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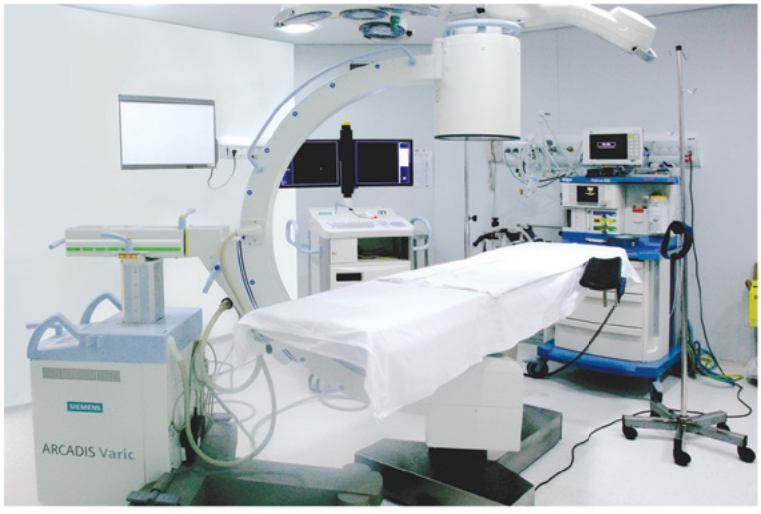

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Constipation. An old new problem

Chinzon D, Chinzon M. Constipation. An old new problem. Arq Gastroenterol. 2022;59(1):1-2.

Constipation is a common gastrointestinal condition in adults and children characterized by unsatisfactory defecation as a result of infrequent stools, difficult stool passage, or both. Definitions of this condition is influenced by variations in geography, language, culture, and level of education. This can create difficulties in interpretation and standardization of prevalence rates obtained from cross-sectional studies[1].

Clinical assessment of the patient with constipation requires careful history taking, in order to identify any red flag symptoms that would need further investigation with colonoscopy to exclude colorectal malignancy[2].

Global prevalence of functional constipation ranged from 15.3% using the Rome I criteria to 10.1%, when the Rome IV criteria was applied. Perhaps this is the reason why we have a significant difference between the prevalence of functional constipation when its definition has been established by the various consensuses over the years. In addition to updates within the criteria themselves, technological advances have enhanced and expanded methods of data collection[3-5].

The differentiation between constipation-predominant irritable bowel syndrome and functional (or chronic) constipation is not simple because both are remarkably similar in terms of their clinical phenotype and response to therapy, when the presence of abdominal pain, occurring on average at least 1 day/week in the last 3 months, associated with at least two of the following: Change in stool frequency (infrequent bowel movements), Change in stool form (hard stools) and related to defecation is its main differential symptom[6-8].

In this issue of **Archives of Gastroenterology**, two studies discuss relevant aspects related to the difficulties observed in the measurement and evaluation of constipation in terms of quantifying the changes observed in constipation as well as the diversity of therapeutic options and, a third paper seeks to evaluate and relate abdominal pain in children and to possible etiopathogenetic mechanisms, among them constipation.

Taniguchi et al. bring the proposal of a clinical score, adapted and aimed at the Brazilian population, aiming to create an environment to measure and quantify changes in intestinal dysfunction and serve as an initial guide for the choice of the best therapy[9].

Perhaps one of the most important aspects of this work is to be adapted specifically to the Brazilian population because, as stated above, the diagnostic criteria are greatly influenced by the environment, habits, diet, and language comprehension, among other aspects. Patients and clinicians often diagnose functional constipation more pragmatically, based on the assessment of symptoms they consider important for a diagnosis.

In addition, this score system is a metric that can and should be used in the comparison of clinical complaints before and after treatment which will reflect on patient satisfaction. Patient satisfaction is an important metric in conditions such as constipation, and higher satisfaction predicts better clinical outcomes in chronic health conditions[10, 11].

Passos et al., through a narrative review, from the perspective of a group of Brazilian experts cover the various aspects of functional constipation, from its pathophysiology to the current treatments of this condition, also highlighting the various alternatives for the correct diagnosis of this condition[12].

Still within the spectrum of functional diseases, Martins et al. in a retrospective epidemiological study in a child population, evaluate the prevalence of abdominal pain and its different possibilities, concluding that functional abdominal pain is the most frequent etiology followed by constipation[13]. A point of attention observed in children, is the long and extensive duration of the investigation and no evidence based medicine treatment, even in a tertiary care level[14-17].

Functional diseases, particularly constipation, continue an object of intense investigation mainly in order to better understand their pathophysiological mechanisms and establish a rationale treatment based on concrete and objective based evidence[18,19].

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Chinzon D, Chinzon M. Constipação. Um velho novo problema. Arq Gastroenterol. 2022;59(1):1-2.

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ORIGINAL ARTICLE

AG-2021-12
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Cross-cultural adaptation and validation of the Constipation Scoring System for the Brazilian population

Thiago Masashi **TANIGUCHI**, Glicia Estevam de **ABREU**, Matheus Mascarenhas **PORTUGAL** and Ubirajara **BARROSO JUNIOR**

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ABSTRACT – Background – Beyond Rome IV Criteria, the assessment of functional constipation in clinical practice can also be obtained by the Constipation Scoring System (CSS). By accessing the CSS, health professionals are able to measure this dysfunction, guiding initial therapeutic approach and post-treatment response. In addition, the CSS enables the standardization of results concerning functional constipation research. **Objective –** To promote translation, cross-cultural adaptation and validation of the CSS for the Brazilian population. **Methods –** To attain the score in Portuguese, the adaptation was accomplished in four steps (translation, back translation, application and adjustments). Afterward, the validation and adaptation to the Brazilian population was performed through test-retest. **Results –** For adults, the convergent validity of the Brazilian version of the CSS showed a significant correlation to the Rome IV Criteria evinced by the positive Spearman correlation (r^2) of 0.816 (P<0.001). Between the test-retest responses, the translated version of the score had a Cronbach's Alpha of 0.972. A high level of internal consistency was also obtained when each item of the questionnaire was assessed separately, revealing an adequate internal reliability. **Conclusion –** The CSS was well adapted and accepted by the Brazilian population, demonstrating the linguistic and psychometric validity of this Portuguese version of the score.

Keywords – Functional constipation; questionnaires; validation study.

INTRODUCTION

Affecting nearly 15% of the general adult population[1-3], constipation is the most prevalent digestive symptom in general population[1]. It is related to high costs for health services[1,4,5] and impacts negatively on patients' quality of life[6]. Functional constipation (FC) is a functional bowel disorder characterized by the predominance of obstruction defecation symptoms and/or reduced spontaneous bowel movements[7].

The major problem in FC research is the dependence on patients' perception of their bowel habits and the range of variations accepted as a normal pattern for each one[8]. Consequently, FC diagnosis tends to be interpretated in different concepts between patients and health professionals, and symptoms of constipation are underestimated in many times by patients themselves[8-10]. For this reason, the current diagnosis of FC and others functional gastrointestinal disorders is obtained in a standardized manner, using clinical aspects listed as Rome Criteria[7,11,12],with Rome IV being the most recent one, published in 2016[7,11,12].

Beyond Rome IV Criteria, the Constipation Scoring System (CSS) can also get FC's assessment in clinical practice. This score is usually used for adult population and that evaluates eight clinical aspects, varying from 0 to 30 points[13]. The advantage of this tool is to quantify the intestinal dysfunction, what guides the initial therapeutic approach and post-treatment response[14]. In addition, the CSS enables the standardization of results on FC research.

However, those scores require linguistic and cultural adjustments to personalize the approach to each population. Although the CSS seems to have a good applicability and acceptance in studies with the Brazilian population[15,16], it has never been translated and adapted for this usage. Therefore, the aim of this study is to promote translation, cross-cultural adaptation and validation of the CSS for the Brazilian population.

METHODS

This is an adaptation and validation study conducted with patients over 18 years receiving care at an outpatient clinic specializing in the diagnosis and treatment of colorectal diseases between July to November 2019. This medical service receives patients referred by gastroenterologists, other specialties or spontaneous demand. Patient with anatomical abnormalities (anorectal and colonic diseases), neurological diseases (central nervous system lesions, Parkinson disease), gastrointestinal tract neuropathy (autonomic neuropathy, Hirschsprung disease, amyloidosis), metabolic disorders (diabetes, hypothyroidism, hyperparathyroidism, metabolic and electrolytes imbalance) or evident psychiatric changes were excluded. All patients enrolled in the study denied receiving a

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previous diagnosis of constipation or treatment for constipation or being referenced with the diagnosis of constipation refractory to the initial treatment. Moreover, they were not submitted to any anorectal physiological examination or radiological exam to differentiate the subtypes of intestinal constipation.

After patient signed the informed consent, a trained researcher applied a sociodemographic characteristic's questionnaire, the CSS's translated version, Rome IV Criteria, as well as a picture of the Brazilian version of Bristol Stool Chart[17]. The study was submitted to the Ethics Committee and obtained approval under the reference of CAAE 15331819.10000.5544.

Diagnostic tests

Gold standard test

The gold standard test for the diagnosis of FC in adults was Rome IV Criteria[12]. Patients were constipated when they presented at least two positive criteria: straining during more than 25% of defecations, lumpy or hard stools (Bristol types 1 or 2) more than 25% of defecations, sensation of incomplete evacuation for more than 25% of defecations, sensation of anorectal obstruction/blockage for more than 25% of defecations, manual maneuvers to facilitate more than 25% of defecations, less than three spontaneous bowel movements per week. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Comparing test

The CSS is a score developed by Agachan et al.[13] that consists in a questionnaire with eight questions about symptoms and clinical signs related to the bowel habits. The usage and the validation of this tool have been authorized by one of the authors of the CSS.

Steps of the study

This study was developed in three steps (FIGURE 1): (1) assessment of equivalence, (2) application in the target population, (3) final evaluation of the pre-test version and final version.

Step 1: assessment of equivalence

Two independent certified translators (translators one and two) produced a Portuguese version from the CSS original English version. The comparative analysis of these translations originated a Portuguese score version, which was translated back to English by a medical professional that was native to the English language and fluent in Portuguese (translator three). Therefore, translator three performed the translation without prior knowledge of the original version.

Subsequently, the original text of the CSS was compared to the one translated from Portuguese, which allowed the inference on the quality of the Portuguese version of CSS. A multidisciplinary team composed of specialists in Pediatric Urology, Coloproctology, pelvic floor physiotherapy, psychology, portuguese and grammar discussed this preliminary version. This preliminary version was modified based on the consensus among the experts' opinions.

Because the original CSS utilizes technical terms not commonly used by the Brazilian population, to expressions like "bowel movements", "abdominal pain" and "constipation" (on topics 1, 4 and 8) were added synonyms such as "evacuations", "bellyache" and "irregular intestinal habit", respectively. Frequency terms were also modified by the consensus of experts and words previously translated as "occasionally" and "regularly" were replaced by expressions more commonly used by Brazilians, such as "sometimes" and "often", respectively. Following the same idea, the term "enema" (on item 6) was substituted for "intestinal lavage", and the term "never" (on item 7) was replaced for "no attempt".

Step 2: application in the target population

The second Portuguese version was adapted by adding an extra alternative answer to each question, which was "I did not understand". After that, a primary test was carried out in a group of 40 patients in order to define the incidence of responses indicating incomprehension about the questionnaire, and the version obtained by this method, denominated as pre-test version, was subsequently evaluated in the third step of this study, in which were assessed the validity and reliability of the Brazilian version of CSS, in Portuguese.

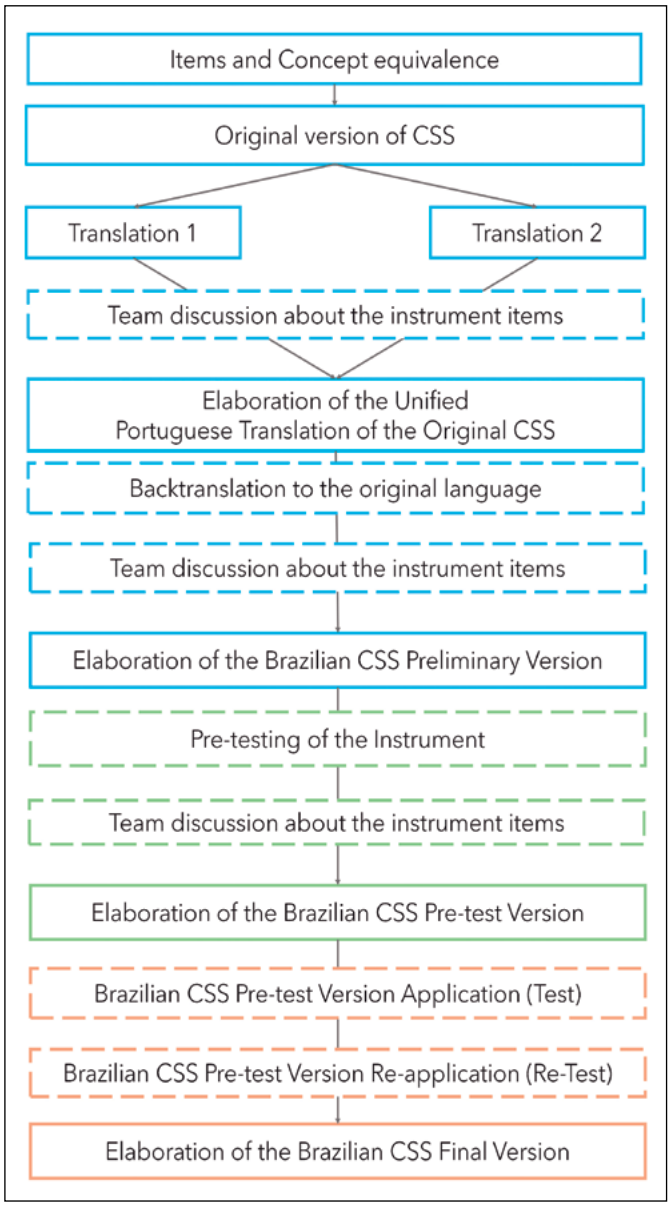

FIGURE 1. Steps of the study.

Step 3: final evaluation of the pre-test version

In the third step, the Brazilian CSS was applied in all patients that fulfilled the study's criteria from the general medical school clinic. The score was applied during medical consults in a private room by a trained researcher. Since the Rome IV Criteria is the gold standard test for the diagnosis of FC in adults, it was applied on the sample and the results of both tests were compared in order to evaluate the correlation between them.

The internal consistency of the Brazilian CSS was assessed by the test-retest method. Patients were submitted to an interview with an examinator who applied the translated version of CSS, and this first evaluation was denominated "First Score". 30 days after, without any further intervention, patients were re-interviewed by a telephone call and this second evaluation was denominated "Second Score".

The protocol used to attempt telephone contact was based on three calls per day, in three different days, and in different times, in a bid to make it possible for patients to participate in the survey. In cases the contact was not succeeded, it was considered loss of follow-up. After evaluating the correlation and the internal consistency, this final version of the Brazilian CSS was considered validated.

Statistical analysis

Categorical variables were expressed in absolute and percentage values. Quantitative variables were described in mean and standard deviation or median and interquartile range, according to their distribution pattern (normal or non-normal) assessed by Kolmogorov-Smirnov test.

The convergent validity of the questionnaire was assessed analyzing the correlation between First CSS score and the quantity of positive variables of the Rome IV by using Spearman or Pearson (r) coefficient, depending on the distribution pattern of variables. Moreover, the internal consistency of the score was evaluated by obtaining a Cronbach's Alpha for First and Second CSS scores, and also for the eight questions that compose the score.

Furthermore, expecting a positive correlation between Rome IV and the Brazilian CSS, it was necessary a sample of 62 patients to obtain a correlation coefficient (r) of 0.35, with bilateral α of 0.05 and β of 0.20 (statistical power of 80%), and thereby validate the tool for the adult population. For precaution, predicting a probable loss of follow-up of about 10% of patients, recruitment of 68 patients was estimated.

Statistical analysis was accomplished by SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp. and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium). The level of significancy was set at 5% for all tests.

RESULTS

Application in the target population

Of the 120 patients enrolled in the study, between July 01, 2016 and November 30, 2019, a total of 40 participated in the step 2 (application in the target population) and 80 in the step 3 (final evaluation of the pre-test version).

In this step, age ranged from 18 to 77 years old (mean =49.55±15.0) and 27 (67.5%) participants were female. Regarding the comprehension of the score, questions 1, 2, 4, 6 and 8 were understood by 100% of patients. In contrast, questions 3, 5 and 7 had a comprehension rate of 85%, 97.5% and 75%, respectively. In view of that, since the level of incomprehension of items three and seven was high, those questions were modified, generating the pre-test version of the Brazilian CSS, in Portuguese.

Final evaluation of the pre-test version

During the final evaluation, 80 patients evaluated in this phase, age ranged from 19 to 84 years old (mean =39.38±15.0) and 66 (82.5%) participants were female.

In convergent validity analysis, the pre-test version of Brazilian CSS showed a significant agreement with the Rome IV criteria for constipation (FIGURE 2), with a positive correlation (r) of 0.816 (P<0.0001). Individual scoring of each Rome IV Criteria is available in TABLE 1.

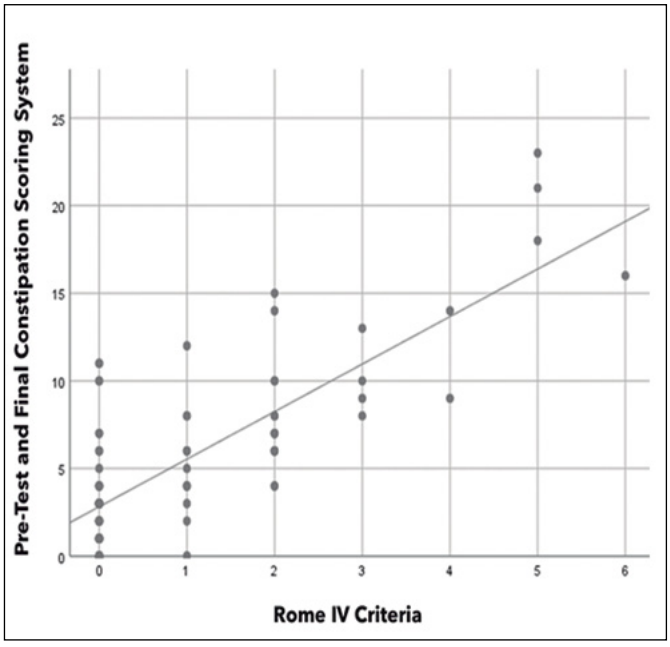

FIGURE 2. Correlation beteween The Rome IV criteria and the pre-test version of Brazilian Constipation Scoring System.

TABLE 1. Individual criteria scoring at the Rome IV Criteria during the final evaluation of the pre-test version.

Rome IV Criteria	N of patients with positive criteria (%)
Straining	24 (30%)
Lumpy or hard stools	12 (15%)
Sensation of incomplete evacuation	23 (29%)
Sensation of anorectal obstruction/ blockage	6 (7.5%)
Manual maneuvers to facilitate defecation	8 (10%)
<3 spontaneous bowel movements per week	8 (10%)

N: number.

In test-retest phase, 14 (17.5%) patients did not complete the second application of the questionnaire. Cronbach's Alpha of the translated version of the scale was 0.972 (TABLE 2). A high concordance was also observed when each item of the questionnaire was assessed separately. The final version of the CSS validated for the Brazilian population is available in TABLE 3.

TABLE 2. Internal consistency of Constipation Scoring System between first and second Scores, and for each question of the scale, obtained by Cronbach's Alpha.

Variables	Test	Correlation
First and Second Scores (total)	Cronbach's Alpha	0.972
First and Second Scores for each question:		
Frequency of bowel movements	Cronbach's Alpha	0.797
Difficulty: painful evacuation effort	Cronbach's Alpha	0.769
Completeness: feeling incomplete evacuation	Cronbach's Alpha	0.780
Pain: abdominal pain	Cronbach's Alpha	0.793
Time: minutes in lavatory per attempt	Cronbach's Alpha	0.798
Assistance: types of assistance	Cronbach's Alpha	0.809
Failure: unsuccessful attempts for evacuating	Cronbach's Alpha	0.798
Per 24 hours		
History: duration of constipation	Cronbach's Alpha	0.797

DISCUSSION

The results obtained by this study showed that the CSS, translated to Portuguese and adapted to the Brazilian population, has a high level of internal consistency and an excellent reliability as an instrument to evaluate constipation in clinical practice.

When created, questionaries are intended to be applied in a specific population, what means that American scores, produced in English, are developed based on American characteristics[13]. Globalization may facilitate the access to these tools. However, since professionals cannot guarantee that aspects are being explored in the right way, literal translations during the clinical practice may represent an error, especially when it comes to symptoms or its impacts on the quality of life[18].

Although constipation is a very prevalent symptom, its definition is quite difficult once it depends on cultural aspects that varies with each population[19,20]. Because of that, the creation of a simple, practical, effective and objective criterion for the diagnosis of this condition is extremely important for clinical practice. Rome IV criteria could satisfy these demands and it standardized the definition of constipation worldwide[7,21,22]. However, it stills has limitations. The inflexibility of dichotomous criteria hampers the diagnosis of constipation as it hinders quantification and comprehension of symptoms impact on quality of life.

CSS was developed in 1996[13], and although it is a simplified tool, this score complements Rome IV Criteria because it quantifies clinical aspects of constipation, allowing health professional to understand and individualize therapeutics approaches for each patient. Besides that, because of its score structure, CSS could also be used as a tool of post-treatment evaluation, monitoring improvement, maintenance or even worsening of cases[14].

TABLE 3. Final Portuguese version of Constipation Scoring System.

Sistema de Pontuação de Constipação	Pontuação*
Frequência de evacuações (fazer cocô)	
1 a 2 vezes a cada 1 a 2 dias	0
2 vezes por semana	1
1 vez por semana	2
Menos do que uma vez por semana	3
Menos que uma vez por mês	4
Dificuldade: esforço com dor para evacuar	
Nunca	0
Raramente	1
Às vezes	2
Quase sempre	3
Sempre	4
Completude: sensação de evacuação incompleta	
Nunca	0
Raramente	1
Às vezes	2
Quase sempre	3
Sempre	4
Tempo: minutos no banheiro por tentativa (para fazer cocô)	
Menos que 5 minutos	0
5 a 10 minutos	1
10 a 20 minutos	2
20 a 30 minutos	3
Mais que 30 minutos	4
Assistência: ajuda para evacuar	
Sem assistência	0
Laxantes estimulantes	1
Assistência digital ou lavagem intestinal	2
Fracasso: tentativas malsucedidas de evacuação por 24 horas	
Nenhuma tentativa	0
1 a 3 tentativas	1
3 a 6 tentativas	2
6 a 9 tentativas	3
Mais que 9 tentativas	4
Histórico: duração da constipação (prisão de ventre)	
<1 ano	0
1 a 5 ano(s)	1
5 a 10 anos	2
10 a 20 anos	3
Mais que 20 anos	4

*Pontuação mínima: 0; pontuação máxima: 30

Despite being an excellent tool, the use of CSS had never been validated for the Brazilian context. Aspiring to guarantee the same effectiveness of the score among our population, the core of this study was to adapt the CSS not only to the Brazilian linguistic aspects, but also to their cultural specifications. For this reason, the methodology of this article was carefully planned and based

on the opinion of health experts and a Portuguese language specialist, what allowed us to structure the questionnaire conciliating technical issues with the peculiarities of Brazilian culture, and that was reflected on the high level of comprehension observed during the pre-test.

Similar results were also found on studies that aimed to validate other scales for the Brazilian population. The Bristol Stool Scale was validated by Martinez et al. (2012)[17], while the Wexner Incontinence Score was adapted by Meinberg (2014)[23]. Methodology utilized in these studies were quite similar to ours and both of them obtained a good internal consistency with significant correlation between the adapted version and the gold standard test that was adopted. Furthermore, this study demonstrated a positive linear correlation of 0.816, which is higher than the obtained on the validation of Wexner Incontinence Score (negative linear correlation of 63%) that adopted the Fecal Incontinence Quality of Life (FIQL) as the gold standard test[23].

Moreover, the validation of Bristol Stool Scale also counted with the inclusion of health professionals on test-retest phase[22], which was not done in this study because our objective was to adapt CSS in terms of complexity and linguistic adequacy, in order to guarantee the comprehension by patients and professionals. On the other hand, Leite et al. (2018)[24] assumed to get a satisfactory validation once the internal consistency was about 0.8. Since this study showed an internal consistency of 0.972, it is possible to admit an excellent functionality of the CSS adapted version.

Difficulty of follow-up can be highlighted as the major limitation of this study. Once the second application of the questionnaire was accomplished by a telephone call, 17.5% of the sample did not complete this tool. However, this was a predicted limitation, and some measures were taken to contain it: the protocol of telephone contact involved different days and times, and sample calculation was done with a safety margin of 10%. The small sample size could also be taken as a limitation, but 80 patients was sufficient when considering sample calculation based on the expected correlation, allowing analysis with significance and satisfactory statistical power. Moreover, it is important to mention that despite of its large usage in Brazil, the Rome IV Criteria, adopted as the gold standard, have not been officially translated to Portuguese yet. However, we emphasize that the Rome IV criterion is a score of dichotomous responses. In turn, the CSS, evaluating the intensity of the symptoms, presents about five response options. Thus, respondents may find it more difficult to understand its literal translation.

Besides, despite the significant correlation between the CSS and the Rome IV Criteria for Functional Constipation, is not possible to affirm that this same correlation significance would be applicable to each bowel constipation subtype (FC, defecatory dysfunction, and colonic inertia). However, none of the patients included in this study had a medical record of FC refractory of any initial constipation management that indicated further examination with anorectal physiology workup or radiological exams. This approach is consonant with the American Gastroenterological Association (AGA) medical position statement on constipation which indicates additional examination when there is an inadequate response to the therapeutic trial (fiber ± laxatives)[25]. Moreover, in a large cohort study with more than 1.400 adults with FC[26], the normal transit constipation represented the most frequent subtype (65%), followed by the dyssynergic defecation type (30%), and colonic inertia, which represents only (5%) of the constipation subtypes[26].

In conclusion, this study demonstrated the linguistic and psychometric validity of the Brazilian CSS, reinforcing the importance of this tool for diagnosis and management of constipated patients in Brazil. The translation to Portuguese had an excellent adequacy and it was well accepted by the population due to it's simplified structure associated with questions more immersed in symptoms impact on quality of life.

Authors' contribution

Taniguchi TM: data collection, survey execution, writing of text, statistical analysis. Abreu GE: data collection, survey execution, review. Portugal MM: writing of text, translation and review. Barroso Junior U: writing of text, review.

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RESUMO – Contexto – Além dos Critérios de Roma IV, a avaliação da constipação funcional também pode ser obtida por meio do *Constipation Scoring System* (CSS). Ao acessar o CSS, o profissional de saúde consegue mensurar a constipação funcional, orientando a abordagem terapêutica inicial e a resposta pós-tratamento. Além disso, o CSS possibilita a padronização dos resultados das pesquisas sobre esta disfunção. **Objetivo –** Promover a tradução, adaptação transcultural e validação do CSS para a população brasileira. **Métodos –** Para obtenção da versão do CSS em português, a adaptação foi realizada em quatro etapas (tradução para o inglês, retrotradução para o português, aplicação e ajustes). Posteriormente, foi realizada a validação e adaptação para a população brasileira por meio de teste-reteste. **Resultados –** Para adultos, a validade convergente da versão brasileira do CSS apresentou correlação significativa com os critérios de Roma IV evidenciada pela correlação de Spearman positiva (r) de 0,816 (P<0,001). Entre as respostas do teste-reteste, a versão traduzida do escore apresentou um Alpha de Cronbach de 0,972. Um alto nível de consistência interna também foi obtido quando cada item do questionário foi avaliado separadamente, revelando uma confiabilidade interna adequada. **Conclusão –** O CSS foi bem adaptado e aceito pela população brasileira, demonstrando a validade linguística e psicométrica da versão em português do escore.

Palavras-chave – Constipação funcional; questionários; estudo de validação.

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ORIGINAL ARTICLE

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Risk factors associated with fracture of the lumbosacral spine and its compromise in the quality of life of cirrhotics

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ABSTRACT – Background – Chronic hepatic disease is associated with osteoporosis, osteopenia or osteomalacia. Osteoporosis and fractures due to bone fragility present high prevalences and are more frequent in patients with liver cirrhosis than in the general population. The search for a diagnosis of osteopenia and osteoporosis in this population may allow early intervention and modify unfavorable outcomes. **Objective –** To know the prevalence of osteopenia or osteoporosis and of fracture due to bone fragility in individuals with liver cirrhosis, the associated risk factors, and its compromise in their quality of life (QoL). **Methods –** Observational, transversal study performed with 71 liver cirrhosis patients of the Hepatology Service of the *Hospital de Base do Distrito Federal*, Brasília, DF, Brazil, between July 2017 and December 2018. The patients were submitted to bone densitometry (DXA) of the lumbar spine and of the femoral neck, to x-ray of the lumbosacral spine and to the Chronic Liver Disease Questionnaire (CLDQ) for the evaluation of quality of life (QoL). The Fracture Risk Assessment (FRAX) major was calculated for patients >50 years old. The analyses were performed for the evaluation of the risk factors associated with lumbosacral spine fracture. **Results –** The majority (62%) of the 71 evaluated patients was diagnosed with osteoporosis or osteopenia on DXA. Of the 44 patients with osteopenia or osteoporosis, 52.3% were female, with a mean age of 62.6±9.51 years old, with the majority (72.7%) being Child A, cirrhotics of alcoholic etiology (36.4%), and with an intermediate QoL according to the CLDQ (3.3). Regarding the patients with lumbosacral spine fracture, the mean age was 61.6±11.1 years old, 60% were female, most of them Child A (66.7%), of alcoholic etiology (46.7%), and with an intermediary QoL according to the CLDQ (3.5). The presence of osteopenia and/or osteoporosis was associated with lumbosacral fracture (P<0.001), without correlation with the other analyzed variables: age, body mass index, gender, presence and absence of ascites, Child-Pugh classification, vitamin D, calcium, and phosphorus serum concentration, cirrhosis etiology and FRAX major. **Conclusion –** The prevalence of hepatic osteodystrophy was high, and the occurrence of lumbosacral spine fracture was more associated with osteoporosis and/or osteopenia among the cirrhotic patients studied. The QoL was intermediate and with no differences between cirrhotics with and without fracture.

Keywords – Osteoporosis; liver cirrhosis; bone fractures; quality of life.

INTRODUCTION

The development of liver cirrhosis occurs when the hepatic parenchyma acquires a nodular form as a result of the fibrosis consequent to chronic hepatic damage[1]. While this occurs, complications secondary to this process also appear, such as bone mineral disease, one of the main complications of chronic hepatic disease[2,3].

The term hepatic osteodystrophy, which is controversial in the literature, but is still cited in recent publications, is used to define the bone disease associated with chronic hepatic disease, and includes osteoporosis, osteopenia and, more rarely, osteomalacia[4-6]. Bone disease occurs when there is an imbalance in bone remodeling, followed by the reduction in osteogenesis and higher bone resorption[7,8]. Therefore, in advanced cases, the bone mass will reduce, and the risk of fracture will increase[9].

Osteoporosis and fractures due to bone fragility are more frequent in patients with liver cirrhosis than in the general population[10], even in the absence of risk factors such as cholestasis or alcohol abuse[11]. The prevalence of osteoporosis among patients with chronic hepatic disease is reported to be between 12 and 55%[4,12], depending on the criteria used for the diagnosis, as well as on the etiology, nutritional status, age group, and degree of hepatic disease[2,4].

As such, a better approach is mandatory to evaluate the prevalence of osteopenia or osteoporosis and of fractures due to bone fragility in individuals with liver cirrhosis, the associated risk factors, as well as to evaluate the interference in the quality of life (QoL) of these individuals.

METHODS

Initially, a total of 146 cirrhotics was included in the present observational, transversal study performed in the hepatology ambulatory care facility of the *Hospital de Base do Distrito Federal* (HBDF, in the Portuguese acronym), Brasília, DF, Brazil, in the period between July 2017 and December 2018, established for data

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collection. Out of this total, 46 patients were excluded because they had a previous diagnosis of osteopenia and/or osteoporosis and were already being treated for this condition. These patients were excluded because they were already in treatment (either with or without medication) for osseous alterations and, therefore, were under a lower risk of fracture, and because this was a confounding factor in the prevalence of osseous fracture in the studied sample. Besides, this could also generate a bias in the QoL questionnaire.

The sample consisted of 71 patients with liver cirrhosis of the hepatology service of the HBDF, selected during routine ambulatorial consultations. All patients had liver cirrhosis from any etiology, were >18 years old, had not presented hospital internment in the previous 30 days, and signed the free and informed consent form. All subjects were informed of the objectives of the present research.

The research project was approved by the Ethics and Research Committee of the *Fundação de Ensino e Pesquisa em Ciências da Saúde* (FEPECS, in the Portuguese acronym). The patients were ensured of the anonymity and confidentiality concerning the provided information. The present research was approved under CAAE opinion number 78583417.2.0000.5553.

The exclusion criteria were pregnancy, patients with neoplasia in any site and bone metastasis, use of medication that interfere in bone metabolism, and previous osteoporosis or osteopenia under treatment.

The following clinical data were collected: etiology of liver cirrhosis, gender, and age; and the Child-Turcotte-Pugh score[13] and body mass index (BMI) were calculated. From blood retrieved from the antecubital vein, after night fasting of 8 hours, the following markers were measured: calcium (o-cresolphthalein complexone [oCPC] method) corrected by serum albumin, with normal values between 8.5 and 10.2 mg/dL, and phosphorus (phosphorus phosphomolybdate method), with normal values between 2.5 and 4.5 mg/dL, and 1.25-dihydroxycholecalciferol vitamin (quimioluminescence method; normal values between 30 and 60 ng/mL). Serum concentrations of 25-hydroxyvitamin D (vitamin D) <30 ng/mL[14] were considered hypovitaminosis D for higher-risk patients, such as patients with chronic hepatic disease.

For the evaluation of bone mineral density (BMD), bone densitometry (DXA) of the lumbar spine and of the femoral neck was performed with an explorer QDR bone densitometer (Hologic, Inc., Marlborough, MA, USA). The diagnostic parameters used in standard deviation (SD) were in accordance with the 2008 guidelines of the *Sociedade Brasileira de Densitometria Clínica*[15]. Premenopausal women and males <50 years old who presented a Z-score ≤2.00 were defined as having a BMD below the estimated value for this age group. Those with a Z-score >2.00 were considered as having a BMD within the estimated value for this age group. Postmenopausal women and males >50 years old with a T-score ≤ -1 were classified as having a normal BMD, those with a T-score between -1 and -2.5 were considered as having osteopenia, and those with a T-score ≤2.5 were considered as having densitometric osteoporosis.

The diagnosis of fracture due to bone fragility was made by radiography of the lumbosacral spine, in anteroposterior and profile incidences, which was performed in all patients, both symptomatic and asymptomatic. Fracture due to bone fragility was defined as a vertebral body fracture due to minimal trauma, such as fall from one's own height or even without identification of the trauma.

The FRAX-Brazil score of patients >50 years old was calculated. The probability of fracture within 10 years was calculated from data such as age, gender, BMI, and risk factors such as a history of fractures due to bone fragility, family history of fracture of the femur, smoking, prolonged use of corticosteroids, rheumatoid arthritis, other causes of secondary osteoporosis and high alcohol intake[16-18]. The DXA was also used for the calculation of the FRAX. In the present study, we calculated the FRAX major of the patients during the consultation, without knowing which patients had fractures, with the aim of correlating higher FRAX scores for major fracture in the patients subsequently diagnosed with fracture of the lumbosacral spine. For the calculation of the FRAX, we only included patients >50 years old or postmenopausal women, because for its calculation, only the T-score of the femoral neck is used, and not the Z-score[19].

The Chronic Liver Disease Questionnaire (CLDQ) was applied by a single examiner and it was translated into Portuguese considering the cultural adaptation of this instrument for its use in Brazil. The authors translated it from English into Portuguese, and its equivalence was evaluated by a bilingual translator. The patients responded to the 29 questions distributed into six domains, and each question had seven levels of answers: from one (all the time) to seven (never). The six domains evaluated were abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worrying[20]. It was considered that the closer the score is to seven, the higher the QoL of the patient, and the closer the score is to one, the worse the QoL of the patient, and intermediate values correspond to an intermediate QoL. The correlation between the presence or absence of bone fracture and QoL was studied. The authors have opted for the use of the CLDQ because it is validated for patients with liver disease.

The diagnosis of liver cirrhosis was defined by biopsy or by the combination of clinical, radiological, laboratory and/or endoscopic findings compatible with liver insufficiency and portal hypertension.

The Child-Turcotte-Pugh score was used for the evaluation of the severity of the disease, according to the following scores: Child-Pugh A (5 and 6 points); Child-Pugh B (7–9 points); and Child-Pugh C (10–15 points)[13].

Continuous variables with normal and nonnormal distribution were presented in mean (standard deviation [SD]) and median (interquartile range [IQ]), and categorical variables were presented in percentage. Categorical variables were compared using the chi-squared test, and continuous variables were compared using the *t*-test or the Mann-Whitney test, according to their distribution. A *P*-value <0.05 was considered statistically significant. Thus, the analysis of the bivariate models were performed. Those who presented an altered DXA (presence of osteopenia or osteoporosis) were categorized in a single variable, called altered femoral and lumbosacral spine DXA, and its distribution was assessed in relation to the following variables: age, gender, BMI, Child-Pugh, etiology of cirrhosis, ascites, CLDQ, and serum concentrations of vitamin D, calcium, and phosphorus. The individuals were categorized as with presence or absence of bone fractures (BFs) in the x-ray of the lumbosacral spine. The FRAX major was compared with the presence or absence of fractures in order to try to establish a correlation by the Student *t*-test.

RESULTS

A total of 29 patients diagnosed with and under treatment for hepatocellular carcinoma was also excluded, since these patients could present with secondary osseous compromise or be using

medication that interfere with bone metabolism and, therefore, could also be a confounding factor in the prevalence of hepatic osteodystrophy and spontaneous bone fracture. Besides, the presence of a neoplasm and the possibility of the use of sorafenib may cause asthenia and interfere in the result of the CLDQ. The final sample consisted of 71 patients who fulfilled the inclusion criteria of the present study (FIGURE 1).

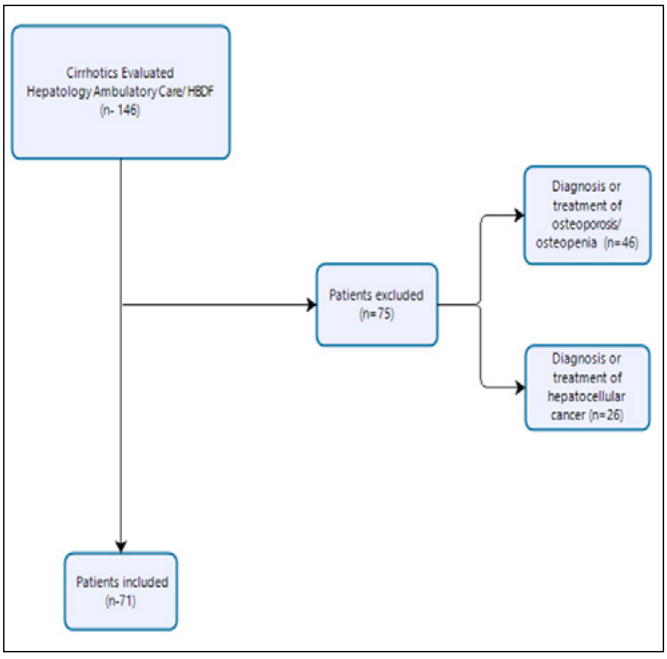

FIGURE 1. Patient inclusion and exclusion algorithm.

The epidemiological, clinical, and laboratory characteristics of the 71 patients are presented in TABLE 1. It is observed that the patients were adults and that there was a discrete predominance of males. Most participants were classified as Child-Pugh A and did not present ascites. The mean BMI was 25.9 kg/m^2. The mean serum concentrations of vitamin D, ionized calcium, and phosphorus were within the parameters of normality. The average CLDQ score was 3.9, characterizing an intermediate QoL in the total sample.

The basal characteristics of the 27 (38%) patients without hepatic osteodystrophy (osteopenia/osteoporosis) and of the 44 (62%) patients with hepatic osteodystrophy are shown in TABLE 2.

In the normal DXA group, the patients were adults, with a predominance of males, and the main etiology of hepatic disease was cirrhosis of viral etiology. Most of the patients were Child A and did not present with ascites. The mean BMI and the mean serum concentration of phosphorus, calcium, and vitamin D were within the parameters of normality. The average CLDQ score was 3.4, characterizing an intermediary QoL in these patients.

In the altered DXA group, the patients were adults, with a discrete predominance of females. The main etiology of hepatic disease in these patients was cirrhosis of alcoholic etiology, and the minority by nonalcoholic steatohepatitis (NASH). Most of the patients were Child A and did not present with ascites. The mean BMI and the mean serum concentrations of phosphorus, calcium and vitamin D were within the parameters of normality. The average CLDQ score was 3.3, characterizing an intermediate QoL in this sample.

TABLE 1. Epidemiologic, clinical and laboratory characteristics of 71 patients with liver cirrhosis.

	Total
n	71
Age (years old), SD	57.46±12.38
Male (n)	54.9% (39)
BMI (kg/m^2), SD	25.9±3.9
Etiology of cirrhosis	
Virus (n)	29.6% (21)
Alcohol (n)	29.6 % (21)
AIH (n)	14.1% (10)
NASH (n)	12.6% (9)
Cryptogenic (n)	5.63% (4)
BCS (n)	2.82% (2)
PBC (n)	2.82% (2)
Drug (n)	1.40% (1)
WD (n)	1.40% (1)
Child A (n)	74.6% (53)
Child B (n)	16.9 % (12)
Child C (n)	8.5% (6)
Ascites	
Absent (n)	81.7% (58)
Present (n)	18.3% (13)
Vitamin D (mg/dL), SD	30.3±16.5
Calcium (mg/dL), SD	9.2±0.6
Phosphorus (mg/dL), SD	3.6±0.8
CLDQ	3.9±1.2

BMI: body mass index; AIH: auto immune hepatitis; NASH: nonalcoholic steatohepatitis; BCS: Budd Chiari Syndrome; PBC: primary biliary cirrhosis; WD: Wilson's disease; CLDQ: chronic liver disease questionnaire; SD: standard deviation.

TABLE 2. Comparison between clinical and laboratory characteristics of patients with and without densitometric alteration.

	Normal DXA (n=27)	Altered DXA (n=44)	*P*-value
Age (years old), SD	49±11.95	62.66±9.51	<0.001[1*]
Male (n)	66.6% (18)	47.7% (21)	
BMI (kg/m^2), SD	25.9±4.81	25.94±3.46	0.96
Etiology of cirrhosis (n)			0.36[2]
Virus (n)	37% (10)	25% (11)	
Alcohol (n)	18.5% (5)	36.4% (16)	
AIH	14.8% (4)	13.6% (6)	
NASH (n)	11.1% (3)	13.6% (6)	
Cryptogenic (n)	7.4% (2)	4.5% (2)	
BCS (n)	7.4% (2)	0% (0)	
PBC (n)	0% (0)	4.5% (2)	
Drug (n)	0% (0)	2.3% (1)	
WD (n)	3.7% (1)	0% (0)	
Child-Pugh %			0.53[2]
Child A (n)	77.7% (21)	72.7% (32)	
Child B (n)	11.1% (3)	20.5% (9)	
Child C (n)	11.1% (3)	6.8% (3)	
Presence of ascites	18.5% (5)	18.2% (8)	0.97[2]
Vitamin D (mg/dL), SD	28.31±12.33	31.22±18.3	0.60[1]
Calcium (mg/dL), SD	9.26±0.70	9.30±0.64	0.83[1]
Phosphorus (mg/dL), SD	3.6±0.78	3.7±0.94	0.92[1]
CLDQ, SD	3.4±1.2	3.3±1.3	0.20[1]

BMI: body mass index; AIH: auto immune hepatitis; NASH: nonalcoholic steatohepatitis; BCS: Budd chiari syndrome; PBC: primary biliary cirrhosis; WD: Wilson's disease CLDQ: chronic liver disease questionnaire; DXA: bone densitometry; SD: standard deviation.
*significance at $P<0.05$. [1]Student *t*-test; [2]Mann-Whitney U-test

Comparing both groups, we observed that the age was significantly higher in the altered DXA group compared with the normal DXA group. The other parameters examined were not significantly different between both groups.

We present and compare the clinical and laboratory characteristics between the group of patients who had fractures and those who did not have fractures in TABLE 3. It is observed that there was no significant difference between both groups in any of the examined characteristics, except for the presence of osteopenia and/or osteoporosis on DXA as an associated factor to lumbosacral fracture ($P<0.001$).

TABLE 3. Comparison between clinical and laboratory characteristics of patients with and without bone fracture.

	Presence or absence of bone fracture		
	Presence	Absence	*P*-value
Patients (n)	21.1% (15)	78.9% (56)	
Age (years old), SD	61.6±11.1	56.3±12.5	0.1
BMI (kg/m^2), SD	24.9±2.7	26.2±4.2	0.1
Male (n)	40% (6)	58.9% (33)	0.1
Ascites			0.8
Absent (n)	80% (12)	82.1% (46)	
Present (n)	20% (3)	17.9% (10)	
Child-Pugh			0.6
A (n)	66.7% (10)	76.8% (43)	
B (n)	20% (3)	16.1% (9)	
C (n)	13.3% (2)	7.1% (4)	
Lumbar spine and femur DXA			0.001
Normal (n)	0% (0)	32.1% (18)	
Osteopenia (n)	13.3% (2)	44.7% (25)	
Osteoporosis (n)	86.6% (13)	23.2% (13)	
Vitamin D (mg/dL), SD	39.6±26.3	27.2±10.9	0.1
Calcium (mg/dL), SD	9.6±0.6	9.1±0.9	0.1
Phosphorus (mg/dL), SD	3.7±0.7	3.6±0.9	0.8
CLDQ	3.5±1.3	4.0±1.1	0.1
Etiology			0.4
Virus (n)	20% (3)	32.1% (18)	
Alcohol (n)	46.7% (7)	25% (14)	
AIH (n)	13.3% (2)	14.3% (8)	
NASH (n)	13.3% (2)	12.5% (7)	
Cryptogenic (n)	0% (0)	7.1% (4)	
BCS (n)	0% (0)	3.6% (2)	
PBC (n)	0% (0)	3.6% (2)	
Drug (n)	6.7% (1)	0% (0)	
WD (n)	0% (0)	1.8% (1)	

BMI: body mass index; AIH: auto immune hepatites; NASH: nonalcoholic steatohepatitis; BCS: Budd chiari syndrome; PBC: primary biliary cirrhosis; WD: Wilson's disease CLDQ: chronic liver disease questionnaire; DXA: bone densitometry; SD: standard deviation.

The FRAX major of all patients >50 years old was calculated. Of the 15 fractured patients, two patients <50 years old were excluded. In the FRAX major and lumbosacral spine fracture association (Student *t*-test), we found a *P*-value of 0.051, and a confidence interval (CI) of 0.0005–2.094.

DISCUSSION

In the present study, we have shown that individuals with liver cirrhosis present a high incidence of osteoporosis and osteopenia, as well as of BFs in the lumbar spine. Most of the patients were classified as Child A, did not present with ascites, and their serum concentrations of vitamin D, calcium, and phosphorus were within the normality parameters. The QoL of the patients was intermediate. The only significant difference in the evaluation of the patients with and without fractures was a normal DXA in those who did not have fractures.

In the last decades, with the advancement in the management of the complications of cirrhosis and the offer of liver transplantation, it became possible to have higher survival and QoL rates in

cirrhotic patients. Currently, a compensated cirrhotic reaches an average survival rate of 12 years after the diagnosis of liver cirrhosis[21]. However, the higher survival rate of these patients increased the risk of extrahepatic complications, such as osteoporosis[22,23].

In the present study, we have shown that liver cirrhosis patients of various etiologies, but mainly of viral or alcoholic etiologies, present a high rate of osteoporosis or osteopenia (62%).

Regardless of the etiology of chronic hepatic disease, the presence of cirrhosis implies in a twofold higher risk of BF in relation to the noncirrhotic population[4], and the etiology of these disorders is complex and multifactorial[2]. In a study[24] that followed 97 liver cirrhosis patients of several etiologies, the prevalence of hepatic osteodystrophy was of 78.4%, corroborating the hypothesis, like the present study, that liver cirrhosis patients may have a higher chance of presenting altered DXA, regardless of the etiology of the hepatic disease.

In the present study, we observed that more advanced age was more associated with altered DXA. The pathogenesis of the bone disorders in cirrhotic patients remains not completely elucidated[11], but already established that risk factors for osteoporosis, such as advanced age, alcohol abuse, smoking, previous fractures, denutrition, and loss of muscular mass, are frequent in patients with liver cirrhosis[25].

It was also possible to observe the diagnosis of lumbosacral spine fracture on x-ray in 21% of these cirrhotic patients. In a literature review, the prevalence of fractures in patients with chronic hepatic disease varied between 7 and 35%[26]. Many of the differences in frequency found between what we have observed and what has been observed in other studies are related to the selection of patients. In the analysis of risk factors, no significant difference was found between patients with and without fracture in relation to age, gender, BMI, presence of ascites, Child-Pugh classification, serum concentrations of vitamin D, calcium, and phosphorus, etiology of the cirrhosis, and FRAX major. However, the presence of osteopenia or osteoporosis on DXA was significantly correlated with lumbosacral fracture (P<0.001).

The detection of osteoporosis requires a high level of clinical suspicion for its diagnosis, since around one-third of vertebral spine fractures are asymptomatic and will only be detected radiologically[4]. Both conditions, osteoporosis and BF, have a significant impact on these patients, for they cause fractures that may result in chronic pain, prolonged immobility, deformities, and may affect the QoL and even the survival rate[2,4,27]. Bone fracture implies in a higher risk of refracture[28], which may impact even more the morbidity and the worsening of the QoL of the patient with liver cirrhosis[4,29].

With the development of DXA, it has become possible to measure the BMD and, thus, to evaluate which patients would be under a higher risk of BF. Conventional diagnostical radiographies also are an important component in the evaluation of osteoporosis, since they are useful in the detection of fractures due to fragility, such as fractures due to vertebral compression, regardless of the DXA[4].

According to the 2014 Clinical Protocol and Therapeutic Guidelines for Osteoporosis (PCDT, in the Portuguese acronym) of the Brazilian Ministry of Health, the tracing of osteoporosis in women ≥65 years old and in men >70 years old is indicated, regardless of the presence of risk factors[30]. In this manual, liver cirrhosis is not included as a risk factor for osteoporosis, only primary biliary cholangitis (PBC), not contemplating other individuals with chronic hepatic disease, as has been commented in previous studies[31].

According to the data presented in the present study, we have observed an average age of 61.6±11 years old among osteoporosis or osteopenia patients with lumbosacral fracture, which could have been avoided if this tracing had been established earlier. Besides, fractures in liver cirrhosis patients who presented only with osteopenia were found. In 13.3% of the sample of fractured patients, lumbosacral spine fracture occurred in osteopenia patients.

A study evidenced a prevalence of 27% of fractures in liver cirrhosis patients of various etiologies, being higher in the osteoporosis group than in the group without this ailment (P<0.001)[32]. It is interesting that any type of previous fracture was considered, which may have overestimated this result, but it had a slightly higher result than what we have observed evaluating only fractures due to bone fragility.

Clinical tools may also be useful in the assessment of the risk of fracture due to bone fragility, such as the FRAX algorithm. This score was developed by the World Health Organization (WHO) with the aim of evaluating the probability of bone fracture in the next 10 years (the probability of hip fracture and of major fracture is expressed in percentage) and of evaluating the decision regarding the initiation of medical treatment for osteoporosis[33,34].

In the present work, the FRAX major of the patients >50 years old was calculated in the first consultation, without knowledge of the results of the lumbosacral spine x-ray, as an attempt to avoid observation bias. Afterwards, no correlation was found between higher FRAX major scores in patients with lumbosacral spine fracture on x-ray (P=0.051). However, the long CI (0.005–2.094) suggests that this correlation may be possible with a larger sample of patients. A limitation of this tool is that in order to calculate the FRAX, the femoral T-score is used, being possible to include only men >50 years old and/or menopausal women. In the present study, the calculations of the FRAX of 2 of the 15 fractured patients were excluded because they were <40 years old.

According to the data described here, age, gender, presence of ascites, Child score, serum concentrations of vitamin D, calcium, and phosphorus, and the etiology of liver cirrhosis were not predictors of the development of BF diagnosed with lumbosacral spine x-ray. Only the DXA of the lumbar spine and/or of the femoral neck evidencing osteopenia or osteoporosis was a common characteristic in all fractured patients.

A meta-analysis of prospective studies showed that the risk of fracture increases progressively with BMD reduction[35]. The DXA has high specificity for fracture, but low sensibility[36]. Therefore, associating lumbosacral spine x-ray with DXA, as we have done in the present work, may be a strategy to increase the diagnostic sensibility of fracture due to bone fragility, which is often asymptomatic[37].

Regarding the QoL related to BF, it is known that vertebral fractures are often asymptomatic or lightly symptomatic, but that, in the long term, they may affect substantially the QoL of the patients[37]. Osteoporosis increases the risk of fractures and compromises the QoL of the patients due to pain and deformities[38-40].

In the present study, an inferior QoL was not observed in fractured patients. The QoL analysis was performed with the CLDQ, an approved questionnaire for the use in liver cirrhosis patients, which allows the evaluation of six domains related to the life of the patient[41].

However, this questionnaire, in our critical evaluation, has important limitations, being very subjective, with answers that may be very similar to one another, but with different scores that may alter the final result of the questionnaire. Besides, only the

previous 2 weeks of the lives of the patients are evaluated, which may difficult the global evaluation of their QoL. Perhaps, with the use of other questionnaires that may be more objective and that evaluate a longer period of the life of the patient, we may find data that better evaluate the QoL of these patients. This is because it has been shown that the QoL of fractured patients, which was evaluated by three different questionnaires, was compromised[41].

Regarding vitamin D serum concentrations, it is known that vitamin D deficiency is widely diagnosed in patients with chronic hepatic disease[42,43]. Its origin is multifactorial and is correlated with the severity of hepatic disease[24,42,44]. Low serum concentration of vitamin D is associated with osteoporosis and with a high risk of BF, especially in elderly patients[45,46]. However, in our sample, it was not possible to correlate low vitamin D serum concentration with fractures. Perhaps, this may be explained by the small sample size or by the fact that the patients live in a region where solar exposure is much higher than that of the locations of other studies.

Regardless of the Child-Pugh score, of the etiology of chronic liver disease and of vitamin D serum concentration, we should consider the risk of already fractured patients presenting with a new fracture. This has been reported by a study[28] that evidenced that the risk of refracture is 1.73 times higher in patients with previous vertebral fracture. It may be possible that this risk is even higher in liver cirrhosis patients; however, to our knowledge, this data is not available in the literature. If the fractured is not detected and approached early, in the future the fracture may evolve to refracture and impact significantly the QoL of these patients.

Even though the sample was small, this present study draws attention to the hypothesis that the high prevalence of hepatic osteodystrophy in liver cirrhosis patients and the higher risk of BFs secondary to low BMD raises questions about considering tracing these patients at a lower age than that of the general population. This way, we will be able to identify and to intervene in the risk factors associated with bone disease and to institute an early therapeutic program. Therefore, we will be able to avoid negative outcomes that compromise the QoL and the life expectancy of this population.

CONCLUSION

The rate of lumbosacral spine fracture was high in our casuistry, and it is correlated with the presence of osteoporosis and/or osteopenia. This suggests that liver cirrhosis patients should undergo DXA and lumbosacral spine x-ray for early diagnosis and treatment. The QoL of patients with hepatic osteodystrophy is intermediate and there is no difference between patients with and without fracture, but this may reflect the limitations of the CLDQ, which was used in the present research.

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Authors' contribution

Siqueira MMLG: data collection, research conduction and writing of the text. Casulari LA: research conduction and writing of the text. Freitas WM: statistical analysis. Carneiro MV: research conduction and data collection. Mendes LSC: research conduction, data collection and writing of the text.

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Siqueira MMLG, Casulari LA, Freitas WM, Carneiro MV, Mendes LSC. Fatores de risco associados à fratura de coluna lombossacra e seu comprometimento na qualidade de vida em cirróticos. Arq Gastroenterol. 2022;59(1):9-15.

RESUMO – Contexto – A doença hepática crônica associa-se com osteoporose, osteopenia ou osteomalácia. A osteoporose e as fraturas por fragilidade óssea têm altas prevalências e são mais frequentes em pacientes com cirrose hepática do que na população geral. A busca por osteopenia e osteoporose nesta população pode permitir a intervenção precoce e modificar os desfechos desfavoráveis. **Objetivo –** Conhecer a prevalência de osteopenia ou osteoporose e de fraturas por fragilidade óssea em portadores de cirrose hepática, fatores de risco associados e seu comprometimento na qualidade de vida. **Métodos –** Estudo observacional e transversal realizado com 71 pacientes portadores de cirrose hepática do Serviço de Hepatologia do Hospital de Base do Distrito Federal, Brasília, DF, Brasil, no período de julho de 2017 a dezembro de 2018. Os pacientes foram submetidos à densitometria óssea de coluna lombar e colo de fêmur, raio-x de coluna lombo sacra e ao questionário *Chronic Liver Disease Questionnaire* (CLDQ, na sigla em inglês) para avaliação de qualidade de vida. Foi calculado o escore de Fracture Risk Assessment Tool "FRAX Maior" nos pacientes >50 anos. As análises foram realizadas para a avaliação dos fatores de risco associados à fratura de coluna lombo sacra. **Resultados –** Dos 71 pacientes avaliados, a maioria (62%) foi diagnosticada com osteoporose ou osteopenia à densitometria. Dos 44 portadores de osteopenia ou osteoporose, 52,3% eram do sexo feminino, com idade média de 62,6±9,51 anos, sendo a maioria (72,7%) Child A, cirróticos de etiologia alcoólica (36,4%) e com qualidade de vida intermediária ao CLDQ (3,3). Dos pacientes com fratura de coluna lombo sacra, a média de idade foi de 61,6±11,1 anos, 60% eram do sexo feminino, a maioria Child A (66,7%), de etiologia alcoólica (46,7%), e apresentaram qualidade de vida intermediária ao CLDQ (3,5). A presença de osteopenia e/ou osteoporose esteve associada à fratura lombo sacra (P<0,001), sem correlação com as demais variáveis analisadas: idade, índice de massa corporal (IMC), gênero, presença e ausência de ascite, classificação de Child-Pugh, concentrações séricas de vitamina D, cálcio e fósforo, etiologia da cirrose e "FRAX maior". **Conclusão –** A prevalência de osteodistrofia hepática foi elevada, e a ocorrência de fratura de coluna lombo sacra esteve mais associada à osteoporose e/ou osteopenia entre cirróticos estudados. A qualidade de vida se mostrou intermediária e sem diferença entre cirróticos com e sem fratura.

Palavras-chave – Osteoporose; cirrose hepática; fraturas ósseas; qualidade de vida.

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Small as well as large colorectal lesions are effectively managed by endoscopic mucosal resection technique

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ABSTRACT – **Background** – Endoscopic mucosal resection (EMR) is an easy-to-use treatment option for superficial colorectal lesions, including lesions ≥20 mm. **Objective** – To evaluate the effectiveness of EMR. **Methods** – We evaluated 430 lesions removed by EMR in 404 patients. The lesions were analyzed according to their morphology, size, location, and histology. Lesions <20 mm were resected en bloc, whereas lesions ≥20 mm were removed by piecemeal EMR (p-EMR). Adverse events and recurrence were assessed. **Results** – Regarding morphology, 145 (33.7%) were depressed lesions, 157 (36.5%) were polypoid lesions and 128 (29.8%) were laterally spreading lesions, with 361 (84%) lesions <20 mm and 69 (16%) ≥20 mm. Regarding histology, 413 (96%) lesions were classified as neoplastic lesions. Overall, 14 (3.3%) adverse reactions occurred, most commonly in lesions removed by p-EMR (P<0.001) and associated with advanced histology (P=0.008). Recurrence occurred in 14 (5.2%) cases, more commonly in lesions removed by p-EMR (P<0.001). **Conclusion** – EMR is an effective technique for the treatment of superficial colorectal lesions, even of large lesions.

Keywords – Colonic polyps; adenoma; colonoscopy; endoscopic mucosal resection; large lesions; colorectal neoplasm.

INTRODUCTION

Endoscopic removal of colorectal lesions reduces the incidence and mortality of colorectal cancer (CRC), proving to be a decisive tool in its prevention[1]. A number of techniques have been proposed, ranging from a simple polypectomy to endoscopic submucosal dissection (ESD). Endoscopic mucosal resection (EMR) is considered the first-line treatment for most superficial lesions[2,3].

Inject-and-cut EMR is the most commonly used EMR technique. Currently, in addition to saline solution, colloid solutions are most commonly used.

It is important to recognize the individual characteristics of the lesions to be resected, as well as the predictive histological diagnosis in order to select the most appropriate approach. EMR represents a major advance in endoscopic treatment by allowing en bloc resection of superficial lesions <20 mm. Lesions ≥20 mm pose a greater challenge as they require a resection piece by piece, called piecemeal EMR (p-EMR). The main criticisms of p-EMR are higher recurrence or residual lesion rates. ESD is also an option for these lesions, allowing en bloc resection with lower recurrence; however, it is associated with a higher risk of perforation and requires a long learning curve[4].

For the management of large non-pedunculated colorectal neoplasms, the European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline suggests that most of these lesions can be treated with p-EMR[5]. To reduce this risk caused by local recurrence after EMR, it is recommended that the first follow-up be performed between two and six months after endoscopic resection[6,7].

The objective of the present study was to evaluate the effectiveness of EMR.

METHODS

Study design

This prospective cross-sectional study was conducted in the Department of Endoscopy at *Hospital Santa Casa de Caridade de Bagé*, Brazil. It was approved by the Research Ethics Committee of the institution and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual participants.

Patients

From January 2008 to December 2019, 430 EMRs of the colon and rectum were performed in 404 patients. Mean patient age was 62.4±10.4 years (range, 34–94 years), and 206 (51%) were men.

Equipment

After detection with white-light imaging, magnification chromoendoscopy with 0.4% indigo-carmine or image-enhancement endoscopy (IEE) were used for pit and capillary pattern analysis. High-definition colonoscopes were used, including LASEREO system since 2015.

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Lesions' characteristics

All lesions showed an endoscopic appearance that suggested the depth was limited to the mucosa or submucosa. The Paris classification was used to describe the morphology of the lesions[8]. According to Kudo et al.[9], LSLs were classified as granular (LSL-G), divided into homogeneous (LSL-G-H) and nodular mixed (LSL-G-N) subtypes and non-granular (LSL-NG), subclassified into flat elevated (LSL-NG-FE) and pseudo-depressed (LSL-NG-PD) subtypes.

Lesions subjected to EMR had pit and capillary patterns, according to the Kudo-Kimura and Teixeira classifications, respectively, suggestive of neoplastic lesion without massive submucosal invasion and were, therefore, amenable to endoscopic treatment[10-12]. All lesions were analyzed by an endoscopist with experience in IEE.

Advanced histology was defined as high-grade dysplasia or early carcinoma.

Endoscopic procedures

EMR was indicated in cases of superficial depressed lesions, sessile lesions ≥10 mm in diameter and LSLs. The inject-and-cut technique used a hypertonic saline solution – 4% sodium chloride. Lesion characteristics such as size, morphology, location, and histology were evaluated, as well as adverse events and recurrence of the endoscopic procedure. Lesion size was measured with open biopsy forceps. Location was divided into the right colon segment (from the transverse colon to the cecum) and the left colon segment (from the rectum to the descending colon).

For histological analysis, specimens were mounted on Styrofoam plates, fixed in 10% formalin, and then evaluated according to the World Health Organization classification for histopathology[13].

Lesions <20 mm were resected en bloc, whereas lesions ≥20 mm were removed by p-EMR (FIGURE 1) in a single session. Bleeding was divided into intraprocedural and delayed (after discharge from the endoscopy department). Prophylactic clipping was not performed to close the post-EMR defect.

Recurrence (or residual neoplasm) was defined as the presence of neoplastic tissue in the area of previous resection, as diagnosed by follow-up colonoscopy. Patients underwent follow-up at 3–6 and 12 months. Recurrent/residual mucosal lesions were treated with a second EMR and identified by the scar.

Argon plasma coagulation (APC) was used in the resection margin in 46 lesions ≥20 mm in a sequential, non-randomized manner. APC was not used in the first 23 lesions ≥20 mm.

Statistical analysis

Statistical analysis was performed using Stata, version 15.1. Categorical variables were expressed as absolute and relative frequencies and analyzed by Fisher's exact test. Numerical variables were expressed as mean and standard deviation and analyzed by analysis of variance (ANOVA). The significance level was set at 5% for two-tailed tests.

RESULTS

EMR was performed in 430 lesions, of which 145 (33.7%) were depressed lesions, 157 (36.5%) were polypoid lesions and 128 (29.8%) were LSLs. The mean lesion size was 12.2±9.8 mm; 361 (84%) lesions were < 20 mm and 69 (16%) were ≥20 mm, removed en bloc and by p-EMR, respectively. Distribution of lesions' size is shown in TABLE 1. Regarding histology, 413 (96%) as neoplastic lesions (adenomas and early carcinomas) (TABLE 2). Advanced histology was more frequently observed in lesions removed by p-EMR than in lesions resected en bloc (50.7% vs 19.5%, P<0.001). Descriptive analysis of lesions with advanced histology is shown in TABLE 3.

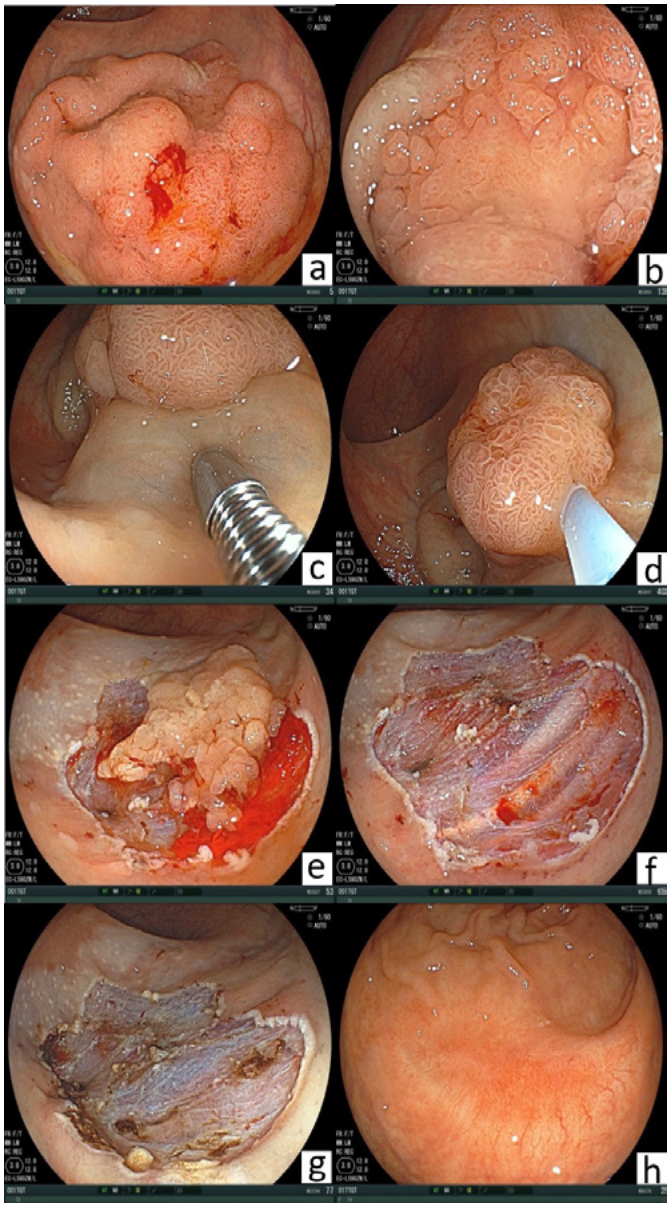

FIGURE 1. A) LSL-G-N subtype; **B)** Fibrosis area; **C)** Injection of 4% NaCl under the lesion; **D-E)** Piecemeal EMR; **F)** Post-resection; **G)** Post-resection and APC; **H)** Scar.

A total of 128 LSLs were removed endoscopically. Granular LSL-G-N subtype were significantly larger (P<0.001) and were more commonly subjected to p-EMR (P=0.003), with higher recurrence (P=0.02) and more adverse events (P=0.03). Advanced histology was more frequently observed in the pseudo-depressed (62.5%) and nodular mixed (53.9%) subtypes, with statistical significance in relation to the other subtypes (P<0.001) (TABLE 4).

TABLE 1. Distribution of lesion size.

Size (mm)	N	%
<10	146	33.9
10–19	215	50.0
20–29	39	9.1
39–39	13	3.0
≥40	17	4.0

TABLE 2. Descriptive analysis of colorectal lesions.

Characteristic	N	%
Sex (n=404)		
Female	198	49.0
Male	206	51.0
Age (mean; SD)	62.4	10.4
Age (years) (n=404)		
<50	41	10.2
≥50	363	89.8
Size (mean; SD)	12.2	9.8
Size (mm)		
<20	361	84.0
≥20	69	16.0
Morphology		
Depressed lesion	145	33.7
Polypoid	157	36.5
LSL	128	29.8
Location		
Left colon segment	196	45.6
Right colon segment	234	54.4
Pathology		
Non-neoplastic	17	4.0
Neoplastic	413	96.0
Technique		
En bloc	361	84.0
Piecemeal	69	16.0
Adverse reactions		
No	416	96.7
Yes	14	3.3
Follow-up		
No	158	36.7
Yes	272	63.3
Recurrence (n=272)		
No	258	94.8
Yes	14	5.2
Total	430	100

SD: standard deviation; LSL: laterally spreading lesion.

TABLE 3. Descriptive analysis of lesions with advanced histology.

Characteristic	% advanced histology	*P*-value
Sex (n=101)		<0.001
Female	17.2 (n=34)	
Male	32.5 (n=67)	
Age (years) (n=101)		0.257
<50	17.1 (n=7)	
≥50	25.9 (n=94)	
Size (mm)		<0.001
<20	19.4 (n=70)	
≥20	50.7 (n=35)	
Morphology		0.100
Depressed lesion	25.5 (n=37)	
Polypoid	28.7 (n=45)	
LSL	18.0 (n=23)	
Location		0.072
Left colon segment	28.6 (n=56)	
Right colon segment	20.9 (n=49)	
Technique		<0.001
En bloc	19.4 (n=70)	
Piecemeal	50.7 (n=35)	
Adverse events (n=105)		0.05
No	23.6 (n=98)	
Yes	50.0 (n=7)	
Follow-up		<0.001
No	5.7 (n=9)	
Yes	35.3 (n=96)	
Recurrence		0.259
No	34.5 (n=89)	
Yes	50.0 (n=7)	
Total	24.4 (n=105)	-

LSL: laterally spreading lesion.

TABLE 4. Characteristics of laterally spreading lesions.

Group	LSL-G-H (n=69)	LSL-G-N (n=13)	LSL-NG-PD (n=8)	LSL-NG-FE (n=38)	*P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	62.9 (10.6)	67.2 (13.8)	61.0 (9.4)	63.0 (11.0)	0.5*
Size (mm)	18.3 (10.5) a	36.8 (15.3) b	15.8 (4.9) a	16.8 (7.9) a	<0.001*
	%	%	%	%	
Advanced histology					<0.001**
No	88.4	46.2	37.5	92.1	
Yes	11.6	53.9	62.5	7.9	
Technique					0.003**
En bloc	68.1	15.4	75.0	65.8	
Piecemeal	31.9	84.6	25.0	34.2	
Adverse reactions					
No	95.6	69.2	100.0	94.7	0.03**
Yes	4.4	30.8	0.0	5.3	
Recurrence					0.02**
No	91.3	61.5	1000	94.7	
Yes	8.7	38.5	0.0	5.3	

LSL-G-H: granular laterally spreading lesion of the homogeneous subtype; LSL-G-N: granular laterally spreading lesion of the nodular mixed subtype; LSL-NG-PD: non-granular laterally spreading lesion of the pseudo-depressed subtype; LSL-NG-FE: non-granular laterally spreading lesion of the flat elevated subtype. *Analysis of variance (b>a). **Fisher's exact test.

Overall, 14 (3.3%) adverse reactions occurred, most commonly in lesions removed by p-EMR (17.4% vs 0.6%, $P<0.001$) and associated with advanced histology ($P=0.008$). Intraprocedural bleeding occurred in 13 (3%) of all EMRs, with 11 cases of minor bleeding, controlled with injection therapy or APC. There were two cases of major bleeding. One occurred after p-EMR of a LSL-G-H subtype, measuring about 40 mm and located in the cecum, which was controlled with APC. After 36 hours, the patient developed pneumoperitoneum and was referred for surgery. The other case of major bleeding occurred after en bloc EMR of a polypoid intramucosal adenocarcinoma with superficial submucosal invasion, located in the rectum, and was controlled with the application of endoclips. There were no cases of delayed bleeding.

Post-EMR micro-perforation occurred in one case of a LSL-G-N subtype, measuring about 50 mm and located in the rectum. The case was managed conservatively with hospitalization, hydration, and antibiotics. There were no deaths.

A total of 272 (63.3%) lesions were followed up, with the first follow-up at 3–6 months, and then at 12 months after the index EMR, being 210 lesions (58.2% of lesions <20 mm) that were resected en bloc and 62 lesions (89.9% of lesions ≥20 mm) that were removed by p-EMR. Recurrence occurred in 14 (5.2%) cases, all detected at first follow-up, and was more common in lesions removed by p-EMR (17.4% vs 0.6%, $P<0.001$). Thirteen (92.9%) of the residual/recurrent lesions were successfully treated with a second EMR.

Of 69 lesions ≥20 mm, 46 received complementary APC in the resection margin. This group had a 15.2% recurrence rate, whereas the group that did not receive APC had a 21.7% recurrence rate ($P=0.5$).

DISCUSSION

EMR is a safe and effective tumor resection technique, even for large lesions. This approach offers an interesting alternative to surgery, including treatment of early carcinomas with superficial submucosal invasion. Chromoendoscopy and IEE are considered effectives resources in the characterization of colorectal lesions and in the risk stratification of submucosal invasion through pit and capillary pattern analysis[14-16]. Proficiency in the use of IEE techniques has been suggested and recommended for endoscopic recognition of submucosal invasion[5]. Kawaguti et al.[17] demonstrated 96.7% accuracy in the assessment of large lesions suspicious for submucosal invasion using pit pattern analysis for the predictive endoscopic diagnosis. In the present study, the endoscopist had expertise in IEE. Seventeen (4%) hyperplastic lesions with a type II-O pit pattern were resected, i.e., with high specificity for sessile serrated adenoma/polyp (SSA/P). The high variability that still exists among pathologists in the differential diagnosis of hyperplastic polyps and SSA/Ps may explain this difference in diagnosis.

Yandrapu et al.[18] demonstrated higher rates of en bloc resection ($P=0.02$) and lower rates of residual lesions ($P=0.02$) with the use of colloid solution compared with normal saline solution for lesions >20 mm. In the present study, hypertonic saline solution was used in all cases.

Advances in endoscopic resection techniques should reduce the rate of surgical indication in lesions amenable to endoscopic treatment, decreasing the rate of adverse events, and costs. Peery et al.[19] reported an increase in the incidence of surgery for non-malignant polyps from 5.9 to 9.4 per 100.000 adults. In a series of 262.843 surgical procedures for non-malignant colorectal polyps, the morbidity was 25.3%, and patients developing a postoperative adverse event had increase in mean hospital length of stay ($P<0.0001$) and in mean hospitalization costs ($P<0.0001$)[20]. Hassan et al.[21] showed that 14% of the patients were immediately referred for surgery before any attempt at endoscopic resection, mainly because of the endoscopic appearance suggestive of submucosal invasion. In the present study, one patient was referred for surgery, in whom bowel perforation was detected 36 hours after the use of APC to control post-EMR massive bleeding.

A meta-analysis showed that most large LSLs are non-invasive

(91.5%) and, therefore, can be treated with p-EMR. LSLs measuring 20–29 mm and ≥30 mm have a 9.2% and 16.5% risk of submucosal invasion, respectively, and that invasive lesions are more common in the pseudo-depressed (31.6%) and nodular mixed (10.5%) subtypes[22]. In the present study, advanced histology was more frequently observed in the pseudo-depressed (62.5%) and nodular mixed (53.9%) subtypes, with statistical significance (P<0.001). Overall, advanced histology was more noticeable in lesions that were resected by the piecemeal technique (P<0.001).

ESD presents significant adverse events in the initial training phase, and its use is limited to centers of excellence in Western countries. Russo et al.[23] showed similar results for EMR and ESD of LSLs in terms of complete resection and curative resection. Bleeding occurred in 9.6% of EMRs and 2.8% of ESDs, especially immediate minor bleeding. Bleeding was more frequent in the removal of LSL-G than LSL-NG (OR 2.46). The present study found a rate of 3.3% of adverse reactions, which were more frequent in lesions removed by p-EMR (P<0.001) and associated with advanced histology (P=0.008). EMR of LSL-G-N subtype resulted in more complications (P=0.03). Intraprocedural bleeding occurred in 3% of all EMRs, with minor bleeding in 11 of the 13 cases, controlled with endoscopic therapy. There were two cases of major bleeding, progressing to perforation after APC, and the other occurred after en bloc EMR of an invasive carcinoma and was controlled with the application of endoclips.

A recent meta-analysis concluded that routine use of prophylactic clipping does not reduce the overall risk of bleeding after polypectomy, but it showed a reduced risk of bleeding after resection of lesions ≥20 mm (P=0.02) or located in the proximal colon (P<0.001)[24]. Prophylactic clipping was not used in any of our patients.

Perforation is one of the most feared adverse events of endoscopic resection. In a recent meta-analysis, the risk of perforation was higher in ESD than in EMR (5.9% vs 1.2%)[23]. We had one case of micro-perforation in a giant LSL-G-N subtype, which was successfully treated conservatively.

The main criticism of EMR is the relatively high recurrence rate. In a meta-analysis, Belderbos et al.[25] identified a significantly higher risk of recurrence after p-EMR than after en bloc resection (P<0.0001). Most recurrences (88%) were found during the first follow-up colonoscopy, with a higher prevalence among carcinomas (P<0.001), and p-EMR was recognized as the only risk factor associated with recurrence. In previous studies by our group, we showed a significant association of the recurrence of lesions removed by p-EMR and with advanced histology[2,26]. In the present study, recurrence was 5.2% and associated with p-EMR (P<0.001). Although recurrence occurred often (almost a fifth of the cases) after p-EMR in larger lesions, they could be successfully managed by a new EMR during follow-up. When only LSLs were analyzed, recurrence was associated with the nodular mixed subtype (P=0.02), and in all cases the residual lesion was relatively small and amenable to successful endoscopic retreatment. There were no cases of late recurrence in the present study.

The use of APC remains controversial. A multi-center study showed lower recurrence at first follow-up in patients undergoing thermal ablation of the post-EMR mucosal defect than in controls receiving no additional treatment (P<0.001), which was directly related to the p-EMR (P<0.001) and lesion size ≥40 mm (P=0.001)[27]. In the present study, 69 lesions ≥20 mm were removed by p-EMR; of these, 46 received complementary APC of the post-EMR mucosal defect margin. Lower recurrence was observed in this group, but without significance (P=0.5).

The present study has some limitations. First, the study was conducted in a single endoscopy unit. Second, all procedures were performed by the same endoscopist. Third, the endoscopist had experience in EMR, which may have contributed to the low rate of serious complications. Fourth, the endoscopist had expertise in chromoendoscopy and IEE, correctly recognizing the lesions that had an indication for endoscopic resection.

In conclusion, this study showed that EMR is a safe and effective procedure for removing superficial neoplasms of the colon and rectum, remaining a viable option in the 21st century, and even allowing the curative resection of large lesions and early carcinomas with a low rate of serious adverse events.

Authors' contribution

Santos CEO: project management; Nader LA, Sanmartin IDA: formal analysis; Scherer C: conceptualization; Furlan RG: data preservation; Santos CEO: writing; Santos CEO, Pereira-Lima JC: review and editing.

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RESUMO – **Contexto** – Ressecção endoscópica da mucosa (REM) é uma opção fácil para o tratamento das lesões superficiais do cólon e reto, inclusive para as lesões ≥20 mm de diâmetro. **Objetivo** – Avaliar a efetividade da REM. **Métodos** – Este estudo prospectivo observacional avaliou 430 lesões ressecadas por REM em 404 pacientes. As lesões foram analisadas de acordo com a morfologia, tamanho, localização e histologia. Lesões <20 mm foram removidas em bloco, enquanto lesões ≥20 mm foram ressecadas em *piecemeal* REM (p-REM). Eventos adversos e recorrência foram avaliados. **Resultados** – Quanto à morfologia, 145 (33,7%) eram lesões deprimidas, 157 (36,5%) eram lesões polipoides e 128 (29,8%) eram lesões que se espalham lateralmente, com 361 (84%) lesões <20 mm e 69 (16%) ≥20 mm. Em relação à histologia, 413 (96%) foram classificadas como lesões neoplásicas. Globalmente tivemos 14 (3,3%) de reações adversas, mais presente nas lesões ≥20 mm removidas por p-REM (P<0,001) e associadas com histologia avançada (P=0,008). A recorrência ocorreu em 14 (5,2%) casos, sendo mais observada em lesões removidas por p-REM (P<0,001). **Conclusão** – REM é uma técnica efetiva para o tratamento das lesões colorretais superficiais, até mesmo para as grandes lesões.

Palavras-chave – Pólipos colônicos; adenoma; colonoscopia; ressecção endoscópica; grandes lesões; neoplasia colorretal.

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Evaluating the impact of early nutritional assessment and intervention in hospitalized liver cirrhosis patients

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ABSTRACT – **Background** – Malnutrition is common in liver cirrhosis patients that is correlated with early complications, morbidity and mortality. **Objective** – The purpose of the study was to assess nutritional status, impact of nutritional screening and intervention in liver cirrhosis patients by evaluating their actual energy and protein intake during hospital stay. **Methods** – A cross sectional study was conducted wherein all patients' nutritional status was defined by Subjective Global Assessment tool. Adequate energy and protein supply were planned and executed by using individualized nutritional plan for patients with dietitian's collaboration. Anthropometric measurements included height, weight, body mass index, mid upper arm circumference, hand grip strength and triceps skin-fold thickness. Biochemical tests included haemoglobin, mean corpuscular haemoglobin, volume and concentration, albumin and liver function tests. To record the daily food intake, a 24-hour dietary recall was used. **Results** – Overall 83 patients (mean age 55) were included, among them 46% of patients were moderately malnourished, 12% were normal, while 42% of cirrhotic patients were severely depleted according to Subjective Global Assessment. The mean intake of calories and protein was improved during stay in hospital after nutritional intervention and critical monitoring (P<0.05). Anthropometric measurements at baseline and discharge showed significant differences (P <0.05) in weight, body mass index, triceps skin fold thickness and mid upper arm circumference values, but not in hand grip strength that was associated with malnourishment among patients. **Conclusion** – Providing individualized nutritional intervention and its monitoring by qualified dietitians during hospital stay helps to improve intake in patients that prevent further risk of malnutrition and related complications.

Keywords – Cirrhosis; dietary intake; malnutrition; nutrition assessment; nutritional intervention.

INTRODUCTION

The prevalence of protein energy malnutrition in liver cirrhosis patients has been devastatingly high during the past years. Data available from the year 2010 represents more than one million deaths caused due to liver cirrhosis worldwide[1]. Malnutrition is one of the contributing factors that enhances the chance of severe complications in liver cirrhosis patients. In the year 2012, the prevalence of protein-energy malnutrition has reached 50 to 90 % in liver cirrhosis patients[2].

Major etiological factors of liver cirrhosis include chronic hepatitis (particularly hepatitis B and C), liver steatosis, alcoholic liver disease, non-alcoholic steatohepatitis and non-alcoholic fatty liver disease (NAFLD). All these persistent conditions lead to progressive chronic liver disease, liver cirrhosis and end stage liver disease. In Pakistan, the prevalence of acute and chronic hepatitis (B and C) has been tremendously increased[3]. According to World Health Organization (WHO), there are approximately 12 million hepatitis patients and 150,000 newly diagnosed patients of hepatitis each year.

Nutritional status of majority of liver cirrhosis patients is compromised due to various contributing factors like anorexia, early satiety, excessive alcohol consumption, maldigestion, malabsorption and poor quality of diet. Inadequate dietary intake in cirrhosis patients is also linked with the altered taste, possibly due to certain medications and anorexia. Other factors for decreased oral intake include hepatic encephalopathy, ascites, abdominal distention, dietary restrictions and starvation for various tests and procedures[4].

Liver cirrhosis patients with altered nutritional status have longer duration of hospital stays as compared to normal patients. In patients with advanced liver disease there is visible loss of fat mass and muscle mass[5]. Malnutrition is a critical issue due to lack of nutritional care in clinical practice in Pakistan. From the onset of disease restricted diet, low socioeconomic status, less nutritional awareness and inadequate oral intake lead to malnutrition that additionally worsens the disease condition and develop early complications.

According to ESPEN (European Society of Clinical Nutrition and Metabolism) 2006, identification of malnutrition in cirrhosis patients can be assessed by using various tools including Subjective Global Assessment (SGA), hand grip strength and anthropometric analysis[2]. Hand grip strength is non-invasive and easy tool to assess nutritional and functional status of patients by detection of loss of muscle strength[6].

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Different strategies should be planned to improve nutritional status of hospitalized liver cirrhosis patients. Delivery of adequate supply of nutrition regarding macronutrients and micronutrients will help to improve the nutritional status and decrease the rate of complications. The recommended daily intake of macronutrients for patients with liver cirrhosis has been approved by ESPEN Guidelines on enteral nutrition specifically for liver disease. Cirrhosis patients should consume adequate amount of energy calculated as 35–40 kcal/kg body weight/day, similarly the daily protein requirements for liver cirrhosis patients is 1.2–1.5 g/kg body weight[7]. According to the guidelines, in condition of inadequate oral intake regardless of nutritional counselling all patients should be provided with Oral Nutritional Support (ONS). Advanced liver disease patients with malnutrition should be provided with enteral nutrition in transitions of oral feeding to fulfil energy and protein requirements and decrease malnutrition effects on complications[8].

Main aim of this study was to assess the nutritional status of cirrhotic patients admitted in hospital at first stage and then apply individualized medical nutrition therapy. Further we compared actual energy and protein intake with standard requirements of hospitalized liver cirrhosis patients.

METHODS

Study was approved by the Institutional Review Committee for Biomedical Research of University of Veterinary and Animal Sciences, Lahore. Site of study was Department of Gastroenterology and Liver Transplant of Sheikh Zaid Hospital in Lahore from July 2018 to January 2019. A total of 100 adult liver cirrhosis patients participated in the study after giving written and verbal consent. Inclusion criteria of the study was patients aged >40 years suffering with liver cirrhosis. Patients with critical conditions, those who needed mechanical ventilation and/or with chronic heart failure (chronic heart failure is an independent cause of mortality so that co-morbidity factors can be diverse with liver cirrhosis) were excluded from the study.

Anthropometric measurements weight, height, mid upper arm circumference (MAUC), triceps skin fold thickness (TSF) and hand grip strength were weekly recorded for each individual patient until discharge. Weight of the patient was measured using a weighing scale with accuracy of 0.1 kg. The patient's height was measured using stadiometer or tape measurement with accuracy of 0.1 cm. Body mass index (BMI) was calculated by using estimated dry weight of the patients following by ascites and paracentesis by Mendenhall, 1992. Mid upper arm circumference (MUAC) was measured using measuring tape with accuracy of 0.1 cm. In order to measure skin fold thickness, first mid arm circumference measured between the olecranon and acromial processes by using a measuring tape with accuracy of 0.1 cm, then on the marked point from the surface of triceps patient's subcutaneous fat was pulled off and measured using a skin fold thickness calliper with accuracy of 1 mm[9].

Hand grip strength shows the maximum strength derived from the contraction of both intrinsic and extrinsic muscles of hand. Hand grip strength of the patients was assessed by using hand grip dynamometer (phisiopadic hand grip dand, China).

Subjective global assessment is one of the most commonly used tools to assess nutritional status of liver disease patients. It is non-invasive, inexpensive and easy tool to assess the extent of malnutrition in liver cirrhosis patients[10]. SGA is further categorized in various portions including dietary intake, weight change, signs and symptoms and functional capacity. SGA classified the data in three types; normally nourished, moderately malnourished and severely malnourished as A, B and C groups respectively.

Biochemical parameters of patients included haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), albumin, liver function tests (ALT, AST) were measured at baseline as well as at end of the study. Blood glucose level and blood pressure was also recorded at proposed interval. All biochemical tests values were taken from hospital record of each patient.

The 24-hour dietary recall is an easy method to assess dietary intake of population[11]. It consists of all the foods and beverages consumed in duration of last 24 hours. A 24-hour dietary recall was taken from participants on day 1, day 3, day 7 of assessment and on discharge day.

All patients' nutritional status was assessed using Subjective Global Assessment and BMI. Adequate energy and protein supply were planned according to ESPEN guidelines for individual patients. Advice on supplemental formulas, enteral or parenteral nutrition when appropriate with dietitian's collaboration in the hospital was also provided. Cirrhotic patients were recommended with supplemental formulas to achieve their optimum protein and energy requirements. Approximately these formulas provide 7 g of protein per serving which leads to an increased total intake of patients. Some other supplements provide an adequate amount of energy (250 kcal), protein (9 g), fats (9 g) and carbohydrates (34 g) per serving. The formulas were also loaded with multiple minerals and vitamins. Thus, these formulas were of great importance due to rich nutritional constituent that helps patients to restore their nutritional status. Individualized patient's energy requirements were determined by using Harris Benedict's Equation[12]. Patient's protein requirements were advised based on standard amount that is 0.8–1.2 g/kg body weight or 1.2–1.5 g/kg body weight. All patients were followed up on day 1, 3, and 7 until discharge[8]. Patients were critically monitored on alternative days for their intake and supplementation use. Appropriate nutrition education was given to the patients regarding their dietary intake and nutritional status with collaboration of dietitian in the hospital. Descriptive statistics on the data was presented as mean and standard deviation. Baseline data (day 1) of anthropometry was compared with data on discharge by using paired sample *t* test in order to find difference after the medical nutrition therapy during hospital stay. Analysis of variance (ANOVA) was applied to find statistical significance in mean intake of patients at different intervals. Chi square test was applied to find out association between different parameters. All these tests were performed by using SPSS version 21 software (IBM Corporation). $P<0.05$ was statistically significant.

RESULTS

A total of 100 individuals participated in this study and 83 (83%) patients completed the study and shared information on their discharge from hospital while 13 participants left and did not provide appropriate information on discharge day. Death of few patients (n=04) was reported during the study. The average age of included participants was 55 years among them 60% of patients were male as showed in baseline characteristics (TABLE 1).

TABLE 1. Baseline characteristics of liver cirrhosis patients on hospital admission (n=83).

Baseline Characteristics	Mean ± SD
Age (years)	55±9.2
Weight (kilogram)	68±13.5
Height (inches)	65±2.1
BMI (kg/m^2)	24.5±4.8
MUAC (cm)	25±4.5
TSF (mm)	13.5±6.6
Blood glucose level (mg/dL)	197±89

SD: standard deviation; BMI: body mass index; MUAC: mid upper arm circumference; TSF: triceps skin fold thickness.

The present study was specifically planned to critically monitor the patients for the nutrition intervention in the duration of their hospital stay. Appropriate diet plans and nutrition education was provided to the patients after early nutritional screening. Patients were critically monitored on alternative days 1, 3, 7 and on discharge. Analysis of variance showed improvement in the macronutrients intake of patients recorded by 24-hour dietary recall. Post hoc test (TABLE 2) showed statistical significance in total calories and protein intake of patient till discharge.

Results (TABLE 3) were categorized on the basis of Subjective Global Assessment, patients were categorized into three groups according to SGA; normally nourished 12% (Category A), moderately malnourished 46% (Category B) and severely malnourished 42% (Category C). Outcomes explained that in severely malnourished patients, mean of BMI was improved from baseline to discharge while other anthropometric measurements (MUAC, TSF) were not much improved at the discharge. The BMI and MUAC values of normal patients were decreased at the discharge and no changes were recorded in the normal weight patients. Dietary intake of all patients (despite of SGA categorization) was improved at discharge where the calories and proteins intake increased. Liver function tests are important to assess medical condition and risks of liver complications, the results represented that the levels of ALT and AST in the blood were significantly reduced at the discharge.

After applying paired *t* test, results showed significant decrease (P<0.01) in the MUAC value of overall patients at discharge day compared to the baseline data. Significant reductions (P<0.02) were observed in the BMI and weight of patient at the discharge. Values of triceps TSF was also found statistical significant while hand grip strength showed no significant differences at the baseline and discharge day as stated in TABLE 4.

TABLE 2. Analysis of variance of mean caloric and protein intake of cirrhosis patients at different intervals of hospital stay.

Parameters	Day 1 Mean ± SE	Day 3 Mean ± SE	Day 7 Mean ± SE	Discharge Mean ± SE	*P* value
Total calories intake (kcal/day)	1030.83±57.99^c	1100.05±55.94^c	1391.57±46.48^b	1544.83±42.22^a	0.000*
Total protein intake (g/day)	35.10±2.69^c	39.20±2.62^c	56.55±2.43^b	64.73±2.11^a	0.000*

SE: standard error. *highly significant P value <0.05; $^{a, b, c}$ statistical difference between calories and protein intake at each interval by post hoc test.

TABLE 3. Mean of various parameters at baseline and discharge of participants categorized on the basis of body mass index.

Parameters	Normal		Moderately malnourished		Severe malnourished	
	Baseline Mean ± SD	Discharge Mean ± SD	Baseline Mean ± SD	Discharge Mean ± SD	Baseline Mean ± SD	Discharge Mean ± SD
Anthropometric measurements						
BMI (kg/m^2)	27.9±5.6	24.8±4.0	23.6±4.2	23.2±4.5	20.5±4.8	21.1±3.8
MUAC (cm)	26.7±4.9	25.6±4.1	22.6±3.9	23.3±3.9	20.2±6.0	20.8±4.4
TSF (mm)	15.9±9.3	13.6±5.2	10.4±6.5	11.5±6.1	9.5±5.0	9.7±6.9
Hand grip strength (force/kg)	16.5±17.4	15.6±9.0	15.7±15.5	15.8±17.8	13.9±15.2	12.5±16.2
Nutrients Intake						
Calories Intake (kcal/day)	1383.4±389.9	1742.5±333.9	1082.7±532.6	1510.1±365.1	917.2±473.9	1516.2±407.4
Protein Intake (g/day)	53.9±19.2	69.7±13.4	39.6±23.3	62.5±15.9	28.4±21.7	65.1±23.4
Biochemical parameters						
Haemoglobin (g/dl)	12.3±3.1	10.6±1.9	12.8±14.6	10.5±2.2	10.8±2.0	10.9±1.9
ALT (IU/L)	38.5±19.9	33.1±2.2	86.2±161.3	56.7±88.1	65.3±75.1	39.2±14.9
AST (IU/L)	58.4±40.1	49.7±20.3	78.6±102.1	58.3±52.9	105.8±107.6	45.5±20.7
Albumin (g/dL)	3.0±0.4	2.7±0.7	2.2±0.8	2.6±0.5	2.5±0.5	2.8±0.5

SD: standard deviation; BMI: body mass index; MUAC: mid upper arm circumference; TSF: triceps skin fold thickness; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

TABLE 4. Mean comparison of anthropometric measurements at baseline and discharge of patients by using paired *t* test.

Parameters	Mean± SD (baseline)	Mean ± SD (discharge)	*P* value
Weight (kg)	68.54±13.90	67.13±12.03	0.001*
BMI (kg/m²)	24.78±4.93	24.27±4.16	0.002*
MUAC (cm)	25.43±4.46	24.82±4.16	0.000**
TSF (mm)	13.92±6.69	13.69±6.37	0.018*
Hand grip strength (force/kg)	15.02±16.26	14.98±16.23	0.940

SD: standard deviation; BMI: body mass index; MUAC: mid upper arm circumference; TSF: triceps skin fold thickness. *significant value, P value < 0.05, **highly significant value.

Subjective global assessment (SGA) covers the important parameters in evaluation that effect nutritional status like weight change, nutrient intake, GI symptoms and functional capacity. After applying chi square test, results showed that there was significant association between SGA scoring and nutrient intake (TABLE 5). Patients who were categorized as severely malnourished had minimal intake or fluid diet during previous days. Approximately 15% and 22% of moderately malnourished patients were taking inadequate or minimal nutrient intake, respectively. While, 47% severely malnourished patients were taking the minimal nutrient intake. There were no significant changes ($P>0.05$) in weight change according to SGA scoring. There was a significant association between functional capacity and SGA scoring represented that that patient who were severely malnourished had decrease functional capacity as compared to normally nourished patients.

DISCUSSION

Results of this study showed that approximately 42% of patients were malnourished classified according to Subjective Global Assessment tool. Previous study was conducted by Brazilian scientist Figueiredo FA et al. to assess nutritional status by using different tool in liver cirrhosis patients showed that 31.6% of patients were malnourished when assessed by using SGA, interpreting that early incidence of malnutrition in liver cirrhosis patients leads to increased complications, morbidity and mortality[13]. Results regarding prevalence of malnutrition in liver cirrhosis patients waiting for liver transplant showed that 35.6% patients of pre liver transplant were in Class C (severely malnourished) and 46.7% patients were in Class B (moderately malnourished) while 17.8% patients were normally nourished (Class A) assessed by SGA tool.

TABLE 5. Nutrition screening by using Subjective Global Assessment tool in liver cirrhosis patients.

Parameters / Defined variables	Category A% n=10	Category B % n=38	Category C % n=35	*P* value	X^2 value
Nutrient intake					
No change	4	1	0		
Inadequate	3	15	5	0.000*	42.214
Minimal intake	3	22	47		
Nutrient intake (past 2 weeks)					
Adequate	5	1	0		
Improved	4	31	7	0.000*	85.275
No improvement	1	6	45		
Weight change					
Less than 5%	8	31	47		
5 to 10%	2	5	3	0.451	3.682
>10%	0	2	1		
Weight change (past 2 weeks)					
Increased	1	2	1		
No change	6	21	26	0.658	2.427
Decreased	3	15	24		
GI symptoms					
None	1	2	0		
Mild	9	32	23	0.000*	23.240
Severe	0	4	24		
GI symptoms (past 2 weeks)					
Resolution	1	2	0		
Improving	7	22	1	0.000*	44.918
No improvement	2	14	46		
Functional capacity					
No dysfunction	5	12	2		
Difficulty in Ambulation	4	24	30	0.000*	26.578
Bed or chair	–	–	–		
Ridden	1	2	20		
Functional capacity (past 2 weeks)					
Improved	5	10	1		
No change	5	27	21	0.000*	45.024
Decreased	0	1	30		

Category A: normal; category B: moderately malnourished; category C: severely malnourished. *highly significant value, *P* value<0.05.

In liver cirrhosis patients' protein to energy ratio is an important concern to reduce frequency of malnutrition[14]. A study was conducted in Malaysian advanced cirrhosis patients showing lower caloric intake (mean value 15.2 /kg body weight per day) during hospitalization depicting it as one of the cause of malnutrition[15]. In the present study after critical monitoring of hospitalized patients regarding macronutrient intake results showed that there was significantly improvement in intake of patients during their stay, there was significant improvements on day 1, day 3, day 7 and discharge. Another study was conducted in stable liver cirrhosis patients to investigate the effect or oral diet on energy metabolism for short duration in Albert Chenevire Hospital, France. Results showed that mean calories and protein intake was improves in the patients ($P<0.01$)[16].

Protein intake of liver cirrhosis patients is another important concern. The improvement in dietary protein intake may be explained as during early days of hospitalization patients were having unstable clinical condition and inability to eat due to anorexia, nausea, vomiting and other GI symptoms and non-supplementation. On day 3 and day 7 patients were improving regarding medical condition and GI symptoms therefore patients were able to tolerate oral supplementation. While at discharge some patients were recovered resulting a mean increased in calories and protein intakes.

The results of this study were supported by a French scientist Campillo et al. that enhanced oral intake of cirrhosis patients (especially severely malnourished patients) for the duration of one month and observed changes in energy metabolism and other indices. Results showed improvement in the nutritional status of the patients assessed using creatinine height index, TSF, MAMC and total body fat mass. For biochemical parameters decrease in the level of C reactive protein (CRP) was reported. In this study there was change in patient's Child Pugh score after 1 month of dietary intervention and monitoring. Therefore, the study determined that increasing energy intake improved the nutritional status of severely malnourished patients and thus supported the patients to combat against disease and prevent further complications[17].

In order to completely assess nutritional status of the patient's, anthropometric measurements are also very noteworthy. Change in dry weight and other body measurements can be used as one of the monitoring parameters in liver cirrhosis patients. Body mass index is one of the indicators to assess nutritional status of liver patients, the mean of BMI of 24.7 kg/m^2 in patients in this study. Another study was conducted in Brazil to assess anthropometric measurements in patients of cirrhosis showed that the mean of BMI of patients was 28.5 kg/m^2, explaining that liver cirrhosis patients' gain more weight at this stage causing BMI ranges in overweight compared to normal BMI patients in present study[18]. To eradicate weight error due to ascites and edema in liver cirrhosis patients, in this study dry weight of patients was estimated to calculate as possible as accurate body mass index[19].

Another study was conducted in France to validate BMI for assessment of nutritional status in liver cirrhosis patients who were categorized as preserved nutritional status, moderately malnourished and severely malnourished based on their nutritional status. BMI in all the categories were 20.3 kg/m^2, 23.5 kg/m^2 and 27.2 kg/m^2 respectively. This displayed that patients who were severely malnourished had the least BMI as compared to other groups (moderately malnourished and normal nutritional status). As compared to current study, results were similar showing the least mean value of BMI in underweight patients and highest BMI in overweight/obese patients[20].

Other anthropometric parameters used in this study include mid upper arm circumference and triceps skin fold thickness. Results of the current study that was conducted in Pakistan showed that there is higher MUAC value for both genders than those reported by an Australian study conducted on hospitalized patients[21].

In results when triceps skin fold thickness distributed against gender parameter it represents that TSF values were higher in females compared to males. The higher TSF values depict higher fat mass that can relate to overweight and obesity. Almost 80% of female liver cirrhosis patients were in normal ranges depicting normal fat mass in the body, while 20% of liver cirrhosis female patients were above the normal ranges showing increased fat mass and interrelate with greater BMI[22]. Additional analysis was performed to find out relationship between nutritional status of patients and survival rate during hospital stay. Results represented that on the basis of percentiles of TSF or MAMC, 26% patients were overly nourished with >75th percentile, 34% patients were severely malnourished with <5th percentile and 20% patients were moderately malnourished with <10th percentile. Study concluded that patients were severe and moderate malnourishment during their disease duration had less survival rated as compared to the normal and overweight patients[23].

Hand grip strength was measured using hand grip dynamometer apparatus to assess muscle strength of hospitalized patients[9]. Results showed decreased muscle strength as compared to standard available in an additional study. Majority of females participated in the study were having decreased muscle strength compared to values 14 kg or less force. In males only 22.4% patients were having good muscle strength as values represented as 15 to 30 kg force while 53.4% patients were having decrease muscle strength compared to standard that is ≤24 kg were categorized as decrease muscle strength[24].

In liver cirrhosis patient's major complications included ascites and edema that directly affect the measurement of body mass index depicting nutritional status of patients as described earlier. As compared to it, subjective global assessment is a universal tool to assess nutritional status of cirrhotic patients. SGA evaluate the patients not only for weight change but also with dietary intake and functional capacity. Thus, combining both tools is necessary to critically assess the patients in order to improve their dietary intake, nutritional status and decrease complications.

In this study, comparison of nutrient intake at discharge and baseline showed that there was improvement in the protein servings in all patients that include different protein enriched sources like egg whites, lentils and chicken complement with vegetables. Furthermore, protein supplementation was a good source to increase the protein intake of patients till discharge from hospital. The daily calories intake of patients was also improved by suggesting multiple snacks, adequate food servings, food from all food groups and supplementation[25]. The use of oral dietary supplements can be a good option in liver cirrhosis patients; as suggested by a Japanese study that investigated the effect of regular snacks enriched with branched chain amino acids (BCAA) on cirrhosis patients for the duration of 3 months and it found there was an improvement in the serum albumin levels and other parameters of the patients who were consuming evening snacks with BCAA. Among patients consuming normal snacks and intervention group there was no significant change in the total energy intake of snacks[26].

CONCLUSION

In hospitalized liver cirrhosis patients, malnutrition is a predominant issue. Dietary consumption is one of the most considerable characteristics in the nutrition indices and outcome of hospitalized patients. Providing individualized nutritional intervention during the hospital stay helps to improve mean macronutrients intake (especially calories and protein) of patients that prevented from further malnourishment. Nutritional therapy and critical monitoring of liver cirrhosis patients for longer duration of time will help the patients to completely improve their nutritional status as well as decrease the chance of malnutrition and complications.

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Authors' contribution

Nida Javaid: compiled the literature review before start of the study, performed data collection in the hospital, entered data in software, statistical analysis and write up the initial draft of the paper. Khan Z: conceptualized and supervised the complete research as well as review and edit the document at each stage. Ali MA: helped with the validation of methodology and supervised the study. Tahir SK: helped with the statistical analysis and data curation and revision of manuscript.

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RESUMO – **Contexto** – A desnutrição é comum em pacientes com cirrose hepática e está correlacionada com complicações precoces, morbidade e mortalidade. **Objetivo** – O objetivo do estudo foi avaliar o estado nutricional, o impacto da triagem nutricional e a intervenção em pacientes com cirrose hepática, avaliando sua ingestão real de energia e proteína durante a internação hospitalar. **Métodos** – Foi realizado um estudo transversal em que o estado nutricional de todos os pacientes foi definido pela ferramenta de Avaliação Global Subjetiva. O fornecimento adequado de energia e proteína foi planejado e executado por meio de plano nutricional individualizado para pacientes com colaboração de nutricionista. As medidas antropométricas incluíram: altura, peso, índice de massa corporal, circunferência do braço médio, força de aderência da mão e espessura da dobra da pele tríceps. Os testes bioquímicos incluíram: hemoglobina, volume e concentração da hemoglobina corpuscular média, albumina e testes de função hepática. Para registrar a ingestão diária de alimentos, foi utilizado um recall dietético de 24 horas. **Resultados** – Ao todo foram incluídos 83 pacientes (média de 55 anos), entre eles 46% dos pacientes estavam moderadamente desnutridos, 12% estavam normais, enquanto 42% dos pacientes cirróticos estavam severamente depletados de acordo com a Avaliação Global Subjetiva. A ingestão média de calorias e proteínas foi melhorada durante a internação hospitalar após intervenção nutricional e monitoramento crítico (P<0,05). As medidas antropométricas na linha de base e descarga apresentaram diferenças significativas (P< 0,05) em peso, índice de massa corporal, espessura da dobra da pele do tríceps e valores médios de circunferência do braço, mas não na força de aderência da mão que estava associada à desnutrição entre os pacientes. **Conclusão** – Proporcionar intervenção nutricional individualizada e seu acompanhamento por nutricionistas qualificados durante a internação hospitalar ajuda a melhorar a ingestão em pacientes que previnem maior risco de desnutrição e complicações relacionadas.

Palavras-chave – Cirrose; ingestão alimentar; desnutrição; avaliação nutricional; intervenção nutricional.

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ORIGINAL ARTICLE

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Factors associated with difficult biliary cannulation in a training center for endoscopic intervention of the biliary tract

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ABSTRACT – Background – This paper aims to determine factors associated with difficult biliary cannulation (DBC) that are identifiable before procedures. **Methods –** This is a nested case-control study within a historical cohort in adult patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) from 2015–2019 in the Hospital Universitario San Ignacio, Colombia. This study assessed the associations among variables that could be identified before or at the beginning of procedures and the probability of DBC. These associations were evaluated through a bivariate and multivariate analysis. The study used criteria for DBC defined by the European Society of Gastrointestinal Endoscopy. **Results –** A total of 498 ERCP performed in 376 patients were analyzed. Of all procedures, 144 (29%) fulfilled criteria for DBC. The multivariate analysis showed an association between DBC and the acute care hospital setting (OR:2.92; CI95% 1.70–5.01; $P<0.001$), redundant papilla (OR:7.26; CI95% 3.38–15.61; $P<0.001$), or peridiverticular papilla (OR:2.45; CI95% 1.38–4.36; $P=0.002$). No association was found between DBC and endoscopist's experience, bilirubin levels, or dilation of the biliary tract. **Conclusion** –– The DBC is a frequent event. Alterations in the papilla and ERCP performed in the acute care hospital setting are the principal factors associated with DBC. This information might be useful to predict DBC and establish healthcare and administrative strategies to reduce its implications.

Keywords – Difficult biliary cannulation; endoscopic retrograde cholangiopancreatography.

INTRODUCTION

Despite technological advances in endoscopic retrograde cholangiopancreatography (ERCP), the technique continues to be difficult and requires a high level of experience from the endoscopist. In reference centers, as many as 35% of biliary cannulations are unsuccessful. General complications in biliary cannulation patients are about 2% in centers with expertise in this population, compared to 7% in centers with low volume ($P<0.001$)[1,2].

The concept of difficult biliary cannulation (DBC) has changed over time[3-5]. Recently, the European Society of Gastrointestinal Endoscopy (ESGE) redefined DBC as more than five contacts with the papilla, unsuccessful cannulation longer than 5 minutes, or more than one unintentional cannulation/opacification of the pancreatic duct (PD)[6]. Even in patients with normal anatomy and easily visible papilla, multiple cannulation attempts can cause mechanical trauma to the papilla and make subsequent attempts more difficult[7]. The resulting edema may obstruct the PD. Also, chemical injury from the inadvertent injection of contrast media in the PD increases the risk of post-ERCP pancreatitis (PEP)[8].

Several factors have been associated with DBC, including the experience level of the endoscopist and the patient's anatomy (type of papilla, altered anatomy, or anatomical variant)[7,9]. Information on this subject, however, continues to be limited. There has not been an assessment based on ESGE's new definition of how factors identifiable before the procedure would be associated with the probability of a DBC. This information might be very useful in ERCP planning, allowing necessary precautions to improve the probability of success.

The objective of this study is to analyze the associations among factors identifiable before or at the beginning of ERCP procedures and DBC probability at a training center for endoscopic intervention of the biliary tract in Bogotá, Colombia.

METHODS

This observational, analytical, case-control study was nested in a historical cohort. The study included adult patients undergoing ERCP for any indication in the Gastroenterology Unit of the San Ignacio University Hospital, Colombia, between 2015 and 2019. Exclusion criteria were a history of upper digestive tract surgery and any procedures ended before a biliary cannulation attempt. The Ethics Committee of the San Ignacio University Hospital and the Pontificia Universidad Javeriana approved the study.

All patients undergoing ERCP in the study period were identified from a database where all procedures performed in the Gastroenterology Unit are systematically registered. All patients were taken to ERCP after preparation with fasting of at least 8 hours,

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withdrawal of anticoagulant medications within the safety times established by international recommendations. All patients received general anesthesia after pre-anesthetic evaluation. According to the preference of the professional in charge, we proceeded in supine or left lateral decubitus. The equipments used in the study were the Duodenum olympus TJF 160 duodenoscope and Duodenum olympus TJF Q180.

A randomized sample completed the calculated sample size. The demographic characteristics, ERCP indication, laboratory test results, and complications after the procedure until hospital discharge were obtained from the electronic clinical histories. Criteria for DBC, the expertise of the endoscopist, anatomical variants, and complications during the procedure were obtained from reports performed by each endoscopist at the end of ERCP.

Difficult biliary cannulation was defined as one of the following, according to ESGE recommendations: more than five contacts with the papilla, unsuccessful cannulation attempts for longer than 5 minutes, or an unintentional cannulation or opacification of the PD on two or more occasions[6]. The definition of papilla contacts establishes the intentional and continuous contacts of the cannulation accessory. The endoscopist's degree of expertise was defined as senior professional or junior endoscopist. Senior professionals had fulfilled the biliary tract training curve (>200 ERCP and >40 ERCP/year). Junior endoscopists were professionals who had not fulfilled that criterion. The cannulation time and the cannulation space available to endoscopists in training to decide the need for intervention by the expert endoscopist, was counted using the clock displayed on the endoscopy monitor, after marking the start of the procedure. Technical success for cannulation was defined as achieving selective biliary cannulation using any technique. Technical success for ERCP was defined as the fulfillment of the technical purpose of the ERCP given the pathological condition intervened. Clinical success was defined as cessation of signs and symptoms after the endoscopic intervention. Evaluated complications during and/or after the ERCP included bleeding, gastrointestinal perforation, cholangitis, and post endoscopic pancreatitis, defined as abdominal pain and enzymes significant elevation.

For description of patients' sociodemographic and clinical characteristics, central tendency and dispersion measures were used, depending on data distribution. The Shapiro Wilk test was used to evaluate the normal distribution assumption. For categorical variables, absolute numbers and proportions were reported. For group comparison, the X^2 test or the Mann-Whitney U test was used, according to the type of variable. Association between each factor and DBC was assessed first in a bivariate analysis, calculating 95% odds ratio and confidence intervals. A subsequent multivariate analysis aiming to identify independent factors was performed, using a logistic regression model with the backward stepwise method. This included variables showing statistically significant association in the bivariate analysis (P<0.05). All the statistical analysis was performed with the statistical analysis package Stata 15®.

RESULTS

FIGURE 1 shows the process for patient selection. A total of 498 ERCP, performed in 376 patients, were analyzed. Clinical and sociodemographic characteristics of the patients are presented in TABLE 1. Of the sample, 54% were women, median age 69 years (interquartile range 57–79), and 66.5% were hospitalized at the time of the procedure. Choledocholithiasis was the most frequent indication for the ERCP (71%). 32.5 % of patients underwent the procedure more than once.

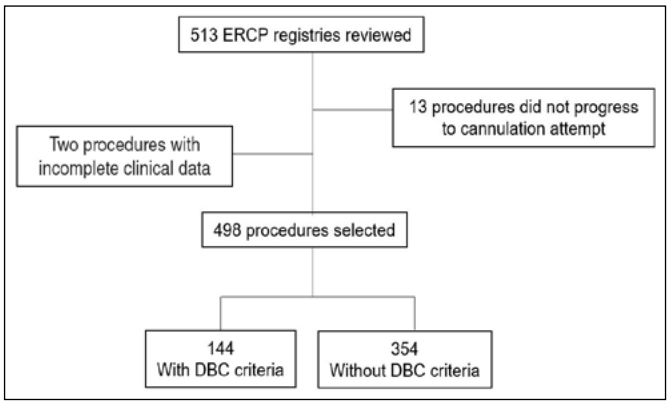

FIGURE 1. Patient selection.

TABLE 1. Clinical and sociodemographic characteristics of patients undergoing ERCP.

Characteristics	n=376
Gender (female), n (%)	203 (54.0)
Age (years), median (IQR)	69 (57–79)
Hospital environment, n (%)	250 (66.5)
ERCP indication, n (%)	
Choledocholithiasis	238 (71.0)
Cholangitis	21 (6.7)
Post-surgical biliary stenosis	21 (6.7)
Pancreatic cancer	14 (4.2)
Biliary pancreatitis	10 (3.0)
Number of ERCP performed, n (%)	
1	254 (67.5)
2	90 (23.9)
3	24 (6.4)
4	4 (1.1)
5	3 (0.8)
6	1 (0.3)

IQR: Interquartile range; ERCP: Endoscopic retrograde cholangiopancreatography.

Technical and clinical outcomes, and complications

Of the 498 ERCP performed, 29% (144) fulfilled DBC criteria, with more than five cannulation attempts the most frequent 1 (52%). TABLE 2 shows the comparison between the procedures with and without this outcome. A higher proportion of DBC was observed in women (49.4 vs 62.5%, P=0.008) and hospitalized patients (64.1 vs 82.6%, P< 0.001). Also, significant differences were found between groups for ERCP indications and for the proportion of redundant/peridiverticular papilla (14.7 vs 34%, P< 0.001), the latter being more frequent in the DBC group. Procedures performed by a senior professional had a similar percentage for both groups (51.7 vs 55.5%; P=0.397). The most frequently used cannulation technique after failure of conventional techniques was double cannulation (42.3%), followed by precut (15.4%).

TABLE 2. Comparison of ERCP with and without DBC criteria.

	Non-difficult cannulation (n=354)	Difficult cannulation (n=144)	*P* value
Gender (female), n (%)	175 (49.4)	89 (62.5)	0.008
Age, median (IQR)	69 (57–78)	69 (58–76)	0.88
Acute care hospital setting, n (%)	227 (64.12)	119 (82.63)	<0.001
Senior professional, n (%)	183 (51.69)	80 (55.5)	0.397
DBC criterion			
>5 attempts		75 (52.08)	
>5 minutes		16 (11.11)	
MPD cannulation/opacification		53 (36.81)	
ERCP indication, n (%)			
Choledocholithiasis	223 (70.54)	79 (62.70)	
Cholangitis	23 (7.28)	11 (8.73)	
Biliary neoplasia	5 (1.58)	0 (0)	
Pancreatic cancer	10 (3.16)	13 (10.32)	
Acute biliary pancreatitis	8 (2.53)	2 (1.59)	0.002
Chronic/recurrent pancreatitis	7 (2.22)	0 (0)	
PO biliary fistula	9 (2.85)	6 (4.76)	
PO biliary stenosis	23 (7.82)	4 (3.17)	
Other	8 (3.17)	11 (8.72)	
Papilla, n (%)			
Usual	293 (82.76)	80 (55.5)	
Redundant	12 (3.38)	25 (17.36)	<0.001
Peri-diverticular	40 (11.29)	24 (16.66)	
Anatomical variation, n (%)	9 (5.54)	7 (4.86)	0.08
Surgically altered anatomy, n (%)			
Hepatic surgery	2 (0.56)	0 (0)	0.14
Total bilirubin >10 g/dL	26 (12)	17 (14.53)	0.507
Dilated biliary tract >6 mm	265 (82.55)	58 (76.32)	0.209
Technical success, ERCP, n (%)	345 (98.3)	82 (56.9)	<0.001
Technical success, cannulation, n (%)	346 (98.9)	83 (57.6)	<0.001
Clinical success, n (%)	348 (98.8)	142 (98.6)	0.704
Complications, n (%)			
Mild bleeding	11 (3.1)	12 (8.3)	0.011

ERCP: endoscopic retrograde cholangiopancreatography; IQR: interquartile range; MPD: main pancreatic duct; PO: post-operative; DBC: difficult biliary cannulation.

Patients with DBC had a lower rate of technically successful ERCP (98.3 vs 56.9%, *P*<0.001) and lower rate of technically successful biliary cannulation (98.9 vs 57.6%, *P*< 0.001). There were not statistically significant differences between groups regarding clinical success of the procedure. Bilirubin level above 10 mg/dL, biliary tract dilation, or the number of previous ERCP were not associated with DBC.

Regarding complications, mild bleeding (without transfusion requirement) was the most frequent in the DBC group (3.1 vs 8.3%, *P*=0.01 (TABLE 2). There were no post endoscopic pancreatitis, gastrointestinal perforations, or cholangitis.

Bivariate and multivariate analysis

Bivariate analysis showed an association between DBC and female gender (OR 1.70; CI95% 1.12–2.49; *P*=0.01), procedures performed in the acute care hospital setting (OR 2.75; CI95% 1.68–4.49, *P*<0.001), pancreatic cancer (OR 3.52; CI95% 1.50–8.25, *P*=0.004), and the presence of redundant or peridiverticular papilla (TABLE 3).

The multivariate analysis evidenced a direct and independent association between DBC and acute care hospital setting (OR 2.92; CI95% 1.70–5.01; *P*<0.001) and the presence of redundant papilla (OR 7.26; CI95% 3.38–15.61; *P*<0.001) or peridiverticular

TABLE 3. Association between difficult cannulation and clinical variables of patients undergoing ERCP. Bivariate and multivariate analysis.

	Bivariate analysis			Multivariate analysis		
	OR	**CI 95%**	***P* value**	**OR**	**CI 95%**	***P* value**
Gender (female)	1.70	[1.12;2.49]	0.01	1.44	[0.93;2.23]	0.104
Age	1.00	[0.98;1.01]	0.85			
Acute care hospital setting	2.75	[1.68;4.49]	<0.001	2.92	[1.70;5.01]	<0.001
Senior professional	1.20	[0.81;1.78]	0.349			
Papilla						
Usual	Reference					
Redundant	7.63	[3.67;15.85]	<0.001	7.26	[3.38;15.61]	< 0.001
Peri-diverticular	2.35	[1.34; 4.11]	0.002	2.45	[1.38;4.36]	0.002
Anatomical variant	2.4	[0.87;6.6]	0.08			
Total bilirubin >10 g/dL	1.24	[0.64;2.4]	0.508			
ERCP indication						
Pancreatic cancer	3.52	[1.50;8.25]	0.004			
Biliary tract >6 mm	0.68	[0.37;1.24]	0.211			

ERCP: endoscopic retrograde cholangiopancreatography.

papilla (OR 2.45; CI95% 1.38–4.36; *P*=0.002). Analysis of the endoscopist's experience did not show any association with DBC (TABLE 3).

DISCUSSION

The percentage of DBC found in the analysis of this study was 29%, which is consistent with the frequency reported in medical literature of between 10–35% of procedures performed by experienced endoscopists[1].

The definition for DBC has changed in the last decades and varies among studies. For this study, ESGE criteria were selected, considering that they have allowed a more generalized identification of DBC[6]. There is, however, controversy over the best definition. Some authors consider it more appropriate to determine the length of the procedure than the number of cannulation attempts, given the relationship between procedure length and rate of complications[10]. A prospective study evaluating 907 ERGP reported that, in expert hands, 80% of cannulations were possible within the first 2 minutes by conventional technique. After 5 minutes without achieving cannulation, the success rate reduces dramatically to as low as 8%[11]. The analysis in this study showed that, in this Gastroenterology Unit, the criterion number of cannulation attempts was more frequent than the criterion time to achieve successful cannulation. These results address the need for establishing quality parameters adapted in the training of new endoscopists, with strict time measurement for cannulation from the moment of first contact with the papilla and/or cannulation/opacification of the PD.

As lengthier procedures are associated with higher risk of complications, the authors propose a 10-minute limit for a cannulation attempt in endoscopist training[12]. Also, when DBC is anticipated, early strategies should be used to minimize the risk of complications and adjust the role of involved endoscopists.

The findings in this study are consistent with medical literature on the association between papilla alterations and DBC probability[13]. Intra- and peri-diverticular papilla are difficult to identify, and they can relate to common bile duct obstruction, pancreatitis, perforation, hemorrhage, and, rarely, carcinoma. Intra- and peri-diverticular papilla presence predicts that cannulation will need extra time, the use of advanced techniques, and the participation of a more experienced endoscopist[14]. There are several classifications for periampullary diverticula. Recent comparison between classifications has shown that Li-Tanaka classification has a clinical advantage as a tool for the endoscopist in cannulation planning and in the evaluation of potentially difficult cases[15].

This study also identified the acute care hospital setting as a DBC predictor, which might relate to the severity of the ailment being treated. Previous studies have also demonstrated that failed ERCP increase the risk of intra-hospital mortality. It has been proposed that the presence of more severe diseases and the complications from their management, might explain such an increase in mortality[16].

Female gender is acknowledged as a risk factor for post endoscopic pancreatitis, and there is no strong evidence on the underlying mechanisms. The DBC is a possible explanation, although there is no strong evidence that cannulation is more problematic in women than in men[17]. In this study, the bivariate study suggested an association between female gender and DBC, but this association was not statistically significant in the multivariate analysis. A prospective study that analyzed 364 ERCP performed by expert endoscopists in native papilla found a tendency toward prolonged times and a higher requirement of alternative techniques to achieve successful cannulation in women. This difference, however, was not statistically significant (*P*=0.061 y=0.054, respectively)[18]. Further studies with a larger sample are required to clarify this association.

Several studies have researched the number of ERCP required to achieve the necessary skills for selective biliary cannulation in patients with native papilla. An 80% success rate in biliary cannulation has been proposed as the goal for ERCP training[19]. An experience of more than 200 procedures has been considered adequate in the ERCP learning curve of an endoscopist. That number is considered the threshold for a significant increase in cannulation success rate (36% at the start compared to 85% after

200 procedures, $P<0.001$)[20]. Other authors report that successful cannulation rate increases from 43% at the start of training to values above 80% after 350 to 400 supervised procedures[21]. Mandai et al. suggested in 2017 that an experience of 300 procedures or less and malignant biliary stenosis due to pancreatic cancer were associated with prolonged time lengths for biliary cannulation[22].

There have been contradictory data regarding student participation in ERCP having a negative impact on cannulation success. A study in 2017 did not find significant differences in cannulation rates between procedures with a learner compared to those without a learner (91% vs 93%, $P=0.8$). However, the average time for biliary cannulation with the presence of a learner was 7 minutes, compared to 5 minutes without a learner[23]. Given that teaching ERCP is the most difficult task in an endoscopic training program, further study is required to clarify that association and to design standardized, structured, and effective ERCP training programs[24].

It has been proposed that the higher the bilirubin level, the higher the DBC risk, this under the assumption that a very high bilirubin is associated with a more severe obstruction, and so to a higher difficulty in passing the catheter. However, DBC mechanisms are not completely elucidated, and DBC can occur with proximal lesions, malignant etiologies, or in the presence of normal bilirubin levels. This study did not find an association between DBC and a high bilirubin level. The number of patients with levels higher than 15 mg/dL, however, was very limited. Further studies are required to determine if such patients do have a higher risk of DBC.

The number of analyzed procedures and DBC events detected is a strength of the study. The main limitation is retrospective data collection. The amount of lost data in the clinical history registries and procedure reports was low, however, so the authors consider lost data irrelevant to the study's conclusions.

This study found DBC a frequent event. Also, it identified papilla variations and performing ERCP in the acute care hospital setting as the two main factors associated with DBC. This information might be useful to predict DBC and establish healthcare and administrative strategies to reduce DBC's implications. Such strategies would include supply preparation and performance of the procedure by senior endoscopists, among others.

Authors' contribution

Cáceres-Escobar D, Muñoz-Velandia OM and Rubio RV: study conception, design, and analysis; writing, revision and editing. Caceres-Escobar D: data collection.

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Cáceres-Escobar D, Muñoz-Velandia OM, Rubio RV. Fatores associados à difícil canulação biliar em um centro de treinamento para intervenção endoscópica do trato biliar. Arq Gastroenterol. 2022;59(1):29-34.

RESUMO – **Contexto** – Este artigo tem como objetivo determinar fatores associados à dificuldade de canulação biliar que sejam identificáveis antes dos procedimentos. **Métodos –** Trata-se de um estudo de caso-controle dentro de uma coorte histórica em pacientes adultos submetidos a colangiopancreatografia retrógrada endoscópica (CPRE) de 2015 a 2019 no Hospital Universitário San Ignacio, em Bogotá, Colômbia. Avaliou-se as associações entre variáveis que poderiam ser identificadas antes ou no início dos procedimentos e a probabilidade de difícil canulação biliar (DCB). Essas associações foram avaliadas por meio de análise bivariada e multivariada. O estudo utilizou critérios para DCB definidos pela Sociedade Europeia de Endoscopia Gastrointestinal. **Resultados –** Foram analisados 498 CPRE em 376 pacientes. De todos os procedimentos, 144 (29%) preencheram critérios para DCB. A análise multivariada mostrou associação entre a DCB e o ambiente hospitalar de atenção aguda (OR:2,92; CI 95% 1,70–5,01; $P<0,001$), papila redundante (OR:7,26; CI95% 3,38–15,61; $P<0,001$), ou papila peridiverticular (OR:2,45; CI95% 1,38–4,36; $P=0,002$). Não foi encontrada associação entre a DCB e a experiência do endoscopista, dos níveis de bilirrubina ou da dilatação do trato biliar. **Conclusão –** A DCB é um evento frequente. Alterações na papila e CPRE realizadas no ambiente hospitalar de cuidados agudos são os principais fatores associados a DCB. Essas informações podem ser úteis para prever a DCB e estabelecer estratégias de saúde e administrativas para reduzir suas implicações.

Palavras-chave – Canulação biliar difícil; colangiopancreatografia retrógrada endoscópica.

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ORIGINAL ARTICLE

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Colonoscopy findings in liver transplantation candidates

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ABSTRACT – Background – Mandatory colonoscopy in liver transplantation (LT) candidates is recommended but still controversial. **Objective –** To investigate the frequency of colonoscopy lesions in order to support colorectal cancer (CRC) screening in a real-world pre-LT cohort. **Methods –** Retrospective study conducted at a single-center included 632 subjects who underwent pre-transplantation colonoscopy. **Results –** Median age was 56.9 years (yr.) old (82.3% were ≥50 yr.). Primary sclerosing cholangitis (PSC) occurred in 4.6%. Colonoscopy was abnormal in 438 (69.3%) by detection of polyps (37.7%), vascular changes (29.9%), diverticulosis (18.4%), inflammatory bowel disease features (5.2%) and CRC (0.6%). Histology was available in 66.8% of polyps: hyperplastic (47.8%), low-grade dysplasia (56.6%) and high-grade dysplasia (3.8%). High-risk adenomas occurred in 8.2% of the 594 subjects evaluated. Individuals ≥50 yr. were more likely to present abnormal colonoscopy and polyps. High-grade dysplasia and CRC were only found in individuals ≥50 yr. Patients with high-risk adenomas were more likely to be ≥50 yr. – there was no association between high-risk adenomas detection and liver disease etiology or PSC diagnosis. **Conclusion –** Most LT candidates presented abnormal colonoscopy examination, especially by polyps presence. All cases of high-grade dysplasia and CRC occurred in patients ≥50 yr., regardless of disease etiology.

Keywords – Liver transplantation; colonoscopy; colorectal cancer; dysplasia; polyps.

INTRODUCTION

Colonoscopy is recommended as part of the standard screening for neoplastic lesions in patients who are candidates for liver transplantation (LT) according to international guidelines[1,2], although the prevalence of colorectal cancer (CRC) in LT candidates is still unclear. The frequency of premalignant lesions, such as high risk adenomas, vary from 5% to 14%[3-6] in this population, and their removal is recommended, since immunosuppressive therapy after LT can potentially accelerate progression to CRC.

Previous studies have reported that cirrhotic patients and LT candidates are more likely to develop polyps, adenomas and high risk pre-malignant lesions than the overall population[4,7,8]. However, this association is still divergent in the literature[5,9,10] and most studies present remarkable limitations such as usage of sigmoidoscopy[10], small patient sample and inclusion criteria of age >45 or >50 years old[11-13]. Therefore, it is still uncertain if end-stage liver disease patients would benefit from referral to colonoscopy and at what age, since it can be a high risk procedure in this group.

The aim of this study is to evaluate the frequency of abnormal colonoscopy findings in LT candidates of a Brazilian referral center, as well as to report the observed lesions and to investigate its association with age and cirrhosis etiology.

METHODS

Study design and patients

A retrospective study was performed at the Liver Transplantation Outpatient Clinic, *Hospital das Clínicas da Universidade Federal de* Minas Gerais, Brazil. We selected 632 patients evaluated for LT eligibility who received colonoscopy assessment between January 2008 and November 2016. At our institution, LT candidates ≥50 years routinely undergo screening colonoscopy[1,2]. Also, patients with risk factors for CRC, such as inflammatory bowel diseases, primary sclerosing cholangitis (PSC) or family history of colonic neoplasia were submitted to colonoscopy at any age, as advised by guideline recommendations[1,2]. In cases of fulminant hepatitis, colonoscopy is not required.

This study was approved by the institution's Ethics Committee (CAAE 37895220.0.0000.5149). Informed consent was waived due to the retrospective design of the study. All procedures performed were in accordance with the 1964 Helsinki declaration.

Clinical characteristics at the time of colonoscopy including sex, age, liver disease etiology and diagnosis of concomitant schistosomiasis infection or hepatocellular carcinoma were collected. Liver disease etiology was classified as: ethanolic, chronic hepatitis C and B, cryptogenic, autoimmune liver disorders (i.e., autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis) and other causes (i.e., nonalcoholic steatohepatitis, hemochromatosis, Budd-Chiari syndrome and alpha-1-antitrypsin deficiency).

Data of the colonoscopy procedure was recorded, including presence of polyps, tumors, diverticulosis, features of inflammatory bowel disease (IBD) and vascular changes. Vascular changes included hemorrhoids, angiodysplasia and portal hypertension colopathy. If histopathological study was available, polyps were

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classified according to their histological characteristics, grade of dysplasia (i.e., low or high) and presence of CRC. High risk adenomas were defined as presence of any of the following features: (i) high-grade dysplasia, (ii) presence of three or more adenomas, (iii) adenomas ≥1 cm, or (iv) villous histologic subtype[14]. Histopathological study was not available in all cases due to the retrospective nature of the study. Also, in the following situations biopsy was unavailable: patients with coagulopathy or severe thrombocytopenia, small lesions non suggestive of CRC, loss of the tissue sample after resection or if the material was insufficient to pathological analysis. All patients with CRC received proper treatment.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (IBM, USA). Data are expressed as mean ± standard deviation for normally distributed continuous variables, as median and interquartile range (IQR) when distribution was skewed, or as absolute number and percentage for qualitative variables. Missing data were handled by pairwise deletion. Continuous variables distribution was assessed by the Shapiro-Wilk test. Student's *t*-test or non-parametric test (i.e., Mann-Whitney U-test) were used to compare quantitative data, as appropriate. Chi-square test or Fisher's exact test were used for comparison of categorical data, as appropriate. All tests were two-tailed and *P*-values <0.05 were considered significant.

RESULTS

Cohort comprised 632 patients. The study population was 69.8% male, median age was 56.9 (IQR 51.3–62.1) years old and 82.3% were ≥50 years old. Liver disease etiology frequency was: ethanolic (36.1%), chronic hepatitis C (27%), cryptogenic (20.8%), autoimmune liver disorders (10.3%, from those 44.6% was PSC), other causes (7.9%) and chronic hepatitis B (4.5%). Other baseline characteristics are presented in TABLE 1. Patients were separated in two groups according to their age (<50 yr. vs ≥50 yr.).

Colonoscopy examination presented abnormal findings in 438 (69.3%) subjects, as described: polyps in 238 (37.7%), vascular changes in 189 (29.9%), diverticulosis in 116 (18.4%), IBD features in 33 (5.2%) and CRC in 4 (0.6%) individuals. Histopathological examination was available in 159 (66.8%) of the polyps. From those, hyperplastic polyps were observed in 76 (47.8%), low-grade dysplasia in 90 (56.6%) and high-grade dysplasia in 6 (3.8%). From the total cohort of 632 patients, high risk adenomas occurred in 49 of the 594 subjects evaluated (8.2%) – 38 individuals did not have histopathology exam available, so they could not be classified. Colonoscopy macroscopic and microscopic findings are expressed in TABLE 2.

When comparing individuals <50 yr. vs ≥50 yr. (TABLE 3), we found no differences between sex (male 66% vs 71%, respectively, *P*=0.203) and availability of polyps histopathology (83.3% vs 64.6%, *P*=0.698). Patients ≥50 yr. were more likely to present hepatocellular carcinoma (18.5% vs 8.0%, *P*=0.007), abnormal colonoscopy examination (73.7% vs 49.1%, *P*<0.001), portal hypertension colopathy (32.1% vs 19.6%, *P*=0.009), diverticulosis (21.3% vs 4.5%, *P*<0.001) and polyps (41.2% vs 21.4%, *P*<0.001), when compared to those <50 yr. Polyps were present in 24 (21.4%) of the patients <50 yr., and 20 (83.3%) of those had histopathology exam available; whereas polyps were found in 214 (41.2%) of the participants ≥50 yr., and histopathology exam was available in 139

TABLE 1. Cohort baseline demographic and clinical characteristics.

Variable	Total cohort (n=632)
Male sex n (%)	441 (69.8)
Age	
Median	56.9 (51.3–62.1)
≥50 yr. n (%)	520 (82.3)
Range of age n (%)	
<45 yr.	66 (10.4)
45–50 yr.	46 (7.3)
50–55 yr.	142 (22.5)
55–60 yr.	157 (24.8)
60–65 yr.	138 (21.8)
≥65 yr.	83 (13.1)
Liver disease etiology n (%)	
Ethanolic	228 (36.1)
Chronic hepatitis C	171 (27.0)
Chronic hepatitis B	28 (4.5)
Cryptogenic	131 (20.8)
Autoimmune liver disorder	65 (10.3)
PSC	29 (4.6)
Other causes	50 (7.9)
Associated hepatosplenic schistosomiasis	21 (3.3)
Hepatocellular carcinoma	105 (16.6)

Yr.: years old; PSC: primary biliary cholangitis.

TABLE 2. Cohort colonoscopy macroscopic and microscopic data.

Variable n (%)	Cohort (N=632)
Normal examination	194 (30.7)
Abnormal examination	
Colorectal cancer	4 (0.6)
IBD features	33 (5.2)
Vascular changes	189 (29.9)
Diverticulosis	116 (18.4)
Polyp	238 (37.7)
Polyps	
Available polyp histopathology	159 (66.8)
Hyperplastic polyp	76/159 (47.8)
Low-grade dysplasia	90/159 (56.6)
High-grade dysplasia	6/159 (3.8)
High risk adenomas	49/594 (7.8)

IBD: inflammatory bowel disease.

TABLE 3. Comparison between clinical and histopathological data of patients < 50 vs ≥ 50 years old.

Variable n (%)	Patients <50 yr. (n=112)	Patients ≥50 yr. (n=520)	*P*-value
Male sex	74 (66.1)	367 (70.6)	0.203
Liver disease etiology			
Ethanolic	31 (27.6)	197 (37.8)	0.040*
Hepatitis C	22 (19.6)	149 (28.6)	0.052
Hepatitis B	5 (4.5)	23 (4.4)	>0.999
Cryptogenic	17 (15.2)	114 (21.9)	0.110
Autoimmune liver disorder	33 (29.5)	32 (6.1)	<0.001*
PSC	20 (17.9)	9 (1.7)	<0.001*
Other causes	8 (7.1)	42 (8.1)	0.740
Associated hepatosplenic schistosomiasis	2 (1.8)	19 (3.7)	0.317
Hepatocellular carcinoma	9 (8.0)	96 (18.5)	0.007*
Normal examination	57 (50.9)	137 (26.3)	<0.001*
Abnormal examination			
Colorectal cancer	0 (0)	4 (0.8)	0.003*
IBD features	15 (13.4)	18 (3.5)	<0.001*
Vascular changes	22 (19.6)	167 (32.1)	0.009*
Diverticulosis	5 (4.5)	111 (21.3)	<0.001*
Polyp	24 (21.4)	214 (41.2)	<0.001*
Polyps			
Available polyp histopathology	20/24 (83.3)	139/214 (64.6)	0.698
Hyperplastic polyp	7/20 (35.0)	69/139 (49.6)	0.220
Low-grade dysplasia	15/20 (75.0)	75/139 (53.9)	0.075
High-grade dysplasia	0/20 (0)	6/139 (4.3)	0.025*
High risk adenomas	3/109 (2.7)	46/485 (9.5)	0.020*

IBD: inflammatory bowel disease. $P<0.05$ was considered significative (*).

(64.6%) of those. All patients with high-grade dysplasia (4.3%) or CRC (0.8%) were ≥50 yr. (FIGURE 1).

The group of patients with high risk adenomas had a mean age of 57.2 (±5.9) yr. Those who presented high risk adenomas, when compared to subjects without high risk adenomas, were more likely to be ≥50 yr. (93.9% vs 80.6%, *P*=0.021), and to show absence of vascular changes (83.7% vs 69.2%, *P*=0.033). Only three individuals <50 years old presented high-risk adenomas, which were incidental findings in all cases, since there was no known risk factor for their occurrence. There was no difference between frequency of liver disease etiology (*P*=0.678), PSC diagnosis (*P*=0.155), ≥45 yr. vs <45 yr. (*P*=0.115) and sex (*P*=0.566).

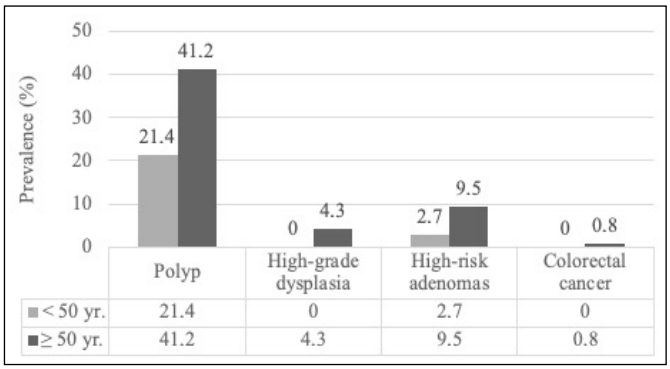

FIGURE 1. Colonoscopy prevalence of polyps and colorectal cancer in liver transplantation candidates with <50 vs ≥50 years old.

DISCUSSION

This study demonstrated that abnormal findings on colonoscopy are common in LT candidates. The most frequent abnormality was the presence of polyps. Cohort's frequency of high risk adenomas was 7.8%, and CRC was found in four patients (i.e., 0.6%). Patients ≥50 yr. were more likely to present abnormal colonoscopy, polyps, high-grade dysplasia and CRC than those <50 yr. In fact, all patients with high-grade dysplasia or CRC were ≥50 yr.

In absolute terms, Brazil is the country that most performs LT in Latin America, although organ donation availability is far below the demand due to the increasing population and inadequate donor organ supply[15]. Thus, selecting adequate LT candidates is extremely relevant for public health, and for this purpose cancer screening is required for eligibility assessment, since extrahepatic cancer can be a contraindication for LT, besides that the immunosuppressive post-transplantation therapy is associated with malignancies development[16-18]. Since CRC incidence is known to be increased after solid organ transplantation[19], including LT patients[20], colonoscopy is recommended for all LT candidates aged 50 years or older or having PSC[1,2].

In end-stage liver disease patients, colonoscopy is a high-risk invasive procedure, with potential morbimortality, besides high cost[21]. Although the procedure has not demonstrated relevant intraoperative complications in a previous cross-sectional study[6], further prospective investigation has shown that after colonoscopy there was an increased risk for renal failure and gastrointestinal bleeding especially in advanced liver disease patients[5]. Therefore, the reconsideration of current guidelines has been suggested and alternative colorectal screening strategies have been proposed[5].

In order to support future recommendations, previous studies have described the frequency of abnormal findings in LT candidates' colonoscopy[3-6,9-13]. The prevalence of polyps ranged from 19–46% in these studies, while high-grade dysplasia was detected in 2–5%[3,9], high risk adenoma in 5–14%[3-6] and CRC in 0–4%[3,5,6,9,10,12,13]. Our cohort presented similar results which corroborated previous studies. However, the previous studies presented remarkable limitations, as follows: examination with only sigmoidoscopy[10], selection criteria of LT candidates 45 or 50 years and older[11-13], lack of detailed polyp histopathological description[6,10,12] and small patients sample[3,9-13]. Our study presented a larger cohort sample and the selected patients were all submitted to total colonoscopy per protocol, which assured reliability to our findings, compared to previous investigations.

A recent study evaluated colonoscopic screening in LT candidates in Egypt[22]. Authors observed polyp prevalence of 8.7%, of which 4.2% were adenomas. Moreover, prevalence of adenoma was significantly higher in patients ≥50 yr. Our study found a higher prevalence of polyps than described in that study and corroborated the finding that being ≥50 yr. is associated with a higher risk of polyp detection.

It is noteworthy that PSC diagnosis was not associated with the occurrence of high risk adenomas in our study, however this might have been observed because PSC patients undergo early colonoscopy examination in order to search for or assess remission of IBD. Thus, early treatment of previous intestine lesions may have an impact on polyps prevalence in those patients.

All high-grade dysplasia adenomas and CRC were observed in subjects ≥50 yr., which can suggest that screening subjects older than 50 yr. may be an adequate strategy. Further studies should compare colonoscopic screening between ≥50 yr. and ≥45 yr. by specific methodology design in order to clarify if LT candidates would benefit from earlier colonoscopic examination. Also it is important to consider the benefits of screening compared to the potential harms of performing an invasive exam in a cirrhotic patient, most of the times decompensated. Although our study did not evaluate data on colonoscopy side effects or complications, our findings on the prevalence of pre-neoplastic lesions was relevant, since high frequency of abnormal findings can support colonoscopy performance.

To the best of our knowledge, this is the first study that investigated colonoscopy findings in LT candidates screening in the Brazilian population. CRC and the adenoma-carcinoma sequence are multifactorial and influenced by lifestyle, genetic and environmental factors, thus its occurrence is heterogeneous around the world[23]. Thereby, investigating the Brazilian population is relevant in order to support future guidelines recommendations. In fact, CRC is the second most incident cancer in both sex in our study geographical region in Brazil, excluding non-melanoma skin cancer[24].

There are limitations to this study. The investigation design was retrospective, data collection was based on patient records and the study did not enroll liver healthy controls. Moreover, there was a considerable lack of histopathological data regarding polyps examination for reasons previously described, although there was no statistical difference between available biopsy samples in <50 yr. and ≥50 yr. Missing data may have reduced statistical power of our study, but pairwise deletion was performed in order to avoid selection bias and keep the population representative. Lastly, in Brazil CRC surveillance in the general population is recommended to be performed after 50 yr. old, so this can have an impact on data analysis in the population studied.

In conclusion, most LT candidates presented abnormal colonoscopy examination, especially by polyps presence. There was a considerable frequency of high-grade dysplasia and CRC in our cohort, which were all detected in patients ≥50 yr. These findings suggest that CRC screening should be performed in LT candidates with 50 yr. or older and colonoscopy might be an adequate strategy for detecting high-risk pre-malignant and malignant lesions. Further investigation by prospective and controlled studies is needed to better analyze the CRC screening in LT candidates.

Authors' contribution

Osório FMF and Lima AS designed the study; Osório FMF, Maia LG and Rodrigues RAT collected data; Osório FMF, Nardelli MJ, Penna FGC and Lima AS analyzed data; Osório FMF and Nardelli MJ wrote the paper; Penna FGC and Lima AS critically reviewed the manuscript for intellectual content; all authors approved the final version of the manuscript.

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Osório FMF, Nardelli MJ, Maia LG, Rodrigues RAT, Penna FGC, Lima AS. Achados da colonoscopia em candidatos a transplante hepático. Arq Gastroenterol. 2022;59(1):35-9.

RESUMO – Contexto – Colonoscopia mandatória em candidatos a transplante hepático (TH) é recomendada, mas ainda é controversa. **Objetivo –** Investigar a frequência de lesões detectadas pela colonoscopia para endossar o *screening* de câncer colorretal (CCR) em uma coorte pré-TH de mundo real. **Métodos –** Estudo retrospectivo conduzido em um centro único que incluiu 632 indivíduos submetidos a colonoscopia pré-TH. **Resultados –** Idade mediana foi 56.9 anos (82,3% eram ≥50 anos). Colangite esclerosante primária (CEP) estava presente em 4.6%. Colonoscopia foi anormal em 438 (69,3%) por: detecção de pólipos (37,7%), alterações vasculares (29,9%), diverticulose (18,4%), características de doença inflamatória intestinal (5,2%) e CCR (0,6%). Histologia estava disponível em 66,8% dos pólipos: hiperplásicos (47,8%), displasia de baixo grau (56,6%) e displasia de alto grau (3,8%). Adenomas de alto risco ocorreram em 8,2% dos 594 indivíduos avaliados. Indivíduos ≥50 anos eram mais prováveis de apresentar colonoscopia anormal e pólipos. Displasia de alto grau e CCR foram encontrados somente em indivíduos ≥50 anos. Pacientes com adenoma de alto risco eram mais prováveis de ter ≥50 anos – não houve associação entre a detecção de adenomas de alto risco e a etiologia da hepatopatia ou o diagnóstico de CEP. **Conclusão –** A maioria dos candidatos a TH apresentaram achados anormais na colonoscopia, principalmente pela presença de pólipos. Todos os casos de displasia de alto grau e CCR ocorreram em pacientes ≥50 anos, independente da etiologia da hepatopatia.

Palavras-chave – Transplante hepático; colonoscopia; câncer colorretal; displasia; pólipos.

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High prevalence of non-adherence to ulcerative colitis therapy in remission: knowing the problem to prevent loss

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ABSTRACT – Background – Ulcerative colitis (UC) is a chronic inflammatory disease whose manifestations can drastically affect the individual's quality of life, and therefore adherence to treatment is important in order to keep it in remission. **Objective –** To verify the prevalence of non-adherence and the influence of sociodemographic, clinical and pharmacotherapeutic characteristics associated with non-adherence to treatment of UC in remission. **Methods –** Cross-sectional study conducted with 90 individuals diagnosed with UC in remission. The information was collected through interviews during medical consultations at Medical Clinic of Gastroenterology of *Hospital Universitário da Universidade Federal de* Juiz *de Fora*. To verify the association of the variables under study with the outcome of interest and its measure of association, Student's *t*-test or Pearson's chi-square non-parametric test ($P<0.05$) was used and prevalence ratio and confidence interval were calculated. **Results –** A high prevalence of non-adherence (77.8%) was found among patients with UC in remission. The individuals most likely to not adhere to the treatment were those aged less than 50 years, who were not engaged in paid work, with high scores for anxiety and who used more than one medication as part of the treatment of UC. **Conclusion –** These findings reinforce that acknowledging the factors that influence the non-adherence behavior is of paramount importance for the development of strategies by health care professionals, assuring that those will be really effective to prolong, as much as possible, one of the most successful ways to maintain the UC remission period: the use of medications.

Keywords – Chronic disease; ulcerative colitis; drug therapy; proctocolitis; treatment adherence and compliance.

INTRODUCTION

Ulcerative colitis (UC) and proctocolitis are classified as a chronic, idiopathic inflammatory disease, characterized by recurrent inflammation of the intestinal mucosa that can extend from the rectum to the colon, causing diarrhea, rectal bleeding and other complications related to these primary symptoms[1]. It is a disease that affects men and women in the same proportion, in the age group of 30 to 40 years, causing an important limitation in these patients of working age[1,2].

The incidence of UC is increasing worldwide, with concern about the impact of Western lifestyle as a risk factor for the disease[3]. The number of diagnosed patients has been growing in countries in Europe and North America, as well as newly westernized countries in Asia, South America and the Middle East[3,4]. Specifically in Brazil, the same trend observed globally follows, with an increase in the prevalence of UC from 0.24/100,000 between 1986–1990 to 14.1/100,000 in 2014[5].

There is no cure for the disease and its treatment is chronic in order to induce and maintain remission of UC. The clinical remission is defined as the resolution of rectal bleeding and diarrhea, and endoscopic remission defined as a Mayo endoscopic subscore of 0 or 1[6]. Pharmacological options are chosen according to the severity of the disease, and aminosalicylates are considered as first-line for the treatment of mild to moderate UC[2,7,8].

For patients who do not respond to aminosalicylate monotherapy or with moderate to severe manifestations, the use of glucocorticoids and immunosuppressants to induce and/or maintain remission of symptoms should be included in the therapeutic regimen[8-10]. However, they all have limited beneficial effects and the risk of adverse reactions and side effects[11,12]. Despite this, adherence to treatment is essential to reach the state of remission, being thus considered a critical point in the management of patients with UC[13].

Non-adherence to treatment is considered a barrier for inducing remission and, therefore, for the patient's clinical improvement[13]. Multiple factors have been suggested to contribute to non-adherence in inflammatory bowel disease (IBD) including age, marital status, employment, gender, new patient status, duration of disease, multiple medications use, three times or more daily dosing, and comorbidities, but still varied form[14,15].

Adherence to drug treatment can be understood as the process by which patients take their medications as prescribed and it is composed of initiation, implementation and discontinuation. The patient is considered as non-adherent when is verified non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen or early discontinuation of the treatment[16]. Thus,

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understanding individual barriers and adherence behaviors is critical for designing effective interventions to improve adherence. The objective of the present study was to verify the prevalence of non-adherence, as well as the influence of socio-demographic, clinical and pharmacotherapeutic factors in this behavior among patients with UC in remission that were seen at the Clinical Gastroenterology of *Hospital Universitário da Universidade Federal de Juiz de Fora* (HU-CAS UFJF).

METHODS

Scenario and study population

The study was conducted at the Medical Clinic of Gastroenterology of Center for IBD at HU-CAS UFJF. This service is considered a regional reference for specialized assistance and approximately 600 patients diagnosed with an IBD have benefited in 2018 from the service.

It was a cross-sectional, observational study, carried out between August 2017 and January 2018, a period that allowed all adult patients (>18 years old) of both genders with a diagnosis of UC made on the basis of routine clinical, radiological, endoscopic and histopathological criteria[17] to attend at least once for an outpatient consultation. At the time of the approach, the patient should be in a period of remission of the disease. To be classified as in clinical remission, a criterion used was that the individual should have a number ≤3 bowel movements per day, free of pus or blood, in addition to the absence of systemic symptoms[17].

Patients with UC who came for their routine appointments were asked to answer a semistructured questionnaire that started witha question about the activity status of their disease. If in remission, they were invited to proceed. Therefore, the following exclusion criteria were established: presenting active status of the disease, being on anti-TNF-α therapy, being in a period of pregnancy or lactation, and disinterest in participating in this research. Thus, 90 patients were considered eligible to participate.

This research was reviewed and approved by the Ethics Committee of the *Universidade Federal de Juiz de Fora*, MG Brazil (protocol number: 2.157.931).

Instruments and data analysis

The selected patients were invited to answer a semi-structured questionnaire so that the socioeconomic characteristics of each patient (age, gender, race, education level, occupation, marital status and region of residence) and personal history (smoking, alcoholism, comorbities, previous surgery in gastrointestinal tract, depression and anxiety) were evaluated.

Questions about clinical characteristics of UC and medications (anatomical extension of UC, time since diagnosis of UC, time in remission, time in clinical follow-up, acces to medications by public health system, total and kinds of medications and daily pills) presented in the same questionnaire that could not be answered by patients for some reason were later verified in their medical records.

The following instruments were used to collect the data: a questionnaire prepared by the authors of this article containing questions about socio-demographic aspects; the eight-item Morisky Medication Adherence Scale (MMAS-8)[18]; Beck depression inventory (BDI)[19]; and a depression and anxiety scale (Hopitalar Anxiety and Depression Scale - HADS-A)[20].

As in another study, we chose to group patients according scores in MMAS-8. Medium and low adherers (score <8) were grouped together and labelled them as MMAS-8 non adherers as there is neither a clear definition of medium and high adherence in the literature nor a clear clinical discrimination between the scores 6 to 8[18,21]. Anyway, scores <8 indicate failure in the following treatment. Thus, only those patients who presented 8 points on the MMAS-8 were considered as adherent to pharmacotherapy. The prevalence of non-adherence was calculated, therefore, by the number of non-adherent patients divided by the total population that participated in the study. For the assessment of depression and anxiety, scores ≥15 for BDI and ≥8 for HADS-A were considered relevant.

Statistical analysis was performed using GraphPad Prism 6.0 software. Quantitative variables were expressed as mean ± SD when normally distributed and significant differences between groups using Studen *t*-test were considered when $P<0.05$. Descriptive statistics of all relevant variables were calculated. All variables were dichotomized and then a descriptive analysis of the data was performed, presented in the form of tables of absolute and relative frequency. The association between variables under study with the outcome of interest was checked by Pearson's chi-square test (significance level of 5%) also being calculated prevalence ratio (PR) and 95% confidence interval (CI95%).

RESULTS

The epidemiological profile found for the population with UC in remission (n=90) showed gender equivalence (n=45, 50% male and n=45, 50% female), age 50.41±12.94 years, white (n=73, 81.1%), with some degree of literacy (n=87, 96.7%), engaged in paid activity (n=69, 76.7%), and married or in a consensual marriage (n=49, 54.4 %). The predominant region of residence, interestingly, was in cities neighboring the municipality where the outpatient service was offered (n=49, 54.4%). Comorbidities were present in 46 (51.1%) individuals, with no history of gastrointestinal surgery (n=87, 96.7%). The prevalence of depression and anxiety was 15.6% and 36.7%, respectively. The sociodemographic characteristics were described in table below (TABLE 1).

The prevalence of non-adherence in the sample was 77.8% and the socio-demographic variables that were related to the non-adherence behavior were age (between 18 and 50 years, 48.2±1.5 years) and not being engaged in paid activity, observing that younger individuals and those who were not engaged in paid activity were, respectively, 2.6 and 5.5 times more likely to show non-adherence behavior. In addition, it was observed that anxiety also was a factor that increased the chance of this behavior by 3.3 times.

With regards to general clinical features of UC, no characteristics were found to interfere with non-adherence behavior. There was a great variation in the times of diagnosis, period in remission and time of follow-up at the clinic. Regarding the anatomical extent of inflammation, cases of panconlitis predominated (46.7%, n=42). These data are described in TABLE 2.

The analysis of the pharmacotherapy aspects showed the most prescribed medication was mesalazine (5-ASA) (54.4%). The number of medications used influenced the non-adherence behavior, and those who used only one type of medication were more adherent than those who used two or more types ($P=0.041$). The quantity of daily pills and daily dosage did not influence in non-adherence behaviour ($P=0.11$ and $P=0.48$, respectivaly). There was a predominance of free supply of medications through the public health system, however this aspect was not relevant in adherence behaviour ($P=0.316$) (TABLE 3).

TABLE 1. Distribution of patients with UC in remission according to sociodemographics characteristics.

Sociodemographic characteristics	Adherence		Total	PR (CI)	*P*
	Yes (n=20)	No (n=70)			
Age (years) (mean±SD)	58.2±2.3	48.2±1.5	-	-	0.002#
Distribution by age group					
18-50 years	6 (6.7%)	41 (45.6%)	47 (52.2%)	2.6 (1.121–5.983)	0.04*
>50 years	14 (15.6%)	29 (32.2%)	43 (47.8%)		
Gender					
Female	8 (8.9%)	37 (41.1%)	45 (50%)	-	0.44
Male	12 (13.3%)	33 (36.7%)	45 (50%)		
Race					
White	17 (18.9%)	56 (62.2%)	73 (81.1%)	-	0.86
Non-white	3 (3.3%)	14 (15.6%)	17 (18.9%)		
Education level					
Illiterate	1 (1.1%)	2 (2.2%)	3 (3.3%)	-	0.81
Literate	19 (21.1%)	68 (75.6%)	87 (96.7%)		
Occupation					
In activity (formal or informal employement)	13 (14.4%)	14 (15.6%)	27 (30%)	4.3 (1.986–9.523)	0.0002*
No activity (unemployed or retired)	7 (7.8%)	56 (62.2%)	63 (70%)		
Marital status					
Single	6 (6.7%)	35 (38.9%)	41 (45.6%)	-	0.18
Married/consensual marriage	14 (14.4%)	35 (38.9%)	49 (54.4%)		
Region of residence					
Juiz de Fora	7 (7.8%)	34 (37.8%)	41 (45.6%)	-	0.41
Neighboring cities	13 (14.4%)	36 (40%)	49 (54.4%)		
Smoking					
Yes	1 (1.1%)	7 (7.8%)	8 (9.9%)	-	0.80
No	19 (21.1%)	63 (70%)			
Alcoholism					
Yes	1 (1.1)	2 (2.2%)	3 (3.3%)	-	0.81
No	19 (21.1%)	68 (75.6%)	87 (96.7%)		
Comorbities					
Yes	12 (13.3%)	34 (37.8%)	46 (51.1%)	-	0.52
No	8 (8.9%)	36 (40%)	24 (26.7%)		
Previous surgery in gastrointestinal tract					
Yes	1 (1.1)	2 (2.2%)	3 (3.3%)	-	0.81
No	19 (21.1%)	68 (75.6%)	87 (96.7%)		
Depression					
Yes	4 (4.4%)	10 (11.1%)	14 (15.6%)	-	0.79
No	16 (17.8%)	60 (66.7%)	76 (84.4%)		
Anxiety					
Yes	5 (5.5%)	42 (46.7%)	47 (52.2%)	3.3 (1.371–8.150)	0.01*
No	15 (16.7%)	28 (31.1%)	43 (47.8%)		

PR: prevalence ratio; CI: confidence interval; UC: ulcerative colitis. #*P*: significant value for Student test-*t*; **P*: significant value for Pearson's chi-square test.

TABLE 2. Distribution of patients with UC in remission according to clinical characteristics.

Clinical characteristics	Adherents patients (n=20)	Non-adherents patients (n=70)	Total sample (n=90)	*P*
Anatomical extension of ulcerative colitis				
Pancolitis	9 (10%)	33 (36.7%)	42 (46.7%)	0.99
Other	11 (12.2%)	37 (41.1%)	48 (53.3%)	
Diagnosis of the disease (months)				
Up to 10 years	12 (13.3%)	37 (41.1%)	49 (54.4%)	0.61
>10 years	8 (8.9%)	33 (36.7%)	41 (45.6%)	
Time in remission (months)				
Up to 3 years	7 (7.8%)	34 (37.8%)	41 (45.6%)	0.42
>3 years	13 (14.4%)	36 (40%)	49 (54.4%)	
Time in clinical follow-up				
Up to 7 years	14 (15.6%)	54 (60%)	68 (75.6%)	0.56
>7 years	6 (6.7%)	16 (17.8%)	22 (24.4%)	

**P*: significant value for Pearson's chi-square test. UC: ulcerative colitis.

TABLE 3. Distribution of patients with UC in remission according to clinical characteristics.

Pharmacotherapeutic characteristics	Adhesion		Total sample (n=90)	PR (CI**)	*P*
	Yes (n=20)	No (n=70)			
Total access to medications by Public Health System					
Yes	19 (17.1%)	58 (52.2%)	77		0.32
No	1 (1.1%)	12 (13.3%)	13 (14.4%)		
Total of medications					
One medication	15 (16.7%)	31 (34.4%)	46 (51.1%)	2.9 (1.202–7.144)	0.02*
More than one medication	5 (5.6%)	39 (43.3%)	44 (48.9%)		
Kinds of medications***					
Azatioprine	7 (7.8%)	27 (30.0%)	34 (37.8%)		0.80
Glycocorticoid	2 (2.2%)	10 (11.1%)	12 (13.3%)		0.72
Mesalazine	11 (12.2%)	38 (42.2%)	49 (54.4%)		>0.99
Sulfasalazine	7 (7.8%)	28 (31.1%)	35 (38.9%)		0.62
Daily pills (mean, range)					
Up to five pills/day	14 (15.6%)	32 (35.6%)	46 (51.1%)	-	0.07
More than 5	6 (6.7%)	38 (42.2%)	44 (48.9%)		

**P*: significant value for Pearson's chi-square test. UC: ulcerative colitis. **CI: confidence interval; PR: prevalence ratio. ***The chi-square test was done with each class compared to the class 'others'. A patient could be using more than one drug class.

DISCUSSION

RCU is a chronic condition requiring lifelong medication to minimize the incidence of symptomatic recurrences, need of surgery, hospitalization and several issues such as colorectal cancer[10]. Nevertheless, a large proportion of patients are non-adherent to their prescribed therapeutic regimen as demonstrated by this study, which found a high non-adherence prevalence (77.8%). Other investigations with Brazilian populations showed high non-adherence prevalence (63.3%) of a similar way to what we found among patients with UC in remission[22]. This issue has also been demonstrated for Chron disease, although with a slightly lower prevalence[22,23]. The quality of life of patients affected by UC can be severely impaired during phases of active disease but often returns to normal levels during remission, hence the importance of patients staying adherent to therapy[13,24].

Some common demographic variables such as age, marital status, living alone, gender, race, income, occupation, number of dependents, level of education or personality type have been the subject of controversial statements about their impact on non-adherence behavior in different treatments for chronic diseases[15,25]. In this study, however, out of the twenty one variables analyzed, only four were found to be related to non-adherence behavior: age, occupation, anxiety and quantity of medications used.

Increasing age, for example, has already been associated with low adherence to some treatments, such as arterial hypertension[26]. In contrast, in our data as well as in other studies on UC[10,27], younger patients demonstrated a lower degree of adherence and this may be a peculiarity of this type of chronic disease[20,28]. In this study, the medium age of non-adherents patients (48.2±1.5 years) was lower than adherents (58.2±2.3 years) and this finding is in agreement to described by D'Inca et al.[28] and De Castro et al.[19] in non-active IBD outpatients.

The portion of the sample individuals identified as having anxiety was highlighted in this study. In another survey involving patients with IBD, a frequency of 24.4 to 31.9% of anxiety in these patients was estimated[29], while our findings pointed to 36.7% of individuals with this disorder. According to Choi et al., the appearance of disorders such as anxiety and depression is related to the status of having a chronic disease diagnosis, but also to several individual circumstances[30] - which may include lack of exercise and being engaged in paid activity, a factor associated with low adherence in the sample. However, such comorbidities can also result from the use of some drugs and, in this case, especially glucocorticoids[30]. In general, anxiety can worsen the manifestations of UC and, as shown, be associated with non-adherence behavior.

As already demonstrated, the impact of these factors can produce different results according to the patients in question. Thus, the most assertive way to deal with non-adherence in a specific population is through in-depth knowledge of how much they can be affected by these variables[25,31].

Other complementary criteria for sociodemographic, clinical and pharmacotherapy features were investigated but also had not been associated with this issue. Our results were similar to Cornelio et al., who investigated risk factors to non-adherence to therapy in Chron's disease patients, without significant findings[23].

There are many reasons for not adhering to medical recommendations; however, some of them are directly related to the choice of an appropriate therapy. The ineffectiveness, the low quality of life of the patient and the high cost of therapy are also negative influences for adherence[32], although they are absent in this study sample. Within the group in question, adherence was achieved demonstrating the effectiveness of the treatment, mostly obtained due to the public health service being free of charge and by significantly improving these individuals' quality of life.

On the other hand, both the occurrence and the fear of side effects also impair adherence. The remission phase, especially, can encourage the belief that potential risks related to the medications surpass the need to maintain their use, since the patients perceive themselves as free from their long-term symptoms[33]. Some medications used for IBD have been associated with a non-adherent behavior to therapy. So, we hypothesized that the possibility of adverse events related to long-term use of medications, even without symptoms of active disease, may be a strong influence on the abandonment or noncompliance of therapy in this sample.

For this reason, an important role is played by the assistant physician that, when planning pharmacological treatment, must select drugs with the utmost care to eliminate risk factors that may contribute to therapeutic failure and encourage the patient to actively participate in the entire process[31,32]. It was realized that using more than one type of medication contributes to non-adherence and, whenever possible, treatments with drug combinations should be reduced in length as much as possible. Although it did not reach statistical significance, consuming more than five pills daily indicated a trend towards possible non-adherence behavior. Alternatives must be considered by the medical team aiming such reduction.

Regarding the limitations of this investigation, it should be noted that the present study did not focus on assessing the quality and the understanding of the information received about the treatment from the patient's perspective. Thus, the knowledge about health literacy of this group is an important point to be considered for future investigations. On this subject, it has already been mentioned that low levels of cooperation and adherence can also result from the action of health care providers. In this case, the perception that the patient has that they are not receiving attention for a long enough period, the lack of intensification of therapy, long waiting times for consultations and the absence of adequate communication between health care providers and the patient must be emphasized[34].

In addition, despite the fact that MMAS-8 has been established with excellent validity and reliability in patients with chronic diseases[21] and also as the first validated compliance scale in IBD, there are still conflicting data on its performance in such patients[35,36]. Thus, it is suggested that more specific studies be carried out with different populations affected by UC, including the use of other tools to measure adherence, such as screening the drug metabolite or counting pills. Using self-report as a method of assessing adherence is simple, inexpensive and useful in clinical practice, but tends to overestimate patient compliance. The combination of different methods increases the measurement's accuracy[37].

Based on the analyzed data, the present study identified that high proportions of patients with UC in remission presented non-adherence behavior to therapy. Patients over 50 years old, who were not engaged in paid activity, with symptoms of anxiety and who used more than one type of medication were identified as having the highest risk for non-adherence behavior among UC patients in remission.

These findings reinforce that acknowledging the factors that influence the non-adherence behavior is of paramount importance for the development of strategies by health care professionals, assuring that those will be really effective to prolong, as much as possible, one of the most successful ways to maintain the UC remission period: the use of medications.

Authors' contribution

Franco FCZ: data's colect and text writer; Oliveira MCC: text writer. Gaburri PD: text writer and review; Franco DCZ: data analyse, text writer and review; Chebli JMF: Research conductor and final review.

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Franco FCZ, Oliveira MCC, Gaburri PD, Franco DCZ, Chebli JMF. Elevada prevalência de não adesão ao tratamento da colite ulcerativa em remissão: conhecer o problema para prevenir o prejuízo. Arq Gastroenterol. 2022;59(1):40-6.

RESUMO – Contexto – Colite ulcerativa é uma doença inflamatória crônica que pode apresentar manifestações graves que afetam drasticamente a qualidade de vida do indivíduo e, dessa maneira, a adesão ao tratamento é importante a fim de manter a doença em remissão. **Objetivo –** Verificar a prevalência de não adesão e a influência de características sociodemográficas, clínicas e farmacoterapêuticas associadas a não adesão ao tratamento da colite ulcerativa em remissão. **Métodos –** Estudo transversal envolvendo 90 indivíduos diagnosticados com colite ulcerativa em remissão. As entrevistas foram conduzidas durante as consultas médicas realizadas na Clínica Médica de Gastroenterologia do Hospital Universitário da Universidade Federal de Juiz de Fora. Para verificar a associação entre as variáveis com o desfecho de interesse, foi aplicado teste-*t* de Student ou teste não-paramétrico qui-quadrado de Pearson ($P<0,05$) e também razão de prevelência e intervalos de confiança foram calculados. **Resultados –** Uma elevada prevalência de não adesão (77,8%) foi encontrada dentre os pacientes com colite ulcerativa em remissão. Os indivíduos mais propensos ao comportamento em questão foram aqueles com menos de 50 anos, sem trabalho remumerado, com escores mais elevados no teste de ansiedade e que utilizavam mais de um medicamento para o tratamento da colite ulcerativa. **Conclusão –** Estes achados reforçam que o conhecimento de fatores que influenciam o comportamento de não adesão é de grande importância para o desenvolvimento de estratégias para a equipe de saúde, garantindo que estas sejam realmente eficazes para prolongar, tanto quanto possível, uma das formas mais bem-sucedidas de manter o período de remissão da colite ulcerativa: o uso de medicamentos.

Palavras-chave – Doença crônica; colite ulcerativa; terapia medicamentosa; proctocolite; adesão e adesão ao tratamento.

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ORIGINAL ARTICLE

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Normal values of esophageal 24-hour impedance-pH ambulatory in an Argentine cohort of healthy volunteers

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ABSTRACT – Background – There are no data of reference values on 24-hour multichannel intraluminal impedance and pH (pH-MII) monitoring in Argentinian populations. **Objective** – Our aim was to obtain the normal values of pH-MII variables among healthy asymptomatic volunteers in a metropolitan Health Care Center of Argentina, and to compare them with data already published from other regions around the world. **Methods –** A cross-sectional study was undertaken in a tertiary referral center in Buenos Aires. We enrolled healthy subjects and asked them to undergo esophageal pH-MII 24hours monitoring. pH-MII variables were recorded and described. **Results –** Median reflux events was 20.5 (25–75%, 95%) interquartile range: (14–46, 50) and proximal reflux episodes was 2.5 (0–10, 11). Sixty percent were acid reflux episodes: 12 (5–29, 38), representing a relatively low value when compared to those reported in European, American and Chinese populations. **Conclusion –** Our study shows the first reference of normal values of gastroesophageal reflux in an Argentinian population. We found a total number of reflux events and a total number of proximal reflux events lower than what was reported until this date by other authors.

Keywords – Normal values; esophagus; 24-hour impedance-pH ambulatory.

INTRODUCTION

Montreal consensus establishes that gastroesophageal reflux disease (GERD) is present when gastric content reflux produces bothersome symptoms and/or complications in the esophagus or respiratory tract[1].

GERD, which is a prevalent condition, may not only lead to an impairment in the quality of life, but it can also predispose to the development of Barrett's esophagus, a preneoplasic entity that can be present in up to 15% of GERD patients[2,3]. Barrett's esophagus with high-grade dysplasia has been related to an incidence rate of esophageal adenocarcinoma of 7%, whereas its association with low-grade dysplasia has shown an incidence rate of 0.7%[4].

Twenty-four-hour impedance- pH (MII-pH) testing is considered to be the best diagnostic tool for GERD, it is considered to be the gold standard when considering those GERD patients without erosive disease on upper endoscopy or among those patients with refractory GERD. This diagnostic tool can measure the number of reflux episodes as well as the chemical characteristics of reflux content, whether it is proximal or distal reflux and its association with symptoms.

Olmos et al.[5] published the only Argentinian epidemiological study assessing the prevalence of GERD based on symptoms and endoscopic findings. Accordingly, studies from the United States and Europe have shown that GERD prevalence can vary from 10 to 20% among adults[6,7].

To our knowledge, there is a lack of studies assessing the values esophageal impedance-pH among asymptomatic subjects from South America. This type of information becomes relevant when defining which values should be taken as abnormal – historically, in our region the normal values from European studies have been taken as a formal guide when analyzing MII-pH[8,9]. It could be hypothesized that the normal values of the aforementioned studies may vary from region to region, a phenomenon related to dietary factors among others. However, recently published studies showed similar MII values among asymptomatic Chinese[10] and South-African[11] subjects when compared to the ones from Europe or North America.

Our aim was to obtain the value of MII variables among healthy asymptomatic volunteers, and to compare them with data already published from other parts of the world.

METHODS

Design and study population

A cross-sectional study was undertaken between January 2014 and February 2015 at the Gastroenterology Department of the "Hospital de Alta Complejidad en Red – El Cruce" located at the metropolitan area of Florencio Varela, Buenos Aires, Argentina. Healthy volunteers were asked to participate. After signing informed consent, standard extensive questionnaire was administered in order to rule out GERD symptoms[12]. Subjects would be excluded if they exhibited at least one of the following features:

- Symptoms of typical (pyrosis, regurgitation) or atypical (chronic cough, chest pain, asthma aerofagia) GERD.
- History of previous gastrointestinal surgeries – excluding appendectomy.

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- Use of proton pump inhibitors or prokinetics.
- Smokers (more than 40 cigarettes per day).
- History of neurologic diseases, hypothyroidism, diabetes mellitus, Chagas disease, inflammatory bowel disease.
- Alcohol consumption (more than 40 gr per day).

The study was conducted following Declaration of Helsinki (2013) recommendations; it was reviewed and approved by our local Ethics Committee. Study participation was always voluntary.

Study procedures

Healthy volunteers who fulfilled inclusion criteria were asked to assist to our institution with an 8-hour fasting before pH-metry with impedance test. There were advised to follow their regular diet during the lenght of the study.

A high-resolution esophageal manometry was initially performed in each subject to rule out esophageal motor disorders and to accurately locate lower esophageal sphincter. A local anaesthetic was used (lidocaine), and pH-metry+impedance catheter was placed transnasally with the distal sensor located 5 cm above the proximal border of the lower esophageal sphincter.

During the length of the study, subjects would have to register in a diary times of food ingestion, as well as body position changes. They were asked to avoid chewing gum and predominantely-acid food or beverages. After 24 hours, subjects would return and the catheters were removed. Diaries were delivered by the subjects and their data were reviewed by the investigators.

Equipment

- High-resolution manometer – Sandhill Scientific, Insight G3, Denver, CO, USA.
- Twenty-four-hour impedance-pH monitor – Sandhill Scientific ZAI-S61C01E.

Catheters with impedance channels at 3; 5; 7; 9; 15 and 17 cm from distal tip. The system includes a portable device and catheters with an antimonium pH electrode located 5 cm above their distal tip and 8 pairs of electrodes at 2; 4; 6; 8; 10; 14; 16; 18 cm above lower esophageal sphincter. Impedance amplificators release a voltage equivalent to 1–2 kHz, and their flux depend on changes of intraluminal impedance – pH sensors were calibrated using four and seven buffers and reference sensor was placed on the anterior chest wall of the patient. Tests results were analyzed by two esophageal motility fellows with advanced training and an expert in esophageal motility. In case of disagreement, the expert's criteria prevailed. Sandhill Scientific software BioVIEW, version 5.7.00 was used and the following variables were retrieved and analyzed per subject:

- Percentage of total time with pH <4 (acid exposure time - AET).
- Number of reflux episodes: total, distal and proximal.
- Acid, weakly acid reflux episodes, mixed and liquid.
- Daytime and nocturnal reflux episodes.
- Mean time of bolus transit and mean time of acid clearance.

Subjects who showed one of the following were excluded from the study:

- Pathologic values (AET>7%).
- Catheter migration.
- Technical artifacts during impedance-pH recording.

Definitions

- Distal reflux: a retrograde fall of at least 50% from basal impedance value in the last two channels. Chemical characteristics of reflux were defined according to expert consensus[13] criteria from Porto, 2002.
  - Acid reflux: pH decreases below four (which is equivalent to >12 mEq HCl/L) or occurring when the esophageal pH is already <4.
  - Superimposed acid reflux: reflux episode occurring while pH is still below four before acid clearance occurs.
  - Weakly acid reflux: a reflux episode with the esophageal pH of 4–6.5.
  - Non-acid reflux: pH increases over seven or remains above seven during reflux episode (0 mEq/L of HCl/L).
  - Bolus clearance: volume clearance of a single reflux episode.
  - Chemical clearance: acid clearance of a single reflux episode.

Statistical analysis

Stata software was used for this purpose (v11.1, Statacorp, College Station, TX, USA). Categorical variables were described as percentages and numerical variables as median with their 25–75% interquartile range; additionally, 95% quartile was described. Mean with its standard deviation was eventually used according to the fashion used in previously published studies assessing normal values. For the comparison of categorical variables, Fisher test was used. For the comparison of numerical variables, Student *t* test or Mann Whitney test were accordingly used. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

Thirty healthy subjects were consecutively enrolled [12 men, mean age 33 (range 19–59) years]. After impedance-pH test, six were excluded: two because of abnormal findings (AET>50%), one due to catheter migration and two dues to technical artifacts. (FIGURE 1).

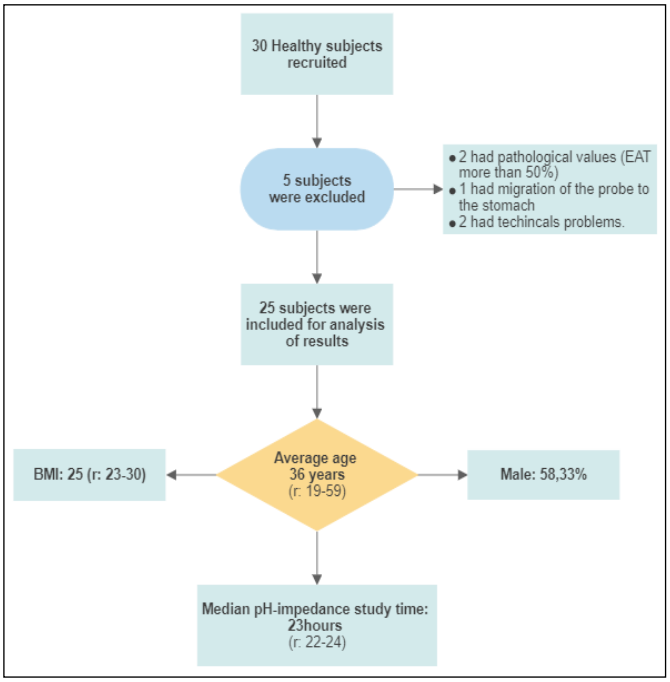

FIGURE 1. Healthy subjects enrolment flowchart.

Overall, 84% of included subjects reported consumption of "mate" (Illex paraguarensis) on a regular basis. The periods of mate were manually excluding, since they had pH drop. Tolerance to pH-metry was acceptable. Consequently, 25 subjects were finally included for analysis. Demographic features are shown in TABLE 1. Median time of study was 23 hours (25–75% IQR, 22–24 hours).

TABLE 1. Demographic data of included subjects.

Age[a] (years)	36 (19–59)
Gender (% M)	58.33
Occupation (% employees)	66.66
Body mass index[b]	25 (23–30)

[a]Results described as median and range. [b]Results described as median and 25–75% interquartile range.

Overall, 632 reflux episodes were registered among included subjects, with a mean of 22.15 reflux episodes per subject.

Supine-position total reflux episodes (95% quartile) was five of these, four were acid reflux episodes.

Median number of reflux events according to impedance testing was 20.5 (median 25–75%, 95%) interquartile range: (14–46, 50). Sixty percent were acid reflux episodes: 12 (5–29, 38); 37% were non-acid: 5, 5 (1–17, 30) and 3% were weakly-acid reflux episodes (TABLE 2).

TABLE 2. Type of reflux episodes in 24 hour-time among included subjects.

	Total reflux episodes	Acid reflux episodes	Weakly-acid reflux episodes
Total median (25th,75th) 95th	20.5 (14–46) – 50	12 (5–29) –38	5.5 (1–17) – 30
Erect	19 (14–35) – 50	11.5 (6–24) – 38	5 (2.5–12) – 25
Supine	2 (0–3) – 5	0 (0–1) – 4	0.5 (0–2) – 4

Results described as median and 25–75% interquartile range-95%.

Median proximal reflux episodes were 2.5 (0–10, 11) which represented 16% of the total number of reflux episodes. Esophageal volume clearance time was shorter than chemical esophageal clearance time: 18.5 versus 91 seconds, respectively (TABLE 3).

TABLE 3. Clearance time according to body position variation. Reflux proximal extension.

	Bolus clearance time	Reflux proximal extension
Total (median 25th, 75th, 95th)	18.5 (12–29) – 58	3 (1–5.5) –10
Erect (median 25th, 75th, 95th)	22 (13–35.5) – 99	0 (0–3) – 14
Supine (median 25th, 75th, 95th)	10.5 (0–42) – 107	0 (0–1) – 5

According to body position, reflux events on supine position were 53; 37% were proximal and 49% were acid. Acid clearance time was shorter in erect position (2758 vs 1735 seconds). TABLE 4 describes the acid reflux variables according to impedance.

TABLE 4. Acid reflux variables according to impedance.

	% of acid exposure time	Acid clearance time	Number of acids reflux events
Total (median 25th, 75th, 95th)	1 (0.2–3.4) – 5.5	91 (47–184) – 382	12 (5–29) – 38
Erect (median 25th, 75th, 95th)	1.7 (0.2–5.3) – 10.3	85 (47–169) – 382	11.5 (6–24) – 38
Supine (median 25th, 75th, 95th)	0 (0–0.9) – 2.3	0 (0–161) – 285	0 (0–1) – 4

Women showed a slightly increased number of reflux episodes (median 3.25 vs 2.44, P=0.08); however, men showed a greater but non-significant proportion of acid reflux episodes (1 vs 0.68, P=0.1).

Subjects with less than 47 years of age showed a greater number of total reflux episodes (mean 29.66 vs 18.57, P=0.04).

TABLE 5 describes the results of pH and impedance variables found among included subjects.

TABLE 5. pH and impedance variables among included subjects.

% of time with pH<4 (AET)	1 (0.2–3.4) – 5.5
% of time with pH<4 erect	1.7 (0.2–5.3) – 10.3
% of time with pH<4 supine	0 (0–0.9) – 2.3
DeMeester score	3.45 (1.2–10.7) – 14.7
Total number of reflux episodes	20.5 (14–46) – 50
Total number of acid reflux episodes	12 (5–29) – 38
Total number of non-acid reflux episodes	5.5 (1–17) – 30
Total number of proximal reflux episodes	2.5 (0–10) –11
Total number of proximal acid reflux episodes	1.5 (0–4) – 11
Total number of superimposed acid reflux episodes	0 (0–0) – 2
Bolus clearance time	18.5 (9–46) – 57
Bolus clearance time, erect	19.5 (9–45) – 63
Bolus clearance time, supine	9 (0–51) – 78
Mean acid clearance time total	91 (47–184) – 382
Mean acid clearance time, erect	85 (47–169) – 382
Mean acid clearance time, supine	0 (0–161) – 285
Nocturnal reflux, 1st quarter	0 (0–1) – 3
Nocturnal reflux, 2–4th quarter	0 (0–0) – 2

Results described as median, 25–75% interquartile range, 95% quartile. AET: acid exposure time.

TABLE 6 describes the gastroesophageal reflux comparison to similar studies expressed by Ndebia et al. and adapted with Argentina values comparison.

TABLE 6. Gastroesophageal reflux comparison to similar studies (Ndebia et al. Adapted with Argentina values).

	South Africa	Europe	China	USA	Argentina
All reflux	49 (29.65) – 97	44 (25.58) – 75	40 (31.53) – 75	30 (18.45) – 73	20.5 (14–46) – 50
Acid reflux	15 (5.31) – 55	22 (10.35) – 50	22 (7.36) – 54	18 (7.31) – 55	12 (5–29) – 38
Weakly acid reflux	17 (9.28) – 55	11 (5.18) – 33	16 (10.24) – 40	9 (6.15) – 26	5.5 (1–17) – 30
Weakly-alkaline reflux	8 (4.13) – 36	3 (1.7) – 15	0 (0.1) – 4	0 (0.0) – 1	0 (0–1) – 13

Results described as median, 25–75% interquartile range, 95% percentile.

DISCUSSION

Impedance-pH monitoring is considered the most accurate diagnostic tool for the detection of reflux events; noticeably, there are no references on normal values published so far in Argentina. We have documented the values of impedance-pH among healthy subjects without GERD.

So far, normal values were taken from the experiences published in North America and Western Europe, but our populations differ in terms of dietary habits in Argentina, dinner time is usually at a later time and a Mediterranean type of diet is usually followed; this elements could have a significant impact on what is considered as a normal pattern of reflux events.

Noticeably, median reflux events were 20.5, a relatively low value when compared to those reported in European, American and Chinese populations. Our study shows a total number of reflux events and a total number of proximal reflux events that are lower than reported until this date by other authors. We hypothesize that many variables may have influenced these findings: dinner times, genetic susceptibility and issues regarding age, gender, geographical distribution of the participants and the size of the population studied.

Recently, Sifrim et al.[14] published the first consensus of impedance-pH normal values around the world, in which we participated, with 391 tracings analyzed and the median reflux events number anlyzed with Diversatek pH-MII System (Inc.) was 21 (95% interquartile range: 10–34, 55). Comparatively, these mentioned values are closer to our results (20.5 (14–46) –50). Another possible cause of different results could be pH-monitoring and analyzing systems used around the world (e.g. Diversatek Inc. or Laborie Corp.). Concerning the low number of proximal events, it could be due to the fact that asymptomatic healthy volunteers do not usually present high volume reflux events, which is the most likely element to reach the proximal esophagus[15]. Age influence on reflux patterns is still a matter of debate. Some authors have suggested a positive association between age and reflux patterns[16], while others did not observe any influence of it[17]. We found a possible influence of age on the number of total reflux episodes in our cohort, but only 16 patients were younger than 47 years old so we cannot rule out the possibility of the presence of type 2 error in the analysis. On the other hand, another regional differences concluded in this important work[14], was the difference between the baseline level of impedance results. This levels, were elevated in some regions such as Asia, and low in others. Since this parameter is related to the mucosa integrity and that depends on microscopic intraluminal factors, it could be modified by the ultrastructural genetics of the esophageal mucosa, and related to the geographic region.

Regarding AET, the 95% percentile was 5.5%, which is in accordance to the Lyon consensus[18] statement that considers an AET over 6% as definitively abnormal. Our finding enforces the concept that normal AET values should have a cutoff of 6%.

DeMeester score values published 30 years ago may not be applicable nowadays because of the changes experienced not only in terms of life expectancy, but also in terms of qualitative and quantitative changes in dietary habits and modifications in body mass index.

Cutoff values for weakly-acid reflux events was seven, which could explain the relatively low prevalence of such events in our population[13]. Although considered to be infrequent, weakly-acid reflux events may represent actual acid reflux events that are easily neutralized by saliva clearance or esophageal clearance. Our findings showed that proximal reflux events represented 16% of total reflux events, whereas among Chinese subjects they represented a proportion near 26%[19]; 22% among Belgian subjects included in the study by Zerbib et al.[20] or 6% in a South African study[10]. Clinical relevance of proximal reflux is far from clear; its association with extra-esophageal reflux symptoms has been questioned. On the other hand, Cicala et al.[21] showed that both erosive reflux disease as well as non-erosive reflux disease patients had a significantly higher number of proximal reflux events when compared to subjects without GERD.

Included subjects did not follow any restraints in terms of diet during the study. Even though some local dietary habits that could have an impact in reflux events, such as mate consumption or late dinner times, we did not find an apparently increased number of acid reflux events when compared to previously published studies. Lyon consensus proposes that >80 reflux episodes in 24 hours is abnormal, whereas less than 40 is within physiological range. Intermediate values are inconclusive. Nevertheless, it becomes more relevant the association between reflux episodes and the occurrence of symptoms in each subject. The number of reflux events in our study seems to be relatively lower than what has been published so far.

An Argentinean study carried out by Olmos et al.[5] in which we participated, included 397 GERD patients who underwent upper endoscopy; prevalence of esophagitis in this cohort of patients was 35%. The clinical features significantly associated with erosive lesions were nocturnal symptoms [OR 2.55 1.55–4.18)] and a body mass index over 25 kg/m^2 [OR 1.91 (1.03–3.55)]. These findings are in concordance with previously published evidence. However, a lower number of reflux episodes could potentially be associated in the relatively lower prevalence of esophageal adenocarcinoma that is witnessed in Argentina and/or Latin-America as well as the discrepancies observed in terms of it distribution according to age and gender[22,23]. Evidence supporting this hypothesis is needed.

An often-neglected aspect of studies such as ours is the median time of acid clearance the time that takes for pH to increase over four after an acid reflux episode. This is a phenomenon that is related to several mechanisms, like esophageal peristaltic movements as well as pH and volume of reflux content. In our study, median clearance time was 91 seconds, which was four times longer

than bolus clearance time (18.5 seconds). This indicates that reflux content is cleared first and then acid residue becomes cleared which depends on secondary peristalsis as well as saliva buffering. The automatic analysis of these parameters is very weak. It depends on the accurate identification of reflux episodes and the accurate identification of start and end of reflux. In general, the software's are very bad for this and it is very time consuming to do it manually.

Limitations should be mentioned. First of all, our sample may not be representative of the whole Argentinean population. In addition, the size of study population is relatively scarce so it turns out to be a weakness of this study to be taken into account. There are several difficulties to achieve a greater number of population sample such as the lack of interest of healthy subjects to enroll, lack of economics resources to carry out the studies or many technical difficulties to correctly analyze the tracings (e.g., tracings excluded because of wrong catheter placement). Maybe for that reason, there are several recognized publications about "impedance-pH normal values" from different regions around the world with relatively scarse sample size population too[8,9].

To our knowledge, this is the first study to assess MII-pH values among non-GERD patients in Argentina. This type of studies is of utmost importance to define normal values and cutoffs of the different variables that are measured in these types of diagnostic tools, which are essential in the management of certain GERD patients.

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Authors' contribution

Ramos RI: planning and conducting the study, collecting and interpreting data, drafting the manuscript. Cernadas G: interpreting data and drafting the manuscript. Curvale C: interpreting data and drafting the manuscript. Matano R: drafting the manuscript.

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RESUMO – Contexto – Não há dados de valores de referência sobre o monitoramento de impedância intraluminal multicanal 24 horas e monitoramento de pH (pH-MII) em populações argentinas. **Objetivo** – O objetivo foi obter os valores normais das variáveis pH-MII entre voluntários assintomáticos saudáveis em um centro metropolitano de saúde da Argentina, e compará-los com dados já publicados de outras regiões do mundo. **Métodos –** Estudo transversal foi realizado em um centro de referência terciário em Buenos Aires. Foram recrutados indivíduos saudáveis para se submeterem ao monitoramento esofágico pH-MII 24 horas. As variáveis pH-MII foram registradas e descritas. **Resultados –** A média de eventos de refluxo foi de 20,5 (25–75%, 95%) entre os episódios interquartis: (14–46, 50) e os episódios de refluxo proximal foram de 2,5 (0–10, 11). Sessenta por cento foram episódios de refluxo ácido: 12 (5–29, 38), representando um valor relativamente baixo quando comparado com os relatados em populações europeias, americanas e chinesas. **Conclusão –** Nosso estudo mostra a primeira referência de valores normais de refluxo gastroesofágico em uma população argentina. Encontramos um número total de eventos de refluxo e um número total de eventos de refluxo proximal menor do que o relatado até esta data por outros autores.

Palavras-chave – Valores normais; esôfago; impedância-pHmetria de 24 horas.

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ORIGINAL ARTICLE

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The prognosis of the different esophageal neuroendocrine carcinoma subtypes: a population-based study

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ABSTRACT – Background – Neuroendocrine neoplasms are extremely rare and account for 0.4% to 2% of all malignant esophageal neoplasms. The burden of the neuroendocrine histological type on the patients' prognosis and survival is poorly debated. This study aimed to compare the survival rates of primary neuroendocrine neoplasms compared with adenocarcinoma and squamous cell carcinoma of the esophagus. **Methods –** This is a retrospective cohort from the Surveillance, Epidemiology, and End Results Program database. Overall survival and cancer-specific survival were evaluated with Kaplan-Meier curves and logrank tests. Proportional Cox regression models were used to evaluate variables related to overall survival. **Results –** After eligibility criteria, 66,528 patients were selected. The mean follow-up was 22.6 months (SD 35.6). Adenocarcinoma was predominant (62%), followed by squamous cell carcinoma (36%). Large cell carcinoma, small cell carcinoma, and mixed adenoneuroendocrine carcinoma each account for less than 1% each. On the long-term overall survival analysis, esophageal adenocarcinoma showed a better prognosis than all the other histologic types (*P*-value for logrank test <0.001). With adenocarcinoma as a reference, HR was 1.32 for large cell carcinoma (95%CI 1.2 to 1.45) and 1.37 for small cell carcinoma (95%CI 1.23 to 1.53). The HR was 1.22 for squamous cell carcinoma (95%CI: 1.2 to 1.24); and 1.3 for adenoneuroendocrine carcinoma (95%CI 1.01 to 1.66). For multivariate Cox regression analysis, besides age and stage, the neuroendocrine subtypes large cell carcinoma and small cell carcinoma were considered independent prognostic variables. **Conclusion –** In the esophagus, large cell carcinoma and small cell carcinoma show poorer long-term survival rates than squamous cell carcinoma and adenocarcinoma.

Keywords – Neuroendocrine tumors; neuroendocrine carcinoma; esophageal neoplasms.

INTRODUCTION

Adenocarcinoma and esophageal squamous cell carcinoma (ESCC) comprise 98% of the esophageal cancers histological types[1]. Neuroendocrine neoplasms (NENs) are extremely rare[2] and account for 0.4% to 2% of all malignant esophageal neoplasms[3-6]. These tumors are epithelial neoplasms with predominant neuroendocrine differentiation[3]. They originated from the peripheral neuroendocrine cell system[3]. Gastrointestinal NENs have shown an increased incidence rate over the last decades[7], but NENs are still far more common in the lungs[8], and a significant part of the knowledge of the disease, its presentation, classification, and therapeutic options are based on those utilized for neuroendocrine lung tumors[9].

The World Health Organization (WHO) 2019 classification[10] categorized in well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NETs can be subdivided into grades (G1, G2, and G3), according to the WHO grading system (G3 is defined as having a mitotic rate higher than 20/2 mm^2 or Ki67 higher than 20%)[10]. NECs are all considered high grades and can be subdivided into large-cell type (LCNEC) and small-cell type (SCNEC), according to the nucleus-cytoplasm ratio, and other variables such as cell shape, chromatin, nucleoli[11] besides, there are the mixed neoplasms, such as the mixed adenoneuroendocrine carcinomas (MANECs)[10].

In the esophageal neoplasms, the burden of the neuroendocrine histological type on the patients' prognosis and survival is poorly debated. This study aimed to compare the survival rates of primary esophageal NECs compared with adenocarcinoma and squamous cell carcinoma of the esophagus.

METHODS

Data source and studied population

This is a retrospective cohort from the Surveillance, Epidemiology, and End Results Program (SEER) database. Data were collected from 2000 to 2018. SEER database covers over one-third of the USA population. Patients submitted to esophagectomy were included. The specialized database "Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat database: incidence – SEER research data, 18 registries, Nov 2020 Sub (2000–2018) – linked to county attributes – time dependent (1990–2018) income/rurality, 1969–2019 counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the

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November 2020 submission". Was applied to extract data using the SEER*Stat Software, version 8.3.5 (released on 6 March 2018). The staging was based on the SEER Summary Stage 2000, classifying the disease as localized (cancer does not extend beyond the primary organ); regional (cancer extends to adjacent organs, regional lymph nodes, or both); and distant (cancer with distant dissemination).

These data are publicly available, and we obtained access to the SEER data by signing the SEER Research Data Agreement. Consequently, local Ethics Committee waived informed consent. The study followed the Ethical Standards of the Brazilian Association of Research Companies (resolution 466/2012).

Data extraction

The following data were collected: 1) age; 2) sex; 3) follow-up; 4) overall and cancer-specific survival; 5) grade of cellular differentiation; and 6) histology. Only adenocarcinoma, ESCC, LCNEC, SCNEC, and MANEC were included. Esophageal carcinomas or neuroendocrine tumors with no information of the subtype of the tumor were excluded.

Statistical analysis

The statistical analysis was performed using STATA 16.1 software (StataCorp, College Station, Texas). A 95% confidence interval (95%CI) was adopted. Categorical variables were expressed as absolute numbers or percentages, and differences between groups were evaluated with the Person chi-squared test. Overall survival and cancer-specific survival were evaluated with Kaplan-Meier curves and logrank test. Proportional Cox regression models were used to evaluate variables related to overall survival. Hazard ratios (HRs) and their corresponding lower and upper 95%CI limits were informed for each independent variable. Only the preoperative clinical and histopathological data with *P*-value <0.05 in the univariate analysis were incorporated in the multivariate analysis.

RESULTS

Baseline characteristics

After applying inclusion criteria, 73,456 patients were selected. After excluding patients with no information regarding neuroendocrine subtype, carcinoma with no specification of the neuroendocrine subtype, and patients with no survival data, 66,528 patients were included (see flow diagram in FIGURE 1).

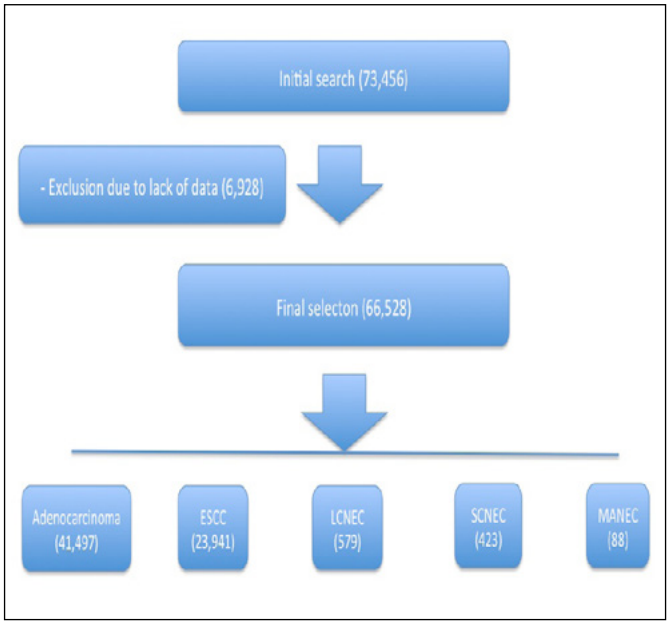

FIGURE 1. Flow diagram of the patients' selection.
ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

The mean follow-up was 22.6 months (SD 35.6). Adenocarcinoma was predominant (62.4%), followed by ESCC (36%). LCNEC, SCNEC, and MANEC account for less than 1% each. LCNEC and SCNEC presented a higher rate of elderly (>65 years old). Adenocarcinoma and MANEC had a higher proportion of men (86 and 80%, respectively) than the other subtypes. TABLE 1 shows the baseline characteristics of the patients according to the histology.

Survival analysis

On the long-term overall survival analysis, esophageal adenocarcinoma showed a better prognosis than all the other histologic types (*P*-value for logrank test <0.001). Overall survival Kaplan-Meier curves can be seen in FIGURE 2. For cancer-specific survival rates, similar findings were obtained (*P*-value for logrank test <0.001) (see FIGURE 3).

TABLE 1. Baseline characteristics.

	Adenocarcinoma	ESCC	LCNEC	MANEC	SC NEC	*P*-value
N (%)	41497 (62.4)	23941 (36)	579 (<1)	88 (<1)	423 (<1)	<0.001
Age						
>65 years (%)	58.8	58	62	55.7	61	<0.001
Male (%)	85.8	64.1	67.5	79.5	65	<0.001
Summary stage (%)						
Localized	25	25	22	9	15	<0.001
Regional	34	40	35	27	22	
Distant	41	35	43	64	63	
Grade of cellular differentiation						
I	17	10	0	0	0	0.413
II	47	50	0	0	0	
III	36	40	100	100	100	

ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

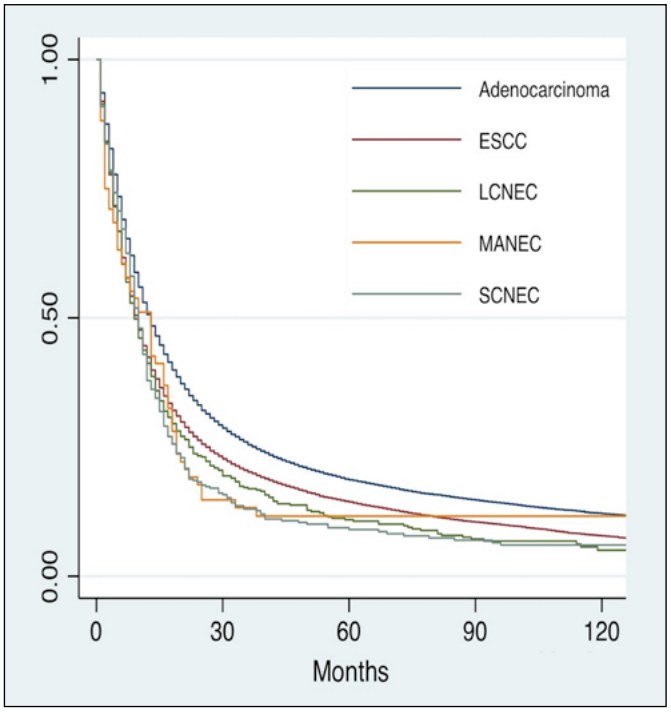

FIGURE 2. Overall survival Kaplan-Meier curves. *P*-value for logrank test <0.001.
ESCC: esophageal squamous cell ca=rcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

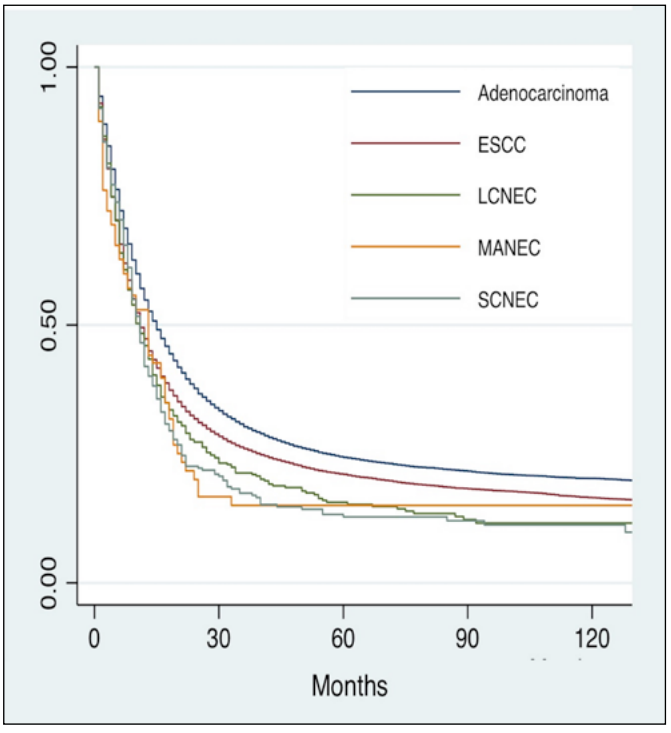

FIGURE 3. Cancer-specific survival Kaplan-Meier curves. *P*-value for logrank test <0.001.
ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

For pairwise multiple logrank comparisons for overall survival, adenocarcinoma showed a better prognosis than all the other studied subtypes (P<0.05). LCNEC and SCNEC showed equivalent overall survival rates (P=0.583). No significant difference was noted between MANEC and ESCC, LCNEC, and SCNEC (see TABLE 2).

TABLE 2. Pairwise multiple survival comparison with logrank test.

P-value for logrank	Adenocarcinoma	ESCC	LCNEC	SCNEC
Adenocarcinoma	x	x	x	x
ESCC	<0.001	x	x	x
LCNEC	<0.001	0.07	x	x
SCNEC	<0.001	0.03	0.583	x
MANEC	0.031	0.619	0.883	0.565

ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

The hazard for death for LCNEC and SCNEC was higher than the other histological subtypes. With adenocarcinoma as a reference, HR was 1.32 for LCNEC (95%CI 1.2 to 1.45) and 1.37 for SCNEC (95%CI 1.23 to 1.53). The HR was 1.22 for ESCC (95%CI: 1.2 to 1.24); and 1.3 for MANEC (95%CI 1.01 to 1.66). For multivariate Cox regression analysis, besides age and stage, the neuroendocrine subtypes LCNEC and SCNEC were considered independent prognostic variables (see TABLE 3).

DISCUSSION

The results of this population-based cohort showed that primary esophageal neuroendocrine carcinomas present poorer survival rates than adenocarcinoma and ESCC. Knowing the long-term survival outcomes for NECs subtypes helps stratify their risk and determine prognosis. The determination of the prognosis before deciding on any specific therapy is crucial to predict patient outcomes.

Currently, there is still no standardized treatment for NECs[3,6,12]. Most classification and therapeutic strategies are adapted from neuroendocrine lung cancer. The NECs subtypes were not contemplated in the 8th edition of the AJCC/UICC TNM staging system for esophageal cancer[13]. Consequently, the results of the present study fill a gap in the esophageal carcinoma staging system. The staging system has two main roles in esophageal cancer: decision-making and prognostication[13], and the present study helps stratify the prognosis of NEC of the esophagus. Clinicians should be aware that carcinomas with neuroendocrine differentiation have a poor long-term outcome, and consequently, an early and aggressive therapy should be considered.

The European Society for Medical Oncology[14] proposed a guideline for the management and risk assessment of neuroendocrine management. They recommend staging according to the adenocarcinoma criteria. Besides the traditional TNM staging and grade of cellular differentiation, they recommend evaluating the Ki-67 and mitotic index as prognostic histopathological variables. For evaluation of the disease extension, 68Ga/64Cu-SSTR-PET-CT and 18F-FDG PET/CT are complementary and should be used for

TABLE 3. Univariate and multivariate Cox proportional-hazards analysis for overall survival.

	Univariate					Multivariate				
	HR	SE	*P*	95%CI		HR	SE	*P*	95%CI	
				Lower	Upper				Lower	Upper
Age										
>65 years	1.259	0.011	<0.001	1.236	1.281	1.331	0.013	<0.001	1.306	1.356
Sex										
Female	1									
Male	0.996	0.011	0.696	0.975	1.017					
Summary stage										
Localized	1					1				
Regional	1.389	0.018	<0.001	1.354	1.425	1.406	0.018	<0.001	1.371	1.443
Distant	2.869	0.037	<0.001	2.796	2.943	2.98	0.388	<0.001	2.905	3.058
Histology						1				
Adenocarcinoma	1									
ESCC	1.218	0.011	<0.001	1.196	1.24	1.214	0.012	<0.001	1.19	1.238
LCNEC	1.322	0.061	<0.001	1.206	1.447	1.252	0.062	<0.001	1.135	1.38
MANEC	1.296	0.162	0.038	1.014	1.656	1.068	0.143	0.624	1.024	1.289
SCNEC	1.373	0.075	<0.001	1.233	1.528	1.149	0.068	0.018	1.024	1.289

ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

and 64% of disseminated disease at diagnosis, contributing to poor overall survival. Ku et al.[19], reporting their experience, showed that the most common sites of distant metastasis were lymph nodes, liver, lung, adrenal, and bone marrow. However, the Cox regression models in the present study demonstrated that independently of the extension of the disease, the LCNEC or SCNEC differentiation imposes a negative impact on long-term survival analysis. LCNEC and SCNEC have equally poor prospects.

Neuroendocrine carcinomas can also be associated with adenocarcinoma or squamous cell carcinoma subtypes[3]. Only 88 adenoneuroendocrine tumors were identified in the present cohort, limiting the statistical power of any of their analyses. These subtypes of neuroendocrine neoplasms represent a heterogeneous group, and thus, the prognosis of these tumors is probably poorly predictable. The proportion of neuroendocrine and adenocarcinoma or squamous cell carcinoma in the tumor (and, consequently, the prognosis) may vary in the mixed tumors. Also, chemoradiation response may depend if the neuroendocrine tumor is associated with squamous cell carcinoma or adenocarcinoma[21]. Besides, the site of lymph nodal and hematogenous metastasis may depend if the mixed tumor is associated with adenocarcinoma or squamous cell carcinoma[22].

The present cohort has some limitations. As with any population-based data, the present study is vulnerable to information bias and selection bias due to potential registry flaws[23,24]. Besides, esophageal cancer varies significantly worldwide, depending on the most frequent risk factors in each location. ESCC is the most common type in Asia and South America[25]. Tobacco and alcohol are the main risk factors in these places[25]. Adenocarcinoma is increasing its incidence, especially in developed countries, and obesity and gastroesophageal reflux disease are the main risk factors[25]. The SEER database covers the United States of America (USA) population, where adenocarcinoma is the most frequent histology[25]. In our analysis, adenocarcinoma covers 62.4% of the included patients. Knowing the expressive influences the environment imposes in esophageal cancer development, probably, NECs subtypes' incidence and causation factors may also be influenced according to each geographic location. Consequently, the external validity of the present results may be harmed.

Future studies evaluating populations other than the North-American are needed. These studies should also evaluate other potential prognostic variables, such as the molecular-based pre-treatment data, essential for the accurate risk stratification of neuroendocrine esophageal cancer.

CONCLUSION

Esophageal SCNEC, LCNEC, and MANEC have unique clinical features, including age, sex, and stage, and differ from the adenocarcinoma and squamous cell carcinoma regarding prognosis. This information should be taken into account in prognostication during the staging of esophageal cancer patients.

Statements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. These data are publicly available, and we obtained access to the SEER data by signing the SEER Research Data Agreement.

Authors' contribution

Tustumi F: contributed to the conception and design of the work. Stefanie Marques SSB: contributed to the acquisition of the data. Barros EF: contributed to the analysis and interpretation of data for the work. Henriques AC: contributed to data analysis.

Waisberg J: contributed to data extraction. Dias AR: contributed to supervision. All authors contributed to this study and participated in the writing or critically revised it for relevant intellectual content. All authors have approved the final and submitted version to be published and assumed joint accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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RESUMO – **Contexto –** As neoplasias neuroendócrinas são extremamente raras e representam 0,4% a 2% de todas as neoplasias malignas do esôfago. A determinação prognóstica e avaliação de sobrevida para o tipo histológico neuroendócrino é pouco debatida. Este estudo teve como objetivo comparar as taxas de sobrevida de neoplasias neuroendócrinas primárias comparadas com adenocarcinoma e carcinoma espinocelular de esôfago. **Métodos –** Este é um estudo coorte retrospectivo do banco de dados do *Surveillance, Epidemiology, and End Results Program*. A sobrevida global e a sobrevida específica do câncer foram avaliadas com curvas de Kaplan-Meier e testes de logrank. Modelos de regressão de Cox proporcional foram utilizados para avaliar as variáveis relacionadas à sobrevida global. **Resultados –** Após critérios de elegibilidade, foram selecionados 66,528 pacientes. O seguimento médio foi de 22,6 meses (DP 35,6). O adenocarcinoma foi predominante (62%), seguido pelo carcinoma espinocelular (36%). Carcinoma de grandes células, carcinoma de pequenas células e carcinoma adenoneuroendócrino misto representam menos de 1% cada. Na análise de sobrevida global, o adenocarcinoma de esôfago apresentou um prognóstico melhor do que todos os outros tipos histológicos (*P* valor para teste de logrank < 0,001). Com adenocarcinoma como referência, HR foi de 1,32 para carcinoma de grandes células (IC95% 1,2 a 1,45) e 1,37 para carcinoma de pequenas células (IC95% 1,23 a 1,53). O HR foi de 1,22 para carcinoma espinocelular (IC95%: 1,2 a 1,24); e 1,3 para carcinoma adenoneuroendócrino (IC95% 1,01 a 1,66). Para a análise multivariada da regressão de Cox, além da idade e do estadiamento, os subtipos neuroendócrinos carcinoma de grandes células e carcinoma de pequenas células foram considerados variáveis prognósticas independentes. **Conclusão –** No esôfago, o carcinoma de grandes células e o carcinoma de pequenas células apresentam menores taxas de sobrevida a longo prazo do que o carcinoma espinocelular e o adenocarcinoma.

Palavras-chave – Tumores neuroendócrinos; carcinoma neuroendócrino; neoplasias esofágicas.

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ORIGINAL ARTICLE

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Immunohistochemical assessment of lymphatic vessels in human livers with chronic hepatitis C – relation to histological variables

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ABSTRACT – Background – Viral hepatitis C is a significant public health challenge. The disease may remain clinically silent in both acute and chronic forms, and chronic infections may progress to advanced disease such as cirrhosis and hepatocellular carcinoma, requiring costly treatment, compromising the patient's quality of life and even leading to death. For this reason, it is one of the most frequent indications for liver transplantation. Although treatment with direct-acting antivirals represents remarkable progress, many patients are still infected and even those who cleared the viral infection must be followed due to their previous hepatic lesions, especially regarding the disturbances of lobular architecture and the sanguineal and lymphatic vessels. **Objective –** To assess immunohistochemical aspects of lymphatic sprouts and mature lymphatic vascularity with histological variables of liver injury attributable to hepatitis C virus (HCV) and fatty disease. **Methods –** The present study included 72 liver biopsies of cases with chronic hepatitis C. Morphologic changes reflecting "staging" and "activity" were analyzed. Immunohistochemical reactions were performed with monoclonal antibody D2-40 anti-podoplanin. Major histological variables were also semiquantified so as to enable the search for possible associations among histological and Immunohistochemical criteria, as well as with genotypes 1 and 3 of HCV. **Results –** Histological findings showed that the different degrees of strutural changes were well represented in this casuistic. Intralobular/parenchymal necro-inflammatory activity was predominantly mild to moderate. Most cases did not show major evidences of fatty disease, which was found significantly higher in cases infected with HCV genotype 3. The amount of portal lymphatic sprouts increased along with the progression of structural changes, maximal at cirrhosis. Portal lymphatic sprouts as well as portal mature lymphatic vessels also showed an increase parallel to the increase in the degree of portal/septal inflammatory infiltrate. In the present study, no significant association was found between the proportion of portal lymphatic sprouts or portal mature lymphatic vessels and the degree of periportal/periseptal activity. No significant relations were detected between lymphatic sprouts/mature vessels and periportal or parenchymal inflammatory activity, nor with infections due to HCV genotype 1 or 3. **Conclusion –** Visualization and semiquantitation of sprouts and mature lymphatic vessels were clearly yielded by Immunohistochemical staining with monoclonal antibody D2-40. The amount of lymphatics was increased along fibrogenic process, significantly related to progression of liver disease and maximal at cirrhosis. No significant relations were detected with necro-inflammatory activity at interface or in the parenchyma.

Keywords – Hepatitis C; chronic; immunohistochemistry; lymphatic vessels; lymphangiogenesis; liver; pathology.

INTRODUCTION

Although the introduction of treatment with direct-acting antivirals (DAA) represents a remarkable progress, chronic hepatitis C remains an important challenge in Public Health, both worldwide and more especifically in Brazil[1-10].

Pathological presentation of chronic hepatitis C includes various degrees of inflammation, necrosis and liver injury, resulting in different prognosis[4,11].

Despite poorly studied in chronic hepatitis C, the lymphatic system is essential to maintain tissue homeostasis by collecting excess fluid from the tissues and returning it to the bloodstream, providing a favorable environment for immune cells to find and respond to antigens in the peripheral lymphoid tissues. The lymphatics also play an important role in lipid absorption and transportation[12-15].

In chronic liver diseases, increased lymphatic flow is an important mechanism by which fluid can circumvent the increased sinusoidal/post-sinusoidal resistance in animals[16]. The sinusoidal hydrostatic pressure increases due to the increase in sinusoidal blood resistance and consequently, the filtered plasma components that form lymph increase[13].

Impaired lymphatic drainage was reported by Ribera et al.[17] in cirrhotic rats with ascites suggest that regulation of NO in lymphatic endothelial cells of cirrhotic rats causes long-term lymphatic remodeling, which is characterized by a loss of surrounding smooth muscle cells.

An increase in vasodilation combined with intrahepatic vascular resistance due to fibrosis results in portal hypertension[18]. Oikawa et al.[19] report that the area of portal lymphatic vessels increases in idiopathic portal hypertension (IPH) and speculate

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that the formation of new lymphatic vessels in cirrhosis occurs as a mode of adaptation to increased lymph flow. This compensatory lymphangiogenic response may help reduce the elevated portal pressure seen in both idiopathic portal hypertension and portal hypertension that develops in liver cirrhosis.

In many occasions, the lymphatic capillaries are difficult to identify, sometimes because they are collapsed, sometimes because they are dilated, have a delicate wall, with an endothelial coating very similar to that of small blood vessels, supported by delicate conjunctive tissue[20-22].

Both in the study of inflammatory diseases and of neoplasms, discrimination between blood vessels and lymphatic vessels has been performed via immunohistochemical markers for lymphatic vessels, but the most sensitive and specific marker for the endothelium of lymphatic vessels is podoplanin, identified using the D2-40 monoclonal antibody[20,21,23].

The present study aims to assess how lymphatic sprouts and lymphatic vessels relate to histological aspects of liver lesions in several stages of chronic hepatitis C, to hepatitis C virus (HCV) genotype and to evidence of fatty liver disease.

METHODS

The study was approved by the Ethics Committee for Analysis of Research Projects of *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* (HC-FMUSP) on 11/24/2016 under online registration number 15847.

This was a retrospective study of liver samples obtained by needle biopsy archived at the Division of Anatomic Pathology (DAP) of HC-FMUSP, ensuring confidentiality of personal data, and no interference in diagnostic or in therapeutic procedures.

As depicted at FIGURE 1, from a universe of 190 HCV-infected patients, cases with the following criteria were selected: diagnosis of HCV infection previously established by serological and virological methods and sufficient amount of residual tissue sample in the paraffin block for histopathological and immunohistochemical studies, defining the minimum tissue length as 1 centimeter and/or the identification of at least 10 portal tracts in the sample. All cases with HCV co-infection with Hepatitis B virus (HBV) or with human immunodeficiency virus (HIV) or with evidences of autoimmune hepatitis were excluded. According to these criteria, the casuistic of the present study includes 72 patients assisted at the Gastroenterology and Infectious Diseases Outpatient Services of HC-FMUSP in the period from 2000 to 2015. Twenty-nine (40%) patients were male and 43 (60%) were female, with a mean age of 48.7 years old, ranging from 22 to 78 years old.

Information about the Genotype of HCV was available in all 72 cases.

Liver samples were collected by 16-gauge needle biopsy and fixed in 4% buffered formalin saline solution at pH=7.4.

The slides were stained with hematoxylin-eosin and picrosirius red and submitted for collaborative histopathological analysis by two experienced liver pathologists (APF and VAFA).

Morphologic changes related to "staging" and "activity" were analyzed, meaning structural alterations and necro-inflammatory findings, respectively.

The histological alterations were semi-quantitated acccording to the proposal by Gayotto et al.[24] in the classification of the Brazilian Society of Pathology, which grades from 0–4 changes related

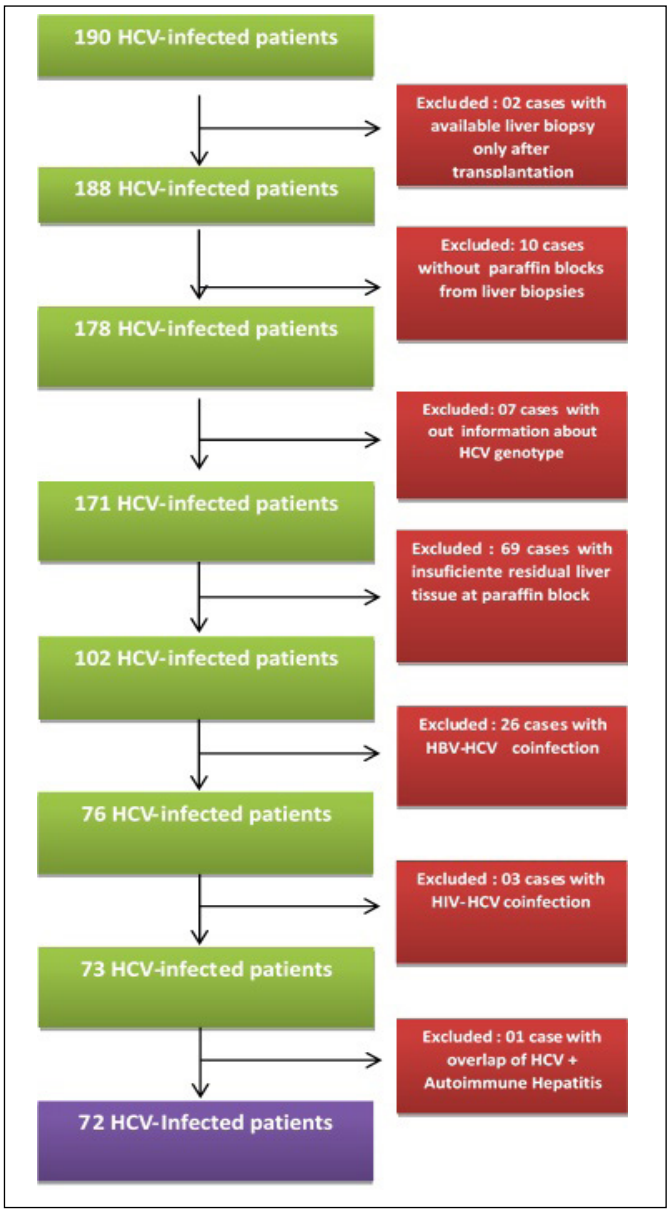

FIGURE 1. Flowchart of hepatitis C infected patients included in the present study.

to lobular architecture, portal inflammation, periportal interface inflammatory activity and parenchymatous necro-inflammation.

As hepatitis C may present features associated with fatty liver disease and also due to the possible comorbidity with metabolic syndrome, we also searched for histological criteria related to fatty liver disease as proposed by Kleiner et al.[25]: steatosis, hepatocytic ballooning, Mallory-Denk bodies and intralobular inflammation were annotated, as well as classification of perivenular and pericellular fibrosis defined as 0= absent, 1= present, slight or 2= marked (or severe).

Immunohistochemical reactions were performed manually with antigen retrieval (Citrate buffer, ph6.0, Spring, 100x) in a steamer for 35 minutes, followed by blocking of endogenous tissue peroxidase with hydrogen peroxide (H2O2) 20 volumes and

methyl alcohol in volume/volume proportion in three incubations for 10 minutes each. After washings in water followed by 0.01M phosphate buffered saline (PBS) pH 7.4, the sections were incubated with non-specific binding blocker (Cas Block, Life Technologies) in an incubator at 37°C for 10 minutes. The primary anti-podoplanin antibody (mouse monoclonal, clone D2-40, DAKO M3619, dilution 1:100) was incubated at 37°C for 30 minutes and then further incubated at 4°C "overnight" for 16 hours. Signal amplification was performed by polymer-based immunoperoxidase method (Novolink Max Polymer DS, Leica Biosystems/Novocastra) at 37°C for 30 minutes, developed with diaminobenzidine (100 mg/100 mL) for 5 minutes and counterstained with Harris hematoxylin.

The detected lymphatic vessels were quantified in the following components: portal lymphatic sprout (PLS), portal lymphatic vessel (PLV), lymphatic sprout at interface, lymphatic vessel at interface, lymphatic sprout in parenchyma and lymphatic vessel in parenchyma. Quantification was performed on digital images acquired by scanning the immunostained slides. Morphometric analysis of the images was performed using Image Pro Plus© 4.1 software.

In each case, five fields estimated as presenting the highest concentration ("hot spots") of sprouts or lymphatic vessels in the region of the portal spaces were analyzed using the 20x objective. Only the sprouts and vessels with well-defined markings were considered (FIGURE 2).

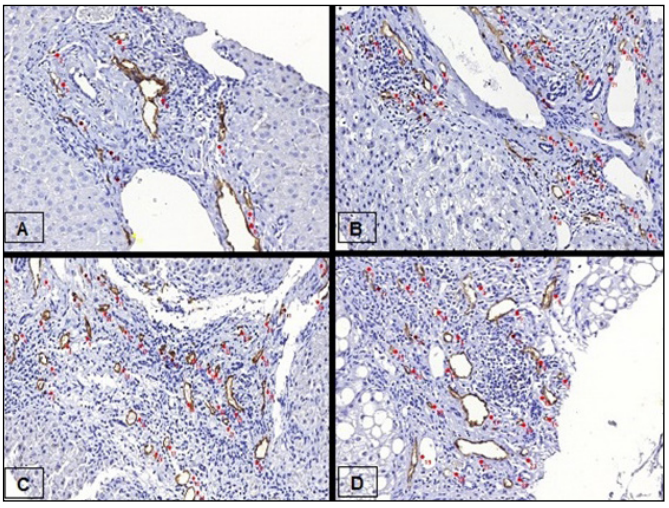

FIGURE 2. Immunohistochemical aspects of lymphatic vessels in chronic hepatitis C.

A) Presence of several lymphatic vessels and few lymphatic sprouts in a portal tract with minor structural alteration IHC, x200. B) expanded portal tract (F2) with moderate periportal necro-inflammation presenting many lymphatic vessels. IHC, x200. C) Fibrovascular septum (F3) with moderate periportal necroinflammation depicting many sprouts and mature lymphatic vessels IHC, x200. D) wide fibrovascular septum (F4) showing many sprout and mature lymphatic vessels, moderate inflammatory infiltrate and mild periportal activity and minimal parenchymal activity. Presence of grade 3 steatosis and steatohepatitis. IHC, x200.

Since the section from one of the cases did not show portal tracts (case with fibrous expansion of portal tracts – stage 1), the expression of podoplanin in the lymphatic endothelium was assessed in 71 cases.

The distribution of values obtained by counting sprouts and lymphatic vessels in both the portal tracts and the interface in each of the 71 cases were presented as medians of the mean positivities, thus grading the cases as "low grade" and "high grade".

In order to assess associations between the immunohistochemical variables related to the pattern of lymphatic vessels and the histological criteria of chronic hepatitis C and the histological criteria of fatty liver disease the chi-square test adopting the significance index as $P<0.05$.

RESULTS

Histological criteria for chronic hepatitis C

Among the 72 HCV serologically positive patients, 7 (10%) cases showed architectural stage 0 (no significant injury in lobular architecture), 19 (26%) cases stage 1 (fibrous expansion of portal tracts), 15 (21%) cases stage 2 (portal expansion with portal-port septa), 16 (22%) cases stage 3 (porto-portal septa and porto-central septa and incomplete nodular formation), whereas 15 (21%) cases were already at stage 4 (cirrhosis, fully identified or predominance of nodular areas over remaining lobules).

Regarding portal/septal inflammatory infiltrate, we found no cases with rare portal lymphocytes (grade 0), whereas 12 (17%) cases had mild lymphocytic infiltrate (grade 1), 31 (43%) cases depicted moderate portal lymphocytes (grade 2), 25 (35%) cases with major portal lymphocytic infiltrate (grade 3). Only 4 (5%) cases presented an exhuberant portal lymphocytic infiltrate (grade 4).

As to the histological variable peri-portal/peri-septal activity, or interface activity, we found 8 (11%) cases with no interface activity (grade 0), 8 (11%) cases presenting only "spill over" of lymphocytes without true hepatocytic lesion (grade 1). True interface lesion with so-called "piece-meal necrosis" (grade 2) was found in 23 (32%) cases, 31 (43%) cases presented moderate interface hepatitis (grade 3), whereas only 2 (3%) cases showed extensive interface hepatitis (grade 4).

As expected for a cohort of chronic hepatitis C cases, intralobular/parenchymal necro-inflammatory activity was mild to moderate in most cases: The hepatocytes were almost normal and lobular infiltrate was not evident in 3 (4%) cases, 28 (39%) cases presented mild lymphohistiocytic infiltrate, and rare hepatocytic apoptosis or focal necrosis (grade 1), 29 (40%) cases with several figures of focal hepatocytic necrosis surrounded by lymphocytes and histiocytes (grade 2). Higher lobular necro-inflammation was detected in 11 (16%) cases presenting grade 3 lesions, whereas only 1 (1%) case showed extensive/multiple confluent necrosis (grade 4).

Histological criteria for fatty liver disease

Twenty-five (35%) cases presented grade 0 steatosis (absence or up to 5% of hepatocytes with macrovesicular steatosis, 27 (38%) cases showed up to 30% of hepatocytes with steatosis (grade 1), whereas 14 (19%) cases had steatosis in 40–60% of hepatocytes (grade 2), and 6 (8%) cases with more than 70% of hepatocytes with steatosis (grade 3).

As for the presence or absence of steatohepatitis, 54 (75%) cases did not present diagnostic criteria sufficient for the diagnosis of steatohepatitis (grade 0) while 18 (25%) cases were diagnosed as steatohepatitis (grade 1).

Ballooning was not present in 35 (49%) cases (grade 0), was mild in 20 (28%) cases (grade 1), and was moderate to severe in 17 (24%) cases (grade 2).

Genotype of hepatitis C virus

Genotype 1 was detected in 50 (69%) cases. In two cases, genotype 1 was reported without other specification (3%), 24 cases geno-

type 1a (33%), 23 cases genotype 1b (32%), and one case genotype 1a/1b (1%). The remaining 22 cases were positive for genotype 3: 18 cases genotype 3a (25%) and four cases with genotype 3 without other specification (6%).

Immunohistochemical detection of podoplanin

The distribution of values obtained by counting sprouts and lymphatic vessels in both the portal tracts and the interface in each of the 71 cases were presented as medians of the mean positivities, thus grading the cases as "low grade" and "high grade".

The median of the average number of portal lymphatic sprouts (PLS) was 2: 40 cases were classified as low grade and the other 31 as high grade.

The median of the average number of mature portal lymphatic vessels was 7: 39 cases were classified as low grade and 32 cases as high grade.

The immunohistochemical study of D2-40 did not identify lymphatic sprouts at the interface. Regarding mature lymphatic vessels, the median was also 0 vessels / 5 fields. Only two cases presented median = 1 vessel / field at the interface. The data shows that lymphangiogenesis was very low at the interface, not allowing comparison with histopathological variables indicating stage and inflammatory activity in the various compartments of the liver lobules.

The search for sprouts or lymphatic vessels in the parenchyma resulted negative in all 71 cases, which prevents its comparative analysis with the other immunohistochemical variables and histological criteria.

With the exception of one case, the TABLE 1 show the distribution between the patterns of portal lymphatic sprouts and portal mature lymphatic vessels was almost identical, demonstrating the direct relationship between the two types of findings.

TABLE 1. Comparison between the values of portal lymphatic sprouts and portal lymphatic vessels.

	Portal lymphatic sprouts			*P*
	PLS low grade	PLS high grade	Total	
Portal lymphatic vessels				
PLV low grade	39	0	39	
PLV high grade	1	31	32	*P*<0.01
Total	40	31	71	

PLV: portal lymphatic vessels; PLS: portal lymphatic sprouts.

TABLES 2 and 3 show the distribution of cases with lower or higher proportion of portal lymphatic sprouts and portal mature lymphatic vessels according to histological variables indicating staging and inflammatory activity in the various compartments of the liver lobules.

The proportion of cases with more portal lymphatic sprouts showed an increase along with the progression of structural alterations. Such an increase was shown to be significant in the grouped analysis, and it was also apparent that the increase occurred at each degree of increasing structural injury, suggesting early and sustained activation of portal lymphangiogenesis.

The proportion of cases with more portal lymphatic vessels was significantly higher in the group of cases with major structural alterations, with an apparent discontinuity of this increase among the cases with grade 3 structural alterations.

TABLE 2. Distribution of portal lymphatic sprouts and portal mature lymphatic vessels marked by expression of podoplanin in lymphatic endothelium according to structural alteration and portal/septal inflammatory infiltrate.

Structural alteration	**F0**	**F1**	**F2**	**F3**	**F4**	***P***
Portal lymphatic sprouts						
Low grade	6	12	9	7	6	0.03
High grade	1	6	6	9	9	
Portal lymphatic vessels						
Low grade	7	13	7	9	3	0.01
High grade	0	5	8	7	12	
Portal/septal inflammatory infiltrate	**0**	**1**	**2**	**3**	**4**	***P***
Portal lymphatic sprouts						
Low grade	0	10	20	9	1	<0.01
High grade	0	1	11	16	3	
Portal lymphatic vessels						
Low grade	0	9	20	9	1	0.01
High grade	0	2	11	16	3	

TABLE 3. Distribution of portal lymphatic sprouts and portal mature lymphatic vessels marked by expression of podoplanin in lymphatic endothelium according to periportal/perisseptal activity and parenchymal activity.

	0	**1**	**2**	**3**	**4**	***P***
Periportal/perisseptal activity						
Portal lymphatic sprouts						
Low grade	8	6	10	16	0	0.21
High grade	0	1	13	15	2	
Portal lymphatic vessels						
Low grade	8	4	12	14	1	0.13
High grade	0	3	11	17	1	
Parenchymal activity						
Portal lymphatic sprouts						
Low grade	3	21	12	3	1	<0.01
High grade	0	6	17	8	0	
Portal lymphatic vessels						
Low grade	3	19	14	3	1	<0.01
High grade	0	8	15	8	1	

The proportion of cases with more portal lymphatic sprouts as well as with more portal mature lymphatic vessels showed an increase parallel to the increase in grade of portal/septal inflammatory infiltrate. This association was shown to be significant in the grouped analysis, and it was also apparent that the increase occurred at each degree of increase in portal inflammatory infiltrate, suggesting a direct relationship between inflammatory activity and portal lymphangiogenesis.

In the present study, no significant association was found between the proportion of portal lymphatic sprouts or portal mature lymphatic vessels and the degree of periportal/perisseptal activity. However, a remarkable increase in cases presenting more portal

lymphatic sprouts and portal mature lymphatic vessels was detected starting with grade 2 necro-inflammatory activity.

Acknowledging that only one case presented with grade 4 inflammatory activity in the parenchyma, the proportion of cases presenting more portal lymphatic sprouts as well as mature portal lymphatic vessels was significantly related to the increase in parenchymal necroinflammatory activity. It is also evident that the increase with each degree of parenchymal activity. In particular, the transition from grade 1 to 2 parenchymal activity, which is highly significant on histopathology, was accompanied by greater activation of portal lymphangiogenesis.

TABLE 4 show the distribution of cases with lower or higher proportion of portal lymphatic sprouts and portal mature lymphatic vessels according to the grade of steatosis and to histological criteria of steatohepatitis, respectively.

TABLE 4. Distribution of portal lymphatic sprouts and portal mature lymphatic vessels marked by expression of podoplanin in lymphatic endothelium according to steatosis and presence of steatohepatitis diagnostic criteria.

Steatosis	0	1	2	3	*P*
Portal lymphatic sprouts					
Low grade	15	13	8	4	0.69
High grade	10	13	6	2	
Portal lymphatic vessels					
Low grade	19	11	7	2	0.29
High grade	6	15	7	4	
Steatohepatitis	**Absence**		**Presence**		***P***
Portal lymphatic sprouts					
Low grade	32		8		0.37
High grade	22		9		
Portal lymphatic vessels					
Low grade	32		7		0.19
High grade	22		10		

The proportion of cases with more portal lymphatic sprouts as well as with more portal mature lymphatic vessels was not significantly related to either steatosis or to the presence of histological criteria of steatohepatitis.

TABLE 5 depicts the distribution of lymphatic structures according to HCV genotypes. Despite the proportion of cases with a higher quantity of portal lymphatic sprouts and portal mature lymphatic vessels being apparently higher in patients infected with HCV genotype 1, this difference was not statistically significant.

TABLE 5. Distribution of portal lymphatic sprouts and portal mature lymphatic vessels marked by expression of podoplanin in lymphatic endothelium according to HCV genotype.

HCV genotype	1	3	*P*
Portal lymphatic sprouts			
Low grade	25	15	0.17
High grade	24	7	
Portal lymphatic vessels			
Low grade	28	11	0.57
High grade	21	11	

HCV: hepatitis C virus.

DISCUSSION

Studies addressing the morphological variations of the lymphatic system in liver biopsy samples throughout the span of major liver lesions in chronic hepatitis are scarce. For this, we aimed to assess the presence of lymphatic vessels and sprouts in chronic hepatitis C marked by the semiquantitative immunohistochemical assessment of podoplanin with the monoclonal antibody D2-40, expecting that the present data may inspire future studies in which further analysis and morpho-molecular correlations may be possible.

Although the experimental data presented in the introduction raise some intriguing questions about lymphangiogenesis in chronic liver disease, Saxena et al.[26], cautioned about the large differences in liver microvasculature between animal and human models. Furthermore, none of the mentioned studies employed quantitative or semiquantitative morphological approaches to study lymphatic shoots and mature lymphatic vessels.

In the present study, the assessment of lymphatic vessels through immunohistochemical labelling with podoplanin yielded the definition of sprout as solid aggregates of lymphatic endotelial cells, versus mature lymphatic vessels which are thin structures with a lumen without red blood cells. The attempt to identify each of these components in different compartments of hepatic lobules was only partially successful, since lymphatic sprouts and mature vessels were identified and quantitated only at portal tracts in early stages of chronic hepatitis C and at fibrous septa in advanced stages, including cirrhosis. Our hypotheses of finding lymphatic structures at the periportal interface and in the hepatic lobule was not substantiated with the present immunohistochemical approach. While acknowledging these important drawbacks, the present study demonstrated several interesting associations.

The almost identical distribution of lymphatic sprouts and mature lymphatic vessels clearly demonstrate by immunohistochemistry and light microscopy that these structures are directly related. It reinforces the concept that a morphological sequence of lymphangiogenesis is reflected in the portal spaces and fibrous septa, starting with the activation of podoplanin-positive lymphatic endothelial cells that give origin to lymphatic sprouts. This relationship is maintained from early stages of chronic hepatitis to advanced stages of HCV-associated cirrhosis. Also, in future studies, the presence of either of these structures may be chosen as a marker of the hepatic lymphatic system.

The increase of both portal sprouts and mature lymphatic vessels was significantly associated to the progression of liver structural alterations. Interestingly, we found that such increase occurs in each step of disturbance in lobular architecture, not only immediately preceding cirrhosis. This may be useful in future studies aiming at the prevention of pathological lymphangiogenesis, which should be started early in the progression of chronic liver disease.

Our analysis of liver lymphangiogenesis in human samples collected by needle biopsy shows many similarities to those reported in animal experiments by Vollmar et al.[16], to the study of Yamauchi et al.[27] in human liver biopsy samples with chronic hepatitis B and C and Yokomori et al.[23] in surgical samples of human livers with HCV cirrhosis.

Using high-resolution fluorescence microscopy, Vollmar et al.[16] simultaneously evaluated hepatic blood macromolecular exchange from the sinusoidal microvasculature and the hepatic lymphatic system in rats in the early stages after exposure to the hepatotoxic drug CCl4.

Those rats were characterized by a progressive delay in the exchange of hepatic macromolecules into blood, implying the development of diffusion barriers inside the fibrotic and cirrhotic liver.

In parallel, in those animals, a marked increase in both lymphatic vessel density and lymphatic vessel area was observed. Linear regression analysis revealed a significant correlation between impairment of sinusoidal macromolecular exchange and density of the lymphatic network. Thus, the lymphatic network increased in agreement with the fibrotic alterations in rats.

Since there were no reports that the data from Vollmar et al.[16] was applicable to the human liver, Yamauchi et al.[27] studied, by morphometric methods, the alterations that occur in human hepatic lymphatic vessels in chronic viral hepatitis B and C and its progression to cirrhosis using 62 liver samples. Those authors investigated the relationship between the degree of liver fibrosis, the activity of liver inflammation, and changes in lymphatic as well as in blood vessels.

Besides number of vessels, Yamauchi et al.[27] studied the area of each lymphatic vessel, finding that such area was significantly higher in cirrhosis than in lower degrees of fibrosis (mild, moderate, and severe, but not cirrhosis). It is intriguing that no differences were found by Yamauchi et al.[27] regarding both the area of each vessel or the number of vessels between the groups with mild, moderate, and severe fibrosis. However, the number of lymphatic vessels in each section tended to increase in association with staging progression. Their finding of a strong correlation of the number of portal/septal lymphatic vessels with the degree of expansion of the portal space was remarkably similar to what we observed in the present study.

The histochemical and morphometric analyses by Yamauchi et al.[27] produced results in agreement with the results of the study by Vollmar et al.[16], showing that lymphatic vessels in the liver increase in size and number with the progression of fibrosis in chronic hepatitis.

Beyond the relationship between architectural disturbance and lymphatic vessels, our present study also disclosed a correlation between the proportion of portal sprouts and lymphatic vessels and the degree of portal inflammation and parenchymal activity. These findings clearly demonstrate that even in early stages of hepatitis, the necroinflammatory activity elicits lymphangiogenesis, a fact to be considered in future studies. In particular, the transition of periportal activity from grade 1 to 2 in both sprouts and portal lymphatic vessels, and from grade 2 to 3 in portal lymphatic vessels highly valued on histopathology, apparently accompanied by more activation of portal lymphangiogenesis.

Thus, in the item "inflammatory activity", our result differed from that obtained by Yamauchi et al.[27] who concluded that the number and area of lymphatics did not differ significantly with hepatitis activity. On the other hand, the findings of the present study and those of Yamauchi et al.[27] were similar regarding the association of greater formation of lymphatic vessels in cases of hepatitis C in more advanced architectural stages.

The present study also aimed at the search of potential relation of lymphangiogenesis and other important pathological variables. However, in the present study, periportal/perisseptal activity, viral genotype, and variables related to comorbidities such as steatosis and steatohepatitis were not found to be associated with the pattern of lymphatic sprouts or mature vessels.

As previously characterized in the normal liver, the tools applied in the present study did not allow identification of lymphatic vessels in the parenchymal region in any stage of chronic hepatitis C/cirrhosis. Similarly, in a study of 16 surgical samples Yokomori et al.[23] had reported finding few or no lymphatic vessels in the parenchyma in both normal livers and cirrhotic livers with HCV-associated hepatocellular carcinoma.

Finally, our current study also attempted to identify possible Mall spaces by assessing the presence of any podoplanin-expressing lymphatic endotelial cells at the portal-parenchymal interface, especially because of the recently introduced concepts of hepatic interstitium[28,29]. However, only rare, isolated cells were found at the interface, leading to a median number of zero lymphatic sprouts. The same occurred with mature lymphatic vessels, since only two cases showed more evident lymphatic vessels at the interface. Therefore, no conclusions could be drawn regarding the interstitial space of Mall and lymphatic sprouts/vessels in the current study.

Our study may serve as a basis for future analyses attempting to correlate histological and immunohistochemical findings with molecular data, considering that several growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF) have been implicated in angiogenesis. We hope our findings may usher in further studies and promote better knowledge about lymphatic endothelial cell proliferation and lymphatic vessel formation.

Authors' contribution

Assato AK: designed and performed the research and the immunohistochemistry reactions, analyzed the data, and wrote the manuscript. Pasinato APBF: helped in obtaining samples and analyzed the histological variables. Cirqueira CS: analyzed the data. Wakamatsu A: supervised all laboratorial activity. Alves VAF: designed and performed the research, analyzed the data, wrote the manuscript, and supervised all the research steps.

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RESUMO – Contexto – A hepatite C é um relevante problema de saúde pública. A doença pode permanecer clinicamente silenciosa tanto na forma aguda como na crônica e as infecções crônicas podem progredir para doenças avançadas, tais como cirrose e carcinoma hepatocelular (CHC), requerendo tratamentos dispendiosos, comprometendo a qualidade de vida do paciente e até mesmo levando à morte. Por esta razão, é uma das indicações mais frequentes para o transplante hepático. Apesar da introdução do tratamento com antivirais de ação directa (AAD) representar um progresso notável, muitos pacientes não receberam o tratamento e continuam infectados, e mesmo aqueles que eliminaram a infecção viral devem ser seguidos devido às lesões hepáticas anteriores, especialmente no que diz respeito às alterações da arquitetura lobular e dos vasos sanguíneos e linfáticos. **Objetivo** – Avaliar os aspectos imuno-histoquímicos dos brotos linfáticos e dos vasos linfáticos "maduros" com variáveis histológicas de lesão hepática atribuíveis ao vírus da hepatite C (VHC) e à doença gordurosa. **Métodos** – O presente estudo incluiu 72 biópsias hepáticas em pacientes com hepatite C crônica. Foram analisadas alterações estruturais relativas a "estadiamento" e "atividade". Reações imuno-histoquímicas foram realizadas com anticorpo D2-40 anti-podoplanina. As principais variáveis histológicas também foram semiquantificadas, de modo a permitir a procura de possíveis associações entre os critérios histológicos e imunohistoquímicos, bem como com os genótipos 1 e 3 do VHC. **Resultados** – Os achados histológicos mostraram que os diferentes graus de alterações estrutural estavam bem representados nesta casuística. A atividade necro-inflamatória lobular/parenquimatosa foi predominantemente leve à moderada. A maioria dos casos não apresentava grandes evidências de doença gordurosa, que foi encontrada significativamente mais elevada nos casos infectados com o genótipo 3 do VHC. A quantidade de brotos linfáticos portais aumentou com a progressão de alterações estruturais, sendo máxima na cirrose. Os brotos linfáticos portais, bem como os vasos linfáticos "maduros" portais também mostraram um aumento paralelo ao aumento do grau de infiltrado inflamatório portal/septal. No presente estudo, não foi encontrada qualquer associação significativa entre a proporção de brotos linfáticos portais ou vasos linfáticos maduros portais e o grau de atividade periportal/periseptal. Não foram detectadas relações significativas entre os brotos linfáticos/vasos maduros e a atividade inflamatória periportal ou atividade inflamatória parenquimatosa, nem com infecções devido ao genótipo 1 ou 3 do VHC. **Conclusão** – A reação imunohistoquímica com anticorpo monoclonal D2-40 possibilitou a visualização e a semiquantitação de brotos e vasos linfáticos "maduros" nas amostras obtidas por biópsia hepática. A quantidade de linfáticos aumentou ao longo do processo fibrogênico, significativamente relacionada com a progressão da doença hepática e máxima na cirrose. Não foram detectadas relações significativas com a atividade necro-inflamatória periportal ou parenquimatosa.

Palavras-chave – Hepatitie C crônica; imuno-histoquímica; vasos linfáticos; linfangiogênese; fígado; patologia.

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ORIGINAL ARTICLE

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Hepatic alterations in kidney transplant recipients from the largest kidney transplant center in Brazil

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ABSTRACT – Background – Kidney transplant is the treatment of choice for patients with end-stage renal disease and is associated with lower mortality when compared to dialysis methods. Brazil is the country with the second largest number of kidney transplants in the world and among these patients it has been observed that liver abnormalities are common. The frequency of liver abnormalities ranges from 20–50% post-transplantation, and have an important impact on the survival and quality of life of these patients. There are scarce data about the frequency, causes and characteristics of these alterations. **Objective –** To determine the prevalence of the different causes of hepatic abnormalities in kidney transplant recipients, to associate the characteristics of these abnormalities with demographic, epidemiological and clinical variables, to compare the characteristics of hepatic alterations between different etiologies, and to evaluate possible changes in diagnosis over two different periods of time. **Methods –** Descriptive, cross-sectional observational, epidemiological study was conducted at the outpatient "Hepato-Rim"clinic of Hospital São Paulo (EPM/UNIFESP), a center providing specialized care for patients with hepatic abnormalities and underlying kidney diseases. **Results –** Five-hundred eighty-one transplant patients were evaluated. The most prevalent etiologies of liver abnormalities were hepatitis C and B, iron overload, nonalcoholic fatty liver disease (NAFLD), and drug-induced liver injury (DILI). The most common cause – hepatitis C – was analyzed in greater detail. Compared to the other causes, this infection was more frequent in older patients, female patients, and patients with a longer time since transplantation and hemodialysis. Analysis of the two periods showed that patients of period 1 (P1 – 1993 to 2005) were older and were more frequently referred because of positive serology; referral due to aminotransferases abnormalities predominated during period 2 (P2 – 2006 to 2018). The predominant diagnoses were hepatitis C and B during P1 and NAFLD and DILI during P2. **Conclusion –** Assessment of the main hepatic alterations in kidney transplant recipients is important because it permits better management of these patients in terms of diagnostic investigation and treatment and contributes to the prevention of complications in this special population.

Keywords – Kidney transplant, hepatic alterations, liver disease.

INTRODUCTION

Kidney transplant is the treatment of choice for patients with end-stage renal disease (ESRD) and is associated with lower mortality when compared to dialysis methods[1]. Infections have been the main causes of mortality during early kidney transplantation worldwide. These complications have been controlled over time and the life expectancy of kidney transplant recipients (KTR) started to increase progressively. Other causes of mortality such as cardiovascular complications, acute rejection, complications of immunosuppressive therapy and decompensation of comorbidities have also declined, especially because of advances in diagnostic and therapeutic methods[2].

Acute and chronic hepatic abnormalities have been recognized in KTR since the 1970s[3] and have contributed to the increasing morbidity and mortality of these patients. It is well known that KTR are at increased risk for viral liver diseases caused by parenterally transmitted viruses, especially because of the previous period of hemodialysis[4] when the patients were exposed to contamination with hepatitis B (HBV) or C virus (HCV) through blood transfusion or, more frequently, environmental contamination. Furthermore, in KTR the liver damage caused by these viruses is frequently aggravated by the immunosuppression[5].

Several other potential causes of liver disease are also present among KTR, such as the use of a large spectrum of medications including immunosuppressive drugs, comorbidities (diabetes, hypertension, dyslipidemia) frequently associated with non-alcoholic fatty liver disease, iron overload remaining from the dialysis period, and even alcohol abuse.

Kidney transplants are the most frequent organ transplantation in Brazil, and 95% of kidney transplants are performed within the Brazilian Unified Health System (SUS)[6]. Brazil is nowadays the country with the second largest number of kidney transplants in the world, surpassed only by the United State[7]. In 2019 6.283 kidney transplants were performed in Brazil and the largest transplant center in that year was *Hospital do Rim e Hipertensão*[8].

This hospital is the largest kidney transplant center in the world, performing up to 900 procedures annually[9]. This is more than dou-

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ble the number of procedures performed by the best international institutions of this specialty. Founded in 1998 and administrated by the *Fundação Oswaldo Ramos*, the hospital performs 20% of all kidney transplants in the country. In view of the attendance of this large number of patients, hepatic abnormalities are frequently detected, including altered liver enzymes, positive viral serology, or altered liver imaging findings. These cases are referred to hepatology specialists for investigation. The present study was undertaken to better understand the causes and characteristics of these hepatic alterations.

Therefore, the objectives of the present study were 1) to determine the prevalence of the different causes of hepatic alterations in KTR; 2) to associate the characteristics of hepatic abnormalities with demographic, epidemiological and clinical variables; 3) to compare the characteristics of the hepatic abnormalities between hepatitis C and other etiologies, and 4) to evaluate possible changes in the causes of hepatic alterations of KTR over two different periods of time.

METHODS

This is a descriptive, cross-sectional, observational, epidemiological study conducted at the outpatient "Hepato-Rim" clinic of Hospital São Paulo (EPM/UNIFESP), a center providing specialized care for patients with hepatic abnormalities and underlying kidney diseases.

Characteristics of the sample

Kidney transplant patients referred mainly by the kidney transplant outpatient clinic of *Hospital do Rim e Hipertensão* were evaluated retrospectively and prospectively.

Patients of both genders older than 18 years were included, regardless of the disease that led to kidney failure. All patients who had at least one medical consultation at the Hepato-Rim outpatient clinic between January 1993 and March 2018 were included. For the evaluation of changes over time, the characteristics of patients referred during two different periods were analyzed: P1 – from 1993 to 2005 and P2 – from 2006 to 2018.

Patients younger than 18 years, patients who lost the graft, and patients without exams defining the diagnosis in the medical record were excluded.

This study was approved by the Research Ethics Committee the from *Universidade Federal de* São Paulo with the number 3.006.733 of November 7th, 2018.

Method

The cause for referral was evaluated in all patients: positive serology, (anti-HCV, HBsAg, anti-HBc), altered enzymes (aminotransferases, alkaline phosphatase, bilirubin, and gamma-glutamyl transferase – GGT), or altered imaging findings (ultrasonography, tomography, or magnetic resonance).

Demographic, epidemiological, clinical and laboratory data were obtained from the standard medical records used for consultation at the outpatient clinic.

Variables evaluated for final diagnosis

Demographical: sex, age, naturalness; epidemiological: etiology of kidney disease, dialysis time before transplantation (in years), transplant time (in years), type of kidney graft (living or deceased donor); clinical: main comorbidities; laboratorial: alanine aminotransferase (ALT) (normal values for women <33U/L and men <41U/L), aspartate aminotransferase (AST) (normal values for women <32U/L and men <40U/L), alkaline phosphatase (FA) (normal values for women <105U/L and men <130U/L) and gamma glutamyl transferase (GGT) (normal values for women <40U/L and men <60U/L). Enzymes were expressed as an index (times upper limit of normality – ULN), iron profile (serum iron, ferritin and transferrin saturation), autoantibodies (anti-nucleus (ANA), anti-smooth muscle (AML), anti-mitochondria (AMA), Other laboratory measurements: blood count, blood glucose, bilirubin, creatinine, albumin, prothrombin time/INR, copper ceruloplasmin, TSH, immunoglobulins, Serologies (HBsAg, anti-HBc, anti-HBs and anti-HCV).

Diagnosis of hepatitis C was determined by the presence of anti-HCV positive and/or viral load or genotype detected. (Hepatitis B: presence of reagent HBsAg and/or detectable viral load, ferric overload: presence of ferritin ≥500 ng/dL and/or transferrin saturation ≥50%, non-alcoholic fatty liver disease: ultrasound alteration, liver biopsy and other etiologies ruled out, drug-induced liver injury: alteration of liver enzymes, drug use during the period of alteration and excluding other causes) The evaluation also included image exams (ultrasonography, computed tomography, magnetic resonance imaging and upper digestive endoscopy) immunosuppressive regimen; evaluation of the main immunosuppression regimens was made.

Fibrosis degree was established by liver biopsy, transient liver elastography or APRI calculation (AST to platelet ratio index – AST in times the upper limit of normal divided by the number of platelets).

Statistical analysis

Categorical variables are expressed as frequency. Numerical variables are reported as mean and standard deviation. Normality was analyzed using measures of skewness and kurtosis. The chi-squared test was used for the comparison of categorical variables. Normally distributed variables were compared by the Student *t*-test and non-normally distributed data by the nonparametric Mann-Whitney test. A level of significance of 0.05 was adopted. Descriptive levels (*P*) less than this value were considered significant. The collected data were stored and managed using the SPSS 20 program.

RESULTS

Between January 1993 and March 2018, 1558 patients were evaluated at the Hepato-Rim outpatient clinic. Of these, 964 (62%) had CKD and received conservative or dialysis treatment and 594 (38%) were KTR. Thirteen of these 594 patients had no exams reported and were excluded from the study. Thus, 581 patients were eligible for analysis (FIGURE 1).

Among the 581 patients, 383 (66%) were male and 198 (34%) were female. The mean age was 56.9±10.8 years. The patients were mainly from the southeastern region (n=282, 48.5%), followed by the northeastern region (n=152, 26.2%). Transplantation was performed with grafts of deceased donors in 52.8% and with grafts from living donors in 40.4%; no information about the type of graft was observed in 6.7% of the cases.

The etiologies of CKD were indeterminate causes in 41.7%, systemic arterial hypertension in 29.8%, nephritis in 12.9%, and diabetes mellitus in 4.3%. The mean time since transplantation was 9.7±7.05 years. These data are shown in TABLE 1.

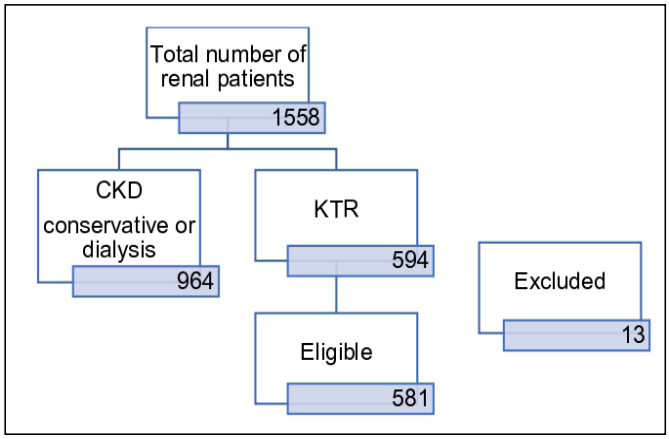

FIGURE 1. Patients eligible for the study.
CKD: chronic kidney disease; KTR: kidney transplant recipients.

TABLE 1. Demographic and epidemiological characteristics of the patients studied (n=581).

Variable	
Age in years (mean ± SD)	57.0±10.8
Male gender	66%
Origin	
Southeast	48.5%
Northeast	26.2%
Others	25.3%
Etiology of kidney disease	
Indeterminate	41.7%
Arterial hypertension	29.8%
Nephritis	12.9%
Diabetes mellitus	4.3%
Polycystic disease	3.4%
Systemic lupus erythematosus	1.2%
Recurrent urinary tract infection	1.5%
Donor type	
Deceased	52.8%
Living	40.4%
Time since transplantation in years (mean ± SD)	9.7±7.05
Duration of hemodialysis in years (mean ± SD)	5.3±4.43

Analysis of the present sample showed 17 different etiologies of hepatic abnormalities, with a higher frequency of HCV, HBV, iron overload, NAFLD, and DILI. The most frequent etiology was hepatitis C, as can be seen in TABLE 2.

Hepatitis C was the most frequent diagnosis. Alone or associated with other liver diseases hepatitis C was observed in 310 (53.3%) cases. HCV genotyping was performed in 161 (51.9%) cases and the most frequent genotypes were: genotype 1a in 60 (37.2%) cases, genotype 1b in 46 (28.5%), indeterminate genotypes in 29 (18%), genotype 1a/1b in 15 (9.3%), genotype 3 in 10 (6.2%), and genotype 4 in 1 (2.4%) case.

TABLE 2. Diagnoses in the kidney transplant recipients studied (n=581).

Final diagnosis	Number of patients with the diagnosis
Hepatitis C	310
Hepatitis B	133
Iron overload	107
Nonalcoholic fatty liver disease	54
Drug-induced liver injury	50
Alcohol	35
Schistosomiasis	14
Cholestasis	8
Hepatocellular carcinoma	3
Polycystic disease	3
False-positive HCV	2
Primary biliary cholangitis	1
Primary sclerosing cholangitis	1
Amyloidosis	1
Cured hepatitis B	1
Liver hemangioma	1
Benign cholestasis of pregnancy	1
Total	725

HCV: hepatitis C virus.

Hepatitis C was associated with other diagnoses in 118 cases: iron overload (n=46), HBV (n=24), NAFLD (n=22), DILI (n=9), alcoholic liver disease (n=8), schistosomiasis (n=4), cholestasis (n=3), and HCC (n=2).

Patients with hepatitis C (n=310) were compared to patients with other etiologies (n=271) and the following differences were: patients with HCV were older than those without HCV (57.8±10.4 vs 55.9±11.1 years; P=0.04). In addition, the duration of hemodialysis (5.7±4.3 vs 4.8±4.4 years; P=0.005) and the time since kidney transplantation (10.7±7.4 vs 8.6±6.4 years; P<0.001) were longer in patients with HCV. Laboratory parameters [ALT (1.3±1.4 vs 1.8±2.5; P=0.15), alkaline phosphatase (1.6±2.2 vs 1.4±1.2; P=0.62) and GGT (4.2±8.9 vs 5.2±8.4; P=0.17)] did not differ significantly between patients with and without HCV. Liver fibrosis evaluated by APRI (aspartate aminotransferase-to-platelet ratio index) was significantly lower in KTR with HCV compared to the other patients (0.8±0.9 vs 0.9±1; P=0.005). TABLE 3 shows the comparison of these parameters between KTR with and without hepatitis C.

The proportion of type 2 diabetes mellitus as etiology of pre-transplant CKD was similar in KTR with and without HCV (4.5% vs 4.1%; P=0.84). The same was observed for hypertensive nephrosclerosis (13.5% vs 12.7%; P=0.71) and nephritis (27.4% vs 32.5%; P=0.20).

Regarding immunosuppression, the main immunosuppressors used were azathioprine (AZA; 38%), cyclosporine (CYA; 42%), mycophenolate sodium (MMF; 35.8%), tacrolimus (FK; 41.3%), and prednisone (98.3%). The most frequent combinations were AZA, CYA and prednisone (n=132, 22.7%); MMF, FK and prednisone (n=113, 19.4%); AZA, FK and prednisone (n=57, 9.8%); CYA, MMF and prednisone (n=53, 9.1%); CYA, FK and pred-

TABLE 3. Epidemiological and laboratory parameters of kidney transplant recipients with and without hepatitis C virus.

Parameter	HCV + (n=310)	HCV – (n=415)	*P*
Age in years	57.8±10.4	55.9±11.1	0.04
Male gender	61.9%	70.5%	0.03
Etiology of CKD			
DM2	4.5%	4.1%	0.84
SAH	13.5%	12.7%	0.71
Nephritis	27.4%	32.5%	0.20
Time since transplantation in years	10.7±7.4	8.6±6.4	<0.001
Duration of hemodialysis in years	5.7±4.3	4.8±4.4	0.005
APRI	0.8±0.9	0.9±1	0.005
ALT	1.3±1.4	1.8±2.5	0.15
AP	1.6±2.2	1.4±1.2	0.62
GGT	4.2±8.9	5.2±8.4	0.17

HCV: hepatitis C virus; CKD: chronic kidney disease; APRI: aspartate aminotransferase-to-platelet ratio index; ALT: alanine aminotransferase; AP: alkaline phosphatase; GGT: gamma-glutamyl transferase; DM2: type 2 diabetes mellitus; SAH: systemic arterial hypertension; *P*: level of statistical significance.

nisone (n=1, 0.2%), and AZA, MMF and prednisone (n=1, 0.2%). The use of AZA (44.5% vs 45.4%; *P*=0.87) and MMF (37.3% vs 35.4%; *P*=0.66) was similar in patients with and without HCV. On the other hand, CYA was more frequently used by patients with HCV (47.2% vs 39.2%), but the difference was not statistically significant (*P*=0.06).

Comparison of the older (P1 – 1993 to 2005) and more recent periods (P2 – 2006 to 2018) revealed differences in the causes of liver abnormalities of the patients studied, which are shown in TABLE 4 and 5. Patients of P2 were younger, most of them were from the Southeastern and Northeastern regions, and had a shorter time since kidney transplantation. Twenty-seven patients were excluded from this analysis because of the lack of data of the first consultation.

During P1, the main etiologies were HCV infection (59.5%) and HBV infection. (23.4%). On the other hand, during P2, HCV decreased to 38.8%, HBV to 12.9% and there were more cases referred to investigate abnormal liver enzymes, corresponding to iron overload, NAFLD and DILI (7.7% in P1 and 26.3% in P2). The differences between periods were significant in all cases (*P*<0.001).

DISCUSSION

Literature data show that almost 25% of renal transplant patients (KTR) have evidence of hepatic disfunction[10]. In the present study 581 renal KTR referred to a hepatology specialized center to investigate liver abnormalities (positive viral serology, abnormal liver enzymes or image exams showing hepatic damage) were analyzed. The main diagnoses were hepatitis C, hepatitis B, iron overload, NAFLD and DILI.

HCV was the most prevalent condition, detected in 310 (53.3%) cases. Hepatitis C is common in KTR and its prevalence is higher than in the general population, ranging from 3 to 80% depending on the country and sample studied[11-12]. This high prevalence is the result of the acquisition of infection during the period of dialysis, with high prevalence rates that range from 3 to 10% in developed countries and from 15 to 80% in developing countries. These rates are much higher than those found in the general population of each region[13]. Genotype 1a predominated in the present population, as also observed in another series[14].

Hepatitis C is an important condition in KTR because it is one of the causes of nephropathy (generally associated with cryoglobulinemia causing membrane-proliferative glomerulonephritis) or, more frequently, a consequence due to the prolonged period of dialysis in CKD patients[15,16]. Infection with HCV is associated with post-transplant diabetes and chronic allograft nephropathy and is also a risk factor for acute rejection, although not a very common cause[13].

Treatment of HCV in KTR is no longer based on interferon-containing regimens whose efficacy ranged from 18 to 34%. In addition to its low response, this therapeutic regimen resulted in a risk of rejection of 12.5 to 51% and was therefore previously used

TABLE 4. Demographic and epidemiological characteristic of the patients studied divided into two periods [P1 (1993–2005) and P2 (2006–2018)] (n=554).

Variable	P1 (n= 299)	P2 (n=255)	*P*
Age in years (mean ± SD)	58.4±10.8	55.2±10.7	<0.001
Male gender	62.4%	68.6%	0.18
Origin			
Southeast	41.5%	57.6%	<0.001
Northeast	24.1%	27.8%	<0.001
Others	34.4%	14.5%	<0.001
Etiology of kidney disease			
Diabetes mellitus	3.3%	5.5%	0.24
Arterial hypertension	28.8%	30.6%	0.64
Nephritis	12.4%	13.3%	0.8
Donor type			
Deceased	52.8%	51%	0.59
Living	41.1%	40.8%	0.59
Time since transplantation in years (mean ± SD)	10.3±6.9	8.8±7.1	0.05

SD: standard deviation; *P:* level of statistical significance.

TABLE 5. Final diagnoses of kidney transplant recipients in periods [P1 (1993–2005) and P2 (2006–2018)] (n=554).

Diagnostic	P1 (n=299)	P2 (n=255)	*P*
HCV	64.9%	40.9%	<0.001
HBV	68.5%	49.5%	<0.001
Iron overload	55%	49%	0.31
NASH	37.3%	55.7%	<0.005
DILI	33.3%	55.8%	0.005

HCV: hepatitis C virus; HBV: hepatitis B virus; NASH: nonalcoholic fatty liver disease; DILI: drug-induced liver injury.

only in higher-risk KTR[13,17]. In 2013, a new class of drugs, direct-acting antivirals, were approved and became the best option for treating HCV in KTR, with a cure rate higher than 90%[13]. Most patients of the present series were treated or are being treated with these drugs.

The duration of hemodialysis was longer in KTR with hepatitis C compared to the other etiologies. Studies have shown that the prevalence of hepatitis C increases progressively with increasing dialysis duration due to the higher risk of contracting the infection. This risk has been declining over time due to improved cleaning processes during hemodialysis and the use of adequate screening tests for the disease and strategies to reduce transmission[13]. Furthermore, patients with HCV were older than those with other etiologies. This finding can be explained by the fact that patients with hepatitis C generally contracted the disease in the past and are therefore older.

Laboratory parameters (ALT, alkaline phosphatase and GGT) did not differ between KTR with HCV and those with other diagnoses. There was also no difference in diabetes mellitus or nephritis. A higher frequency of these two conditions might be expected as they can be consequences of the direct action of HCV[18], but this was not observed in the present study. Analysis of fibrosis by the noninvasive APRI method showed a lower degree of fibrosis in patients with HCV compared to the other etiologies, suggesting that the evolution of hepatitis C might be slower in KTR when compared to patients with NAFLD, DILI or iron overload. On the other hand, when compared to the non-immunosuppressed population, the progression of liver disease seems to be faster in KTR[19]. However, this disease progression during immunosuppressive therapy may be related to the use of high doses of corticosteroids and "old" immunosuppressants, which can increase viral replication[12,20,21,22].

The use of immunosuppressive drugs did not differ between KTR with HCV and patients with the other etiologies, regardless of the immunosuppressant used (AZA, MMF or CYA). However, there was a greater tendency to use CYA, probably because the patients were older and had a longer time since transplantation and this drug was more frequently used in the past.

Comparison of the two periods showed a larger number of patients with HCV during P1 (1993–2005). This finding reflects a higher frequency of HCV at hemodialysis services during this period as a result of environmental transmission of the virus[23,13]. HBV infection was also frequent, identified in almost 25% of the cases.

In the more recent period (2006–2018) HCV showed a decrease in frequency, but still the main reason for referral and HBV reduced its frequency by 50%. However, patients referred due to abnormal liver enzymes were more frequent, corresponding to iron overload, NAFLD and DILI. Iron overload is observed in 10% of KTR patients, as observed in other studies[24], as a consequence of iron administration during hemodialysis period that persists after transplantation[25].

Non-alcoholic fatty liver was also more frequent in P2, resulting from metabolic abnormalities, such as diabetes, dyslipidemia, hypertension and overweight. Furthermore, prolonged immunosuppression with corticosteroids and calcineurin inhibitors can also contribute to the development of NAFLD[26].

DILI was also frequent among referred patients and similarly to the present study, Guo (2012) identified this condition in 10% of KTR. The main drugs associated with this finding were azathioprine and sulfamethoxazole-trimethoprim[27].

In conclusion, the present study could evaluate hepatic laboratory and clinical abnormalities of several causes in a large casuistic of kidney transplant recipients, who require a more in-depth assessment because of their complexity. Early evaluation of possible hepatic alterations in these patients is important in order to prevent complications, acute liver failure and even progression to chronic liver disease.

Over time, the distribution of the various etiologies of liver disorders has changed, with a lower proportion of hepatitis B and C and a higher proportion of diagnoses of non-alcoholic fatty liver disease and drug-induced injury, showing the impact of control over time of viral infections in dialysis units.

Authors' contribution

Vieira GA: study design, data analysis, article writing. Amaral ACC: data collection, patient care. Carvalho-Filho RJ: data collection, patient care. Souza ALS: data collection, patient care. Medina-Pestana JO: provision of data relating to the casuistry. Ferraz MLG: study design, data analysis, article writing.

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RESUMO – Contexto – O transplante renal é o tratamento de escolha para pacientes com doença renal terminal e está associado a menor mortalidade quando comparado aos métodos dialíticos. O Brasil é o país com o segundo maior número de transplantes renais do mundo e, entre esses pacientes, observa-se que as alterações hepáticas são comuns. A frequência das alterações hepáticas varia de 20 a 50% pós-transplante e tem importante impacto na sobrevida e qualidade de vida desses pacientes. Existem poucos dados sobre a frequência, causas e características dessas alterações. **Objetivo –** Determinar a prevalência das diferentes causas de anormalidades hepáticas em receptores de transplante renal, associar as características dessas anormalidades a variáveis demográficas, epidemiológicas e clínicas, comparar as características das alterações hepáticas entre diferentes etiologias e avaliar possíveis alterações no diagnóstico em dois períodos diferentes de tempo. **Métodos –** Estudo epidemiológico descritivo, transversal, observacional, realizado no ambulatório "Hepato-Rim" do Hospital São Paulo (EPM/UNIFESP), centro de atendimento especializado a pacientes com anormalidades hepáticas e doenças renais de base. **Resultados –** Quinhentos e oitenta e um pacientes transplantados foram avaliados. As etiologias mais prevalentes de anormalidades hepáticas foram hepatite C e B, sobrecarga de ferro, doença hepática gordurosa não alcoólica e lesão hepática induzida por drogas. A causa mais comum – hepatite C – foi analisada em maiores detalhes. Em comparação com as outras causas, essa infecção foi a mais frequente em pacientes mais velhos, pacientes do sexo feminino e pacientes com mais tempo de transplante e hemodiálise. A análise dos dois períodos mostrou que os pacientes do período 1 (P1 – 1993 a 2005) eram mais velhos e encaminhados com maior frequência devido à sorologia positiva; encaminhamento devido a anormalidades de aminotransferases predominou durante o período 2 (P2 – 2006 a 2018). Os diagnósticos predominantes foram hepatite C e B durante P1 e doença hepática gordurosa não alcoólica e lesão hepática induzida por drogas durante P2. **Conclusão –** A avaliação das principais alterações hepáticas em receptores de transplante renal é importante, pois permite melhor manejo desses pacientes na investigação diagnóstica e no tratamento e contribui para a prevenção de complicações nesta população especial.

Palavras-chave – Transplante renal, alterações hepáticas, doença hepática.

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ORIGINAL ARTICLE

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Does COVID-19 cause pancreatitis?

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ABSTRACT – **Background** – Viral infections can cause acute pancreatitis. Idiopathic pancreatitis has an important proportion in the etiology of acute pancreatitis. **Objective –** To investigate the rate of development of acute pancreatitis (AP) in COVID-19 patients and to determine the rate of idiopathic pancreatitis in the etiology of this pancreatitis. **Methods** – A total of 6.467 patients hospitalized with the COVID-19 diagnosis were included in the study. Patients diagnosed with AP based on the Atlanta criteria were identified. Etiological factors were determined in patients who developed acute pancreatitis and compared with the etiological factors in 315 patients with non-COVID-19, hospitalized with the diagnosis of AP before the COVID-19 pandemic. AP was detected in 0.1% of patients with COVID-19. While gallstone was the etiologic factor in 2 (28.6%) of seven patients who developed acute pancreatitis during COVID-19, hyperlipidemia was the factor for 1 (14.3%) patient. Moreover, the etiologic factor could not be determined in 4 (57.1%) patients, and they were regarded as idiopathic pancreatitis patients. Biliary pancreatitis was the most common etiologic factor in 315 (78.4%) patients admitted to the hospital for AP before the COVID-19 pandemic. Idiopathic pancreatitis was ranked second with 16.8%. **Conclusion** – It was observed that there was a significant difference in the incidence of idiopathic pancreatitis between patients with COVID-19 and non-COVID-19 (P=0.015). Results suggest that the SARS-Cov-2 virus may be among the factors leading to AP.

Keywords – COVID-19; acute pancreatitis; acute pancreatitis incidence; etiology.

INTRODUCTION

Coronavirus disease (COVID-19) is a viral infection that mainly affects the upper respiratory tract and lungs. It is known that this virus enters cells by attaching to angiotensin-converting enzyme two (ACE-2) receptors[1]. The ACE-2 receptor is found not only in the respiratory system but also in many organs and tissues, mainly in the liver, biliary tract, intestine, and pancreas[2].

Acute pancreatitis (AP) is a necroinflammatory disease of the pancreas. Many factors play a role in the etiology, while some consist of viral causes (such as mumps). Regarding the majority of acute pancreatitis cases, the underlying factors are unidentified. Idiopathic pancreatitis is defined as acute pancreatitis cases whose etiology is unclear despite detailed history, physical examination, biochemical tests, and screening methods such as abdominal ultrasonography/computed tomography. Idiopathic pancreatitis accounts for 8–44% of all pancreatitis cases[3,4].

Although the virus was isolated in pancreatic tissue in the autopsies of people who died due to SARS-Cov infection, acute pancreatitis was not reported in these patients[5]. First acute pancreatitis cases were reported in COVID-19 patients in China, then similar cases were reported from other parts of the world[6]. Nonetheless, due to the absence of a clear definition of pancreatitis and limited retrospective studies, also the lack of emphasis on Atlanta criteria, it was not possible to present a straightforward conclusion.

Therefore, this study aims to determine the frequency of AP in patients with COVID-19 and to investigate whether COVID-19 causes AP.

METHODS

The data consists of 6467 patients admitted to Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital between April 2020 and January 2021 due to COVID-19 was analyzed retrospectively. Followingly, the data of seven COVID-19 patients diagnosed with AP were selected and scrutinized further. The etiological factors in patients with AP and COVID-19 were compared with the etiological factors in 315 acute pancreatitis patients followed up in our hospital between May 2016 and November 2019 prior to the COVID-19 outbreak. Finally, the incidence of idiopathic pancreatitis was compared across the patients with acute pancreatitis with and without COVID-19.

Patients were diagnosed with acute pancreatitis according to the revised Atlanta criteria. Therefore, patients were diagnosed with acute pancreatitis if at least two of following the criteria; 1- abdominal pain consistent with AP; (displaying posteriorly in the right upper quadrant and epigastric region); 2- amylase or lipase level increased more than three times the upper limit of average level; 3- AP-specific imagining findings (with ultrasound, computed tomography or magnetic resonance imaging) were present[7].

A group of patients was excluded from the study; for instance, patients with a diagnosis of chronic pancreatitis, with a diagnosis of hereditary pancreatitis, previous pancreatic or biliary tract surgery, patients with pancreatic and other organ malignancies, patients with sepsis, septic shock, and multiorgan dysfunction.

The study was carried out per the declaration of Helsinki, and

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permission for the study was obtained from the Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee. (Date 16.10.2020 and issue number 611).

Statistical analysis

While mean and standard deviation values were stated for continuous variables, categorical variables were expressed as %. Student's *t*-test and Mann Whitney U test were used to compare the factors between patients who developed pancreatitis during non-COVID-19 and COVID-19 infection. All tests were bilateral, and a *P*-value <0.05 was considered statistically significant. Statistical analyzes were performed using the SPSS26.0 for Windows (SPSS Inc.Chicago, IL, USA) package program.

RESULTS

Acute pancreatitis developed during hospitalization in 7 (0.1%) of 6467 patients with COVID-19. Of these patients, three were female, and four were male, with a mean age of 51.4. One of the patients had diabetes, and one had hypertension. Of 315 patients without COVID-19 were hospitalized for acute pancreatitis, 212 (67.3%) were female, and 103 (32.7 %) were male. 4 (1.2%) of these patients hospitalized due to acute pancreatitis died. Of all the patients, at least one comorbid disease was present in 116 (36.8%), and the most common ones were hypertension, diabetes, and coronary artery disease (TABLE 1).

Biliary pancreatitis was the most common etiologic factor in 315 (78.4%) patients admitted to the hospital for AP before the COVID-19 pandemic. Idiopathic pancreatitis was ranked second with 16.8%. While gallstone was the etiologic factor in 2 (28.6%) of seven patients who developed acute pancreatitis during COVID-19, hyperlipidemia was the factor for 1 (14.3%) patient. Moreover, the etiologic factor could not be determined in 4 (57.1%) patients, and they were regarded as idiopathic pancreatitis patients. It was observed that there was a significant difference in the incidence of idiopathic pancreatitis between patients with COVID-19 and non-COVID-19. (*P*=0.015) (TABLE 2). Five patients with acute pancreatitis with COVID-19 had computed tomography for diagnosis or follow-up during the pancreatitis attack. According to the Baltahazar classification, one patient was moderate, and the others were mild pancreatitis. Considering Atlanta classification, pancreatitis was mild in five patients and moderate in two patients. Finally, all patients recovered with treatment (TABLE 3).

TABLE 1. Demographic data and clinical characteristics of acute pancreatitis patients with COVID-19 and non COVID-19.

Feature	COVID-19	Non COVID-19 acut pancreatitis
N	7	315
Age	51.4±12.5	57.17±19.1
Gender		
Female	3 (42.9%)	212 (67.3 %)
Male	4 (57.1%)	103 (32.7 %)
Exitus	0 (0.0%)	4 (1.2%)
Comorbid diseases		
HT	1 (14.3 %)	40 (12.7%)
DM	1 (14.3 %)	33 (10.4%)
CAD	–	24 (7.6%)
CRF	–	10 (3.1 %)
COPD	–	7 (2.2%)
Malignancy	–	2 (0.6 %)

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, CRF:chronic renal failure, COPD: chronic obstructive pulmonary disease.

DISCUSSION

An increasing number of pancreatitis cases have been reported in the literature developed during or after COVID-19 infection[8-11]. In addition, it was stated that pancreatic damage occurs parallel with the severity of the disease in COVID-19 patients. It was acknowledged that 1–2% of mild COVID-19 patients and 17% of severe COVID-19 patients had pancreatic damage[12]. In another study, amylase and lipase elevations were reported to range from 8.5% to 17.3% in COVID-19 patients. Likewise, enzyme elevation was observed to be correlated with the severity of COVID-19[13,14]. However, it has not been fully revealed if this enzyme elevation expresses clinical pancreatitis. On the other hand, focal pancreatitis was detected in significant numbers of the patients in autopsy studies[15,16]. In the COVID PAN study investigating the severity of pancreatitis in patients with COVID-19, the rate of idiopathic pancreatitis was higher in patients with COVID-19 than in the control group, 24% 14%, respectively[17].

The incidence of acute pancreatitis is reported to be approximately 40–50/100,000[18]. In hospitalized COVID-19 patients, AP occurred two times higher than the rate stated above (0.1%). Supporting the related literature, in this study, we observed that AP developed in 0.1% of the patients hospitalized with COVID-19. Etiology was not found in 4 (57.1%) of these APs and was regarded as idiopathic pancreatitis. The rate of idiopathic pancreatitis was 16.8% in 315 patients diagnosed with AP in our hospital before the COVID-19 pandemic. However, the rate of idiopathic pancreatitis was higher in patients with COVID-19, and the difference was statistically significant. Although there is no evidence between COVID-19 and acute pancreatitis, data suggests that the SARS-Cov-2 virus may also play a role in the etiology of APs.

Since the beginning of the epidemic, COVID-19 has spread extensively all over the world. Therefore, we emphasize the importance of considering acute pancreatitis as a new etiological factor of the SARS-Cov-2 virus. Furthermore, to reveal the relationship between COVID-19 and AP, further multicenter, randomized, and controlled studies are needed.

TABLE 2. Etiological causes of patients with acute pancreatitis (COVID-19 and non-COVID-19).

Etiology	Non-covid pancreatitis	COVID19+ pancreatitis	*P* value
Biliary	247 (78.4 %)	2 (28.6%)	0.009
Idiopathic	53 (16.8%)	4 (57.1 %)	0.015
Hyperlipidemia	3 (0.9 %)	1 (14.3%)	0.020
Post ERCP	6 (1.9 %)	–	–
Drugs	4 (1.2 %)	–	–
Other	2 (0.6 %)	–	–
Total	315 (100 %)	7 (100 %)	

ERCP: endoscopic retrograde cholangiopancreatography.

TABLE 3. Demographic and biochemical characteristics of patients who developed acute pancreatitis during COVID-19.

Feature	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7	Total
Age	71	57	60	33	42	51	46	51.4±12.5
Gender F/M	M	F	M	F	M	F	M	3/4
Atlanta	Mild	Mild	Mild	Mild	Moderate	Mild	Moderate	
Etiology	Idiopathic	Bilier	Bilier	Idiopathic	Hiperlipidemi	Idiopathic	Idiopathic	
CT (Balthazar)	2	–	–	2	5	1	3	
Amylase (U/L)	3510	2755	972	1246	188	3306	2070	2006±1256
Lipase (IU/L)	1662	1229	578	729	39	1662	1144	1006±595
ALT (IU/L)	18	238	305	23	19	105	66	110±115
AST (IU/L)	90	207	273	40	28	188	74	128±93
ALP (IU/L)	53	279	302	80	98	79	101	141±103
GGT (IU/L)	28	317	448	19	35	16	23	126±178
LDH (IU/L)	317	507	439	208	261	335	252	331±107
T.Bil (mg/dL)	0.8	2.6	2.1	0.9	0.8	0.7	1.0	1.27±0.75
D.Bil (mg/dL)	0.3	1.9	1.7	0.3	0.2	0.2	0.3	0.70±0.75
Glucose (mg/dL)	134	280	143	120	178	116	95	152±61
Urea (mg/dL)	42	38	45	27	30	78	50	44.2±16.9
Creatinine (mg/dL)	0.7	0.6	0.8	0.9	0.6	1.3	1.0	0.84±0.25
Calcium (mg/dL)	8.2	8.8	9.5	9.1	8.0	9.0	8.6	8.74±0.52
Triglyceride (mg/dL)	328	205	277	172	1758	253	195	455±576
WBC (cell/μmL)	4600	10500	7700	16000	10200	13500	6800	9900±3940
Neutrophil (cell/μmL)	3700	8900	6300	13900	8100	11100	5500	8214±3477
Lymphocyte (cell/μmL)	660	970	1120	1660	1700	1380	720	1187±405
CRP (mg/L)	108	23	75	59	37	43	177	74.5±53.1

CT: computerized tomography; ALT: alanina aminotransferase; AST: aspartato aminotransferase; ALP: fosfatase alcalina; GGT: gama glutamil transpeptidase; LDH: lactato desidrogenase; T.Bil: bilirubin; D.Bil: direct bilirubin; WBC: white blood cells; CRP: C-reactive protein.

Authors' contribution

Ebik B: idea/concept, data collection and processing. Ekin N: design, analysis, interpretation and manuscript writing. Bacaksız F: supervision/consultancy, literature review, materials, critical and review.

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RESUMO – **Contexto** – Infecções virais podem causar pancreatite aguda (PA). A pancreatite idiopática tem uma proporção importante na etiologia da pancreatite aguda. **Objetivo** – Investigar a taxa de desenvolvimento de pancreatite aguda em pacientes com COVID-19 e determinar a taxa de pancreatite idiopática na etiologia desta pancreatite. **Métodos** – No estudo foram incluídos 6.467 pacientes internados com o diagnóstico de COVID-19. Foram identificados pacientes diagnosticados com PA com base nos critérios de Atlanta. Fatores etiológicos foram determinados em pacientes que desenvolveram pancreatite aguda e comparados com os fatores etiológicos em 315 pacientes sem COVID-19, hospitalizados com o diagnóstico de PA antes da pandemia COVID-19. A PA foi detectada em 0,1% dos pacientes com COVID-19. Enquanto o cálculo biliar foi o fator etiológico em 2 (28,6%) dos sete pacientes que desenvolveram pancreatite aguda durante o COVID-19, a hiperlipidemia foi o fator para 1 (14,3%) paciente. Além disso, o fator etiológico não pôde ser determinado em 4 (57,1%) pacientes, sendo considerados pacientes com pancreatite idiopática. A pancreatite biliar foi o fator etiológico mais comum em 315 (78,4%) pacientes internados no hospital para PA antes da pandemia COVID-19. A pancreatite idiopática ficou em segundo lugar com 16,8%. **Conclusão –** Observou-se que houve diferença significativa na incidência de pancreatite idiopática entre pacientes com COVID-19 e não COVID-19 (*P*=0,015). Os resultados sugerem que o vírus SARS-Cov-2 pode estar entre os fatores que levam à pancreatite aguda.

Palavras-chave – COVID-19; pancreatite aguda; incidência aguda de pancreatite; etiologia.

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Serum procalcitonin as a prognostic marker in acute severe ulcerative colitis: a prospective study

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ABSTRACT – **Background** – Procalcitonin may be increased in active ulcerative colitis (UC). We investigated the role of procalcitonin in predicting response in acute severe UC (ASUC). **Methods –** Consecutive patients with ASUC diagnosed on basis of Truelove and Witts criteria were enrolled. Serum procalcitonin levels for consecutive patients were measured at admission and day 3. We assessed role of procalcitonin values at presentation and at day 3 in assessing response on day 3 (Oxford's criteria) and need for second line therapy (day 28). **Results –** Of fifty patients (23 males, mean age: 35.98±13.8 years), 16 did not respond (day 3). Ten (20%) patients required second-line therapy. Baseline procalcitonin was significantly associated with response on day 3 (*P*=0.016). There was no association between day 1 or day 3 procalcitonin and need for second-line rescue therapy. **Conclusion –** Serial procalcitonin is not an effective biomarker for predicting outcomes or need for second line therapy in ASUC.

Keywords – Inflammatory bowel disease; colectomy; surgery; outcomes; ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease which usually has a relapsing remitting course[1]. Acute severe ulcerative colitis (ASUC) is a severe presentation of the disease and requires aggressive medical therapy or colectomy[2]. Up to 25% of patients with UC experience at least one episode of ASC in their lifetime[3,4]. Mortality from ASUC has drastically decreased with the use of corticosteroids in such patients, however a third of all patients may not respond to medical therapy and need an urgent colectomy[5]. Oxford's criteria has been used extensively to predict the risk of colectomy, but its components are subjective (stool frequency) and correlate poorly with mucosal inflammation[6]. Many parameters and composite scores have been evaluated for accurate prediction of response to medical therapy[7,8]. As the armamentarium of drugs available for medical therapy expands, it is important to timely recognize patients who may not respond to intravenous corticosteroids and may benefit from early institution of second line medical rescue therapy.

Procalcitonin is a peptide molecule which is a precursor of the endocrine hormone calcitonin. Calcitonin is primarily synthesized in the C cells of the thyroid gland and plays a regulatory role in calcium homeostasis. In patients with acute inflammation, there is an increased concentration of procalcitonin in the circulation[9]. This is attributed to an increased synthesis of procalcitonin across many extra thyroid organs as well as decreased cleavage of procalcitonin to calcitonin molecule[10]. Initially used as a biomarker of gram-negative infections, application of procalcitonin has gradually expanded to prognostication of other inflammatory diseases as well[11-13]. It is a useful tool to differentiate infective gastroenteritis from a flare of UC[14]. Although level of procalcitonin in patients with UC does not increase to the same extent as in patients with infective colitis, it is an effective marker for differentiating a severe flare from mild and moderately active disease[15]. Procalcitonin has been evaluated as a predictor of outcomes in patients with ASUC previously. Baseline procalcitonin was 73% accurate in predicting intravenous corticosteroid failure when a cut off of 0.1 mcg/mL was taken[16]. It correlated positively with the baseline UCEIS score and could be incorporated effectively into a model to predict response to intravenous corticosteroids[16].

The purpose of this study was to evaluate the role of procalcitonin as a biomarker for the severity of disease in patients who presented with ASUC and to assess its accuracy in predicting the response to intravenous corticosteroids and need for second line therapy.

METHODS

We have previously reported a randomised controlled trial at our center to evaluate the added impact of intravenous antibiotics (ceftriaxone and metronidazole) as compared to standard of care in patients with acute severe ulcerative colitis. The present report includes the same subset for whom we report the association between serum procalcitonin at admission and at day 3 with outcomes in these patients[17]. The study included patients admitted with a diagnosis of acute severe ulcerative colitis at a tertiary center from 1st April 2019 to 4th March 2020. Written informed consent was taken from all patients prior to inclusion and the study was approved by the Institute Ethics Committee, the work vide letter no NK/3148/Res/32.

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Patients

Patients with active colitis (presence of blood mixed stools) were screened and those with ASUC, as defined by the modified Truelove and Witt's criteria were evaluated further. Thus, our study included patients who presented six or more bloody stools per day with one or more of the following: pulse rate >90/min, temperature >37.8 C, hemoglobin <10.5 g/dL, erythrocyte sedimentation rate >30mm at 1 hour or C-reactive protein >30 mg/L. Patients with age <12 years, had suspicion or evidence of infection or sepsis, toxic megacolon, patients with chronic uncontrolled comorbidities, pregnant or lactating mothers were excluded.

All patients received the standard of treatment including intravenous methylprednisolone 60 mg once daily, anticoagulation prophylaxis, intravenous fluids and were allowed orally on a soft diet. Since the patients were enrolled from a RCT[17], antibiotic regime was decided by randomization. In addition to the standard of treatment mentioned above, half of the patients received intravenous ceftriaxone 1 gm twice a day and metronidazole 500 mg thrice a day, while the other half received placebo infusions. Clinical features of all patients were noted, including the stool frequency, severity of bleeding, presence of toxic symptoms and baseline disease characteristics. Blood and stool investigations were done on admission, including inflammatory biomarkers: serum C-reactive protein, serum procalcitonin and fecal calprotectin. All patients underwent an unprepared sigmoidoscopy with rectal biopsy. Plain abdomen X-ray was done to rule out megacolon and perforation.

Response to treatment was assessed on day 3 as per the Oxford criteria[18]. Patients who had a partial or no response were managed according to the treating physician's discretion and the patient's choice. Second line rescue therapies which were offered included intravenous infliximab (5 mg/kg), intravenous cyclosporine (2 mg/kg/day) given once daily for five days or colectomy. Patients who responded to intravenous corticosteroids were discharged on oral prednisolone (40 mg/day) and azathioprine. Patients who were successfully treated with cyclosporine were subsequently prescribed oral cyclosporine (4 mg/kg) and azathioprine. Patients were followed up for 4 weeks after discharge from the hospital.

Measurement of serum procalcitonin

Procalcitonin was measured on admission which was taken as day 1, and at day 3 of therapy with intravenous corticosteroids. Non heparinized blood samples were drawn in pyrogen free polypropylene tubes. Samples were stored at room temperature and were processed within 6 hours of collection. In the event of delay in processing, samples were stored at -20°C. Samples containing precipitates were centrifuged before performing the assay. Serum procalcitonin levels were measured via electrochemiluminescence immunoassay (Elecsys BRAHMS PCT, Cobas E; Roche diagnostics, Switzerland) according to the manufacturer's instructions. Measurement range for the assay if from 0.02 ng/mL to 100 ng/mL.

Outcomes

Primary outcome was the response on day 3 as per the Oxford criteria. Secondary outcome was the need for second line rescue therapy.

Baseline procalcitonin levels were compared between those who had a complete response on day 3 and those who did not. Both day 1 and day 3 procalcitonin levels were compared between patients who eventually required second line therapy and those who responded. Day 1 and day 3 procalcitonin levels were also compared between patients who received antibiotic therapy and those recieving placebo infusions. Receiver operating characteristic (ROC) curve was plotted to analyse the accuracy of baseline procalcitonin for predicting non response and need for second line therapy.

Statistical analysis

Data entry and analysis was done using SPSS 20.0 software. Continuous variables were expressed using mean with standard deviation or median and IQR. Qualitative variables were expressed as proportions. Mann Whitney U test was used to compare quantitative data between two groups. *P* value <0.05 was considered statistically significant.

RESULTS

Fifty patients enrolled (23 males, mean age: 35.98±13.8 years). Mean disease duration was 41.1 (48.7) months. Baseline features of the cohort are described in TABLE 1.

TABLE 1. Baseline characteristics of the patients.

Parameter	Total (n=50)
Age (years)	35.98±13.8
Male	22 (44%)
Disease duration (months)	41.11 (48.17)
Extensive colitis (n, %)	22 (50%)
First presentation (n, %)	13 (26%)
Previous UC related hospitalization (n, %)	19 (38%)
Steroid used previously	23 (46%)
Azathioprine used	12 (24%)
Endoscopic Mayo score	2.68 (0.47)
Partial Mayo score	7.44 (0.97)
Complete Mayo score	10.1 (1.13)
Fulminant disease	23 (46%)
Severe Mayo	17 (34%)
Laboratory parameters	
Hemoglobin (gm/dL)	9.99±2.9
Total leucocyte count (cells/μL)	8586±3513
S.Creatinine (mg/dL)	0.68±0.189
S. albumin (mg/dL)	3.2±0.86
ESR (mm/h)	49.48±20.49
C reactive protein (mg/L)	51.8±112.6
Fecal calprotectin (μg/gm)	784.64±343.18

UC: ulcerative colitis; ESR: erythrocyte sedimentation rate.

Complete response at day 3 was observed in 13 (26%), partial response in 21 (42%) and no response in 16 (32%) patients. Twenty-seven of partial/non-responder patients responded to steroids with the median time to response being five[4-6] days. Ten patients required second line rescue therapy, of which seven were given intravenous cyclosporine while three patients underwent colectomy. None of the patients opted for infliximab, primarily due to financial constraints.

Role of procalcitonin in acute severe ulcerative colitis

Serum procalcitonin concentration in the serum was measured on day 1 and day 3 of intravenous corticosteroid therapy. Median procalcitonin level on admission of all patients was 0.049 [0.02–0.122] µg/L. The median procalcitonin on day 3 was 0.057 [0.021–0.114].

Prediction of response on day 3 as per Oxford day 1 procalcitonin was significantly higher in patients who showed no response on day 3. Median baseline procalcitonin level in non-responders was 0.098 [0.031–0.217] while it was 0.03 [0.02–0.095] µg/L in patients who had a partial or complete response (*P*=0.016). Four out of sixteen non-responders had procalcitonin >0.1 µg/mL (25%) as compared to 12 out of 34 (35%) responders (*P* value=0.466). The median change of procalcitonin from day 1 to day 3 was -0.002 (-0.018–0.003) mcg/L for the non-responder group and it was 0.005 (-0.008–0.036) mcg/L for the responder group (*P* value=0.062) ROC curve for accuracy of day in procalcitonin in predicting non-response on day 3 showed an area of 0.71 (0.553, 0.866) (*P*=0.018). Using a cut off of 0.109 µg/L, the sensitivity for day 3 non-response was 50 % and specificity was 80 %. While a cut off 0.4 µg/L yielded a sensitivity of 63% and specificity of 100% (FIGURE 1) for predicting overall need for second line rescue therapy.

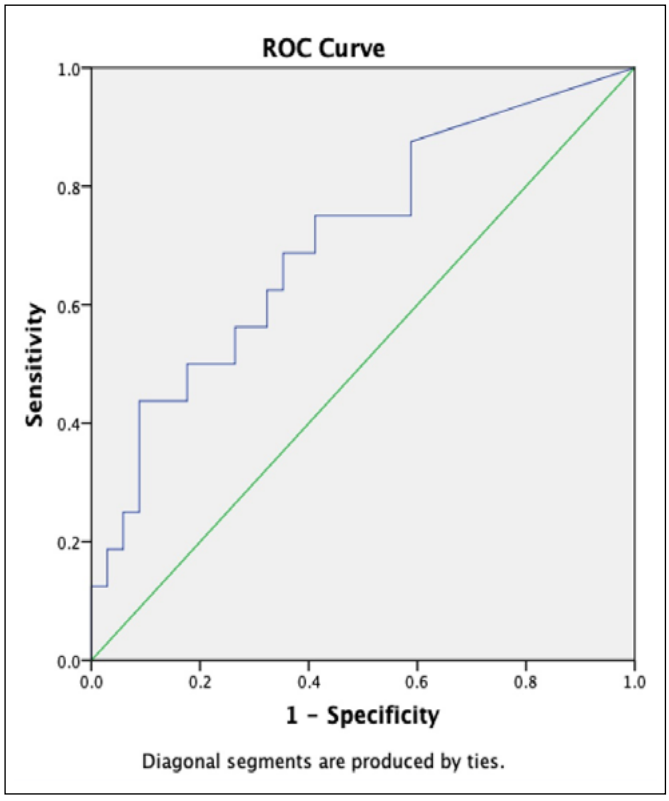

FIGURE 1. Receiver operating characteristic curve for procalcitonin levels for prediction of response as per Oxford Criteria on day 3.

Neither day 1 nor day 3 procalcitonin was significantly associated with the eventual need for second line rescue therapy by day 28 (TABLE 2). Also, the decline in serum procalcitonin did not seem to differ between the groups receiving antibiotics or placebo (TABLE 3).

TABLE 2. Serum procalcitonin levels between those responding to steroids and those requiring second line therapy.

Need for second line	Yes (n=10)	No (n=40)	*P* value
Day 1 procalcitonin (µg/L)	0.105 (0.025–0.258)	0.105 (0.025–0.258)	0.092
Day 3 procalcitonin (µg/L)	0.1045 (0.03–0.2)	0.045 (0.02–0.105)	0.181

TABLE 3. Serum procalcitonin levels between in patients on antibiotics vs placebo.

Procalcitonin	Antibiotic (n=25)	Control (n=25)	*P* value
Day 1 procalcitonin (µg/L)	0.065 (0.417)	0.026 (0.344)	0.173
Day 3 procalcitonin (µg/L)	0.07 (0.029)	0.039 (0.69)	0.815

DISCUSSION

In our evaluation of the role of procalcitonin as a biomarker in acute severe ulcerative colitis, all the patients had a value lower than the standard cut off 0.5 µg/L. The levels were significantly higher in patients who did not show any response on day 3 as per the Oxford criteria. However, in contrast to the previously reported optimal cut off of 0.1 µg/mL, we did not see a similar predictive value for this cut-off[16]. There was no difference in the baseline or day 3 procalcitonin levels between those patients who required second line rescue therapy and those who eventually responded to intravenous corticosteroids.

Ulcerative colitis is a chronic inflammatory disease and dysbiosis has been implied in the pathophysiology of the disease. Fecal microbiome analysis in patients with acute severe colitis has demonstrated a reduced overall diversity with high intra cohort variation[19]. A decrease in *Firmicutes* and increase in genera of *Gammaproteobacteria* class is noted, which is distinct from the microbiome signature of healthy controls or people with mild to moderately active UC[20]. This shift in microbiome and the increased level of TNF receptors may have lead to the procalcitonin levels which were observed. Since we had excluded patients with sepsis or those with evidence of *Clostridioides difficile* infection, we did not expect a drastic increase in procalcitonin levels. Furthermore, Aeromonas caviae was grown on stool culture of a single case (2% of entire cohort). Hence, the patients in our cohort did not seem to be infected with gram negative enteric bacteria, further explaining the relatively low levels of procalcitonin. Gut microbiome has been associated with the response to treatment in patients with ulcerative colitis. Microbiome rich in OTUs from *Clostridioides* order have been linked to a response to 5-ASA and corticosteroids[21,22]. The differences in baseline procalcitonin between patients who showed a complete or partial response on day 3 may be attributed to the differences in severity of inflammation as well as the degree of dysbiosis. However, the lack of correlation with the eventual need for second line rescue therapy highlights the importance of the trend of biomarkers rather than the absolute baseline value, when evaluating for the response to therapy. It also suggests that procalcitonin may not be the perfect biomarker for prognosticating these patients.

The only possible value of performing serum procalcitonin may be to differentiate self-limited infective colitis from a flare of inflammatory bowel disease, and may suggest the presence of other infective complications as well[23]. Wu et al. evaluated the role of procalcitonin in predicting response in patients with ASUC. They found that baseline procalcitonin level >0.1 μg/mL positively correlated with failure of corticosteroid therapy, failure of second line medical therapy and could accurately predict the need for colectomy[16]. Although the infection profile of their patients has not been mentioned, one third of the patients had received steroids previously, and a higher percentage of patients in the surgical group had previously been on immunomodulators and biologics. In comparison, none of the patients in our study had received biologicals previously and 26% had presented for the first time. Further almost 46.7 % of the patients in the previous study failed steroids which is much higher than the usually reported steroid failure rate. Thus, the baseline features may account for the difference observed.

Our study has a few limitations, including a small sample size and that we did not evaluate the gut microbiome. Also, we excluded patients with suspected sepsis or those with toxic megacolon to ensure homogeneity of patients and to ensure the analysis only in patients with disease activity rather than underlying infection.

In conclusion, the present study shows that although serum procalcitonin of patients with ASUC may accurately predict non response to steroids as per Oxford criteria, it is not an accurate biomarker to predict the need for second line rescue therapy.

Authors' contribution

Mishra S: data collection, initial draft, literature review. Ram S and Sharma AK: laboratory support and revision of manuscript. Prasad KK: histopathology and revision of manuscript. Dutta U: clinical care of patients, revision. Sharma V: conception, study design, manuscript revision. All authors approved the final version.

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Mishra S, Ram S, Prasad KK, Sharma AK, Dutta U, Sharma V. A procalcitonina sérica como marcador prognóstico na colite ulcerativa aguda. Um estudo prospectivo. Arq Gastroenterol. 2022;59(1):75-9.

RESUMO – **Contexto** – A procalcitonina pode estar aumentada em colite ulcerativa ativa. Investigamos o papel da procalcitonina na previsão de resposta na colite ulcerativa aguda grave. **Métodos –** Foram inscritos pacientes consecutivos com colite ulcerativa aguda grave diagnosticados com base nos critérios de Truelove e Witts. Os níveis de procalcitonina sérica dos pacientes foram medidos consecutivamente na internação e no terceiro dia. Avaliamos o papel dos valores procalcitonina na apresentação e na avaliação da resposta no terceiro dia (critérios de Oxford) e necessidade de terapia de segunda linha (dia 28). **Resultados –** Dos 50 pacientes (23 homens, idade média: 35,98±13,8 anos), 16 não responderam (terceiro dia). Dez pacientes (20%) necessitaram de terapia de segunda linha. A procalcitonina de linha de base foi significativamente associada à resposta no terceiro dia (*P*=0,016). Não houve associação entre o primeiro dia ou o terceiro dia de procalcitonina e necessidade de terapia de resgate de segunda linha. **Conclusão –** A procalcitonina sérica não é um biomarcador eficaz para prever desfechos ou necessidade de terapia de segunda linha em colite ulcerativa aguda grave.

Palavras-chave – Doença inflamatória intestinal; colectomia; cirurgia; desfechos; colite ulcerativa.

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Validation of the Rockall score in upper gastrointestinal tract bleeding in a Colombian tertiary hospital

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ABSTRACT – Background – Rockall score is the most widely used prognostic scale for assessing risk of complications from non-varicose upper gastrointestinal bleeding (UGIB). Several studies have been conducted in adult populations with non-varicose UGIB in different parts of the world, with conflicting findings regarding the extent of association between the score and some morbidity and mortality outcomes. Also, there is controversy regarding the best cut-off point for the score. Moreover, no studies validating this score in Colombia have been carried out. **Objective –** To assess the diagnostic performance of the Rockall score in predicting rebleeding and mortality in patients with non-varicose UGIB. **Methods –** A prospective cohort study was conducted in patients requiring upper gastrointestinal endoscopy (UGIE) for non-varicose bleeding. The pre-and post-endoscopy Rockall scores were calculated and outcomes, including mortality, UGIB-associated mortality and in hospital rebleeding were determined at the 1 and 3-month time points. The association between the scores and these outcomes was assessed using the chi^2 or the Fisher test, whereas the discrimination ability of the score was determined using the areas under the ROC curve (AUC). High discrimination ability was considered to exist in cases in which an AUC ≤0.7 with α=0.05 could be rejected. **Results –** Overall, 177 patients were analyzed. In-hospital outcomes at 1 and 3 months were 12%, 17% and 23% for general mortality, 6%, 12% and 15% for UGIB mortality, and 19%, 30% and 37% for rebleeding. The post-endoscopy Rockall score was associated with the three outcomes at the three time points assessed, while the pre-endoscopy score was only associated with general mortality at the three time points, and rebleeding at 1 and 3 months. Regarding discrimination ability, although the AUC was greater than expected by randomness (0.5) in all cases, only one AUC ≤0.7 was rejected in the post-endoscopy score for in-hospital UGIB mortality (AUC=0.901; 95%CI: 0.845–0.958), at 1 month (AUC=0.836; 95%CI: 0.717–0.954) and at 3 months (AUC=0.869; 95%CI: 0.771–0.967), and for rebleeding at 1 month (AUC=0.793; 95%CI: 0.725–0.861) and at 3 months (AUC=0.806; 95%CI: 0.741–0.871). **Conclusion –** An association was found between the Rockall score and rebleeding and mortality in patients with non-varicose UGIB. Only the post-endoscopy score had a high predictive ability for rebleeding and UGIB mortality.

Keywords – Upper gastrointestinal tract; gastrointestinal hemorrhage; sensitivity and specificity; prognosis; endoscopy; mortality.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) tract is defined as any gastrointestinal (GI) bleeding occurring above the ligament of Treitz, including the esophagus, the stomach and the proximal duodenum[1]. It is the most frequent medical emergency in gastroenterology[2]. It has been associated with preventable risk factors, primarily alcohol consumption, *H. pylori* infection and the use of non-steroidal anti-inflammatory agents (NSAIDs)[3,4].

Despite breakthroughs in management, advances in endoscopic techniques and the introduction of proton pump inhibitors (PPIs), UGIB is still associated with significant morbidity and mortality and represents a substantial cost for the health system[5]. Mortality rate between 5% and 10% has been described[6-7], with higher rates found in patients hospitalized for other causes who develop bleeding during their hospital stay[7]. Moreover, close to 20% of patients will develop rebleeding after the first hemostatic endoscopy, which is also an important predictor of mortality, with a 10-fold increase in risk[8]. Medium-term outcomes in these patients are also worse because both the bleeding episode as well as potential adjustments to chronic medications (including platelet aggregation inhibitors) act as decompensation factors. This impacts prognosis and increases the risk of mortality even months after the acute episode[9]. Mortality has been described to increase 27 times during the first month after hospital admission, and although this increased risk remains over time, it is considerably less significant after four months[10]. Consequently, UGIB is a public health problem, creating the imperative need to develop strategies designed to identify patients who require urgent upper GI endoscopy as well as closer surveillance.

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Rockall score is the most widely used prognostic scale for assessing risk of complications from non-varicose UGIB. This score can be applied before or after upper gastrointestinal endoscopy (UGIE), the latter being the preferred timing because it allows to include endoscopic findings in the calculation as the best predictors for decision-making in these patients[11]. According to Rockall's initial study with 4,000 patients, there is a correlation between rebleeding and the score[12]. The score has been reviewed in various settings around the world. The first independent validation was a cohort study in New Zealand which established a cut-off point of four to distinguish between high and low mortality risk patients[13]. However, several studies have been conducted over the past few years in adult populations with non-varicose UGIB in different parts of the world, with conflicting findings regarding the extent of association between the score and some morbidity and mortality outcomes. There is also a controversy regarding the best cut-off point for the score[14-16]. Moreover, no studies validating this score in Colombia have been carried out.

The objective of this study is to assess the performance of the Rockall score in predicting in-hospital mortality and rebleeding in patients with non-varicose UGIB at 1 and 3 months. Secondary objectives include determining the association between the score and the need for transfusion, and its correlation with how fast the endoscopic assessment is performed.

METHODS

This study was approved by the Ethics and Research Committee of La Samaritana Hospital, Bogotá DC, Colombia. La Samaritana Hospital is a tertiary teaching hospital, and local referral center. A prospective cohort study was conducted using convenience sampling in a population consisting of patients undergoing UGIE due to suspected UGIB at La Samaritana Hospital between September 1, 2019, and January 31, 2021. The primary sources of information included clinical records, official UGIE reports and phone calls made 1 and 3 months after the endoscopic procedure. The study population consisted of patients ≥18 years of age hospitalized in the emergency service or the general ward undergoing UGIE during their stay because of UGIB, with completed follow-up by telephone call. Patients with varicose UGIB and patients with GI bleeding during their stay in intensive or step-down units were excluded. All the patients were informed and signed the informed consent form.

Admission sociodemographic and clinical variables were collected, including the variables comprising the pre-endoscopy Rockall score. Endoscopic variables were also collected, including need for, and type of, hemostatic therapy provided, as well as the variables comprising the post-endoscopy Rockall score. Moreover, outcome variables for in-hospital rebleeding and mortality, both general as well as UGIB-specific, were also collected.

With α=0.05 error and assuming an area under the ROC curve (AUC) =0.85 and a positive outcome in 20% of patients, it was estimated that a sample of 155 patients would have 80% power to detect an AUC >0.7, considered as a cut-off point with high discrimination ability.

A univariate analysis was performed using absolute and relative frequencies for qualitative variables and medians and inter-quartile ranges (IQR) for quantitative variables, given the non-normal distribution of the latter according to the Shapiro-Wilk test. A bivariate analysis was then performed between exposure and outcome variables. Chi^2 tests were used for qualitative exposure variables if the expected values in less than 20% of the cells were <5 and <1 in none, and Fisher's test was used in the opposite case; and given their non-normal distribution, the U-Mann-Whitney test was used for quantitative variables.

To validate pre- and post-endoscopy Rockall scores, an association test was initially performed in 2 x n tables between the results of each of the scores and the outcome variables, also using chi^2 or Fisher's tests, as appropriate. The AUC was then estimated in order to evaluate discrimination ability. For those outcomes in which H_0 was rejected (AUC ≤0.7), sensitivity, specificity, LR+ and LR- of the different cut-off points of the score were described, ROC curves were plotted and the proportion of positive outcomes for each score was tabulated. The Spearman coefficient was used to assess the correlation between the two scores and the time from the onset of symptoms until UGIE and length of stay.

Data sources were reviewed again for completion of missing data, and only complete data were finally analyzed. All statistical analyses were performed using the Stata 13.0 (Stata Corporation, College Station, TX, USA) software package and two-tailed calculations were used for all *P* values, which were considered significant if lower than 0.05.

RESULTS

Data from 177 patients were collected. TABLE 1 summarizes the sociodemographic, clinical and outcomes characterization for these patients, as well as their results in the Rockall score.

The bivariate analysis found that place of origin (other departments), heart rate (HR) and mean arterial pressure (MAP) on admission, shock status, aspirin (ASA) use, and Hb on admission were associated with the need for transfusion before UGIE, and with rebleeding (TABLES S1 and S2 of the supplementary material). Moreover, some UGIE findings were associated with rebleeding (TABLE S2): the presence of major recent bleeding stigmata, endoscopic diagnosis (GI malignancy or other diagnoses, in their order, compared with Mallory-Weiss tear or no findings) and the need for endoscopic hemostasis. Mortality was found to be associated with age, the presence and number of comorbodities, HR and MAP on admission, shock status, ASA use, Hb and leukocytes on admission, the need for transfusion before UGIE, major recent bleeding stigmata on UGIE and GI malignancy on UGIE (TABLE S3).

Regarding validation of the Rockall score, it was found that the post-endoscopy score was associated with all outcome variables, whereas the pre-endoscopy score reached significance only for predicting the need for pre-endoscopy transfusion, in-hospital death, and rebleeding and death at 1 and 3 months (TABLE 2). However, although in all cases the AUC was higher than randomly expected (0.5), only one AUC ≤0.7 was rejected in the post UGIE score for outcomes: in-hospital death due to UGIB at 1 month, and at 3 months, and rebleeding at 1 month and at 3 months (TABLE 2). Sensitivity, specificity, LR+ and LR- for these outcomes are shown in TABLE 3, the ROC curve graphs are shown in FIGURE 1, and the tabulation of the proportion of positive outcomes for each score is shown in TABLE 4. Finally, there was poor correlation with both the time from the onset of symptoms to UGIE as well as with the length of stay: *P*=-0.001 and *P*=0.217 for the pre-endoscopy score, and *P*=-0.131 and *P*=0.170 for the post-endoscopy score, respectively.

TABLE 1. General population characterization.

Characteristics	Median (IQR) or frequency (%)	95%CI
Sociodemographic		
Age	66 years (49–78)	62–70 years
Male sex	110 (62%)	55–69%
Place of origin		
Bogotá	51 (29%)	23–36%
Cundinamarca	31 (18%)	13–24%
Other departments	95 (54%)	46–61%
Clinical		
Any comorbidity	150 (85%)	79–89%
Heart rate[a]	85 BPM (74–95)	82–86 BPM
SBP[a]	117 mmHg (106–133)	115–122 mmHg
DPB[a]	72 mmHg (66–78)	70–74 mmHg
Shock status[b]		
No	120 (68%)	60–74%
Tachycardia	35 (20%)	15–26%
Hypotension	22 (12%)	8–18%
NSAID use	44 (25%)	19–32%
ASA use	47 (27%)	21–34%
Hb[a]	10.7 g/dL (7.2–13.6)	9.6–11.2 g/dL
Leukocytes[a]	9560 x µL (6980–13540)	8630–10054 x µL
Pre-UGIB transfusion[c]	61 (35%)	28–42%
Length of hospital stay	7 days (3.2–15.2)	5.7–8.6 days
Time from onset of symptoms to UGIE	15 hours (4–27)	13–18 hours
Endoscopic		
Major stigmata of recent bleeding[d]	55 (31%)	25–38%
Endoscopic diagnosis[b]		
Mallory-Weiss	3 (2%)	1–5%
No lesions or bleeding stigmata	57 (32%)	26–40%
Other diagnoses	104 (59%)	51–66%
Upper GI malignancy	13 (7%)	4–12%
Hemostatic therapy provided		
None	139 (79%)	72–84%
Argon plasma	1 (1%)	0–4%
Only adrenaline	17 (10%)	6–15%
Only hemoclip	3 (2%)	1–5%
Adrenaline + hemoclip	17 (10%)	6–15%
Outcomes during hispitalization		
Deaths	22 (12%)	8–18%
Death from UGIB[e]	10 (6%)	3–10%
Rebleeding	33 (19%)	14–25%
Outcomes at 1 month		
Deaths	30 (17%)	12–23%
Deaths from UGIB[e]	12 (7%)	4–12%
Rebleeding	53 (30%)	24–37%

Continuation →

Characteristics	Median (IQR) or frequency (%)	95%CI
Outcomes at 3 months		
Deaths	41 (23%)	17–30%
Deaths from UGIB[e]	15 (9%)	5–14%
Rebleeding	66 (37%)	30–45%
Rockall		
Pre-endoscopy		
0	12 (7%)	4–12%
1	10 (6%)	3–10%
2	31 (18%)	13–24%
3	47 (27%)	21–34%
4	43 (24%)	18–31%
5	21 (12%)	8–18%
6	12 (7%)	4–12%
7	1 (1%)	0–4%
Post-endoscopy		
0	8 (5%)	2–9%
1	4 (2%)	1–6%
2	10 (6%)	3–10%
3	38 (21%)	16–28%
4	30 (17%)	12–23%
5	27 (15%)	11–21%
6	28 (16%)	11–22%
7	17 (10%)	6–15%
8	7 (4%)	2–8%
9	6 (3%)	2–7%
10	2 (1%)	0–4%

SBP: systolic blood pressure; DBP: diastolic blood pressure; NSAID: non-steroidal anti-inflammatory agents; ASA: admission shock status, aspirin; UGIE: upper gastrointestinal endoscopy; UGIB: upper gastrointestinal bleeding; GI: gastrointestinal. [a]On admission. [b]According to Rockall score. [c]≥2 red blood cell unit. [d]According to Rockall score: blood, clot or visible or bleeding vessel. [e]Death from bleeding that could not be controlled endoscopically and/or patients with refractory hypovolemic shock or with no other diagnosis as the main cause of death recorded in the death certificate.

TABLE 2. Associations between the Rockall score and outcome variables and discrimination ability.

Outcome	Pre-endoscopy Rockall			Post-endoscopy Rockall		
	P[a]	AUC	95%CI	*P*[a]	AUC	95%CI
In-hospital						
Pre-endoscopy transfusion[b]	0.041	0.621	0.536–0.706	–	–	–
Rebleeding	0.069	0.653	0.551–0.755	0.001	0.748	0.665–0.832
Death	<0.001	0.784	0.694–0.874	0.017	0.775	0.685–0.864
Death from UGIB	0.124	0.769	0.640–0.898	<0.001	0.901	0.845–0.958
At 1 month						
Rebleeding	0.018	0.653	0.566–0.738	<0.001	0.793	0.725–0.861
Death	<0.001	0.756	0.657–0.855	0.004	0.746	0.654–0.838
Death from UGIB	0.273	0.665	0.492–0.839	0.003	0.836	0.717–0.954
At 3 months						
Rebleeding	0.007	0.631	0.548–0.714	<0.001	0.806	0.741–0.871
Death	<0.001	0.762	0.679–0.845	0.001	0.744	0.661–0.827
Death from UGIB	0.077	0.708	0.562–0.855	<0.001	0.869	0.771–0.967

UGIB: upper gastrointestinal bleeding; AUC: rea under the curve; 95%CI: 95% confidence interval. [a]chi^2 or Fisher test [b]≥2 red blood cell unit.

TABLE 3. Sensitivity, specificity, LR+ and LR- of the post-endoscopy Rockall score.

Outcome	AUC	Cut-off	Sensitivity	Specificity	LR+	LR-
In-hospital mortality from UGIB	0.901	≥0	100.0%	0.0%	1.00	
		≥1	100.0%	4.8%	1.05	0.00
		≥2	100.0%	7.2%	1.08	0.00
		≥3	100.0%	13.2%	1.15	0.00
		≥4	100.0%	35.9%	1.56	0.00
		≥5	100.0%	53.9%	2.17	0.00
		≥6	100.0%	70.1%	3.34	0.00
		≥7	80.0%	85.6%	5.57	0.23
		≥8	40.0%	93.4%	6.07	0.64
		≥9	20.0%	96.4%	5.57	0.83
		≥10	10.0%	99.4%	16.70	0.91
Mortality from UGIB at 1 month	0.836	≥0	100.00%	0.00%	1.00	
		≥1	100.00%	4.85%	1.05	0.00
		≥2	100.00%	7.27%	1.08	0.00
		≥3	100.00%	13.33%	1.15	0.00
		≥4	91.67%	35.76%	1.43	0.23
		≥5	91.67%	53.94%	1.99	0.15
		≥6	91.67%	70.30%	3.09	0.12
		≥7	66.67%	85.45%	4.58	0.39
		≥8	33.33%	93.33%	5.00	0.71
		≥9	16.67%	96.36%	4.58	0.86
		≥10	8.33%	99.39%	13.75	0.92
Mortality from UGIB at 3 months	0.869	≥0	100.00%	0.00%	1.00	
		≥1	100.00%	4.94%	1.05	0.00
		≥2	100.00%	7.41%	1.08	0.00
		≥3	100.00%	13.58%	1.16	0.00
		≥4	93.33%	36.42%	1.47	0.18
		≥5	93.33%	54.94%	2.07	0.12
		≥6	93.33%	71.60%	3.29	0.09
		≥7	73.33%	87.04%	5.66	0.31
		≥8	40.00%	94.44%	7.20	0.64
		≥9	26.67%	97.53%	10.80	0.75
		≥10	6.67%	99.38%	10.80	0.94
Rebleeding at 1 month	0.793	≥0	100.00%	0.00%	1.00	
		≥1	100.00%	6.45%	1.07	0.00
		≥2	100.00%	9.68%	1.11	0.00
		≥3	100.00%	17.74%	1.22	0.00
		≥4	92.45%	45.16%	1.69	0.17
		≥5	77.36%	62.90%	2.09	0.36
		≥6	66.04%	79.84%	3.28	0.43
		≥7	39.62%	91.13%	4.47	0.66
		≥8	20.75%	96.77%	6.43	0.82
		≥9	9.43%	97.58%	3.90	0.93
		≥10	3.77%	100.00%		0.96
Rebleeding at 3 months	0.806	≥0	100.00%	0.00%	1.00	
		≥1	100.00%	7.21%	1.08	0.00
		≥2	100.00%	10.81%	1.12	0.00
		≥3	98.48%	18.92%	1.21	0.08
		≥4	90.91%	48.65%	1.77	0.19
		≥5	75.76%	66.67%	2.27	0.36
		≥6	65.15%	84.68%	4.25	0.41
		≥7	37.88%	93.69%	6.01	0.66
		≥8	18.18%	97.30%	6.73	0.84
		≥9	9.09%	98.20%	5.05	0.93
		≥10	3.03%	100.00%		0.97

UGIB: upper gastrointestinal bleeding; LR +: positive likelihood ratio; LR-: negative likelihood ratio.

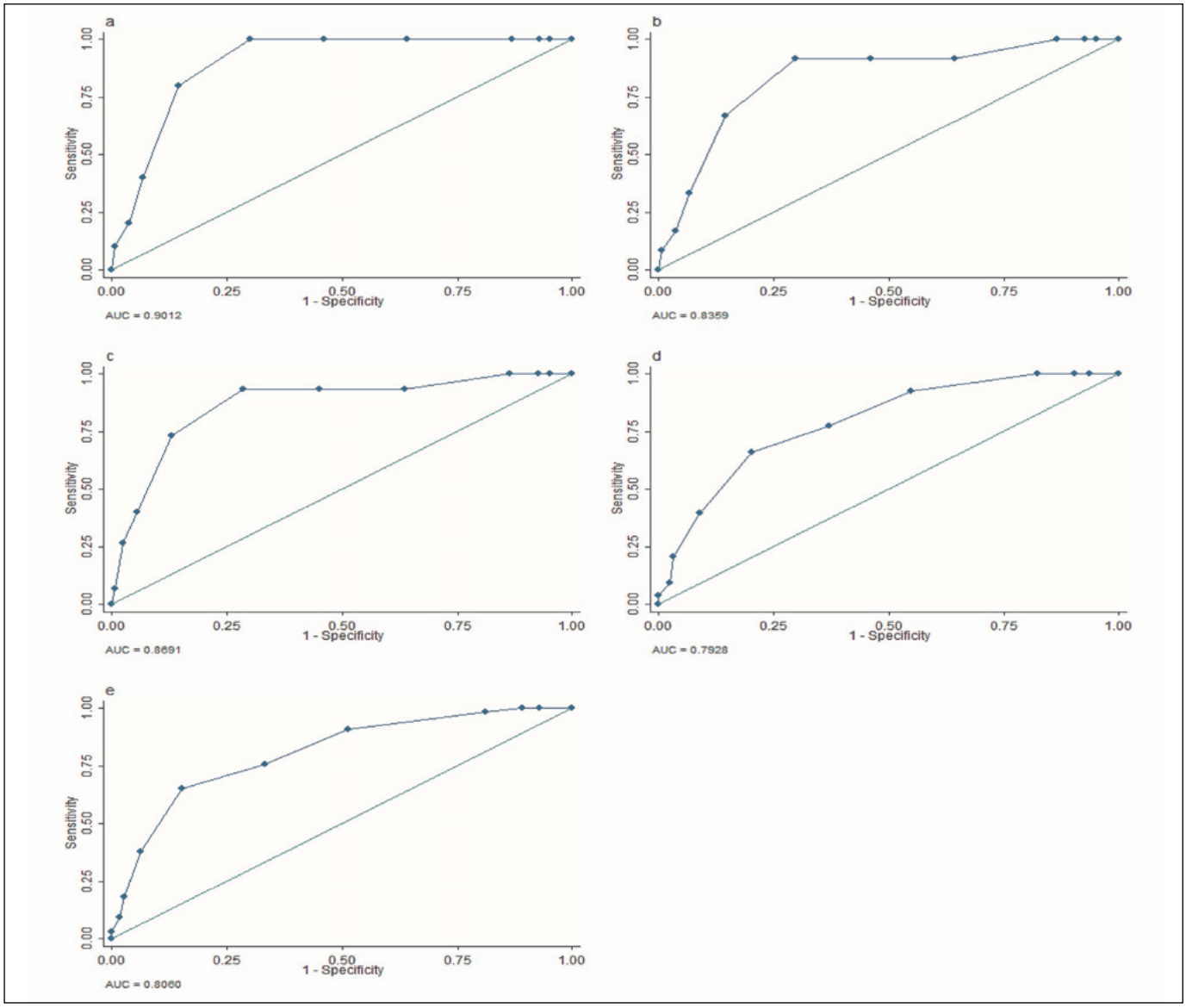

FIGURE 1. Post-endoscopy Rockall score ROC. **A)** In-hospital mortality from UGIB; **B)** Mortality from UGIB at 1 month; **C)** Mortality from UGIB at 3 months; **D)** Rebleeding at 1 month; **E)** Rebleeding at 3 months. AUC: area under the ROC curve; UGIB: upper gastrointestinal bleeding.

TABLE 4. Proportion of positive outcomes based on post-endoscopy Rockall score.

Score	In-hospital mortality from UGIB	Mortality from UGIB at 1 month	Mortality from UGIB at 3 months	Rebleeding at 1 month	Rebleeding at 3 months
0	0.0%	0.0%	0.0%	0.0%	0.0%
1	0.0%	0.0%	0.0%	0.0%	0.0%
2	0.0%	0.0%	0.0%	0.0%	10.0%
3	0.0%	2.6%	2.6%	10.5%	13.2%
4	0.0%	0.0%	0.0%	26.7%	33.3%
5	0.0%	0.0%	0.0%	22.2%	25.9%
6	7.1%	10.7%	10.7%	50.0%	64.3%
7	23.5%	23.5%	29.4%	58.8%	76.5%
8	28.6%	28.6%	28.6%	85.7%	85.7%
9	16.7%	16.7%	50.0%	50.0%	66.7%
10	50.0%	50.0%	50.0%	100.0%	100.0%

UGIB: upper gastrointestinal bleeding.

DISCUSSION

This is the first study to validate the Rockall score in Colombia. This was achieved using a prospective design to evaluate its association with outcomes and its discrimination ability.

Both the pre-endoscopy and post-endoscopy scores showed an association with general mortality, mortality from UGIB and rebleeding at the three time points of the study. However, the superiority of the latter was evident as shown not only by higher AUCs for each of these outcomes, but also because it was the only one to reach high discrimination ability for some of those outcomes (in-hospital UGIB-related death at 1 month and 3 months, and rebleeding at 1 month and 3 months). Best performance is expected with the combined use of clinical and endoscopic information given that endoscopic findings are the best predictors for decision-making in these patients and have been associated with rebleeding, mortality and need for therapeutic endoscopic intervention in observational studies[11,17,18]. Moreover, it is consistent with the associations found in our study between endoscopic findings that comprise the post-endoscopy score and the assessed outcomes (TABLES S2 and S3).

Based on ROC curve analyses of the post-endoscopy Rockall score for those outcomes in which discrimination ability was high, the cut-off points with a better balance between sensitivity and specificity for predicting UGIB-related mortality appear to be ≥6 or ≥7, while ≥5 or ≥6 would be the prediction cut-off points for rebleeding. However, the definition of the ideal cut-off point for any score must consider the implications of false negative and false positive results. In this setting, false negatives (patients with low risk based on the score but who develop the outcome) would have worse implications as they would result in early discharges or less stringent surveillance in patients who would eventually re-bleed or die from UGIB[19]. Bearing this in mind, the ≥6 cut-off could be proposed so that the score can be used as a tool in deciding discharge of a patient with lower values, considering that it was shown to have 100% sensitivity, equal to an LR- of 0, for in-hospital mortality from UGIB, indicating that this outcome did not occur in any of the patients with a score <6 in our study. On the other hand, the ≥3 could be more useful for less intense follow-up in patients with lower values, given its 100% sensitivity for predicting UGIB-related mortality at 1 month and 3 months and for rebleeding at 1 month. For 3-month rebleeding, the sensitivity of this cutoff point dropped to a still high 98.5%, with an LR of 0.08. Although it does not rule out the outcome, it does reflect a strong reduction in the likelihood of occurrence. The findings by Morales et al. in 464 Colombian patients affected by UGIB would also support these cut-off points[20], given that patients with scores <3 had 0% mortality, although the objective of the study was not to validate de post-endoscopy Rockall score.

Our findings and conclusions are similar to those reported in other studies in different geographical areas, which have shown an association between the Rockall score and the risk of death and rebleeding and have identified scores between three and four as the best predictors overall. For example, the study by Dicu et al.[21] found that close to 10% of the patients died, all of them with a Rockall score ≥5. Gleeson et al.[22], in a study conducted in Dublin, Ireland, defined patients with a score ≤3 as mild, given that no deaths or new bleeds occurred in these patients who were considered as low risk and candidates for early discharge. Likewise, Dulai et al.[23], in Los Angeles, USA, found that patients with a Rockall score ≤2 had a lower probability of adverse outcomes, with rebleeding and mortality rates of 4% and 0% versus 19% and 2%, respectively. Regarding the Rockall score's ability to predict rebleeding, our results are similar to those of other studies, in that the general conclusion is that this score was originally developed for predicting mortality and not rebleeding, hence the loss of some diagnostic performance[15,24,25]. In our study, reported mortality was 7%, similar to that found in the studies mentioned above, which ranged between 2% and 18.7%, and to the world figure, which is close to 10%[3,12,21].

Our study found a statistically significant association between the pre-endoscopy Rockall score and the need for transfusion, albeit with no high discrimination ability to predict it. Consequently, it is unlikely that this score can be relevant when it comes to determining the benefit of transfusion in these patients, at least beyond the clinical and paraclinical elements that usually guide this decision. In fact, prior studies have reached similar conclusions: Mokhtare et al., for example, found 71.8% sensitivity, 51.8% specificity and 0.528 AUC for this outcome[26], while in the study by Robertson et al., the same estimators were 71%, 55%, and 0.66, respectively[27].

The poor correlation found between the score obtained and length of stay is to be expected, at least for two reasons: 1) just like higher scores can be associated with the need for longer hospitalization, they can also be associated with higher mortality, lowering the correlation; 2) although one of the main abilities of this score is to define a sufficiently low risk as to prompt discharge, clinicians frequently ignore it when it comes to making this and other decisions[19], actually resorting more frequently to the endoscopic findings than to the Rockall score[28]. Among other reasons, this is due to the lack of continuing education, the absence of studies that assess outcomes using the score versus clinical judgement, and the paucity of objective evidence regarding the enhanced use of resources derived from the incorporation of the score in decision-making[19].

Our population was similar to that affected by UGIB in other national and international studies in terms of characteristics such as age, proportion of men, the number of comorbidities, and mortality, among others[2,6,20,29,30]; therefore, it is valid to assume that our findings would not lack external validity. Likewise, our study found an association between the outcomes and several of the risk factors reported previously: age, the presence of comorbidities, use of NSAIDs or ASA, shock status, endoscopic findings, among other variables, most of which are part of the post-endoscopy Rockall score[2,19,20,31].

A low percentage of patients with low Rockall scores was found in our study when compared to the study by Morales et al.[20]. A likely explanation is that, in the context of the current health system, access to hospital admission is relatively difficult, and it is not beyond reason that many of these patients had been managed on an outpatient basis, considering this study was conducted mostly during the COVID-19 pandemic. This fact may also have prevented patients from visiting the hospital out of fear of leaving their homes during the pandemic.

The study has some limitations that could undermine the validity of the estimated ROC curves. For example, discrimination ability could have been negatively affected at least in three ways: 1) follow-up bias, derived from the fact that patients who did not complete telephone follow-up, and who may have had both higher scores as well as worse outcomes, were excluded; 2) selection bias due to the inclusion of only in-hospital UGIB, because outpatients

could have had better outcomes and lower scores; 3) selection bias due to the exclusion of patients in the intensive care or step-down unit, who could also have had higher scores and worse outcomes. However, our results are a more accurate reflection of the clinical settings in which the Rockall score would be useful, rendering those exclusions necessary. Moreover, in this setting, as in most settings, a type II error is preferable over a type I error. On the other hand, a single-center study could have limited external validity: for example, the population served in this center is usually of middle-to-low socioeconomic status which confers several particular exposures and characteristics. However, most of the variables assessed, at least those with the highest clinical relevance, were similar to those used in previous studies, particularly to those reported in the past by other institutions in this country. Verification of the clinical record data by at least two researches could have resulted in a lower risk of transcription bias. Finally, although a potential classification bias may have existed in relation to patient classification in the Rockall score, given experience variability among the six endoscopists who performed the endoscopic procedure, this would be a non-differential bias, which usually moves associations towards nil value. Therefore, again, a type II error would be favored, not invalidating the positive associations actually found.

CONCLUSION

Both the pre-endoscopy as well as the post-endoscopy Rockall scores were associated with rebleeding and mortality in patients with non-varicose UGIB. Discrimination ability was high only for the post-endoscopy score and specifically for the outcomes of death from in-hospital UGIB at 1 month and 3 months, and rebleeding at 1 month and 3 months. A post-endoscopy Rockall score <6 appears to be useful for making the decision of discharging these patients, while a score <3 appears to be useful for less stringent outpatient follow-up decisions.

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Authors' contribution

Frías-Ordoñez JS, Arjona-Granados DA and Urrego-Díaz JA: development of the pre-project and all of the research stages (review of the literature, data collection, data analysis, and composition). Briceño-Torres M: contributed for data collection. Martínez-Marín JD: contributed for composition, supervision, and guidance.

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Frías-Ordoñez JS, Arjona-Granados DA, Urrego-Díaz JA, Briceño-Torres M, Martínez-Marín JD. Validação da pontuação Rockall no sangramento do trato gastrointestinal superior em um hospital terciário colombiano. Arq Gastroenterol. 2022;59(1):80-8.

RESUMO – Contexto – O escore de Rockall é a escala de prognóstico mais amplamente usada para avaliar o risco de complicações de sangramento gastrointestinal superior não varicoso. Vários estudos foram conduzidos em populações adultas com sangramento gastrointestinal superior não varicoso em diferentes partes do mundo, com achados conflitantes quanto à extensão da associação entre o escore e alguns desfechos de morbimortalidade. H**á** também controvérsias em relação ao melhor ponto de corte para a pontuação. Além disso, não foram realizados estudos que validem essa pontuação na Colômbia. **Objetivo –** Avaliar o desempenho diagnóstico do escore de Rockall na previsão de ressangramento e mortalidade em pacientes com sangramento gastrointestinal superior não varicoso. **Métodos –** Um estudo de coorte prospectivo foi conduzido em pacientes que necessitaram de endoscopia digestiva alta (EDA) para sangramento não varicoso. Os escores de Rockall pré e pós-endoscopia foram calculados e os resultados, incluindo mortalidade, mortalidade associada ao sangramento gastrointestinal superior não varicoso e ressangramento intra-hospitalar foram determinados nos pontos de tempo de 1 e 3 meses. A associação entre os escores e esses desfechos foram avaliados pelo teste de chi^2 ou Fisher, enquanto a habilidade de discriminação do escore foi determinada pelas áreas sob a curva ROC (AUC). Alta capacidade de discriminação foi considerada existente nos casos em que uma AUC ≤0,7 com α=0,05 poderia ser rejeitada. **Resultados –** No geral, 177 pacientes foram analizados. Os desfechos hospitalares em 1 e 3 meses foram de 12%, 17% e 23% para mortalidade geral, 6%, 12% e 15% para mortalidade com hemorragia digestiva alta e 19%, 30% e 37% para ressangramento. O escore de Rockall pós-endoscopia foi associado aos três desfechos nos três momentos avaliados, enquanto o escore pré-endoscopia foi associado apenas à mortalidade geral nos três momentos, e ressangramento em 1 e 3 meses. Em relação à capacidade de discriminação, embora a AUC fosse maior do que o esperado pela aleatoriedade (0,5) em todos os casos, apenas uma AUC ≤0,7 foi rejeitada no escore pós-endoscopia para mortalidade com hemorragia digestiva alta intra-hospitalar (AUC =0,901; 95%IC: 0,845–0,958), em 1 mês (AUC =0,836; 95%IC 0,717–0,954) e em 3 meses (AUC =0,869; 95%IC: 0,771–0,967), e para ressangramento em 1 mês (AUC =0,793; 95%IC: 0,725–0,861) e aos 3 meses (AUC =0,806; 95%IC: 0,741–0,871). **Conclusão –** Foi encontrada associação entre o escore de Rockall, ressangramento e mortalidade em pacientes com hemorragia digestiva alta não varicosa. Apenas o escore pós-endoscopia teve alta capacidade preditiva para ressangramento e mortalidade por sangramento gastrointestinal superior não varicoso.

Palavras-chave – Trato gastrointestinal superior; hemorragia gastrointestinal; sensibilidade e especificidade; prognóstico; endoscopia; mortalidade.

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ORIGINAL ARTICLE

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Rational for continuing terlipressin after endoscopic variceal ligation in acute variceal haemorrhage needs further evidence: a pilot study

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ABSTRACT – **Background** – Variceal hemorrhage (VH) is a medical emergency. Prompt endoscopic variceal ligation (EVL) is therapeutic. Terlipressin is used in VH and continued for 2–5 days even after EVL. As hemostasis is primarily achieved by EVL, the benefit of continuing trelipressin after EVL is unknown. **Objective** – To evaluate the efficacy of continuing terlipressin after EVL to prevent re-bleed and mortality. **Methods** – In this pilot study, after EVL 74 patients of VH were randomized into two treatment groups TG2 & TG5, received terlipressin (1 mg IV bolus q 4 hourly) for 2 days and 5 days respectively and one control group (TG0), received 0.9% normal saline (10 mL IV bolus q 4 hourly) and followed up for 8 weeks. **Results** – A total of 9 (12.6%) patients had re-bleed with maximum 4 (5.6%) patients in TG5 group followed by 3 (4.2%) in TG2 and 2 (2.8%) in TG0 groups (P=0.670). The overall mortality was 15 (21.1%) patients, 6 (8.5%) patients in TG0 group, followed by 5 (7.0%) in TG5 and 4 (5.6%) in TG2 group (P=0.691). Adverse drug reactions were significantly higher in treatment groups with maximum 18 (24.32%) patients in TG5, followed by 8 (10.8%) in TG2 and 2 (2.7%) in TG0 groups (P=0.00). Duration of hospital stay was also significantly higher in treatment group, 6.63 (±0.65) days in TG5 followed by 3.64 (±0.57) in TG2 and 2.40 (±0.50) days in TG0 groups (P=0.00). **Conclusion** – The rational for continuing terlipressin after EVL is doubtful as it didn't have any benefit for the prevention of re-bleed or mortality; rather it increased the risk of adverse drug reactions and duration of hospital stay. Further randomized clinical trials are encouraged to generate more evidence in support or against continuing terlipressin after EVL.

Keywords – Terlipressin; variceal hemorrhage; endoscopic variceal ligation; re-bleed; mortality; adverse drug reaction; portal hypertension; chronic liver disease; cirrhosis; gastrointestinal bleed.

INTRODUCTION

Upper gastrointestinal (UGI) bleed of variceal origin is a frequently encountered medical emergency. Prompt endoscopic variceal ligation (EVL) is therapeutic as well as diagnostic. Terlipressin is a vasopressin analog and widely used (intravenous, 2 mg q 4 hourly) in suspicious cases of variceal hemorrhage (VH) before endoscopic procedure is done, along with volume and blood resuscitative measures. As per guideline, after EVL terlipressin therapy (1 mg IV q 4 hourly) is continued for 2–5 days to prevent re-bleed and mortality[1]. But the extended use of terlipressin is not completely safe, as well as expensive also in resource constraint setting. At present there is no clinical trial available to authenticate the benefit of continuing terlipressin after EVL to prevent re-bleed or mortality in acute VH. During the post marketing surveillance terlipressin had been found to be associated with life threatening complications, like cardiac arrhythmia, myocardial ischemia, critical vasoconstriction of peripheral as well as internal organ leading to ischemia or gangrene, severe hyponatremia, hypertension, fluid overload and pulmonary edema[2-4]. So, the justification of continuing terlipressin for 5 days after EVL is questionable, as haemostasis is primarily achieved by EVL and the risk versus benefit of trelipressin therapy after EVL is still undiscovered. Continuing terlipressin after EVL also prolongs in-hospital care causing further expansion of the health care burden. There is still scarcity of evidence regarding efficacy of continuing terlipressin after EVL in preventing re-bleed or mortality and the incidence of adverse drug reaction in acute VH. The present study was about evaluating the benefit or risk associated with continuing terlipressin after EVL in acute VH.

METHODS

Aims

The aim of the study was to evaluate the efficacy of continuing terlipressin after EVL to prevent re-bleed and mortality in acute VH.

Site of study

The study was carried out in emergency medical outpatient department (EMOD) of post graduate institute of medical education and research (PGIMER), a tertiary care centre in northern India, with collaboration of department of internal medicine, gastroenterology, hepatology and pharmacology.

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Study design

It was an open label randomized controlled clinical trial. The study was carried out in three groups; denoting the duration of terlipressin therapy after EVL, two treatment group TG2 and TG5 and one control group TG0. The TG2 and TG5 groups received terlipressin for 2 days and 5 days respectively while the control group (TG0) received 0.9% normal saline (NS). All the patients of endoscopic proven acute VH presented at emergency were screened and subsequently enrolled in the study as per inclusion and exclusion criteria after taking written informed consent. The participants were followed up for 8 weeks telephonically or physically as and when required. The study was registered in the clinicaltrials.gov (clinicaltrials.gov PRS ID: NCT03584087).

Study duration

The study was conducted during the period of January 2018 to July 2019 after getting prior approval from Institutional Ethics Committee (IEC) of the under the n. IEC/2018/000684.

Inclusion and exclusion criteria

Irrespective of gender with age ≥18 years, all the patients with endoscopy proven acute VH with EVL done within 24 hours of admission were enrolled for the study. Patients with UGI bleed for more than 24 hours, past history of UGI bleed or EVL, chronic kidney disease, pregnancy were excluded from the study. Patients who didn't received pre-EVL terlipressin therapy, couldn't achieve haemostasis during EVL, EVL done beyond 24 hours of admission because of hemodynamic instability or encephalopathy were excluded from the study. Further patients who were receiving blood thinners like antiplatelets, anti-coagulation agents within 4 weeks of presentation, were also excluded from the study.

Methods and intervention

Clinical details were noted and base line blood investigations of all the patients were performed for risk stratification and to formulate further plan of management. For management, initial priority was given to secure airway, breathing and circulation. To ensure hemodynamic stability, crystalloid infusion was given as and when required. Blood transfusion was initiated at the threshold hemoglobin (Hb) of 7g/dL, to maintain target Hb of 7–9 g/dL or with signs of hemodynamic instability despite fluid resuscitation. Intra venous (IV) terlipressin (2 mg q 4 hourly) along with proton pump inhibitor and antibiotic were initiated promptly in all suspicious case of VH before endoscopy. Once the patient was hemodynamically stable and airway secured, endoscopy was done as soon as possible, within 24 hours of the presentation by the experienced gastroenterologists and hepatologists in the institute. Once variceal origin of hemorrhage was confirmed, EVL was done. After EVL patients satisfying the inclusion criteria were randomized into two treatment groups TG2 & TG5 and one control group (TG0) (FIGURE 1). The participants in TG2 and TG5 groups received IV terlipressin 1 mg IV bolus q 4 hourly for 2 and 5 days respectively and participants in control group (TG0) received 10 mL of 0.9% normal saline (NS) IV bolus q 4 hourly in place of terlipressin (FIGURE 1). All the participants were kept under observation and discharged subsequently after stabilization when haemostasis achieved and followed up for 8 weeks through OPD visits or telephonically. In case of re-bleed, terlipressin (1 mg IV bolus q 4 hourly) was re-started in those patients who were not receiving terlipressin at the time of re-bleed,

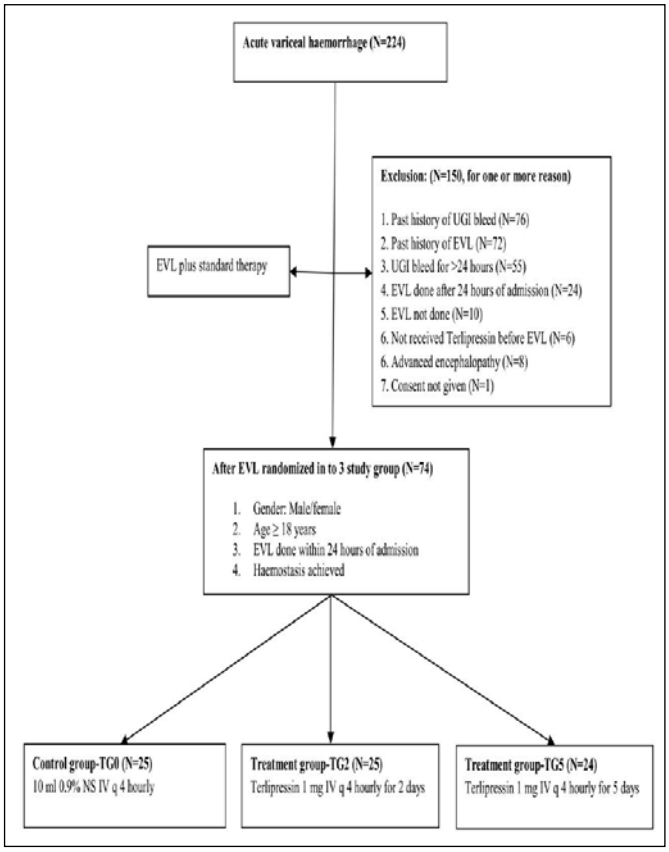

FIGURE 1. Study design.
EVL: endoscopic variceal ligation; UGI: upper gastrointestinal.

both in control as well as treatment groups. Re-bleed was defined as any significant UGI hemorrhage after EVL, leading to repeat endoscopy, hemodynamic instability and significant drop of Hb requiring blood transfusion. In case of re-bleed, another attempt was made for endoscopic hemostasis. Incidence of re-bleed, mortality, need for blood transfusions, duration of hospital stay and ADR were compared between the study groups. ADR incurred in the patients during the study were notified to ADR Monitoring Centre, PGIMER, under the Pharmacovigilance Programme of India (PvPI), National Coordination Centre (NCC) – Indian Pharmacopoeia Commission (IPC), Ministry of Health and Family Welfare, Government of India.

Outcome

Primary outcomes were incidence of re-bleed and mortality among the participant during the 8 weeks follow up. Secondary outcomes were incidence of ADR, duration of hospital stay, cost of therapy and in-hospital complication.

Sample size and statistical analysis

No previous RCT was available for the expected incidence of re-bleed or mortality in the treatment or control group. It was a pilot study. As per available epidemiological evidence, expecting 30% incidence of re-bleed in population with 15% incidence of re-bleed in treatment group, sample size was calculated to be around 70 patients after adjusting α-error of 0.05 with power of 80% and 10% drop out, for the final analysis[5]. A total of 224 patients with

acute VH were screened, out of which 150 patients were excluded as per exclusion criteria (FIGURE 1). Finally, 74 patients of acute VH were enrolled and randomized into three study groups (TG0, TG2, TG5) through computer generated block randomization. The data was managed in database system through Microsoft Excel and statistical analysis was performed by SPSS 24.0 version. The descriptive statistics were summarized as categorical data in the form of percentage, proportions and graphical presentations. The categorical endpoints were analyzed by non-parametric Pearson's chi-square test. Parametric data were presented in the form of mean, range and standard deviation. The mean values were compared for various groups using one-way ANOVA. The *P*-value of less than 0.05 was considered statistically significant. Outcomes were assessed for risk factor by using odds ratio, value more than one was considered significant.

RESULTS

Baseline data of the study population

• Age and Gender

Out of total 74 participants, 61 (82.4%) were male. The mean age of the study population was 48.15 (±11.12) years (range 25 to 71 years). Out of which 12 (16.2%) participants (6, 2 and 4 in TG0, TG2 and TG5 respectively) had age of ≥60 years and 62 (83.8%) participants (19, 23 and 20 in TG0, TG2 and TG5 respectively) were below 60 years of age and comparable between the groups (*P*=0.307). The mean body mass index (BMI) was 23.9 (±3.5) kg/m^2. The distribution of gender, age and BMI were comparable among the study groups (TABLE 1).

• Comorbidity

The most common comorbidity was chronic liver disease (CLD), in 64.9% participants, followed by diabetes mellitus (10.8%), chronic hepatitis C (10.8%) and chronic hepatitis B (9.5%). Two participants had hypertension and one participant had chronic obstructive airway disease (COAD). None of the participants were HIV positive. Total 20.3% participant were smokers and 73% were alcoholic, out of which 67.6% participants consumed alcohol in cirrhogenic dose. The distribution of comorbidities and risk factors were similar among the study groups (TABLE 1). At presentation 51.3% participants had tachycardia (PR ≥100), 20.3% had hypotension (SBP ≤90 mmHg) and 5.4% were hypoxic (SPO2 ≤90%), which were comparable among the study groups (TABLE 1).

• Investigations

Mean Hb, total leucocyte count (TLC) and platelet counts of the study population were 7.76 (±2.3) g/dL, 10.10x10^9/L (±4.8) and 108.5x10^9/L (±85.0) respectively. Clinically significant anemia

TABLE 1. Baseline data of the study population.

Baseline data	TG0 (N=25)	TG2 (N=25)	TG5 (N=24)	*P* value
Males (N=61)	20 (27%)	20 (27%)	21 (28.4%)	0.730
Females (N=13)	5 (6.8%)	5 (6.8%)	3 (4.1%)	0.730
Age (years ±SD)	48.28 (12.005)	48.12 (10.212)	48.04 (11.563)	0.997
BMI (kg/m^2)	23.9 (2.6)	24.1(3.3)	23.8(4.3)	0.906
CLD (N=48)	16 (21.6%)	16 (21.6%)	16 (21.6%)	0.975
DM (N=8)	1 (1.4%)	3 (4.1%)	4 (5.4%)	0.351
Hypertension (N=2)	0	0	2 (2.7%)	0.118
COAD (N=1)	1(1.4%)	0	0	0.370
Hepatitis B (N=7)	3 (4.1%)	2 (2.7%)	2 (2.7%)	0.867
Hepatitis C (N=8)	1 (1.4%)	3 (4.1%)	4 (5.4%)	0.351
Smoking (N=15)	5 (6.8%)	2 (2.7%)	8 (10.8%)	0.088
Alcoholic (N=54)	17 (23%)	17 (23%)	20 (27%)	0.380
Cirrhogenic dose of alcohol (N=50)	14 (18.9%)	16 (21.6%)	20 (27%)	0.111
Tachycardia (PR ≥100) (N=38)	12 (16.2%)	12 (16.2%)	14 (18.9%)	0.707
Hypotension (SBP ≤90) (N=15)	3 (4.05%)	6 (8.1%)	6(8.1%)	0.448
Hypoxia (SPO2 ≤90%) (N=4)	1 (1.4%)	2 (2.7%)	1 (1.4%)	0.780
Cirrhosis (N=66)	22 (29.7%)	22 (29.7%)	22 (29.7%)	0.893
Ascites (N=32)	12 (16.2%)	9 (12.2%)	11 (14.9%)	0.660
Spontaneous bacterial peritonitis (N=3)	1 (1.4%)	2 (2.7%)	0	0.365
Significant anemia (Hb ≤7 gm/dL) (N=28)	13 (17.6%)	7 (9.5%)	8 (10.8%)	0.186
Thrombocytopenia (N=52)	20 (27%)	18 (24.3%)	14 (18.9%)	0.246
Acute kidney injury (N=18)	6 (8.1%)	4 (5.4%)	8 (10.8%)	0.368
Transaminitis (N=48)	15 (20.3%)	18 (24.3%)	15 (20.3%)	0.547
Jaundice (N=40)	12 (16.2%)	15 (20.3%)	13 (17.1%)	0.696
Hypoalbuminemia (N=49)	14 (18.9%)	20 (27%)	15 (20.3%)	0.937
Coagulopathy (N=40)	15 (20.3%)	10 (13.5%)	15 (20.3%)	0.219

BMI: body mass index; CLD: chronic liver disease; DM: diabetes mellitus; COAD: chronic obstructive airway disease.

requiring PRBC transfusion was considered with a Hb ≤7 gm/dL, which was detected in 37.8% participants. Thrombocytopenia was present in 70.3% participants. In coagulation profile mean prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and prothrombin time index (PTI) were 22.9 (±6.5) second, 38.49 (±11.34) seconds, 1.63 (±0.43) and 61.12 (±14.75) % respectively. Coagulopathy (INR >1.5) was present in 54.6% patients. Mean serum urea and creatinine level were 52.5 (±26.06) mg/dL and 1.0 (±0.6) mg/dL respectively and 24.3% patients had renal dysfunction (creatinine of ≥1.5 mg/dL). Liver function test was comparable between the study groups with mean serum bilirubin, aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT) and albumin were 3.99 (±6.0) mg/dL, 91.69 (±68.4) IU/L, 57.21 (±39.5) IU/L and 2.87 (±0.5) g/dL respectively. Jaundice (total serum bilirubin ≥2 mg/dL) was present in 54.6% patients. Transaminitis (SGOT/SGPT>40 IU/L) and hypoalbuminemia (serum albumin <3.5 gm/dL) were present in 64.9% and 66.2% patients respectively. Baseline investigations were comparable among the study groups (TABLE 1 and 2). Ultrasonography proven cirrhosis with portal hypertension was present in 66 (89.2%) participants with 43.2% had ascites and 4.1% patients had spontaneous bacterial peritonitis (TABLE 1).

TABLE 2. Baseline investigations of the study population.

Baseline investigation	TG0 (N=25) (Mean ±SD)	TG2 (N=25) (Mean ±SD)	TG5 (N=24) (Mean ±SD)	*P* value
Hemoglobin (gm/dL)	6.93 (1.63)	8.22 (2.60)	8.14 (2.41)	0.086
TLC ($\times 10^9$/L)	9.22 (5.0)	10.62 (5.0)	10.48 (4.3)	0.529
Platelets($\times 10^9$/L)	87.56 (62.45)	115.2 (118.32)	123.38 (59.194)	0.304
Urea (mg/dL)	51.68 (25.32)	50.88 (30.37)	55.17 (22.66)	0.834
Creatinine (mg/dL)	0.91 (0.37)	0.89 (0.48)	1.22 (0.86)	0.120
Bilirubin (mg/dL)	3.13 (3.59)	3.31 (3.98)	5.60 (9.03)	0.285
SGOT (IU/L)	110.9 (84.78)	93.16 (69.83)	71.68 (43.42)	0.260
SGPT (IU/L)	60.64 (45.59)	61.39 (41.76)	48.58 (30.24)	0.563
Albumin (g/dL)	2.79 (0.71)	2.90 (0.56)	2.93 (0.45)	0.780
PT (seconds)	22.5 (5.4)	22.0 (6.2)	24.3 (7.9)	0.446
PTI (%)	61.08 (15.95)	63.56 (13.42)	58.52 (14.96)	0.503
INR	1.63 (0.39)	1.55 (0.40)	1.71 (0.50)	0.477
aPTT (seconds)	35.83 (5.79)	37.36 (7.93)	42.60 (16.98)	0.097

TLC: total leucocyte count; SGOT: aspartate aminotransferase; SGPT: alanine aminotransferase; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; PTI: prothrombin time index.

TABLE 3. Comparison of outcome among the different treatment and control groups.

Outcomes	TG0	TG2	TG5	*P* value
Re-bleed (N=9)	2 (2.8%)	3 (4.2%)	4 (5.6%)	0.670
Early re-bleed (N=1)	0	0	1 (1.4%)	0.348
Late re-bleed (N=8)	2 (2.8%)	3 (4.2%)	3 (4.2%)	0.888
Mortality (N=15)	6 (8.5%)	4 (5.6%)	5 (7.0%)	0.691
Early mortality (N=2)	0	1 (1.4%)	1 (1.4%)	0.592
Late mortality (N=13)	6 (8.5%)	3 (4.2%)	4 (5.6%)	0.447
Mean units of PRBCs transfusion (N=40)	1.60 (± 1.22)	1.04 (±1.27)	1.00 (±1.38)	0.198
Mean units of FFPs transfusion (N=7)	0.36 (±0.99)	0.24 (±0.83)	0.25 (±0.89)	0.876
Patients with ADR (N=28)	2 (2.7%)	8 (10.8%)	18 (24.3%)	0.00
Diarrhoea (N=25)	2 (2.7%)	7 (9.5%)	16 (21.6%)	0.00
Hypokalemia (N=10)	0	2 (2.7%)	8 (10.8%)	0.002
Bradycardia (N=8)	0	2 (2.7%)	6 (8.1%)	0.016
Abdominal pain (N=7)	1 (1.4%)	3 (4.1%)	3 (4.1%)	0.518
Shock (N=7)	2 (2.7%)	0	5 (6.8%)	0.043
Encephalopathy (N=6)	1 (1.4%)	2 (2.7%)	3 (4.1%)	0.552
Sepsis (N=4)	1 (1.4%)	2 (2.7%)	1 (1.4%)	0.780
Mechanical ventilation (N=3)	0	1 (1.4%)	2 (2.7%)	0.335
Hospital acquired pneumonia (N=1)	0	0	1 (1.4%)	0.348
Duration of hospital stay (days)	2.40 (±0.50)	3.64 (±0.57)	6.63 (±0.65)	0.000
Cost of therapy (INR)	10480 (±3216)	15880 (±2437)	29166 (±4931)	0.000

PRBC: packed red blood cells; FFP: fresh frozen plasma; ADR: Adverse drug reaction; INR: Indian rupee.

Rest of the 8 (10.8%) participants had either Budd Chiari syndrome or extrahepatic portal venous obstruction or grade -3 fatty liver on Ultrasonography.

• Primary outcomes

Out of 74 participants, 71 participants could be followed up for 8 weeks. Three participants (2 in TG0 and 1 in TG5) were lost from follow up after 7 days.

• Re-bleed

Total 9 (12.6%) patients had re-bleed during 8 weeks follow up. Maximum re-bleed occurred in TG5 (5.6%) group followed by TG2 (4.2%) and TG0 (2.8%) groups (TABLE 3). But it was not statistically significant (*P*=0.670). Re-bleed was further divided into early re-bleed (within 7 days) and late re-bleed (after 1 week to 8 weeks). All 74 participants could be followed up for 7 days and early re-bleed occurred in only 1 (1.4%) patient, which was in TG5 group. Rest of 8 (11.3%) patients had late re-bleed, 2.8%, 4.2% and 4.2% in TG0, TG2 and TG5 groups respectively (TABLE 3), which was not statistically significant (*P*=0.888). We found that patients in treatment group (TG2 and TG5 groups) had higher incidence (N=7, 9.9%) of re-bleed as compared to the patients (N=2, 2.8%) in control group (TG0), but statistically insignificant (*P*=0.485). Re-endoscopy was done in six patients out of nine; two in each group. One patient in each group underwent repeat EVL and hemostasis was achieved.

• Mortality

The overall mortality was 21.1% (15 patients) during 8 weeks follow up. Maximum mortality was in TG0 group (8.5%), followed by TG5 (7.0%) and TG2 (5.6%) groups (TABLE 3). But it was not statistically significant (*P*=0.691). All 74 patients could be followed up for 7 days. Early mortality (within 7 days) occurred in 2 (2.7%) patients, one each in TG2 and TG5 groups and none in the control (TG0) group (TABLE 3), but it was not statistically significant (*P*=0.592). Rest of 13 (18.3%) patients had late mortality (after 7 days within 8 weeks), 8.5%, 4.2% and 5.6% in TG0, TG2 and TG5 groups respectively (TABLE 3), which was not statistically significant (*P*=0.447). When comparing the treatment groups (TG2 and TG5) with the control group (TG0), we found that mortality was higher in treatment group (N=9, 12.7%) than control group (N=6, 8.5%) but statistically insignificant (*P*=0.485).

• Cause of death

Most commonly patients died because of CLD related complications 9 (60.0%). Cause of death was re-bleed in 4 (26.7%) patients, hepatic encephalopathy in 3 (20%) patients, refractory shock in 1 (6.7%) patient and re-bleed with aspiration pneumonia in 2 (6.7%) patient. One (6.7%) patient died of traumatic head injury. Cause of death was not clear in 5 (33.3%) patients who died at home. Two patients had in-hospital early mortality due to hepatic encephalopathy (TG2 group) and refractory shock (TG5 group). Both of these patients did not have evidence of re-bleed. One patient under TG5 group had late mortality from in-hospital early re-bleed and subsequent aspiration pneumonia requiring mechanical ventilation.

Secondary outcomes

• Blood component transfusion requirement

Total 40 (54.1%) patients required Blood component transfusion in the form of packed red blood cells (PRBC) and fresh frozen plasma (FFP). FFP was transfused in 7 (9.5%) patients who also required PRBC and 33 (44.6%) patients required only PRBC transfusion. Mean number of PRBC and FFP units transfusion (TABLE 3) were not significantly different between the study groups (*P*=0.198). None of the patients required platelets transfusion.

• Adverse drug reaction

Out of 74 patients, ADR was noted in 28 (37.5%) patients. Most commonly in TG5 group (24.3%), followed by TG2 (10.8%) and TG0 (2.7%) study groups (TABLE 3). ADRs were significantly higher in treatment group than control group (*P*=0.000). Most Common ADR was diarrhea, followed by hypokalemia and bradycardia and 15 patients reported two or more ADR. ADR was significantly higher in treatment groups than control group (TABLE 3).

• In-hospital complications

Most common in-hospital complication was shock (seven patients), followed by encephalopathy (six patients) and sepsis (four patients). Total three patients required mechanical ventilation and one patient developed hospital acquired pneumonia (TABLE 3). Though the incidence of in-hospital complication was higher in TG5 group but it was statistically significant only for shock (*P*=0.043).

• Duration of hospital stay

Mean duration of hospital stay for all patients was 4.19 (±1.86) days. Mean duration of hospital stay was 2.40±0.50 days, 3.64±0.57 days and 6.63±0.65 days in TG0, TG2 and TG5 groups respectively (TABLE 3). Duration of hospital stay was significantly prolonged as the number of days of terlipressin therapy was increased (*P*=0.000).

• Cost of therapy

Mean cost of therapy for the study participants was INR 18364.86 (±8647.70) which was INR 10480 (±3216), INR 15880 (±2437) and INR 29166 (±4931) in TG0, TG2 and TG5 group respectively (TABLE 3). As the duration of hospital stay and duration of terlipressin therapy was increased, cost of therapy also significantly increased (*P*=0.000).

DISCUSSION

Acute VH is a medical emergency and mostly secondary to CLD leading to cirrhosis and portal hypertension. Mortality from VH varies from 20–80%, depending upon whether the patients present with isolated event of VH or with ascites or encephalopathy[6]. The immediate goal of therapy is to control bleeding, prevent early recurrence and prevent 6-week mortality[7]. Prompt EVL is therapeutic as well as diagnostic. Before EVL, the initial priority is to assess airway, breathing and maintain circulatory volume with crystalloids for hemodynamic stability. Blood transfusion is indicated to target Hb of ≥7 g/dL[8]. Endoscopy is done as soon as possible, preferably within 24 hours of the presentation. During endoscopy when variceal origin of bleeding is confirmed, EVL should be done promptly. But re-bleed is not unusual and it may be as high as 30–40% of cases[9]. In case of re-bleed another attempt of endoscopic hemostasis is tried. In refractory bleeding definite treatments with transjugular intrahepatic portosystemic shunt is

under taken. Terlipressin along with proton pump inhibitor and antibiotic have been widely used as adjuvant pharmacotherapy in acute VH. Terlipressin is a vasopressin analog. Its pharmacological effect is mediated through stimulation of vasopressin-1 receptors of vascular smooth muscle, causing vasoconstriction of splanchnic circulation leading to decrease in portal flow and hepatic venous pressure gradient[2]. As per guideline terlipressin (2 mg IV q 4 hourly) is promptly used in any suspicious case of VH before endoscopic procedure and continued (1 mg IV q 4 hourly) for 2–5 days after EVL to prevent re-bleed and mortality[1]. But the prolong use of terlipressin is not completely safe. It increases in-hospital care burden and expenses in resource constraint setting like India. Terlipressin is also known to be associated with some life threatening cardiovascular, ischemic, pulmonary and electrolytes imbalance like complication[2-4]. So the benefit of continuing terlipressin for 5 days after EVL is debatable, as haemostasis is primarily achieved by EVL. The present pilot study was a prospective, open label randomized controlled clinical trial. Primary end point of this study was to evaluate re-bleed and mortality benefit of terlipressin therapy after successful EVL in acute VH.

Re-bleed

In 1989, Freeman et al. found that 60% of VH were controlled with terlipressin compared to 37% with placebo[10]. Re-bleed was also more common in the placebo group and 5 days bleeding remained under control in 54% of patients with terlipressin therapy compared to 19% with placebo (P<0.025). Blood transfusion requirement was similar in the two groups. However, the sample size was 29 patients only. In 1990, Sodurlund et al. concluded that 90.3% of VH was controlled with terlipressin therapy for duration of 24 hours to 36 hours as compared to 58.6% with placebo[11]. Blood transfusion requirement was also fewer in terlipressin group. But unlike our study both of these studies did not consider EVL and use of terlipressin after EVL. Y Peng et al. in 2013, compared efficacy of EVL combined with 1 mg/day of terlipressin for 5 days and EVL combined with 10 mg/day of oral propranolol for 5 days[12]. Early (5-day) re-bleeding was significantly lower in EVL plus terlipressin group than in EVL plus propranolol group (2.1% vs 12.5%). There was no significant difference in 3-month re-bleeding rate between two groups (4.2% vs 14.6%). As compared to Y Peng et al. the dose of terlipressin used in our study was significantly higher. As per guidelines, terlipressin is continued for 2-5 days after EVL at a dose of 1 mg every 4 hours[1]. Presently there is no clinical trial available to define the duration & rational of terlipressin therapy after EVL. In our study, we compared the different duration of terlipressin therapy after successful EVL. There was no significant differences in the re-bleed rate (TABLE 3) in different groups in our study (P>0.05). In our study, re-bleed occurred in 9 (12.6%) patients. Only one patient had early re-bleed, which was in TG5 group, received terlipressin for 5 days. Overall 7 (9.9%) patients in treatment group (TG2 & TG5) had re-bleed as compared to 2 (2.8%) patients in control group (TG0). So re-bleed was more in patients who received terlipressin for longer duration after EVL, though the data was not statistically significant (P=0.485). Since all the patients underwent EVL within 24 hours of their arrival, early re-bleeding was less in our study compared to the above studies. Since hemostasis could be achieved with EVL, use of terlipressin after EVL to prevent re-bleed was not beneficial in our study. According to our study, using terlipressin after EVL did not offer advantage in terms of controlling re-bleed.

Mortality

Mortality from VH varies from 20–80%[6]. In 1992, Arcidiacono et al. found that re-bleed was significantly higher in sclerotherapy alone group than sclerotherapy plus terlipressin group (29.5% vs 12.7%) though the mortality rate was similar (10.5% vs 9.8%) in both the groups[13]. But in this study none of the patient underwent EVL. In our study, overall mortality was 21.1% (15 patients) and two patients had early mortality; one each from TG2 & TG5 groups. None of the patients in control group had early mortality. In present study there was no significant differences in the early or late mortality (TABLE 3) in different study groups (P>0.05). As per present study overall mortality was higher in treatment group (N=9, 12.7%) than control group (N=6, 8.5%) but statistically insignificant (P=0.485). As in other studies, most common cause of death in present study was also CLD related complications, like re-bleed and hepatic encephalopathy, followed by shock and aspiration pneumonia. At present there is no other major clinical trial available regarding mortality benefit of terlipressin therapy after EVL. As per present study continuing terlipressin after EVL did not yield any mortality benefits. Smoking, alcohol, presence of ascites, jaundice and coagulopathy were associated with increased risk of re-bleed and mortality as per our study (supplementary file).

Blood component transfusion

As per Freeman et al., PRBC transfusion requirement was similar in both terlipressin and placebo groups[10], whereas Soderlund et al. found that PRBC transfusion requirement was more in placebo group than in terlipressin group[11]. In present study mean number of PRBC (P=0.198) and FFP (P=0.876) units transfusion were not significantly different between the study groups (TABLE 3). According to present study, terlipressin therapy after EVL did not show any major benefit for the need for PRBC or FFP transfusion.

Adverse drug reactions and in-hospital complications

Sodurlund et al. noted gastrointestinal cramps, diarrhea, bradycardia and ECG changes, hypertension as common ADR associated with terlipressin therapy[11]. Similar side effects were also noted by Arcidiacono et al.[13]. Similar ADR was noted in the present study. Most common was diarrhea, followed by hypokalemia, bradycardia and non-specific abdominal pain (TABLE 3). There were some reports of terlipressin associated ischemic complication of peripheral as well as internal organ including heart[1,3,4]. None of the participants in our study complained of chest pain and features suggestive of ischemic heart disease, as well as peripheral ischemia. Most of the ADR was common in TG5 group as compared to TG2 and control group (P=0.000). So, our study showed using terlipressin for longer duration may result in number of ADR. These ADR were mainly minor, self-limiting and subsided, requiring close observation. Similarly, in-hospital complications such as need of mechanical ventilation, sepsis, encephalopathy, shock were more in the patients admitted for longer duration and received terlipressin therapy after EVL, though the data was statistically not significant.

Recently published meta-analysis with systematic review concluded that terlipressin along with EVL was effective in bleeding control and preventing in-hospital mortality in acute VH but terlipressin alone was not effective therapy for acute VH[14]. Same study also showed that terlipressin was not completely safe and free of complications[14]. So EVL is the definitive form of therapy to achieve primary hemostasis and terlipressin is bridging the interval before the definitive therapy with EVL is done. At present there is no

clinical trial available to prove the efficacy of continuing terlipressin after EVL in acute VH to prevent re-bleed or mortality. As per index study continuation of terlipressin after achieving haemostasis with EVL was not beneficial for preventing re-bleed, mortality and need for blood product transfusion, in fact it increased the risk of ADR, duration of hospital stay, in-hospital complications and cost of the therapy. Continuing terlipressin even after achieving hemostasis with EVL also prevents early discharge and increases health care burden for the already congested emergency facilities, like our institute. Further randomized double blind study with larger sample size is required to verify the efficacy of the continuing terlipressin after EVL in acute VH.

Limitations of the study were first, it was an open label study. We could not do blinded study because as per guidelines, in acute VH terlipressin is recommended to be continued after EVL for 2 to 5 days. So, we did not get ethical clearance for blinded study because of risk of re-bleed involved in the study participants. This study, which to our knowledge is the only clinical trial tried to evaluate the rational of continuing Trelipressin after EVL in acute VH. Secondly the sample size was small because of strict exclusion criteria. PGIMER, being tertiary care centre, caters many patients referred from multiple northern states of India and arrival in the institute for definitive therapy may take several hours. Acute VH is medical emergency and any delay in intervention may influence the outcome of the patients. So we excluded all the patients with recurrent bleed and bleeding for more than 24 hours to prevent bias and maintain uniformity in the study groups.

We conclude that in acute VH, terlipressin should be used as a bridging therapy before definite EVL is done to achieve haemostasis. Rational for continuing terlipressin after EVL in acute VH is doubtful as it did not have any benefit for prevention of re-bleed or mortality, rather it increased the risk of ADR, duration of hospital stay, in-hospital complications and cost of the therapy. However, further randomized control studies with larger sample size are recommended to establish and verify the rational of continuing terlipressin after EVL to prevent re-bleed or mortality in acute VH.

Authors' contribution

Poudel RC: plan execution, data analysis, protocol, and manuscript writing. Dhibar DP: concept, design, data analysis, protocol and manuscript writing. Sharma N: patient management and guidance. Sharma V: patient management, endoscopic intervention. Taneja S: patient management, endoscopic intervention. Prakash A: randomization, statistical analysis, ADR monitoring. Each author has contributed significantly to the submitted work.

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SUPPLEMENTAL

TABLE 4. Risk factors for re-bleed & mortality.

Risk factors	Re-bleed (N=9)	Risk factors	Mortality (N=15)
Male (N=8) vs female (N=1)	OR–1.597 95%CI 0.233–10.936	Male (N=14) vs female (N=1)	OR–2.847 95%CI 0.413–19.647
Alcoholic (N=7) vs non-alcoholic (N=2)	OR–1.234 95%CI 0.340–4.472	Alcoholic (N=13) vs non-alcoholic (N=2)	OR–2.277 95%CI 0.590–8.781
Smoker (N=3) vs non-smoker (N=6)	OR–1.234 95%CI 0.766–1.986	Smoker (N=5) vs non-smoker (N=10)	OR–1.259 95%CI 0.865–1.883
Hb ≤7 gm/dL (N=4) vs Hb >7 gm/dL (N=5)	OR–0.722 95%CI 0.213–2.453	Hb ≤7 gm/dL (N=8) vs Hb >7 gm/dL (N=7)	OR–1.454 95%CI 0.822–2.572
With TCP (N=5) vs without TCP (N=4)	OR–0.871 95%CI 0.320–2.374	With TCP (N=7) vs without TCP (N=8)	OR–0.853 95%CI 0.652–1.116
With CP (N=7) vs without CP (N=2)	OR–2.323 95%CI 0.668–8.073	With CP (N=12) vs without CP (N=3)	OR–2.768 95%CI 0.979–7.824
With jaundice (N=8) vs without jaundice (N=1)	OR–4.645 95%CI 0.721–29.945	With jaundice (N=11) vs without jaundice (N=4)	OR–1.942 95%CI 0.808–4.665
With ascites (N=5) vs without ascites (N=4)	OR–1.379 95%CI 0.647–2.939	With ascites (N=11) vs without ascites (N=4)	OR–2.545 95%CI 1.079–6.003

OR: odd ratio, CI: confidence interval, TCP: thrombocytopenia, CP: coagulopathy, Hb: haemoglobin.

Risk factors for re-bleed & mortality

In our study re-bleed (OR–1.597, 95%CI 0.233–10.936) and mortality (OR–2.847, 95%CI 0.413–19.647) were more common in males than in females. This may be due to the fact that most of the patients were male who were alcoholic with CLD. Similarly smoker (OR–1.234, 95%CI 0.766–1.986), alcoholic (OR–1.234, 95%CI 0.340–4.472), patient with jaundice (OR–4.645, 95%CI 0.721–29.945), ascites (OR–1.379, 95%CI 0.647–2.939) and coagulopathy (OR–2.323, 95%CI 0.668–8.073) had increased risk for re-bleed and mortality as compared to non-smoker (OR–1.259, 95%CI 0.865–1.883), non-alcoholic (OR–2.277, 95%CI 0.590–8.781),

patients without jaundice (OR–1.942, 95%CI 0.808–4.665), ascites (OR–2.545, 95%CI 1.079–6.003) and coagulopathy (OR–2.768, 95%CI 0.979–7.824) respectively. In our study patient with significant anemia (Hb ≤7 gm/dL) had increased risk of death within 8 weeks (OR–1.454, 95%CI 0.822–2.572) but there was no relation with re-bleed (OR–0.722, 95%CI 0.213–2.453) as compared to the patients with Hb >7 gm/dL. In our study there were no relation of re-bleed (OR–0.871 95%CI 0.320–2.374) and mortality (OR–0.853, 95%CI 0.652–1.116) with thrombocytopenia as compared to the patients without thrombocytopenia.

Poudel RC, Dhibar DP, Sharma N, Sharma V, Taneja S, Prakash A. O uso contínuo da terlipressina após a ligadura endoscópica em hemorragia varicosa aguda necessita de mais evidências: um estudo piloto. Arq Gastroenterol. 2022;59(1):89-96.

RESUMO – **Contexto** – A hemorragia varicosa (HV) é emergência médica. A ligadura endoscópica imediata das varizes (LEV) é terapêutica. A terlipressina é usada em HV e contínua por 2–5 dias mesmo após a LEV. Como a hemostasia é alcançada principalmente pela LEV, o benefício do uso contínuo da terlipressina após o evento é desconhecido. **Objetivo** – Avaliar a eficácia da terlipressina contínua após a LEV para evitar o ressangramento e a mortalidade. **Métodos** – Neste estudo piloto, após a LEV, 74 pacientes com HV foram randomizados em dois grupos de tratamento TG2 & TG5, que receberam terlipressina (1 mg EV em bolus a cada 4 horas) durante 2–5 dias, respectivamente, e um grupo controle (TG0), que receberam soro fisiológico normal de 0,9% (10 mL EV em bolus a cada 4 horas) e foram seguidos por 8 semanas. **Resultados** – Um total de 9 (12,6%) pacientes tiveram ressangramento, 4 (5,6%) no grupo TG5, seguidos por 3 (4,2%) no TG2 e 2 (2,8%) no grupo TG0 (*P*=0,670). A mortalidade geral de pacientes foi de 15 (21,1%), 6 (8,5%) no grupo TG0, seguidos por 5 (7,0%) no TG5 e 4 (5,6%) no TG2 (*P*=0,691). As reações adversas de medicamentos foram significativamente maiores em grupos de tratamento em 18 (24,32%) pacientes no TG5, seguidos por 8 (10,8%) no TG2 e 2 (2,7%) em grupo TG0 (*P*=0,00). A duração da internação hospitalar também foi significativamente maior no grupo de tratamento, 6,63 (±0,65) dias no TG5, seguido por 3,64 (±0,57) em TG2 e 2,40 (±0,50) dias em grupos TG0 (*P*=0,00). **Conclusão** – O uso racional para a continuação da terlipressina após a LEV é duvidoso, pois não teve qualquer benefício para a prevenção de ressangramento ou mortalidade; pelo contrário, aumentou o risco de efeitos adversos e duração da internação hospitalar. Outros ensaios clínicos randomizados são necessários para gerar mais evidências em apoio ou contra a terlipressina contínua após a LEV.

Palavras-chave – Terlipressina; hemorragia varicosa; ligadura endoscópica de varizes; ressangramento; mortalidade; reação adversa a medicamentos; hipertensão portal; doença hepática crônica; cirrose; sangramento gastrointestinal.

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ORIGINAL ARTICLE

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Functional abdominal pain is the main etiology among children referred to tertiary care level for chronic abdominal pain

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ABSTRACT – **Background** – Chronic abdominal pain (CAP) carries a significant burden of disease. The last edition of the Rome Criteria (Rome IV) allows the diagnosis of functional gastrointestinal disorders (FGIDs) according to symptoms-based criteria; however, patients continue to experience a delay in their diagnosis and to be submitted to different interventions before the establishment of a positive diagnosis. **Objective** – We aimed to characterize etiology, clinical features, and interventions in a pediatric cohort of patients with CAP secondary to FGIDs, who were referred to our tertiary care university-affiliated hospital, in Brazil. **Methods** – A retrospective descriptive study of children and adolescents (aged 20 years and younger) referred to our institution, from January/2013 to December/2018, for CAP, and who fulfilled criteria for FGIDs classified according to Rome IV criteria. **Results** – Three hundred twenty-eight patients with CAP were screened, of which 67.9% (223 patients) fulfilled the criteria for FGIDs and were included in the study. Sixty percent were female, with a mean age of 8.3 years. At the time of referral, the mean duration of symptoms was 2.8 years. Length/height for age and weight for age mean z-scores were -0.08±1.87 and -0.38±1.62, respectively. Functional abdominal pain not otherwise specified was overall the most common diagnosis (70.4%). Before establishing the diagnosis of FGIDs, multiple pharmacological interventions were described, while after, the mainstay of therapy was education/reassurance and dietary interventions. Thirty-two percent of patients did not further require specialized follow-up. **Conclusion** – Even at the tertiary care level, FGIDs were still the most common etiology of chronic abdominal pain, particularly functional abdominal pain not otherwise specified. Despite the relatively long duration of symptoms at referral, cessation of specialized care follow-up was possible in approximately a third of the cases.

Keywords – Children; adolescents; abdominal pain; functional disorders; Rome IV.

INTRODUCTION

Chronic abdominal pain (CAP) in childhood constitutes a significant time-consuming clinical problem for healthcare practitioners, and it carries an important psychosocial burden for patients and their families[1]. Among school-age children, the prevalence of CAP reported ranges widely from 10 to 45%[2-6], and it is estimated that CAP accounts for up to 5% of pediatric primary care visits[7]. It is estimated that around 90% of children with chronic abdominal pain do not have an organic cause for their abdominal pain, and even though the diagnosis of functional etiology could be established in children without any alarm symptoms or "red flags", still at least one-quarter of these children undergo diagnostic testing[8].

Functional gastrointestinal disorders (FGIDs) are diagnosed following well-established clinical principles summarized in the Rome Criteria for childhood functional gastrointestinal disorders, last updated in 2016[9,10]. The most substantial contribution of Rome IV was to present evidence and systematization of clinical criteria to support a "symptom-based diagnosis", which led to the end of an era in which the diagnosis of functional disorders had to be preceded by the exclusion of organic diseases'.

Despite the relatively benign nature of the symptoms in FGIDs and the growing evidence that supports taking away the focus on testing, in many instances patients still undergo extensive testing, receive treatments that are not supported by an evidence-based approach, and/or are referred for specialist (further) evaluation and follow up. In that context, we aimed to describe the demographics, etiology, and interventions in a pediatric cohort of patients with CAP secondary to FGIDs, referred to a tertiary care university-affiliated hospital, in Brazil.

METHODS

A descriptive retrospective cohort study of children and adolescents referred to tertiary care for CAP from January/2013 to December/2018. Patients were identified from their ambulatory visits to the divisions of General Pediatrics and/or Pediatric Gastroenterology, in the Department of Pediatrics at *Faculdade de Ciências Médicas*, *Universidade Estadual de Campinas* (UNICAMP), Campinas, SP, Brazil.

Inclusion criteria were as follows: 1) children and adolescents younger than 20 years of age, 2) reason for referral having CAP

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as the main complaint, 3) diagnosis of FGIDs following Rome IV criteria definitions for childhood FGIDs[9,10], 4) absence of chronic diseases or the use of medications that could cause abdominal pain. Patients were excluded from the analysis if on follow-up there were diagnosed with any condition known to cause abdominal pain, for example, with lactose intolerance.

Data collected included gender, age, anthropometrics, clinical presentation, classification of FGIDs according to Rome IV criteria, interventions, and resolution of symptoms with discontinuation of follow-up in the tertiary care setting. Among the interventions, we collected data on additional tests used to investigate organic causes, as well as dietary changes, the use of medication and non-pharmacological measures to treat functional abdominal pain. Data were summarized with descriptive statistics.

This study was approved by our Institutional Research Ethics Board.

RESULTS

During the study period, 328 patients with CAP were referred to our center, of which 223 patients (67.9%) fulfilled the criteria for FGIDs as per Rome IV criteria definitions[9,10]. The majority of patients were female (60%), with a mean age of 8.3 years (between 2 months and 20 years old). At the time of initial evaluation in our institution, the mean duration of symptoms was 2.8 years. Length/height for age and weight for age mean z-scores were -0.08±1.87 and -0.38±1.62, respectively.

Among the FGIDs, functional abdominal pain not otherwise specified was by far the most common diagnosis, in 70.4% of cases, followed by functional constipation – 13.9%, and functional dyspepsia – 9.4%. The Rome IV diagnostic classification of all patients who fulfilled the criteria for FGIDs is summarized in TABLE 1.

TABLE 1. Rome IV diagnostic classification of 223 patients with functional gastrointestinal disorders referred to tertiary care for chronic abdominal pain.

Functional gastrointestinal disorder	Overall number (n=223)	Percentage (%)
Functional abdominal pain not otherwise specified	157	70.4%
Functional constipation	31	13.9%
Functional dyspepsia	21	9.4%
Abdominal migraine	10	4.5%
Functional diarrhea	6	2.7%
Irritable bowel syndrome	5	2.2%
Cyclic vomiting syndrome	2	0.9%
Rumination syndrome	1	0.4%
Infant colic	1	0.4%

All the 328 patients with CAP underwent additional tests to investigate organic causes. The most frequent were abdominal ultrasound in 48% of cases, complete blood count – 43%, urinalysis – 35%, upper digestive endoscopy – 35%, serum amylase – 25%, stool for ova and parasite – 25%, and abdominal radiography – 9%.

Before establishing the diagnosis of FGIDs, many treatments had been trialed, including: antiparasitic drugs, proton pump inhibitors (PPIs), and histamine H2-receptor antagonists (before ranitidine products were withdrawn from the market in Brazil) were the most common therapies used, in 18.2%, 26% and 19.2% of cases, respectively. Less commonly, the use of prokinetic agents (such as domperidone) – in 12.5%; analgesics (acetaminophen and dipyrone) – in 4.9%, and, other interventions, including *H. pylori* eradication treatments and dietary interventions – in 4.9% were also described. The relative frequency of all the main treatment modalities trialed in children with FGIDs before establishing the diagnosis of a functional disorder is presented in FIGURE 1.A.

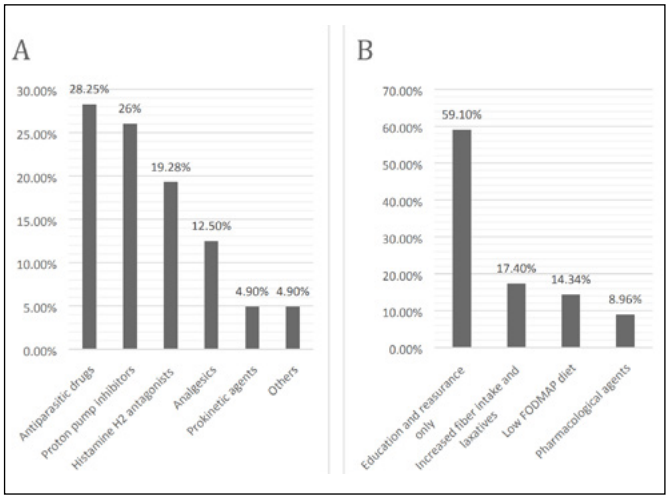

FIGURE 1. Relative frequency of the main interventions prior to establishing the diagnosis (A) of functional abdominal pain vs. interventions later established at tertiary care (B).
FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Meanwhile, interventions established at the tertiary care level once the diagnosis of FGIDs was established mainly focused on patient/parental education and reassurance – in all cases and reported as the only therapeutic intervention in 59.1% of cases. In selected cases, other dietary and pharmacological interventions were used, such as increased fiber intake and laxatives – in 17.4%; low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet – in 14.3%; and the use of other pharmacological agents targeting FGIDs – in 8.9%. The relative frequency of interventions established at tertiary care, after diagnosis of FGIDs is presented in FIGURE 1.B. Adjustments of dietary fiber intake and laxatives (polyethylene glycol, lactulose, and magnesium hydroxide) were reserved for cases of functional constipation; while a low FODMAP diet or reduction in the consumption of FODMAPs was recommended for selected cases in which clinical history was suggestive that the ingestion of these carbohydrates triggered the abdominal pain. Pharmacological treatment targeting FGIDs was highly individualized and included: amitriptyline, flunarizine, and cyproheptadine. Almost a third of patients (32.7%) had complete resolution of their symptoms and did not require further follow-up for this complaint.

DISCUSSION

It is well known that the overwhelming majority of children with chronic abdominal pain has no underlying organic disease – 90 to 95%[8,11]. However, it would be intuitive to expect a lower percentage among patients whose symptoms' severity, duration

and/or burden had led to a referral to tertiary specialized care. Indeed, in our study, we found that amidst 328 patients with CAP referred to a tertiary care university-affiliated hospital in Brazil, approximately 68% of patients fulfilled Rome IV criteria for FGIDs. Female predominance (60%) and the mean age of 8.3 years were compatible with previous literature reports recently summarized in a systematic review of the literature[6]. On initial assessment at specialized care, nutritional status – inferred grossly from length/height for age and weight for age z-scores – was overall normal, despite the relatively prolonged duration of symptoms (mean duration at referral of 2.8 years), as it would be expected given the benign nature of FGIDs[11]. And even though the current knowledge on FGIDs support a "symptom-based diagnosis" – well-characterized on Rome IV[9,10], we report some investigation to exclude organic causes were performed in all cases. We hypothesize that this finding could be explained by the long duration of symptoms and also a referral bias of a tertiary center.

As the majority of the studies so far have focused on epidemiology and clinical features of the general pediatric population with FGIDs, little is known about those patients who are not retained at the primary care setting and are referred to specialized care. Our study focuses on this specific setting at a tertiary care university-affiliated hospital in Brazil. By far, the most commonly observed diagnosis was functional abdominal pain not otherwise specified. Interestingly, even though the reason for referral was CAP, functional constipation not previously identified was found in 13.9% of cases. These findings differed from those previously published in a Colombian cross-sectional study, also on FGIDs diagnosed based on Rome IV criteria, which reported that functional dyspepsia and irritable bowel syndrome (IBS) were more frequent than FAP-NOS and functional constipation[12]. We hypothesize these differences are likely explained by the fact that their cohort reflected a broad pediatric population, while our study population is narrower – i.e. patients referred to tertiary care level. Our study found a relatively low prevalence of IBS (five patients – 2.2%), compared to other pediatric publications[13] – we hypothesize that this finding relates to the fact that IBS is diagnosed in older children, while our population patients had a mean age of 8.3 years. Regarding constipation, since the mean duration of symptoms before referral was 2.8 years, it is arguable whether or not it was the initial presentation or whether it developed later reflecting maladaptive behavioral responses or dietary changes. Regardless, it is important to remember that the burden of constipation is often underestimated[14], and it should be considered in the differential diagnosis even if the main complaint is abdominal pain. Functional constipation was recently reported among the most common FGIDs, especially in infants and toddlers[15]. Finally, another intriguing finding was that some of the diagnosis found (summarized in TABLE 1) were not FGIDs in which abdominal pain is typically an associated symptom but not a main complaint, such as functional diarrhea, cyclic vomiting syndrome and rumination syndrome.

Multiple mechanisms have been proposed and studied among the different disorders that fall under the umbrella of FGIDs. To this date, no single mechanism can explain its pathogenesis – and it is unlikely that we will ever find an isolated explanation: these disorders are heterogeneous, and seem to result from a complex interaction between genetics and environmental factors, such as gastrointestinal infections and inflammation, visceral hypersensitivity, psychological stressors, abnormal intestinal motility, among others[16]. The understanding of these specific pathophysiologic mechanisms is an evolving area: while earlier studies focused on alterations in motility and visceral hypersensitivity, more recently the focus has changed to the underlying role of the intestinal microbiota and host immune responses, the bidirectional communication between the central and the enteric nervous systems and genetic factors[17,18].

Our current knowledge does not allow the precise indication of specific interventions to target-directed mechanisms when treating FGIDs. It is, however, well documented that some of the commonly used pharmacological interventions used in this context have minimal or no effect[19-21], and therefore, should not be routinely recommended. Some of these therapies, such as PPIs, ranitidine, domperidone and others, were often used in our cohort of patients before to establishing the diagnosis of FGID. Specifically, regarding *H. pylori* eradication, the joint North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN, respectively) guidelines recently published categorically affirmed that studies in children do not support a role for *H. pylori* infection in functional disorders, and strongly recommended against diagnostic testing for *H pylori* infection in children with functional abdominal pain, based on high-quality evidence[22].

On a different note and as a reality which is more specific to resource-limited countries, the use of antiparasitic drugs was very common in our cohort – even though such practice should be directed only to cases when the cause of abdominal symptoms is proven to be related to a parasitic infection[23], hence not to treat FGIDs.

With a well-established diagnosis of FGID and under specialized care, less than 10% of patients in our study received any pharmacological treatment – amitriptyline, cyproheptadine and flunarizine were used in selected patients. The evidence for the use of those drugs remains controversial – for example, there is data supporting the use of low-dose amitriptyline to treat functional gastrointestinal disorders[24], while other studies have shown results similar to placebo[20,25,26].

General principles for the management of functional gastrointestinal disorders must include first and foremost the establishment of a "positive diagnosis" (i.e. not based on the need to exclude other gastrointestinal conditions), reassurance of patients and families, with education on the benign nature of the diagnosis, appropriate adjustment of expectations, and acknowledgment of the symptoms and their impact in the quality of life; beyond that, lifestyle, dietary, pharmacological and non-pharmacological interventions should be established in an individualized basis[17,27]. Failing to provide or delaying the diagnosis, following the "traditional diagnostic approach" of ruling out a series of other conditions leads to inappropriate tests and treatments, and adds to parental concerns and frustration, increasing the burden of the disease and health care costs.

Among the non-pharmacological interventions, cognitive behavioral therapy (CBT) is the most studied. It has been demonstrated that CBT is effective to address dysfunctional emotions, maladaptive behaviors, and cognitive processes in FGIDs[16,28]. Unfortunately, at our center, as most centers in the Public Health System in Brazil, we cannot offer CBT – the reason why this modality of treatment was not reported in our study.

A healthy lifestyle and diet are always recommended as part of a "well-child" visit and these recommendations deserve special attention in the evaluation of children with FGIDs, as often pitfalls

and triggers can be identified. Despite the recognition of the role of diet in the treatment of childhood FGIDs, a recent study reported that most patients do not receive dietary recommendations, and that there is great variability in the guidance provided when these recommendations are given[29]. The most common dietary interventions are high-fiber diet or dietary fiber supplementation and low-FODMAP diet[20,29,30]. However, the overall data on fiber supplementation is functional abdominal pain disorders is inconclusive. Recently, special attention has been devoted to low FODMAPs diet as a strategy to treat FGIDs: it is hypothesized that these poorly absorbed short-chain carbohydrates may trigger gastrointestinal symptoms in patients with visceral hypersensitivity, as they exert osmotic effects in the intestinal lumen, and are rapidly fermented by bacteria[31]. In our cohort, all patients had an assessment of their diet and were provided some general guidance/education on their diet, but fiber supplementation or low-FODMAP diet were recommended on an individualized basis, in 17.4% and 14.3% of cases, respectively.

Our study limitations include the well-known weaknesses of retrospective and single-center studies. Given the retrospective nature, we have to recognize that documentation, especially of non-pharmacological interventions and education may be underestimated. Furthermore, our study reflects the practice of a single pediatric healthcare tertiary institution, and therefore, our findings should be confirmed in additional similar healthcare settings. However, the strengths of this study include our relatively large sample size, and the novelty of focusing on a population of patients different than the typically described in studies on childhood chronic abdominal pain or FGIDs, since all the patients had previously been evaluated in the primary healthcare setting.

In conclusion, functional gastrointestinal disorders still represented the majority of the cases of chronic abdominal pain referred to tertiary care, particularly functional abdominal pain not otherwise specified – this is an intriguing finding, which can be perhaps explained by the fact it is probably easier to give a positive diagnosis of a "well-defined" functional abdominal pain disorder (such as functional dyspepsia or irritable bowel syndrome) rather than a less specific one. Despite the relatively long duration of symptoms at referral, cessation of specialized care follow-up was possible in approximately a third of the cases.

Authors' contribution

Martins GP and Bellomo-Brandão MA: conceptualized the manuscript and obtained REB approval. Martins GP: collected the data and drafted the initial manuscript. Sandy NS and Alvarenga LR: supported data curation, production of the manuscript, and revision of the manuscript. Lomazi EA and Bellomo-Brandão MA: supported supervision of all stages, reviewed and edited the manuscript. All authors approved the final version as submitted.

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Martins GP, Sandy NS, Alvarenga LR, Lomazi EA, Bellomo-Brandão MA. Dor abdominal funcional é a principal etiologia em crianças encaminhadas ao nível de atenção terciária por dor abdominal crônica. Arq Gastroenterol. 2022;59(1):97-101.

RESUMO – Contexto – A dor abdominal crônica (DAC) pode acarretar importante morbidade. A última edição dos Critérios de Roma (Roma IV) permite o diagnóstico de distúrbios gastrointestinais funcionais (DGIFs) de acordo com critérios baseados em sintomas; no entanto, esses pacientes continuam a apresentar atraso no diagnóstico e a serem submetidos a diferentes intervenções antes do estabelecimento de um diagnóstico. **Objetivo** – Caracterizar a etiologia, características clínicas e intervenções de crianças com DAC que não são mantidas na atenção primária e que foram encaminhadas ao nosso hospital universitário de nível terciário, no Brasil. **Métodos** – Estudo retrospectivo descritivo de crianças e adolescentes (com idade igual ou inferior a 20 anos) encaminhados a nossa instituição, entre janeiro/2013 e dezembro/2018, por DAC e que preenchiam os critérios para DGIFs conforme o consenso de Roma IV. **Resultados** – Trezentos e vinte e oito pacientes com DAC foram triados, 67,9% (223 pacientes) preencheram os critérios para DGIFs e foram analisados. Sessenta por cento do sexo feminino, com idade média de 8,3 anos. A duração média dos sintomas no encaminhamento era de 2,8 anos. Os escores z médios de estatura para idade e peso para idade foram -0,08±1,87 e -0,38±1,62, respectivamente. Dor abdominal funcional sem outra especificação foi o diagnóstico mais comum (70,4%). Antes do diagnóstico de DGIFs, múltiplas intervenções farmacológicas foram descritas, enquanto depois, a base da terapia foi a educação, passar segurança à família e intervenções dietéticas. Trinta e dois por cento dos pacientes apresentaram resolução dos sintomas e receberam alta do acompanhamento especializado. **Conclusão** – Mesmo no nível terciário, as desordens gastrointestinais funcionais ainda constituem a etiologia mais comum da DAC, particularmente a dor abdominal funcional não especificada. Apesar da duração longa dos sintomas, alta do serviço especializados foi possível em aproximadamente um terço dos casos.

Palavras-chave – Crianças; adolescentes; dor abdominal; distúrbios funcionais; Roma IV.

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ORIGINAL ARTICLE

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Analysis of healthcare associated and hospital acquired infections in critically ill patients with cirrhosis

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ABSTRACT – Background – Bacterial infections occur in 43–59% of cirrhotic patients admitted to the intensive care unit with impact in morbidity and mortality. An increase in the frequency of multidrug-resistant (MDRO) and extensively drug-resistant (XDRO) organisms has been described in bacterial infections in cirrhotic patients with an adverse impact on survival. **Objective –** To characterize community-acquired (CA), healthcare-associated (HCA), and hospital-acquired (HA) infections in cirrhotic patients and their impact in the occurrence of adverse outcomes. **Methods –** This study included all cirrhotic patients admitted in an intensive care unit specialized in liver and gastrointestinal diseases in Brazil between January 2012 and June 2018. Frequency and topography of infections were retrospectively evaluated, as well as the frequency of MDRO and XDRO organisms, and their impact in occurrence of acute kidney injury, hepatorenal syndrome, acute-on-chronic liver failure, sepsis and mortality. **Results –** A total of 374 infections were observed and classified as CA (22%), HCA (34%) and hospital-acquired (44%). Eighty-nine (54%) episodes of hospital-acquired infections were second infections. Spontaneous bacterial peritonitis (32%) and urinary tract infection (23%) were the most common infections. Culture-proven infections were positive in 61% of the cases, mainly gram-negative bacteria (73%). Acute kidney injury, hepatorenal syndrome and sepsis were observed, respectively, in 48%, 15% and 53% of the cases. MDRO and XDRO were seen, respectively, in 35% and 16%, mainly in HCA (48% vs 26% in CA infections, P=0.02) and hospital-acquired (58% vs 26% in CA infections, P=0.0009). Adverse outcomes were more frequently observed in subjects with hospital-acquired infections when compared to HCA and CA infections. Hospital-acquired, HCA and second infections were independently associated with in-hospital mortality. **Conclusion –** Hospital-acquired, HCA and second infections are increasingly associated with either MDRO and/or XDRO and are independent predictors of in-hospital mortality. Their recognition and proper selection of appropriate empiric antibiotic regimens are important measures to reduce in-hospital mortality.

Keywords – Liver cirrhosis; bacterial infections; morbidity; mortality; intensive care unit.

INTRODUCTION

Bacterial infections occur in 43% to 59% of critically ill patients with cirrhosis[1,2] either with acute decompensation (AD) due to variceal hemorrhage (VH), hepatic encephalopathy (HE) and ascites, or with acute-on-chronic liver failure (ACLF). In fact, infections in patients with cirrhosis are considered to be the major trigger for the development of severe complications of cirrhosis, including ACLF, and to be associated with a four-fold increase in mortality mainly due to sepsis and multi-organ failure[3-5].

The epidemiology of bacterial infections in patients with cirrhosis has changed in recent years with the emergence of gram-positive[1,6,7] and multidrug (MDRO) and extended drug (XDRO) resistant organisms, particularly in those subjects with healthcare-associated (HCA) and hospital-acquired (HA) infections[8]. Not surprisingly, HCA infections are increasing in number since cirrhotic patients are frequently hospitalized and readmitted to the hospital in short time intervals[9,10]. Treating those patients with empiric antibiotic regimens recommended for community-acquired (CA) infections with inadequate coverage for MDRO and XDRO may lead to treatment failure with a detrimental effect on survival[11-13]. Several reports have highlighted that MDRO and XDRO are significantly associated with worse response to initial antibiotic therapy, higher progression to sepsis and septic shock, organ dysfunction development, and increased mortality[13-15].

The purpose of the study was to characterize the frequency of MDRO and XDRO in cirrhotic patients admitted to the intensive care unit (ICU) with CA, HCA, and HA infections and to assess their impact on clinical in-hospital outcomes.

METHODS

All admissions in the electronic database of the Unit of Gastroenterology and Hepatology of the Portuguese Hospital of Salvador, Brazil, from January 2012 to June 2018 were retrospectively reviewed in search of AD of cirrhosis or ACLF as the cause for hospitalization. This ICU is a reference unit for critically ill patients with cirrhosis.

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The diagnosis of cirrhosis was based on clinical, biochemical, and echographic findings, as well as on liver histology, whenever liver biopsy results were available. The etiology of cirrhosis and the reason for hospitalization were established in all patients. When there was more than one reason for admission, the main cause was reckoned based on the following hierarchy: VH, bacterial infections, HE, tense ascites and others. All cirrhotic patients admitted in the postoperative period of abdominal surgery, including liver transplantation, intra-arterial chemoembolization for hepatocellular carcinoma, and subjects with co-infection with HIV were excluded from the study. Fungal infections were also not taken into consideration.

Data at admission regarding demographics; clinical and laboratory parameters; prognostic variables such Child-Pugh (CPS), MELD, APACHE II, SOFA and CLIF-SOFA scores and the updated Charlson comorbidity index[16]; etiology of cirrhosis; the main cause of admission, either AD of cirrhosis or ACLF were collected in all subjects with clinical or microbiological evidence of bacterial infections.

The occurrence of CA, HCA, and HA infections was reckoned in every patient. Infections were classified as HA when acquired 48 hours after hospital admission and CA when diagnosed at admission or up to 48 hours of admission to the hospital. Community-acquired were considered as HCA infection in those subjects who fulfilled any one of the following criteria: 1) attendance in a dialysis facility in the last thirty days; 2) hospitalization for at least 48 hours, surgery or residence in a nursing home or assisted living facilities in the last 3 months. Second infections were categorized as a new nosocomial infection apart from one first infection, either CA, HCA or HA infection[10].

Bacterial infections were defined according to established international criteria. Briefly, spontaneous bacterial peritonitis (SBP) were considered in the presence of polymorphonuclear (PMN) cell count in the ascitic fluid of more than 250 cells/mm^3; spontaneous bacterial empyema if the fluid analysis showed a positive culture and more than 250 neutrophils/mm^3 or a negative culture and more than 500 neutrophils/mm^3, in the absence of lung infection; secondary bacterial peritonitis in the presence of PMN of more than 250 cells/mm^3 associated with evidence of imaging and/or surgical evidence for an intra-abdominal source of infection; urinary tract infection (UTI) as the occurrence of more than 10 leukocytes per field with positive urinary culture or numerous leukocytes per field along with fever or urinary symptoms and a negative urinary culture; pneumonia as clinical signs of infection associated with new pulmonary infiltrates on x-rays or chest CT scans; tracheobronchitis as clinical signs of infection without lung infiltrates with positive sputum cultures; skin and soft infections (SSTI) in the presence of clinical signs of infection associated with swollen, red and tender area in the affected skin; cholangitis in the presence of fever and/or right upper quadrant pain associated with jaundice or laboratory signs of cholestasis and radiological evidence of biliary obstruction; spontaneous bacteremia, characterized by positive blood cultures in the absence of an identified source of infection associated or not with invasive procedures whenever performed 24 hour prior to its diagnosis. The diagnosis of catheter-associated UTI, ventilator-associated pneumonia (VAP) or tracheobronchitis, or central line-associated bloodstream infections were considered according to Centers of Disease Control criteria. Infections were described as suspected whenever clinical and laboratory signs of infection elicited antibiotic therapy without any identified source or positive blood culture results.

Bacterial cultures and antimicrobial susceptibility testing were performed according to standard methods. Briefly, MDRO, XDRO and pan-drug resistant (PDRO) organisms were considered, respectively, in the presence of nonsusceptibility to at least one agent in at least three categories of antimicrobials, to at least one agent in all but less than two antimicrobial categories, and to all antimicrobial classes of drugs. As previously stated, well-known intrinsic resistance to a particular antimicrobial was not considered to establish antimicrobial resistance patterns[17].

Infections were treated using therapeutic regimens based on international guidelines[18,19].

The presence of AKI, HRS and ACLF, sepsis, septic shock and death was evaluated and compared to the occurrence of CA, HCA, HA and a second infection. Diagnosis of AKI, HRS and ACLF was established based on international criteria[20,21]. Sepsis and septic shock were considered based on current criteria according to physician's discretion[22,23]. Patients were followed until death or hospital discharge.

The study was approved by the Ethics Committee in Research of the Portuguese Hospital of Salvador, Bahia.

Statistical analysis

Categorical or nominal variables are presented in the text and tables as numbers and percentages and were compared using the chi-square test or Fisher's test, when appropriate. Continuous variables are reported as mean and standard deviation (SD) if the distribution was normal or median and interquartile range if not and, were compared using the Student *t*-test or the Mann-Whitney U test when appropriate. A *P*-value ≤0.05 was considered significant. Univariate analysis was performed to assess the influence of CA, HCA and HA infections and other well-recognized prognostic predictive variables on the development of in-hospital mortality. Variables associated with mortality at univariate analysis with a *P*-value of <0.10 were entered in multivariate logistic regression modeling using stepwise elimination. The software used for analysis was the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, EUA), version 14.0 for Windows.

RESULTS

From January 2012 to June 2018, 784 consecutive patients were admitted to the ICU due to AD of cirrhosis or ACLF. Bacterial infections were identified in 285 (36%) patients (147 males, mean age 67±11 years). Demographics and clinical features of those patients are depicted in TABLE 1. Most of the patients were male with Child-Pugh C cirrhosis with a high index of comorbidities. Acute kidney injury, HRS and ACLF were recorded on admission, respectively, in 48%, 15% and 45% of the patients. Sepsis and septic shock were observed in 152 (53%) and 120 (42%) patients at the time of hospitalization. The mean in-ICU and in-hospital length of stay (LOS) were 8 [3–12] and 8 [8–19] days. One hundred and twenty-five (44%) subjects died. The main causes of death were septic shock (n=95), ACLF (n=16), hypovolemic shock (n=8), acute respiratory distress syndrome (n=5) and acute kidney injury (n=1).

Three hundred and seventy-four episodes of infections were recorded. According to the site of acquisition, 81 (22%), 129 (34%) and 164 (44%) were classified as CA, HCA and HA infections. Eighty-nine (54%) episodes of HA infections were a second infection after CA (n=19), HCA (n=41) and HA (n=29) infections. Demographics, severity of liver disease assessed by CPS and MELD

TABLE 1. Demographics, clinical features and outcomes of cirrhotic patients with bacterial infections at admission in the intensive care unit.

Age (years)	67±11
Male sex	147 (72%)
Etiology of cirrhosis	
Alcohol liver disease	68 (33%)
Undefined	49 (24%)
Hepatitis C virus	39 (19%)
Non-alcoholic steatohepatitis	24 (12%)
Mixed	11 (6%)
Others	12 (6%)
Child-Pugh Score	11±2
CPS A	2 (1%)
CPS B	75 (26%)
CPS C	208 (73%)
MELD score	23±8
Apache II score	16±7
SOFA	5±3
Charlson Comorbidities Index	8±3
Concurrent hepatocellular carcinoma	63 (22%)
Main reason for ICU admission	
Bacterial Infection with sepsis or septic shock	108 (38%)
Hepatic encephalopathy	91 (32%)
Ascitis	54 (19%)
Variceal hemorrhage	28 (10%)
Other causes	4 (1%)
Outcomes	
Acute Kidney Injury	138 (48%)
Hepatorenal syndrome	42 (15%)
Dialysis during hospitalization	46 (16%)
ACLF	128 (45%)
Sepsis	152 (53%)
Septic shock	120 (42%)
ICU length of stay	8 (3–12)
Hospital length of stay (days)	8 (8–19)
Mortality	125 (44%)

ACLF: acute-on-chronic liver failure; APACHE II: *acute* physiology; CPS: Child Pugh Score; ICU: intensive care unit; MELD: Model for End – Stage Liver Disease; SOFA: Sequential Organ Failure Assessment.

scores and CCI were similar in those subjects with CA, HCA and HA infections, but patients with HA infections had higher APACHE II scores when compared to their counterparts with CA infections (17±7 vs 14±5 in CA infections, *P*=0.01) (TABLE 2).

The most frequent bacterial infections were SBP (32%), UTI (23%), pneumonia (14%) and SSTI (7%) (FIGURE 1). Spontaneous bacterial peritonitis was more frequently observed in HCA infections when compared to HA infections, pneumonia in HA infections when compared to CA infections and SSTI in CA

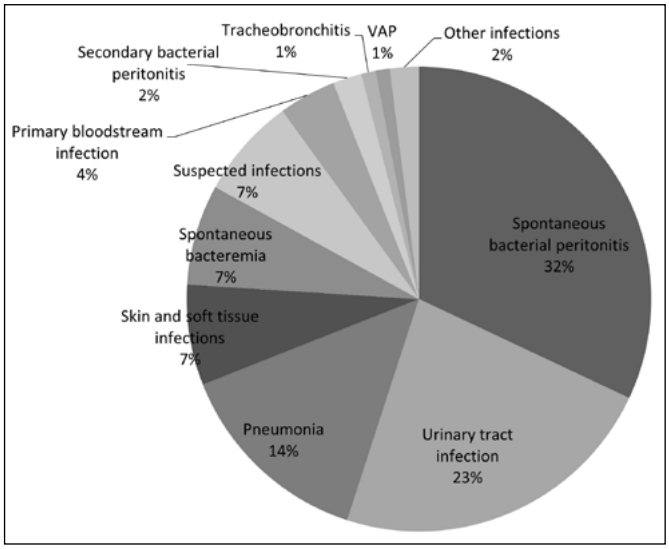

FIGURE 1. Characterization of bacterial infections in cirrhotic patients admitted to the intensive care unit (n=374).
VAP: ventilator associated pneumonia.

infections when compared either with HCA or HA infections (TABLE 2). Two hundred and thirty (61%) patients with clinically suspected bacterial infections had positive cultures, much more frequently in HA infections when compared to CA and HCA infections (TABLE 2). Gram-negative bacteria (GNB) were the most common microorganisms (73%), mainly *Klebsiella pneumoniae* and *Escherichia coli* (TABLE 3), irrespective of the site of acquisition of infection (TABLE 2). Gram-positive bacteria (GPB) were observed in 27% of the isolates, mainly *Enterococcus faecalis*, *coagulase-negative Staphylococcus* and *Staphylococcus aureus* (TABLE 3). The frequencies of MDRO and XDRO in CA, HCA and HA infections were 20% and 6%, 31% and 19%, 41% and 17%, respectively. The frequencies of MDRO and/or XDRO were similar in HCA infections when compared to HA infections (TABLE 2). Both types of organisms were observed more often in HCA (48% vs 26% in CA infections, *P*=0.02) and HA infections (58% vs 26% in CA infections, *P*=0.0009) when compared to CA infections. However, considering only MDRO, the difference remained significant only when HA infections were compared to CA infections (41% vs 20% in CA infections, *P*=0.03). Most MDRO were extended-spectrum beta-lactamase (ESBL) producing-*Klebsiella pneumoniae* and ESBL producing-*Escherichia coli*, whereas all XDRO gram-negative bacteria were carbapenemase-producing *Enterobacteriaceae* (TABLE 3).

Regarding outcomes, patients with HA-infections compared to their counterparts with CA and HCA infections, had a respectively higher frequency of HRS (15% vs 6% in CA infections, *P*=0.03) and a higher need for dialysis (16% vs 9% in HCA infections, *P*=0.04), but the occurrence of AKI and ACLF at the time of infection was similar in all groups of patients. On the contrary, sepsis, septic shock, in-ICU and in-hospital LOS and mortality were significantly higher in those subjects with HA infections when compared to their counterparts with CA and HCA infections (TABLE 4). Those adverse outcomes were even more overrepresented in those patients with a second infection. When compared to their counterparts with a single HA infection, patients with a second infection had more AKI (71% vs 49% in single HA infection, *P*=0.006), more sepsis

TABLE 2. Demographics, clinical and microbiological features of patients with bacterial infections according to site of acquisition.

	CA infections (n=81)	HCA infections (n=129)	HA infections (n=164)	*P*
Age (years)	68±11	68±12	69±10	0.50
Child-Pugh Score				
A	2 (3%)	0 (0%)	0 (0%)	–
B	27 (33%)	32 (25%)	41 (25%)	0.30
C	52 (64%)	97 (75%)	123 (75%)	0.15
MELD	23±7	23±8	23±8	0.80
APACHE II	14±5	16±8	17±7	0.01[b]
Charlson Comorbidities Index	8±3	8±3	8±2	0.08
SOFA	5±3	5±2	5±3	0.60
Types of infections				
Spontaneous bacterial peritonitis	27 (33%)	51 (40%)	40 (24%)	0.02[c]
Urinary tract infection	19 (23%)	33 (26%)	34 (21%)	0.60
Pneumonia	6 (7%)	16 (12%)	31 (19%)	0.04[b]
Skin and soft tissue infection	14 (17%)	9 (7%)	5 (3%)	<0.001[ab]
Infection with undefined site	6 (7%)	10 (8%)	9 (5%)	0.70
Spontaneous bacteremia	2 (2%)	7 (5%)	17 (10%)	0.05 [b]
Primary bloodstream infection	0 (0%)	0 (0%)	16 (10%)	–
Secondary bacterial peritonitis	2 (2%)	1 (1%)	6 (4%)	0.20
Tracheobronchitis	0 (0%)	0 (0%)	4 (2%)	–
Ventilator-associated pneumonia	0 (0%)	0 (0%)	2 (1%)	–
Other infections	5 (6%)	2 (2%)	0 (0%)	–
Microbiological results				
Positive cultures (n=230)	35 (43%)	70 (54%)	125 (76%)	<0.001[b c]
Bacterial profile				
Gram-negative	25 (71%)	48 (69%)	95 (76%)	0.50
Gram-positive	10 (29%)	22 (31%)	30 (24%)	0.50
Multidrug-or extensively drug resistant organisms	9 (26%)	34 (48%)	72 (58%)	0.003[a,b]
Multidrug-resistant organisms	7 (20%)	22 (31%)	51 (41%)	0.03[b]
Extensively drug-resistant organisms	2 (6%)	13 (19%)	21 (17%)	0.20

CA: community-acquired; HCA: healthcare-associated; HA: hospital acquired. [a]$P<0.05$ when comparing CA vs HCA infections; [b]$P<0.05$ when comparing CA vs HA infections and [c]$P<0.05$ when comparing HCA vs HA infections.

TABLE 3. Frequency of Gram-negative bacteria and Gram-positive cocci according to patterns of microbiological resistance.

	All (n=230)	CA infections (n=35)	HCA infections (n=70)	HA infections (n=125)
Gram-negative bacteria	169 (73%)	26 (74%)	48 (69%)	95 (76%)
Klebsiella pneumoniae	13 (6%)	3 (9%)	3 (4%)	7 (6%)
Escherichia coli	29 (13%)	10 (29%)	10 (14%)	9 (7%)
Aeromonas hydrophila	3 (1%)	2 (6%)	–	1 (1%)
Enterobacter cloacae	5 (2%)	–	2 (3%)	3 (2%)
Pseudomonas aeruginosa	8 (3%)	–	2 (3%)	6 (5%)
Burkholderia cepacia	4 (2%)	1 (3%)	–	3 (2%)
Stenotrophomonas maltophilia	3 (1%)	–	–	3 (2%)
Proteus mirabilis	2 (1%)	–	–	2 (2%)
Others	9 (4%)	2 (6%)	1 (1%)	6 (5%)
Acinetobacter Baumanni	2 (1%)	–	–	2 (2%)
MDR Gram-negative bacteria	60 (26%)	6 (17%)	19 (27%)	35 (28%)
ESBL-producing *Klebsiella pneumoniae*	34 (15%)	6 (17%)	10 (14%)	18 (14%)
ESBL-producing *Escherichia coli*	16 (7%)	–	8 (11%)	8 (6%)
Enterobacter cloacae	3 (15)	–	–	3 (2%)
Brevundimonas diminuta	2 (1%)	–	–	2 (2%)
Proteus mirabilis	3 (1%)	–	–	3 (2%)
Others	2 (1%)	–	1 (1%)	1 (1%)
XDR Gram-negative bacteria	31 (13%)	2 (6%)	11 (16%)	18 (14%)
Carbapanemase-producing *Klebsiella pneumoniae*	25 (11%)	2 (6%)	10 (1%)	13 (10%)
Carbapanemase-producing *Escherichia coli*	3 (1%)	–	–	3 (2%)
Others	3 (1%)	–	1 (1%)	2 (2%)
Gram-positive cocci	61 (27%)	9 (26%)	22 (31%)	30 (24%)
Streptococcus pneumoniae	10 (4%)	4(12%)	6 (9%)	–
Staphylococcus aureus	8 (3%)	2 (6%)	4 (6%)	2 (2%)
Coagulase negative *Staphylococcus*	9 (4%)	–	4 (6%)	5 (4%)
Enterococcus faecalis	9 (4%)	2 (6%)	3 (4%)	4 (3%)
MDR Gram-positive cocci	20 (9%)	1 (3%)	4 (6%)	15 (12%)
Methicilin-resistant *Staphylococcus aureus*	4 (2%)	–	2 (3%)	2 (2%)
Coagulase negative *Staphylococcus*	11 (5%)	–	1 (1%)	10 (8%)
Enterococcus faecalis	5 (2%)	1 (3%)	1 (1%)	3 (2%)
XDR Gram-positive cocci	5 (2%)	–	1 (1%)	4 (3%)
Coagulase negative *Staphylococcus*	1 (0%)	–	–	1 (1%)
Enterococcus faecalis	4 (2%)	–	1 (1%)	3 (2%)

CA: community-acquired; HCA: healthcare-associated; HA: hospital acquired; MDR: multidrug-resistant; XDR: extensively drug-resistant.

TABLE 4. Outcomes of patients with bacterial infections according to site of acquisition.

Outcomes	Community-acquired infections (n=81)	Healthcare-associated infections (n=129)	Hospital-acquired infections (n=164)	*P*
ICA-AKI	36 (44%)	65 (50%)	75 (46%)	0.70
Hepatorenal syndrome	5 (6%)	12 (9%)	25 (15%)	0.07[b]
Dialysis requirement	8 (10%)	11 (9%)	27 (16%)	0.09 [c]
ACLF	28 (35%)	64 (50%)	75 (46%)	0.09[a]
Sepsis	22 (27%)	41 (32%)	89 (54%)	<0.01[b,c]
Septic shock	13 (16%)	31 (24%)	76 (46%)	<0.01[b,c]
Hospital length of stay (days)	11 (7–15)	11 (8–17)	17 (11–28)	<0.001[b,c]
ICU length of stay (days)	5 (3–11)	6 (3–10)	10 (4–15)	<0.001[b,c]
Mortality	15 (19%)	32 (25%)	78 (48%)	<0.001[b,c]

ICA-AKI: International Club of Ascitis Acute Kidney Injury criteria; ACLF: acute on chronic liver failure. [a]$P<0.05$ when comparing community-acquired vs healthcare-associated infections; [b]$P<0.05$ when comparing community-acquired vs hospital acquired infections and [c]$P<0.05$ when comparing healthcare-associated vs hospital acquired infections.

(72% vs 45% in single HA infection, *P*<0.001), septic shock (62% vs 39% in single HA infection, *P*=0.004), higher mortality (64% vs 39% in single HA infection) and a longer stay at the hospital (24 [13–27] vs 16 [10–29] days in single HA infection, *P*<0.001) and in ICU LOS (14 [6–17] vs 9 [3–14] days in single HA infection, *P*<0.001). In addition, subjects with a second infection, when compared to those with single HA-infection, also had higher CCI (10±3 vs 7±2 in single HA infection, *P*=0.01), higher frequency of primary bloodstream infection (15% vs 4% in single HA infection, *P*=0.02), culture-positive infection (98% vs 51% in single HA infection, *P*<0.001) and MDRO (49% vs 21% in single HA infection, *P*=0.002).

TABLE 5 discloses the variables associated with mortality in multivariate analysis. The parameters associated with mortality in univariate analysis were female sex, in-ICU and in-hospital LOS, baseline leukocyte count, baseline MELD, APACHE II and SOFA scores, HCA and HA infections, second infections, HE and VH at admission, dialysis during hospitalization, SBP, pneumonia, secondary bacterial peritonitis and infections by XDRO. However, on multivariate analysis, only female gender (odds ratio [OR] 2.24, confidence interval [CI] 95%CI 1.05–4.77 *P*=0.04), MELD (OR 1.15, 95%CI 1.09–1.21, *P*<0.001), APACHE II (OR 1.12, 95%CI 1.06–1.19, *P*<0.001), HCA (OR 2.30, 95%CI 1.00–5.29, *P*=0.04), HA infection (OR 3.64; 95%CI: 1.46–9.11; *P*=0.006), pneumonia (OR 2.71; 95%CI: 1.11–6.61, *P*=0.03), SBP (OR 0.24; 95%CI: 0.12–0.52, *P*<0.001), second infection (OR 2.47, 95%CI 1.11–5.47, *P*=0.03) and in-ICU LOS (OR 1.13, 95%CI 1.06–1.20, *P*<0.001) were independently associated with mortality.

TABLE 5. Logistic regression model for the prediction of in-hospital mortality in critically ill patients with cirrhosis.

	OR	95%CI		*P*
Healthcare-associated infections	2.30	1.00	5.29	0.04
Pneumonia	2.71	1.11	6.61	0.03
Second infections	2.47	1.11	5.47	0.03
Hospital-acquired infections	3.64	1.46	9.11	0.006
Female sex	2.24	1.05	4.77	0.04
MELD	1.15	1.09	1.21	<0.001
In-ICU length of stay	1.13	1.06	1.20	<0.001
APACHE II	1.12	1.06	1.19	<0.001
Spontaneous bacterial peritonitis	0.24	0.12	0.52	<0.001

APACHE II: *acute* physiology, age, chronic health evaluation II; MELD: Model for End – Stage Liver Disease; ICU: intensive care unit.

DISCUSSION

Bacterial infections are life-threatening events in patients with cirrhosis. They can worse the clinical course of the disease, triggering the development of organ failure and ACLF. In this study, infections were observed in one-third of the patients with cirrhosis admitted to a single-center ICU in Brazil. In agreement with other reports, most of those infections were SBP, UTI and pneumonia[5,8,10,24-26]. Nosocomial infections were observed in almost half of the patients, but two-thirds of the remaining infection episodes contracted before hospital admission were considered HCA infections due to prior exposure to healthcare facilities in the previous three months. This is in consonance with previous data showing that HCA infections, whenever adequately investigated, are increasing in prevalence in hospitalized subjects with cirrhosis due to frequent admissions and readmissions of those patients to the hospital[6,7,9,27]. When compared to other studies[5,8,10,13], more patients in the present cohort developed a second infection, probably due to advanced age and a higher presence of comorbidities leading to prolonged in-hospital LOS. As previously described, pneumonia was more commonly observed in HA-infections, particularly in subjects admitted to the ICU[1,2] or with a second infection[10]. As expected, primary bloodstream infections, SBP and SSTI were more frequently seen in patients with a second infection, HCA and CA infection, respectively. In accordance with the literature, culture-proven infections were observed in 60% of the cases[7,8,28,29], with a higher frequency observed in those subjects with HA infection[5,25], particularly a second infection.

Regarding the site of acquisition, no difference in the frequency of GNB or GPC was disclosed. In contrast to other studies which reported a higher frequency of GPC[1,6,10,29] or *Escherichia co*li as the main isolated microorganism[14,15,27,30], most of the isolates in the present investigation were GNB, particularly MDR and XDR *Klebsiella pneumoniae.* In this study, MDRO and XDRO were responsible for 35% and 16% of the bacterial infections, respectively. However, their frequency was shown to vary sharply when subjects with either HCA or HA infections when compared to their counterparts with CA infections. This is in accordance with recent studies showing a sharp increase in the frequency of MDRO in the last 2 decades[24,26]. One recent global multicenter study also disclosed a frequency of MDRO and XDRO in 35% and 8% of those hospitalized with cirrhosis, with higher frequencies observed in countries from South America and Asia, particularly India[7]. Besides geographical location, other independent predictors of infections by MDRO disclosed by those authors were UTI, pneumonia, cellulitis, previous use of antibiotics, occurrence of HCA and HA infection. They also observed an adverse impact on survival associated with the presence of MDRO, probably due to the use of ineffective empiric antibiotic regimens[8]. Not surprisingly, the frequencies of MDRO and XDRO in the current study were similar in subjects with HCA and HA infections, mainly due to ESBL-producing and cabarpamenase producing *Klebsiella pneumoniae.*

Bacterial infections are well-recognized triggers for AKI, HRS and ACLF in cirrhosis[8,25]. In those studies, sepsis and septic shock were reported to occur in 22%–26% and 13%–15% of the patients, respectively. When compared to other studies, our patients had similar rates of in-hospital AKI and ACLF[25,29,31,32], a lower rate of HRS[9,10,26], but a higher frequency of sepsis and septic shock[8,25,32], which may be due to the employment of distinct criteria for sepsis assessment in those different studies over the years, as well as enrollment of sicker critically-ill patients with cirrhosis in the present study. There was no difference in severity of liver disease evaluated by CPS or MELD in those patients with CA, HCA and HA infections, but patients with HA and HCA infections tended to have more AKI and ACLF when compared to their counterparts with CA infections. On the other hand, sepsis and septic shock development were significantly higher in those with HA infections than those with CA or HCA infections. It is also worth mentioning that those adverse outcomes were even more pronounced in those with a second infection. These findings may be ascribed to the increase in MDRO infections observed in those with HA infection, as pointed out by others[24,32], but also due to the prescription of ineffective empiric antibiotic regimens, which were not evaluated in our study[14].

Approximately half of our patients died due to septic shock or ACLF. Lower mortality rates were observed in other reports involving mainly hospitalized cirrhotic patients with infections outside the ICU[5,10,14,15], but similar death rates were described in critically-ill cirrhotic subjects[2,33]. Mortality[26,27] and in-hospital LOS[29] were significantly higher in those subjects with HA infection when compared to those patients either with CA or HCA infection. Patients with a second infection also had higher mortality when compared to their counterparts with HA infection[10].

Independent predictors of in-hospital mortality disclosed in the present study were MELD and APACHE II scores reflecting disease severity, HCA and HA infection and occurrence of pneumonia and a second infection[8,27]. Unlike previous reports, infections with either MDRO or XDRO, which were more common in HCA, HA and a second infection, were not shown to be independent predictors of mortality. Those discrepancies could be ascribed to a recent shift favoring the use of broad-spectrum antibiotics with adequate coverage against ESBL-producing GNB, particularly in HCA infections, according to updated international guidelines. As previously reported, SBP was associated with a lower risk[10], while pneumonia and a second infection to a higher risk for mortality[7,10].

This study, being retrospective, has some limitations. We were unable to assess previous hospitalizations either due to AD of cirrhosis or bacterial infections. None of the patients were on rifaximin because the drug was not marketed in Brazil, but some could be using norfloxacin for SBP prophylaxis. The antibiotic regimens used in these individuals for both prophylaxis and treatment have not been evaluated. The study also did not assess the use of intravenous albumin during hospitalization, which could impact the clinical outcomes of cirrhotic patients with infection.

In summary, HA and HCA-related infections are increasingly associated with either MDRO or XDRO, with an adverse impact on survival. Recognition of HCA infections and proper selection of appropriate empiric antibiotic regimens tailored to local antibiotic resistance patterns are of utmost importance since those bacterial infections are associated with an increased risk for mortality.

Authors' contribution

D'Oliveira RAC: conceptualization, formal analysis, investigation, methodology project administration, supervision, writing-original draft, writing-review and editing. Pereira LCD: investigation. Codes L: formal analysis, writing review and editing. Rocha MS: conceptualization. Bittencourt PL: conceptualization, methodology, project administration, writing review and editing.

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RESUMO – **Contexto –** As infecções bacterianas ocorrem em 43–59% dos pacientes cirróticos internados em unidade de terapia intensiva com impacto na morbimortalidade. Um aumento na frequência de bactérias multirresistentes e com resistência estendida foi descrito em infecções bacterianas em pacientes cirróticos, com um impacto adverso na sobrevida. **Objetivo –** Caracterizar as infecções adquiridas na comunidade, relacionadas aos cuidados de saúde (RCS) e hospitalares em pacientes cirróticos e seu impacto na ocorrência de desfechos adversos. **Métodos –** Este estudo incluiu todos os pacientes cirróticos internados em uma unidade de terapia intensiva especializada em doenças hepáticas e gastrointestinais no Brasil entre janeiro de 2012 e junho de 2018. A frequência e topografia das infecções foram avaliadas retrospectivamente, bem como a frequência de bactérias multirresistentes e resistência estendida, e seu impacto na ocorrência de lesão renal aguda, síndrome hepatorrenal, insuficiência hepática crônica agudizada, sepse e mortalidade. **Resultados –** Um total de 374 infecções foram observadas e classificadas como infecções adquiridas na comunidade (22%), RCS (34%) e infecções hospitalares (44%). Oitenta e nove (54%) episódios de infecções hospitalares foram identificadas como segunda infecção. Peritonite bacteriana espontânea (32%) e infecção do trato urinário (23%) foram as infecções mais comuns. As infecções comprovadas por cultura foram positivas em 61% dos casos, principalmente ocasionadas por bactérias gram-negativas (73%). Lesão renal aguda, síndrome hepatorrenal e sepse foram observados respectivamente, em 48%, 15% e 53% dos casos. Bactérias multirresistentes e resistência estendida foram observadas respectivamente, em 35% e 16%, principalmente nos RCS (48% vs 26% em infecções adquiridas na comunidade, *P*=0,02) e infecções hospitalares (58% vs 26% em infecções adquiridas na comunidade, *P*=0,0009). Os resultados adversos foram observados com mais frequência em indivíduos com infecções nosocomiais em comparação com infecções relacionadas aos cuidados de saúde e comunitárias. Infecções hospitalares, RCS e ocorrência de uma segunda infecção foram independentemente associadas à mortalidade intra-hospitalar. **Conclusão –** Infecções hospitalares, relacionadas aos cuidados de saúde e reinfecções estão cada vez mais associadas a bactérias multirresistentes e/ou resistência estendida e são preditores independentes de mortalidade intra-hospitalar. Seu reconhecimento e seleção adequada de regimes antibióticos empíricos apropriados são medidas importantes para reduzir a mortalidade intra-hospitalar.

Palavras-chave – Cirrose hepática; infecções bacterianas; morbidade; mortalidade; unidade de terapia intensivo.

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ORIGINAL ARTICLE

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Should routine liver biopsy be considered in bariatric surgical practice? An analysis of the limitations of non-invasive NAFLD markers

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ABSTRACT – Background – Non-invasive markers are useful and practical tools for assessing non-alcoholic fatty liver disease (NAFLD), but liver biopsy remains the gold-standard method. Liver biopsy can be easily obtained on individuals undergoing bariatric surgery, but there is no ultimate evidence on the relationship between costs, risks and benefits of its systematic performance. **Objective –** To compare the diagnostic accuracy of non-invasive methods with liver biopsy for detection and staging of NAFLD in obese individuals undergoing bariatric surgery. **Methods –** This is a cross-sectional, observational and descriptive study which enrolled individuals who underwent bariatric surgery from 2018 through 2019 at a public tertiary university hospital. Ultrasound scan, hepatic steatosis index, Clinical Non-Alcoholic Steatohepatitis Score (C-NASH), hypertension, alanine aminotransferase (ALT) and insulin resistance (HAIR), aspartate aminotransferase (AST) to Platelet Ratio Index (APRI), NAFLD Fibrosis Score (NFS) and body mass index, AST/ALT ratio, and diabetes (BARD) were the methods compared with the histopathological examination of wedge liver biopsies collected during surgery. **Results –** Of 104 individuals analyzed, 91 (87.5%) were female. The mean age was 34.9±9.7 years. There was no biopsy-related morbidity. The respective overall accuracies of each marker analyzed were: ultrasound scan (79.81% for steatosis), hepatic steatosis index (79.81% for steatosis), HAIR (40.23% for steatohepatitis), C-NASH (22.99% for steatohepatitis), APRI (94.23% for advanced fibrosis), NFS (94.23% for advanced fibrosis), and BARD (16.35% for advanced fibrosis). **Discussion –** Given the high prevalence of liver disease within this population, even the most accurate markers did not present enough discretionary power to detect and/or rule out the NAFLD aspects they were designed to assess in comparison with liver biopsy, which is safe and easy to obtain in these patients. **Conclusion –** Wedge liver biopsy during bariatric surgery helps to diagnose and stage NAFLD, presents low risks and acceptable costs; given the limitations of non-invasive methods, it is justifiable and should be considered in bariatric routine.

Keywords – Non-alcoholic fatty hepatopathy; fatty liver; obesity; bariatric surgery; liver function tests.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as the abnormal deposition of fat in the liver without significant alcohol consumption and/or other secondary causes. NAFLD may present with different forms within a histopathological spectrum, from simple steatosis to liver cirrhosis, and can even evolve to hepatocellular carcinoma. In 2030, it is believed to be the main indication for liver transplantation in the world. Weight loss is one of the most effective treatments for NAFLD, which can be obtained by surgical, pharmacological and/or dietary-behavioral means[1].

Due to its broad histopathological spectrum, biopsy is the ideal test to define and stage this disease. Biopsy during abdominal operations can be performed by wedge resection of a small fragment of the periphery of the liver, of about two centimeters in length, followed by its cauterization to control hemostasis. It is a simple procedure, which does not prolong the operation and can be performed in both open and laparoscopic procedures. In addition to this method, it can be performed by means of needle puncture to search for a core fragment of the liver[2,3].

However, in situations where it is not performed during an abdominal surgery, biopsy is an invasive, high-cost procedure that presents risks and, for these reasons, several indirect, non-invasive diagnostic methods have been proposed to replace it. These can be obtained by means of laboratory, anthropometric analysis, and imaging tests[4].

Considering that NAFLD is an extremely prevalent disease, and the gold standard diagnostic method is invasive, widespread routine use of liver biopsy for the entire population with high risk for NAFLD is not feasible. Non-invasive markers can assist in screening for detection and/or exclusion of the disease. At our facility, liver biopsy is performed routinely on all individuals undergoing bariatric surgery (BS), but there is no ultimate evidence on the relationship between costs, risks, and benefits of its systematic performance.

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This study aims at comparing the diagnostic accuracy of non-invasive methods with liver biopsy for detection and staging of NAFLD in obese individuals undergoing BS and at proposing the routine performance of liver biopsy during BS.

METHODS

Study design

This is a cross-sectional, observational, and descriptive study. Data were collected through the analysis of medical records of individuals who underwent BS (open Roux-en-Y gastric bypass) from 2018 through 2019 at a public tertiary university hospital. The study protocol was approved by the local institutional review board and all participants provided informed consent.

Work developed at Department of Surgery – Faculty of Medical Sciences – State University of Campinas (UNICAMP), Campinas (SP), Brazil.

Study population

Inclusion criteria were patients who underwent BS indicated according to the National Institutes of Health criteria (body mass index [BMI] greater than 40 kg/m^2 or BMI greater than 35 kg/m^2 with comorbidities associated with obesity), of any gender, aged between 18 and 70 years[5]. Exclusion criteria were use of alcohol and hepatotoxic drugs, chronic viral hepatitis or serological abnormalities, bile duct obstruction and incomplete medical records. All individuals underwent a preoperative mandatory weight loss program and surgery was performed when a minimal 10% weight loss was achieved.

Variables

The data collected were age, gender, weight, BMI, results of abdominal ultrasound (US) scan and liver biopsy findings. The following laboratory tests were consulted: glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, high-density lipoprotein (HDL), triglycerides, insulin, alkaline phosphatase (ALK), gamma-glutamyl transferase (GGT), platelets and albumin.

Non-invasive methods

US, hepatic steatosis index (HSI), Clinical Non-Alcoholic Steatohepatitis Score (C-NASH), Hypertension, ALT and Insulin Resistance (HAIR), AST to Platelet Ratio Index (APRI), NAFLD Fibrosis Score (NFS) and BMI, AST/ALT ratio, and diabetes (BARD) were the methods evaluated. TABLE 1 summarizes their rationales and outcomes[6-13].

Liver biopsy technique and histopathological evaluation

Wedge liver biopsy was performed during surgery after the main surgical proceeding. A 2-cm fragment was extracted with blunt scissors from segments III or IV.

NAFLD-related features were classified into categories: 1) steatosis (absent, mild, moderate or severe); 2) fibrosis (according to the Kleiner-Brunt classification): 0- absent; 1- perisinusoidal or periportal alone; 2- periportal and perisinusoidal; 3- presence of fibrous septa ("bridging fibrosis"); 4- cirrhosis); 3) steatohepatitis (classified in grades: 0, 1+, 2+, 3+)[1].

Statistical analysis

Calculations of diagnostic accuracy tests were performed: sensitivity, specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios and overall accuracy. The gold standard was the histopathological evaluation. The software SAS Release 8.2 (SAS Institute Inc., Cary, NC) was used to perform the analysis.

RESULTS

Of 104 individuals selected for study, 91 (87.5%) were female. The mean age was 34.9±9.7 years. The main comorbidity was hypertension (34.6%), followed by dyslipidemia (24%) and type 2 diabetes (21.2%). The mean BMI was 36.1±3.5 kg/m^2. There were no biopsy-related complications.

The main NAFLD-related histopathological aspects were steatosis (80.8%), fibrosis (82.7%) and steatohepatitis (81.7%). Most individuals presented mild macrovesicular steatosis (55.8%), whereas the commonest stages of fibrosis were 1a and 2 (both 36.5%). Most individuals with steatohepatitis presented mild acinar inflammation (55.8%) and/or mild portal inflammation (58.7%). The details of histopathological and biochemical findings are shown in TABLE 2.

The respective overall accuracies of each marker analyzed were: US (79.81% for steatosis), HSI (79.81% for steatosis), HAIR (40.23% for steatohepatitis), C-NASH (22.99% for steatohepatitis), APRI (94.23% for advanced fibrosis), NFS (94.23% for advanced fibrosis), and BARD (16.35% for advanced fibrosis). TABLE 3 presents the complete diagnostic accuracy analyses of the non-invasive markers evaluated.

DISCUSSION

The current study focused on a highly prevalent disease in the population, especially in the group of individuals with obesity, with a risk of progression to chronic liver disease and high morbidity and mortality in advanced stages, mainly liver cirrhosis, including the risk of developing hepatocellular carcinoma. Individuals with an indication for BS surgery according to the NIH criteria are likely to present metabolic abnormalities and consequent abnormal deposit of fat in the liver, thus constituting a high-risk population for NAFLD. As such, the possibility of an early diagnosis of NAFLD could lead to relevant benefits, such as receiving guidance on risks, prognosis and evolution of the disease. A previous study by our group found a prevalence of over 50% of liver fibrosis in a population undergoing BS[14].

That is, in obese individuals, in addition to the usual investigation for type 2 diabetes, dyslipidemia and other metabolic co-morbidities, they could benefit from an eventual screening for NAFLD, especially through a method with the possibility of defining the different aspects of this disease. With this aim in mind, an ideal diagnostic method with few risks and low cost, in addition to high accuracy and high availability in clinical practice is highly sought. Given the high observed prevalence of steatohepatitis, significant (≥F2) and advanced (≥F3) fibrosis within the population of the current study, an accurate assessment of NAFLD becomes even more important in this context.

US scan is a low-cost, non-invasive and operator-dependent method, which is also highly available. An important factor to be highlighted in the US of obese patients is the technical difficulty in individuals with severe obesity, due to the thick subcutaneous tissue. It presented high sensitivity (99%) and high positive predictive value (81%). Despite this, it proved to be an ineffective method to

TABLE 1. Main characteristics of each non-invasive score assessed.

Score	Rationale	How to perform or calculate	Cut-off values and interpretation
US	Used to determine the presence of liver steatosis[5].	Qualitative visualization of hepatic echogenicity, measurement of the difference of the hepatic parenchyma compared to the renal parenchyma, evaluation of the penetration of the deep portion of the liver and through the determination of the hepatic structures, for example.	Subjective: normal, mild, moderate or severe.
HSI	Created to predict the occurrence of steatosis in the general population[6].	HSI =8 x ALT/AST + BMI (+2 if T2DM, +2 if female)	A score >36 indicates the presence of steatosis, while a score <30 indicates absence of steatosis.
NFS	Designed for prediction of advanced fibrosis in NAFLD patients[6].	NFS =-1.675 + 0.037 X age (years) + 0.094 X BMI (kg/m²) X IGT/T2D (Yes =1 OR No =0) +0.99 X AST/ALT – 0.013 X Platelet count (X 10^9/L) – 0.66 X Albumin (g/dL)	A score over 0.676 indicates advanced fibrosis, while a score below -1.455 excludes advanced fibrosis.
APRI	Developed to predict advanced fibrosis and cirrhosis in patients with hepatitis C, it was then validated for detection of advanced fibrosis in NAFLD[6].	APRI = {[(observed AST/AST (upper limit in iU/L)] / Platelet count (10^9/L)} x 100	A score 0.98 indicates advanced fibrosis.
BARD	Derived to detect advanced fibrosis in a population comprised exclusively of individuals with biopsy-proven NAFLD[7].	BMI greater than or equal to 28 earns 1 point, AST/ALT ratio greater than or equal to 0.8 earns 2 points and presence of diabetes earns 1 point.	**BARD Score** / **Risk of advanced fibrosis** 0–1 / Low 2–4 / High
HAIR	Developed to detect steatohepatitis in bariatric surgery patients[8].	The variables used are the presence of hypertension, ALT greater than 40 and an insulin resistance index greater than 5. Each variable earns 1 point.	A sum of points ≥2 indicates a high probability of NASH.
C-NASH	Designed to predict the occurrence of NASH based in clinical characteristics[6].	**Clinical aspect** / **Points** BMI (kg/m²) 40–45 / 1 >45 / 2 AST >40 iU/L / 2 Triglycerides >140 mg/dL / 1	A sum of points ≥3 indicates the presence of steatohepatitis.

NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic fatty liver steatohepatitis; US: ultrasound scan; HSI: hepatic steatosis index; NFS: non-alcoholic fatty liver disease fibrosis score; APRI: AST-to-platelet ratio index; C-NASH: clinical score for non-alcoholic steatohepatitis; HAIR: hypertension, ALT and insulin resistance index; BARD: BMI, AST/ALT ratio and diabetes score; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index.

TABLE 2. Non-alcoholic fatty liver disease related features and biochemical examinations observed in the study population.

	N (%)
Steatosis	84 (80.8%)
Macrovesicular	83 (79.8%)
Mild	58 (55.8%)
Moderate	21 (20.2%)
Severe	3 (2.9%)
Microvesicular	30 (28.8%)
Fibrosis	86 (82.7%)
0	18 (17.3%)
1a	38 (36.5%)
1b	4 (3.8%)
1c	2 (1.9%)
2	38 (36.5%)
3	4 (3.9%)
4	0 (0%)
Steatohepatitis	85 (81.7%)
Acinar inflammation	80 (76.9%)
Mild	58 (55.8%)
Moderate	19 (18.3%)
Severe	3 (2.9%)
Portal inflammation	84 (80.8%)
Mild	61 (58.7%)
Moderate	22 (21.2%)
Severe	1 (1%)
Fasting glucose (mg/dL)	91.5±27.8
Aspartate aminotransferase (U/L)	22.9±11.1
Alanine aminotransferase (U/L)	28±22.8
Alkaline phosphatase (U/L)	65.2±18.2
Gamma-Glutamyl Transferase (U/L)	23.1±14.7
Platelet count (x10^9/L)	271.7±81.6
Albumin (g/dL)	4.3±0.3
Insulin (mU/L) (N=87)	15.6±10.7
Triglycerides (mg/dL)	106.9±55.9
High density lipoprotein (mg/dL)	38.2±8.5
Total cholesterol (mg/dL)	166.8±33.5
Homeostasis model assessment – insulin resistance (HOMA-IR) (N=87)	3.5±2.6

rule out the occurrence of steatosis, which would be important in a population with high prevalence. Hernaez et al., in a meta-analysis that analyzed 49 studies (4,720 individuals), observed that US is an accurate and reliable method for detecting moderate to severe NAFLD in the general population, with sensitivity and specificity greater than 80%[15]. Almeida et al., in a cross-sectional study in which 105 obese individuals were analyzed, demonstrated that US was not an accurate method for the diagnosis of NAFLD in obese individuals, with 65% sensitivity, 91% specificity, 98% positive predictive value and a negative 23%, with a limitation comparable to that observed in the current study[16]. Thus, the main strength of US, which is to detect the presence of NAFLD becomes almost dispensable in a population in which the overall prevalence of NAFLD is extremely high; discarding its occurrence and staging its characteristics would be more important, but the US did not have enough discretionary power for these purposes. Similarly to US, the results of the HSI score for the detection of steatosis demonstrated high sensitivity (99%), but low specificity. In a population with a high prevalence of hepatic steatosis at some level, a negative HSI result has low significance. Therefore, the HSI's discretionary power to rule out steatosis in this population was not satisfactory. Lind et al., analyzing HSI in different contexts, observed that its accuracy is higher in populations at high risk compared to populations at low risk for steatosis (78% vs 74%)[17].

In regard to methods for the evaluation of steatohepatitis, the HAIR score showed an accuracy of only 40%. In clinical practice, a negative result is of little significance, while a positive result will be correct in approximately 80% of cases. On the other hand, the C-NASH score showed high specificity; despite that, a negative result has little significance, since due to the high prevalence of steatohepatitis in the obese population, there is a high chance that it is a false negative result. Thus, its accuracy is only 23%. Therefore, both tests do not present enough accuracy for widespread use in this population.

APRI demonstrated high specificity, 98%, and a negative predictive value of 96.8%. Therefore, this non-invasive score, created to assess patients with fibrosis in viral hepatitis, proved to be effective in ruling out significant fibrosis, but little accurate for its detection. Its accuracy reached 94.23% and proved effective for advanced fibrosis. De-Cleva et al. similarly observed that the APRI is highly accurate for advanced fibrosis in obese patients undergoing BS[18]. The NFS showed similar results to the APRI, presenting similarly usefulness in clinical practice to rule out advanced fibrosis, but also failing to detect incipient fibrosis, an aspect that would be of greater interest in this population. Singh et al., in a study with 1,319 individuals with biopsy-proven NAFLD, observed that the NFS showed a specificity of 93% and sensitivity of 44%, demonstrating little use in a high-risk population[19]. However, it is unusual for patients with advanced fibrosis, who present the risk of chronic liver failure, to undergo elective BS. The detection of incipient fibrosis, which would be more relevant in the context of the individual undergoing BS, is not possible with both these scores. Similarly, the BARD scoring system showed high sensitivity, but low specificity, which provides an accuracy of only 16%. In this way, it becomes a method that is difficult to interpret when assessing the presence of advanced fibrosis. De Carli et al., in a study that analyzed 323 individuals with morbid obesity, observed that the BARD showed an accuracy of 44%; the population studied in that study had a higher prevalence of advanced fibrosis than in the current study (9%), which may explain its greater accuracy[20].

TABLE 3. Diagnostic accuracy of each non-invasive method for assessment of NAFLD aspects.

	Test/disease	Present	Absent	Total
Ultrasound scan (diagnosis of steatosis)	**Present**	True positive: 83	False positive: 20	103
	Absent	False negative: 1	True negative: 0	1
	Total	84	20	104
	Sensitivity: 98.81%; specificity: 0; positive predictive value: 80.58%; negative predictive value: 0; positive likelihood ratio: 0.99; negative likelihood ratio: 0; overall accuracy: 79.81%.			
HSI (diagnosis of steatosis)	**Present**	True positive: 83	False positive: 20	103
	Absent	False negative: 1	True negative: 0	1
	Total	84	20	104
	Sensitivity: 98.81%; specificity: 0; positive predictive value: 80.58%; negative predictive value: 0; positive likelihood ratio: 0.99; negative likelihood ratio: 0; overall accuracy: 79.81%.			
HAIR (diagnosis of steatohepatitis)	**Present**	True positive: 26	False positive: 7	33
	Absent	False negative: 45	True negative: 9	54
	Total	71	16	87
	Sensitivity: 36.62%; specificity: 56.25%; positive predictive value: 78.79%; negative predictive value: 16.67%; positive likelihood ratio: 0.84; negative likelihood ratio: 1.13; overall accuracy: 40.23%.			
C-NASH (diagnosis of steatohepatitis)	**Present**	True positive: 4	False positive: 0	4
	Absent	False negative: 67	True negative: 16	83
	Total	71	16	87
	Sensitivity: 5.63%; specificity: 100%; positive predictive value: 100%; negative predictive value: 19.28%; positive likelihood ratio: 0; negative likelihood ratio: 0.94; overall accuracy: 22.99%.			
APRI (diagnosis of advanced fibrosis)	Present	True positive: 0	False positive: 2	2
	Absent	False negative: 4	True negative: 98	102
	Total	4	100	104
	Sensitivity: 0; specificity: 98%; positive predictive value: 0; negative predictive value: 96.08%; positive likelihood ratio: 0; negative likelihood ratio: 1.02; overall accuracy: 94.23%.			
NFS (diagnosis of advanced fibrosis)	**Present**	True positive: 0	False positive: 2	2
	Absent	False negative: 4	True negative: 98	102
	Total	4	100	104
	Sensitivity: 0; specificity: 98%; positive predictive value: 0; negative predictive value: 96.08%; positive likelihood ratio: 0; negative likelihood ratio: 1.02; overall accuracy: 94.23%.			
BARD (diagnosis of advanced fibrosis)	**Present**	True positive: 4	False positive: 87	91
	Absent	False negative: 0	True negative: 13	13
	Total	4	100	104
	Sensitivity: 100%; specificity: 13%; positive predictive value: 4.40%; negative predictive value: 100%; positive likelihood ratio: 1.15; negative likelihood ratio: 0; overall accuracy: 16.35%.			

NAFLD: non-alcoholic fatty liver disease; HSI: hepatic steatosis index; HAIR: Hypertension, ALT, Insulin Resistance; C-NASH: Clinical Non-alcoholic Steatohepatitis; APRI: AST to platelet radio index; NFS: NAFLD fibrosis score; BARD: Body mass index, AST/ALT ratio, diabetes.

Therefore, the scores for the detection of advanced fibrosis should be analyzed with caution, being more useful in populations with a higher prevalence of individuals with severe and already manifest forms of NAFLD. A meta-analysis conducted by Xiao et al. demonstrated that the FIB-4 score tends to present an accuracy higher than APRI and comparable to NFS; thus, it might also be considered as an option[21].

Most scores analyzed were not developed specifically to assess obese populations at high risk for NAFLD, especially those whose objective is to analyze liver fibrosis. Their initial scopes were to evaluate patients with advanced chronic liver diseases, mostly viral hepatitis. The natural history of these diseases and the evolution of non-NAFLD fibrosis are different, with a more insidious evolution in the group of patients analyzed in the current study. A recent study conducted by our group also showed that the accuracies of these markers are variable according to BMI status, pointing another difficulty in their interpretation[22].

Other non-invasive methods, such as ultrasound elastography or magnetic resonance imaging, are promising in the attempt to define which NAFLD patient will progress to fibrosis without the need for percutaneous biopsy. However, elastography itself is a high-cost and largely unavailable diagnostic tool in our country. In addition, its accuracy when performed by ultrasound is considerably lower in obese individuals[23].

Considering all these flaws, liver biopsy during BS assumes an important role. During BS, the patient is already undergoing an invasive procedure. The biopsy under direct vision does not add significant operative time and risk. It is not associated with prolonged hospital stay, postoperative pain and the cost is only due to histological analysis. Khorgami et al. observed that intraoperative needle liver biopsy was significantly associated with an increased cost in bariatric procedures, but this increase was an average 17% higher, which our group considers fair in relation to the benefits, also considering that wedge biopsies are even safer and less expensive[24]. In addition to promoting early diagnosis of NAFLD and its severe forms, liver biopsy helps to understand their postoperative evolution[2-4]. Hence, there are several reasons for performing a wedge liver biopsy during a bariatric operation. The operated patient presents with a high-risk for NAFLD, the biopsy proceeding is safer in this surgical context, the increase in costs is not prohibitive and, most importantly, the method is the most accurate for these goals. Liver biopsy, in addition to promoting early diagnosis of both NAFLD and severe forms such as liver cirrhosis, helps to understand the natural evolution of the disease. BS usually causes changes in the evolution of this condition, causing improvement in most patients[25,26]. There is no consensus on the most appropriate technique for obtaining liver biopsy specimens during surgery, whether it should be by means of wedge or either needle techniques. Ooi et al. demonstrated that there is an appropriate agreement between these approaches, but a weaker agreement in the assessment of fibrosis stage[27].

This study, due to its cross-sectional design, has its methodological limitation since this type of study does not allow causal links to be established. The lack of consensus in the literature to systematize liver biopsy during BS shows the need for prospective studies to increase knowledge about this discussion. Since it is not standard at our facility, there was no data available on the Nonalcoholic Steatohepatitis Clinical Research Network (CRN) classification, which uses the NASH Activity Score (NAS) as its most important parameter. Another limitation is the preoperative weight loss to which patients in our service are subjected and, therefore, the BMI at the time of the analysis has a low average. The general bariatric population is also very specific, with no patients with advanced liver disease who underwent surgery at our facility. On the other hand, it is possible to safely say that liver biopsy, according to the findings of the current study, leads to considerable benefits in relation to the detection of different aspects of the histopathological spectrum of NAFLD in a high-risk population.

Given the high prevalence of liver disease within this population, even the most accurate markers did not present enough discretionary power to detect and/or rule out the NAFLD aspects that they were designed to assess in comparison with liver biopsy, which is safe and easy to obtain in these patients.

CONCLUSION

Wedge liver biopsy during bariatric surgery helps to diagnose and stage NAFLD, presents low risks and acceptable costs; given the limitations of non-invasive methods, it is justifiable and should be considered in bariatric routine.

Authors' contribution

Concon MM collected the data and wrote the first draft. Gestic MA, Utrini MP and Chaim FDM collected the data and performed the biopsies and operations. Chaim EA provided critical intellectual inserts and reviewed the final draft. Cazzo E conceived and designed the analysis, performed the analysis and wrote the final draft.

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RESUMO – Contexto – Marcadores não-invasivos são ferramentas úteis e práticas para avaliar a doença hepática gordurosa não alcoólica (DHGNA), porém, a biópsia hepática continua sendo o método padrão-ouro. A biópsia pode ser facilmente obtida em indivíduos submetidos à cirurgia bariátrica, mas não há evidências definitivas acerca da relação entre custos, riscos e benefícios de sua realização sistemática. **Objetivo –** Comparar a acurácia diagnóstica de métodos não-invasivos com a biópsia hepática para detecção e estadiamento da DHGNA em obesos submetidos à cirurgia bariátrica. **Métodos –** Trata-se de um estudo transversal, observacional e descritivo que envolveu indivíduos que se submeteram à cirurgia bariátrica de 2018 a 2019 em um hospital universitário público terciário. Ultrassonografia (US), índice de esteatose hepática (HSI), Escore Clínico de Esteato-hepatite Não-Alcoólica (C-NASH), Índice de Hipertensão, alanina aminotransferase (ALT) e resistência à insulina (HAIR), Razão entre aspartato aminotransferase (AST) e plaquetas (APRI), Escore de Fibrose da DHGNA (NFS) e índice de massa corporal (IMC), relação AST/ALT e diabetes (BARD) foram os métodos comparados com o exame histopatológico de biópsias hepáticas em cunha coletadas durante a cirurgia. **Resultados –** De 104 indivíduos analisados, 91 (87,5%) eram do sexo feminino. A média de idade foi de 34,9±9,7 anos. Não houve morbidade relacionada à biópsia. As respectivas acurácias globais de cada marcador analisado foram: US (79,81% para esteatose), HSI (79,81% para esteatose), HAIR (40,23% para esteato-hepatite), C-NASH (22,99% para esteato-hepatite), APRI (94,23% para fibrose avançada), NFS (94,23% para fibrose avançada) e BARD (16,35% para fibrose avançada). **Discussão –** Considerando a alta prevalência de doença hepática nesta população, mesmo os mais acurados destes marcadores não apresentaram poder discricionário suficiente para detectar e/ou descartar os aspectos da DHGNA que foram desenvolvidos para avaliar em comparação com a biópsia hepática, que é segura e de fácil obtenção nestes pacientes. **Conclusão –** A biópsia hepática em cunha durante a cirurgia bariátrica auxilia no diagnóstico e estadiamento da DHGNA, apresenta baixo risco e custos aceitáveis e, dadas as limitações dos métodos não-invasivos, é justificável e deve ser considerada na rotina bariátrica.

Palavras-chave – Hepatopatia gordurosa não alcoólica; fígado gorduroso; obesidade; cirurgia bariátrica; testes de função hepática.

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ORIGINAL ARTICLE

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Small bowel is largely affected in Behçet's disease: a long-term follow-up of gastrointestinal symptoms

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ABSTRACT – Background – Behçet's disease is a rare immune-mediated disorder that can affect the gastrointestinal tract. The prevalence and extension of small bowel involvement is largely unknown. **Objective** – The aim of this study was to describe the small bowel lesions diagnosed by double-balloon enteroscopy (DBE) and to verify if these findings were associated to the presence of gastrointestinal symptoms and disease activity after long-term follow-up. **Methods** – This study included 19 Behçet's disease patients who underwent DBE. After a mean follow-up of 15 years the endoscopic findings were associated to the presence of gastrointestinal symptoms, disease activity and current therapy through collection of electronic medical records. **Results** – A total of 63.2% patients were female and the mean age was 37 years at the time of DBE. Mean disease duration at baseline was 24 years. 11 patients had no gastrointestinal symptoms and eight patients presented either abdominal pain, gastrointestinal bleeding or diarrhea. The average procedure time was 1 hour and 30 minutes and the ileum was achieved in all patients but one. Small bowel ulcers were diagnosed in 78.9%, with 63.1% of jejunal involvement. Two patients presented only small bowel edema and two were normal by DBE. Eight patients had concomitant gastric ulcers. Gastrointestinal symptoms prior to DBE were present in 36.8% of the patients and, after follow-up, all of them persisted with some of the symptoms. Bleeding was reported by three patients at baseline and persisted in only one patient. The frequency of treatment with steroids and immunomodulators was 31.6% and 57.9% at baseline, respectively, and 21% in both at the end of the follow-up. No patient was treated with biologics at the time of the DBE procedure and the current rate of biologic use is 21%. **Conclusion** – Small bowel involvement in Behçet's disease was frequently demonstrated by DBE even in asymptomatic patients. Understanding clinical evolution of the disease over the years and the impact of such diagnosis still represents a challenge, possibly with the need for novel treatment.

Keywords – Behçet's disease; double-balloon enteroscopy; ulcers; small intestine; long-term.

INTRODUCTION

Behçet's disease (BD) was first described by Hulusi Behçet in 1937, and represents a rare chronic immune-mediated disorder usually manifested by oral and genital ulcers and uveitis[1]. It is characterized by relapses and clinical remissions cycles which can lead to life-threatening depending on the involved complications[2].

The International Group for the Study of Behçet's Disease (ISGBD) defined a criteria for BD diagnosis, with 85% sensitivity and 96% specificity. ISGBD criteria requires recurrent oral ulcer with at least three episodes in 12 months, associated with two of the following findings: genital ulcer, eye lesions, skin lesions and positive pathergy test, which is characterized by the development of a wheal or pustule at the needle prick site within 48 hours[3].

BD is mainly diagnosed between the third and fourth decade of life[4,5] and it has been reported worldwide, although some cases cluster along the old "Silk Road", which extends from East Asia to the Mediterranean basin[6].The estimated prevalence of BD on the "Silk Road" is 14 cases per 100,000 inhabitants[7]. One of the highest incidence has been reported in Anatolia, Turkey, estimated at 420 cases per 100,000 inhabitants[8]. Japan also has a different rate than Western countries, 15 cases per 100,000 inhabitants. On the other hand, it was observed in countries such as United Kingdom, USA, Germany and Portugal with incidence rates of 0.6, 0.12, 4.16 and 2.4 cases per 100,000 inhabitants, respectively[9-11]. Although controversial, some studies have shown that men and women are equally affected[9], with arthritis occurring more frequently in the female population[12].There is an association between the major histocompatibility complex HLA–B51 allele and BD, which is present in 67.3% of cases[13,14] but the association with environmental factors has also been described[15].

The frequency of gastrointestinal tract (GIT) involvement among patients with BD varies from 2.8% to 58% in different cohorts[16]. Peker et al. highlighted three reasons why the BD diagnosis of GIT lesions is a challenge: first, it is a rare disease; second, mild symptoms may be overlooked; and lastly, the absence of symptoms despite of the presence of GIT lesions[17]. Moreover, other diseases, like Crohn's disease, have similar BD symptoms making differential

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diagnosis difficult[18]. Thus, in patients presenting GIT symptoms, abdominal imaging is required, such as barium study x-ray[19], computed tomography[20], and magnetic resonance enterography[17].

Zou et al., who performed upper and lower gastrointestinal endoscopies on 168 Chinese patients, showed that 35.1% of them presented GIT lesions, including some asymptomatic patients[21]. Few studies have evaluated the small bowel in patients with BD by video capsule endoscopy[22-24], however there is a paucity of studies with balloon-assisted enteroscopy, either double balloon enteroscopy (DBE) or single-balloon enteroscopy, which has already been described as a safe, and effective method for this kind of assessment[25].

Given that GIT manifestations of BD are associated with significant morbidity and mortality, the appropriate staging of small bowel involvement is of ultimate importance for the proper management of the disease. Thus, the aim of this study was to describe the GIT small bowel lesions diagnosed by DBE and to verify if these findings were associated to the presence of GIT symptoms and disease activity after 15 years of follow-up.

METHODS

This is a single-center prospective analysis of a retrospectively collected database cohort. (FIGURE 1).

Nineteen patients, aged over 18 years, with an established diagnosis of BD, according to the International Study Group for Behçet's disease criteria[26], underwent DBE between 2005 and 2006 for small bowel assessment. Medical evaluation, including anamnesis and physical exam regarding the presence of abdominal pain, diarrhea and gastrointestinal bleeding was assessed within a 30-day period previously to the performance of DBE. All DBE procedures were performed by a single experienced endoscopist. BD patients were treated according to the outpatient clinic protocol.

Between January and June 2020 these patients were re-evaluated for the presence of abdominal pain, diarrhea and gastrointestinal bleeding. All patients were followed by a single physician in the outpatient clinic.

Ethical approval was obtained from institutional and national Ethics Committee, registered under CAAE 35869520.9.0000.0068.

RESULTS

DBE was performed in 19 patients with an established diagnosis of BD, under deep sedation without complications. Twelve (63.2%) patients were female, and the mean age was 37 years (34 to 80 years-old) at the time of DBE. Mean disease duration at baseline was 24 years (18–40).

Eleven patients had no GIT symptoms, and eight patients presented either abdominal pain, gastrointestinal bleeding or diarrhea.

The average procedure time was 1 hour and 30 minutes (ranging of 1 to 3 hours), and the ileum was achieved in all patients but one. Small bowel ulcers were diagnosed in 78.9% (15/19), with 63.1% of jejunal involvement (12/19). Two patients presented only small bowel edema and two were normal by DBE (FIGURE 2 and FIGURE 3). Eight patients had concomitant gastric ulcers.

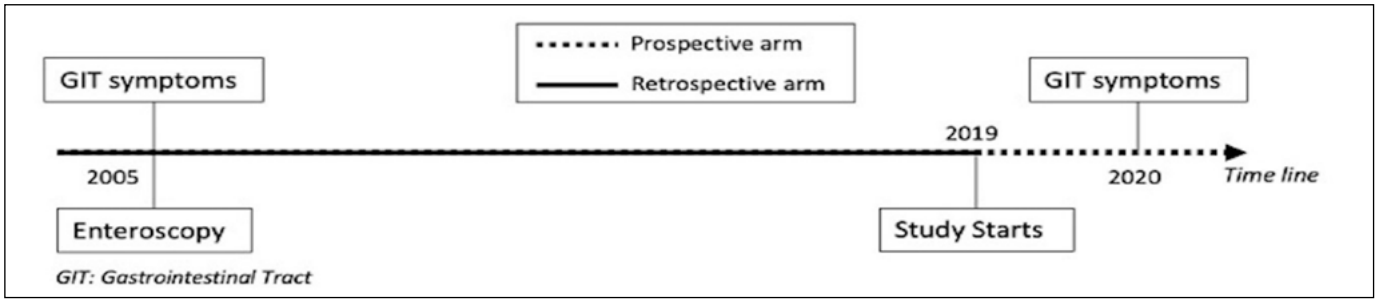

FIGURE 1. Algorithm of the Study Design.

Case	Gender	Current Age (years)	Current Disease Durantion (years)	Enteroscopy Gain	Enteroscopy Findings	Distribution Pattern
1	F	37	25	Medium Ileum	Ileal ulcers < 5 mm	Multiple
2	F	41	18	Medium Ileum	Duodenal and Jejunal ulcers < 5 mm	Multiple
3	F	54	20	Proximal Ileum	Duodenal and Jejunal ulcers < 5 mm	Multiple
4	F	45	25	Proximal Ileum	Jejunal Edema and Lymphangiectasis	Multiple
5	F	48	18	Proximal Ileum	Normal	–
6	M	58	22	Proximal Ileum	Gastric and Jejunal ulcers < 5 mm	Multiple
7	M	59	34	Proximal Ileum	Duodenal and jejunal ulcers < 5mm	Multiple
8	M	51	20	Proximal Ileum	Ileal Edema	–
9	F	56	30	Proximal Ileum	Duodenal, Jejunal and Ileal ulcers < 5 mm	Multiple
10	M	44	20	Proximal Ileum	Gastric, duodenal and jejunum ulcers >5, < 10 mm	Multiple
11	F	80	40	Medium Ileum	Gastric and Jejunal ulcers < 5 mm	Multiple
12	M	58	19	Proximal Ileum	Gastric and Jejunal ulcers < 5 mm	Multiple
13	F	62	19	Terminal Ileum	Gastric ulcers < 5 mm	Multiple
14	M	43	27	Proximal Ileum	Duodenal and Jejunal Ulcers < 5 mm	Multiple
15	F	41	18	Medium Ileum	Gastric and Duodenal ulcers < 5 mm	Multiple
16	F	58	29	Proximal Jejunum	Jejunal ulcers > 5, <10 mm	Multiple
17	F	75	19	Terminal Ileum	Gastric, Duodenal, Jejunal and Ileal ulcers < 5 mm	Multiple
18	M	51	21	Distal Ileum	Ileal ulcers < 5 mm	Mulitple
19	F	34	29	Proximal Ileum	Gastric, Duodenal and Jejunal ulcers < 5 mm	Mulitple

FIGURE 2. Clinical features of patients with Behçet's Disease and Enteroscopy Findings.

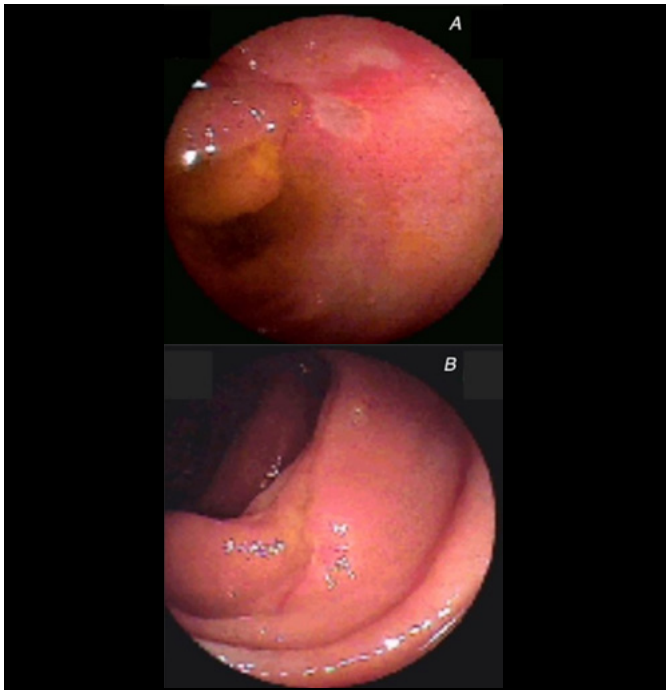

FIGURE 3. A) Case 18: multiple ulcers in distal ileum. **B)** Case 10: Jejunal ulcer.

GIT symptoms prior to DBE were present in 36.8% of the patients and, after follow-up, all of them persisted with some of the symptoms (FIGURE 4). Bleeding was reported by 3/19 patients at baseline and persisted in only one patient.

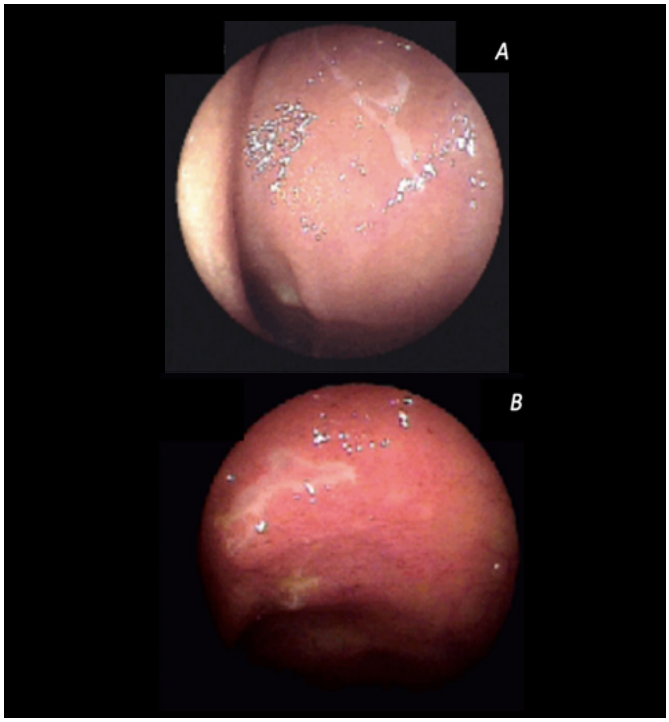

FIGURE 4. A) Case 19: Superficial ulcer covered by fibrin in the duodenum. **B)** Case 17: Presence of ulcers covered by fibrin in the ileum.

Treatment at baseline and at the end of follow-up is described in FIGURE 5. The frequency of treatment with steroids and immunomodulators was 31.6% and 57.9% at baseline, respectively, and 21% in both at the end of the follow-up. There was no patient using immunobiologicals at the time of the DBE procedure, and currently, about 21% of them are using them.

	Gastrointestinal symptons in 2005-06			Gastrointestinal symptons in 2020		
Case	Abdominal Pain	Diarrhea	Gastrointestinal Bleeding	Abdominal Pain	Diarrhea	Gastrointestinal Bleeding
1	–	–	–	–	–	–
2	–	–	–	–	–	–
3	+	+	+	+	–	–
4	+	+	+	+	–	–
5	–	–	–	–	–	–
6	–	–	–	–	–	–
7	+	–	–	+	–	–
8	–	–	–	–	–	–
9	–	–	–	–	–	–
10	–	–	–	–	–	–
11	+	–	–	+	+	–
12	–	–	–	–	–	–
13	–	–	–	–	–	–
14	–	–	–	–	–	–
15	+	–	–	+	–	–
16	+	–	–	+	–	–
17	–	–	–	–	–	–
18	–	–	+	–	–	+
19	–	–	–	–	–	–

FIGURE 5. Previous and Current Gastrointestinal Symptoms of patients with Behçet's Disease.

At the time of DBE, all patients were taking some medication (FIGURE 6). Eleven patients were using immunosuppressants, being one on immunosuppressive monotherapy and nine on immunosuppressants associated with prednisone and colchicine. There were also three patients using colchicine associated with thalidomide. Over the 15-years follow-up, six patients have used at least one immunobiological.

DISCUSSION

Small bowel ulcers were frequently diagnosed by DBE in BD patients, even in those asymptomatic from the gastrointestinal point of view. However, the impact of this finding still represents a challenge on the long-term clinical progression of the disease.

Small bowel endoscopy have been useful in detecting and staging lesions involving the GIT in BD. DBE allows the assessment of the entire small intestine[27], with direct visualization of the lesion, tissue biopsies and, possible, treatment[25,28,29]. Nowadays, small intestine assessment through DBE has been rarely performed in BD patients, since video capsule endoscopy represents a less invasive procedure, despite of not allowing biopsies.

In the present study, DBE demonstrated that the jejunum was the most affected region, although the duodenum and the ileum could also present some ulcers[30]. Accordingly, a Brazilian study using capsule endoscopy, demonstrated that the jejunum was affected in 80%, presenting erosions and ulcers[24].

Of all asymptomatic patients (12/19) at the time of DBE, 52.6% of them presented lesions in the small intestine. This rate is considerable higher than the reported frequencies ranging from 3% to 25%[2,31-33] from studies that evaluated only lower and upper GIT, reinforcing the importance of total small bowel evaluation. Ileocecal region was previously described as the most commonly affected region[16].

Case	Treatment at DBE period	Current Treatment	Surgical History
1	colchicine and azathioprine	colchicine	No
2	azathioprine, chloroquine, colchicine and prednisone	gabapentin, colchicine and amitriptyline	No
3	colchicine, fluoxetine and methotrexate	azathioprine, chloroquine, amitriptyline, cyclobenzaprine, fluoxetine and prednisone	No
4	prednisone and sulfasalazine	certolizumab 200mg every 15 days, methotrexate, prednisone, gabapentin and amitrptyline	No
5	cyclosporine, colchicine and sulfasalazine	infliximab every 10 weeks	No
6	cyclosporine and prednisone	colchicine	No
7	colchicine, indomethacin, methotrexate, prednisone and benzathine penicillin monthly	methotrexate	No
8	colchicine	without medication	No
9	colchicine and thalidomide	without medication	Cholecystectomy
10	chlorambucil, thalidomide, colchicine, chloroquine and benzathine penicillin monthly	infliximab every 10 weeks	No
11	raloxifene	without medication	Cholecystectomy
12	colchicine, prednisone, amitriptyline and thalidomide	colchicine	No
13	amitriptyline, azathioprine, chloroquine, colchicine and pentoxifylline	amitriptyline and colchicine	No
14	cyclosporine, prednisone and colchicine	colchicine	No
15	colchicine and amitriptyline	without medication	No
16	methotrexate, fluoxetine, chloroquine and pentoxifylline	amitriptyline, gabapentin and colchicine	Cholecystectomy
17	azathioprine	methotrexate, prednisone and secukimumab	No
18	cyclosporine, pentoxifylline and colchicine	without medication	No
19	colchicine	prednisone and colchicine	Appendectomy

FIGURE 6. Previous and Current treatment of patients with Behçet's Disease.

Stomach is usually lesser affected in BD. However, one study of Twain, including 28 patients, demonstrated a prevalence of 43% of gastric involvement, besides isolated duodenal ulcers or both[34]. Higher rates of minor gastric ulcers were also observed during anterograde DBE in the present study, and the majority had concomitant small bowel segment involved.

The most prevalent described GIT manifestations associated with BD are abdominal pain, diarrhea and bleeding[35], mostly being mild symptoms[36]. After long-term follow-up and clinical management, only one patient persisted with bleeding. It is important to mention that the presence of small bowel ulcers or erosions might cause occult bleeding leading to anemia in these patient population.

Although BD may progress with severe GIT complications, such as fistulas or perforations[37], no major complication was detected in this cohort followed over a 15-year period.

The treatment for GIT manifestations in BD is not standardized, with different classes of medications being used for each symptom presented, and it is also based on severity and complications[38]. Even though the majority of patients included in this analysis were asymptomatic, it was observed a high proportion of small bowel lesions. Such endoscopic findings might be relevant, since small intestine lesions may contribute to a worse prognosis over the years, increasing the morbidity and mortality[16]. However, whether the proactive management of small bowel lesions in asymptomatic patients aiming changing in disease course is unknown. Noteworthy, for other immune-mediated diseases affecting GIT, such as Crohn's disease, early intervention and disease monitoring is associated with better long-term outcomes[39]. In this study, it was not possible to evaluate disease progression, as patients were not reassessed by DBE, but it is important to highlight that and the proportion of patients presenting GIT symptoms remained stable over time.

The most widely used medications, such as five aminosalicylic acid, corticosteroids and immunomodulators[40], anti-tumor necrosis factors, including infliximab and adalimumab, have recently been included in the arsenal of new treatments of different manifestations of BD, including GIT, with good efficacy and safety[38,41]. This temporal trend was clearly demonstrated in this cohort with a marked increase in the use of biological therapy over time. Other promising immunobiologicals, such as anti-interleukin 1, 6, 17 and 12/23 need further studies to demonstrate their effectiveness in treating GIT symptoms of BD[42].

This study showed that there are patients who presented GIT symptoms and patients that do not presented GIT symptoms, as recently suggested by some authors, concerning different inflammatory pathways for distinct BD phenotypes[43,44]. This fact corroborates the complexity of the disease and the difficulty of its treatment and management.

The study has some limitations, including the small sample size and the fact that data was obtained from one single institution. However, the strong points are the long-term follow-up of a rare disease and the evaluations carried out by a single professional.

CONCLUSION

The early diagnosis of small bowel lesions in BD patients, even in asymptomatic patients, might have an impact on therapeutic management.

Thus far, there is no curative treatment to BD. Understanding clinical evolution of the disease over the years and the impact of such diagnosis, still represents a challenge, possibly with the need for novel treatment.

New studies with long-term endoscopic follow-up will be able to determine whether the disease progresses or not endoscopically.

Authors' contribution

Facanali CBG: substantial contributions to the conception, acquisition, interpretation of data work. Facanali Junior MR: formal analysis of data for the work. Ribeiro Junior U: drafting the work and revising it critically for important intellectual content. Queiroz NSF: drafting the work and revising it critically for important intellectual content. Carlos Sobrado Junior CW: final editing/end reviewing. Safatle-Ribeiro AV: project administration, supervision, enteroscopy examination. Final approval of the version to be published. Guarantor of the article.

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Facanali CBG, Facanali Junior MR, Ribeiro Junior U, Queiroz NSF, Sobrado Junior CW, Safatle-Ribeiro AV. O intestino delgado é amplamente afetado na doença de Behçet: um acompanhamento de longo prazo dos sintomas gastrointestinais. Arq Gastroenterol. 2022;59(1):117-22.

RESUMO – **Contexto** – A doença de Behçet é uma doença imunomediada rara que pode afetar o trato gastrointestinal. A prevalência e extensão do envolvimento do intestino delgado é desconhecida. **Objetivo** – O objetivo deste estudo foi descrever as lesões do intestino delgado diagnosticadas por enteroscopia de duplo balão (EDB) e verificar se esses achados estavam associados à presença de sintomas gastrointestinais e atividade da doença após seguimento de longo prazo. **Métodos** – Este estudo incluiu 19 pacientes com doença de Behçet que foram submetidos a EDB. Após seguimento médio de 15 anos, os achados endoscópicos foram associados à presença de sintomas gastrointestinais, atividade da doença e terapia atual por meio de coleta de prontuário eletrônico. **Resultados –** Um total de 63,2% dos pacientes eram do sexo feminino e a média de idade era de 37 anos no momento da EDB. A duração média da doença no início do estudo foi de 24 anos. 11 pacientes não apresentaram sintomas gastrointestinais e oito pacientes apresentaram dor abdominal, sangramento gastrointestinal ou diarréia. O tempo médio do procedimento foi de 1 hora e 30 minutos e o íleo foi atingido em todos os pacientes, exceto em um. Úlceras de intestino delgado foram diagnosticadas em 78,9%, sendo 63,1% de acometimento jejunal. Dois pacientes apresentaram apenas edema de intestino delgado e dois apresentaram EDB normais. Oito pacientes tinham úlceras gástricas concomitantes. Sintomas gastrointestinais prévios à EDB estavam presentes em 36,8% dos pacientes e, após o seguimento, todos persistiram com alguns dos sintomas. Sangramento foi relatado por três pacientes no início do estudo e persistiu em apenas um paciente. A frequência de tratamento com esteroides e imunomoduladores foi de 31,6% e 57,9% no início do estudo, respectivamente, e 21% em ambos ao final do seguimento. Nenhum paciente foi tratado com biológicos no momento da EDB e a taxa atual de uso de biológicos é de 21%. **Conclusão** – O envolvimento do intestino delgado na doença de Behçet foi frequentemente demonstrado por EDB mesmo em pacientes assintomáticos. Compreender a evolução clínica da doença ao longo dos anos e o impacto de tal diagnóstico ainda representa um desafio, possivelmente com a necessidade de novos tratamentos.

Palavras-chave – Doença de Behçet; enteroscopia com duplo balão; úlceras; intestino delgado; longo prazo.

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REVIEW

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Probiotic, prebiotic or symbiotic supplementation impacts on intestinal microbiota in patients with nonalcoholic fatty liver disease: a systematic review

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ABSTRACT – **Background** – Supplementation with probiotics, prebiotics and symbiotics has shown positive effects on clinical markers and risk factors for non-alcoholic fatty liver disease (NAFLD). **Objective** – To evaluate the effect of supplementation with probiotic, prebiotic or symbiotic on intestinal microbiota in NAFLD patients. **Methods** – Two investigators conducted independently search for articles in the Medline databases, via PubMed, Web of Science, Embase, Scopus, Lilacs, Central Cochrane Library, Clinical Trials.gov and on the Ovid platform for the gray literature search. **Results** – A total of 3,423 papers were identified by searching the electronic databases; 1,560 of them were duplicate and they were excluded; 1,825 articles were excluded after reading the title and abstract. A total of 39 articles were select to reading, however only four articles met the eligibility criteria to include in this systematic review. Three of the included studies that used prebiotic or symbiotic supplementation showed that after the intervention there were changes in the intestinal microbiota pattern. Only in one study such changes were not observed. A high risk of bias was observed in most assessments. **Conclusion** – Although there is a possible change in the gut microbiota of individuals with NAFLD after supplementation with symbiotics or prebiotics, a clinical indication as part of NAFLD treatment is not yet possible.

Keywords – Non-alcoholic fatty liver disease; probiotics; prebiotics; symbiotics; intestinal microbiome.

INTRODUCTION

The relationship between the intestine and disease predisposition has been the subject of many studies, especially in experimental animal studies[1]. When there is a dysregulation of intestinal homeostasis, the increase in intestinal permeability, as well as an increase in the amount and/or change in the type of bacteria in the gastrointestinal tract, leads to a bacterial translocation with transport of bacteria and bacterial products from the intestinal lumen to the blood[2].

This bacterial translocation seems to be one of the mechanisms that can predispose to non-alcoholic fatty liver disease (NAFLD)[3], which is characterized by the accumulation of triglycerides in the cytoplasm of hepatocytes in patients with no history of alcohol intake or little intake (less than 20 g/day), presenting a evolutionary potential that can vary from isolated hepatic steatosis, to non-alcoholic steatohepatitis (NASH), progressing to varying degrees of necroinflammation[4].

NAFLD is currently considered the most common cause of chronic liver disease, with an estimated worldwide prevalence of 25% of the general population. The adoption of new diagnostic criteria has been discussed, as well as a new nomenclature called fatty liver disease associated with metabolism[5].

There is still no drug therapy that can control the evolution of NAFLD, and lifestyle interventions, including changes in diet and regular exercise, are the only effective and recommended measures[4].

Studies show that patients with NAFLD appear to present changes in the intestinal microbiota, and an increase in the occurrence of bacterial overgrowth of the small intestine (SIBO). These changes seem to be associated with the severity of NAFLD[6-8]. Thus, in an attempt to intervene in the intestinal microbiota of these patients with NAFLD, the use of probiotic, prebiotic or symbiotic supplements has been the subject of recent studies[9-11].

Recent systematic reviews have evaluated the effect of supplementation of probiotics, prebiotics or symbiotics on clinical markers and risk factors for NAFLD[9-12]. The results of these studies are promising, since the use of these supplements was favorable in reducing fasting blood glucose and insulin[9,11], total cholesterol[11,12], triglycerides[11], alanine aminotransferase (ALT), aspartate aminotransferase (AST)[10-12], as well as in tumor necrosis factor alpha (TNF-α)[11,12]. However, all studies highlight the importance of more evidence that can evaluate the dose-response effect of supplementation, as well as the probiotic strains used.

This systematic review aimed to evaluate the impact of pro-

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biotic, prebiotic or symbiotic supplementation on gut microbiota of NAFLD patients, being conducted according to the guidelines for a systematic review.

METHODS

The study was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) as a systematic review and meta-analysis under registration number CRD42019133407. Preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) were used as a reference for protocol writing[13].

The research articles that contained the following search terms in the title or abstract fields were identified in the Medline via PubMed, Web of Science, Embase, Scopus, Lilacs, Central Cochrane Library, ClinicalTials.gov, and the Ovid Gray Literature Platform, between the months of April 2019 to May 2021. Thus, the descriptors were defined based on the Medical Subject Heading (MeSH); health science descriptors (DeCS) and the EMTREE. Boolean operators "AND" and "OR" were used in all combinations. Thus, the search was carried out using the following terms: ("nonalcoholic fatty liver disease" OR "NAFLD" OR "nonalcoholic fatty liver disease" OR "fatty liver, nonalcoholic" OR "fatty livers, nonalcoholic" OR "liver, nonalcoholic fatty" OR "livers, nonalcoholic fatty" OR "nonalcoholic fatty liver" OR "nonalcoholic fatty livers" OR "nonalcoholic steatohepatitis" OR "nonalcoholic steatohepatitides" OR "steatohepatitides, nonalcoholic" OR "steatohepatitis, nonalcoholic") AND ("probiotics" OR "probiotic") AND ("symbiotic") AND ("prebiotics" OR "prebiotic).

The included studies were not limited to the language and year of publication.

Two authors independently decided which studies should be included in this review. Any disagreements were resolved by discussion or mediation by third parties. Only the terms for the components I (intervention) and P (population) were used in the data search.

Were included clinical trials involving adults over 18 years of age and under or equal to 65 years of age, of both sexes and with clinical diagnosis of NAFLD, hepatic statosis by abdominal ultrasound or computed tomography or magnetic resonance imaging or liver biopsy, excluding other liver diseases and alcohol consumption <20 g/day, were included in this study. Animal studies, in vitro, review articles, case reports, conference abstracts and proceedings, observational studies, studies in which individuals used antibiotics or had other clinical conditions such as SIBO or those that did not meet the inclusion criteria, were excluded.

For the intervention group, supplementation with probiotics, prebiotics or symbiotics was considered, being allowed the use of any probiotic strain, without limiting the dose administered and duration of follow-up. For the comparison group, the treatment was not specified. Regarding the evaluation of the intestinal microbiota, there was no restriction on the method used.

The titles and abstracts were initially read to exclude irrelevant articles. The relevant articles were read in full and evaluated according to the eligibility criteria. The reference lists of the articles found and thematic reviews were also searched.

The original articles included in the final list were read in full and the information contained in them was recorded in a specific Excel® spreadsheet, created by a single researcher and standardized for synthesis of evidence.

The risk of bias in the studies included in this review was assessed by two independent reviewers, according to the Cochrane Collaboration criteria for the development of systematic intervention reviews.

This tool consists of two parts, which contain seven domains. Judgment on bias risk for each of the domains analyzed was classified into three categories: bias low risk, bias high risk or bias uncertain risk. Subsequently, the results were entered into the Review Manager 5.3 tool to create figures that could summarize the judgment of risk of bias in the clinical trials included in this review[14].

The results presented by the included articles were not combinable, limiting the meta-analysis execution.

RESULTS

Selection and characteristics of studies

A total of 3,423 references were identified by searching the electronic databases. Of these, 1,560 articles were deleted after duplicate removal and 1,825 articles were deleted after reading the title and abstract. The complete reading was performed in 39 articles of electronic search and manual search in the references of thematic reviews. After reading in full, only four articles met the eligibility criteria and were included in this systematic review. The reasons for the exclusion of the articles were due to the non-assessment of the effect of supplementation on the characteristics of the microbiota (n=9), literature review articles (n=17), studies with animals (n=6), studies with results unpublished (n=2) and full article not available in the database (n=1) (FIGURE 1).

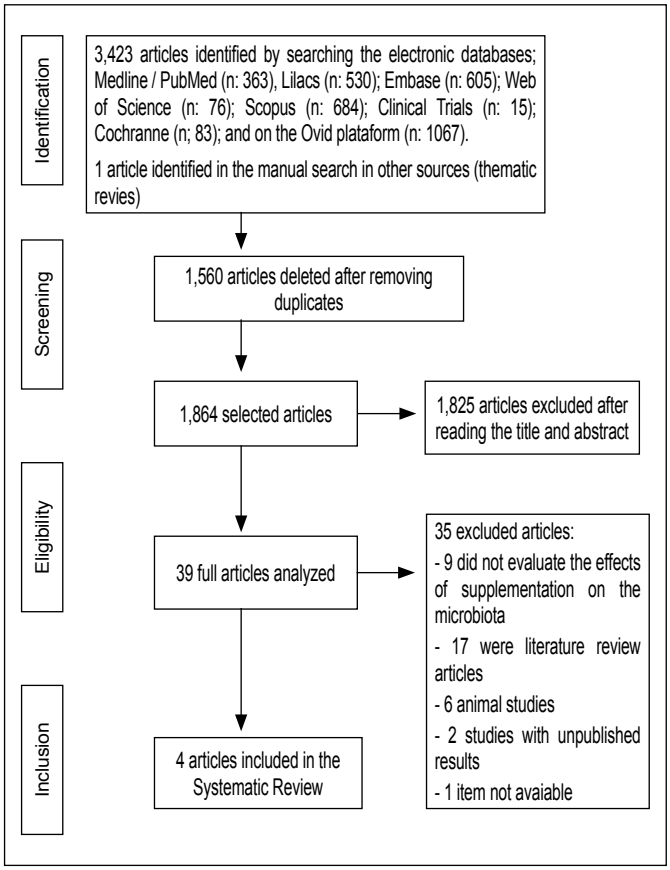

FIGURE 1. Flowchart for selecting articles included in this Systematic Review.

The included studies were carried out in China[15], Ukraine[16], Canada[17], and England[18]. Information was collected between 2009 and 2020 and the intervention time ranged from 1 month to 12 months. Wong et al.[15], Manzhalii et al.[16], and Scorlett et al.[18] used symbiotic supplementation containing a mixture of probiotics with prebiotics and Bomhof et al.[17] used isolated probiotic. The studies involved the only adult population and manuscript published in English.

Population characteristics

The four included studies totaled a sample of 194 patients evaluated, comprising 98 from the intervention group and 96 from the control group, 102 (52.6%) of whom were male. Manzhalii et al.[16] did not include obese individuals (BMI >30 kg/m^2), nor those with any associated comorbidity, such as diabetes and hypertriglyceridemia (TABLE 1).

Methods for characterization of intestinal microbiota

For the characterization of the intestinal microbiota, indirect methods were used, based on the count of bacteria in the fecal sample. Wong et al.[15], Bomhof et al.[17] and Scorlett et al.[18] characterized the fecal microbiota through the analysis of DNA samples for sequences of 16S rRNA by pyose sequencing. Manzhalii et al.[16] did not describe the technique used, only mention that the microbial composition in the feces was quantified.

Intervention characteristics

Three studies used symbiotic preparations[15,16,18], and Bomhof et al.[17] used prebiotic supplementation. All preparations differed in composition, dosage and intervention time. Only in the studies by Wong et al.[15] and Manzhalii et al.[16] the participants were instructed to make specific dietary changes. As for the prebiotic, all used fructooligosaccharide (FOS) and oligofructose (TABLE 2).

Effect of intervention on intestinal microbiota

Wong et al.[15] observed according to the quantification of bacteria in fecal samples, that after the intervention there was no significant change in bacterial biodiversity (P<0.05). Prior to the intervention, all NASH patients had a composition of 67.6% *Bacteroidetes* and 22.3% *Firmicutes*, and after 6 months of dietary

TABLE 1. Characteristics of the population and studies included in this Systematic Review.

Author	Country/ year	Study design	N	Age (years)	Sex (M/F)	NAFLD diagnostic method	BMI (≥25kg/m^2)	Method for evaluation of intestinal microbiota
Wong et al.	China 2013	Randomized controlled trial	I: 7 C: 9	I: 46±6 C: 56±9 P=0.03	I: 5/2 C: 4/5 P=0.36	Liver biopsy	I: 29.8±5.3 C: 28.6±6.1 P=0.69	Microbial composition in fecal sample
Manzhalii et al.	Ukraine 2017	Unblinded prospective randomized controlled trial	I: 38 C: 37	I: 44.3±1.5 C: 43.5±1.3 P=0.62	I: 11/27 C: 16/21 P=0.20	Upper abdominal US and elastography	I: 26.4±0.8 C: 26.6±0.7 P=0.85	Microbial composition in fecal sample
Bomhof et al.	Canada 2019	Pilot clinical trial	I: 8 C: 6	I: 45.3±5.6 C: 53.3±4.8	I: 5/3 C: 3/3	Liver biopsy	I: 33.7±3.0 C: 34.8±2.2	Microbial composition in fecal sample
Scorletti et al.	England 2020	Double-blind, randomised, placebo-controlled trial	I: 45 C: 44	I: 50.2±12.4 C: 51.6±13.1	I: 31/14 C: 27/17	Magnetic resonance spectroscopy	I: 32.9±5.5 C: 33.2±4.9	Microbial composition in fecal sample

N: total population; M: male; F: female; NAFLD: Non-Alcoholic Fatty Liver Disease; BMI: body mass index; I: intervention; C: control; US: ultrasound.

TABLE 2. Main results of studies included in this Systematic Review after intervention with probiotic, prebiotic or symbiotic supplementation.

Author	Intervention	Dose/duration of intervention	Treatment for the control group	Diet composition	Characteristics of the intestinal microbiota
Wong et al.	Symbiotic 10^8 CFU L. plantarum + L. *Bulgaricus* + *L. acidophilus* + *L. rhamnosus* + *B.bifidum* + FOS	13 g (02 times a day) 6 months	Diet + exercise	Low in carbohydrates and fats	There was no significant change in bacterial biodiversity after treatment
Manzhalii et al.	Symbiotic 10^8 CFU *L. casei* + *L. rhamnosis* + *L. bulgaris* + *B. longum* + *S. thermophiles* + FOS	1 capsule 3 months	Diet + exercise	Low fat: 30 to 90 g/day low calories: 1800 kcal/day	Increased bacterial abundance toward normal range compared to healthy individuals (P<0.05)
Bomhof et al.	Oligofructose	8 g/d/ 12 sem. 16 g/d/24 sem	Maltodextrin 8 g/d / 12 week 16 g/d / 24 week	Usual diet	Increased *Bifidocaterium sp.* (P=0.017) and reduction of *Clostridium cluster* (P=0.03)
Scorletti et al.	Symbiotic 10^8 CFU *B. animalis* subsp. *lactis* BB-12 + FOS	1 capsule + 4 g (02 times a day) 12 months	Maltodextrin 4 g (2 times a day)	Usual diet	Significant increase in the abundance of *Bifidobacterium* (P<0.001)

CFU: colony forming units; FOS: fructooligosaccharide.

intervention, patients in the control group had a reduction in *Bacteroidetes* to 63.8% and an increase in the number of *Firmicutes* to 24.3%. The presence of adverse effects due to supplementation has not been investigated.

In the study by Manzhalii et al.[16] an increase in bacteria toward the normal range was observed ($P<0.05$) after symbiotic intervention when compared to standard distribution in healthy subjects. No adverse effects have been reported.

Bomhof et al.[17] observed after supplementation during the 36 weeks of intervention, there was an increase in the abundance of *Bifidobacterium spp*. ($P=0.017$) and reduction of *Clostridium cluster* ($P=0.03$) compared to placebo. Both prebiotic and placebo supplementation were associated with increased *L. leptum*, *Faecali bacterium prausnitzii* ($P=0.017$). The presence of adverse effects due to supplementation has not been investigated.

Scorlett et al.[18] found an increase in *Bifidobacterium* abundance ($P<0.001$) in the symbiotic group but not in the placebo group, considering that at the beginning of the study, both groups had no difference in the abundance of *Bifidobacterium* ($P=0.5$). The presence of adverse effects due to supplementation has not been investigated.

Other effects of the intervention

The Manzhalii et al. study[16] showed improvement after treatment in other parameters, reducing total cholesterol, triglycerides, body mass index (BMI), liver enzymes (ALT and AST) and degree of steatosis ($P<0.05$). However, Wong et al.[15] and Bomhof et al.[17] found no changes in serum liver enzyme values and body composition ($P<0.05$), and Scorlett et al.[18] also found no difference in the reduction of liver fat ($P=0.08$), in circulating levels of lipopolysaccharide ($P=0.08$), in the concentrations of short-chain fatty acids (SCFA) ($P=0.21$), nor in bacteria classically linked to inflammation, obesity and NAFLD.

Bias risk assessment

The study by Scorlett et al.[18] was the only one classified as having a low risk of bias in almost all items evaluated. The other studies[15-17] obtained a high risk of bias at the end of the judgment, as they presented answers that led to doubts about the impact of their results or insufficient and/or absent information, preventing proper judgment. The information was considered insufficient or was not present for the following items: generation of the random sequence[16,17], concealment of allocation[16,17], blinding of participants and personnel[15,16], blinding of outcome evaluators[15-17], incomplete results[18], report of selective outcome[14-16], and other sources of bias[15-18]. In relation to other risks of bias, the four studies[15-18] showed a high risk of bias due to the lack of data on the lifestyle of the patients included, no quantitative specification of the dietary intervention and lack of clarity regarding the classification of hepatic steatosis (FIGURE 2).

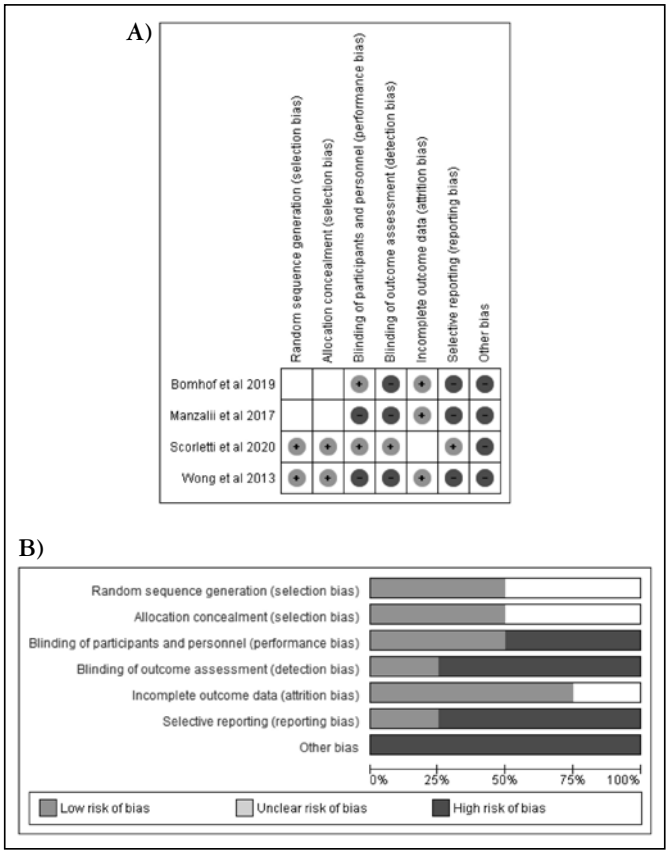

FIGURE 2. Bias risk assessment. **A)** Bias risk summary: review of each bias risk item for each included study. **B)** Bias risk graph: review of each bias risk item (%) for all included studies.

DISCUSSION

This systematic review included studies in which researchers assessed the effect of the symbiotic or prebiotic on the intestinal microbiota in NAFLD patients. Although some studies have shown a change in the abundance of certain strains of bacteria in the intestinal microbiota, the evidence is still not consistent.

For the interpretation of the results on changes in the intestinal microbiota, it is important to highlight that there is no parameter when it comes to a healthy intestinal microbiota, since the most accepted definition is the increase in bacterial diversity and the resilience capacity, that is, the capacity of this microbiota return to a state of equilibrium after a certain disturbance. Thus, it seems very simplistic to define the healthy intestinal microbiota only by specific microorganisms[19].

All studies evaluated here used different techniques for gut microbiota evaluation, as well as differences in the description of results, limiting the conclusion to similar results. This diagnostic limitation is relevant considering the small number of human studies available in the scientific literature and included in this review. Another fact is that patients usually have other associated diseases that may interfere with the composition of the intestinal microbiota[20].

The differences between the techniques of sample evaluation may have contributed to the divergences between the results found, since even being performed the fecal sample analysis the results were described differently between the studies[15-18]. In addition, the small sample size was another factor that may have contributed to the conflicting results between studies.

Participants in the intervention group, in addition to supplementation, were instructed on food intake. For the control group, some received guidance on behavioral changes in relation to regular physical exercise and changes in diet[15,16] and in others the recommendation was to keep the usual diet[17,18]. However, for those who had dietary modifications, it was possible to observe quantitative

variations in the recommendations, which was already expected, as these studies were carried out on different continents, presenting a great cultural diversity. In general, everyone prioritized the food calorie deficit[15,16].

A common feature of most of the included studies was had NASH patients in sample[14-16] which is a more advanced degree of hepatic steatosis in the presence of an inflammatory process. Experimental study[3] show that changes in the intestinal microbiota favor the increase of intestinal permeability and SIBO. There seems to be a relationship between the positive regulation of the toll-like liver receptor (TLR-4) which when bound to lipopolysaccharides, one of the pathogenic bacteria-derived products, activates inflammatory mediators responsible for the development or progression of NASH.

Only one study investigated adverse effects after the use of symbiotic or probiotic, not observing any adverse effects[16]. A recent review evaluated the adverse effects of probiotic strains in humans, concluding that there is heterogeneity between studies in terms of lifestyle, differences in the intestinal microbiota, relevant genetic differences, sex and age of the participants evaluated, and difference in the treatment period or length of stay treatment. And all these factors can lead to divergent results, and more studies are available to elucidate such effects and mechanisms, as this has been one of the treatments for the safe use of supplementation with probiotic strains[21].

As for the other results found, one study[16] observed at the end of the intervention with symbiotic a reduction in the degree of steatosis. However, it is not possible to know that such intervention is effective as part of the treatment of NAFLD[22].

Most studies showed a high risk of bias[15-17], a small sample size[14,16] and heterogeneity as to the type of probiotic strains used, as well as the dose administered and the intervention time[15,16,18]. Such are in line with the results found regarding the effect of supplementation on the intestinal microbiota.

This systematic review presented as limitation the small number of included studies, given the difficulty to evaluate the established outcome and the heterogeneity regarding the methodology and results presented between the studies.

CONCLUSION

This systematic review has shown that although there is a possible change in the intestinal microbiota of individuals with NAFLD after symbiotic or prebiotic supplementation, a clinical indication as part of NAFLD treatment is not yet possible. The factors that most contributed to this result were the heterogeneity between the techniques used for intestinal microbiota evaluation, as well as the small sample size of these studies. It also observed the lack of standardization regarding the type and quantities of probiotic strains, the different dose administered and the duration of treatment. All these observations suggest that more consistent studies are needed to elucidate the real benefits as well as the long-term consequences of the use of probiotics, prebiotics or symbiotics on the intestinal microbiota in NAFLD.

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Authors' contribution

Souza CA: building the protocol, bibliographic search, analyzing the data and building the manuscript. Rocha R: bibliographic search, data input. Almeida NS: bibliographic search, data input. Farias PRF: study design, critical review of draft. Cotrim HP: study design, critical review of draft.

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Souza CA, Rocha R, Costa PRF, Almeida NS, Cotrim HP. Impacto da suplementação com probióticos, prebióticos e simbióticos na microbiota intestinal em pacientes com doença hepática gordurosa não alcoólica: uma revisão sistemática. Arq Gastroenterol. 2022;59(1):123-8.

RESUMO – **Contexto** – A suplementação com probióticos, prebióticos e simbióticos mostrou efeitos positivos sobre marcadores clínicos e fatores de risco para doença hepática gordurosa não alcoólica (DHGNA). **Objetivo** – Avaliar o efeito da suplementação com probióticos, prebióticos ou simbióticos na microbiota intestinal em pacientes com DHGNA. **Métodos** – Dois pesquisadores realizaram buscas independentes de artigos nas bases de dados Medline, via PubMed, Web of Science, Embase, Scopus, Lilacs, Biblioteca Central Cochrane, Clinical Trials.gov e na plataforma Ovid para busca de literatura cinza. Os títulos e resumos foram lidos para excluir artigos irrelevantes. Em seguida, os artigos selecionados foram lidos na íntegra e avaliados de acordo com os critérios de elegibilidade. O risco de viés foi avaliado de acordo com a Cochrane. **Resultados** – Um total de 3.423 artigos foram identificado por meio de busca nas bases de dados eletrônicas; 1.560 deles eram duplicados e foram excluídos; 1.825 artigos foram excluídos após a leitura do título e do resumo. Um total de 39 artigos foram selecionado para leitura, porém apenas quatro artigos atenderam aos critérios de elegibilidade para inclusão nesta revisão sistemática. Três dos estudos incluídos que utilizaram suplementação de prebióticos ou simbióticos mostraram que após a intervenção ocorreram mudanças no padrão da microbiota intestinal. Apenas em um estudo tais mudanças não foram observadas. Um elevado risco de viés foi observado na maioria das avaliações. **Conclusão** – Embora haja uma possível alteração na microbiota intestinal de indivíduos com DHGNA após a suplementação com simbióticos ou prebióticos, uma indicação clínica como parte do tratamento da DHGNA ainda não é possível.

Palavras-chave – Doença hepática gordurosa não alcoólica, probióticos, prebióticos, simbióticos, microbiota intestinal.

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REVIEW

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Better living donor liver transplantation patient survival compared to deceased donor – a systematic review and meta-analysis

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ABSTRACT – Background – Deceased donor liver transplantation (DDLT) is the first choice, but living donor transplantation (LDLT) is an alternative to be considered in special situations, such as lack of donated organs and emergencies. So far, there is no consensus on which transplantation method provides better survival and fewer complications, which is still an open point for discussion. **Methods –** This meta-analysis compared the 1, 3, and 5-year patient and graft survival rates of LDLT and DDLT. We included studies published from April-2009 to June-2021 and adopted the generic model of the inverse of variance for the random effect of hazard ratios. The adequacy of the studies was determined using the Newcastle-Ottawa Scale – NOS (WELLS). **Results –** For patient survival analysis, we included a total of 32,258 subjects. We found a statistically significant better survival for the LDLT group at 1, 3 and 5 years, respectively: 1.35 HR (95%CI 1.10–1.66, *P*=0.005), 1.26 HR (95%CI 1.09–1.46, *P*=0.002) and 1.27 HR (95%CI 1.09–1.48, *P*=0.002). Our meta-analysis evaluated a total of 21,276 grafts. In the overall analysis, the 1-year survival was improved in favor of the LDLT group (1.36 HR, 95%CI 1.16–1.60, *P*<0.0001), while the 3-year survival (1.13 HR, 95%CI 0.96–1.33, *P*<0.13), and 5 (0.99 HR, 95%CI 0.74–1.33, *P*<0.96), did not differ significantly. **Conclusion –** This metanalysis detected a statistically significant greater 1-, 3- and 5-years patient survival favoring LDLT compared to DDLT as well as a statistically significant difference better 1-year graft survival favoring the LDLT group.

Keywords – Liver transplantation; living donor liver transplantation; deceased donor liver transplantation.

INTRODUCTION

The success of solid organ transplants may be superior when using organs from living donors[1]. However, it is necessary to take into account and obtain a balance between the risk/benefit ratio of the recipient and donor in several points: non-existent supply of organs from deceased donors; availability of a close relative willing to serve as a donor; a candidate with a potentially fatal disease for which the transplant saves lives or standardizes referrals; and the belief that the psychological benefit experienced by the donor would outweigh the physical damage and risk of mortality associated with the donation[1,2].

Liver transplantation is a complex medical procedure due to many factors. It is associated with several well-known surgery-related complications, as well as immunosuppression issues. Also, there is a worldwide disproportion between donors and recipients. Therefore, many patients perish during the waiting list period awaiting an organ[3,4].

Worldwide, most liver transplants utilize deceased donors. Living donor liver transplantation has emerged as an alternative due to organ shortage[5,6]. One-year and 5-year patient and graft survival rates of liver transplant patients from deceased and living donors might be similar. Nevertheless, there are still some controversies regarding this issue. Post-operative complications appear to occur more frequently after living donor transplantation (LDLT). Hence, there is still no consensus on which of the two types of transplants is better in terms of survival and complications[6].

In this meta-analysis, we compared patient and graft survival rates of living and deceased donor liver transplantation to amplify the knowledge of this relevant issue.

METHODS

Eligibility criteria

We included studies published from April 2009 to June 2021. Inclusion criteria were patients older than 18 years old undergoing liver transplantation who received grafts from living or deceased donors; patient and graft survival comparison. We did not include cases reports and series as well as publications with insufficient data for analysis.

Search strategy

We searched PubMed/Medline databases up to June 30th, 2021, and used Medical Subject Headings (MeSH) descriptors during the process. The systematic review was performed according to PRISMA protocol[7]. All descriptors were organized and crossed according to the boolean operators "and" and "or". The following search strategy was performed: ("transplant recipients"

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[MeSH] OR "liver transplantation" [MeSH]) AND ("tissue donors" [MeSH] OR "living donors" [MeSH]) AND ("survival" [MeSH] OR "mortality" [MeSH] OR "mortality" [Subheading]) OR "survival analysis" [MeSH] OR "survival rate" [MeSH] OR "tissue survival" [MeSH] OR "graft survival "[MeSH] OR" Kaplan-Meier estimate "[MeSH]). We also searched the references of the identified studies to retrieve other relevant studies.

Data extraction

Two independent researchers selected the articles by title and abstracts, and we further considered eligible studies for a complete reading. If there was uncertainty about the inclusion of any investigation, we designated another evaluator to do the analysis. We collected the data using a predefined collection form which was then revised.

The variables evaluated in the included studies were the title and principal investigator, year of publication, sample size, the average age of donors and recipients, Model for End-stage Liver Disease (MELD) and Child-Pugh scores pre-transplant, patient and graft survival, early post-surgical complications, and liver disease etiology.

Selection of papers

We researched for papers for the last time on May 30, 2021. In the first stage of the search, we found 344 studies and excluded 284 (74 studies had non-compatible study designs and 210 articles dealt with other topics). We selected 60 studies for full reading and ruled out 32 (31 for not addressing the outcome of interest and one for not being available) (FIGURE 1).

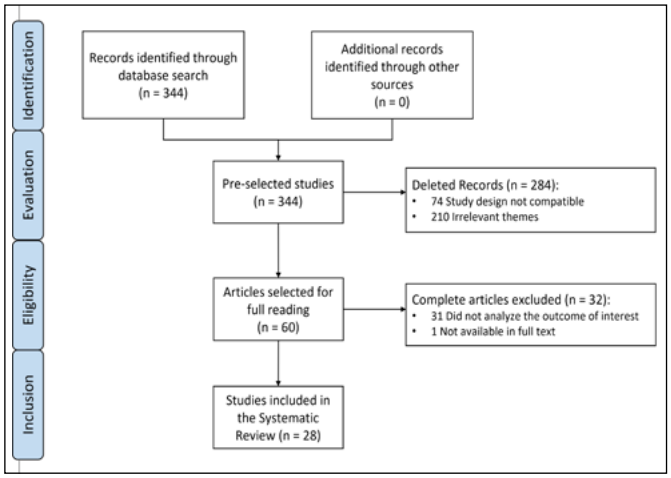

FIGURE 1. Flowchart reporting the process for selection of papers for inclusion in the meta-analysis.

Study risk of bias assessment

The adequacy of the included studies was determined using the Newcastle-Ottawa Scale – NOS (WELLS)[8]. This scale consists of eight questions in three domains, selection, comparability, and exposure or outcome.

Meta-analysis

Survival analysis was determined by extracting hazard ratios (HR) and their respective 95% confidence intervals (95%CI). The studies that did not describe the data of interest descriptively in the text were estimated using Kaplan-Meier graphs when reported; we extracted the information using the online domain application WebPlotDigitizer 4.4[9].

We did the meta-analysis using the Review Manager software (RevMan 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014)[10]. We adopted the generic model of the inverse of variance for the random effect of HR data. The heterogeneity between the included studies was considered as Cochrane's Q, assuming a level of statistical significance of 0.10 for heterogeneity and the I^2 for inconsistencies in the effect size in the treatments, with I^2 <50% low heterogeneity, ≥50% heterogeneity accepted as substantial, and >75%, high heterogeneity[11]. Visual inspection was adopted, using the improved funnel plot with contour for risk of publication bias when the analysis included ten studies[11]. The asymmetry of the plots was evaluated by the Begg and Egger tests[12,13]. We adopted influence analysis by Baujat plot and leave-one-out analysis to evaluate heterogeneity[13]. We used the software R version 3.5.2 (The R Foundation for Statistical Computing)[14]. The Baujat plot is a graph that diagnoses the contribution of individual studies to heterogeneity[14], while the leave-one-out re-analyzes the results by omitting one study per time. For subgroup analysis, we utilized the following characteristics: recipients' age (<50 years; >50 years).

RESULTS

Patients survival

One, 3- and 5-years survival

A total of 32,258 patients were studied, of which 83% corresponded to the Deceased donor liver transplantation (DDLT) group[3,5,12-19,20-27]. When analyzing the HR distribution in the Forrest plot graphs (FIGURE 2), the results demonstrated a statistically significant better survival for the LDLT group (six studies in the 1-year follow-up, seven papers in the 2-year, and 6 in the 3-year follow-up) (FIGURE 2). Of note, the study of Kulik et al.[19] found a better significant survival for the DDLT group at 1-year follow-up (FIGURE 2.A).

The grouped analyzes showed substantial heterogeneity for survival in 1, 3 and 5 years (I^2=73%, 64% and 72% respectively). In the general analysis, it was observed that, for the periods of 1, 3 and 5 years, there was a greater survival of LDLT patients with, respectively: 1.35 HR (95%CI 1.10–1.66, P=0.005), 1.26 HR (95%CI 1.09–1.46, P=0.002) and 1.27 HR (95%CI 1.09–1.48, P=0.002).

When investigating heterogeneity using the Baujat graphic analysis (FIGURE 3), we identified the study by Xiao et al.[3] as the one that most contributed to the heterogeneity in the 1-year follow-up and as the most influential study on the overall results, while Wong et al.[4] was the one that most contributed for the 3-year analysis. The articles by Wong et al.[4] and Hu et al.[5] were the ones that most contributed to the heterogeneity of the 5-year follow-up, respectively.

Applying the leave-one-out method for sensitivity analysis (FIGURE 4), in the one-year survival analysis, we removed the study by Xiao et al.[3], which explained 32% of the heterogeneity, resulting in a favorable effect for the LDLT group, with 1.45 HR (95%CI 1.21–1.73, I^2=40.9%, P<0.0001). In the 3-year survival analysis, the exclusion of the study by Wong et al.[4] explained 20% of the heterogeneity, but it had little influence on the results initially obtained (1.22 HR, 95%CI 1.08–1, 37, I^2=43.5%). When evaluating the 5-year survival, the withdrawal of the studies by Hu et al.[5] and

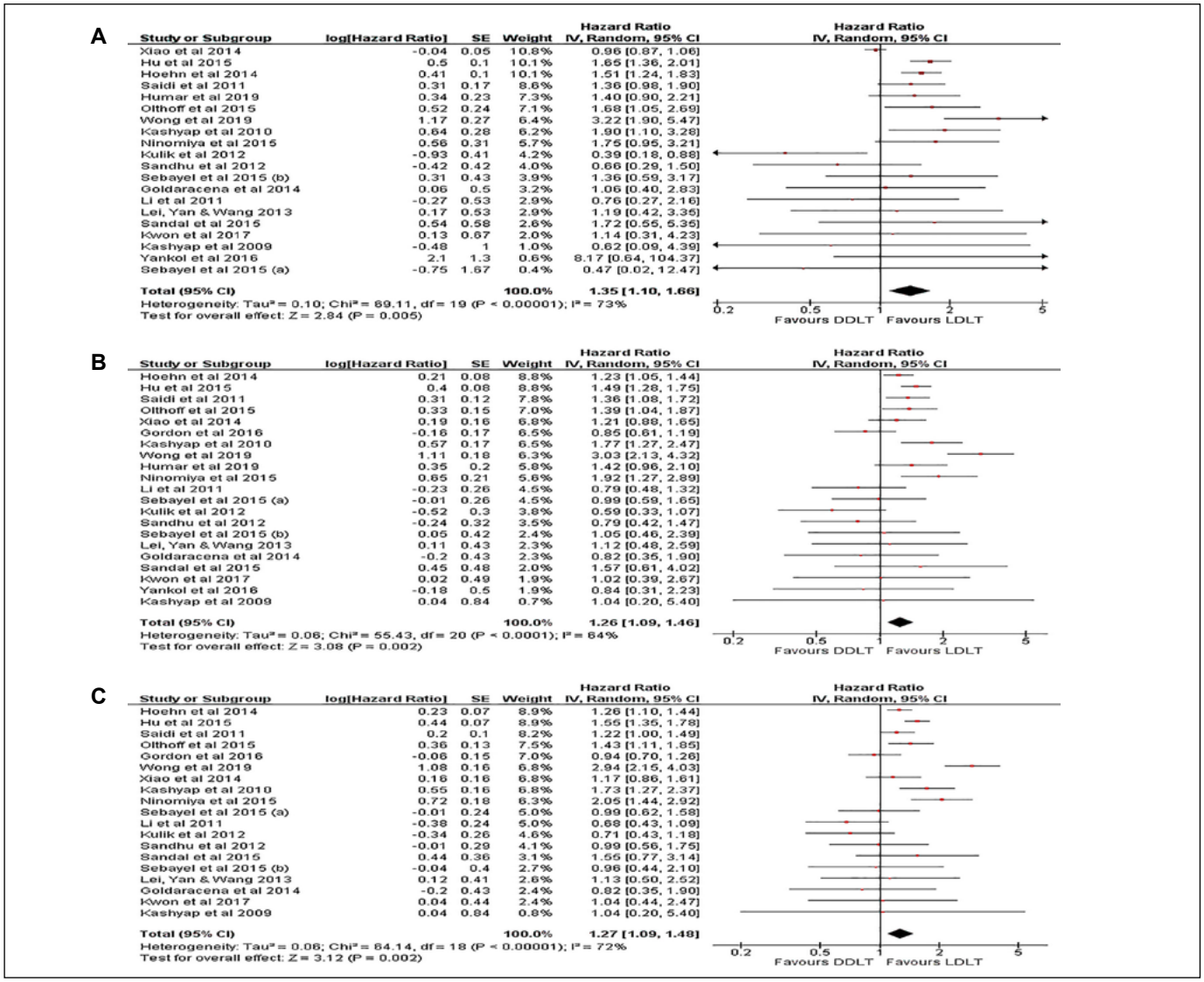

FIGURE 2. Survival of the patient considering the living or deceased donor for liver transplantation: a) 1-year survival, b) 3-years survival and c)-5 years survival.

DDLT: deceased donor liver transplant; LDLT: living donor liver transplant.

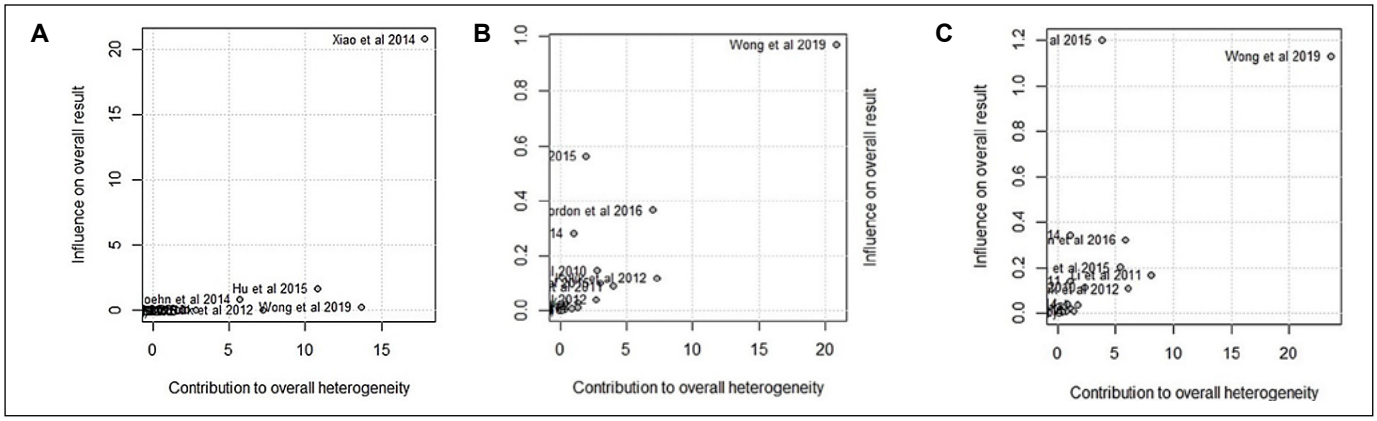

FIGURE 3. Analysis of the heterogeneity by Baujat plot, evaluating survival of patients undergoing liver transplantation: a) 1-year survival, b) 3-years survival and c)-5 years survival.

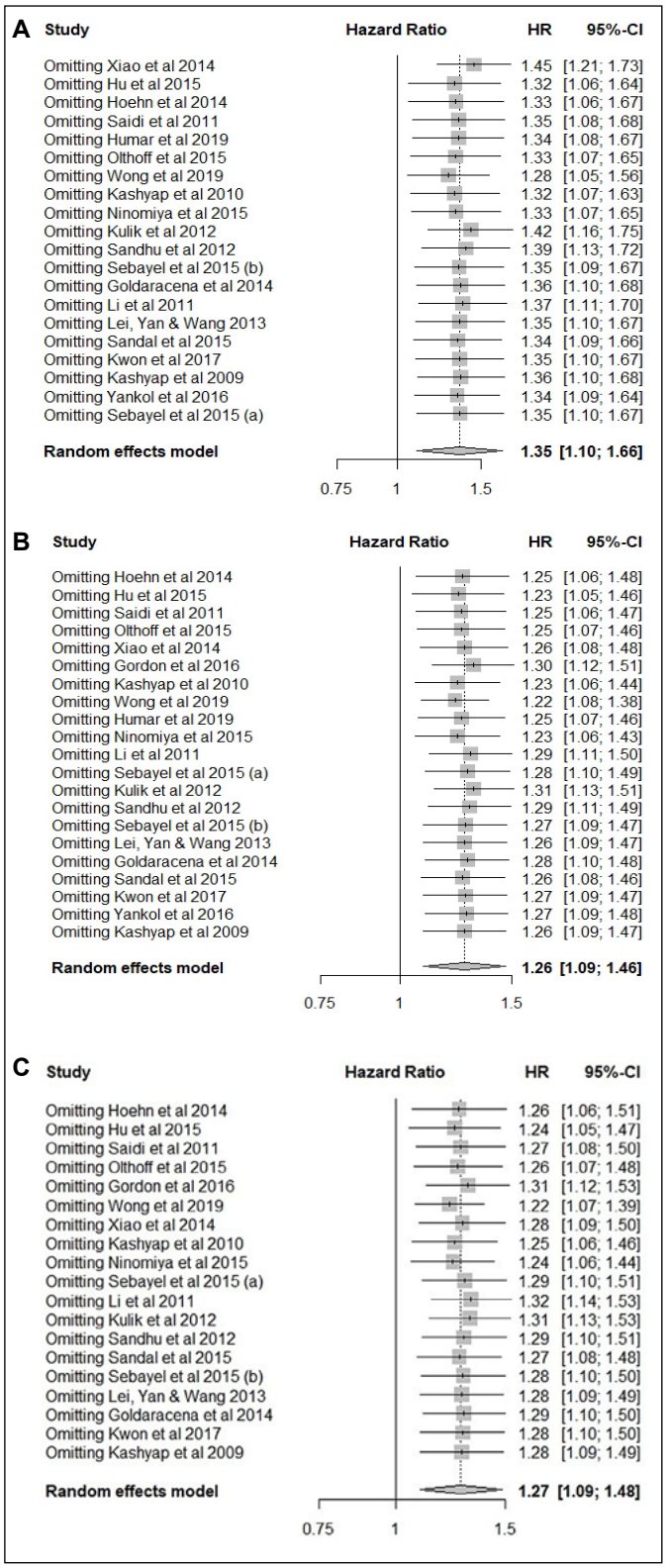

FIGURE 4. Survival analysis of patients undergoing liver transplantation with deceased or living donors, using the leave-one-out method: a) 1-year survival, b) 3-year survival and c) 5-year survival. DDLT: deceased donor liver transplant; LDLT: living donor liver transplant.

Wong et al.[4] did not explain the heterogeneity found (1% and 15%, respectively) as well as did not change the data either, maintaining favorable results for LDLT (1.24 HR, 95%CI 1.04–1.47, I^2=71.2%, *P*=0.0117 and 1.22 HR, 95%CI 1.08–1.38, I^2=56.9%, *P*=0.0022).

We assessed asymmetries by visually inspecting the funnel plots of patient survival at 1, 3, and 5 years of follow-up. However, we did not confirm any asymmetry by the statistical tests of Egger and Begg[12,13].

Regarding the subgroup analysis, we identified an improved patient survival with statistical significance for individuals over 50 years of age in favor of the LDLT group at intervals of 3 and 5 years with, respectively, 1.23 HR (1.04–1.44, I^2=33%, *P*=0.01) and 1.22 HR (1.01–1.48, I^2=58%, *P*=0.04) (TABLE 1).

TABLE 1. Survival analysis considering a subgroup of patients with an age cut-off.

Subgroup (age)	k	Hazard ratios	CI95%	I^2	Weight	*P*
Patient survival at 1 year						
<50	4	1.08	0.68–1.71	72%	31.3%	0.73
≥50	12	1.26	0.95–1.66	68%	68.7%	0.11
Patient survival at 3 years						
<50	4	1.15	0.89–1.49	55%	33.9%	0.29
≥50	12	1.23	1.04–1.44	33%	66.1%	0.01
Patient survival at 5 years						
<50	4	1.18	0.99–1.39	34%	32.6%	0.06
≥50	11	1.22	1.01–1.48	58%	67.4%	0.04

Graft survival

Nine studies were meta-analyzed for graft survival at 1 and 3 years[15,16,19,20,25,28-31], and seven for 5-year survival[15,19,20,25,28,30,31]. Overall, our meta-analysis evaluated 21,276 grafts, 85% of which correspond to the DDLT group. When assessing the HR individual distribution in the Forrest plot, only the studies by Hoehn et al.[31] and Kashyap et al.[20] showed statistical significance in favor of LDLT in the first year. On the other hand, the study from Hoehn et al.[31] was the only one that found statistically significant results, which favored the DDLT group in the fifth year (FIGURE 5.A and 5.C).

The grouped analyzes showed low heterogeneity for survival at 1 and 3 years (I^2=0% and 34% respectively), and high heterogeneity for 5 years (I^2=78%). In the overall analysis, the 1-year survival evaluation showed a statistically significant difference between the groups, favoring the LDLT group (1.36 HR, 95%CI 1.16–1.60, *P*<0.0001), while the 3-year survival (1.13 HR, 95%CI 0.96–1.33, *P*<0.13), and 5 (0.99 HR, 95%CI 0.74–1.33, *P*<0.96), did not differ significantly.

Baujat's graphical analysis (FIGURE 6) identified the study from Hoehn et al.[31] as the main contributor to heterogeneity in 3 and 5 years. The leave-one-out method (FIGURE 7) assessed the impact on the results after removal from the study of Hoehn et al.[31]. It found a statistically significant effect in favor of LDLT in 3 years (1.24 HR; 95%CI 1.08–1.4, I^2=0%, *P*=0.0023), while follow-up at one year there were no differences among groups. At 5-year analysis it was detected a non-statistically significant increase in the effect [1.12 HR (95%CI 0.97–1.28, I^2=0%, *P*=0.11)].

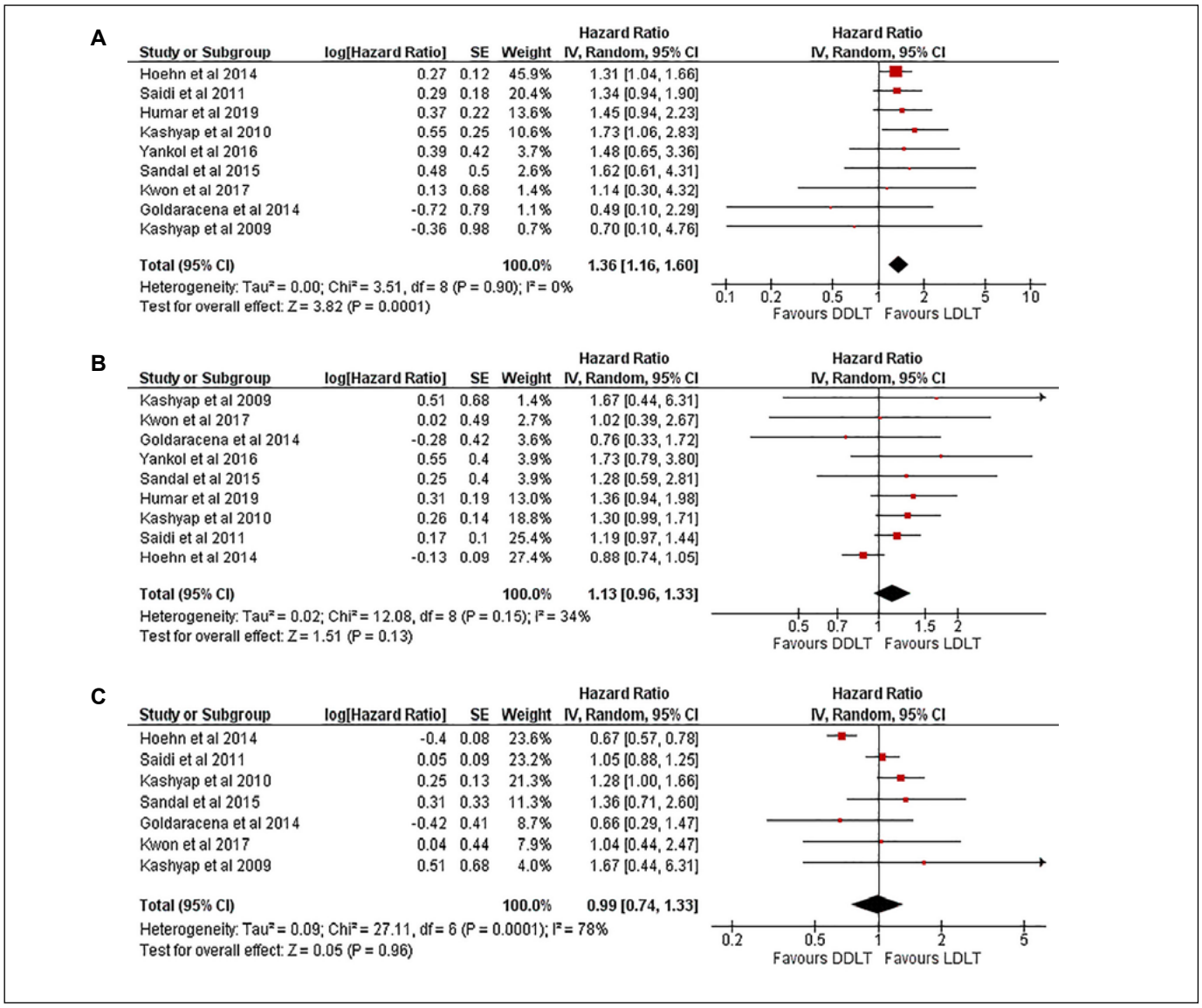

FIGURE 5. Survival of the liver graft considering the type of living or deceased donor: a) survival at 1 year, b) survival at 3 years and c) survival at 5 years.

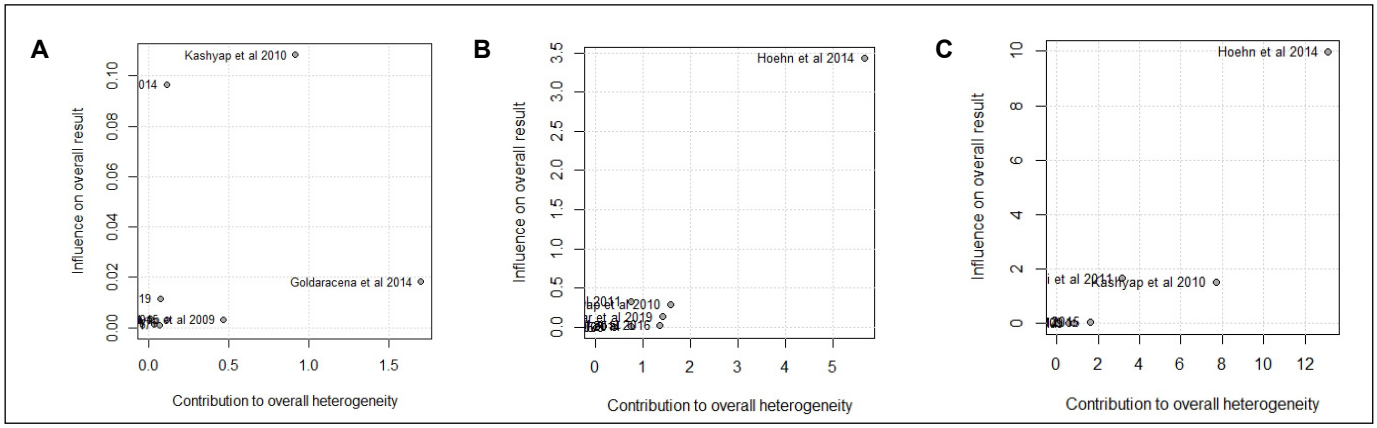

FIGURE 6. Analysis of heterogeneity using the Baujat graph, assessing graft survival in patients undergoing liver transplantation: a) 1 year survival, b) 3-year survival and c) 5-year survival.

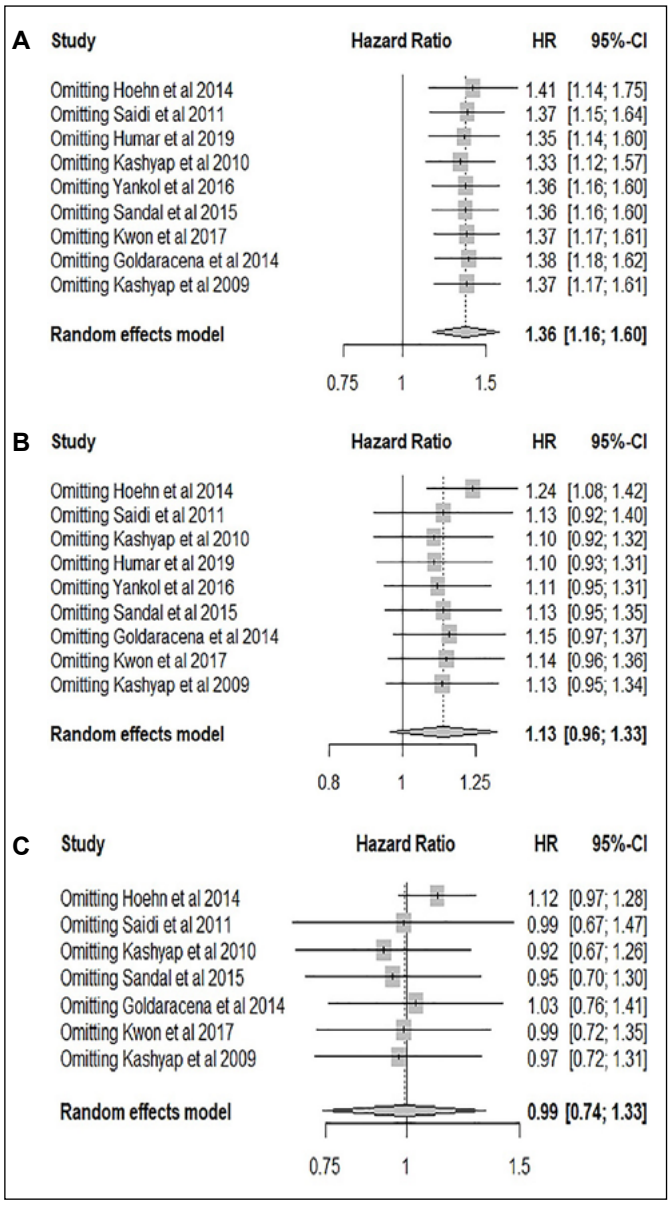

FIGURE 7. Survival analysis of grafts from patients undergoing liver transplantation with a deceased or living donor, using the leave-one-out method: a) 1-year survival, b) 3-year survival and c) 5-year survival.

In the subgroup analysis, we found a significant HR effect of 1.31 (1.08–1.59, I^2=0%, *P*=0.007) in favor of the LDLT group for individuals 50 years old at one-year follow-up (TABLE 2).

TABLE 2. Survival analysis of graft considering a subgroup of patients with an age cut-off.

Subgroup (age)	k	Hazard ratios	CI95%	I^2	Weight	*P*
Graft survival at 1 year						
<50	3	1.31	1.08–1.59	0%	91.5%	0.007
≥50	3	1.15	0.61–2.18	0%	8.5%	0.66
Graft survival at 3 years						
<50	3	1.04	0.79–1.36	64%	82.8%	0.80
≥50	3	1.13	0.68–1.86	5%	17.2%	0.64
Graft survival at 5 years						
<50	3	0.89	0.58–1.35	87%	77.1%	0.57
≥50	2	0.81	0.45–1.46	74%	22.9%	0.49

DISCUSSION

Many authors have explored several strategies to improve the number of donors without compromising the recipient results. Thus, it is necessary to know and compare the outcomes of living and deceased donor liver transplantation, including the ideal technique, results, and ethics. In this study, we meta-analyzed studies that evaluated an overall large number of patients undergoing liver transplantation, assessing the patient and the graft survival according to the type of donor, living or deceased (N=32,258 for survival analysis and N=21,276 for graft analysis).

Liver transplantation with a graft from a deceased donor is the most performed, but the supply is lower than the demand. Our meta-analysis detected a better survival at 1, 3, and 5 years in adult liver transplant patients who received an LDLT graft. When considering individuals over 50 years old, patients undergoing LDLT also had better survival results. The analysis of graft survival varied according to adjustments performed, showing better 1-year survival for LDLT recipients when compared to DDLT, including receivers older than 50 years. The 5-year graft survival was similar among groups.

Literature data differ in terms of survival analysis considering the different types of donors in liver transplantation. Kashyap et al.[20] evaluated patients with chronic autoimmune liver disease (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis). Similarly, to our study, they observed a better patient survival for LDLT, being the patient survival at 1, 3, and 5 years, respectively, of 95.5%, 93.6%, and 92.5% for LDLT, and 90.9%, 86.5%, and 84.9% for DDLT (*P*=0.002). The graft survival at 1, 3 and 5 years was 87.9%, 85.4% and 84.3% for LDLT and 85.9%, 80.3% and 78.6% for DDLT (*P*=0.123). On the other hand, Hoehn et al.[31] evaluated 14,282 patients undergoing DDLT and 715 patients undergoing LDLT and found no differences in survival rates over the years (patient survival at 1, 3 and 5 years were, respectively: DDLT – 90.1 %, 80% and 72.6% and LDLT – 90.1%, 84.1% and 78.6%; graft survival at 1, 3 and 5 years: DDLT – 90%, 80% and 78% and LDLT -85%, 78% and 70%). In Hoehn's analysis, individuals submitted to LDLT had a greater chance of readmission 30 days after discharge (rate of 44% vs 37.1%; *P*=0.001).

Gavriilidis et al.[6] also performed a systematic review and network meta-analysis on survival following right lobe split graft, living- and deceased-donor liver transplantation in adult patients[6]. A pairwise meta-analysis demonstrated that there were no significant differences in graft and patient survival outcomes. Bayesian network meta-analysis showed no significant differences in 1, 3, and 5-year graft and patient survival between the three alternative liver transplantations. Such differences, found in both the results of patient and graft survival, may be associated with the sample size since the authors included fewer studies in their review. For the analysis of graft survival, the meta-analysis by Gavriilidis et al.[6] included six studies referring to the follow-up of 1, 3, and 5 years while the present analysis has used data from eight studies for the

follow-up of 1 and 3 years, and seven studies for the follow-up of 5 years. Regarding patient survival, Gavriilidis et al.[6] evaluated eight studies for the follow-up of 1, 3, and 5 years, while we obtained twice as many studies.

In another meta-analysis that evaluated controlled studies, Wan P et al.[32] compared LDLT and DDLT outcomes. The authors included 19 studies totaling 5,450 patients. They analyzed five postoperative complications: biliary and vascular, intraabdominal bleeding, perioperative death, and re-transplantation. They also evaluated the following four perioperative outcomes: duration of the recipient operation, red blood cell transfusion requirement, length of the hospital stay, and cold ischemia time.

The study found no significant difference in the perioperative mortality between LDLT and DDLT recipients. On the other hand, LDLT had a higher rate of surgical complications after transplantation. However, it is interesting to mention that the authors reported their data using the odds ratio, which considers only the number of events and not the time in which they have occurred, being less appropriate to analyze the results from time to time, according to Tierney et al.[33]. In our review, we used HR, suggested as the most appropriate method to analyze survival.

The results of previous studies, including earlier metanalysis, associated with the results of our own reinforce the usefulness of utilizing living donor living livers and reassurance that patient and graft survival are the same as or greater for LDLT compared to DDLT[34-36].

This meta-analysis used the process of searching and selecting articles by two independent researchers. It also followed the Prism Declaration, an internationally recognized guideline. It utilized the Newcastle-Ottawa Scale to assess the risk of bias of each included article. The outcomes of interest were analyzed using HR, considering the temporal influence on them. This meta-analysis may have some limitations. Our study could have suffered the influence of publication bias or language bias. Data from "grey literature" has not been evaluated. Moreover, part of the results was analyzed using HR, which may overestimate or underestimate the variable effect.

In conclusion, we observed better patient survival at 1, 3, and 5 years among patients who received living donor liver transplantation (LDLT), compared to DDLT, as well as better 1-year graft survival. Thus, the present study provides further support to maintain the indications for living donor liver transplantation when appropriate since it is a viable option with acceptable patient and graft survival rates.

Authors' contribution

Cavalcante LN participated in the project design, selection, and review of articles, as well as writing of the scientific article. Queiroz RMT performed search and selection of articles, review of eligibility criteria and writing. Paz CLSL performed the statistical analysis of the data. Lyra AC contributed to the discussion and final review of the manuscript.

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Cavalcante LN, Queiroz RMT, Paz CLSL, Lyra AC. Sobrevida de pacientes submetidos ao transplante hepático com enxerto de doador vivo é melhor em comparação com doador falecido – uma revisão sistemática e meta-análise. Arq Gastroenterol. 2022;59(1):129-36.

RESUMO – Contexto – O transplante de fígado com doador falecido é a primeira escolha, mas o transplante de doador vivo é uma alternativa a ser considerada em situações especiais, como falta de órgãos doados e emergências. Até o momento, não há consenso sobre qual método de transplante proporciona melhor sobrevida e menos complicações, sendo, ainda, um ponto em aberto para discussão. **Métodos –** Esta meta-análise comparou as taxas de sobrevida de pacientes e enxertos de 1, 3 e 5 anos de transplante de doador vivo e transplante de fígado com doador falecido. Incluímos estudos publicados de abril de 2009 a junho de 2021 e adotamos o modelo genérico do inverso da variância para o efeito aleatório das razões de risco. A adequação dos estudos foi determinada por meio da Escala de Newcastle-Ottawa – NOS (WELLS). **Resultados –** Para análise de sobrevida do paciente, incluímos um total de 32.258 indivíduos. Encontramos uma melhor sobrevida estatisticamente significativa para o grupo de transplante de fígado de doador vivo em 1, 3 e 5 anos, respectivamente: 1,35 HR (IC95% 1,10–1,66, *P*=0,005), 1,26 HR (IC95% 1,09–1,46, *P*=0,002) e 1,27 HR (IC95% 1,09–1,48, *P*=0,002). Nossa meta-análise avaliou um total de 21.276 enxertos. Na análise geral, a sobrevida em 1 ano foi melhorada em favor do grupo de transplante de doador vivo (1,36 HR, IC95% 1,16–1,60, *P*<0,0001), enquanto a sobrevida em 3 anos (1,13 HR, IC95% 0,96–1,33, *P*<0,13) e 5 (0,99 HR, IC95% 0,74–1,33, *P*<0,96), não diferiram significativamente. **Conclusão –** Esta meta-análise detectou uma sobrevida estatisticamente significativa maior do paciente em 1, 3 e 5 anos favorecendo o transplante de doador vivo em comparação com o transplante de fígado com doador falecido, bem como uma diferença estatisticamente significativa melhor na sobrevida do enxerto em 1 ano favorecendo o grupo de transplante de doador vivo.

Palavras-chave – Transplante de fígado; transplante de fígado de doadores vivos; transplante de fígado de doador falecido.

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REVIEW

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Diagnosis and management of chronic idiopathic constipation: a narrative review from a Brazilian expert task force

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ABSTRACT – Background – Chronic idiopathic constipation (CIC) is a condition that widely affects the global population, represents relevant healthcare resource utilization and costs, and impacts the individual's well-being. **Objective –** To review the consensus of expert societies and published guidelines on the diagnosis and treatment of CIC in adults, seeking to assist reasoning and decision-making for medical management of patients with CIC and provide a practical reference material. **Methods –** A Brazilian medical task force searched the scientific literature in the following electronic databases: MEDLINE/PubMed, SciELO, EMBASE and Cochrane, using the following descriptors: chronic constipation, diagnosis, management of chronic constipation. In addition, a review of articles on the mechanism of action, safety, and efficacy of therapeutic options available in Brazil was carried out. **Results –** The diagnostic approach and the understanding of the pathophysiology present in CIC are essential items to indicate the appropriate therapy and to understand the ecosystem of the patient's needs. **Conclusion –** CIC is a common condition in adults, occurring more frequently in the elderly and in women. Proper management is defined by detailed medical history and physical examination, together with appropriate therapeutics, regardless pharmacological or not, and depending on the best moment of indication. This way, the impact on quality of life is also optimized.

Keywords – Chronic idiopathic constipation; functional constipation; diagnosis; treatment.

INTRODUCTION

Chronic constipation (CC) is a common and persistent condition with 14% of global prevalence[1,2]. It is often associated with older age, female gender, and lower socioeconomic status[2-4]. Characterized by infrequent bowel movements, CC encompasses symptoms such as excessive straining at stool, abdominal pain and bloating, a sense of incomplete evacuation, lengthy (or failed) attempts to defecate, use of digital manoeuvres for evacuation of stool, and hard consistency of stools[1,5]. CC results in significant economic burden and substantial healthcare utilization, affects work, productivity, school attendance, and patients may suffer from impaired psychological well-being and poor quality of life (QoL)[6,7]. Half of the patients with CC reports symptoms for more than 5 years[8].

After examining secondary causes for CC (organic or systemic diseases, or medications in use), chronic idiopathic constipation (CIC), also called primary constipation, can be divided into three subtypes: a) dyssynergic defecation (DD); b) normal-transit constipation (NTC), the most common subtype, that include functional constipation (FC)[5]; and c) slow-transit constipation (STC). These classifications are not mutually exclusive and significant overlap exists. Classification of CC is shown in FIGURE 1[1], and risk factors are presented in BOX 1[9].

Although we recognise that FC often overlaps with irritable bowel syndrome–constipation predominant (IBS-C), the latter would call for a specific material as it has a particular pathophysiology and therapeutic implications. In this article, we aimed to briefly describe the pathophysiology of CIC, with emphasis on FC and its frequent symptoms, diagnostic methods, and current options of treatment to offer a practical reference material.

In this work, we searched the literature in electronic databases such as MEDLINE/PubMed, SciELO, EMBASE and Cochrane, using the following terms: "chronic constipation", "diagnosis", "management" and "surgical treatment". After reviewing the published literature, a Brazilian medical task force, experts in gastroenterology, discussed the findings aiming to briefly describe the pathophysiology of CIC, its frequent symptoms, diagnostic

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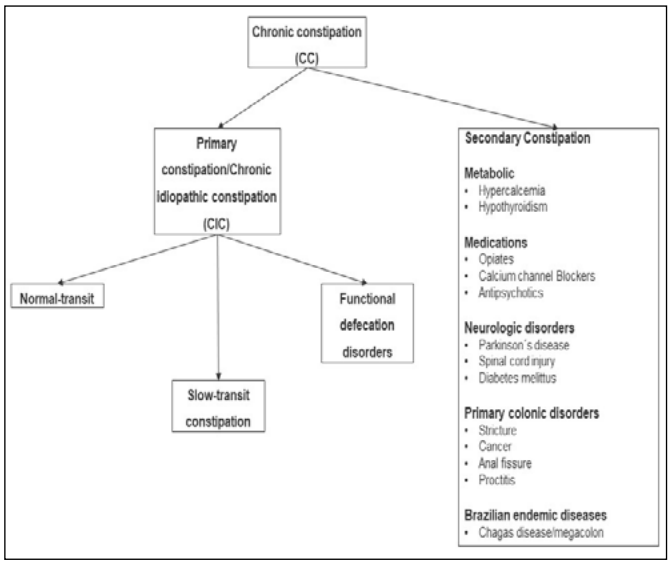

FIGURE 1. Classification of chronic constipation.

BOX 1. Risk factors for chronic constipation*.

- Depression.
- Low calorie intake (high-fiber diet may be protective).
- Low income and low education levels.
- Medications.
- Physical and sexual abuse and inactivity.
- Aging (although, constipation is not necessarily a consequence of normal aging).
- Female sex.
- Inactivity (physical exercise may be protective).

Adapted from Lindberg et al., 2011[1]. *Association with these risk factors is not necessarily causative.

methods, and current options for treatment, to offer a practical reference guiding material with special emphasis in the options available locally. In addition, we reviewed current North American and European guidelines and recommendations to provide a comparison between them, whenever relevant.

Normal colonic physiology

To understand CIC, it is worthwhile to consider the normal functioning of the colon. Colonic motility is controlled by the entry of food into the small intestine, and intrinsic somatic movements are the main mechanism of propulsive motility that leads to defaecation[10]. Motility of the bowel can be divided, basically, in low- or high-amplitude propagated activity and this latter is mainly related to large amounts of colonic contents and defecation[11]. The primary motor pattern associated with these mass movements, which originate from the inhibition of distal haustral segments and contractions of the proximal bowel wall, is called high-amplitude propagating contraction (HAPC), and arise from the contraction of colonic smooth muscle[12]. The HAPCs usually occur after meals (there is evidence that fat and carbohydrate may influence the occurrence of HAPC), but they can also be induced by stimulant laxatives (e.g., bisacodyl)[11,13]. In turn, peristalsis is mediated by serotonin (5-HT), which is synthesized in enterochromaffin cells in the mucosa, and antagonists of 5-HT receptors can inhibit/block peristalsis, reducing propulsion of contents[14]. Contents in the colon can also move in a retrograde direction, specially following a meal, a mechanism that prevents rapid rectal filling. Though, there is also an increase in the post-prandial colonic motor activity (gastro-colic reflex)[15]. The colon also plays an important role in managing fluids and electrolytes, as it reabsorbs approximately 1.5–2 litres of fluid per day, which is important for pharmacological treatment[16].

Pathophysiology of chronic idiopathic constipation

The cause of CIC is multifactorial. Motility disturbances of the colon and dysfunctions of the pelvic floor are usually the main causes of CIC, but diet, changes in the microbiome and anatomical issues may also contribute to the condition[17]. Life style, behaviour, psychological factors, or medications, may be involved in FC[18,19].

In addition, CIC may be a result of rectal evacuation disorders such as DD (the most common cause of rectal evacuation disorder)[5]. When coordination of rectal muscles is impaired, failure of anal relaxation happens or there is an inadequate rectal and abdominal propulsive force, DD may arise[20]. DD often results from dysfunctional toilet habits, being considered then a learned behavioural problem[21]. History of abuse (physical and sexual) is often present, with 29% of men and 32% of women reporting physical abuse and 22% reporting sexual abuse[21]. Rectal evacuation problems may coexist with structural causes (e.g., rectal prolapse, rectal intussusception, rectocele)[22]. STC – a delay in the emptying of the proximal colon[23,24] and reduction or absence of HAPCs[24-26] – may occur concurrently[27].

Clinical evaluation of chronic idiopathic constipation

A detailed clinical history should be obtained, including time of symptoms' onset, dietary/fiber intake characteristics as well as history of physical/sexual abuse and obstetric events. According to Rome IV criteria, CIC is diagnosed based on symptoms, such as straining during more than 25% of defecations, sensation of incomplete evacuation more than 25% of defecations and other symptoms[28]. Symptoms such as the sense of anal blockage during defecation or a sense of incomplete evacuation after defecation usually suggest DD[29]. Abdominal bloating or discomfort, may be associated with abdominal distention, but other symptoms or conditions may also be present (e.g., fatigue, psychosocial distress, fibromyalgia)[30,31]. However, the clinician should bear in mind that, generally, symptoms are not a good guide to the pathophysiology of CIC as they are not specific[9].

The Bristol Stool Form Scale (BSFS)[32] (FIGURE 2) shows stool form as an indirect measure of colonic transit time, changes in intestinal function and ease of defecation, which are influenced by stool form[33]. Frequently, patients misperceive they have constipation because they do not have daily bowel movements[33]. Straining to begin defecation is often found in the presence of hard stools, among constipated women[33]. Patients with severe DD may have problems to pass even severe soft stools or enema fluids[34].

Diagnosis of chronic idiopathic constipation

The diagnosis of CIC can be based mainly on symptoms alone; therefore, a careful medical history is critical and should assess the presence of symptoms, their duration, and progression[32]. Johansson et al. (2007) surveyed patients with CC and found that straining (79%), hard stools (71%), abdominal discomfort (62%), bloating (57%), infrequent bowel movements (57%), and feelings of incomplete evacuation after a bowel movement (54%) were the

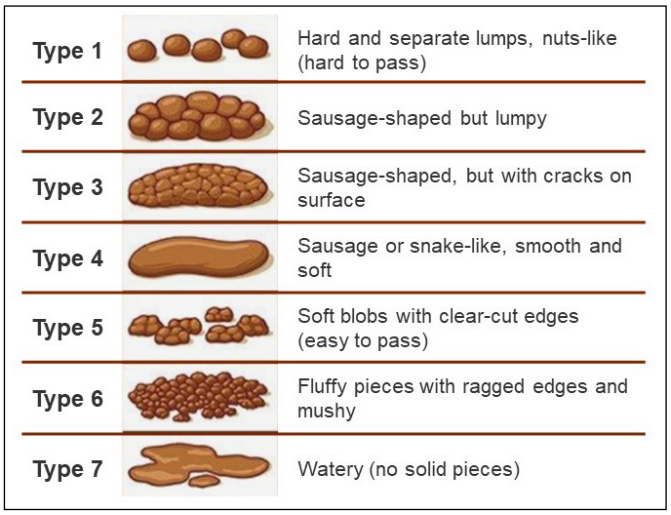

FIGURE 2. Bristol Stool Form Scale.
Adapted from Lewis & Heaton, 1997[2].

most frequent symptoms[35]. Currently, the criteria most in use for definition of CIC are those of the Rome IV[36]. BOX 2 presents the specific diagnostic criteria[36]. One of the most important symptoms to differentiate FC from IBS-C is the presence of abdominal pain[36].

BOX 2. Rome IV diagnostic criteria for functional constipation.

- Must include two or more of the following[b]:
  - Straining during more than 25% of defecations.
  - Lumpy or hard stools (BSFS 1–2) more than 25% of defecations.
  - Sensation of incomplete evacuation more than 25% of defecations.
  - Sensation of anorectal obstruction or blockage more than 25% of defecations.
  - Manual manoeuvres to facilitate more than 25% of defecations.
  - Fewer than 3 spontaneous bowel movements per week.
- Loose of stools are rarely present without the use of laxatives.
- Do not meet criteria for irritable bowel syndrome.

Adapted from Lacy et al., 2016[3]. BSFS: Bristol Stool Form Scale.
[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. [b]For research studies, patients meeting criteria for opioid-induced constipation should not be given a diagnosis of chronic idiopathic constipation because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognise that these two conditions might overlap.

Medical history is an important part of the diagnosis and should include: age, family history of colon cancer (or familial polyposis syndromes), frequency of bowel movements, associated symptoms (e.g. abdominal pain, bloating, or distension), an assessment of stool consistency, stool size, and degree of straining during defecation[37]. Objective measures such as stool frequency, daily stool weight (<35 g/d), colonic transit, and anorectal function can also be performed and should be done while the patient is not under laxatives[32].

For patients presenting with new onset constipation, causes of secondary constipation such as mechanical obstruction, medications (BOX 3)[9], and systemic illnesses should be explored[32,36]. The presence of alarm features (BOX 4)[9], such as unintentional weight loss (>10% in 3 months) or rectal bleeding (in the absence of bleeding haemorrhoids or anal fissures) among other features, should be investigated[36]. When the clinician suspects organic causes of constipation (especially when alarm symptoms are present), objective tests are recommended to guide treatment[38].

BOX 3. Medications associated with chronic constipation.

- Antacids containing aluminium, calcium.
- Antidepressants.
- Antidiarrheal agents.
- Antiepileptics.
- Antihistamines.
- Antiparkinsonian drugs.
- Antipsychotics.
- Antispasmodics.
- Calcium and iron supplements.
- Calcium channel blockers.
- Diuretics.
- Monoamine oxidase inhibitors.
- Nonsteroidal anti-inflammatory drugs.
- Opiates.
- Sympathomimetics.
- Tricyclic antidepressants.

Adapted from Lindberg et al., 2011[1].

BOX 4. Alarm features.

- Change in stool calibre.
- Rectal bleeds.
- Rectal prolapse.
- Obstructive symptoms.
- Loss of weight.
- Recent onset constipation.
- Heme-positive stool.
- Iron-deficiency anaemia.
- Patients older than 50 years old with no previous screening for colon cancer.

Adapted from Lindberg et al., 2011[1].

Objective testing should be performed if considered necessary to identify underlying pathophysiological mechanisms[32]. Diagnosis of DD may be done by specific questionnaires and physical examination, and is important as it may require different treatment strategies[39,40]. Central nervous system and spinal lesions can be ruled out by physical examination, and the abdomen should be examined for distension and presence of hard stool or a mass in the colon. Rectal examination is also essential to identify fecal impaction, anal stricture, or rectal mass. It should include examination of the perineum at rest and after strains as inappropriate contractions of the puborectalis muscle and/or anal sphincter when simulating an evacuation is consistent with DD[28,39,40].

Functional evaluation should be performed when DD is suspected or in cases that do not respond to initial treatment with fiber supplementation and/or laxatives[41,42]. In addition, anorectal manometry and balloon expulsion tests may help to identify DD[42], as well as defecography may detect anatomic aetiologies that are typical of DD (e.g., intussusception and rectocele with stool retention, or the inability to relax the puborectalis or decrease the

anorectal angle with straining)[43]. Electromyography and pudendal nerve latency testing are supporting techniques[44]. However, testing for DD is not required for all patients, but for those who do not respond to a reasonable number of attempts of treatment.

Some laboratory studies may be necessary, such as complete blood count, thyroid-stimulating hormone and serum calcium, and a colonoscopy might be indicated in patients aged 45 years or older (though the American Gastroenterological Association [AGA] does not recommend this exam in the absence of alarm symptoms)[45]. Radiopaque markers can also be used to evaluate colonic transit[36,46]. Below we specify the most used diagnostic methods and when to used them.

Physical examination

In the evaluation of a patient with CC, it is important to identify diseases that cause constipation and include a detailed physical examination, together with perineal and rectal examination[39,47], which may bring evidence of the presence of haemorrhoids, fissures, scars or skin excoriation as well as some structural abnormalities[39,48]. According to the AGA, digital rectal examination should be performed before referral to anorectal manometry, although a normal result does not exclude defecatory disorders[41]. In patients with DD, when asked to push or bear down with a normal push manoeuvre, at least one of the following responses are absent: relaxation of the external anal sphincter and/or the puborectalis muscle, together with perineal descent and tightening of abdominal muscles[39,48]. Although digital rectal examination is an important part of the diagnosis, showing 75% sensitivity and 87% specificity for detecting DD[39], it is not performed by approximately 50% of the physicians treating constipation[49].

Stool diary

Bowel habits can provide useful information in the evaluation of patients with CC[48]. A stool diary has proven to be a valid instrument[50] for assessing patients and findings such as loose or hard stool, stool frequency (which provides information regarding colonic transit time and therapeutic responsiveness such as number of bowel movements per day), stool consistency (as per the BSFS type 1–7), level of straining, use of digital manoeuvres, feeling of incomplete evacuation, presence of pain and bloating[48,50].

Colonic transit assessment

According to the AGA, colonic transit should be evaluated if anorectal tests do not show defecatory disorders or if after treating them, the symptoms still persist[45]. Colonic transit assessment provides useful information on the overall colonic motor function and can be performed by three different methods: a) radiopaque marker test – performed by the oral administration of a radiopaque marker (the patient typically ingests one capsule containing 24 radio-opaque markers five days before or, depending on the technique used, every day) and then performs the abdominal x-ray between 5 and 6 days later, to determine the number of markers remaining. The exam is considered abnormal if more than 5 (>20%) markers are retained in the colon[51]; b) colonic scintigraphy – a radiolabelled marker is infused and released in the caecum, and images are made at 24 and 48 hours; c) wireless motility capsule – this method potentially provides information about the whole gut and not only about specific regions. The transit of the capsule is measured by documented normative values[52]. DD and STC are conditions that may appear simultaneously, and this test does not differentiate between them (this requires an anorectal test); however, STC can be found in two-thirds of patients with DD[21,48,29].

Anorectal structure and function testing

If no alarm symptoms or symptoms suggesting difficulty with defecation are present, the use of empirical trial with laxatives can be considered prior to colorectal tests[51]. Symptoms alone do not provide much information on underlying pathophysiology; therefore, diagnostic tests are complimentary to clinical assessments[48]. However, although several tests are available to define structural morphology and physiology of defecation, no single test can provide a complete picture, so tests and symptoms should be interpreted together with careful consideration[48].

Anorectal manometry

AGA recommends that anorectal manometry is performed in patients who fail to treatment with laxatives[45]. The anorectal manometry assesses sphincter tone in resting and squeeze, rectoanal reflexes, rectal sensations, and changes in pressure during attempt to defecate[53]. Most changes found are high anal sphincter pressure during rest and impaired relaxation[52]. It is the most reliable test to diagnose DD, especially when the patient is asked to attempt defecation when sitting on a commode[53].

Balloon expulsion test

The balloon expulsion test is a screening test used to identify patients with DD, and the AGA recommendation is that this test is performed if the patient fails to laxatives[45]. Its specificity is high (80–90%), but sensitivity is low (50%)[54,55]. This test is performed by placing a balloon filed with warm water (50 mL) in the rectum, and a stop watch is provided to the patient to assess time required for expulsion, which is less than one minute for healthy individuals[51].

Defecography

In case that anorectal manometry and rectal balloon expulsion tests are inconclusive, the AGA recommends the defecography is performed. Contrast defecography (using barium) or functional magnetic resonance (MR) defecography can provide anorectal imaging. These techniques provide information about anorectal function (e.g., DD) and anatomy (e.g., anal stenosis, rectal intussusception). MR defecography provides additional information about the integrity of anorectal and pelvic floor structures[6].

Treatment of chronic idiopathic constipation

The treatment options and recommendations presented here are not a consensus, but the result of a literature review combined with best practice and experience of the authors and, therefore, should be used as a guide for clinical practice.

Once the diagnosis is made, the initial management of CIC can be done with a symptomatic approach based on lifestyle and diet changes, an increase in fluid intake, and stopping/reducing medications that may cause constipation. The World Gastroenterology Organization describes as a second step, the addition of osmotic laxatives (polyethylene glycol [PEG] or lactulose), as well as new drugs such as lubiprostone, linaclotide and plecanatide, that treat constipation by increasing fluid secretion into the intestinal lumen through direct action on intestinal epithelial cells[6]. Then stimulant laxatives that stimulate colorectal activity (orally or rectally administered), enemas and prokinetic drugs (e.g., prucalopride, which increases the propulsive activity of the colon) can be

alternatives in a next step[9]. Other treatment options may include biofeedback (generally effective to treat patients with features of pelvic floor dyssynergia)[37] and surgery, that is usually restricted to those refractory cases that fail to respond to aggressive medications and biofeedback treatment[48].

Changes in lifestyle and diet

Traditionally, changes in lifestyle such as an increase in physical exercises and dietary interventions have been recommended, as well as an increase in fluid intake; however, the European Society of Neurogastroenterology and Motility (ESNM) guidelines for CC points to conflicting evidence regarding the benefits of physical exercise or overall lifestyle modifications[38].

Fiber

The inclusion of dietary fiber (either ingested as food and/or as medicinal supplement) is recommended by the American College of Gastroenterology (recommendation: strong; quality of evidence: low)[37]. The ESNM also recommends a fiber-rich diet as first-line treatment (recommendation: strong; level of evidence: moderate)[38]. They are delivered to the colon as they are not digested in the small intestine[37]. Depending on how the fiber interacts with water, it is classified as soluble (e.g., psyllium) and insoluble (e.g., bran). Both soluble and insoluble fiber increase the stool frequency in patients with CIC; however, insoluble fiber should be introduced gradually, as it may cause bloating, distension, flatulence, and cramping[37], and with sufficient water intake[56]. Low fluid intake has been associated with reductions in stool frequency in women[57] and is a better predictor for constipation than a fiber-poor diet[58].

Other bulk-forming agents

Bulk-forming agents (e.g., polycarbophil, methylcellulose) are natural or medicinal fiber products that help retain water to increase intraluminal volume[59].

Osmotic laxatives

Patients with constipation frequently present with bloating, which can be due to underlying disorder and/or medications (e.g., fiber and osmotic laxatives). Osmotic laxatives include polyethylene glycol (PEG)-based solutions, products based on magnesium-citrate, sodium phosphate, and non-absorbable carbohydrates[17]. Water retention in the colon can be achieved with poorly absorbed ions which create an osmotic gradient, resulting in improved stool consistency and frequency[52,17].

Magnesium hydroxide and other salts are sparingly absorbed and safe; however, they have not been tested in randomized controlled trials. Patients with renal impairment may present with severe hypermagnesemia[60]. Among non-absorbable carbohydrates, lactulose, and sorbitol presented similar laxative effects in a randomized crossover study of 30 men, but lactulose was associated with more nausea[61].

Dosing of laxatives prescription varies from patient to patient and from agent to agent. The general goal is to improve symptoms reported by patients. Bacterial metabolism of unabsorbed carbohydrate leads to gas production and abdominal cramping, which can limit long-term use. The American College of Gastroenterology's recommendation is strong for both PEG and lactulose, but for the former the quality of the evidence is high, while for the latter, it is low[37] (PEG is also strongly recommended by the ESNM, though lactulose recommendation is weak)[38]. Reported adverse events do not differ from those reported in groups treated with placebo, and include abdominal pain and headache[37].

Stimulant laxatives

Stimulant laxatives are frequently used on a rescue basis and include diphenylmethane derivatives (e.g., bisacodyl and sodium picosulfate) and anthraquinone derivatives (e.g., senna, aloe, cascara sagrada)[17]. Bisacodyl and sodium picosulfate are converted by mucosa deacetylase enzymes and desulfatases of the colonic microbiota, respectively, to bis-(p-hydroxyphenyl)-pyridyl-2-methane, which prevents reabsorption of water and initiates HAPCs in the colon[62]. Anthraquinones also increase colonic motility and alter colonic absorption and secretion[63]. Sodium picosulfate and bisacodyl are recommended by the American College of Gastroenterology and the ESNM (recommendation: strong; quality of evidence: moderate)[38]. The use of these agents is often limited by adverse events (usually abdominal pain and diarrhea)[17]. Another stimulant laxative, docusate sodium (an ionic surfactant) decreases the surface tension at the stool oil-water interface and allows water to penetrate the stool. Although it is often recommended, it has few data to support its use[17].

Prosecretory agents (secretagogues)

Prosecretory agents (e.g., lubiprostone - a bicyclic fatty acid derived from prostaglandin E1 that activates type 2 chloride channels on the apical membrane of epithelial cells) increase secretion of intestinal chloride, stimulate net efflux of ions and water into the intestinal lumen, accelerate transit, and facilitate defecation[52,17]. Lubiprostone, linaclotide, and plecanatide have been approved by the Food and Drug Administration for treatment of CIC; however, only lubiprostone is currently approved in Brazil[64]. Both lubiprostone and linaclotide are prosecretory agents recommended by the American College of Gastroenterology (recommendation: strong; quality of evidence: high)[37]. Nausea, usually mild and well tolerated, is the most common adverse event; therefore, lubiprostone should be taken with food and water (24 mcg twice a day)[65]. Linaclotide and plecanatide therapy have similar efficacy and tolerability[66], and diarrhea is the most common adverse event, but fewer than 5% of the patients have been discontinued from clinical trials due to this reaction[67,68].

Prokinetic drugs

The neurotransmitter serotonin (5-HT) is involved with sensation and motility of the gastrointestinal tract[56]. Several agonists of 5-HT receptors have been studied due to their increase in intestinal motility[56]. Prucalopride, a highly selective 5-HT4 agonist, is reported to be well tolerated, although the use has been associated with headache, abdominal pain, nausea and diarrhea. No significant cardiovascular adverse events have been reported with prucalopride use[17]. Patients in treatment with prucalopride should be monitored for depression and suicidal thoughts[56]. The American College of Gastroenterology recommendation for prucalopride is strong and the quality of evidence is high[37]. In Europe, prucalopride has been approved and used for years and is recommended by the ESNM (recommendation: strong and level of evidence: high)[38].

Probiotics

Although some studies have reported improvement in bowel movements per week with probiotics use, their utility in adults with constipation is unclear[69]. An increasing body of evidence shows that changes in the gut microbiota may contribute to the development of functional bowel disorders that are possibly secondary

to dysbiosis of the gut microbiota[28]. Possibly, the link between constipation and microbiota is the small intestinal bacterial overgrowth, which has been shown to be associated with prolonged small bowel transit time in methane production microbiota[69,70]. More evidence for the effectiveness of specific probiotic strains, and more randomized clinical studies with CIC patients utilizing those well-defined probiotics strains (or combinations) are necessary, as well as education of healthcare professionals on the increased utilisation of probiotics for constipation by the public[69].

Enemas

Despite lack of studies on the use of enemas in CIC, they continue to be used[38,70]. The effect of enemas will depend on the amount of liquid delivered to the rectum (usually between 5–150 mL of glycerine, saline solution, etc.), the intraluminal pressure and the temperature of the enema[70]. However, studies are needed to stablish the real efficacy of enemas in the treatment of CIC.

Biofeedback

Biofeedback aims to restore dysfunctional behaviors that may cause constipation, emphasizing appropriate coordination of abdominal and pelvic floor motion during evacuation (although therapy may include Kegel exercises)[71]. It may vary in methodological techniques but, in general, biofeedback is effective to treat CIC in patients with DD[71]. The patient may learn how to achieve defecation by relaxing the pelvic floor muscles, and to correlate relaxation and pushing during straining[72] through visual or auditory feedback of anorectal and pelvic floor muscle activity, which is recorded with surface electromyographic sensors or manometry. Patients practice by expelling a balloon filled with air, and learn how to recognize weaker sensations of rectal filling[71]. Biofeedback is underutilized as its benefits are not widely recognized, and the recommendation by the American College of Gastroenterology is weak, with low quality of evidence[37]. In addition, the expertise is not widely available. In turn, the ESNM recommendation for biofeedback therapy is strong (level of evidence: moderate)[38].

Surgery

Surgery is usually reserved for patients with debilitating symptoms and refractory CIC presenting with negative effects on their QoL[73]. End sigmoid colostomy may be an option for patients with normal colonic transit and severe refractory pelvic outlet dysfunction constipation[73], but patients with concomitant STC and pelvic dysfunction may consider an ileostomy[74]. In patients with STC, a loop ileostomy to assess benefits may be useful before considering a total abdominal colectomy[73]. However, a patient should not be referred to surgery before a functional evaluation is carried out, including motility assessment of the upper gastrointestinal tract[75].

Quality of life

Quality of life (QoL) tools are helpful to measure physical and emotional burden associated with physical, psychological and social stressors that come with CC[6]. Different measures of QoL and disease-related QoL have been used in studies reporting impaired QoL in patients with CC. The Well-Being Index has been reported to be lower in individuals with CC[7]. Lower QoL scores were reported in a study for patients with constipation who were unemployed or retired than for those who were employed, and symptoms of anxiety and depression were reported risk factors for worse QoL[76]. The Medical Outcomes Short-Form Health Survey (SF–36 and SF–12) instruments used in the general population and in patients in the clinical setting, showed lower physical and mental scores, meaning that individuals with CC had poorer QoL than individuals without constipation[7]. Importantly, individuals with constipation in the community had QoL scores similar to those of individuals with stable inflammatory bowel disease (IBD), chronic allergies and dermatitis. In the clinical setting, patients with constipation had QoL scores that were comparable to those of patients with functional dyspepsia or active IBD[7]. The Psychological General Well-Being Index (PGWBI) scores were as severe as those associated with untreated conditions such as peptic ulcer disease, gastro-oesophageal reflux disease and mild asthma[7].

CONCLUSION

Chronic idiopathic constipation is a highly prevalent condition that is probably multifactorial, more prevalent in women, and has a great impact on patient's QoL. The correct approach for diagnosis starts with diving into details of clinical history, the patient's complaints, as well as a careful physical examination, that are basic points for the diagnosis, which will be even more accurate when supported by the well-stablished Rome IV diagnosis criteria. Alarm symptoms, epidemiological data regarding colorectal cancer surveillance and underlying diseases should also be part of the medical reasoning, so that they can be excluded. Medicine brings new therapeutic innovations and reinforces the most accurate diagnostic methodology possible. Traditional treatment, fluid intake, and a fiber-rich diet greatly helps patients with CIC. The therapeutic options available in Brazil contemplate innovative and traditional molecules (e.g., lubiprostone and prucalopride, respectively) and classic laxatives, but each option should be weighed in relation to efficacy and safety. Prucalopride has been used in refractory cases, and phase III trials have shown lubiprostone as an effective and safe option recently made available locally.

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Authors' contribution

Passos MCF, Alvariz RC, André EA, Barbuti RC, Fillmann HS, Murad-Regadas SM, Rezende Filho J, Perrotti M and Guedes L: conceptualization, data curation, formal analysis, methodology, resources, supervision, validation, visualization and interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have approved the final version of the manuscript.

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Passos MCF, Alvariz RC, André EA, Barbuti RC, Fillmann HS, Murad-Regadas SM, Rezende Filho J, Perrotti M, Guedes L. Diagnóstico e abordagem terapêutica da constipação idiopática crônica: uma revisão de especialistas brasileiros. Arq Gastroenterol. 2022;59(1):137-44.

RESUMO – **Contexto** – A constipação idiopática crônica (CIC) é uma condição que afeta amplamente a população global, representa um grande custo econômico, causa substancial utilização de recursos em saúde e impacta o bem-estar do indivíduo. **Objetivo** – Revisar os consensos de Sociedades de especialistas e diretrizes publicados sobre o diagnóstico e tratamento da CIC em adultos, buscando auxiliar o raciocínio e a tomada de decisão para a conduta médica frente ao paciente e oferecer um material prático de referência. **Métodos** – Uma força tarefa médica brasileira realizou uma busca na literatura científica nas bases de dados eletrônicos Medline/PubMed, SciELO, Embase e Cochrane, tendo sido utilizados os seguintes descritores: *chronic constipation, diagnosis, management of chronic constipation*. Adicionalmente, foi realizada uma revisão de artigos sobre o mecanismo de ação, segurança e eficácia das opções terapêuticas disponíveis no Brasil. **Resultados** – A abordagem diagnóstica e o entendimento da fisiopatologia presente na CIC são itens fundamentais para que seja indicada a terapêutica apropriada e seja compreendido o ecossistema de necessidades do paciente. **Conclusão** – A CIC é uma condição comum em adultos, ocorrendo com maior frequência em idosos e mulheres. O manejo correto é definido pela anamnese e exame físico detalhados, juntamente com a terapêutica apropriada, independentemente de ser farmacológica ou não, conforme o melhor momento de indicação. Desta forma, o impacto na qualidade de vida também é otimizado.

Palavras-chave – Constipação idiopática crônica; constipação funcional; diagnóstico; tratamento.

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BRIEF COMMUNICATION

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Agreement between nutritional screening instruments in hospitalized older patients

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ABSTRACT – Background – The prevalence of hospitalized elderly patients has grown substantially and has impacted the hospital health services. Thus, it is believed that an investigation of the nutritional status associated with different clinical situations in elderly patients could contribute to multidisciplinary hospital intervention and nutritional care actions suitable for this population. **Objective –** To investigate the relationship between two nutritional screening instruments in hospitalized older patients and to compare clinical variables between these two instruments. **Methods –** Retrospective study with hospitalized older patients (n=277), investigating the agreement between two nutritional screening instruments. The data were analyzed using the McNemar, chi-square, Fisher, Mann-Whitney tests and the kappa coefficient for the agreement assessment. **Results –** There was a significant difference (P=0.0002) between the nutritional risk classifications of the two nutritional screening instruments and moderate agreement (k=0.5430) between them. The association between nutritional risk screening and age (P=0.0255), length of hospital stay (P<0.0001), gender (P=0.0365) and illness (P=0.0001) were assessed. There was an association between Mini Nutritional Assessment and length of stay (P<0.0001), illness (P=0.0001) and body weight evolution (P=0.0479). **Conclusion –** The nutritional risk screening and Mini Nutritional Assessment showed moderate agreement in the assessment of elderly patients.

Keywords – Hospitalized elderly patients; nutritional screening; agreement.

INTRODUCTION

There is currently a high increase in the number of hospitalized elderly patients (HEP) and, accordingly, nutritional management[1] of these patients continues to be the object of clinical investigations as evidenced in the literature. Several parameters and models of nutritional diagnosis are still being studied for this purpose[1,2], both alone and in combination[3], as well as comparison and correlation analysis[4] among the nutrition screening tools (NSTs). Some studies also illustrate the impact of the nutritional status and nutritional support on the clinical outcome of HEP[5].

In a recent prospective study with hospitalized elderly patients[6], the priority to be given at identifying the patients' nutritional status using nutritional tracking instruments in clinical practice was confirmed with the aim to reduce morbidity and mortality rates. A prospective study on the application of the Mini Nutritional Assessment (MNA) instrument in hospitalized elderly patients[7], identified 77% malnutrition or malnourishment risk cases. The study also showed a statistically significant association between low albumin, cholesterol and vitamins A and D plasma levels with malnutrition or risk of malnutrition[7].

It is known that there is no single elderly patients' nutritional investigation method; this is why it may be necessary to apply together more than one instrument or indicator to assess the nutritional status in order to better identify the nutritional status of these patients[8,9]. Many studies[10-13], conducted with elderly patients whether hospitalized or not, have carried out a comparison between the different methods and indicators to diagnose already established malnutrition or even an initial depletion of the condition, in order to implement measures or intervention actions to avoid unfavorable clinical outcomes. This is the case of a recent study[12] that also assessed the nutritional status of patients aged ≥65 years, comparing the agreement of the MNA instrument and the nutritional risk screening (NRS 2002) in relation to malnutrition or malnutrition risk. In the study in question[12], the authors reported that no agreement was found between the short-form (MNA-SF) version of the MNA instrument and the (NRS- 2002) (k=-0.12, P<0.001).

As the prevalence of hospitalized elderly patients has grown substantially and impacted hospital health services, it is believed that an investigation of the nutritional status, associated with different clinical situations of elderly patients, could contribute to multidisciplinary hospital interventions and adequate nutritional care for this population. Since the tools for assessing the nutritional status and risk, such as the MNA and the NRS are easily applicable in clinical practice, the interest in the investigation of these screening instruments in hospital clinical practice arose. Thus, the aim of this study was to investigate the relationship between two NSTs in HEPs and to compare clinical variables between the instruments.

METHODS

After approval by the Institution's Research and Ethics Committee of the Pontifical Catholic University of Campinas,

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São Paulo, Brazil (reference number: 3.587.982, CAAE 150277 19.0.0000.5481), a retrospective study was carried out with 277 HEP (≥65 years). Patients with complete medical records and nutritional assessment carried out within the first 48 hours of hospitalization were included. Patients hospitalized only for diagnostic investigation were excluded.

The variables gender, age, kind of disease, length of hospital stay, evolution of body weight during hospitalization, death, NSTs such as the MNA[14] (classifying as eutrophic, risk of malnutrition or malnutrition) and the NRS[15] (classifying as with or without nutritional risk) were investigated.

MNA[14] is a nutritional assessment tool that includes aspects of specific interest for the elderly and addresses issues related to food consumption, changes in body weight, mobility, arm and calf circumference and disease. This instrument consists of 18 questions and a 30 points maximum score, allowing the classification of the patient's nutritional status as malnourished (<17 points), risk of malnutrition (17–23.5 points) and eutrophic (≥24 points)[14].

NRS[15] is a valid method recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN). This instrument addresses issues such as body mass index, weight loss, reduced food intake, disease severity, plus an adjustment factor for people ≥70 years old. The total score of the NRS allows classifying patients by a numerical score namely with nutritional risk (score ≥3) and without nutritional risk (score <3)[15].

The nutritional screening instruments were applied by properly trained and qualified nutritionists for this type of assessment.

To assess agreement between the NSTs, the kappa coefficient was applied. The magnitude of this coefficient indicated excellent agreement for values greater than or equal to 0.75; for values between 0.75 and 0.40: good agreement and values less or equal to 0.40: no agreement. To compare the classifications between the NSTs, the McNemar test was used. To compare proportions, the chi-square or Fisher's exact test was used, when necessary. To compare the numerical measures between the outcomes, the Mann-Whitney test was used. The significance level was 5%[16,17].

RESULTS

The study was conducted with 277 patients, with a mean age of 72.37±5.85 years, 70% (n=194) being male and 30% (n=83) female. The average hospital stay was 7.64±6.83 days. The most frequent diseases were neoplasms of the digestive tract (33.2%, n=92), diseases of the digestive tract (24.2%, n=67), renal and urological neoplasms (23.1%, n=64) and renal and urological diseases (19.5%, n=54). Upon admission, it was found that 45.8% (n=127) of the patients were at nutritional risk by the NRS and 56.7% (n=157) were at risk of malnutrition or malnourishment by the MNA. It was observed that 18.8% (n=52) of the patients lost weight, 63.5% (n=176) maintained their weight and 17.7% (n=49) gained weight during hospitalization. Death occurred in 3.6% (n=10) of the patients.

There was a significant difference (P=0.0002) between the nutritional risk classifications of the two NSTs (MNA and NRS). The MNA showed a higher percentage of malnutrition risk or malnourishment than the NRS. Using the Kappa coefficient, there was moderate agreement (k=0.5430) between the screening instruments (TABLE 1).

A significant association between NRS and age (P=0.0255), length of stay (P<.0001), gender (P=0.0365) and illness (P=0.0001) was observed. There was a significant association between the MNA and length of stay (P<.0001), illnesses (P=0.0001) and evolution of body weight (P=0.0479) (TABLE 2).

DISCUSSION

We investigated the relationship between two NSTs in HEP and our data showed a high percentage of nutritional risk and malnutrition, with more patients malnourished according to the MNA. The findings showed moderate agreement between the two instruments, which may indicate that both could continue to be used routinely in clinical and nutritional hospital practice. Relevant findings were also observed in the association of these instruments with age, gender, length of stay, illness and the evolution of body weight during hospitalization.

These results are in line with other studies published in recent literature[4,5,18]. In a cross-sectional study carried out in Iran with elderly hospitalized patients[4] to detect malnutrition, anthropometric measures such as arm, calf, waist circumference, body mass index, skinfold thickness, laboratory exams as well as nutritional screening tools such as Full MNA (full-MNA) and short MNA (MNA-short form) were used. The authors showed that the full-MNA scores were significantly correlated with the measure of arm, calf, waist circumference and body mass index, and serum albumin was weakly correlated with both nutritional screening tools used in the study[4] in this study the full version of the MNA proved to be more appropriate for tracking malnutrition in hospitalized elderly patients[4]. Such findings are in line with the results found in the present study, where the MNA was also adequate for tracking malnutrition. These instruments were also used in another study conducted in China[5] indicating longer hospital stay in patients at nutritional risk. The authors also showed that nutritional support reduced the length of hospital stay in patients at nutritional risk and with malnutrition[5]. This study was carried out with elderly hospitalized patients[5] and evaluated the impact of nutritional status and nutritional support on clinical outcomes, using the MNA-short form and the NRS for nutritional screening at the beginning of hospitalization. It was shown in the study that in patients at nutritional risk and with malnutrition,

TABLE 1. Agreement between MNA and NRS nutritional screening instruments.

	Mini nutritional assessment		Total
	MR + M N (%)	Eutrophic N (%)	MR + M Eutrophic N (%)
Nutritional risk screening			
With risk	110 (39.71)	17 (6.14)	127 (45.85)
No risk	47 (16.97)	103 (37.18)	150 (54.15)
Total	157 (56.68)	120 (43.32)	277 (100.00)

MR: malnutrition risk, M: malnutrition. P=0.0002 (McNemar test). Kappa = 0.5430, 95%CI (0.4770; 0.6390).

TABLE 2. Descriptive analysis of variables and comparisons with NRS and MNA.

Variables	NRS		*P*-value	MNA	MNA	*P*-value
	With risk (N=127)	No risk (N=150)		E (N=120)	MR+M (N=157)	
Category						
Age						
mean ± SD	73.9 ± 6.35	71.51 ± 5.27	0.0255*	71.84 ± 5.20	72.78 ± 6.30	0.4334*
median	73.00	70.00		71.00	72.00	
LHS						
mean ± SD	9.87 ± 8.41	5.75 ± 4.31	<.0001*	5.65 ± 3.84	9.16 ± 8.11	<.0001*
median	7.00	5.00		5.00	7.00	
Gender						
Male	46 (36.2)	37 (24.7)	0.0365**	29 (24.2)	54 (34.4)	0.0656**
Female	81 (63.8)	113 (75.3)		91 (75.8)	103 (65.6)	
Diseases						
DTD n (%)	28 (22.0)	39 (26.0)	<.0001**	31 (25.8)	36 (22.9)	<.0001**
RUD n (%)	18 (14.2)	36 (24.0)		35 (29.2)	19 (12.1)	
RUN n (%)	19 (15.0)	45 (30.0)		33 (27.5)	31 (19.7)	
NDT n (%)	62 (48.8)	30 (20.0)		21 (17.5)	71 (45.2)	
Weight evolution						
WG n (%)	24 (18.9)	25 (16.7)	0.0525**	16 (13.3)	33 (21.0)	0.0479**
WM n (%)	72 (56.7)	104 (69.3)		86 (71.7)	90 (57.3)	
WL n (%)	31 (24.4)	21 (14.0)		18 (15.0)	34 (21.7)	
Death						
No n (%)	120 (94.5)	147 (98.0)	0.1944***	118 (98.3)	149 (94.9)	0.1950***
Yes n (%)	7 (5.5)	3 (2.0)		2 (1.7)	8 (5.1)	

NRS: Nutritional Risk Screening; M: male; F: female; LHS: length of hospital stay; MNA: Mini Nutritional Assessment; E: eutrophic; MR: malnutrition risk; M: malnutrition; DTD: digestive tract disorders; RUD: renal and urological disorders; RUN: renal and urological neoplasia; NDT: neoplasm of the digestive tract; WG: weight gain; WM: weight maintenance; WL: weight loss. *Mann-Whitney, **Chi-square test, ***Fisher's exact test.

nutritional support reduced the length of hospital stay, and patients experienced a lower incidence of infectious complications[5]. These observations suggest the relevance of assessment and tracking of the nutritional status and malnutrition early during hospitalization, since such measures could contribute to the prevention of unfavorable clinical outcomes in hospitalized elderly patients.

A prospective study[18] with geriatric patients investigated the instruments we actually used in our study with patients of the same age range, but considering prediction of mortality risk[18]. The authors reported that both instruments can predict mortality in hospitalized geriatric patients, but that only the NRS 2002 score was an independent predictor of mortality risk[18].

Other studies carried out with elderly hospitalized patients showed a high risk of malnutrition associated with reduction of muscle mass[19], and malnutrition in this population contributed to the development of frailty[20]. Other studies have also reported that a decline in nutritional status assessed by subjective global assessment and by weight loss was associated with prolonged hospital stay, regardless of other risk factors[21]. Weight loss and other anthropometric indicators are still widely used in hospital clinical practice[22]. Another study[23] that investigated the nutritional risk of hospitalized patients using the tool (NRS 2002) showed 29% of nutritional risk, with different prevalence in different clinical situations and with older age, in addition to the prevalence of malnutrition in those patients with greater morbidity and infections. However, it was noteworthy that nutritional risk was evidenced in patients with normal BMI or overweight[23]. These reports are in line with the need to detect the nutritional status of older patients upon admission. Such actions by hospital health professionals could contribute to the reduction of unfavorable clinical outcomes.

It was not the object of this investigation to identify which was the best nutritional tracking instrument for elderly patients, but to assess whether there was agreement between the two instruments considered. Since both instruments are adequate and easy to apply in hospital clinical practice, they can be applied by health professionals and there is no gold standard for the identification of malnutrition in hospitalized patients; we can consider that each institution could select the tool or other instruments and/or indicators that best apply to each reality, thus contributing to the prevention of unfavorable clinical outcomes. It is important to highlight that both screening tools take into account dietary, clinical and anthropometric aspects[14,15] and studies show that a nutritional

intervention could interrupt weight loss in malnourished elderly people, being also associated with improvements in MNA scores[24].

CONCLUSION

The findings in this study allowed us to conclude that NRS and MNA show moderate agreement for the assessment of hospitalized elderly patients.

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Authors' contribution

Leandro-Merhi VA: developed the methodological design of the study. Almendra AAR: performed the collection and tabulation of the data. AARA and VALM performed the analysis and interpretation of the data. Almendra AAR and Leandro-Merhi VA: wrote the original draft of the manuscript. Almendra AAR, Leandro-Merhi VA and Aquino JLB: performed a critical review, wrote and revised the final version of the manuscript. All authors approved the final version of the manuscript.

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Almendra AAR, Leandro-Merhi VA, Aquino JLB. Concordância entre instrumentos de triagem nutricional em idosos hospitalizados. Arq Gastroenterol. 2022;59(1):145-9.

RESUMO – Contexto – A prevalência de pacientes idosos hospitalizados tem crescido substancialmente e impactado os serviços de saúde hospitalar. Desta forma, acredita-se que uma investigação do estado nutricional, associado a situações clínicas variadas em pacientes idosos, poderia contribuir para ações de intervenção hospitalar multidisciplinares e de cuidado nutricional adequadas para esta população. **Objetivo –** Investigar a relação entre dois instrumentos de triagem nutricional em pacientes idosos hospitalizados e comparar variáveis clínicas entre estes dois instrumentos. **Métodos –** Estudo retrospectivo com pacientes idosos hospitalizados (n=277), sendo investigado a concordância entre dois instrumentos de triagem nutricional. Os dados foram analisados pelos testes McNemar, qui-quadrado, Fisher, Mann-Whitney e o coeficiente kappa para a avaliação de concordância. **Resultados –** Houve diferença significativa (P=0,0002) entre as classificações de risco nutricional pelos dois instrumentos de triagem nutricional e concordância moderada (k=0,5430) entre eles. Verificou-se associação entre triagem de risco nutricional e idade (P=0,0255), tempo de internação (P<,0001), sexo (P=0,0365) e doenças (P=0,0001). Houve associação entre a Mini Avaliação Nutricional e tempo de internação (P<0,0001), doenças (P=0,0001) e evolução do peso corporal (P=0,0479). **Conclusão –** Triagem de risco nutricional e a Mini Avaliação Nutricional apresentam concordância moderada para a avaliação de pacientes idosos.

Palavras-chave – Idosos hospitalizados; triagem nutricional; concordância.

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BRIEF COMMUNICATION

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Pediatric celiac disease diagnosis and adherence to the ESPGHAN 2012 and 2020 guidelines: a single centre experience

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Dear Sir,

The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2012 guidelines for celiac disease (CD) recommended a no-biopsy pathway (NBP) for symptomatic children who meet the so-called 'triple criteria'[1]:

- IgA anti-tissue transglutaminase antibody [TGA-IgA] titer ≥10-times upper-limit-of-normal [ULN] and are IgA sufficient.
- Positive IgA anti-endomysial antibody [EMA-IgA].
- Positive HLA-DQ2/DQ8 haplotype.

Biopsy based diagnosis remained mandatory for diagnosing all other children with suspected CD while remaining on gluten-containing diet[1]. Failure to follow ESPGHAN (2012) guidelines for CD diagnosis (across a range of results) was previously reported including two recently published studies from Southwest England[2,3].

The ESPGHAN guidelines for CD were revised in 2020 recommending that the NBP can be used in all children (symptomatic/asymptomatic) with[4]:

- TGA-IgA ≥10xULN.
- Positive EMA-IgA in a second serum sample.

Biopsy based pathway still remain mandatory for all other children with TGA-IgA is <10xULN.

The aim of this retrospective study (performed in January 2021) was to establish the level of adherence to established ESPGHAN (2012/2020) guidelines[1,4]. Potential cases (n=179) were identified from the laboratory database over an 8-year period (January 2013–December 2020). All patients investigated as per the ESPGHAN 2012 and 2020 guidelines were included in the study. However, children whose TGA-IgA had normalised in the interim period i.e. from the time of initial referral by their general practitioners (GPs) to when they were seen in the paediatric clinic, were excluded from the study (n=31). A further 17/179 children were excluded as they were not referred by their GPs and are currently being been assessed locally within the pediatric services.

FIGURE 1 details the study population managed following the ESPGHAN 2012 guidelines from January 2013 till December 2019; 113 of 118 children (aged <16 years) were diagnosed with CD. The NBP was utilised to diagnose CD in 57/118 (48.3%) and non-adherence to the established ESPGHAN criteria was noted in 20.3% cases (n=24). Five children were diagnosed with CD without biopsy (yet had TGA-IgA <10xULN) because parents were unhappy with gluten challenge despite the need for endoscopic assessment to adhere to ESPGHAN guidelines. Positive HLA-DQ2/

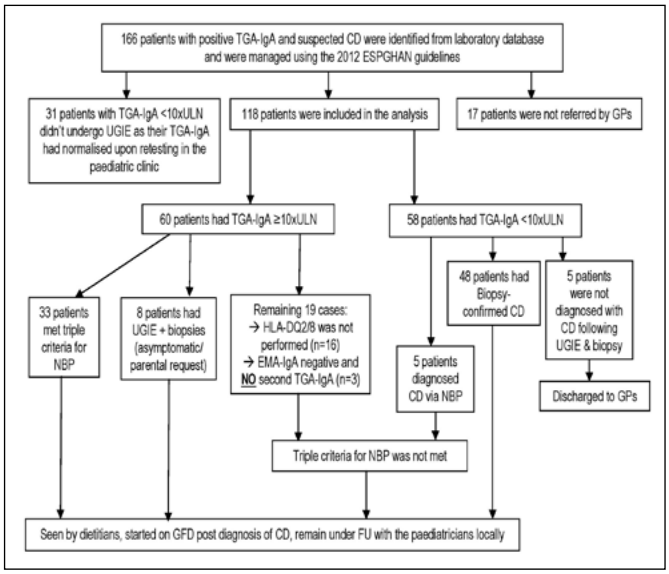

FIGURE 1. Diagnostic pathways used for children with suspected CD. CD: coeliac diseases; EMA-IgA: IgA-based anti-endomysial antibody; FU: follow-up; GFD: gluten-free diet; GPs: general practitioners; HLA: human leukocyte antigen; IgA: immunoglobulin A; NBP: no-biopsy pathway; TGA-IgA: IgA-based anti-tissue transglutaminase antibodies; UGIE: upper gastrointestinal endoscopy; ULN: upper limit of normal.

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DQ8 results (testing for which was requested inappropriately) in four of five patients likely contributed towards non-adherence to the guidelines. Seventeen patients (two with TGA-IgA >10xULN) were not referred by primary care until December 2020 and are being recalled and reassessed for CD.

In 2020, 13 children were diagnosed CD without biopsy: 11/13 met the revised 2020 ESPGHAN criteria for NBP[4]; two (with TGA-IgA <10xULN but >5xULN) were diagnosed using our regional interim COVID-19 NBP pathway.

Of the 126 children diagnosed with CD, there were 39 males and 87 females. The mean and median ages of the 126 children were 8.5 and 8.2 years respectively (range 0.8 year to 15.9 years). Out of 126 children, 106 were symptomatic: 82 had gastrointestinal symptoms (diarrhoea, constipation, abdominal pain, vomiting, faltering growth), fifteen had 15 extra intestinal manifestation (iron deficiency anaemia, tiredness, pubertal delay), and nine had mixed features. Twenty patients who were asymptomatic at diagnosis of CD belonged to high-risk groups: 12 had type 1 diabetes and eight had CD in a first-degree relative.

This study identified significant non-adherence to the 2012 ESPGHAN CD guidelines (n=24). However, some of these cases where non-adherence was noted will be admissible within the 2020 ESPGHAN revision of the CD guidelines[4], given the omission of HLA-DQ2/DQ8 typing (16/24 cases with TGA-IgA ≥10xULN had no HLA-DQ2/DQ8 performed). However, 5/24 cases who had TGA-IgA <10xULN would still require a biopsy diagnosis[4], with similar problems identified in two other English studies[2,3]. Due to the COVID-19 pandemic and limited endoscopy access, two symptomatic children with TGA-IgA <10xULN but >5xULN were diagnosed via NBP in 2020, a strategy suggested by a recently published Italian study[5].

Another issue identified: 17 of 179 (9.5%) children with positive TGA-IgA were not referred for confirmation of CD diagnosis by GPs. While a transient rise in titer is recognised after viral illnesses or in another condition e.g. cow's milk protein allergy, inflammatory bowel disease or other autoimmune conditions, it is quite possible that some were truly celiac and just not referred or may have been inappropriately diagnosed as CD in the primary care and commenced on gluten free diet (GFD). Similar issues were identified in two recently published studies from Southwest England where around 15% of children with a positive celiac serology were not initially referred[2,3], but following a recall, some were subsequently appropriately got diagnosed as CD (SPP personal communication).

Strict adherence to 2012 ESPGHAN guidelines was not seen in 24/118 (20.3%) cases. Considering CD is a life-long condition and GFD has significant challenges, we conclude that detailed understanding of, and tighter adherence to ESPGHAN 2020 guidelines is mandatory amongst general pediatricians involved in the diagnostic process in a non-specialist setting. Education events involving local pediatricians and GPs involved in referring/diagnosing CD are planned to update understanding, through dissemination of 2020 ESPGHAN guidelines, detailing challenging CD scenarios and emphasising the absolute need for referral to pediatricians or pediatric gastroenterologists to confirm a CD diagnosis.

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Authors' contribution

Tashtoush LB: data collection and analysis, prepared manuscript and literature review. Broad SR: project supervision and logistical support, data analysis, edited manuscript. Paul SP: project concept, supervision, edited manuscript and provided expert opinion. All the authors have approved the final manuscript.

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Combined extended right hepatectomy with inferior vena cava resection and reconstruction with Gore-Tex graft

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Malignant liver tumors can directly invade the inferior vena cava (IVC) due to anatomical proximity. In such cases, hepatectomy combined to IVC resection may be required to achieve negative surgical margins[1,2]. This approach becomes more common, due to progress in surgical techniques and perioperative management[3,4].

Herein, we present a case of a 42-year-old woman with a 23 cm hypervascular liver mass located on the right liver, extended to segments one and four, encompassing completely the IVC circumference, near the root of the left hepatic vein (LHV) (FIGURE 1). Preoperative diagnosis was between liver cell adenoma or hepatocellular carcinoma (HCC). Patient was taken to surgery, which was performed through a bilateral subcostal incision with midline extension (E-VIDEO). Initially, we performed a doppler ultrasonography to analyze the relationship between the tumor and vascular structures and assure that the LHV was not involved by the lesion. Next, the liver pedicle and infrahepatic IVC were taped to perform the liver's total vascular exclusion (TVE). Then, the right hepatic artery, right portal vein and right biliary duct were dissected, ligated and divided. Portal and arterial branches to caudate lobe were also divided. Suprahepatic IVC was then isolated and encircled. Hepatotomy was performed through the anterior approach, using an ultrasonic dissector/aspirator. Besides the selective ischemia of the right liver, Pringle maneuver was applied (two periods of 15-minutes clamping with 5-minutes of clamping-free), in order to minimize blood loss and ischemic time.

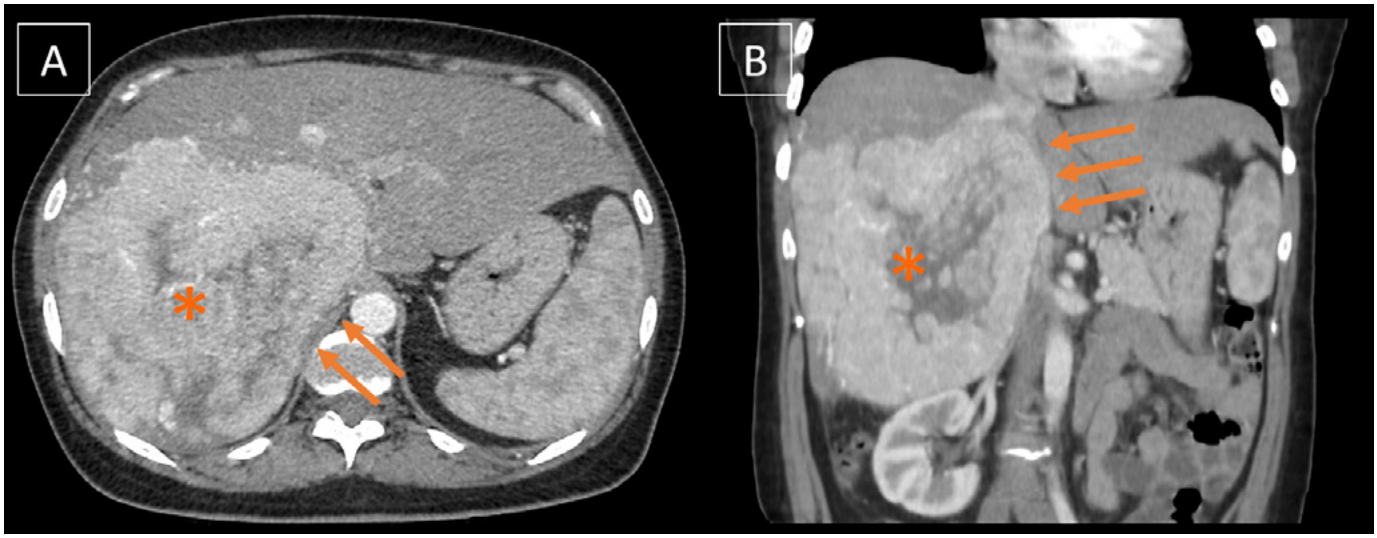

FIGURE 1. Axial **(A)** and coronal **(B)** CT scan images showing a hypervascular liver mass (*) involving the retrohepatic IVC (arrows).

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After identifying the middle hepatic vein in the transection plane, TVE was performed by clamping successively the portal triad, infrahepatic and suprahepatic IVC. Extended right hepatectomy and IVC resection was then completed. The LHV in the native vena cava remained untouched.

IVC was reconstructed with a 20 mm Gore-Tex graft, firstly sutured to the suprahepatic IVC. Sequentially the suprahepatic clamp was released and placed below the insertion of the LHV, allowing unclamping of the hepatic pedicle, for restoration of liver perfusion and diminishing ischemic time. The graft was then sutured to the infrahepatic IVC and the last clamp was released. TVE time was 20 minutes. Patient recovered well and was discharged on the 6th post-operative day. Histopathological analysis confirmed HCC. Patient is still alive 36 months after surgery, with graft patency (FIGURE 2).

Combined extended right hepatectomy and IVC resection is a safe and feasible procedure, that should be performed by a hepatobiliary team experienced in complex hepatectomies and liver transplantation. Despite being an aggressive surgical procedure, it may be the only curative option for patients with massive tumors involving the IVC.

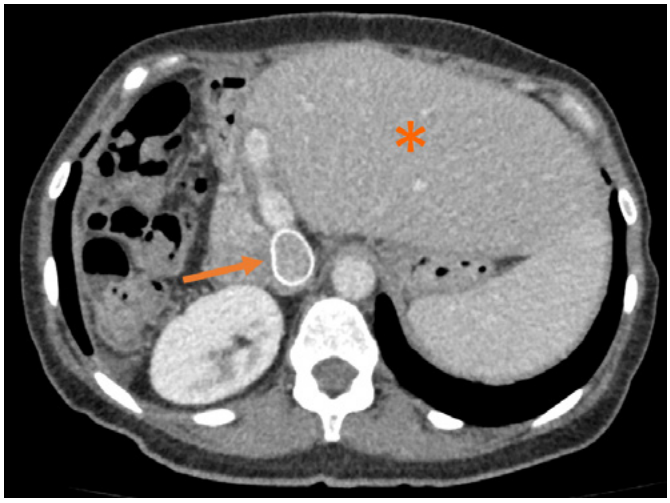

FIGURE 2. Long term postoperative axial CT scan image showing the hypertrophied left lateral liver sector (*) and patent IVC graft (arrow).

Authors' contribution

Steinbrück K, Cano R, Vasconcelos H, Rangel B, Fernandes R and Enne M: participated in the surgical procedure, designed the case report, collected data, wrote the paper, critically reviewed and approved the final version to be published.

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Steinbrück K, Cano R, Vasconcelos H, Rangel B, Fernandes R, Enne M. Hepatectomia direita alargada combinada com ressecção da veia cava inferior e reconstrução com prótese de Gore-Tex. Arq Gastroenterol. 2022;59(1):152-3.

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Robotic approach for the treatment of giant colonic diverticulum

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Keywords – Diverticulum; colon; robotic surgical procedures; colectomy.

INTRODUCTION

Giant colonic diverticulum (GCD) is defined as a diverticulum with more than 4 cm. It is a rare manifestation of colonic diverticulum and appear mostly (90%), but not solely, in the sigmoid and is usually 4–9 cm in diameter (range 5–40 cm)[1].

Abdominal pain is the most common clinical manifestation (69%), while abdominal mass, fever and abdominal tenderness are frequent physical signs[2,3]. Additional symptoms are rectal bleeding, diarrhea, vomiting and constipation[4].

The diagnosis of GCD relies mainly on image studies, such as contrast enhanced computed tomography (CT-scan) and magnetic resonance (MRI). It usually appears as a gas-filled structure containing fluid and with communication with the colon, and the main differential diagnosis is a colonic perforation with abscess formation. These image study modalities may provide important further information, such as wall thickening, infiltration of adjacent fat and localized peritonitis, suggestive of an acute inflammatory complication (diverticulitis)[4]. Diagnostic colonoscopy and barium enema are not usually considered necessary or helpful for the diagnosis of GCD[5].

While a non-surgical conservative approach may be considered for asymptomatic high-risk patients, elective segmental colonic resection with primary anastomosis is recommended for asymptomatic patients and en bloc resection of the diverticulum with terminal temporary colostomy (Hartmann's procedure) is suggested for symptomatic complicated cases[2,4]. Diverticulectomies are the least used option, performed in only 10.2% of the cases[2].

While the adoption of the minimally invasive laparoscopic approach for colonic resection has been slower than to other procedures, it is now widely recognized that it results in decreased use of postoperative analgesics, shorter hospital stays and better short-term outcomes when compared to the traditional open approach[5]. The robotic surgical platform has emerged, in the last two decades, in order to overcome several technical limitations of the laparoscopic approach. Different from the slow initial adoption of the laparoscopic approach, the robotic colorectal surgery paved the way for the spread of this minimally invasive technology, as the benefits of the robotic surgery were first noted without a doubt during left colectomies[6]. It has several advantages when compared to the laparoscopic approach, such as wristed instrumentation, more degrees of motion than even the human hand, improved ergonomics, high definition three-dimensional imaging, control of the camera by the surgeon and tremor filtering with superior dexterity[7,8].

METHODS

In this multimedia article we present the totally robotic approach for the treatment of a symptomatic GCD.

The patient was a 42-year-old woman with previous hypothyroidism and systemic lupus erythematosus admitted with a 2-day history of left lower quadrant abdominal pain, abdominal swelling and nausea. The patient reported episodic abdominal pain for 3 months prior to admission. She did not report any changes in bowel habits. Previous surgeries included an appendectomy in her childhood. The patient's weight was 60 kg, with a body mass index of 23. On clinical examination the abdomen was distended, soft, and mildly tender on the lower abdominal quadrants, where a large palpable mass.

She was submitted to investigation with a CT-scan of the abdomen that disclosed an 6 cm cystic lesion containing air and fluid with communication with the sigmoid colon, with signs of acute inflammation such as surrounding fat stranding and intense wall thickening (FIGURE 1. A, B). After being conservatively treated with analgesics and antibiotics, she was submitted to an abdominal MRI 2 months after, that disclosed enlargement of the cystic lesion to 8 cm, cranial displacement of the mass when compared to the CT-scan and resolution of the signs of acute inflammation (FIGURE 1. C, D). As she presented recurrent symptoms of abdominal pain and nausea, surgical treatment with a totally robotic approach was proposed using the da Vinci Si platform.

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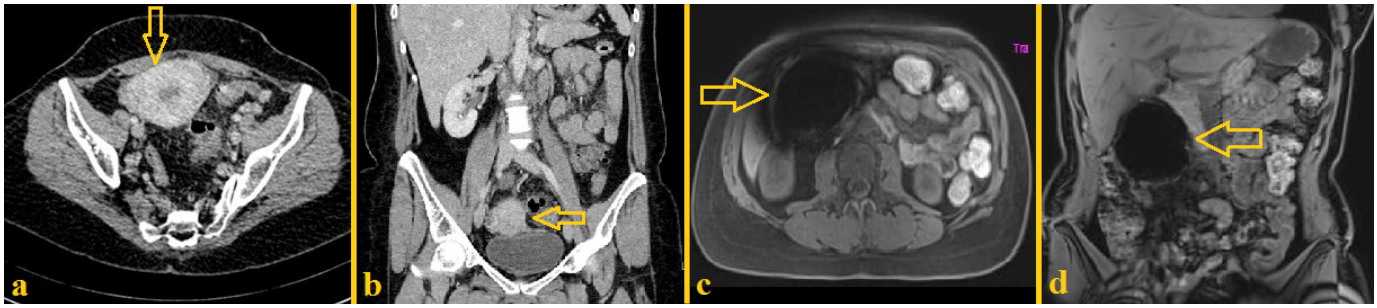

FIGURE 1. Image studies performed on a patient with GCD. **a, b)** CT-scan disclosing a pelvic cystic mass with wall thickening, fat stranding and communication with the sigmoid colon (yellow arrows): **a)** axial plane; **b)** coronal plane. **c, d)** Contrast enhanced MRI performed 2 months after initial presentation disclosing cranial displacement, enlargement, reduction of wall thickening and fat stranding of the GCD (yellow arrows): **c)** axial plane; **d)** coronal plane.
GCD: giant colonic diverticulum; CT-scan: computed tomography; MRI: magnetic resonance.

RESULTS

At inspection, a large diverticulum of the sigmoid colon was found, and the resection of the diverticulum of the sigmoid colon and primary colonic anastomosis were performed (FIGURE 2. a-c, E-VIDEO). The pathology examination showed a 7 cm true GCD with acute and chronic inflammation with no evidence of malignancy (FIGURE 2. d). The postoperative course was uneventful, and the patient was discharged on postoperative day 4. At 12 months follow-up, the patient was asymptomatic without any complication.

It is known that the first description of a GCD dates back to 1946 by Bonvin and Bonte, and the first description by radiologic examination is attributed to Hughes and Greene in 1953[3]. It is a rare presentation of colonic diverticulum, with less than 200 cases described in the literature[1-3]. A segmental colectomy with en-bloc diverticular resection and primary anastomosis with or without a diverting ileostomy is the preferred surgical treatment option. Minimally invasive surgery can be a valuable alternative to open procedures[2,5].

DISCUSSION

While the the first laparoscopic approach for colorectal surgery was performed by Semm at the University of Kiel in 1981 and is the usual approach for the treatment of colonic diverticulum, the robotic colorectal surgery was reported only in 2002 by

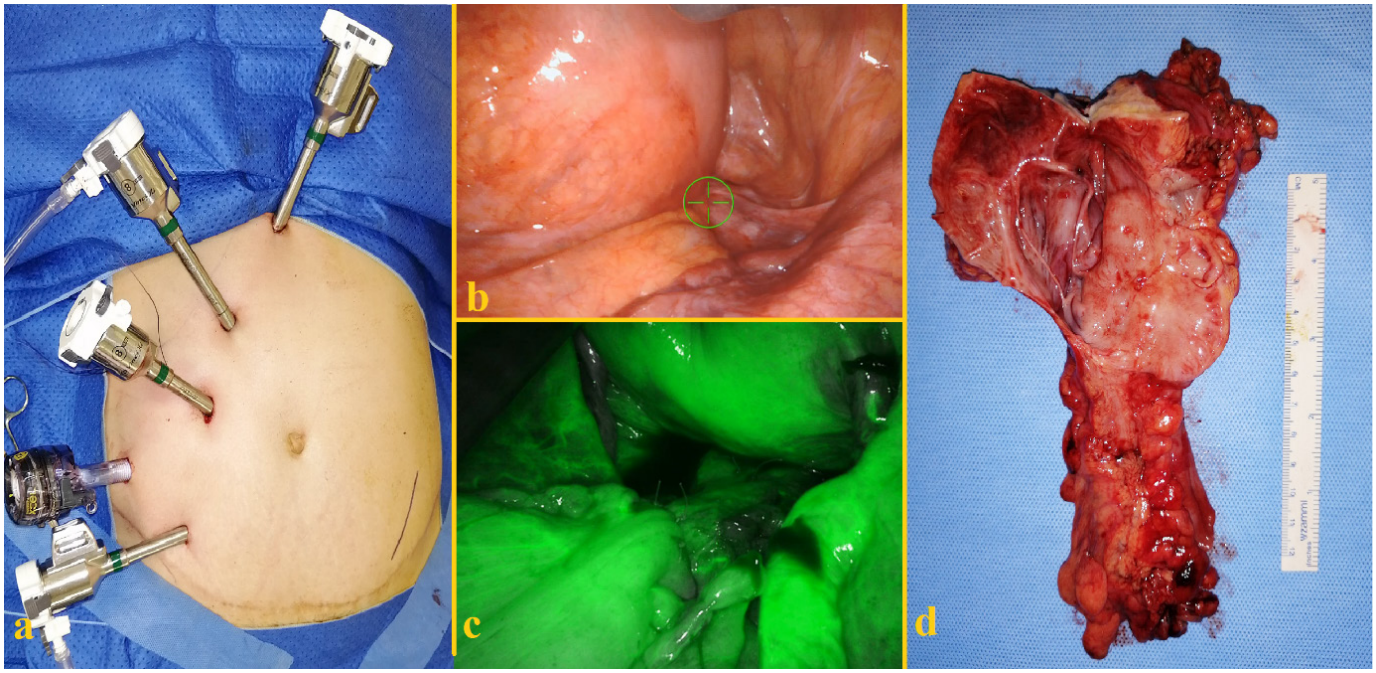

FIGURE 2. Robotic approach for the treatment of a GCD. **a)** Trocar placement; **b)** GCD at inspection; **c)** Fluorescence evaluation of the vascularization of the anastomosis; **d)** Surgical specimen.
GCD: giant colonic diverticulum.

Weber et al. for benign disease and by Hashizume et al. for malignant disease[9,10]. To our knowledge this is only the second GCD treated by the Robotic approach described in the literature[11].

In the current case a robotic atypical colon wedge resection was safely performed. This option might be considered as an alternative to extended resections, such as a formal left colectomy. The use of real-time near-infrared robotic fluorescence using intravenous indocyanine green as contrast agent allowed precise evaluation of the vascularization of the anastomosis, an important feature of atypical colonic resections. Localization of the GCD and the simultaneous existence of diverticular disease are the main criteria for the decision between the different operative approaches[2].

CONCLUSION

Therefore, the totally robotic surgical treatment of GCD with resection of the diverticulum and adjacent colon with primary anastomosis is a feasible and safe alternative, with potential advantages over the conventional open and laparoscopic approaches.

Author's contribution

Bustamante-Lopez LA and Surjan RCT: wrote the article. Surjan RCT and Bustamante-Lopez LA: designed the study. Silveira SP performed data collection. Surjan RCT, Silveira SP and Bustamante-Lopez LA: provided critical advice. All authors discussed the results and commented on the article and take full responsibility on the manuscript.

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Palavras-chave – Divertículo; cólon; procedimentos cirúrgicos robóticos; colectomia.

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Duodenal involvement related to vascular complications: diagnosed by upper gastrointestinal endoscopy

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Keywords – Aortoduodenal fistula; inferior vena cava filter; duodenal fistula; duodenal perforation.

The vascular enteric fistulae are severe. Late diagnosis causes high mortality[1]. The aortoduodenal fistulae are the most frequent (80%) and occur due to an aortic aneurysm[2]. The inferior caval vein filter (ICVF) is indicated when anticoagulation is contraindicated due to the risk of bleeding[3]. Its implantation is not free from short or long term complications[4]. The authors report two cases of vascular enteric fistulae, one derived from an aortic aneurysm and the other by ICVF, both perforated into the duodenum and detected by upper gastrointestinal endoscopy.

A 76-year-old man with abdominal pain, hematemesis and melena for 5 days. He reports aortic aneurysm. He arrived in serious condition, hypotensive (systolic pressure 90 mmHg) and with tachycardia (120 bpm). The rectal examination revealed the presence of living blood. After hemodynamic stabilization, the endoscopy showed a deep and pulsatile ulcer in the second duodenal portion, circumferentially affecting the organ's lumen, covered by fibrin and clots, compatible with aortoduodenal fistulae (FIGURE 1 and E-VIDEO). Computed tomography scan confirmed the finding of an infrarenal aortic aneurysm (7.5 cm) with rupture, in close contact with the duodenum, determining focal compression of the inferior vena cava. There was a new hemodynamic instability a few hours after admission with massive hematemesis and there was no time for surgical approach. He was referred to the intensive care unit and died 24 hours later.

Female, 54 years old, with abdominal pain, abdominal distension and postprandial fullness for 2 months. Physical examination revealed pain on deep palpation in the right flank and epigastrium. Eight years ago abdominal trauma with splenic injury. She had deep venous thrombosis in her lower limb, requiring ICVF implantation. Submitted to endoscopy that revealed an ICVF strut perforating the duodenum wall (E-VIDEO). Computed tomography scan showed the ICVF positioned below the confluence of the renal veins, and with its struts perforating the duodenum, right psoas muscle and attached to the L3 vertebral body (FIGURE 2). The patient underwent surgery, which identified the ICVF (FIGURE 3.A). The ICVF was removed and the duodenal wall sutured (FIGURE 3). The patient evolved well and was discharged on the eighth postoperative day.

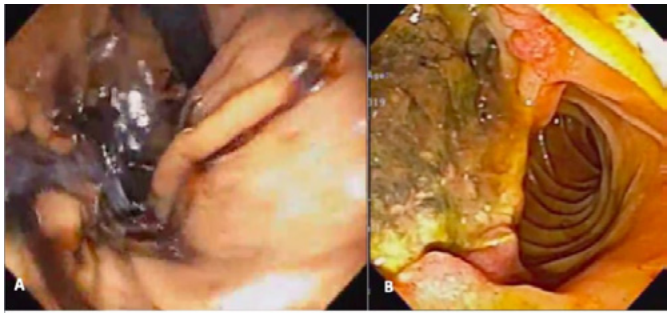

FIGURE 1. A) Hematic residues inside the stomach. **B)** Aortoduodenal fistula.

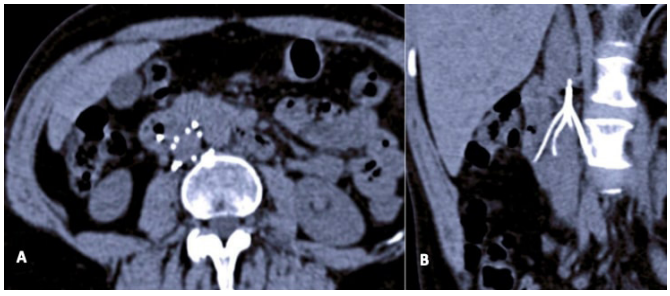

FIGURE 2. A) CT-scan showing inferior vena cava with its larger componetns perforating adjacent structures (duodenum, right psoas muscle and L3 vertebral body) . **B)** CT-coronal view.

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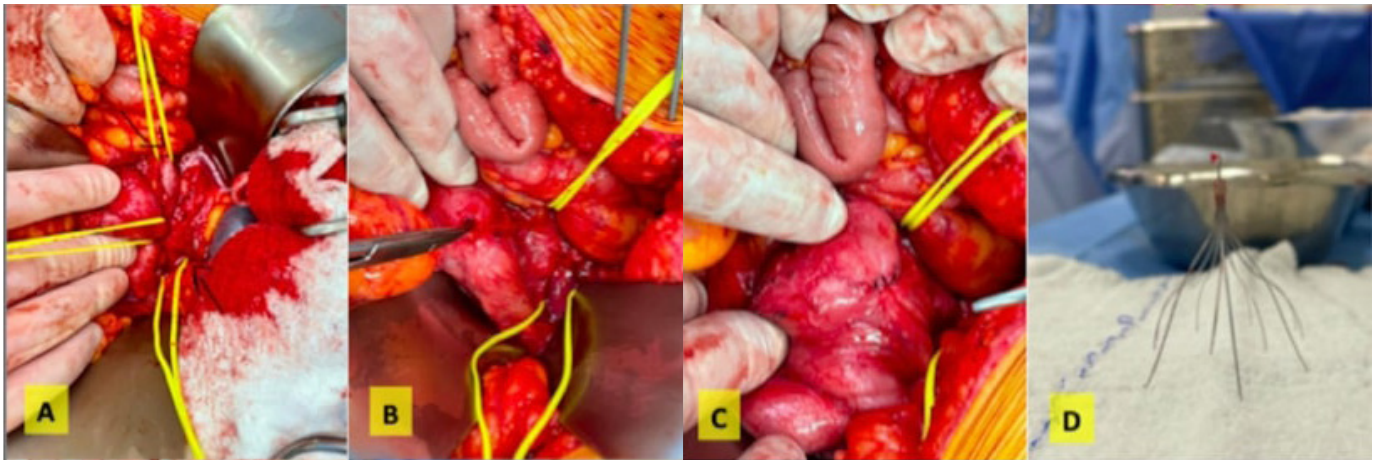

FIGURE 3. Intra-operatory view. **A)** Adherence between the 2nd duodenal portion and the vena cava. **B)** Perforation site in the 2nd duodenal portion. **C)** Suture of the duodenal wall. **D)** Recovered vena cava filter.

We emphasize the importance of valuing complaints reported by patients with these antecedents, in addition to performing a detailed physical examination. The diagnostic iconography must be precise, so that the treatment can be abbreviated. Remember that the close anatomical relationship of the retroperitoneal vascular organs and structures favors the appearance of complications in this topography.

Authors' contribution

Reis ACF designed the study, drafted the article and analyzed and interpreted the data; Romanini SG, Rampazzo Neto A, Trentini B, Aun R and Andengh JC analyzed the data. Ardengh JC approved the final version to be published. All authors read and approved the final manuscript.

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