Portuguese Journal of Gastroenterology

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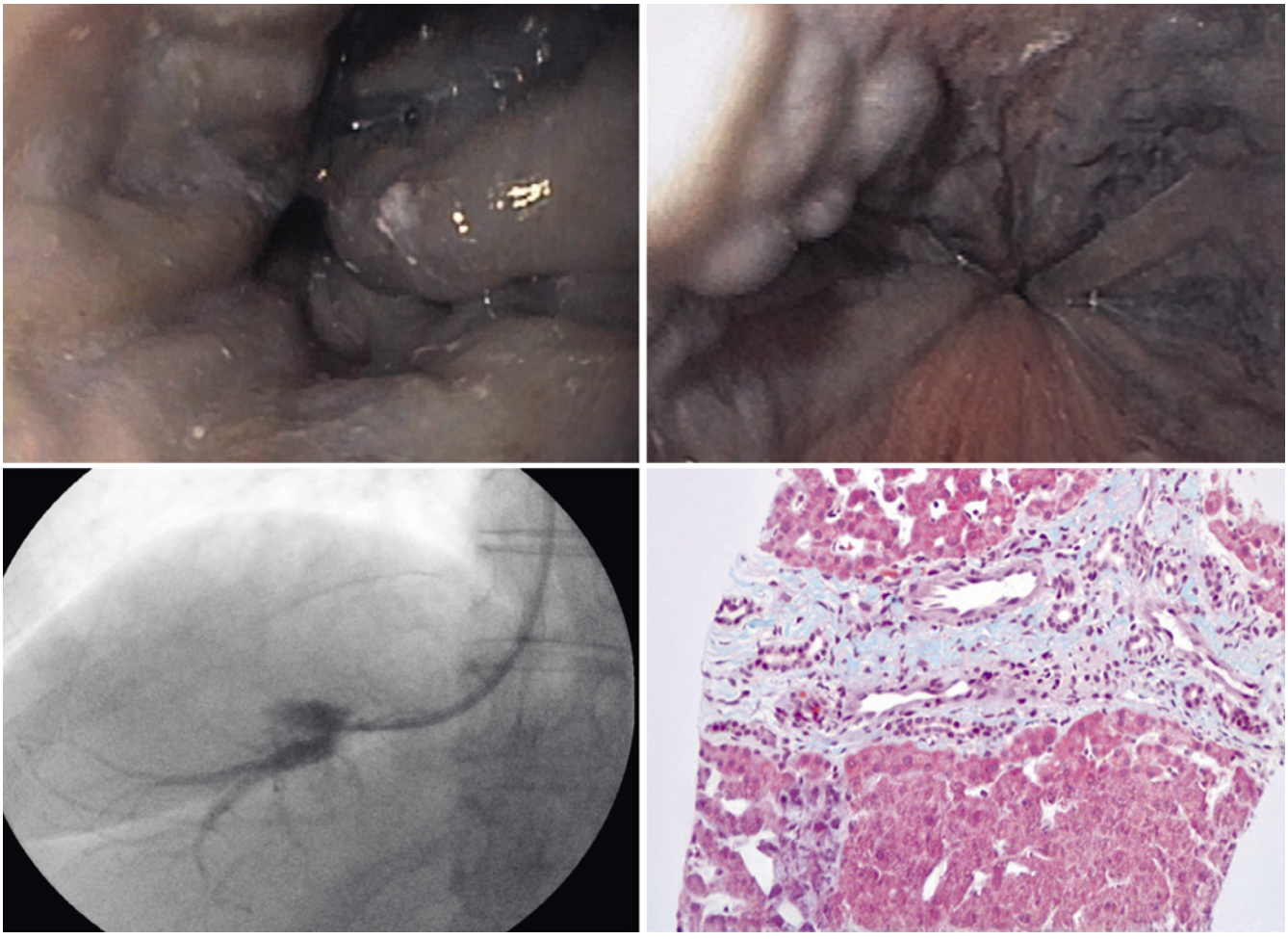

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Research article: Prevalence of Endoscopic and Histological Lesions at Upper Endoscopy: A Cross-Sectional, Multicentre Study

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Aims and Scope

The *GE Portuguese Journal of Gastroenterology* (formerly *Jornal Português de Gastrenterologia*), founded in 1994, is the official publication of Sociedade Portuguesa de Gastrenterologia (Portuguese Society of Gastroenterology), Sociedade Portuguesa de Endoscopia Digestiva (Portuguese Society of Digestive Endoscopy) and Associação Portuguesa para o Estudo do Fígado (Portuguese Association for the Study of the Liver).
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Price per printed issue: Free of charge
ERC-No.: 117866
Editor address: Rua Abranches Ferrão, nº 10–14º, PT–1600-001 Lisbon (Portugal)

ISSN Online Edition: 2387–1954

Journal Homepage: www.karger.com/pjg
Bibliographic Indices: This journal is regularly listed in bibliographic services, including PMC, PubMed, Web of Science, SciELO Citation Index, Google Scholar, DOAJ, Scopus, and WorldCat.

Publication Data: *GE Port J Gastroenterol* is published 6 times a year. Volume 32 with 6 issues appears in 2025.

Karger

GE – Portuguese Journal of Gastroenterology

Vol. 32, No. 1, 2025

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Research Article

GE Port J Gastroenterol 2025;32:1–8
DOI: 10.1159/000537685

Received: October 24, 2023
Accepted: December 8, 2023
Published online: March 12, 2024

Prevalence of Endoscopic and Histological Lesions at Upper Endoscopy: A Cross-Sectional, Multicentre Study in Clinical Practice

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Keywords
Upper endoscopy · Peptic ulcer · Cancer · *Helicobacter pylori* · Precancerous lesions

Abstract
Background/Aim: Prevalence of gastroduodenal endoscopic and histological lesions may modify over time due to different factors. We assessed both macroscopic and histological lesions currently detected at upper endoscopy performed in routine practice. ***Patients and Methods:*** Clinical, endoscopic, and histological data of consecutive adult patients referred for upper endoscopy in the 28 participating centres were analysed. Only patients who underwent the first endoscopic examination were considered. Prevalence of erosive/ulcerative lesions, cancers and extensive precancerous lesions in the stomach, and *Helicobacter pylori* infection was computed. ***Results:*** A total of 1,431 patients underwent endoscopy for gastro-oesophageal reflux symptoms (31.5%), dyspepsia (29.4%), or alarm symptoms (18.5%). Erosive oesophagitis or Barrett's oesophagus was detected in 210 (14.7%) cases, peptic ulcer in 49 (3.4%), and a neoplastic lesion in 17 (1.2%). *H. pylori* was present in 201 (22.6%) cases, and extensive precancerous lesions on gastric mucosa in 46 (5.6%) patients. Gastric lesions were more prevalent in patients aged ≥50 years (26% vs. 18%; $p = 0.001$), and peptic ulcers were more frequently detected in patients with *H. pylori* (9.4% vs. 2.3%; $p = 0.001$) and in males (5.8% vs. 1.6%; $p = 0.001$), while neoplastic lesions in patients with alarm symptoms (3.8% vs. 0.6%; $p = 0.001$). ***Conclusions:*** The overall endoscopic lesions were more prevalent in patients aged ≥50 years, peptic ulcer and erosions were more frequent in *H. pylori*-infected patients, and extensive gastric precancerous lesions were present in less than 6% of cases.

Prevalência de lesões endoscópicas e histológicas na endoscopia digestiva alta: um estudo transversal e multicêntrico na prática clínica

Palavras Chave
Esofagogastroduodenoscopia · Ulcera peptica · Câncer · *H. pylori* · Lesões pré-cancerosas

Resumo
Introdução/Objetivo: A prevalência de lesões endoscópicas e histológicas gastroduodenais pode modificar-se ao longo do tempo devido a alterações de diferentes fatores. Este estudo teve como objetivo avaliar lesões macroscópicas e histológicas e detectadas na esofagogastroduodenoscopia realizada na prática rotineira. ***Pacientes e Métodos:*** Foram analisados dados clínicos, endoscópicos e histológicos de pacientes adultos consecutivos encaminhados para esofagogastroduodenoscopia nos 28 centros participantes. Foram considerados apenas os pacientes que realizaram o primeiro endoscopia. Foi computada a prevalência de lesões erosivas/ulcerativas, cânceres e lesões pré-cancerosas difusas no estômago e infecção por *H. pylori*. ***Resultados:*** Um total de 1,431 pacientes foram submetidos à endoscopia foram sintomas de refluxo gastroesofágico (31.5%), dispepsia (29.4%) e sintomas de alarme (18.5%). Esofagite erosiva ou esôfago de Barrett foram detectadas em 210 (14.7%) casos, úlcera péptica em 49 (3.4%), lesão neoplásica em 17 (1.2%). A infecção por *H. pylori* esteve presente em 201 (22.6%) casos, lesões gastricas pré-cancerosas difusas em 46 (5.6%). As lesões endoscópicas foram mais prevalentes em pacientes com idade ≥50 anos (26% vs. 18%; $p = 0.001$), com úlceras pépticas detectadas com mais frequência em pacientes com *H. pylori* (9.4% vs. 2.3%; $p = 0.001$) e no sexo masculino (5.8% vs. 1.6%; $p = 0.001$), enquanto lesões neoplásicas naqueles que apresentam sintomas de alarme (3.8% vs. 0.6%; $p = 0.001$). ***Conclusões:*** As lesões endoscópicas globais foram mais prevalentes em pacientes com idade >50 anos, úlcera péptica e erosões foram mais frequentes em pacientes infectados por *H. pylori*. Lesoes gástricas pre-cancerosas estiveram presentes em menos de 6% dos casos.

Introduction

Prevalence of different gastroduodenal lesions detected at upper endoscopy is changing over time due to modifications of the main involved aggressive or protective factors. Indeed, prevalence of *Helicobacter pylori* infection – namely, the main aetiologic factor for peptic ulcer (gastric and duodenal) and gastric neoplastic lesions (low-grade B-cell MALT lymphoma, diffuse large B-cell lymphoma, adenocarcinoma) – is decreasing in developed countries [1–3]. Conversely, therapy with non-steroidal anti-inflammatory drugs (NSAIDs) – either as antiaggregant therapy or treatment of chronic rheumatic diseases and chronic pain – is largely used in routine practice, even as out-the-counter therapy [4–7], and its role in damaging gastric mucosa is well documented [8].

Similarly, prevalence of obesity is relentlessly increasing worldwide, and its association with gastro-oesophageal reflux disease (GORD) is recognized [9]. On the other hand, use of proton-pump inhibitors (PPI), the most effective drugs to treat lesions of acid-related diseases, has hugely increased in the last decades [10]. Since gastric cancer remains one of the most prevalent cancer-related causes of mortality and population-based screening programmes are not implemented in Western countries, to search for precancerous lesions in the stomach during endoscopy performed in routine practice is advised to identify patients deserving follow-up [11]. Current guidelines suggest to standard biopsies during appropriate upper endoscopies to assess the presence of extensive atrophy/metaplasia – i.e., involving both antral and gastric body mucosa – on gastric mucosa, because these precancerous lesions distinctly increase gastric cancer risk [11, 12]. Based on these observations, it is clinically worthy updating the diagnostic yield of upper endoscopies performed in routine practice. Indeed, previous large studies on prevalence of endoscopic and histological lesions in routine upper endoscopy performed in our country were published more than 10 years ago [13, 14].

The relevance of this topic is further strengthened when considering that more than 2.5 million of upper endoscopies was performed in Italy yearly, 1.2 million in UK, and 6.9 million in USA [15–17], and that the rate of inappropriate procedures was higher than 20% [18]. Therefore, we performed a multicentre study to assess both macroscopic and histological lesions currently detected at upper endoscopy performed in routine practice.

Materials and Methods

Study Design and Patients

In this cross-sectional study, clinical, endoscopic, and histological data of consecutive adult patients referred for upper endoscopy in the participating centres between October 1 and October 31, 2022, were anonymously reviewed and gathered in a specific Excel database. To better describe routine clinical practice, only data of patients referred by their general practitioners were collected, while those of in-patients were excluded. Moreover, we have taken into account solely patients who underwent the first endoscopic examination for any indication, while endoscopic surveillance procedures not considered. Clinical data collection was focused on the main indication for endoscopy, and ongoing therapies with antithrombotic drugs (antiaggregant or anticoagulant) and PPI. PPI therapy was defined as ongoing when drugs were taken until the previous day before or suspended less than 7 days before endoscopy. Alarm symptoms included anaemia, melena, persistent vomiting, weight loss, and dysphagia, as suggested in guidelines [19, 20]. Data on oesophageal, gastric, and duodenal lesions detected at endoscopy were computed, and a threshold age of 50 years was chosen for comparison, as suggested by Italian guidelines [12, 20]. Histological reports were reviewed to evaluate the prevalence of both *H. pylori* infection and that of extensive precancerous lesions (atrophic or metaplastic pangastritis) in the stomach.

Table 1. Demographic and clinical characteristics of patients

Variable	Finding
Male/female (*N* = 1,431)	584/847
Mean age ± SD (*N* = 1,431), years	55.9±17.2
Main indication for endoscopy (*N* = 1,139)	
GORD	452 (31.5)
Dyspepsia	422 (29.4)
Alarm symptoms	265 (18.5)
Portal hypertension	28 (1.9)
Radiological finding	14 (0.9)
Before bariatric surgery	9 (0.6)
PPI therapy (*N* = 928)	276 (29.7)
Antithrombotic therapy (*N* = 1,070)	173 (16.1)
Gastric biopsies performed (*N* = 1,431)	
Only antrum	90 (6.2)
Antrum plus gastric body	812 (56.7)
Only gastric body	10 (0.6)
Main endoscopic finding (*N* = 1,431)	
Erosive gastritis	228 (15.9)
Erosive oesophagitis	193 (13.5)
Erosive duodenitis	50 (3.5)
Duodenal ulcer	28 (1.9)
Gastric ulcer	21 (1.5)
Barrett's oesophagus	17 (1.2)
Suspected neoplastic mass	17 (1.2)

Statistical Analysis

Frequencies, means, or medians were computed, with their 95% confidence intervals (CIs) and the odds ratios (ORs) calculated for the main observations. Comparison among subgroups was performed by using the χ^2 test with Yate's correction. A p value <0.05 was considered statistically significant.

Results

Descriptive Analysis

A total of 1,431 patients (M/F: 584/847; mean age: 55.9 ± 17.2) underwent first endoscopic examination in the 28 participating centres, including 24 community hospitals and 4 academic hospitals. The main indication for endoscopy was GORD (*N* = 452; 31.5%), dyspepsia (*N* = 422; 29.4%), alarm symptoms (*N* = 265; 18.5%), searching for gastro-oesophageal varices (*N* = 28; 1.9%),

Table 2. Distribution of lesions detected at endoscopy according to the main indication

Finding	Dyspepsia (*N* = 422)	GORD (*N* = 452)	Alarm symptoms (*N* = 265)	Not available (*N* = 292)
Oesophagus				
Erosive oesophagitis	43 (10.1)	90 (10.1)	34 (12.8)	26 (8.9)
Barrett's	1 (0.2)	4 (0.8)	2 (0.7)	10 (3.4)
Suspect neoplasia	–	–	3 (1.1)	–
Varices	–	–	–	9 (3)
Total	44 (10.4)	94 (20.8)	39 (14.7)	45 (15.4)
Stomach				
Erosions	77 (18.2)	71 (15.7)	42 (15.8)	38 (13)
Peptic ulcer	3 (0.7)	8 (1.7)	6 (2.2)	4 (1.3)
Suspect neoplasia	2 (0.4)	2 (0.4)	9 (3.3)	–
Fundal cystic polyps	11 (2.6)	15 (3.3)	10 (3.7)	12 (4.1)
Adenoma	2 (0.4)	2 (0.4)	3 (1.1)	11 (3.7)
Submucosal mass	3 (0.7)	3 (0.6)	–	5 (1.7)
Total	98 (23.2)	101 (22.3)	70 (26.4)	70 (23.9)
Duodenum				
Erosions	17 (4)	16 (3.5)	10 (3.7)	7 (2.3)
Peptic ulcer	8 (1.8)	11 (2.4)	4 (1.5)	5 (1.7)
Suspect coeliac	6 (1.4)	–	6 (2.2)	14 (4.7)
Suspect neoplasia	–	–	–	1 (0.3)
Total	31 (7.3)	27 (5.9)	20 (7.5)	27 (9.2)

N (%). GORD, gastro-oesophageal reflux disease.

suspect radiological finding (*N* = 14; 0.9%), and evaluation before bariatric surgery (*N* = 9; 0.6%), while the information was lacking for the remaining 292 (20.4%) cases. There were 276 (29.7%) out of 928 patients in ongoing PPI therapy, and 173 (16.1%) out of 1,070 patients in antithrombotic, with either antiaggregant (*N* = 135) or anticoagulant (*N* = 38) therapy, when considering only cases with available information (Table 1).

Endoscopic Findings

At endoscopic examination, at least one lesion in the oesophagus, stomach, and duodenum was detected in 222 (15.5%, 95% CI: 13.6–17.3), 339 (23.6%, 95% CI: 21.4–25.8), and 105 (7.3%, 95% CI: 5.9–8.6) patients, respectively. In detail, erosive oesophagitis or Barrett's oesophagus was diagnosed in 193 (13.5%) and 17 (1.2%) cases, gastric erosions in 228 (15.9%), gastric ulcer in 21 (1.5%), duodenal erosions in 50 (3.5%), duodenal ulcer in 28 (1.9%), and coeliac disease in 26 (3.8%) cases, while a neoplastic lesion was overall suspected in 17 (1.2%) cases (Table 1). Therefore, the overall peptic ulcer prevalence was 3.4% (95% CI = 2.5–4.4). The endoscopic lesions according to the main indication for upper endoscopy are listed in Table 2. The distribution of different endoscopic findings according to patients' age, gender, *H. pylori* infection, PPI therapy, and alarm symptoms is provided in Table 3. As shown, the overall endoscopic lesions in the stomach were more prevalent in patients aged ≥50 years (26% vs. 18%; $p = 0.001$; OR: 1.61; 95% CI: 1.23–2.12). Gastric ulcers (3.4% vs. 0.7%; $p = 0.009$), duodenal ulcers (5.9% vs. 1.6%; $p = 0.002$), and duodenal erosions (6.9% vs. 3.2%; $p = 0.02$) were more frequently detected in patients with *H. pylori* infection. Moreover, the prevalence of overall oesophageal (21% vs. 11.6%; $p = 0.001$; OR: 2.01; 95% CI: 1.51–2.69) and duodenal (10% vs. 5.4%; $p = 0.001$; OR: 1.95; 95% CI: 1.31–2.92) lesions was twice in males than in females, while fundal cystic polyps were predominant in females (5% vs. 0.8%; $p = 0.001$). Finally, the prevalence of overall neoplastic lesions was higher in those presenting with alarm symptoms (3.8% vs. 0.6%; $p = 0.001$; OR: 6.49; 95% CI: 2.4–17.2).

Histological Findings

At histological assessment, *H. pylori* infection was overall detected in 201 (22.6%, 95% CI: 19.9–25.4) out of 886 in whom antral biopsies (with or without other sites) were

Table 3. Distribution of lesions detected at endoscopy in different settings

Finding	Age		*p* value	Gender		*p* value	*H. pylori*		*p* value	PPI therapy		*p* Value	Alarm symptoms		*p* value
	<50 yrs (*N* = 488)	≥50 yrs (*N* = 943)		M (*N* = 584)	F (*N* = 847)		Pos (*N* = 201)	Neg (*N* = 685)		Yes (*N* = 276)	No (*N* = 652)		Yes (*N* = 265)	No (*N* = 1,166)	
Oesophagus															
Erosive oesophagitis	70 (14.3)	123 (13)	0.5	107 (18.3)	86 (10.1)	0.001	25 (12.4)	106 (15.4)	0.3	14 (5)	111 (17)	0.001	34 (12.8)	159 (13.6)	0.8
Barrett's	8 (1.6)	9 (0.9)	0.3	7 (1.1)	10 (1.1)	1	3 (1.4)	12 (1.7)	1	2 (0.7)	5 (0.7)	1	2 (0.7)	15 (1.2)	0.6
Suspect neoplasia	1 (0.2)	2 (0.2)	1	2 (0.3)	1 (0.1)	0.7	0 (0)	1 (0.1)	1	0 (0)	3 (0.4)	0.6	3 (1.1)	0 (0)	0.004
Varices	0 (0)	9 (0.9)	0.07	7 (1.1)	2 (0.2)	0.05	–	–	–	1 (0.3)	2 (0.3)	1	0 (0)	9 (0.7)	0.3
Total	79 (16)	143 (15)	0.6	123 (21)	99 (11.6)	0.001	28 (14)	119 (17)	0.2	17 (6)	121 (18)	0.001	39 (15)	183 (15)	0.7
Stomach															
Erosions	61 (12.5)	167 (17.7)	0.01	104 (17.8)	124 (14.6)	0.1	41 (20.3)	122 (17.8)	0.4	41 (14.8)	115 (17.6)	0.3	42 (15.8)	186 (15.9)	1
Peptic ulcer	5 (1)	16 (1.6)	0.4	14 (2.3)	7 (0.8)	0.02	7 (3.4)	5 (0.7)	0.009	6 (2.1)	7 (1)	0.3	6 (2.2)	15 (1.2)	0.3
Suspect neoplasia	1 (0.2)	12 (1.2)	0.08	8 (1.3)	5 (0.5)	0.2	3 (1.4)	1 (0.1)	0.059	4 (1.4)	6 (0.9)	0.7	7 (2.6)	6 (0.5)	0.003
Fundal cystic polyps	7 (1.4)	41 (4.3)	0.001	5 (0.8)	43 (5)	0.001	1 (0.4)	29 (42.3)	0.019	14 (5)	13 (1.9)	0.019	10 (3.7)	39 (3.3)	0.8
Adenoma	10 (2)	8 (0.8)	0.09	8 (1.3)	10 (1.1)	0.9	1 (0.4)	5 (0.7)	1	3 (0.4)	4 (0.6)	0.7	3 (1.1)	9 (0.7)	0.8
Submucosal mass	5 (1)	6 (0.6)	0.6	2 (0.3)	9 (1)	0.2	2 (0.9)	8 (11.6)	0.6	0	3 (0.4)	0.6	0 (0)	19 (1.6)	0.07
Total	89 (18)	250 (26)	0.001	141 (24.1)	198 (23.3)	0.7	55 (27)	168 (24)	0.4	68 (24)	148 (22)	0.5	68 (25)	274 (23)	0.7
Duodenum															
Erosions	11 (2.2)	39 (4.1)	0.09	29 (4.9)	21 (2.4)	0.01	14 (6.9)	22 (3.2)	0.03	8 (2.8)	28 (4.2)	0.4	10 (3.7)	40 (3.4)	0.9
Peptic ulcer	5 (1)	23 (2.4)	0.1	21 (3.5)	7 (0.8)	0.001	12 (5.9)	11 (1.6)	0.002	5 (1.8)	15 (2.3)	0.8	4 (1.5)	24 (2)	0.7
Suspect coeliac	12 (2.4)	14 (1.4)	0.2	9 (1.5)	17 (2)	0.1	–	–	–	–	–	–	6 (2.2)	20 (1.7)	0.7
Suspect neoplasia	1 (0.2)	0 (0)	0.7	0 (0)	1 (0.1)	1	0 (0)	0 (0)	–	1 (0.3)	0 (0)	0.6	0 (0)	1 (0.008)	1
Total	29 (6)	76 (8)	0.1	59 (10.1)	46 (5.4)	0.001	26 (13)	33 (5)	0.001	14 (5)	43 (6)	0.4	20 (7)	85 (7)	0.9

N (%). PPI, proton-pump inhibitor therapy.

Table 4. Distribution of atrophy and/or metaplasia on gastric mucosa in patients with standard (2 antral and 2 gastric body) biopsy sampling

Precancerous lesion	Finding (*N* = 812)
Atrophy only in the antrum	20 (2.5)
Intestinal metaplasia only in the antrum	67 (8.3)
Atrophy both in the antrum and gastric body	19 (2.3)
Intestinal metaplasia both in the antrum and gastric body	27 (3.3)
Atrophy only in the gastric body	4 (0.5)
Intestinal metaplasia only in body	3 (0.3)
None	672 (82.8)

N (%).

taken, and in 185 (22.7%, 95% CI: 19.9–25.6) out of 812 patients for which standard (2 antral and 2 gastric bodies) biopsy sampling of the stomach was available. Prevalence of infection did not differ between patients aged <50 and ≥50 years (71/306, 23.2% vs. 130/580, 22.4%; $p = 0.8$), nor between those taking PPI therapy or not (34/150, 22.6% vs. 99/388, 25.5%; $p = 0.5$). Taking into account data of only patients in whom a standard gastric biopsy sampling was available, the presence of extensive atrophy or metaplasia on gastric mucosa was overall detected in 46 (5.6%, 95% CI: 4–7.2) patients, including extensive atrophy in 19 (2.3%, 95% CI: 1.3–3.3) cases and extensive metaplasia in 27 (3.3%, 95% CI: 2–4.5) patients (Table 4). Prevalence of these extensive precancerous lesions was significantly higher (OR: 8.02; 95% CI: 2.46–26.11; $p < 0.001$) in patients aged ≥50 years (43/534, 8%) than in those <50 years (3/278, 1%), while it did not differ between patients with *H. pylori* infection and those without it (10/185, 5.4% vs. 35/616, 5.6%; $p = 0.9$). All the 3 (0.2%) suspected neoplastic lesions in the oesophagus were eventually diagnosed as adenocarcinoma, the 13 (0.9%) gastric masses were either carcinomas ($N = 12$) or MALT lymphoma ($N = 1$), and the single suspected duodenal lesion was an ampullary adenoma.

Discussion

This large, multicentre study updated data on prevalence of both endoscopic and main histological lesions detected at first upper endoscopy performed in routine practice. We observed that GORD symptoms were the most frequent indication for upper endoscopy, and that erosive oesophagitis was among the most frequent (13.5%) detected lesions. Likewise, this mirrors the relentless increasing of GORD prevalence in the general population, at least in part, linked to the escalation of obesity incidence [21]. However, the prevalence of Barrett's oesophagus (1.2%) we computed would appear not increased when compared to 2.2% and 1.6% reported on 2003 and 2012, respectively [14, 22]. We observed that prevalence of erosive oesophagitis was 3-fold lower in patients in ongoing PPI therapy and near halved in females, while it did not differ between young and older patients or those with or without *H. pylori* infection. Therefore, it may be speculated that an ongoing PPI therapy would reduce diagnosis of erosive oesophagitis leading undiagnosed several patients with a chronic or recurrent disease deserving an appropriate therapy and follow-up [10]. Indeed, current guidelines advise to interrupt PPI therapy at least 2 weeks before diagnostic upper endoscopy [19, 23], a procedure not followed in as many as 20% in our study, even if this value seems to be lower than 36.3–50.7% previously reported in other series [14, 24].

Regarding neoplastic lesions, our data found that the overall prevalence was distinctly higher in patients presenting with alarm symptoms than in those without, confirming that upper endoscopy should be promptly scheduled in patients presenting with these symptoms [19, 20]. In detail, we found that the frequency of oesophageal cancer remains 4-fold lower than that of neoplastic lesions in the stomach.

Another finding of our study was that the overall prevalence (3.4%) of peptic ulcer remained substantially stable when compared to 2.7–5.5% reported in other Italian series through 2010 and 2021 [14, 25]. This occurs even if the 22.6% prevalence of *H. pylori* observed in this study would appear distinctly lower than 34% previously reported in 2012 [14], suggesting a trend towards a relentless reduction of this infection in endoscopic series. Therefore, the expected decrease of peptic ulcer incidence due to the lower prevalence of *H. pylori* is probably offset by the more diffuse use of NSAIDs, even as out-the-counter use [4–7]. Indeed, *H. pylori* infection and NSAID use remain the main pathogenetic factors for peptic ulcer, idiopathic ulcer prevalence being negligible in Italy [13].

Standard sampling on gastric mucosa is advised during routine endoscopy to search for presence and extension of precancerous lesions in the stomach – namely, extensive atrophic or metaplastic gastritis [12, 26]. Our data found a 5.6% prevalence of these extensive precancerous lesions on gastric mucosa, a value consistent with data of previous Italian studies showing a prevalence ranging from 2.3% to 7.8% [27–30]. Therefore, by performing standard sampling of gastric mucosa during endoscopy, it is possible to identify the small subgroup of patients with

extensive precancerous lesions in the stomach at increased risk of developing gastric cancer deserving a scheduled follow-up [11]. Regrettably, our data showed that standard biopsy sampling is performed in only half patients, suggesting that an implementation in routine practice is still needed.

Conclusions

Data of present study found that the overall endoscopic lesions were more prevalent in patients aged ≥50 years, peptic ulcer and erosions were more frequent in *H. pylori*-infected patients, and extensive gastric precancerous lesions deserving follow-up were present in less than 6% of cases.

Statement of Ethics

Since no identification of patients was allowed, no experimental drugs were administered, no additional costs or procedures for the patients were required, and no funds were received, the Investigational Review Boards of Nuovo Regina Margherita Hospital waived formal approval for this retrospective, cross-sectional study performed in clinical practice. Patients signed informed consent for both procedure and anonymous use of their data for scientific purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Vincenzo De Francesco and Angelo Zullo conceived the study and were responsible for the study design, statistical analysis, and drafting the manuscript. Vincenzo De Francesco, Angelo Zullo, Arnaldo Amato, Irene Bergna, Emanuele Bendia, Giorgia Giorgini, Elisabetta Buscarini, Guido Manfredi, Sergio Cadoni, Renato Cannizzaro, Stefano Realdon, Mario Ciuffi, Orazio Ignomirelli, Paola Da Massa Carrara, Giovanni Finucci, Antonietta Di Somma, Chiara Frandina, Mariafrancesca Loria, Francesca Galeazzi, Francesco Ferrara, Carlo Gemme, Noemi Sara Bertetti, Federica Gentili, Antonio Lotito, Bastianello Germanà, Nunzia Russo, Giuseppe Grande, Rita Conigliaro, Federico Cravero, Giovanna Venezia, Riccardo Marmo, Piera Senneca, Angelo Milano, Konstantinos Efthymakis, Fabio Monica, Paolo Montalto, Mario Lombardi, Olivia Morelli, Danilo Castellani, Daniela Nigro, Roberto Festa, Sergio Peralta, Maria Grasso, Antonino Carlo Privitera, Maria Emanuela Di Stefano, Giuseppe Scaccianoce, Mariangela Loiacono, Sergio Segato, Marco Balzarini, Paolo Usai Satta, Mariantonia Lai, and Raffaele Manta were responsible for data and patient collection in each participant centre. Raffaele Manta provided to critical revision of the manuscript with important intellectual support. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data are available following reasonable enquiries directed to the corresponding author, Vincenzo De Francesco.

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GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2025;32:9–17
DOI: 10.1159/000539227

Received: January 19, 2024
Accepted: March 26, 2024
Published online: June 6, 2024

Food-Related Quality of Life in Inflammatory Bowel Disease: Translation and Validation of Food-Related Quality of Life to the Portuguese Language (FR-QoL-29-Portuguese)

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Keywords
Translation · Validation · Nutrition · Inflammatory bowel disease · Patient-reported outcomes

Abstract
Introduction: Food-related quality of life (FR-QoL) has been shown to be an important patient-reported outcome in inflammatory bowel disease (IBD). We aimed to translate and validate a Portuguese version of the FR-QoL-29. ***Methods:*** This was a case-control cross-sectional study undertaken at a tertiary hospital. After obtaining the original authors' authorization, both forward and backward translations of the original FR-QoL-29 were performed by bilingual researchers. After an IBD expert's revision and the input of a small group of patients, a final version was obtained. Portuguese IBD patients were prospectively recruited from the outpatient clinic of a tertiary hospital and completed the questionnaire at two timepoints (0 and 4 weeks). Reliability (internal consistency, test-retest, and intraclass correlation [ICC]), validity (content and convergent validity, and hypothesis testing using Spearman's correlations), and responsiveness (Student *t* tests) were analysed. ***Results:*** 239 patients (mean age 50.1 [SD = 15.3 years], 56.5% female) and 87 (36.4%) patients answered the questionnaire at the first and second timepoints, respectively; 126 controls answered the questionnaire. Overall, the FR-QoL-29-Portuguese showed excellent internal consistency (Cronbach's $\alpha = 0.97$) and good test-retest reliability (ICC = 0.78 [95% CI: 0.64–0.85]). FR-QoL moderately correlated with health-related quality of life, measured by the SIBDQ-PT ($R = 0.49$; $p < 0.05$). Lastly, the questionnaire revealed appropriate responsiveness when patients reported an overall improvement in general well-being (mean improvement 25.88 [SD = 32.50]; $p < 0.05$). ***Discussion/Conclusions:*** We present an adaptation and validation of the FR-QoL-29 tool for Portuguese IBD patients. The FR-QoL-29-Portuguese is a reliable and valid tool shown to be responsive to changes in general well-being.

Qualidade de Vida relacionada com a Dieta na Doença Inflamatória Intestinal: tradução e validação do FR-QoL-29 para Português (FR-QoL-29-Portuguese)

Palavras Chave
Tradução · Validação · Nutrição · Doença inflamatória intestinal · Resultados reportados pelo doente

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Resumo

Introdução: A Qualidade de Vida relacionada com a Dieta é uma medição de resultados reportados pelo doente importante na Doença Inflamatória Intestinal (DII). O nosso estudo teve como objetivo principal a tradução e validação da versão portuguesa do FR-QoL-29. ***Métodos:*** Tratou-se de um estudo caso-controlo transversal num hospital terciário. Após obtermos a autorização dos autores originais, foram realizadas traduções direta e inversa do FR-QoL-29 original por investigadores bilingues. Depois da revisão por uma especialista em DII e o parecer de um pequeno grupo de doentes, alcançou-se a versão traduzida final. Doentes portugueses com DII foram prospectivamente recrutados a partir da Consulta Externa e Hospital de Dia de um hospital terciário, e completaram o questionário em dois momentos (às 0 e 4 semanas). Foram analisadas a fiabilidade (consistência interna, teste-reteste, correlação intraclasse [ICC]), validade (de conteúdo e convergente, e testagem de hipóteses com correlações de Spearman) e a responsividade (testes *t* de Student). ***Resultados:*** ados: 239 doentes (idade média 50.1 [DP = 15,3 anos]; 56.5% mulheres) e 87 (36.4%) doentes, respetivamente, responderam ao questionário no primeiro e segundo momentos; 126 controlos responderam ao questionário. Globalmente, o FR-QoL-29-Portuguese mostrou excelente consistência interna (*α* de Cronbach = 0.97) e boa fiabilidade teste-reteste (ICC = 0.78 [IC 0.64–0.85]). A qualidade de vida relacionada com a dieta correlacionou-se moderadamente com a qualidade de vida relacionada com a saúde, avaliada pelo SIBDQ-PT ($R = 0.49$; $p < 0.05$). Por último, o questionário mostrou ser adequadamente responsivo quando os doentes reportavam uma melhoria global no seu estado geral (melhoria média 25.88 [DP 32.50]; $p < 0.05$). ***Discussão/Conclusões:*** Apresentamos uma adaptação e validação da ferramenta FR-QoL-29 para doentes portugueses com DII. O FR-QoL-29-Portuguese é uma ferramenta fiável e válida, que mostrou ser responsiva a alterações no estado geral dos doentes.

Introduction

Inflammatory bowel disease (IBD) includes both Crohn's disease (CD) and ulcerative colitis (UC). IBD is a worldwide burdensome chronic inflammatory disease of the gastrointestinal tract [1] with a significant impact on patient's quality of life [2]. Nowadays, patient-reported outcomes (PROs) are considered an important tool for personalized clinical management [3], and it is advised to assess PROs early and frequently during IBD course [4]. Patients with IBD often believe diet to have a symptom-triggering role [5–7], which can not only lead to maladaptive dietary modifications but may also affect patients' psychological and social well-being [7]. Recently, food-related quality of life (FR-QoL), which measures dietary restrictions and daily life limitations driven by eating and drinking [8, 9], has been acknowledged as an important PRO in IBD [4]. Indeed, FR-QoL has been shown to be significantly impaired in IBD [9]. However, this is still not routinely assessed by IBD clinicians, neither in clinical practice nor in research. Recently, a FR-QoL questionnaire was developed [5], following qualitative interviews with patients with IBD [8]. This instrument was designed to systematically measure the psychosocial factors surrounding eating and drinking in IBD. Afterward, the FR-QoL-29 questionnaire has been used in different English-speaking countries to show impaired FR-QoL in patients with IBD, both in adults [10–12] and in children [13]. Moreover, this instrument was shown to be valid and reliable for assessing FR-QoL in culturally diverse English-speaking populations (e.g., Hispanics and Caucasians) [14], and there is already a validated translation of the FR-QoL to the Turkish language [15]. To the authors' knowledge, no validated translation to the Portuguese language has been performed. To adequately use the FR-QoL questionnaire in a Portuguese-speaking population, adaptation and validation of a translated version were necessary. We aimed to translate and validate a Portuguese version of the FR-QoL-29 (FR-QoL-29-Portuguese) and to evaluate its reliability, validity, and responsiveness, to assess dietary restrictions and daily life limitations driven by eating and drinking in Portuguese patients with IBD.

Materials and Methods

The FR-QoL Questionnaire

As stressed, the FR-QoL questionnaire addresses the eating and drinking experience of IBD patients. The questions revolve around the feelings and thoughts patients with IBD have around buying and preparing food, and how it affects their lifestyle and social commitments. This includes enjoyment of food, dietary restrictions, social eating situations, and the psychological impact of managing a diet under the constraints of IBD. The questionnaire also addresses fear of food-triggered symptoms, aiming to provide comprehensive insights into the intersection of diet, social life, and

well-being in the context of IBD. This instrument has 29 questions measured on a five-point Likert scale. The sum score ranges from 29 to 145. A higher sum score indicates greater FR-QoL, and a lower sum score indicates a poorer FR-QoL. There are no validated cutoff values [8].

Translation and Adaptation of the FR-QoL to the Portuguese Language

After obtaining permission from the copyright holders (King's College London), the FR-QoL-29 was translated to Portuguese following a thorough methodological approach [16–18]. The original version was independently translated into Portuguese by two bilingual investigators (R.O. and J.R). The research team compared and assessed the two translations for ambiguities or discrepancies between the original version and the forward translations. A single blind back translation to English was then performed by another bilingual investigator (H.T.S.), and this back translation was compared by the research team with the original version to ensure conceptual, semantic, and content equivalence between the source and target language versions. Subsequently, a convenience sample of 3 Portuguese IBD patients evaluated the pre-final version and made suggestions for improving clarity and ease of comprehension. Before the final discussion took place, the teams' IBD expert (H.T.S.) evaluated each item of the questionnaire for content validity. Finally, a discussion between the research team took place to reformulate some items according to the cognitive debriefing of the patients and the expert's revision, and a final translated version (FR-QoL-29-Portuguese) was reached.

Study Design

To perform this validation study, the authors conducted a cross-sectional case-control study to assess differences regarding FR-QoL between a Portuguese IBD population and a control population (patients referred to a Gastroenterology appointment for in-hospital colorectal polypectomies and hospital volunteer blood donors) [19]. Briefly, this was a survey-based study using a multimodal questionnaire that assessed both demographic and clinical data, patients' disease-related QoL and FR-QoL. This study was conducted in a Portuguese tertiary hospital (Algarve University Hospital Centre) between May and July 2022. All outpatient adult IBD patients were invited to participate, as long as they were native Portuguese speakers willing to provide consent, were not receiving parenteral or enteral nutrition, and were not pregnant or breastfeeding.

Participation rate was defined by the ratio of patients who were invited to participate in the study and agreed to do so. Completeness rate was defined as the ratio of participants who completed all the questions of the survey. If more than 20% of answers were missing from a questionnaire, that questionnaire was excluded.

The necessary sample size for any study is dependent on the individual characteristics of the study, and there are no clear guidelines on the ideal sample size for validation studies [20]. Despite this, based on the available literature, we considered a minimum respondent-to-item ratio of 5:1 [18, 21]. Therefore, a minimum of 145 participants would be required to adequately assess the operational properties of the 29-item scale. Allowing for potential dropouts or missing data, and since a larger sample size allows for better quality of psychometric testing, we used a consecutive sample of IBD patients, granting a minimum of 145 patients would be reached.

Patients were asked to complete the FR-QoL at a first timepoint and at a second timepoint 4 weeks later. Additionally, at this first timepoint, demographic and clinical data were collected (sex, age, disease type, disease duration, current medication, history of IBD-related surgery, latest inflammatory biomarker [faecal calprotectin], Harvey-Bradshaw index [HBI] for CD and partial Mayo score [pMS] for UC, patients' body mass index, smoking status, history of nutritional counselling), and patients would also fulfil the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) to assess disease-related QoL [22]. At the second timepoint, the patients were also questioned about whether they felt their general well-being to be "similar, better, or worse" than at baseline. Controls were asked to complete the FR-QoL only once, during outpatient appointments, and simple demographic data were collected (sex, age).

Ethical Considerations

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Algarve University Hospital Centre Administration Board (April 21, 2022) and Research Ethics Committee (April 7, 2022). Written, informed consent was obtained from all patients by one of the investigators after explaining the aims of the present study.

Statistical Analysis

Reliability

Reliability measures the consistency of the survey results. This property was ensured by the questionnaire internal consistency and test-retest reliability. Internal consistency reflects the extent to which the different items of a questionnaire measure the same construct. It was assessed using Cronbach's α coefficient [16]. Test-retest reliability refers to the extent to which individuals' responses to questionnaire items remain relatively stable over time [18]. It was assessed using the intraclass correlation coefficient [23]. An interval of 4 weeks was considered long enough to prevent recall bias. Only patients who reported to maintain the same general well-being as at baseline were used in this analysis to guarantee similar disease status.

Validity

Validity determines whether the questionnaire measures what it was in fact designed to measure [18]. Content validity, which evaluates if the questionnaire items are representative of the theoretical construct that the questionnaire assesses [18], was ensured by an each-item throughout analysis by an IBD expert (H.T.S.) after the final translation, as previously described.

Construct validity was measured through convergent and discriminant validity [18] and hypothesis testing [16]. We hypothesised that the FR-QoL-29-Portuguese overall score would positively correlate with the SIBDQ-PT and negatively correlate with patients' disease activity, as measured by HBI or pMS (symptom-based scores), and faecal calprotectin (inflammatory biomarker). We also hypothesised that having IBD and current disease activity would be associated with lower FR-QoL-29-Portuguese scores, compared with controls and patients with inactive disease. For correlation analysis, Spearman's correlation coefficient was calculated.

Active disease was defined through a HBI ≥5 or a pMS ≥2 [24], and faecal calprotectin above 250 μg/g [4], when a recent (2-month timeframe) faecal calprotectin was available. Disease was considered to be in remission when patients had an HBI <5 or a pMS <2 [24], and faecal calprotectin below 250 μg/g. When faecal calprotectin was unavailable within the predefined timeframe, only symptom-based scores were considered to define disease activity.

Responsiveness

Responsiveness measures the extent to which a questionnaire can detect changes over time in the construct being measured [18]. A Wilcoxon test was used to compare the median overall scores of FR-QoL-29-Portuguese between the first and the second timepoints. According to patients' responses regarding general well-being modifications, three groups of patients were defined: those who referred "an overall worsening of general well-being," those who referred "an overall improvement of general well-being," and those who reported to have "similar general well-being," compared to baseline. A $p < 0.05$ was considered statistically significant.

Results

FR-QoL-29 Translation and Cultural Adaptation

The FR-QoL-29 was translated to Portuguese following a thorough and multiphase process, which included forward translation, reconciliation, blind back-translation, forward and back translation harmonization, comprehensibility assessment by a sample of Portuguese IBD patients, and item per item content validity judgement by a bilingual IBD expert. Finally, the research team discussed the results of the patients' cognitive debriefing and the expert's evaluation, and a final translated version of the questionnaire was reached and proofread.

During the forward and back translation process, minor discrepancies regarding sentence structure and use of synonyms were found and reconciled. Importantly, one major issue concerning the five Likert-scale response options was identified and clarified after a research team meeting. In detail, the first and last Likert-scale response options in the original version are "strongly agree" and "strongly disagree," which would be translated to Portuguese as "concordo fortemente" and "discordo fortemente," respectively. However, because the alternatives "concordo totalmente" and "discordo totalmente" ("totally agree" and "totally disagree," respectively) are more commonly used in Portuguese, those were chosen for the final version, ensuring semantic equivalence.

Both the patients' cognitive debriefing and the expert's evaluation raised concerns about the comprehensibility of the verb tenses used. In fact, the original version has many items written in the present perfect continuous, which is not typically used in spoken Portuguese. As such, to improve the ease of quaestionary comprehensibility, the simple past was chosen as the preferred verb tense.

Regarding content equivalence, the IBD expert considered all items to be either "relevant but needing minor alterations" (namely, the verb tense in use, as explained) or "very relevant and succinct." As so, the questionnaire was considered to have acceptable content-related validity by the expert involved. Lastly, the final version was approved by the original authors of the instrument. The licence to use the FR-QoL-29-Portuguese can be obtained from kevin.whelan@kcl.ac.uk.

Sociodemographic and Clinical Data and Score Results

Two-hundred thirty-nine patients with IBD and 126 controls were included in the study and fulfilled the FR-QoL Portuguese at the first timepoint. The participation rate for IBD patients was 99.6% and the questionnaire completion rate was 100%. Only 1 patient declined to participate in the study as he claimed not to consider it relevant to his situation. As so, all handed questionnaires were complete and included in the analysis. Overall, age and gender were similar between IBD patients and controls. Patients and controls' demographic data, and patients' clinical characteristics are described in Table 1. Faecal calprotectin values were available for 175 (73.2%) of the patients. FR-QoL-29-Portuguese scores were significantly lower for IBD patients than controls (median 99.0 [IQR 76.0–126.0] vs. 136.0 [IQR 102.8–143.0]; $p < 0.001$).

At the second timepoint, 87 (36.4%) patients answered the questionnaire. Sex and patients' clinical characteristics were comparable between timepoints, except for age, which was higher at baseline (Table 1). The median FR-QoL-29 Portuguese scores at the first and second timepoint were 99.0 and 115.0 (IQR 76.0–126.0 and 88.0–132.0; $p = 0.902$) (Table 1).

Reliability

The FR-QoL-29-Portuguese Cronbach's α coefficient was 0.966, indicating excellent internal consistency. Moreover, Cronbach's α coefficient did not significantly improve when items were eliminated one by one, and as such, there was no need to consider eliminating any item of the questionnaire (Table 2). Furthermore, the test-retest reliability revealed a good temporal stability of the FR-Qol-29-Portuguese between the baseline and the second timepoints, considering an intraclass correlation coefficient of 0.767 (95% CI: 0.644–0.848).

Table 1. Sample demographic and clinical characteristics

Characteristic	Baseline				At 4 weeks			*p* value[a]
	all IBD (*n* = 239)	all UC (*n* = 163)	all CD (*n* = 69)	controls (*n* = 126)	all IBD (*n* = 87)	all UC (*n* = 64)	all CD (*n* = 21)	
Female, *n* (%)	135 (56.5)	87 (52.4)	44 (63.8)	58 (46.0)	49 (56.3)	31 (48.4)	16 (76.2)	0.979
Age, years, mean (SD)	50.1 (15.3)	52.0 (15.0)	46.7 (15.5)	50.6 (15.1)	43.4 (29.7)	44.0 (10.9)	41.4 (12.5)	<0.01
Age at diagnosis, years, mean (SD)	37.9 (14.9)	39.0 (14.8)	35.3 (15.0)	NA	33.4 (12.0)	33.9 (11.9)	31.6 (12.4)	0.005
Time since diagnosis, years, median (IQR)	10.0 (4.0–17.0)	10.0 (4.0–17.0)	10.0 (3.5–17.0)	NA	9.0 (3.0–15.0)	8.5 (3.0–13.8)	10.0 (2.5–15.0)	0.179
Nutritional counselling, *n* (%)								
Never	169 (73.2)	122 (73.9)	47 (71.2)	NA	60 (75.0)	48 (77.4)	12 (66.7)	0.883
In the past	47 (20.3)	32 (19.4)	15 (22.7)	NA	16 (20.0)	12 (19.4)	4 (22.2)	
Currently	15 (6.3)	11 (6.7)	4 (6.1)	NA	4 (5.0)	2 (3.2)	2 (11.1)	
UC extent, *n* (%)								
E1, proctitis	NA	39 (23.9)	NA	NA	NA	14 (22.2)	NA	0.828
E2, left side	NA	46 (28.2)	NA	NA	NA	16 (25.4)	NA	
E3, extensive	NA	78 (47.9)	NA	NA	NA	33 (52.4)	NA	
Montreal location, *n* (%)								
L1, ileal	NA	NA	25 (36.2)	NA	NA	NA	9 (42.9)	0.836
L2, colonic	NA	NA	20 (29.0)	NA	NA	NA	7 (33.3)	
L3, ileocolonic	NA	NA	21 (30.4)	NA	NA	NA	5 (23.8)	
L4, isolated upper disease	NA	NA	0 (0.0)	NA	NA	NA	0 (0.0)	
L1 + L4	NA	NA	2 (2.9)	NA	NA	NA	0 (0.0)	
L2 + L4	NA	NA	1 (1.4)	NA	NA	NA	0 (0.0)	
Montreal behaviour, *n* (%)								
B1, non-stricturing non-penetrating	NA	NA	28 (40.6)	NA	NA	NA	9 (42.9)	0.839
B2, stricturing	NA	NA	15 (21.7)	NA	NA	NA	3 (14.3)	
B3, penetrating	NA	NA	23 (33.3)	NA	NA	NA	7 (33.3)	
B2 + B3	NA	NA	2 (2.9)	NA	NA	NA	1 (4.8)	
Faecal calprotectin, µg/g, median (IQR)	81.0 (32.0–256.0)	69.0 (28.0–244.0)	99.0 (36.0–296.0)	NA	NA	NA	NA	NA
FR-QoL-29-Portuguese sum score, median (IQR)	99.0 (76.0–126.0)	99.0 (80.0–127.0)	96.0 (69.0–124.5)	136.0 (120.3–143.0)	115.0 (88.0–132.0)	112.5 (88.3–132.0)	120.0 (83.5–131.5)	0.902
Partial Mayo score, median (IQR)	NA	0.0 (0.0–1.0)	NA	NA	NA	0.0 (0.0–1.0)	NA	0.994

Table 1 (continued)

Characteristic	Baseline				At 4 weeks			*p* value[a]
	all IBD (*n* = 239)	all UC (*n* = 163)	all CD (*n* = 69)	controls (*n* = 126)	all IBD (*n* = 87)	all UC (*n* = 64)	all CD (*n* = 21)	
Harvey-Bradshaw index, median (IQR)	NA	NA	1.0 (0.0–3.5)	NA	NA	NA	0.0 (0.0–2.0)	0.525
Active disease, *n* (%)	35 (14.9)	22 (13.3)	13 (18.8)	NA	12 (14.1)	9 (14.1)	3 (14.3)	0.862

CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile ratio; SD, standard deviation; UC, ulcerative colitis. [a]Comparison for "all IBD" characteristics between the first (baseline) and second (at 4 weeks) timepoints, except for Montreal classification, partial Mayo score, and Harvey-Bradshaw, which have been calculated for all UC or all CD, accordingly.

Validity

We had a priori hypothesised that FR-QoL-29-Portuguese would positively correlate with SIBDQ-PT and negatively correlate with disease activity. These hypotheses were confirmed, as a positive moderate correlation between FR-QoL-29-Portuguese and SIBDQ-PT scores ($R = 0.490$, $p < 0.001$), and a negative correlation between FR-QoL-29-Portuguese and disease activity symptom-based scores ($R = -0.277$ for UC, $R = -0.388$ for CD; $p < 0.001$) and faecal calprotectin were found ($R = -0.150$, $p = 0.041$).

As for questionnaire discriminant validity, patients with IBD scored lower than controls (all IBD: median 99.0 [IQR 76.0–126.0] vs. controls: 136.0 [IQR 102.8–143.0]; $p < 0.001$), and patients with active disease scored lower than patients with inactive disease (active: median 80.0 [IQR 56.0–99.0] vs. inactive: 103.5 [IQR 81.0–128.8]; $p < 0.001$).

Responsiveness

Out of the 87 patients who fulfilled the FR-QoL-29-Portuguese at the second timepoint, 17 (19.5%) reported an "overall improvement of well-being." For these patients, the median sum score on FR-QoL-29-Portuguese was significantly higher than at baseline (114.0 vs. 68.0; $p = 0.007$). A median improvement of 15.0 points (IQR 3–0.48.5) was detected. For the 10 (11.5%) patients who reported an "overall decline of well-being," the median sum score on FR-QoL-29-Portuguese was lower than at baseline, though this difference was not statistically significant (61.5 vs. 81.5; $p = 0.059$). Still, a mean decline of 12.0 points (IQR 23.5–3.5) was observed (Table 3).

Discussion

In this study, we present a translation to the Portuguese language of the FR-QoL-29, after independent forward and back translations, as well as assessment for content and semantic equivalence by both an IBD expert and an IBD patient group. The FR-QoL-29-Portuguese was applied to a Portuguese IBD sample at two timepoints to confirm the questionnaire reliability, validity, and responsiveness to change.

Two-hundred thirty-nine and 87 patients with IBD answered the questionnaire at the first and second timepoint, respectively. Despite the observed drop in response rate between the first and second timepoints, this panel size is in line with previous studies [8, 15] and was considered to be appropriate to evaluate all FR-QoL-29-Portuguese psychometric properties.

The FR-QoL-29-Portuguese showed excellent internal consistency (Cronbach's α value of 0.966). Likewise, the validation studies of the original English FR-QoL-29 tool and the FR-QoL-29-Turkish showed similar properties with a Cronbach's α of 0.959 [8] and 0.96 [15], respectively. Furthermore, the correlation coefficients between individual items and the total sum score of the FR-QoL-29-Portuguese ranged from 0.398 to 0.806, and Cronbach α coefficient did not significantly improve when items were eliminated one by one. As such, the Portuguese version of the FR-QoL-29 has the same items as the original version of the instrument. Lastly, test-retest reliability showed good temporal stability at a 4-week interval. Overall, these measures establish the FR-QoL-29-Portuguese to be a highly reliable tool to measure FR-QoL in the Portuguese population.

The FR-QoL-29-Portuguese construct validity was demonstrated through the confirmation of a priori formulated

Table 2. Results of the internal consistency analysis

FR-QoL-29-Portuguese item	Scale mean if item deleted	Scale variance if item deleted	Corrected item-total correlation	Cronbach's α if item deleted
1	103.96	840.534	0.634	0.965
2	103.72	837.082	0.700	0.965
3	103.09	863.898	0.462	0.966
4	103.38	847.526	0.677	0.965
5	104.17	837.420	0.684	0.965
6	103.38	839.065	0.705	0.965
7	104.70	837.606	0.631	0.965
8	103.37	851.921	0.621	0.965
9	103.34	865.471	0.456	0.966
10	103.50	848.652	0.594	0.966
11	103.39	841.041	0.746	0.965
12	103.88	829.674	0.770	0.964
13	103.67	827.793	0.806	0.964
14	103.49	835.168	0.779	0.964
15	103.36	842.786	0.731	0.965
16	103.90	828.743	0.770	0.964
17	104.08	825.049	0.805	0.964
18	103.36	842.126	0.729	0.965
19	103.94	827.439	0.763	0.964
20	104.16	830.407	0.711	0.965
21	104.27	825.238	0.758	0.964
22	103.77	828.090	0.789	0.964
23	103.91	826.758	0.764	0.964
24	103.18	870.412	0.398	0.967
25	103.37	852.355	0.588	0.966
26	103.65	834.052	0.768	0.964
27	103.75	840.881	0.693	0.965
28	103.51	844.300	0.707	0.965
29	103.64	833.735	0.761	0.964

Table 3. Responsiveness of the FR-QoL-29-Portuguese to changes in overall well-being

Overall well-being at 4 weeks	FR-QoL-29-Portuguese score at baseline, median (IQR)	FR-QoL-29-Portuguese score at 4 weeks, median (IQR)	*p* value*
Overall improvement (*n* = 17)	68.0 (61.5–99.5)	114.0 (83.5–122)	0.007
Overall decline (*n* = 10)	81.5 (54.3–100.8)	61.5 (52.5–94.5)	0.059

**p* values based in Wilcoxon tests.

hypothesis: the FR-QoL-29-Portuguese sum score correlated positively with SIBDQ-PT and negatively with disease activity surrogates (symptom-based scores and faecal calprotectin). In fact, FR-QoL has previously been shown to correlate with disease-specific QoL in IBD [8], and patients with higher symptom burden and clinical activity have been reported to have poorer FR-QoL [8, 10, 12, 15]. Additionally, patients with IBD had significantly lower scores than controls without IBD, demonstrating an excellent discriminant validity of the questionnaire, similar to the original version [8]. Interestingly, in our cohort, both IBD patients and controls reported higher FR-QoL-29 scores than those in other studies [8–10, 12]. Sixty percent of patients scored the maximum points ("totally agree") in question number 24, which concerns feeling comfortable about eating and drinking around people despite their IBD. In the Portuguese culture, it is very common for eating and drinking to occur in a social context, such as at parties, events, and even in the workplace. The tradition of sharing meals and drinks with family, friends, and colleagues is deeply rooted in Portuguese culture. As such, we may elaborate that the importance placed on these social moments around the table

may at least partially explain why Portuguese people scored higher in FR-QoL questionnaires.

The participation rate for IBD patients in this study on FR-QoL was 99.6%, and the questionnaire completion rate was 100%. These results suggest that our IBD population is highly interested in discussing these issues. This tool could be applied during initial evaluations and follow-ups, especially for patients concerned with diet management, those altering their lifestyle due to IBD, or those considering nutritional counselling. This approach would underscore the importance of addressing diet-related issues in clinical practice, despite time constraints during appointments.

This study has several strengths that ought to be highlighted. We recruited a large sample, representative of the outpatient population across all stages of disease, in terms of phenotype, disease activity, and duration. Besides, the case-control design allowed to evaluate the discriminant validity of the Portuguese questionnaire. To our knowledge, this is the first study showing that FR-QoL-29 is responsive to changes in overall well-being, further supporting its role as an important tool to measure FR-QoL in IBD. Nevertheless, the study may have been underpowered to detect responsiveness to an overall decline in well-being, and further validation of responsiveness should be carried out in a larger sample. Moreover, this was a unicentric study, although this sample size allowed complete psychometric assessment of the instrument's properties. Lastly, because we did not have the possibility of using an expert panel, content validity index could not be calculated, and as such, content validity was based on the evaluation of a single IBD expert.

In conclusion, the FR-QoL-29-Portuguese is a valid and reliable tool to evaluate FR-QoL in Portuguese patients with IBD. It is convergent with health-related QoL and disease activity surrogates and responsive to change, highlighting its value in both clinical practice and research.

Acknowledgments

The FR-QoL-29-Portuguese is available upon request from Professor Kevin Whelan (kevin.whelan@kcl.ac.uk).

Statement of Ethics

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and its protocol was reviewed and approved by the Algarve University Hospital Centre Administration Board and Research Ethics Committee (088/CFIC7UAIP/2022). Written, informed consent was obtained from all patients by one of the investigators after explaining the aims of the present study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Raquel Oliveira: study design, data collection, data analysis and interpretation, manuscript drafting, and revision. Viviana Martins: data collection, manuscript revision. Laetitia Teixeira: study design, data analysis and interpretation, manuscript revision. Helena Tavares de Sousa: data collection, manuscript revision. Joana Roseira: study design, data collection, data analysis and interpretation, and manuscript revision. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2025;32:18–24
DOI: 10.1159/000539690

Received: March 3, 2024
Accepted: May 25, 2024
Published online: June 27, 2024

Carbapenem-Resistant Enterobacteriaceae Colonization or Infection Was Not Associated with Post-Liver Transplant Graft Failure: An Observational Cohort Study

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Keywords
Carbapenem · Multidrug resistance · Colonization · Infection · Liver transplantation

Abstract

Introduction: Carbapenem-resistant Enterobacteriaceae (CRE) epidemiology among liver transplant (LT) recipients is variable. We studied the impact of CRE colonization and infection on LT recipients' outcomes. ***Methods:*** This observational cohort study included consecutive adult LT recipients between January 2019 and December 2020 at Curry Cabral Hospital, Lisbon, Portugal. Primary exposures were CRE colonization (rectal swabs under a screening program) and infection within 1 year of index LT. Primary endpoint was graft failure within 1 year of the index LT. ***Results:*** Among 209 patients, the median (interquartile range [IQR]) age was 57 (47–64) years and 155 (74.2%) were male. CRE colonization was identified in 28 (13.4%) patients during the first year posttransplant (median [IQR] number of rectal swabs per patient of 4 [2–7]). CRE resistance genes identified were OXA48 in 8 (3.6%) patients, KPC in 19 (67.9%) patients, and VIM in 1 (3.6%) patient. Any bacterial/fungal and CRE infections were diagnosed in 88 (42.1%) and 6 (2.9%) patients, respectively, during the first year posttransplant. After adjusting for confounders, neither CRE colonization (aOR [95% CI] = 1.83 [0.71–4.70]; $p = 0.21$) nor infection (aOR [95% CI] = 1.35 [0.17–11.06]; $p = 0.78$) was associated with graft failure within 1 year of index LT. ***Discussion/Conclusion:*** Under a screening program, CRE colonization and infection prevalence was low and neither was associated with graft failure.

Colonização ou infecção por Enterobacteriaceae resistentes a carbapenemos não se associaram a falência do enxerto pós-transplante de fígado: um coorte observacional

Palavras Chave
Carbapenem · Multirresistência · Colonização · Infecção · Transplante de fígado

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Resumo

Introdução: A epidemiologia de Enterobacteriaceae resistentes a carbapenemos (CRE) entre receptores de transplante hepático (TH) é variável. Estudámos o impacto da colonização e da infecção por CRE nos resultados dos receptores de TH. ***Métodos:*** Estudo coorte observacional incluindo adultos consecutivos receptores de TH entre Janeiro de 2019 e Dezembro de 2020 no Hospital Curry Cabral, Lisboa, Portugal. As exposições primárias foram colonização por CRE (esfregaços retais sob programa de rastreio) e infecção dentro de um ano após o TH índice. O resultado primário foi a falência do enxerto dentro de um ano após o TH índice. ***Resultados:*** Entre 209 doentes, a idade mediana (IQR) foi de 57 (47–64) anos e 155 (74.2%) eram do sexo masculino. A colonização por CRE foi identificada em 28 (13.4%) doentes durante o primeiro ano após o TH (número mediano (IQR) de esfregaços retais por paciente de 4 [2–7]). Os genes de resistência CRE identificados foram: OXA48 em 8 (3.6%), KPC em 19 (67.9%) e VIM em 1 (3.6%) doente. Infecções a qualquer microrganismo e CRE foram diagnosticadas em 88 (42.1%) e 6 (2.9%) doentes, respectivamente, durante o primeiro ano após o transplante. Após ajuste para fatores de confusão, nem colonização (aOR [95% CI] = 1.83 [0.71–4.70]; $p = 0.21$) nem infecção por CRE (aOR [95% CI] = 1.35 [0.17–11.06]; $p = 0.78$) se associaram com falência do enxerto dentro de um ano após TH índice. ***Discussão/Conclusões:*** No âmbito de um programa de rastreio, a prevalência de colonização e infecção por CRE foi baixa e nenhuma delas se associou com falência do enxerto após TH.

Introduction

Infection still represents the main cause of graft failure within 1 year of liver transplant (LT), despite improvements in the surgical technique, organ support, infection control, and immunosuppression regimens [1]. Nosocomial infection, occurring mainly in the first month after LT, may contribute further to morbidity and mortality [1]. The rising prevalence of multidrug-resistant microorganisms (MDRs) worldwide may make it more difficult to treat nosocomial infections, as effective antimicrobials remain limited [2]. Strategies to prevent infections from such difficult-to-treat microorganisms frequently include institutional protocols for colonization studies.

Factors such as cirrhosis-related gut dysbiosis, exposure to prolonged courses of antimicrobials, or post-LT complications may increase the risk of MDR colonization among LT recipients [3]. Colonization with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus faecium* has been associated with a higher risk of infections among LT recipients [4, 5]. The impact of carbapenem-resistant Enterobacteriaceae (CRE) colonization on the outcomes of LT recipients has been poorly studied [6, 7]. Accordingly, we hypothesized that CRE colonization may negatively impact these patients' outcomes. Therefore, this study's objectives were the following: (1) determine the prevalence of CRE colonization and infection among LT recipients; (2) study the association between CRE colonization and infection with clinical outcomes.

Materials and Methods

Ethics

The Central Lisbon University Hospital Center (CLUHC) Ethics Committee approved the study's protocol and waived the individual informed consent due to its observational character (INV_447). The study's conduct followed the principles of the Declaration of Helsinki [8]. The study's reporting followed the STROBE guideline [9].

Design, Setting, and Participants

This observational retrospective cohort study included all adult (age ≥18 years) patients who underwent LT between January 2019 and December 2020 at Curry Cabral Hospital (CCH), CLUHC.

Definitions, Exposures, and Endpoints

Since 2018, there has been a prospective CRE surveillance protocol in the Transplant Unit at CCH as a tool to prevent cross-contamination among patients in the ward. All patients admitted for LT, whether elective (in the ward) or urgent (in the ICU), performed the first CRE rectal swab <24 h before transplantation. All patients who underwent LT were admitted to the ICU after the surgery. Following that index swab, patients were due to repeat the CRE rectal swab before ICU discharge to the ward or weekly until hospital discharge.

The CRE rectal swab was performed by the nursing staff using a specified kit (COPAN®): the humid swab was rubbed (360° movement) in the patients' anal canal, stored in a predefined involucrum, and sent within 2 h to the CCH laboratory. Afterward, a real-time polymerase chain reaction test was performed to search for 4 genes associated with carbapenemases' production by Gram-negative bacteria in the gut (GeneXpert®, Cepheid®): OXA48, KPC, NDM, or VIM (the IMP1 gene was only added after the study's inclusion period, so it was not considered) [10, 11].

Patients with a CRE-positive rectal swab were placed under contact precautions in a single room or were positioned within a CRE-positive ward cohort, including patients with the same colonizing gene. Contact precautions ceased only once there were

2 consecutive (1 week apart at least) negative rectal swabs. Overall, the following patients' data were collected from their electronic records: age, sex, LT indication, site before LT, urgent LT, comorbidities pre-LT, disease severity scores (model for end-stage liver disease with sodium correction [MELDNa] and Sequential Organ Failure Assessment [SOFA]), immunosuppression post-LT (the local protocol is detailed in online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000539690), body fluids' cultures (blood, urine, ascites, or bile as in online suppl. Table S2), and cytomegalovirus (CMV) serum viral loads (quantification limit of 34.5×10^7UI/mL) requested at clinicians' discretion, known standard risk factors for MDR colonization or infection (hospital stay, MDR colonization or infection, and antibiotics) within 1 year prior to the index hospital admission, and CRE colonization and infection within 1 year following the index LT.

The standard LT antibiotic prophylaxis at CCH was cefotaxime (1 g every 8 h) and ampicillin (2 g every 6 h) for 24 h. There was no decontamination strategy in place for CRE-colonized patients. CRE infection empirical antimicrobial therapy was at clinicians' discretion based on local antibiograms. Antimicrobial therapy was then adjusted at the earliest possible time based on available sensitivity tests.

Primary exposures were CRE colonization and infection within 1 year of index LT. Primary endpoint was graft failure within 1 year of the index LT. This endpoint was selected to better characterize both organs' and patients' morbidity and mortality during the first year post-LT. Additional outcomes considered were all-cause mortality within 1 year of the index LT and index ICU and hospital length of stay. The follow-up time period ended in October 2022.

Statistical Analyses

Descriptive analysis used absolute frequency (%) and median (interquartile range [IQR]) for categorical or continuous variables, respectively. Missing data across all variables were 0.2%, and no multiple imputation was performed.

Univariable comparisons used the χ^2 or Mann-Whitney tests where appropriate. Adjusted associations between CRE colonization or infection and graft failure within 1 year of index LT were studied using logistic regression. Variables were initially included in the models if deemed clinically significant and with a $p < 0.10$ on univariable analysis. A stepwise backward selection process was applied to build the final models. To avoid overfitting, the number of covariables admitted was restricted to one covariable per 10 events. The models' fitness was assessed using the χ^2 test. Statistical significance was defined by $p < 0.05$ (2-tailed). IBM SPSS Statistics (version 28.0; IBM Corp, Armonk, NY, USA) was used for all statistical analyses.

Results

Baseline Characteristics

Between January 2019 and December 2020, there were 239 LT procedures performed in 209 patients at CCH. Thus, there were 30 retransplants during this time period (25 within 1 year of index LT).

Median (IQR) age was 57 (47–64) years, and 155 (74.2%) patients were males. Cirrhosis and hepatocellular carcinoma were the leading causes of LT in 106 (50.7%) and 61 (29.2%) patients, respectively (Table 1). Etiologies of cirrhosis in the absence of hepatocellular carcinoma are presented in online supplementary Figure S1. Elective LT was performed in 175 (83.7%) patients.

Median (IQR) MELDNa pre-LT and SOFA scores upon the end of LT surgery were 15 (12–21) and 6 (4–8), respectively. Immunosuppression induction with basiliximab (antagonist of IL2 receptor) was used in 127 (60.8%) patients. All baseline characteristics are depicted in Table 1.

Exposures and Endpoints

Overall, risk factors for MDR colonization or infection identified within 1 year prior to LT were the following: previous hospital stay in 114 (54.5%), MDR colonization in 6 (2.9%), MDR infection in 13 (6.2%), and antibiotics use in 54 (26.0%) patients (Table 1). With the CRE surveillance program at CCH, 28 (13.4%) patients who underwent LT were diagnosed with CRE colonization during the first year posttransplant. During that time period, the median (IQR) number of CRE rectal swabs performed per patient was 4 (2–7). Moreover, the median (IQR) time to CRE positive rectal swab was 17 (5–39) days post-LT; in fact, 6 (21.4%) patients had a positive test since the day of index LT.

The following CRE resistance genes were identified: OXA48 in 8 (3.6%) patients, KPC in 19 patients (67.9%), and VIM in 1 (3.6%) patient. The NDM gene was not identified in this cohort. Only 1 patient showed colonization with 2 different CRE genes (OXA48 and KPC, with 98 days of interval). Among the 28 patients with CRE colonization, 6 (21.4%) eventually had at least 2 consecutive negative rectal swabs during the follow-up time period. The median (IQR) time between the first positive and negative CRE rectal swabs was 213 (82–530) days.

During the first year post-LT, any bacterial/fungal and CRE infections were diagnosed in 88 (42.1%) and 6 (2.9%) patients, respectively. Abdominal and bloodstream infections accounted for 33.9% (38/112) and 27.7% (31/112) of all diagnosed infections, respectively. The foci of these infections are detailed in online supplementary Table S3. The most prevalent bacteria causing these infections were *Klebsiella pneumoniae* (17.4%), *Enterococcus faecium* (12.8%), and *Escherichia coli* (10.5%). Among CRE infections, 4 were bloodstream infections, one was pneumonia, and another one was a urinary tract infection. Among fungal infections, 5

Table 1. Baseline characteristics of patients who underwent liver transplantation from January 2019 to December 2020 stratified by 1-year post-liver transplantation graft failure

Characteristic (*n* [%] or median [IQR])	*N* total = 209 (100%)	*N* graft failure at 1-year post-LT = 45 (21.5%)	*N* graft viable at 1-year post-LT = 164 (78.5%)	*p* value
Age, years	57 (47–64)	52 (46–62)	58 (46–64)	0.20
Sex, male	155 (74.2%)	32 (71.1%)	123 (75.0%)	0.60
LT indication, *n* (%)	–	–	–	0.86
ALF	10 (4.8)	2 (4.4)	8 (4.9)	–
Cirrhosis*	106 (50.7)	25 (55.6)	81 (49.4)	–
HCC	61 (29.2)	10 (22.2)	51 (31.1)	–
ColangioCa	3 (1.4)	1 (2.2)	2 (1.2)	–
Retransplant	19 (9.1)	4 (8.9)	15 (9.1)	–
FAP	10 (4.8)	3 (6.7)	7 (4.3)	–
Site before LT, *n* (%)	–	–	–	0.032
Home	164 (78.5)	34 (75.6)	130 (79.3)	
Ward	30 (14.4)	4 (8.9)	26 (15.9)	
ICU	15 (7.2)	7 (15.6)	8 (4.9)	
Urgent LT	34 (16.3)	9 (20.0)	25 (15.2)	0.44
Comorbidities pre-LT, *n* (%)				
CKD	17 (8.1)	8 (17.8)	9 (5.5)	0.008
Diabetes	60 (28.7)	13 (28.9)	47 (28.7)	0.98
HIV infection	2 (1.0)	0 (0)	2 (1.2)	0.99
Malignancy	87 (41.6)	18 (40.0)	69 (42.0)	0.80
MELDNa pre-LT (*n* = 208)	15 (12–21)	15 (11–26)	16 (12–20)	0.94
SOFA post-LT	6 (4–8)	8 (3–14)	5 (4–7)	0.005
Basiliximab induction, *n* (%)	127 (60.8)	30 (66.7)	97 (59.1)	0.36
CMV reactivation post-LT, *n* (%)	6 (2.9)	4 (8.9)	2 (1.2)	0.020
Standard risk factors for MDR colonization/infection (1-year pre-LT), *n* (%)				
Hospital stay	114 (54.5)	28 (62.2)	86 (52.4)	0.24
MDR colonization	6 (2.9)	2 (4.4)	4 (2.4)	0.61
MDR infection	13 (6.2)	3 (6.7)	10 (6.1)	0.99
Antibiotics	54 (26.0)	14 (31.1)	40 (24.5)	0.37
CRE colonization/infection (1-year post-LT)				
N swabs during follow-up	4 (2–7)	4 (1–9)	3 (2–6)	0.61
Time to positive swab since LT, days	17 (5–39)	28 (0–65)	14 (6–35)	0.75
CRE colonization, *n* (%)	28 (13.4)	9 (20.0)	19 (11.6)	0.14
Any bacterial/fungal infection (*n* = 206), *n* (%)	88 (42.1)	21 (48.8)	67 (40.9)	0.32
CRE infection (*n* = 207), *n* (%)	6 (2.9)	2 (4.7)	4 (2.4)	0.44
Index LT hospital stay duration				
ICU LOS	4 (3–8)	7 (2–13)	4 (3–6)	0.12
Hospital LOS	20 (14–34)	24 (12–37)	20 (14–33)	0.83

LT, liver transplantation; ALF, acute liver failure; HCC, hepatocellular carcinoma; ACLF, acute-on-chronic liver failure; ColangioCa, cholangiocarcinoma; FAP, familial amyloid polyneuropathy; ICU, intensive care unit; CKD, chronic kidney disease; HIV, human immunodeficiency virus; MELDNa, model for end-stage liver disease with sodium correction score; SOFA, Sequential Organ Failure Assessment score; OR, operating room; CMV, cytomegalovirus; MDR, multidrug-resistant microorganism; CRE, carbapenemases producing Gram-negative bacteria; LOS, length of stay. *Among 106 cirrhosis patients, 6 had ACLF (2.9%) and 5 had graft failure at 1-year post-index LT.

Candida spp. isolates (5.9%) were identified – 3 causing cholangitis, one peritonitis, and another one a bloodstream infection. A complete list of microorganisms isolated is depicted in online supplementary Table S4. Finally, CMV reactivation was detected in 6 (2.9%) patients during the first year post-index LT.

Table 2. Logistic regression multivariable associations between carbapenemase-producing bacteria colonization and 1-year post-liver transplantation graft failure

Covariable	OR (95% CI)	*p* value
Model 1		
ICU at LT	2.11 (0.61–7.33)	0.24
CKD pre-LT	2.50 (0.81–7.73)	0.11
SOFA post-LT	1.13 (1.05–1.23)	0.002
CRE colonization	1.83 (0.71–4.70)	0.21
Model 2		
ICU at LT	2.36 (0.70–7.96)	0.17
CKD pre-LT	2.48 (0.79–7.84)	0.12
SOFA post-LT	1.12 (1.03–1.21)	0.011
CRE infection	1.35 (0.17–11.06)	0.78

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; LT, liver transplantation; CKD, chronic kidney disease; SOFA, Sequential Organ Failure Assessment score; CRE, carbapenemases producing Gram-negative bacteria. Model 1: *n* total = 209, *n* events = 45, $p < 0.001$. Model 2: *n* total = 207, *n* events = 43, $p = 0.002$.

MDR colonization (14.3 vs. 1.1%; $p = 0.003$) or infection (17.9 vs. 4.4%; $p = 0.006$) within 1 year prior to LT was associated with a higher frequency of CRE colonization 1-year post-LT. Also, MDR colonization (33.3 vs. 2.0%; $p = 0.010$) within 1 year prior to LT was associated with a higher frequency of CRE infection 1-year post-LT, but MDR infection prior to LT was not (16.7 vs. 6.0%; $p = 0.33$).

Among all patients included, 26 (12.4%) died within 1 year of LT. Furthermore, 19 (9.1%) required a retransplant but survived that same time period. Therefore, graft failure within 1 year of index LT was 21.5% (45/209 patients). Median (IQR) index ICU and hospital length of stay were 4 (3–8) and 20 (14–34) days, respectively. Overall, the median (IQR) follow-up time period post-index LT was 1,079 (859–1,236) days. All exposures and endpoints are detailed in Table 1.

Association of CRE Colonization and Infection with Graft Failure

Based on univariable comparisons, patients with CRE colonization were more likely to develop any bacterial/fungal (20.5 vs. 8.3%; $p = 0.011$) or CRE (83.3 vs. 11.4%; $p < 0.001$) infections during the first year post-LT than non-colonized ones. Furthermore, patients with graft failure within 1 year of index LT were more likely on ICU before LT (15.6 vs. 4.9%; $p = 0.032$), had more often CKD pre-LT (17.8 vs. 5.5%; $p = 0.008$), had a higher median SOFA score posttransplant surgery (8 vs. 5; $p = 0.005$), had more often positive blood cultures in the OR (24.4 vs. 7.9%; $p = 0.002$), and had more often CMV reactivation during the first year post-LT (8.9 vs. 1.2%; $p = 0.020$) than those alive without retransplant (Table 1).

Based on multivariable logistic regression, after adjusting for significant confounders, namely, ICU at LT, CKD pre-LT, and SOFA score post-LT, CRE colonization was not associated with graft failure within 1 year of index LT (Table 2: model 1: adjusted odds ratio (aOR) [95% CI] = 1.83 [0.71–4.70]; $p = 0.21$). In a similar adjusted analysis, CRE infection was also not associated with graft failure within 1 year of index LT (aOR [95% CI] = 1.35 [0.17–11.06]; $p = 0.78$).

Discussion

Main Findings and Comparisons with Previous Literature

In a large Portuguese cohort of LT recipients subjected to a standardized protocol of CRE screening, CRE colonization and infection rates within 1 year of index transplant were 13.4% and 2.9%, respectively. In an Italian cohort of 553 LT recipients, CRE colonization and infection rates were 25.7% and 10.3%, respectively, figures higher than what has been observed in our cohort [7]. Both country-level and institutional-level features may help explain such differences. While overall CRE prevalence may vary widely with geography, Portugal has been experiencing outbreaks, but rates reported have been lower than in neighboring Southern European countries, such as Spain, Italy, or Greece [10, 11]. Additionally, at our center, strict contact precautions have been enforced in the ICU and ward to help mitigate the risk of cross-contamination among admitted patients. Thus, we speculate that CRE colonization rates may have also benefited from this strict institutional policy.

We also found that CRE-colonized patients were more likely to develop any bacterial/fungal or CRE infections than non-colonized ones during the follow-up period. Previous literature reported on the association between CRE colonization and infection [7, 12]. In fact, post-LT complications, such as biliary leaks or strictures, with often difficult source control and requiring prolonged courses of antimicrobials, as well as multiple-week hospital stays, may create the ideal environment for CRE infection, especially in previously colonized patients. Given the small number of patients with CRE colonization prior to LT, we could not address the association between colonization at such timing and post-LT outcomes. Interestingly, not all CRE-colonized patients ended up developing an infection; therefore the

colonization-infection relationship is far more complex than may be clinically perceived. Among other factors, post-LT evolving gut dysbiosis may play a role in this pathophysiological process [3, 12]. Namely, factors such as gut inflammation related to surgery or critical illness, antimicrobials' pressure, or immunosuppression effects may all contribute to altering the gut microbiome.

In our cohort, almost two-thirds of LT recipients got induction immunosuppression with an anti-IL2 drug (basiliximab) and steroids; following that, almost all patients required maintenance immunosuppression with a calcineurin inhibitor (mostly tacrolimus) and steroids (tapered gradually until eventual discontinuation). Each patient's immune status is very difficult to properly characterize at any sequential time point. Moreover, the association between immunosuppression and clinical outcomes following non-opportunistic infections remains doubtful [13]. Additionally, how clinicians adjust immunosuppressive regimens once there is an infection varies widely [14]. Therefore, it remains unclear how the immune status of these patients may have influenced CRE colonization and infection rates.

Finally, we found that neither CRE colonization nor infection was associated with graft failure within 1 year of index LT. While some studies have reported CRE infection to be associated with higher mortality, the impact of CRE colonization on mortality remains unclear [6, 15]. We speculate that lower rates of both CRE colonization and infection in our cohort may have contributed to the lack of an independent association between these factors and graft failure (an outcome more frequent than mortality). As our sample seemed somewhat comparable to other LT cohorts, in terms of demography, liver disease etiologies and severity, comorbidities, and risk factors for MDR colonization or infection, other factors may have influenced our CRE colonization and infection prevalence. For example, we speculate that our own locally implemented CRE surveillance program, in combination with enforced antibiotic stewardship and infection management protocols, may have helped reduce CRE colonization and infection prevalence and its impact on graft failure.

Limitations, Strengths, and Future Directions

Our results need to be interpreted in the context of the following limitations. First, this was a Southern European single-center observational cohort study, therefore prone to selection bias. However, our consecutive enrollment of patients, with specific inclusion and exclusion criteria, may have helped to minimize such bias and strengthen the study's internal validity. Second, we could not capture data on pre-LT immunosuppressive medication use or on the prescription of antimicrobials during the post-LT period, including transplant-related prophylaxis. Such data could have provided more insights regarding the risk factors for CRE colonization and infection in this context. Third, the study was designed to assess the impact of CRE colonization and infection on graft failure. Thus, while we can speculate about how our CRE surveillance program may have impacted CRE colonization and infection prevalence, this was not actually the purpose of our study [16].

Despite these limitations, our study adds to the literature by documenting the recent CRE colonization and infection prevalence and its impact on clinical outcomes among Portuguese LT recipients in the context of an operational CRE surveillance program. Further studies from other jurisdictions could improve knowledge on the evolving CRE epidemiology and how it affects LT recipients' outcomes [17, 18]. Moreover, further studies dedicated to how CRE colonization and infection affect clinical outcomes may help establish specific thresholds to locally adjust LT-related antimicrobial prophylaxis and CRE infection empirical therapy [19, 20]. Finally, further studies are needed to test how different digestive decontamination strategies could potentially modify gut dysbiosis, CRE colonization and infection prevalence, and clinical outcomes post-LT [21].

Acknowledgments

We thank the clinical staff caring for liver transplant recipients.

Statement of Ethics

Study approval statement: The Central Lisbon University Hospital Center (CLUHC) Ethics Committee approved the study's protocol (INV_447).

Consent to participate statement: The Central Lisbon University Hospital Center (CLUHC) Ethics Committee waived the individual informed consent due to its observational character (INV_447).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Filipe S. Cardoso conceived the idea and wrote the protocol. João Caria, Ana C. Gonçalves, Gonçalo Cristóvão, Maria Carlos, Sara Magalhães, Vasco Almeida, and Filipe S. Cardoso retrieved the data. João Caria and Filipe S. Cardoso performed the statistical analysis and wrote the manuscript. All authors provided content expertise and revised and approved the final manuscript.

Data Availability Statement

Data may be available upon reasonable request directed at the corresponding author.

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GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2025;32:25–36
DOI: 10.1159/000538939

Received: August 25, 2023
Accepted: April 13, 2024
Published online: June 18, 2024

Abdominal Hypoperfusion and Acute Kidney Injury in the Critically Ill Patient with Liver Cirrhosis: A Prospective Cohort Study

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Learning Points

- Acute kidney injury (AKI) has a high prevalence in critically ill patients, especially in patients with liver cirrhosis, ascites, and increased intra-abdominal pressure. Abdominal hypoperfusion is an often underdiagnosed pathophysiological mechanism.
- In critical patients with liver cirrhosis in intensive care, higher serum urea concentration and increased white blood cell count at baseline, and low persisting abdominal perfusion pressure (APP) were independent risk factors for developing AKI
- It is fundamental to maintain an adequate APP, and a target of ≥70 mm Hg may be useful as a therapeutic endpoint to optimize renal perfusion and prevent AKI

Keywords
Acute kidney injury · Liver cirrhosis · Acute-on-chronic liver failure · Abdominal compartment syndrome

Abstract

Background: Reduced abdominal perfusion pressure (APP) is an underdiagnosed potential pathophysiological mechanism for acute kidney injury (AKI) in the patient with liver cirrhosis and ascites. This study aimed to analyze the prevalence of abdominal hypoperfusion (AhP) (APP <60 mm Hg) and the impact of APP on AKI in critically ill patients with liver cirrhosis. ***Methods:*** This was a post hoc analysis from a prospective cohort study set in a general ICU at a tertiary university hospital. Patients were recruited between October 2016 and December 2021. Acute renal failure (ARF) was defined by stage 3 AKI according to the International Club of Ascites. ***Results:***

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Fifty-eight patients where included, with a mean age of 57 (±8.4) years, 79% were male, and 93% had acute-on-chronic liver failure at admission. The prevalence of AhP reached 75%, and 29% of cases had persisting AhP during the first week of ICU stay. Patients with baseline AhP had a higher 28-day mortality compared to those without AhP (respectively, 76% vs. 49%, $p = 0.03$). Acute renal failure developed in 48% of patients. Higher serum urea (aOR: 1.01, 95% CI: 1.00–1.02, $p = 0.04$) and white blood cell count (aOR: 1.1, 95% CI: 1.01–1.2, $p = 0.02$) at ICU admission, as well as low persisting APP (aOR: 0.9, 95% CI: 0.86–0.98, $p = 0.02$) were independent risk factors for ARF. ***Conclusion:*** Critically ill patients with liver cirrhosis presented a high prevalence of ARF, independently associated with higher baseline serum urea and WBC, and lower persisting APP. A structured clinical approach to optimize APP may reduce renal dysfunction in high-risk patients with cirrhosis.

Hipoperfusão abdominal e lesão renal aguda no doente crítico com cirrose hepática – estudo de coorte prospetivo

Palavras Chave
Lesão renal aguda · Cirrose hepática · Doença hepática crónica agudizada · Síndrome de compartimento abdominal

Resumo
Introdução: A pressão de perfusão abdominal (PPA) é um possível mecanismo fisiopatológico para a lesão renal aguda (LRA) frequentemente sub-diagnosticado no paciente cirrótico com ascite. Este estudo teve como objetivo analisar a prevalência de hipoperfusão abdominal (hPA) (PPA <60 mm Hg) e o impacto da PPA na lesão renal aguda em doentes com cirrose e doença crítica. ***Métodos:*** Esta foi uma análise pós-hoc de um estudo de coorte prospetivo de doentes críticos com cirrose hepática realizado numa unidade de cuidados intensivos (UCI) polivalente de um hospital universitário terciário. Os doentes foram recrutados entre outubro de 2016 e dezembro de 2021. A falência renal aguda (FRA) foi definida de acordo com o estadio 3 de LRA do International Club of Ascites. ***Resultados:*** Cinquenta e oito doentes foram incluídos, com uma média de idade de 57 (±8.4) anos, 79.3% eram do sexo masculino e 93.1% apresentavam a síndrome *acute-on-chronic liver failure*. A prevalência de hPA foi de 75.3%, e 29.3% dos casos apresentaram hPA persistente durante a primeira semana na UCI. Os doentes com hPA basal apresentaram um aumento de mortalidade aos 28 dias em comparação com aqueles sem hPA (76.0% vs. 48.5%, $p = 0.03$). Verificou-se FRA na admissão em 48.3% dos pacientes. O aumento da concentração da ureia sérica (aOR 1.01, IC95% 1.001–1.02, $p = 0.04$) e da contagem de leucócitos (CL) (aOR 1.1, 95% IC: 1.01–1.2, $p = 0.02$) na admissão à UCI, bem como a redução persistente da PPA (aOR 0.9, 95% IC: 0.86–0.98, $p = 0.02$) foram fatores de risco independentes para o desenvolvimento de FRA. ***Conclusão:*** Os doentes críticos com cirrose hepática apresentaram uma alta prevalência de FRA, cujos fatores de risco independentes incluíram o aumento da ureia sérica e da CL basais, e a redução persistente da PPA. Uma abordagem clínica estruturada para otimizar a PPA poderá reduzir a lesão renal aguda nos doentes cirróticos de alto risco.

Introduction

Acute kidney injury (AKI) in the patient with liver cirrhosis presents a wide spectrum of pathophysiological mechanisms. It can be divided into hepatorenal syndrome (HRS-AKI), a functional syndrome in advanced portal hypertension, and non-HRS-AKI due to other precipitant events [1]. Particularly, AKI is one of the main clinical features of the acute-on-chronic liver failure (ACLF) syndrome, as described by the CANONIC study, characterized by systemic inflammation, dysregulated immune response, and high short-term mortality [2, 3]. Current AKI therapies are based on treating the precipitant events, preventing hypovolemia, and treating hemodynamic disorders with albumin administration and vasoconstrictors [4, 5].

In the critically ill patient with cirrhosis, ascites and increased intra-abdominal pressure (IAP) are related to portal hypertension. Abdominal perfusion pressure (APP) is the difference between mean arterial pressure (MAP) and IAP. Abdominal hypoperfusion (AhP) (APP <60 mm Hg) is often overlooked as a potential concomitant mechanism for AKI in the critically ill patient with liver cirrhosis, especially if ascites is present [6]. Even more, paracentesis is a safe therapeutic option to treat intra-abdominal hypertension (IAH), thus

optimizing APP and improving organ perfusion [6–10]. This study aimed to analyze the impact of APP on AKI in critically ill patients with liver cirrhosis.

Methods

Design and Settings

This was a post hoc analysis from a prospective observational study of critically ill patients with liver cirrhosis set in a 22-bed general ICU specialized in liver disease in a tertiary university hospital with a regional liver transplant program [11]. Patients were recruited between October 2016 and December 2021 and followed up to hospital discharge.

Data were collected at admission and throughout the ICU stay and included demographic and clinical variables for the calculation of general and liver specific severity scores, as well as liver cirrhosis etiology, acute illness precipitating event, arterial blood lactate concentration and vital organ support with vasopressors, invasive mechanical ventilation (IMV), and renal replacement therapy (RRT). Patient data were retrieved on site or from medical records and collected in an anonymous and protected database. IAP was a routine measurement in our clinical practice.

The study protocol was approved by the Ethics Committee at Centro Hospitalar Universitário Lisboa Central (CES No. 397/2017), and the need for individual informed consent for this observational study was waived. All study procedures followed the principles of the Declaration of Helsinki [12].

Patient Selection

All patients with liver cirrhosis admitted to the ICU were consecutively screened for eligibility for this study. Cirrhosis was defined as bridging fibrosis on previous liver biopsy or a composite of clinical signs and findings provided by laboratory tests, endoscopy, and radiologic imaging [13].

Patient selection used the following inclusion criteria: (1) age ≥18 years, (2) first ICU admission during the index hospital stay, and (3) presence of a bladder catheter. The exclusion criteria were (1) surgical patient or any type of surgery in the 4 weeks preceding the index ICU admission, (2) contraindication for intravesical IAP measurements, (3) patients with ICU stay duration inferior to 24 h, (4) patients with previous liver transplant (LT), and (5) absence of IAP and APP measurements at ICU admission.

Definitions

IAH and abdominal compartment syndrome (ACS) definitions, IAP measurement methodology, and clinical management of these patients followed the updated guidelines by the World Society of Abdominal Compartment Syndrome (WSACS) [7, 14, 15]. Accordingly, IAH was classified into grade I–IV (respectively, 12–15, 16–20, 21–25, and >25 mm Hg), and ACS was defined as IAP >20 mm Hg with an acute organ dysfunction. The definition of hypotension corresponded to a MAP <65 mm Hg, regardless of vasopressor support, and AhP was defined by mean APP lower than 60 mm Hg. Reported pressure values correspond to daily means, unless otherwise stated.

IAP monitoring was prescribed every 6–8 h from the moment of ICU admission and was performed via trans-bladder measurement technique with a maximum of 25 mL of saline solution and zero-pressure reference point set at the phlebostatic axis in the midaxillary line [7]. APP was, thereafter, calculated using the difference between the corresponding MAP and IAP (APP = MAP−IAP).

ACLF and organ failure were defined as described in the CANONIC study [3]. Clinical management of patients with cirrhosis during the study period adhered to updated guidelines [5, 16]. This included withdrawal of all diuretic therapy, nephrotoxic drugs, vasodilators, and nonsteroidal anti-inflammatory drugs in patients with a diagnosis of AKI at admission and/or during the ICU stay.

For this study, acute renal failure (ARF) was defined by stage 3 International Club of Ascites (ICA) AKI criteria in patients with liver cirrhosis, determined by (1) an increase of serum creatinine >3-fold from baseline, (2) serum creatinine ≥4.0 mg/dL (353.6 μmol/L) with an acute increase ≥0.3 mg/dL (26.5 μmol/L), or (3) initiation of RRT [5]. The lowest value of creatinine measured at ICU admission was considered as the reference for the "3-fold increase of serum creatinine," as well as the presence of any day of RRT, for ARF assessment during the study period.

The temporal definition of the term "baseline" corresponds to ICU admission calendar day (D0) plus the following calendar day of ICU stay (D1). Additionally, the term "persisting" refers to the time period from D1 up to D7, specifically, with regard to mean pressure values (i.e., "persisting APP" refers to the 7-day mean APP pressure value). Outcome assessment was performed at D7, unless otherwise stated. The rationale for choosing a study period of 7 days relied upon the observation that the cumulative prevalence of IAH and AhP become relatively stable between days 5–7, and that there is a mean lag of up to 3 days for an increase in creatinine to become apparent after the onset of IAH [11, 17]. Therefore, less than 7 days could exclude patients that developed AhP and subsequent ARF, and more than 7 days could include more cases of ARF or death, potentially unrelated to APP.

Outcomes

The primary outcomes were the prevalence of AhP and ARF. The secondary outcomes included daily urine output, number of renal replacement free days, and survival rate at 28 days, and ICU length-of-stay (LOS). Whenever ICU discharge or LT occurred before D7, the available data prior to these events was used.

To calculate RRT-free days within a 28-day period from ICU admission, we considered, inclusively, the days between the start and the end of RRT (censoring the end date at D28 if it was surpassed) and subtracted this number of days from 28. If death occurred before D28 in patients receiving RRT, the number of RRT-free days considered was zero to penalize the event of death [18].

Statistical Analysis

Outcome variables were compared between groups of patients with and without baseline AhP and persisting AhP during the study period. Continuous variables were reported as mean and standard deviation or as median and interquartile range as appropriate, and categorical variables reported as frequencies and proportions. Mann-Whitney U test was used to compare non-normal distribution continuous variables or, otherwise, *T* test for normal distribution variables, between two independent groups. χ^2 and Fisher's exact tests were used to compare the frequencies of categorical variables between independent groups. Significant

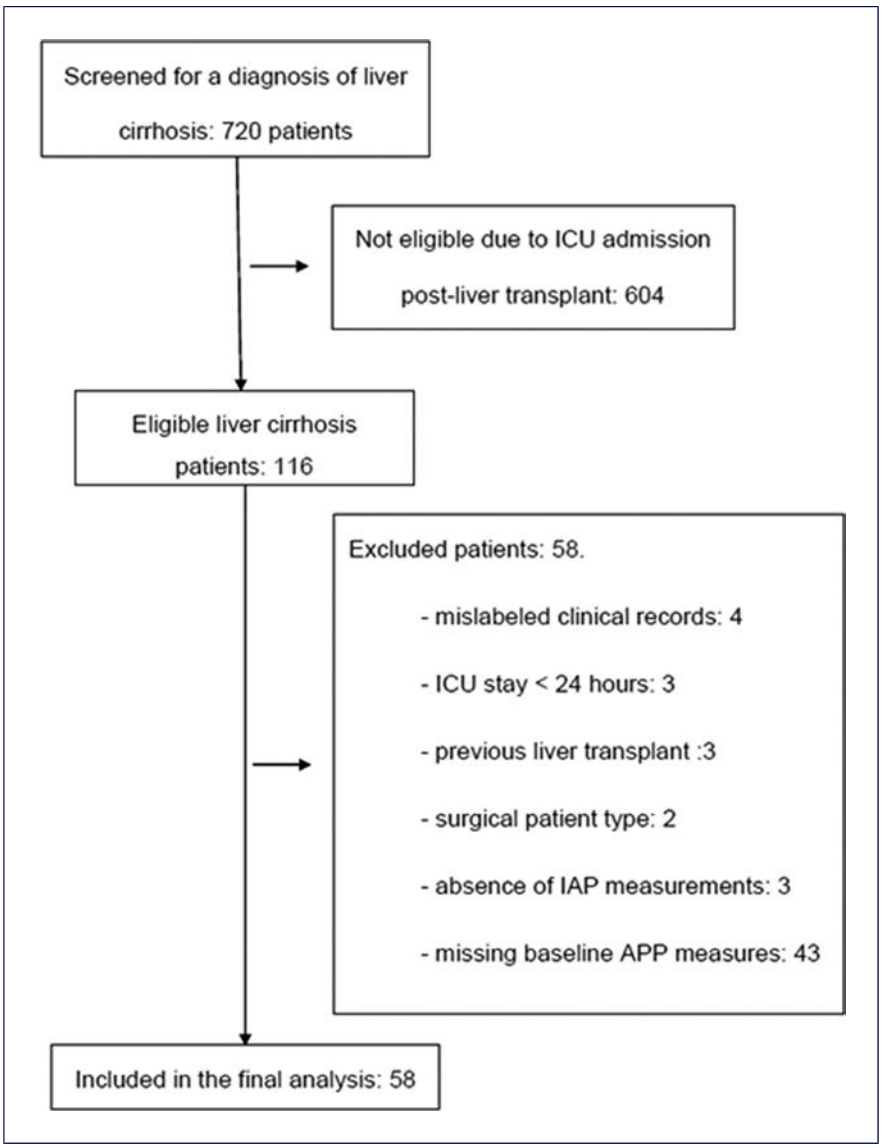

Fig. 1. Study patient flowchart. ICU, intensive care unit; IAP, intra-abdominal pressure; APP, abdominal perfusion pressure.

statistical difference was defined as a two-sided p value ≤0.05. Multivariate analysis was performed, after assessing for statistical assumptions, using backward stepwise logistic regression, and included variables based on clinical importance and statistical significance with p value ≤0.10 in univariate analysis. Statistical software IBM SPSS Statistics for Windows, version 27.0, Armonk, NY, USA, was used for analysis.

Results

Patient Characteristics

For this study, 720 patients were screened, 116 were found eligible, and the final analysis included 58 patients, as detailed in the patient flowchart (Fig. 1). None of the patients had previous ICU admissions nor contraindication for intravesical IAP measures. The total number of measurements of APP was 527, corresponding to approximately 9 per patient during the study period.

Patients in this study had a mean age of 57 (8.4) years, and 79.3% were male. The most frequent liver disease etiologies were alcohol-related (50%), alcohol and hepatitis C virus (14%), nonalcoholic steato-hepatitis (7%), hepatitis C virus-related (5%), and hepatitis B virus-related (5%). Ascites was present at baseline in 93% of patients. Liver neoplasm was present in 22% of cases with 11 confirmed or suspected hepatocellular carcinoma (including 9 patients with three or less lesions and 2 multinodular), 1 lymphoma, and 1 unknown neoplastic

Table 1. Baseline characteristics of critically ill patients with liver cirrhosis at ICU admission

Baseline variables	Overall (n = 58)
Age, years	57 (8.4)
Male gender, %	46 (79)
Liver disease etiology, %	
Alcohol	29 (50.0)
Alcohol + HCV	8 (13.8)
Precipitant event, %	
Infection	22 (37.9)
Bleeding	10 (17.2)
Encephalopathy	5 (8.6)
AKI	6 (10.3)
West-Haven score	2 [0, 3]
Hematocrit, %	24 (6.4)
Leucocytes, cells/μL	13.5 (8.6)
Platelets, cells/μL	65 [42, 115]
INR	2.45 (1.01)
Creatinine, mg/dL[a]	1.8 [0.9, 2.9]
Urea, mg/dL	91 [56, 136]
Bilirubin, mg/dL	6.5 [2.8, 15]
Albumin, g/dL	27.0 (11.1)
Ammonia, μg/dL	240 [164, 306]
C-reactive protein, mg/L	46 [17, 79]
PaO_2/FiO_2	268 (129)
pH	7.34 (0.12)
Lactate, mmol/L	2.6 [1.5, 4.3]
Urine output, mL/24 h	1,230 [483, 2,006]
Fluid balance, mL/24 h	796 [−384, 2,340]
Ascites, %	54 (93)
Paracentesis, %[b]	22 (37.9)
Drained ascites, mL	1,700 [50, 4,375]
IMV, %	30 (52)
Vasopressors, %	42 (72)
RRT, %	13 (22)
SAPS II	49 (16)
MELD-Na	31 [23, 37]
ACLF grade	3 [2, 3]
CLIF-C	53 (11)
IAP	12 (4.9)
MAP	77 (13)
APP	63 [56, 71]

Values are presented in count (%), mean (SD) or median [P_{25}, P_{75}]. IAP, MAP, and APP values correspond to those calculated from ICU admission day (D0) plus the following day (D1). HCV, hepatitis C virus; AKI, acute kidney injury; INR, international normalization ratio; PaO_2, oxygen arterial partial pressure; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; SAPS, simplified acute physiology score, MELD-Na, model for end-stage liver disease sodium; ACLF, acute-on-chronic liver failure; CLIF-C, chronic liver failure consortium; IAP, intra-abdominal pressure; MAP, mean arterial pressure; APP, abdominal perfusion pressure; SD, standard deviation; P, percentile. [a]Highest creatinine value during the initial 24 h of ICU admission. [b]Paracentesis of any type, including diagnostic and large-volume paracentesis.

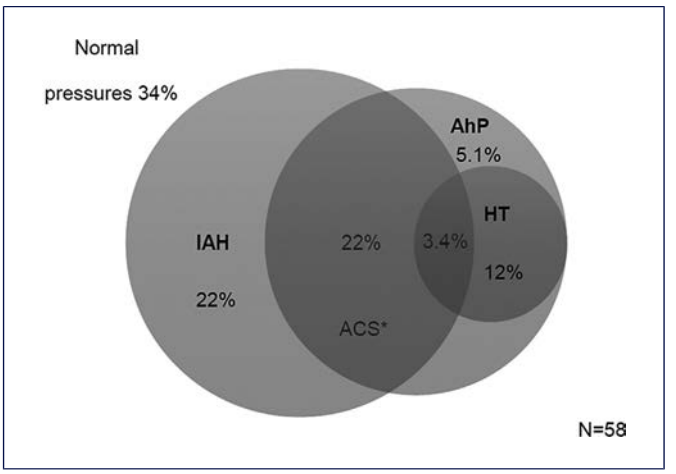

Fig. 2. Venn diagram illustrating baseline critical pressures' distribution in patients with cirrhosis. Illustration of the overlapping distribution (%) of baseline critical pressures in patients with cirrhosis (N = 58) admitted to intensive care. The overall frequency of AhP was 43.1%, IAH was 48.3%, HT was 15.5%, and (*) ACS accounted for 5.1% of patients in the corresponding area. IAH, intra-abdominal hypertension (>12 mm Hg); AhP, abdominal hypoperfusion (APP <60 mm Hg); HT, hypotension (mean arterial blood pressure <65 mm Hg); ACS, abdominal compartment syndrome.

infiltration. The prevalence of chronic kidney disease was 21% (including 12.1% mild, 5.2% moderate, and 3.4% severe), with no patients receiving chronic dialysis. No previous ACLF episodes were documented within the index hospital stay, and 19 patients (33%) had past hospitalization within the previous 12 months. The most frequent precipitant events leading to ICU admission were infection (38%), portal hypertension-related bleeding (17%), AKI (10%), and encephalopathy (8.6%).

At ICU admission, median MELD-Na score was 31 [19, 20], and mean SAPS II score was 49 (±16) and chronic liver failure consortium (CLIF-C) score was 53 (±11). In total, there were 54 (93%) patients with ACLF criteria at baseline, and the clinical severity distribution was grade 1 in 12%; grade 2 in 26%; and grade 3 (with three or more organ failures) in 55% of cases. During the first 24 h of admission, vital organ support was provided using RRT in 22%, IMV in 52%, and vasopressors in 72% of patients (Table 1).

Overall, 28-day mortality was 60%, hospital mortality was 69%, and ICU LOS (days) was 6.5 (2.3, 10.8) with a LT rate of 17.2%. No patients were submitted to transjugular intrahepatic portosystemic shunt. The highest classification of IAH during the first week of ICU was grade 1 in 41.1%, 2 in 24.1%, 3 in 10.3%, and 4 in 3.4%.

Abdominal Hypoperfusion

The prevalence of baseline AhP was 43.1%, with a cumulative prevalence of 75.3% in any given day during the first week of ICU stay. Patients with baseline AhP had higher clinical severity as assessed by SAPS II score, lower pH, and higher lactate concentration and needed IMV more frequently at admission. Comparison between groups of patients with and without baseline AhP is detailed in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000538939).

Critical pressures (hypotension, IAH, and AhP) at baseline overlapped as illustrated in Figure 2. The frequency of persisting hypotension, IAH, and AhP were, respectively, 8 (13.8%), 27 (46.6%), and 17 (29.3%).

Acute Kidney Injury

The prevalence of AKI was 65.5%, as assessed by the APACHE score at ICU admission and did not include 2 CKD patients. At baseline, serum creatinine was above the normal threshold of 1.2 mg/dL in 40 (69.0%) patients, including all CKD patients. Acute kidney failure was accounted in 25.0% of patients starting RRT at admission, in 27.8% (15/54) patients with urinary output of less than 0.3 mL/kg/h in 24 h during the first calendar day of ICU stay, and in 37.0% (20/54) of patients combining both criteria.

During the first week of ICU stay, 48.3% of patients presented ARF, including 5.2% of patients with a 3-fold increase from baseline serum creatinine, 19.0% an increase to over 4 mg/dL of serum creatinine with an acute increase of at least 0.3 mg/dL, and 43.1% initiating RRT. Additionally, 62.1% presented a urinary output less than 0.3 mg/kg/24 h.

Comparison of baseline characteristics of patient with and without ARF during the period is detailed in Table 2. In univariate analysis, baseline variables associated with ARF included lower pH and higher white blood cell (WBC) count, serum urea, arterial blood lactate, and SAPS II score, as well as a trend for higher fluid balance. There were no significant differences in daily APP between patients with and without ARF during the first 7 days in the ICU, as illustrated in Figure 3.

The rate of ARF was similar between patients with and without baseline AhP (respectively, 48.0% vs. 48.5%, p = 1.0) and was significantly higher among those with persisting AhP when compared to those without it (respectively, 70.6% vs. 39.0%, p = 0.04) (Table 3).

Multivariable analysis for the development of ARF, including persisting APP as a continuous variable, and excluding urinary output due to correlation with serum urea, revealed independent association with higher serum urea (aOR: 1.01, 95% CI: 1.001–1.02, p = 0.04), WBC (aOR: 1.10, 95% CI: 1.01–1.19, p = 0.03), and lower persisting APP (aOR: 0.93, 95% CI: 0.86–0.996, p = 0.04) (online suppl. Table 2).

Furthermore, persisting AhP had a good ability to discriminate ARF (ROC AUC: 0.69, SD: 0.07, 95% CI: 0.56–0.83, p = 0.01) (online suppl. Fig. 1), comparable to both persisting IAH and hypotension. Additionally, the optimal persisting APP cutoff value that predicted ARF was ≤69 mm Hg (sensitivity of 0.93, specificity of 0.40, and Youden index of 0.33) [21].

We performed further analysis to assess how the presence of persisting MAP would influence the results. When we included persisting MAP and persisting IAP in the multivariate analysis (n = 58), independent risk factors for ARF were unchanged with persisting APP as a continuous variable (aOR: 0.93, p = 0.04, 95% CI: 0.86–0.996) and baseline WBC (aOR: 1.10, p = 0.03, 95% CI: 1.01–1.19) and urea (aOR: 1.01, p = 0.04, 95% CI: 1.00–1.02). Similar results were observed when we used persisting AhP, persisting hypotension, and persisting IAH as categorical variables, instead of the corresponding continuous values. When we excluded patients with persisting hypotension (all with concomitant persisting AhP) from the multivariate analysis, in a smaller sample (n = 50), independent risk factors for ARF were baseline arterial blood lactate (aOR: 1.75, p = 0.04, 95% CI: 1.03–2.97) and urea (aOR: 1.02, p = 0.005, 95% CI: 1.01–1.03).

Other Results

The number of RRT-free days was comparable within groups of baseline APP and persisting APP. Mortality at 28 days was significantly higher in patients with baseline AhP (respectively, 76.0% vs. 48.5%, p = 0.03) and similar within groups of persisting APP. Finally, ICU LOS (days) was similar within group of baseline APP and was significantly lower among those with persisting AhP (Table 3). Furthermore, ICU LOS was significantly lower among 28-day non-survivors when compared to survivors (respectively, 5 [2, 9] vs. 9 [4, 7], p = 0.047).

Discussion

Main Findings

This is the first study to demonstrate a temporal relation between reduced APP and ARF in critical patients with liver cirrhosis. Our main findings revealed that higher serum urea and WBC at baseline, as well as lower persisting APP were independent risk factors for ARF in critical patients with liver cirrhosis.

Table 2. Comparison of baseline characteristics of patients with and without ARF during the first 7 days in the ICU

	Without ARF	With ARF	*p* value
N = 58	30	28	
Age, years	57 (7.1)	57 (9.7)	1.0
Male gender, %	26 (87)	20 (71)	0.3
Liver disease etiology, %			0.6
Alcohol	16 (53)	13 (46)	
Alcohol + HCV	4 (13)	4 (14)	
Precipitant, %			0.1
Infection	8 (27)	14 (54)	
Bleeding	6 (21)	4 (15)	
Encephalopathy	3 (10)	2 (7.7)	
AKI	3 (10)	3 (12)	
West-Haven score	1 [0, 3]	2 [0, 3]	0.8
Hematocrit, %	24 (7.5)	24 (5.1)	1.0
Leucocytes, cells/μL	11 (7.2)	16 (9.1)	0.01
Platelets, cells/μL	67 [38, 115]	63 [46, 106]	0.6
INR	2.3 (1.0)	2.7 (1.0)	0.1
Creatinine, mg/dL*	1.1 [0.8, 1.8]	2.9 [2.0, 4.6]	<0.001
Urea, mg/dL	76 [45, 96]	127 [72, 193]	0.01
Bilirubin, mg/dL	5.8 [2.9, 12]	9.6 [2.9, 20]	0.5
Albumin, g/dL	26 (13)	28 (8.8)	0.8
Ammonia, μg/dL	210 [156, 299]	253 [181, 306]	0.6
C-reactive protein, mg/L	35 [12, 65]	55 [18, 87]	0.3
PaO_2/FiO_2	279 (139)	257 (118)	0.5
pH	7.39 (0.10)	7.30 (0.12)	0.004
Lactate, mmol/L	2.2 [1.3, 3.6]	3.6 [1.6, 10]	0.04
Urine output, mL/24 h	1,495 [1,096, 2,240]	603 [344, 1,413]	0.004
Fluid balance, mL/24 h	326 [–493, 1,227]	1,367 [327, 2,797]	0.054
Ascites, %	26 (90)	27 (96)	0.4
Paracentesis, %	10 (33)	12 (43)	0.6
Drained ascites, mL	1,435 [238, 4,000]	1,900 [50, 5,538]	0.5
IMV, %	14 (47)	16 (57)	0.6
Vasopressors, %	19 (63)	23 (82)	0.2
RRT, %	0 (0)	13 (46)	<0.001
SAPS II	43 (14)	55 (17)	0.004
MELD-Na	26 [18, 31]	36 [31, 40]	<0.001
ACLF grade	2 [1, 3]	3 [2, 3]	0.01
CLIF-C	48 (10)	59 (9.3)	<0.001
IAP	11 (4.2)	12 (5.6)	0.32
MAP	79 (14)	75 (10)	0.3
APP	64 [57, 80]	62 [56, 69]	0.4

The term "acute renal failure" is defined as stage 3 International Club of Ascites Acute Kidney Injury. Values are presented in count (%), mean (SD) or median [P_{25}, P_{75}]. IAP, MAP, and APP values correspond to the mean calculated from ICU admission day (D0) plus the following day (D1). HCV, hepatitis C virus; AKI, acute kidney injury; INR, international normalization ratio; PaO_2, oxygen arterial partial pressure; FiO_2, fraction of inspired oxygen; IMV, invasive mechanical ventilation; RRT, renal replacement therapy; SAPS, simplified acute physiology score, MELD-Na, model for end-stage liver disease sodium; ACLF, acute-on-chronic liver failure; CLIF-C, chronic liver failure consortium; IAP, intra-abdominal pressure; MAP, mean arterial pressure; APP, abdominal perfusion pressure; SD, standard deviation; P, percentile. *Highest creatinine value during the initial 24 h of ICU admission.

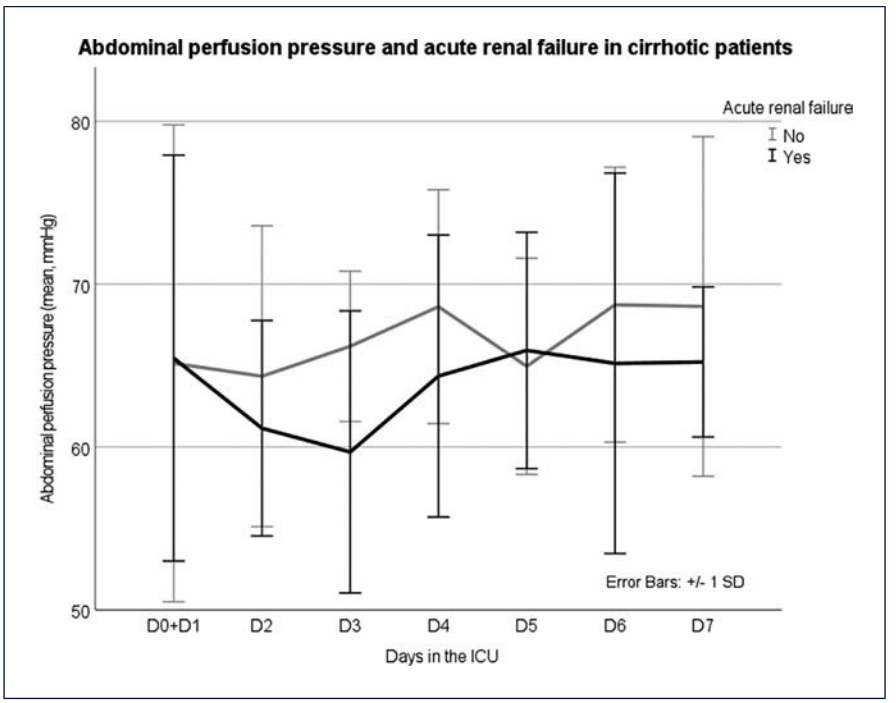

Fig. 3. APP and ARF in patients with cirrhosis. ARF is defined as stage 3 International Club of Ascites acute kidney injury (ICA-AKI).

Table 3. Renal function and outcomes in cirrhotic patients with baseline and persistent AhP in intensive care

	Baseline			Persisting[a]		
	APP <60 mm Hg	APP ≥60 mm Hg	*p* value	APP <60 mm Hg	APP ≥60 mm Hg	*p* value
n = 58	25	33		17	41	
Baseline creatinine, mg/dL[b]	1.4 [1.1, 2.1]	1.2 [0.8, 2.4]	0.4	1.6 [1.1, 2.4]	1.2 [0.8, 2.1]	0.2
Maximum creatinine, mg/dL[a]	2.3 [1.5, 3.6]	2.1 [1.1, 3.6]	0.7	2.3 [1.6, 3.8]	2.1 [1.0, 3.2]	0.2
Urine output, mL/day[a]	1,022 [130, 1,574]	1,056 [474, 1,656]	0.3	205 [87, 804]	1,095 [759, 1,701]	0.003
Anuria, %[a]	17 (68.0)	19 (57.6)	0.6	14 (82.4)	22 (53.7)	0.07
RRT, %[a]	10 (40.0)	15 (45.5)	0.8	10 (58.8)	15 (36.6)	0.2
RRT-free days at 28 days	28 [0, 28]	28 [0, 28]	0.8	0 [0, 28]	28 [0, 28]	0.07
ICA-AKI stages, %[a]			0.8			0.048
No AKI	6 (24.0)	10 (30.3)		1 (5.9)	15 (36.6)	
Stage 1	7 (28.0)	6 (18.2)		4 (23.5)	9 (22.0)	
Stage 2	0 (0)	1 (3.0)		0 (0.0)	1 (2.4)	
Stage 3	12 (48.0)	16 (48.5)	[c]	12 (70.6)	16 (39.0)	[d]
Mortality at 28 days, %	19 (76.0)	16 (48.5)	0.03	12 (70.6)	23 (56.1)	0.3
ICU LOS, days	6 [2, 12]	7 [4, 10]	0.2	2 [1, 4]	8 [5, 12]	<0.001

Abdominal hypoperfusion corresponds to an APP <60 mm Hg. Overall APP reflects the mean of the daily APP values. Variables are presented using median [interquartile range] and count (%). APP, abdominal perfusion pressure; AhP, abdominal hypoperfusion; mm Hg, millimeters of mercury; RRT, renal replacement therapy; ICA, International Club of Ascites; AKI, acute kidney injury; RIFLE, risk, injury, failure, loss of renal function and end-stage renal disease; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcome; ICU, intensive care unit; LOS, length-of-stay. [a]Considering the first 7 days (D1 to D7) in the intensive care. [b]Lowest creatinine value during the initial 24 h of ICU admission, used for acute kidney injury criteria. [c]*p* value of 1.0, when comparing stage 3 ICA-AKI versus non-stage 3 combined categories. [d]*p* value of 0.04, when comparing stage 3 versus non-stage 3 combined categories.

Abdominal Hypoperfusion

The prevalence of baseline AhP in our cohort was high and comparable with other studies (47–70%) [11, 22]. Nearly two-thirds of cases presented critical pressures with either hypotension, IAH, and/or AhP at baseline, and, on one hand, the majority of patients with AhP had concomitant IAH and, on the other hand, all patients with hypotension had AhP.

Acute Kidney Injury

The prevalence of AKI at baseline was higher than expected in our study, affecting approximately two-thirds of patients, and nearly half of the cohort developed ARF during the 7-day study period, with high RRT requirement. Comparatively, the overall incidence of AKI in mixed populations of intensive care patients has been reported between 20 and 50%, including 50% in patients with liver cirrhosis [19, 23, 24]. Our results may be due to the high severity of patients admitted at our ICU (i.e., septic shock (SS) and multiorgan failure) since our center serves as a reference for LT and emergent transplant is a therapeutic option in selected patients.

We demonstrated that reduced persisting APP was predictive of ARF. Few studies reported a temporal relation between the onset of IAH and the development of AKI [17, 25, 26]. More than 2 decades ago, Sugrue et al. [17] described, in surgical patients, the gradual effect of IAH on renal function, with a mean lag period of 2.7 (±6.5) days between the onset of IAH and renal impairment, assessed by the rise of serum creatinine concentration. Regueira et al. [27] found that serum creatinine levels were directly proportional to higher degrees of IAH and inversely related to APP in a surgical-medical mixed population of SS patients. Both these studies used a modified Kron technique for IAP measure [28]. More recently, Dalfino et al. [26], using current standard methodology for IAP measure [7], reported a mean lag period between IAH and ARF onset of 1 (±1.8) day in a medical-surgical mixed population of critically ill patients. Furthermore, Al-Dorzi et al. [22] in their study with 61 patients with liver cirrhosis and SS described IAH as a risk factor for increased RRT requirement [18]. In our study in patients with liver cirrhosis, low persisting APP was an independent risk factor for ARF, even though there were no significant differences in baseline APP (Table 2), nor in discrete daily APP values between groups of patients with and without ARF (Fig. 3). We considered that persisting APP mean value captured the deleterious 7-day cumulative effect of lower APP values on renal function, signaling the impact of the prolonged duration of low APP rather than short-term at baseline. This is in-line with the impact of the duration of IAH on mortality as described by Kyoung et al. [25] in surgical patients with severe sepsis. This is even more relevant since persisting APP remained an independent risk factor for ARF after adjusting for the corresponding persisting IAP and MAP both fundamental variables in the APP equation.

Additionally, we determined an optimal APP cutoff value (persisting APP <70 mm Hg) to predict ARF in our cohort of critically ill patients with liver cirrhosis, and this may be useful in clinical practice. Reports of similar APP cutoff values that predict clinical outcomes have been described, and these add to the generalizability of our results. In their study, Gül et al. [29] described a mean APP threshold of ≤72 mm Hg associated with an increase in Doppler-based renal resistive index, suggested to predict worsening renal perfusion in mechanically ventilated patients. In another study, Bieda et al. [30] reported, in patients with ruptured aortic aneurism, a mean APP cutoff value of 70 mm Hg to discriminate between survivors and non-survivors. Furthermore, Vidal et al. [31] observed, in a medical-surgical mixed population of critically ill patients, that APP was independently associated with hospital survival, with a best cutoff value ≥75 mm Hg, using the modified Kron technique. In two other studies, APP cutoff values of 52 and 50 mm Hg predicted ARF and survival, respectively, although they used the worst APP values (not mean daily values) or did not use current IAP measure methods [26, 32]. Our study in patients with liver cirrhosis suggests that maintaining an APP target of ≥70 mm Hg may be useful as a therapeutic endpoint to optimize renal perfusion and prevent organ failure during the ICU stay, although this requires confirmatory studies.

White blood cell count at baseline was an independent risk factor for the development of ARF in our cohort, but not infection as precipitant event, and this can be interpreted as a surrogate marker for systemic inflammation. The ACLF syndrome is an inflammatory paradigm with mainstay AKI, multiorgan failure, and increased mortality in patients with liver cirrhosis, and WBC count is well acknowledged in the CLIF-C prognostic score [3, 33].

Systemic inflammation is a common feature shared between the two subtypes of AKI, hepatorenal syndrome (HRS)-AKI and non-HRS-AKI, described in liver disease patients [1]. The pathophysiologic mechanism of HRS-AKI is traditionally ascribed to splanchnic vasodilation, cardiac dysfunction, adrenal insufficiency, and inflammation, while non-HRS-AKI is mainly characterized by the role of inflammation and bacterial translocation, bile

acid toxicity, worsening portal hypertension, cardiac dysfunction, and renal hypoperfusion [6].

In an animal model of cirrhosis and HRS, Chang et al. [6] were able to demonstrate causality between increases in IAP and de novo interstitial inflammatory infiltrates in renal histopathology, after merely 24 h of induced IAP of 5 mm Hg, as well as significant increases in serum urea and creatinine at 10 mm Hg of IAP. Most of our patients had IAH and, although there were no data regarding APP, a pathophysiologic mechanism for inflammation and AKI was established.

Urea is one of the oldest biomarkers in nephrology; however, blood urea nitrogen (BUN) is suboptimal for estimation of renal function [34]. Most BUN is generated in the liver as a product of protein metabolism, and an important proportion of urea filtered by the glomerular capillaries is reabsorbed from the tubules. Whereas, virtually all filtered creatinine is excreted in the urine making it a most practical marker. BUN's clearance falls markedly, even though glomerular filtration rate remains normal, at low urinary flow [35]. In our study, serum urea was inversely correlated with urinary output and behaved as early AKI markers at baseline. BUN concentration also depends on nonrenal factors independent of kidney function (i.e., protein intake, catabolic state, upper gastrointestinal bleeding, volume status, and therapy with high-dose steroids), and many of these factors are found in patients with liver cirrhosis [34]. Without surprise, urine output was reduced among those with persisting AhP and with ARF, acting as an early marker of impaired hemodynamics, renal hypoperfusion, and AKI. This is a relevant point that would lead to consider additional scores that include urine output (RIFLE [20], AKIN [36], and KDIGO [37]) and their ability to stratify the severity of AKI in the critically ill cirrhotic patient, although this is outside of the scope of this study. The pathophysiologic complexity of the typical ACLF patient in this cohort is clear, and multiple injury mechanisms coexist, thus justifying the evolving nature of definitions and classifications of AKI [5].

ACLF syndrome is characterized by increased short-term mortality, and our results are comparable with similar cohorts described in the literature [3, 11, 38]. Patients with baseline AhP had higher 28-day mortality, with higher clinical severity SAPS II score and lactate concentration, worst pH, and more IMV at admission. Furthermore, we consider clinically relevant the 28-day mortality rate in patients with persisting AhP when compared with normal persisting APP (respectively, 70.6% vs. 56.1%), although it did not reach statistical significance likely due to a small sample size. The ICU LOS was lower among those with persisting AhP and the deceased, highlighting the link between of APP and outcomes.

Finally, an important proportion of patients during the study period presented persisting critical pressures, particularly IAH, despite paracentesis and vasopressor use, indicating a potential for improved clinical management of AhP. Although our study did not focus on vasopressors, we did confirm that noradrenaline and/or terlipressine used at baseline did not significantly affect APP or ARF up to day 7.

Given the high prevalence of AhP in high-risk patients with liver cirrhosis, APP must not be overlooked. A structured clinical approach for a target APP >70 mm Hg, including the optimization of IAP and MAP (above 75 mm Hg if necessary) may reduce AKI and ARF in critical patients with liver cirrhosis.

Limitations

We acknowledge some limitations: (1) the use of D0 lowest creatinine value as reference for the calculation of AKI criteria may have excluded diagnosis of AKI and ARF already established at baseline; (2) the frequency of contrast-enhanced computed tomography, although uncommonly performed in these patients, was not asserted, nor the subsequent risk for contrast-induced AKI; (3) the relatively small sample size may have been underpowered to detect significant differences in outcomes such as RRT-free days, (4) possible selection bias at ICU admission, since some patients were excluded for not having baseline calculation of APP, and (5) serum creatinine may have underestimated AKI in these patients with liver cirrhosis, whereas cystatin-C may be a better marker; and finally (6) no specific urinary biomarkers were used to differentiate the etiologies of AKI, including acute tubular necrosis, HRS-AKI, and others since we did not use these in our clinical practice.

Conclusion

Critical patients with liver cirrhosis and ACLF presented a very high prevalence of AhP during the first week of ICU stay, and those with baseline AhP had a higher 28-day mortality. Nearly half of the cohort presented ARF, and independent risk factors were high serum urea and WBC at baseline, as well as low persisting APP.

A temporal relation between APP and AKI was observed, with a persisting APP cutoff value predictive of ARF in the ICU. We advocate for a structured clinical

APP approach to assist the physician in the optimization of IAP and MAP for improved outcomes in high-risk patients with liver cirrhosis.

Acknowledgments

We would like to express our gratitude to all the nursing and medical staff at UCIP7, Hospital de Curry Cabral, for their fundamental work and dedication to patient care, and to the Research Center at Centro Hospitalar Universitário Lisboa Central for their support in study design and biostatistics.

Statement of Ethics

This study complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. The Ethics Committee at Centro Hospitalar Universitário Lisboa Central (CES No. 397/2017) approved this study. Informed patient consent to participate was waived by the Local Ethics Committee given the observational nature of this study.

Conflict of Interest Statement

The authors of this study have no conflicts of interest to declare.

Funding Sources

No funding nor financial support was received for this study.

Author Contributions

Rui Pereira designed the study, collected data, performed the analysis, and wrote the manuscript. All authors reviewed and approved the final manuscript.

Data Availability Statement

The dataset used during the current study is available from the corresponding author on reasonable request.

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GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol 2025;32:37–42
DOI: 10.1159/000540117

Received: March 25, 2024
Accepted: June 3, 2024
Published online: August 16, 2024

Real-Time Gastric Juice Analysis to Rule Out the Presence of Autoimmune Gastritis: A Case-Control Study

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Keywords
Autoimmune gastritis · Gastric juice analysis · pH value · Precancerous lesions

Abstract

Background: Autoimmune gastritis (AIG) is an infrequent disease predisposing to both neuroendocrine tumours and cancer. This study aimed to evaluate whether pH measurement of gastric juice allows accurate exclusion of the presence of AIG in real time so that gastric mucosa sampling on normal-appearing mucosa may be avoided. ***Methods:*** This study enrolled patients diagnosed with AIG and matched controls (ratio 1:5) who underwent upper endoscopy with standard gastric mucosa sampling and real-time, gastric juice pH assessment. A threshold of pH less than 4.5 was adopted as cut-off to rule out the presence of a feature of AIG. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall accuracy, positive likelihood ratio (LR+), and negative likelihood ratio (LR–) were calculated. ***Results:*** Data of 40 patients (M/F: 19/21; mean age: 58 years, range: 18–89) with AIG and 212 matched controls were evaluated. Among AIG patients, the feature of atrophy/metaplasia of the oxyntic mucosa was staged as mild in 9 cases, moderate in 9, and severe in the remaining 22 patients. Gastric juice analysis showed a pH value >4.5 in 29 (72.5%) patients and 12 (5.7%) controls. Sensitivity, specificity, accuracy, PPV, NPV, LR+, and LR– were 73% (95% CI = 0.57–0.84), 94% (95% CI = 0.90–0.97), 71% (95% CI = 0.64–0.74), 95% (95% CI = 0.93–0.97), 91% (95% CI = 0.87–0.95), 12.9 (95% CI = 7.19–23.03), and 0.29 (95% CI = 0.18–0.48), respectively. The histological assessment of false-negative cases showed the presence of only mild-moderate atrophy of oxyntic mucosa in 6 (54.5%) cases, and severe in the others. ***Conclusions:*** Our data found that real-time pH evaluation of gastric juice allows ruling out AIG with a very high NPV, but further studies are needed.

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Análise em tempo real do suco gástrico para exclusão de gastrite autoimune - estudo caso-controlo

Palavras Chave
Gastrite auto-imune · Avaliação do suco gástrico · pH · Condições pré-malignas

Resumo
Introdução: A gastrite auto-imune (GAI) é uma condição rara que aumenta o risco de tumores neuroendócrinos e cancro gástrico. Este estudo teve como objetivo avaliar se a medição do pH do suco gástrico permite excluir em tempo real, com acuidade, a presença de GAI, de modo a evitar a realização de biópsias quando os aspetos endoscópicos são normais. ***Métodos:*** Foram incluídos doentes com GAI e controlos emparelhados (rácio 1:5) que realizaram endoscopia digestiva alta com biópsias gástricas padronizadas e medição do pH do suco gástrico em tempo real. O valor de pH <4,5 foi definido como *cut-off* para exclusão de GAI. Foram calculadas a sensibilidade, especificidade, valores preditivos positivos (VPP) e negativos (VPN), acuidade e rácios de verosimilhança (LR). ***Resultados:*** Foram avaliados os dados de 40 doentes com GAI (M/F 19/21; idade média 58 anos, intervalo 18–89) e de 212 controlos emparelhados. Nos doentes com GAI a atrofia/metaplasia intestinal na mucosa oxíntica em foi classificada como leve em 9 casos, moderada em 9 e grave nos restantes 22 doentes). A análise do suco gástrico mostrou um pH >4.5 em 29 (72.5%) dos doentes com GAI (vs. 5.7% nos controlos). A sensibilidade, especificidade, acuidade, VPP, VPN, LR+ and LR- foram de 73% (95% CI = 0.57–0.84), 94% (95% CI = 0.90–0.97), 71% (95% CI = 0.64–0.74), 95% (95% CI = 0.93–0.97), 91% (95% CI = 0.87–0.95), 12.9 (95% CI = 7.19–23.03), e 0.29 (95% CI = 0.18–0.48), respetivamente. A avaliação dos falsos negativos mostrou a presença de atrofia ligeira/moderada em 6 casos (54.5%) e severa nos restantes. ***Conclusão:*** Este estudo sugere que a medição do pH do suco gástrico em tempo real pode ser uma ferramenta promissora para excluir a GAI, embora sejam necessários estudos adicionais.

Introduction

Autoimmune gastritis (AIG) is a chronic, inflammatory disease characterized by progressive atrophy – with or without intestinal metaplasia – and enterochromaffin-like cell hyperplasia of gastric oxyntic mucosa (acid-secreting gastric compartment), sparing the antral mucosa [1, 2]. This condition increases the risk of both neuroendocrine tumours and cancer development in the stomach [3–5]. AIG is usually suspected when either iron or B_{12} deficiency anaemia develops, due to the reduction of gastric acid and intrinsic factor secretion, respectively [6]. Moreover, it is searched for at endoscopy in patients with positive serology to parietal cell autoantibodies, generally screened in patients with other autoimmune diseases, such as autoimmune thyroiditis or type 1 diabetes mellitus [6]. However, some patients with AIG complain of dyspeptic or even gastro-oesophageal reflux symptoms, so AIG may be also diagnosed at gastric biopsies performed during routine endoscopy [7]. According to current guidelines, standard sampling of gastric mucosa should be accomplished in 90% of appropriate upper endoscopies to search for *Helicobacter pylori* infection and gastric precancerous lesions, that is, atrophy and intestinal metaplasia, including AIG [8, 9]. However, these conditions are present in only a minority of patients with normal-appearing gastric mucosa, so the histological results are often clinically unrewarding. Indeed, an AIG prevalence as low as 1.9% was reported in a serology study in the USA [10], and 2.7% in three large endoscopic series from Italy, Australia, and Tunisia [11–13].

The interest towards gastric juice analysis during routine endoscopy has been renewed by the marketing of EndoFaster®, a device that performs a real-time evaluation of both ammonium and H^+ concentrations in the gastric juice, allowing to accurately rule out *H. pylori* and extensive atrophy involving antral and gastric body mucosa [14, 15]. Indeed, negative predictive values of gastric juice analysis as high as 97% on more than 2,000 patients were reported in a recent systematic review [16]. However, no specific data on EndoFaster® performance in AIG patients are available. Therefore, we designed this study to assess whether gastric juice analysis allows accurate exclusion of the presence of AIG in real time so that gastric mucosa sampling on normal-appearing mucosa may be safely and conveniently avoided.

Materials and Methods

Patients

This retrospective study was performed on data prospectively collected in a specific database where information of consecutive adult patients who underwent gastric juice analysis at upper endoscopy was registered. For this study, data of all patients diagnosed with AIG were retrieved and compared to those of matched controls enrolled in the

Fig. 1. The EndoFaster® device.

same database. Inclusion criteria were (a) histologically proven AIG; (b) no use of proton pump inhibitor therapy in the last 2 weeks before endoscopy; (c) absence of *H. pylori* at histology; (d) no previous therapy for *H. pylori* infection. These criteria were adopted to appropriately exclude present or past *H. pylori* infection potentially triggering atrophy/intestinal metaplasia development on gastric mucosa, in order to study only patients with true AIG. For each case, data of 5 controls matched for gender and age (±2 years) and with the same inclusion criteria, but without AIG, were recovered.

Endoscopic Procedures

All patients underwent upper endoscopy with standard (2 antral, 1 *incisura angularis*, 2 gastric body) biopsies on gastric mucosa, according to the updated Sydney system [17]. AIG was diagnosed when glandular atrophy (with or without intestinal metaplasia) with enterochromaffin-like cell hyperplasia was confined to the oxyntic mucosa, and a feature of normal antral mucosa was confirmed at histology [1]. During endoscopy, gastric juice analysis was performed by EndoFaster® (manufacturer: NISO Biomed S.r.l, Turin, Italy; distributor: Waldner Tecnologie Medicali, Trento, Italy). In detail, the device was interposed between the endoscope and the suction system, without causing any discomfort to the patient (Fig. 1). During endoscopy, lumen washing was avoided until the stomach was reached and at least 3 mL of gastric juice was aspirated. The device performs a real-time (within 90 s) gastric juice evaluation of pH values and ammonium concentrations, to suspect atrophic gastritis and *H. pylori* infection, respectively [16]. A threshold of pH less than 4.5 was adopted as cut-off to rule out the presence of atrophy involving the oxyntic mucosa and, then, a feature of AIG [16]. Informed consent was obtained for all the procedures. Since no identification of patients was allowed, no experimental drugs were administered, no additional costs or procedures for the patients were required, and no funds were received, the Investigational Review Boards waived formal approval for this retrospective analysis on medical records.

Table 1. Distribution of patients based on EndoFaster results (positive when pH >4.5) and histological feature of autoimmune gastritis (AIG)

	AIG positive	AIG negative	Total
EndoFaster positive	29	12	41
EndoFaster negative	11	201	212
Total	40	213	253

Statistical Analysis

Frequencies, percentages, and mean values with their 95% confidence intervals were calculated for all observations. Sensitivity, specificity, positive predictive value, negative predictive value (NPV), accuracy, positive likelihood ratio, and negative likelihood ratio were calculated, and Fagan's nomogram accordingly was designed.

Results

Overall, data of 40 patients (M/F: 19/21; mean age: 58 years, range: 18–89) diagnosed with AIG and 212 matched (102/120; mean age: 59 years, range: 19–92) controls were evaluated. Among AIG patients, the feature of atrophy/metaplasia on the oxyntic mucosa was staged as severe in 22 (55%) cases, moderate in 9 (22.5%), and mild in the remaining 9 (22.5%) patients. Gastric juice analysis showed a pH value >4.5 in 29 (72.5%) patients and 12 (5.7%) controls. Sensitivity, specificity, positive predictive value, NPV, and the overall accuracy were 73% (95% CI = 0.57–0.84), 94% (95% CI = 0.90–0.97), 71% (95% CI = 0.64–0.74), 95% (95% CI = 0.93–0.97), and 91% (95% CI = 0.87–0.95), respectively, while the positive likelihood ratio value was 12.9 (95% CI = 7.19–23.03), and the negative likelihood ratio was 0.29 (95% CI = 0.18–0.48). Distribution of patients according to EndoFaster® results and AIG feature is provided in Table 1, and Fagan's nomogram in Figure 2 [2]. Data regarding the 11 false-negative cases are provided in Table 2. As shown, the histological assessment showed the presence of mild-moderate atrophy of oxyntic mucosa in 6 (54.5%) cases, and severe in the remaining 5 cases.

Discussion

Upper endoscopy is largely performed in routine practice for diagnostic, therapeutic, and follow-up purposes [9, 18]. However, the rate of inappropriate

examinations in open-access setting was >20%, with values reaching 61.7% in some series [19]. According to current guidelines, standard gastric biopsies should be performed during routine endoscopy to search for both *H. pylori* infection and precancerous lesions on gastric mucosa, namely atrophy and intestinal metaplasia [8, 9]. AIG, characterized by atrophy and/or metaplasia confined in the oxyntic mucosa of the stomach and increased risk of developing both type I NET and adenocarcinoma in the stomach [1, 2], is a quite infrequent condition. Indeed, a prevalence rate of less than 3% was reported in endoscopic studies performed in different geographic areas [11–13], and ranging between 3% and 9% in serological studies only on Scandinavian populations where the incidence of disease is particularly high [6].

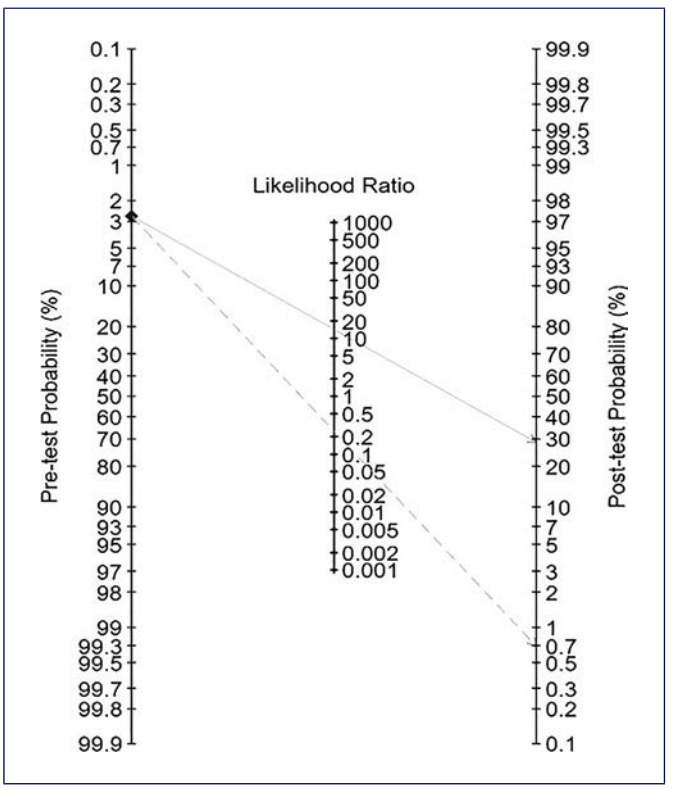

Fig. 2. Fagan's nomogram. The pretest probability indicated in the nomogram was that calculated in endoscopic studies.

Although generally suspected in patients with anaemia (micro- or macrocytic) or with parietal cell autoantibody seropositivity, AIG may be unexpectedly detected at histological assessment of gastric mucosa of patients with dyspepsia, particularly subtype postprandial distress syndrome or even with gastro-oesophageal reflux symptoms [7]. Can the gastric juice analysis be useful to avoid useless biopsies on normal-appearing mucosa without missing AIG? To achieve this purpose, a test with a very high NPV is needed. Real-time pH measurement in gastric juice with EndoFaster® was found to accurately rule out the presence of extensive atrophy/metaplasia involving both antral and gastric body mucosa [16]. To our knowledge, this is the first study on the accuracy of such a device in AIG patients. Our data found that by performing gastric juice analysis it is possible to rule out the presence of AIG with an NPV as high as 95%, so that only 5 patients in every 100 cases with negative EndoFaster® testing would be eventually overlooked for AIG. Of note, we observed that only mild-moderate atrophy on the oxyntic mucosa was present in more than half of patients with false-negative results at pH measurement. Therefore, it could be speculated that the patchy reduction of appropriate acid-secreting gastric glands revealed at histological assessment could be insufficient to markedly impair acid secretion detectable by pH measurement. On the other hand, the diagnosis of mild atrophy on gastric mucosa could represent an over-reporting, when considering that

Table 2. Patients with histological feature of AIG and normal pH values in gastric juice

Gender	Age, years	Gastric pH	Histology
F	46	3.5	Severe atrophy with intestinal metaplasia
F	53	1.3	Mild atrophy with focal intestinal metaplasia
F	66	1.7	Moderate atrophy with intestinal metaplasia
F	44	1.6	Mild atrophy without intestinal metaplasia
M	75	3.2	Severe atrophy with intestinal metaplasia
M	66	1.3	Moderate atrophy with intestinal metaplasia
F	18	2.6	Severe atrophy with intestinal metaplasia
F	60	2.6	Mild atrophy without intestinal metaplasia
M	63	1.6	Severe atrophy with intestinal metaplasia
M	40	1.6	Mild atrophy with focal intestinal metaplasia
F	65	2.8	Severe trophy with intestinal metaplasia

gastric biopsy specimens are not routinely oriented in clinical practice [20] and that interobserver agreement for atrophic gastritis among expert pathologists is only 0.73 [21]. Therefore, an even better performance of EndoFaster® in this setting could be foreseeable. On the other hand, beyond reducing useless biopsies in a negative test, a positive EndoFaster® result would alert the endoscopist to take standard biopsies on antral and gastric body mucosa. Indeed, despite it is recommended that gastric biopsies should be taken in >90% of endoscopies [8, 9, 22], the routine biopsy rate was quoted as low as 23% in a recent Italian study [23].

In the past, a pH 4 cut-off was proposed to rule out atrophy/metaplasia involving gastric oxyntic mucosa, because only few patients with this histological condition showed a pH value of gastric juice lower than 4 [24, 25]. However, a pH 4.5 cut-off was adopted in successive studies to disclose severe hypochlorhydria due to diffuse atrophy on gastric mucosa and, therefore, we cautionarily used the latter cut-off to rule out AIG [14, 15, 26].

Besides pH measurement, gastric juice analysis with EndoFaster® was found to be highly accurate in simultaneously excluding *H. pylori* – namely a type I carcinogen for gastric cancer according to the IARC [27]– by assessing ammonium concentration [16]. Therefore, it is clearly evident the advantage in contemporary discarding *H. pylori* infection and precancerous lesions by real-time gastric juice analysis with EndoFaster®. Moreover, avoiding foreseeable negative gastric biopsies in a definite portion of patients through the gastric juice analysis was found to distinctly reduce the environmental impact of upper endoscopy [28].

Some limitations of the study should be considered. The sample size is quite small, so our findings need to be confirmed in a larger, multicentre study. Although a standard biopsy sampling is routinely performed in our centre, the retrospective design of the study prevents specifically verification of the quality of endoscopic procedures or biopsies protocol in all cases. Finally, we excluded subjects with ongoing PPI use or presence of *H. pylori* infection, two conditions quite frequently encountered in routine practice.

Conclusions

Our data found that real-time pH evaluation of gastric juice allows ruling out AIG with a very high NPV, so that biopsies may be avoided on normal-appearing gastric mucosa. However, our results need to be confirmed in different settings.

Statement of Ethics

Since no identification of patients was allowed, no experimental drugs were administered, no additional costs or procedures for the patients were required, and no funds were received, the Investigational Review Boards of Nuovo Regina Margherita Hospital waived formal approval for this retrospective, cross-sectional study performed in clinical practice. Patients signed informed consent for both procedure and anonymous use of their data for scientific purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Angelo Zullo and Gianluca Esposito conceived the study and were responsible for the study design, statistical analysis, and drafting of the manuscript. Emanuele Dilaghi, Irene Ligato, and Gianluca Esposito were responsible for data and patient collection in each participant centre. Roberta Elisa Rossi, Cesare Hassan, and Bruno Annibale provided critical revision of the manuscript with important intellectual support. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data are available following reasonable inquiries directed to Angelo Zullo.

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GE – Portuguese Journal of Gastroenterology

Review Article

GE Port J Gastroenterol 2025;32:43–50
DOI: 10.1159/000540116

Received: February 22, 2024
Accepted: June 17, 2024
Published online: July 23, 2024

Chronic Intestinal Failure and Short Bowel Syndrome in Adults: Principles and Perspectives for the Portuguese Health System

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Keywords
Intestinal failure · Home parenteral nutrition · Short bowel syndrome

Abstract
Background: Short bowel syndrome is a devastating malabsorptive condition and the most common cause of chronic intestinal failure (CIF). Patients need parenteral support for months or years. Ideally, it should be delivered at home, reducing limitations in everyday life activities. ***Summary:*** The Portuguese Health Directive 017/2020 was the first step in the regulation of home CIF management, and more patients are now being treated in an ambulatory setting. However, much work still needs to be performed in this area. Our country lacks a network of units capable of providing home parenteral nutrition (HPN), and only a few centers have expertise to take care of these complex patients: fluid support, oral, enteral, and parenteral nutrition; disease/HPN-related complications; pharmacologic treatment; and surgical prevention/treatment. Providing adequate transition from pediatric to adult care is a mandatory issue that should only be addressed by expert centers. ***Key Messages:*** Implementation of a national network, as well as the creation of an intestinal failure registry, with an initial focus on adult patients, will start a new era in the identification and management of these complex CIF patients.

Falência Intestinal Crónica e Síndrome do Intestino Curto em Adultos: Princípios e Perspetivas para o Serviço Nacional de Saúde

Palavras Chave
Falência intestinal · Nutrição parentérica domiciliária · Síndrome do intestino curto

Resumo
Contexto: A síndrome do intestino curto constitui uma condição clínica devastadora e mal-absortiva, sendo a causa mais comum de falência intestinal crónica (FIC).

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Estes doentes carecem de suporte parentérico durante meses ou anos, idealmente em ambulatório, reduzindo as suas limitações no seu dia-a-dia. ***Sumário:*** Em Portugal, a Norma 017/2020 constituiu um primeiro passo oficial na abordagem da FIC, abrangendo cada vez mais doentes em contexto de ambulatório. Contudo, em Portugal não existe rede de serviços/unidades que possam providenciar nutrição parentérica domiciliária e apenas alguns centros possuem competência no tratamento de doentes com FIC, nomeadamente no manejo da fluidoterapia, nutrição oral, entérica e parentérica, complicações associadas à doença e/ou à própria nutrição parentérica domiciliária, tratamento farmacológico e ainda na prevenção/tratamento cirúrgico. Proporcionar uma adequada transição da idade pediátrica para a idade adulta constitui um aspeto fundamental que apenas deve ser operacionalizado entre centros de referência. ***Mensagens-chave:*** A implementação de uma rede nacional de FIC, assim como a criação de um registo nacional de FIC, com foco inicial no doente adulto, iniciarão uma nova era na identificação e abordagem adequada destes doentes.

Introduction

Short bowel syndrome (SBS) is a malabsorptive condition that results from the loss of intestinal length due to disease or resection [1]. SBS is the most common cause of chronic intestinal failure (CIF) [2]. Patients need parenteral support during months or years, parenteral nutrition (PN), or hydration/electrolyte supplementation. Parenteral support should be delivered at home, reducing limitations to everyday life activities, including working for adult patients and studying for children and adolescents. Functional classification includes all chronic metabolically stable patients requiring intravenous supplementation (type III) and some less metabolically stable patients requiring intravenous supplementation during weeks or months (type II) that can be effectively managed in an ambulatory setting.

For decades, Portuguese patients with CIF faced multiple barriers in receiving home PN (HPN). PN was considered a pharmacological treatment to be used only in hospital ward. Only a few institutional teams with home hospitalizations or a similar organization can provide HPN to some citizens [3]. In 2020, a new regulation from Portuguese authorities (*Direção-Geral da Saúde*), "Norma 017/2020" [4], set the conditions for home CIF management. Regulation of HPN, procedures, and structure of the nutrition support team (NST) have been organized, and an increasing number of intestinal failure (IF) patients are being treated in an ambulatory setting.

We aimed to address the current Portuguese reality for adult patients with SBS-CIF and the implications of the health directive 017/2020. We also reviewed the composition of multidisciplinary NST and the transition from pediatric to adult care. Finally, on behalf of Núcleo de Nutrição em Gastrenterologia (NNG), there is now a need to develop a national network of skilled centers and to organize SBS-CIF care, including patients requiring all types of parenteral support (PN and/or hydration/electrolyte supplementation). With standardized care, we will certainly contribute to improving the outcomes of these complex patients. Because SBS is the most important etiology of CIF, other causes of CIF will not be covered in this review.

The Current Portuguese Reality for Adult Patients with SBS-CIF

CIF is a rare organ failure worldwide [5], and the estimation of SBS-CIF prevalence is extremely variable. One of the reasons for this variability is the methodology used for the SBS-CIF estimation. Several studies have used HPN as a surrogate marker of SBS-CIF, which is frequent in older studies [6, 7]; however, it carries some setbacks: not all patients needing HPN have SBS-CIF, and not all SBS-CIF need PN. Other studies were based on SBS-CIF hospitalizations [8]. More recent studies are based on national SBS-CIF registries, which are easily accessible to researchers [9]. Another reason for the wide variation is the study or survey period. In Europe, the prevalence varies from 6 to 34 per million citizens in several countries, which is lower than the 2022 American study [10–15]. In contrast, data on CIF are scarce in Portugal. Antunes et al. [16] reported a prevalence of 27 cases per million inhabitants of the pediatric population in 2018. Furthermore, a Portuguese nationwide survey conducted in 2019 found only 20 children and 11 adults undergoing HPN (although 2 known patients were not included for logistic reasons), equivalent to 1 adult patient per million, the lowest European prevalence [17]. This likely reflects the lack of a national registry and the complete absence of a network of units capable of providing HPN and treating patients with SBS-CIF. In fact, the survey only identified five centers that took care of adult patients.

It is expected that the incidence and prevalence of CIF will increase in the coming years due to improvements in care, introduction of new drugs (e.g., teduglutide), and the associated increased life expectancy [5]. However, owing to

its low incidence and prevalence, as well as the complex medical and surgical issues associated with long-term PN, it is essential to establish a wider network of referral centers that are proficient in the management of SBS-CIF patients.

The Portuguese Turning Point – Health Directive 017/2020

As stated, patients with SBS-CIF had major difficulties in accessing PN at home since PN was only considered a hospital-based treatment. In addition, patients living in geographically isolated areas with limited health resources do not have access to HPN. "*Norma 017/2020: Implementação da Nutrição Entérica e Parentérica no Ambulatório e Domicílio em Idade adulta*" [4], a government initiative, was, indeed, a major step in clinical/artificial nutrition in Portugal. It starts with the creation of an NST named *Grupo de Nutrição Entérica e Parentérica* (GNEP), whose main objective is to manage the prescription of enteral nutrition (EN) or PN at the hospital level. For all patients previously identified as suffering from malnutrition or nutritional risk that would benefit from HPN, an individualized nutritional plan should be developed. It aims to achieve enteral autonomy by progressively reducing PN and increasing oral/enteral feeding, if tolerated.

According to Health Directive 017/2020, HPN should be prescribed when EN is contraindicated or when nutritional support is required, but needs cannot be met by the enteral route. Examples of disorders leading to HPN other than SBS in adults in Portugal (stated in the health directive) include the following:

- cancer-associated cachexia (e.g., after intestinal resection and Lisboaradiation/treatment-related enteritis);
- inflammatory bowel disease causing severe malnutrition;
- mesenteric ischemia with abdominal angina;
- proximal enteric fistula;
- chronic dysmotility diseases not controlled by therapy.

Table 1 summarizes the therapies, equipment, and medical devices essential for HPN according to health directive 017/2020, highlighting the complexity, resource intensiveness, and expense to be considered with HPN.

The Interdisciplinary Nutrition Team for SBS-CIF Adult Patients

The most important resource for IF management is multidisciplinary NST [2]. It includes health care professionals with different backgrounds and clinical nutrition training. The NST should include the following:

- Medical doctors, including gastroenterologists and gastrointestinal surgeons [18], are trained in providing the necessary care for digestive diseases. Gastroenterologists should be experienced in the management of medical disorders that cause CIF, such as Crohn's disease, dysmotility, and malabsorption. The experience and training of surgeons should be considered a subspecialty of digestive surgery according to the European Society of Coloproctology [19], and this is of special importance for patients with type II IF. Whenever needed, other specialists, such as radiologists, endocrinologists, and/or pediatricians, should be included in the NST.
- Nurses: They assist patients in a therapeutic manner. A major objective of nurses' interventions is to promote the autonomy and self-care of patients and caregivers in a safe and responsible manner. An individualized educational plan should be made to meet the needs of each patient/caregiver and should address principles of infection control and prevention, central venous catheter (CVC) precautions, training aseptic care of the CVC, and technique of management PN [20]. Nursing intervention is essential in preventing risks and complications associated with CVC, including monitoring inflammatory signs at the CVC insertion site and the integrity of the CVC, assessing the effectiveness and tolerance of PN, and evaluating the skills achieved. CIF nurses are essential to engage patients and caregivers in the management of their illness, promoting a feeling of independence, security, control, responsibility, normality, and trust.
- Dietitians with experience and training in CIF [21]. Most patients with CIF suffer from SBS, with some bowel extension capable of digestion and absorption, and the same scenario may be present in type II IF. Although virtually all patients with SBS-CIF will require PN, more than 50% will be able to be weaned completely from PN within 5 years. Therefore, rehabilitation should be initiated as soon as possible, and dietitians play a major role in this process. Oral feeding plays an important role in global nutrition and is a major contributor to the quality of life and well-being. It provides gut feeding, helps intestinal integrity and function by providing nutrition to enterocytes, and may contribute to the prevention of IF-associated liver disease. Dietitians must provide optimal oral intake, considering the PN, morphology of the remaining bowel, patient preferences, and lifestyle. EN should also be considered, especially in those with low PN dependence who are expected to be weaned off. Furthermore, the importance of restricting the intake of

Table 1. Therapies, equipment, and medical devices essential for HPN

PN equipment/therapies
Standard PN admixtures (two or three compartments) or personalized PN admixtures if the former does not reach nutritional needs
Injectable hydrosoluble and liposoluble vitamins
Bidistilled water
Sodium chloride 0.9% (100 mL and 500 mL)
Heparin
Hypertonic glucose (20 or 30%)
Rapid-onset insulin (if necessary)
Antiseptic (chlorhexidine or iodopovidone)
Disinfectant (alcohol)
Catheter lock with antimicrobial and antifungal properties (taurolidine 2% or equivalent)
Medical devices
Perfusion pump
Filter in line, 0.22 micron (two-chamber PN or admixtures without lipids) or 1.2 micron (three-chamber PN or admixtures with lipids)
Three-way stopcock
Sterile catheter cap
Surgical mask
Scrub cap
Surgical gloves
Sterile fields
Sterile syringe (2, 5, 10, and 20 mL)
Hypodermal needle (12 and 18G)
Sterile dressings (10×5 cm and 7.5 × 7.5 cm)
Film dressings (ex. IV 3000; op-site 3000 10×14 cm)
Container for sharp/cutting medical waste
Disposable medical gown
Other materials
Disinfectant for hand hygiene
Fridge space for storage of PN bags
Metallic support for PN admixture (if necessary)
Support for the perfusion bomb (if necessary)

PN, parenteral nutrition.

low-sodium fluids such as hypotonic fluids (e.g., water, tea, alcohol, and coffee) and hypertonic fluids (e.g., regular soda and fruit juices) should be emphasized.

- Pharmacists' main role is to collaborate and supervise the design, composition of macro- and micronutrients, implementation and monitoring of PN, and prevention of metabolic or catheter-related complications [22]. In addition, they play a very important role in preventing the possible interactions of PN with other medications, as well as the absorption of oral/enteral drugs in the context of intestinal dysfunction. Pharmacists' roles have been expanding beyond the supervision of compounding/dispensing PN, including direct care, consultations of PN patients, and education of patients/caregivers, which results in more adequate nutrition with fewer metabolic complications.
- Besides this core team, other healthcare professionals are also frequently needed. Physiotherapists and exercise professionals are necessary as these patients present with malnutrition and sarcopenia with impaired movement aptitudes. Several cases present with dysphagia or insecure swallowing; evaluation/rehabilitation may require a trained speech therapist. Finally, patients may present with comorbidities that may require a wide range of health professionals [23].

Whenever a department has a patient in a ward who may need HPN, the staff should contact the NST with experience in HPN, whether from the same institution or from another hospital. Together, the department staff and the NST should evaluate the need for HPN, stabilize the patient, and determine the composition of the PN mixture before discharge. After discharge, the patient

should be evaluated in an outpatient clinic on a weekly basis, with clinical and laboratory evaluations to assess the fluid, nutritional, and electrolyte status. When difficulties are recognized during the hospital-home transition, appointments may be more frequent, e.g., twice a week. Gradually, appointments may become less frequent according to HPN stabilization and patient autonomy and empowerment.

The NST should conduct regular audits and prepare regular reports of activities regarding the services provided in the field of HPN in outpatient/home settings. In this regard, the quality of care should be measured to evaluate HPN-related complications, hospital readmissions, weight change, and regular assessments of the patient's quality of life. The NST should promote and facilitate the continuous training of its members, with participation in courses and scientific meetings dedicated to clinical nutrition, such as those promoted by *Associação Portuguesa de Nutrição Entérica e Parentérica*, NNG, and the European Society for Clinical Nutrition and Metabolism.

Transition from Pediatric to Adult Care in SBS-CIF

In the CIF, the transition of care from pediatric to adult health services remains a delicate process, and a planned transition of care is essential. This transition is a planned and purposeful movement of adolescents and young adults with complex medical conditions from a child-centered to an adult-centered healthcare system [24].

The transition period is a time with a potential risk of morbimortality [25, 26], which reinforces the need for an organized, multidisciplinary, and individualized plan of care involving primary healthcare services. The NST must be prepared to provide care to these patients and to maintain, at least, the level of the previous care, which is crucial to maintain clinical stability and quality of life [27].

Children and adolescents with CIF have limited autonomy and dependence on the care provided by caregivers and healthcare teams. Adolescents are a distinct group of children and adults from physical, emotional, and psychological standpoints, making this transition even more complex.

There are different models of transitional care for chronic illnesses [24]. The most suitable model for CIF might be the transition model focused on the illness and their professionals [28].

In Portugal, most pediatricians select the age of 15–19 years as the most appropriate age to initiate the transition, which encompasses the recommended age by the American Academy of Pediatrics from 18 to 21 years [29, 30]. The key principles sustaining a successful transition are (1) information, (2) communication, and (3) planning/coordination [31]. According to the Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the Italian Society of Artificial Nutrition and Metabolism, the aims of this process, known as "acronym of 5 M" are (1) motivate independent choices, (2) move toward adult goals, (3) maintain previous care, (4) minimize the difficulties involved in the transition, and (5) modulate the length of transition [28].

In the first transitional appointment, the adolescent should attend simultaneous consultations with the pediatrician and the adult physician. Subsequent consultations should be performed according to a previously established plan. Initially, the place for consultations should be the usual pediatric environment and afterward, in the adult's environment. Most adolescents and young adults wish to be seen by the adult physician in their pediatric environment, but it is desirable to be familiar with adult facilities [28].

A Portuguese National Network for Adult Patients with SBS-CIF

In complex and rare diseases, it is essential to have dedicated professionals with medical and surgical resources, organized in multidisciplinary teams, and with knowledge and expertise in the management of these patients. In Europe, there are inequalities in accessing HPN, and there are no standardized models of organization or reimbursement. However, some countries have national centers for CIF, such as Denmark, France, and England [32]. In Portugal, most hospitals can provide PN in the setting of hospitalized patients (mainly type I and II IF) but not HPN, and there are only a few specialized centers to manage complex SBS-CIF patients.

Portugal, a country with 10.4 million inhabitants [33], has very few patients under nutritional support at home (related to several reasons including low expertise in the field and the absence of legal support for delivering PN at home, until recently). Owing to its rarity, a total of 50–150 adult CIF patients are expected to be managed with HPN a few years after the implementation of an organized network. To prevent the allocation of a very small number of SBS-CIF patients *per* center, insufficient to provide enough clinical experience to each center, it would be critical to constitute a maximum of 3–5 referral centers for adult CIF patients. These referral centers could work in close relation to support local NST. In geographically isolated areas, telehealth services, outreach clinics, and

Table 2. Main topics in SBS-CIF in Portugal

What is the current Portuguese reality for adult patients with SBS-CIF?
Extremely low prevalence compared with other European countries, reflecting the complete absence of a national registry and a network of reference centers
The Portuguese turning point – what have changed with the health directive 017/2020?
Portuguese SBS-CIF patients had major difficulties in accessing PN at home (no legal support for it)
The health directive 017/2020 was a major step in clinical/artificial nutrition in Portugal
Regulation of HPN, procedures, and structure of the NST were organized
How should an NST be organized?
The NST should be composed of healthcare professionals with different backgrounds and clinical nutrition formation/training
The NST should include medical doctors (e.g., gastroenterologists/digestive surgeons), nurses, dietitians, and pharmacists
Other healthcare professionals may be needed (e.g., physiotherapists, speech therapist)
How to promote a stable transition from pediatric to adult care in SBS-CIF?
Most pediatricians select the age 15–19 years as the most appropriate to initiate the transition
In the first transitional appointment, the adolescent should attend simultaneous consultations with the pediatrician and the adult physician
Pediatric and adult centers may be located in different hospitals, providing that transition is effectively organized
What will change in Portugal regarding SBS-CIF care?
It is suggested to create 3–5 referral centers for adult SBS-CIF patients in relation with the local NST. Also, 2–3 pediatric referral centers should be organized
The organization of a Portuguese CIF Registry is ongoing and will focus initially on SBS-CIF adult patients
Although the pediatric register has not yet started, it may be unified with the adult register in the future

SBS-CIF, short bowel syndrome-chronic intestinal failure; PN, parenteral nutrition; NST, nutrition support team.

shared care models may overcome some challenges in managing these patients. Close collaboration with primary healthcare services, including blood collection and evaluation, may help patients living far from the hospital, although this is still not implemented, and SBS-CIF patients still need to come to the hospital. Sometimes, a "ready-to-use service" provided by an external corporation may be used to deliver several items at the patient's home, including PN admixture, systems, and perfusion bombs for PN delivery. Using such external partners may be useful; however, clinical follow-up must remain with the NST, and regular appointments should not be neglected [34]. Patients were required to have an available telephone number, ideally always available, to answer any emergent problems. Also, 2–3 pediatric referral centers should be organized. Pediatric and adult centers may be located in different hospitals, providing that the transition is effectively organized. These patients may live in different geographical areas, and it is important to offer healthcare in proximity. It is agreed that patients and GNEPs benefit from a large specialist center for discussion of more difficult cases and the promotion of a network model of care. It is crucial that the National Health System promotes this network of care and allocates funds to maintain their clinical practice, ongoing learning, and research with the aim of providing the best care for these patients according to international standards, such as those provided by the European Society for Clinical Nutrition and Metabolism [5].

A Portuguese IF Registry

The organization of the Portuguese SBS-CIF Registry is ongoing under the supervision of NNG, a special interest group in nutrition of the Portuguese Society of Gastroenterology (SPG). This IF Registry will be held on the Cerega platform (Centro Nacional de Registo de Dados em Gastrenterologia) and will use a data collection form similar to other collecting forms of European countries. As a first step, the register focuses on adult patients with CIF. Although the pediatric register has not yet started, it may be unified with the adult register in the future. Table 2 summarizes the main conclusions of this review.

Conclusion

CIF requires a multidisciplinary team composed of healthcare providers with different backgrounds, aiming for the successful treatment of these patients. In our

country, a great deal of work remains to be done in this area, and we hope that the implementation of a nationwide network as well as the creation of a CIF registry will start a new era in the identification and management of SBS-CIF patients.

Acknowledgment

This study was supported by NNG, a special interest group in SPG.

Statement of Ethics

Due to the nature of the article, ethical approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was financially supported by an honoraria grant from Takeda Pharmaceuticals. The study sponsor was not involved in the study design, data collection, or data analysis.

Author Contributions

Francisco Vara-Luiz, Luísa Glória, Ivo Mendes, Sandra Carlos, Paula Guerra, Gonçalo Nunes, Cátia Sofia Oliveira, Andreia Ferreira, Ana Paula Santos, and Jorge Fonseca performed literature review, selection of studies, and writing. Luísa Glória and Jorge Fonseca conceived the study design, structured the content, and critically reviewed the manuscript. All the authors approved the final version of the manuscript.

Data Availability Statement

All the data analyzed during this review are included in this article. Further inquiries can be directed to the corresponding authors.

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GE – Portuguese Journal of Gastroenterology

Endoscopic Snapshot

GE Port J Gastroenterol 2025;32:51–53
DOI: 10.1159/000539021

Received: January 28, 2024
Accepted: April 15, 2024
Published online: June 11, 2024

Beware the Hole: A Trick for Endoscopic Success while Closing an Esophageal Perforation

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Keywords
Esophageal perforation · Esophagus · Bone · Endoscopy · Perforation

Cuidado com o buraco: um truque para o tratamento endoscópico ao encerrar uma perfuração esofágica

Palavras Chave
Perfuração esofágica · Esófago · Osso · Endoscopia · Perfuração

A 79-year-old diabetic woman presented at the emergency room with fever, retrosternal pain, and dysphagia 24 h after choking on pork meat. A chest CT scan without oral contrast revealed a 2 cm dense linear structure crossing the thoracic esophageal wall, with signs of pneumomediastinum and densification of the periesophageal tissues (shown in Fig. 1) – these findings were compatible with mediastinitis due to esophageal perforation by bone.

Upper digestive endoscopy was performed, with CO_2 insufflation in the operating room in the presence of the general surgery team, under orotracheal intubation, and it identified a bone perforation 23 cm from the upper dental arch – the bone was removed with forceps only after unlocking and deflating the endotracheal tube cuff due to space conflict. After extracting the bone, a 15 mm esophageal perforation (shown in Fig. 2) was closed with 4 through-the-scope (TTS) clips (shown in Fig. 3).

It was decided to keep the patient intubated for 72 h; there was a good clinical and analytical evolution during this period. Afterward, a new CT scan was then performed, which showed successful closure of the esophagus, with no extravasation of oral contrast. She was then extubated without complications.

The patient underwent a 12-day nil-by-mouth regimen, under total parenteral nutrition, and 20 days of piperacillin/tazobactam + fluconazole, with good clinical and analytical response. A predischarge CT scan indicated resolution of the inflammatory process without oral contrast leakage.

Esophageal perforations are rare, with an incidence of 3.1 per 1,000,000 per year, but are associated with significant morbimortality [1]. Traditionally, surgery was the therapeutic modality of choice, but endoscopic management is now emerging as its first treatment modality [2, 3]. In the case of infracentimeter perforations, TTS clips can easily be used. In the case of larger perforations, other endoscopic options are primarily available, such as over-the-scope clips, stents, endoscopic suturing, or endoscopic vacuum therapy (when there is also need for infectious control) [1].

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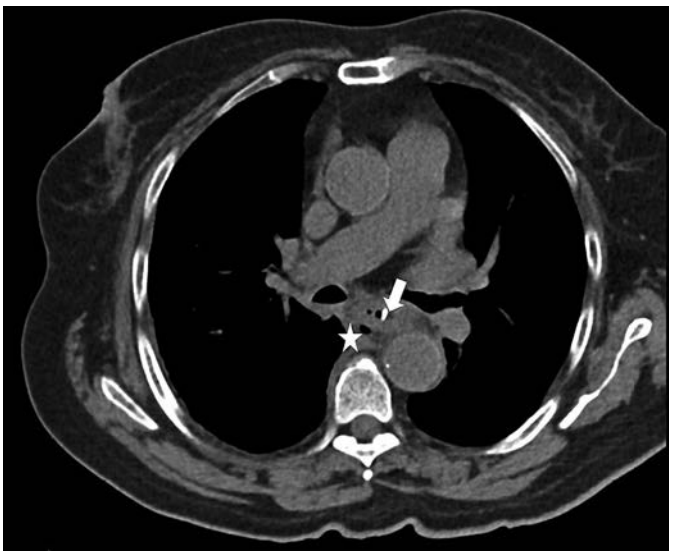

Fig. 1. Axial CT scan of admission showing the 2 cm linear structure crossing the thoracic esophageal wall (arrow) causing densification of periesophageal tissues and signs of pneumomediastinum (star).

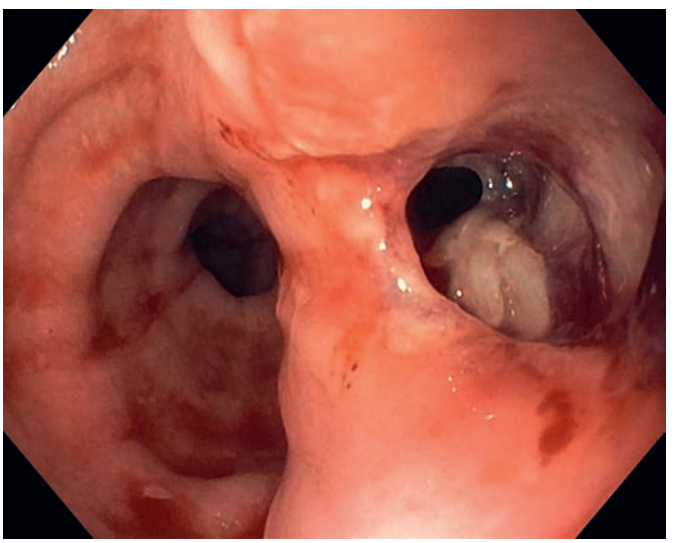

Fig. 2. Esophageal perforation of 15 mm seen after bone extraction.

In this case, it was necessary to unblock and deflate the orotracheal tube cuff due to space conflict, in order to allow for the bone to be removed. Although the size of this perforation was >10 mm, and attending to space conflict, closure with TTS clips was tried and successful – clinical judgment is always imperative. This case underscores the efficacy of endoscopic therapy for esophageal perforations and emphasizes the need for multidisciplinary involvement.

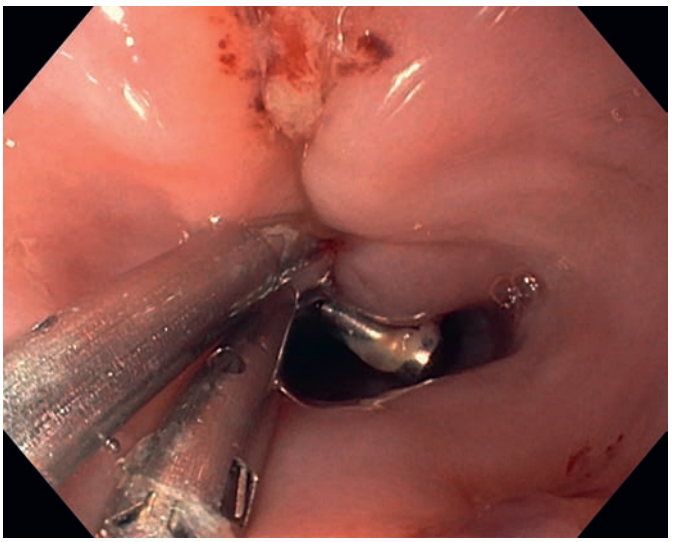

Fig. 3. Successful endoscopic closure of the esophageal perforation.

Statement of Ethics

Ethical approval was not required to this type of manuscript due to local laws. The patient has given written informed consent for publication (including the publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This case report was not supported by any sponsor or funder.

Author Contributions

A.T.F. and S.A. wrote the manuscript; C.C. performed the upper endoscopy; C.C. and I.P. critically reviewed the manuscript. All authors approved the final version of this paper.

Data Availability Statement

The complete data of this case report are not publicly available due to the patient's privacy but are available from the corresponding author upon reasonable request.

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GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2025;32:54–60
DOI: 10.1159/000539092

Received: December 18, 2023
Accepted: February 12, 2024
Published online: June 14, 2024

Porto-Sinusoidal Vascular Disease and Downhill Varices: Separate Clinical Entities?

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Keywords
Porto-sinusoidal vascular disease · Downhill varices · Pulmonary arterial hypertension · Liver hemodynamic study · Transjugular liver biopsy

Abstract

Introduction: Porto-sinusoidal vascular disease (PSVD) is an entity characterized by the absence of histologic liver cirrhosis and the detection of specific or non-specific histological findings, irrespective of the presence of portal hypertension (PHT). The pathogenesis remains poorly understood. Pulmonary arterial hypertension (PAH), independently of the presence of PHT, can be associated with an increase in central venous pressure, which can rarely lead to the development of downhill varices in the proximal esophagus. ***Case Presentation:*** A 53-year-old woman, with an unremarkable medical and pharmacological history, presented with a 3-day history of melena, epigastric pain and hematemesis. Physical examination revealed bilateral peripheral edema of the legs. Laboratory findings included severe anemia, normal hepatic enzymology, and NT-proBNP 1,748 pg/mL. Endoscopy showed large proximal esophageal varices and mild hypertensive gastropathy. A complete liver disease etiology panel was negative. Ultrasound showed an irregular liver surface, splenomegaly, and dilated supra-hepatic veins and inferior vena cava. Echocardiogram revealed significant cardiac valve and cavity abnormalities, especially on the right side, as well as moderate to severe PAH. Diuretics therapy was started with clinical improvement. Beta-blockers were suspended due to intolerance. There were no images suggestive of portosystemic collateralization on angiography. Re-evaluation endoscopy showed large but reduced esophageal varices, without red spots. Cardiopulmonary hemodynamic assessment revealed moderate PAH (40 mm Hg). Liver hemodynamic study revealed non-clinically significant sinusoidal PHT. Transjugular liver biopsy revealed nodular regenerative hyperplasia suggestive of PSVD. ***Discussion/Conclusion:*** The case was complex and presented diagnostic challenges, illustrating the uncommonly reported association between PSVD and porto-pulmonary hypertension and the importance of the transjugular liver biopsy and pressure measurements to confirm both diagnoses.

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Doença vascular porto-sinusoidal e varizes downhill: entidades clínicas distintas?

Palavras Chave
Doença vascular porto-sinusoidal · Varizes downhill · Hipertensão arterial pulmonar · Estudo hemodinâmico hepático · Biópsia hepática transjugular

Resumo
Introdução: A doença vascular porto-sinusoidal (PSVD) é uma entidade caracterizada pela ausência histológica de cirrose hepática e pela detecção de achados histológicos específicos ou inespecíficos, independentemente da presença de hipertensão portal (PHT). A sua fisiopatologia permanece pouco compreendida. A hipertensão arterial pulmonar (PAH), independentemente da presença de PHT, pode estar associada ao aumento da pressão venosa central, o que, raramente, pode levar ao desenvolvimento de varizes *downhill* no esófago proximal. ***Caso clínico:*** Mulher de 53 anos, sem antecedentes pessoais e farmacológicos de relevo, com quadro de melenas, epigastralgia e hematemeses com 3 dias de evolução. O exame físico revelou edema periférico bilateral dos membros inferiores. Os achados laboratoriais revelaram anemia grave, enzimologia hepática normal e NT-proBNP 1748 pg/mL. A endoscopia mostrou varizes esofágicas proximais grandes e gastropatia hipertensiva ligeira. Foi realizado um painel completo de etiologia de doença hepática, que não revelou alterações. A ultrassonografia mostrou uma superfície hepática irregular, esplenomegália e veias supra-hepáticas e veia cava inferior dilatadas. O ecocardiograma revelou alterações significativas nas válvulas e cavidades cardíacas, especialmente no lado direito, bem como PAH moderada a grave. A doente iniciou terapêutica diurética com melhoria clínica. A terapêutica com beta-bloqueantes foi suspensa por intolerância. Não se verificaram imagens sugestivas de colateralização portossistémica na angiografia. A endoscopia de reavaliação mostrou varizes esofágicas grandes, mas reduzidas em relação ao exame anterior, sem *red spots*. A avaliação hemodinâmica cardiopulmonar revelou PAH moderada (40 mm Hg). O estudo hemodinâmico hepático revelou PHT sinusoidal não clinicamente significativa. A biópsia hepática transjugular revelou hiperplasia regenerativa nodular sugestiva de PSVD. ***Discussão/Conclusão:*** Este caso apresentou elevada complexidade e múltiplos desafios diagnósticos, ilustrando a associação incomumente relatada entre PSVD e hipertensão porto-pulmonar e a importância da biópsia hepática transjugular e medições de pressão para confirmar ambos os diagnósticos.

Introduction

Portal hypertension (PHT) is the main clinical manifestation of advanced chronic liver disease. Clinically significant PHT (hepatic venous pressure gradient – HVPG ≥10 mm Hg) [1] predicts complications like variceal bleeding, ascites, jaundice, and encephalopathy [2–4]. These can occur in the absence of cirrhosis (Table 1) [4, 5].

Porto-sinusoidal vascular disease (PSVD) is a rare cause of PHT and is characterized by absence of liver cirrhosis and detection of specific or non-specific histological findings, irrespective of PHT [4, 7]. The presence of other causes of liver disease does not rule it out [4]. The pathogenesis remains poorly understood. Drugs, hematologic and infectious diseases, prothrombotic and immune disorders, and genetic factors have been associated [4, 8]. Imaging and non-invasive tests like liver (LSM) and spleen stiffness measurements (SSM) have a diagnostic role, but hemodynamic study with transjugular liver biopsy (TJLB) is crucial to assess HVPG and obtain liver tissue for histopathology [4].

Pulmonary arterial hypertension (PAH), characterized by elevated mean pulmonary artery pressure (PAP) (>25 mm Hg), is most commonly idiopathic, but may be associated with PHT (porto-pulmonary hypertension-PoPH). PAH and PoPH are histologically indistinguishable [9–11].

PAH can be associated with increased central venous pressure [12], which can rarely lead to downhill varices in the proximal esophagus [13]. Blood flows from the superior vena cava to the esophageal venous plexus [14]. It is a rare etiology for hematemesis (0.1%) [13], due to their localization in the proximal esophageal submucosa [14]. Treatment should be directed at the vascular obstruction's underlying cause [15, 16].

Case Report

A 53-year-old-woman presented with a 3-day history of melena, epigastric pain and hematemesis. Medical history included obesity (BMI 34 kg/m^2) and peripheral vascular

Table 1. Causes of noncirrhotic portal hypertension [6]

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Splanchnic arteriovenous fistula
Splenomegaly (e.g., from lymphoma, Gaucher's disease*)
Intrahepatic
Presinusoidal
Schistosomiasis*
Idiopathic noncirrhotic portal hypertension (including nodular regenerative hyperplasia)
Primary biliary cholangitis
Sarcoidosis*
Congenital hepatic fibrosis
Primary sclerosing cholangitis
Hepatic arteriopetal fistula
Adult polycystic liver disease
Arteriovenous fistulas
Autoimmune cholangiopathy
Vinyl chloride toxicity*
Neoplastic occlusion of the intrahepatic portal vein
Mineral oil granuloma*
Sinusoidal
Arsenic poisoning
Vinyl chloride toxicity*
Drugs (e.g., amiodarone, methotrexate)
Alcoholic liver disease*
Nonalcoholic fatty liver disease
Gaucher's disease*
Zellweger syndrome
Viral hepatitis
Chronic Q fever
Schistosomiasis*
Amyloid or light-chain deposition in the space of Disse
Acute hepatic injury
Mastocytosis
Agnogenic myeloid metaplasia
Acute fatty liver of pregnancy
Postsinusoidal
Sinusoidal obstruction syndrome (venoocclusive disease)
Budd-chiari syndrome*
Alcoholic liver disease*
Chronic radiation injury
Vitamin A toxicity
Epithelioid hemangioendothelioma
Angiosarcoma
Sarcoidosis*
Mycobacterium avium or *M. intracellulare* infection
Mineral oil granuloma*
Posthepatic
IVC obstruction (e.g., Budd-Chiari syndrome*)
Cardiac disease (constrictive pericarditis, restrictive cardiomyopathy)

IVC, inferior vena cava. *May cause noncirrhotic portal hypertension via several mechanisms.

disease treated with bioflavonoids. She denied fever, jaundice, choluria, alcohol consumption, and liver disease. She also denied taking nonsteroidal anti-inflammatory drugs, anti-platelets, or anticoagulants.

Physical examination was unremarkable except for bilateral peripheral edema of the legs. Laboratory findings included severe iron deficiency anemia (hemoglobin 4.1 g/dL), platelet count 188 × 10^9/L, INR 1.13, albumin 4.6 g/dL, normal hepatic enzymes, and raised NT-proBNP (1,748 pg/mL).

Endoscopy showed large proximal esophageal varices, without red spots, and mild portal hypertensive gastropathy (shown in Fig. 1). Abdominal ultrasound revealed slight hepatomegaly with irregular liver surface; no focal lesions; marked echogenicity of the fibrovascular axes and hilum; ectasia of the inferior vena cava (IVC) and hepatic veins; no portal vein abnormalities; mild splenomegaly (14 cm). A comprehensive chronic liver disease etiology panel was negative.

Echocardiograms revealed good systolic function; dilated right heart cavities; mild aortic and mitral insufficiency; moderate tricuspid and pulmonary insufficiency; severe PAH. Furosemide and spironolactone were instituted, with clinical improvement. Perindopril and carvedilol were introduced but the latter was suspended due to intolerance (symptomatic hypotension, lipothmia, platypneia).

Coronary angiography ruled out coronary disease. Thoracoabdominal computed tomography angiography showed enlargement of the pulmonary artery with no evidence of thrombus, as well as absence of porto-systemic collateralizaion, portal vein thrombosis, and structural lung disease. A re-evaluation endoscopy showed large but reduced esophageal varices, without red spots (shown in Fig. 2).

Cardiopulmonary and hepatic hemodynamic (HH) study revealed moderate PAH (mean PAP 40 mm Hg, pulmonary capillary wedge pressure 5 mm Hg) and HVPG of 6 mm Hg, which was suggestive of non-clinically significant sinusoidal PHT (shown in Fig. 3). There were no hepatic vein-to-vein communicants detected during the HH study.

The biopsy fragments obtained with TJLB measured 48 mm in length. Histopathological evaluation revealed nodular regenerative hyperplasia (NRH) and obliterated portal veins, without fibrosis, suggesting PSVD (shown in Fig. 4).

She was discharged on diuretics, with improvement of peripheral edema. Additionally, she was medicated with macitentan and tadalafil. She underwent variceal bleeding prophylaxis with endoscopic band ligation.

Discussion

As previously stated, diagnosis of PSVD requires histological confirmation and exclusion of liver cirrhosis [4, 17]. HH study with TJLB is often performed due to thrombocytopenia, and was key in the diagnostic process [18]. In PSVD, HVPG is normal/slightly elevated and often <10 mm Hg, due to pre-sinusoidal PHT [4, 17, 19] and presence of vena-vena communications [4, 19]. Hence, HVPG is often not correlated with events like variceal bleeding/ascites [17].

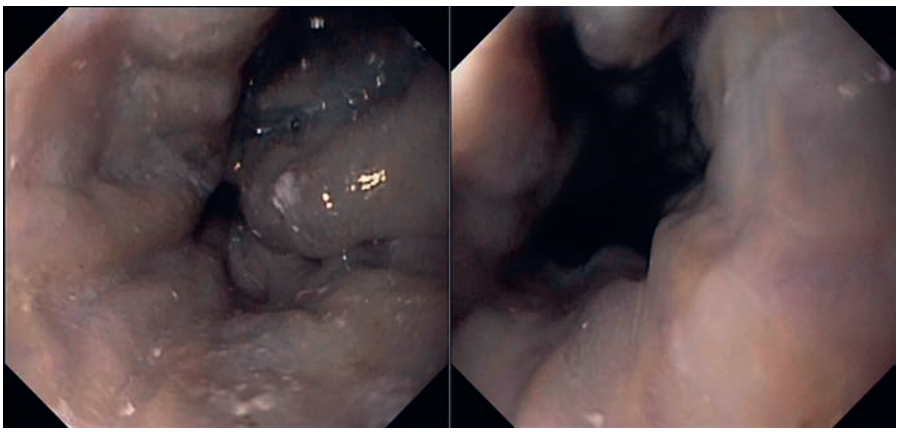

Fig. 1. Large proximal esophageal varices without red spots.

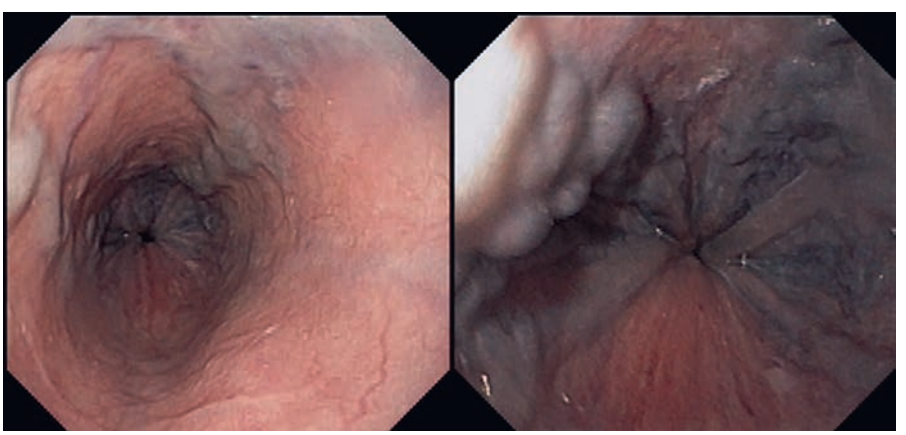

Fig. 2. Large esophageal varices, reduced in size in comparison to the previous evaluation, without red spots.

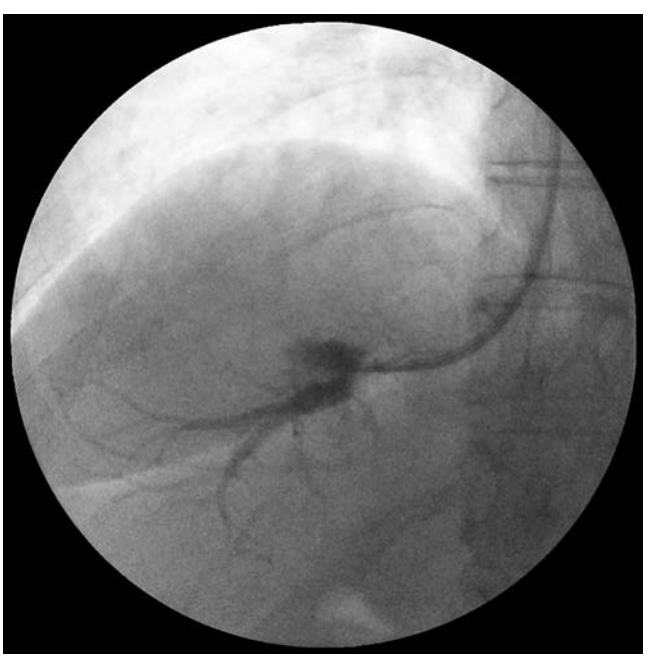

Fig. 3. Wedged supra-hepatic vein pressure measurement with Fogharty balloon catheter.

Specific histologic features include obliterative portal venopathy, NRH (present in this case) and incomplete septal cirrhosis/fibrosis [4, 17]. NRH is a nodular parenchymal transformation with hyperplastic hepatocytes surrounded by atrophic hepatocytes without fibrosis [20].

Abdominal ultrasound features of PSVD include normal/inhomogeneous liver with irregular surface; right hepatic lobe atrophy/hypotrophy; caudate lobe hypertrophy; marginal atrophy; compensatory central hypertrophy; features of PHT (splenomegaly, portosystemic collaterals, portal venous dilation); portal vein abnormalities (portal atypical thickening, hyperechoic walls, and portal vein thrombosis [PVT]) [4, 19], some of which were identified in the abdominal ultrasound performed, as is stated above.

LSM are usually normal/slightly elevated, and SSM are increased [4, 19]. LSM <10 kPa as a cut-off value has good diagnostic performance and low LSM values should prompt a biopsy [21]. A higher spleen-to-liver stiffness may be suggestive of PSVD and should indicate a HH study and TJLB to rule it out [4, 19].

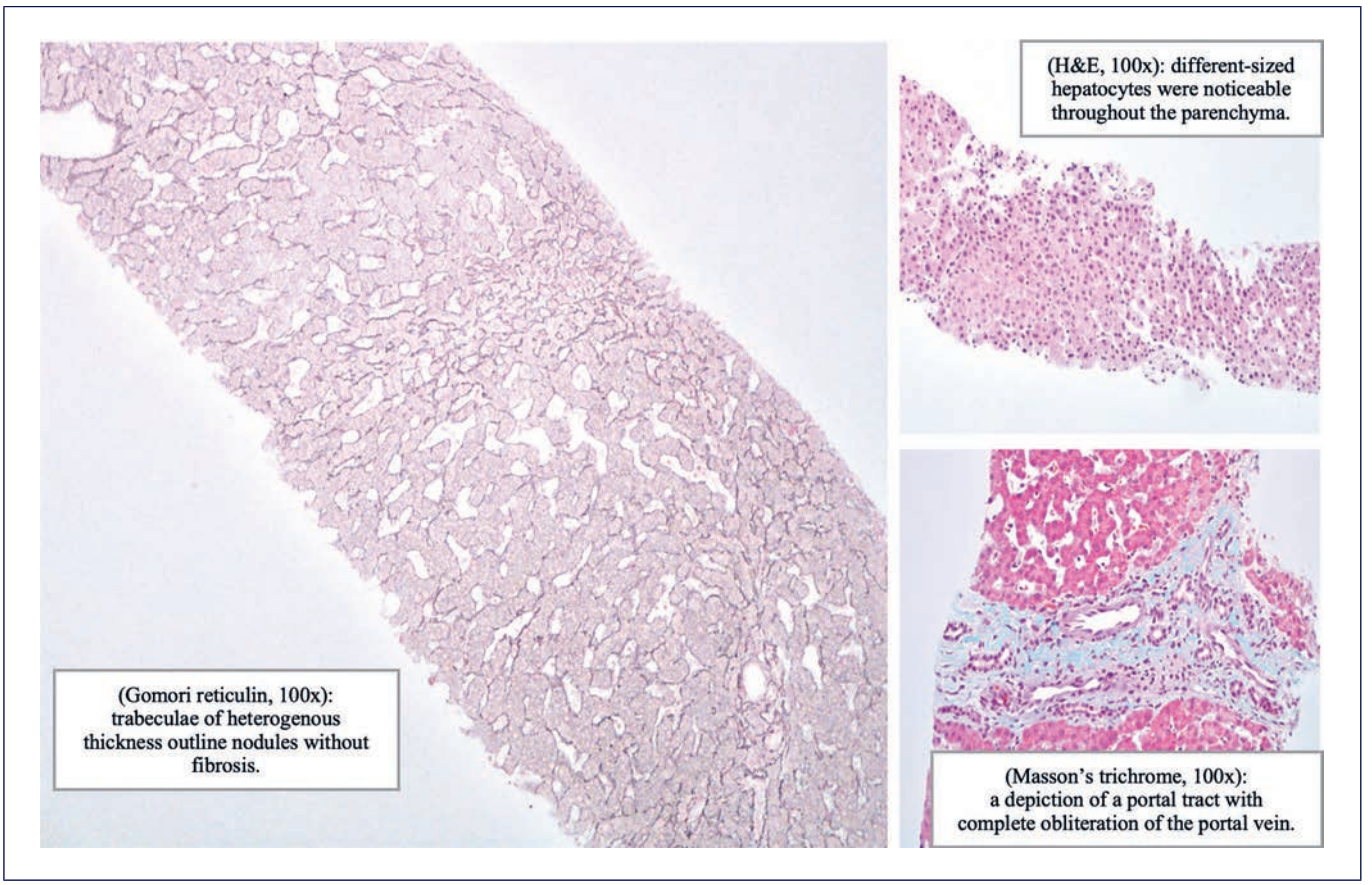

Fig. 4. Liver histological features suggesting PSVD.

Patients with PSVD and PHT are usually asymptomatic until they develop complications. Thrombocytopenia is common and transaminases, alkaline phosphatase and gamma-glutamyltransferase are normal/slightly elevated, but hepatocellular function is relatively preserved (normal serum albumin and bilirubin) [4, 19].

Gastrointestinal bleeding secondary to ruptured varices is a presenting symptom in 20–40% [4, 5, 19]. Esophageal varices are frequently large and gastric varices are more common than in cirrhosis [18]. In our patient, the varices were in the proximal esophagus, a vascular territory less influenced by PHT, raising the possibility of downhill varices. Although the ultrasound showed an irregular liver surface, hyperechoic walls of the fibrovascular axes and splenomegaly (compatible with PSVD), the IVC, and hepatic veins ectasia suggested a cardiovascular disorder. Furthermore, the patient had peripheral leg edema without ascites and the echocardiogram revealed significant cardiac valve and cavity abnormalities and severe PAH. In this case, the cardiopulmonary and HH study and TJLB were essential in confirming both PSVD and PAH.

The risk factors linking PSVD and PoPH are unknown [4], and few cases have been reported. PoPH has a multifactorial pathogenesis (genetic predisposition; pulmonary vascular wall shear stress; dysregulation of vasoactive, proliferative, angiogenic, and inflammatory mediators) [10, 11]. Patients may be asymptomatic but often present with exertional dyspnoea and may have clinical signs of right heart failure when moderate to severe disease develops [22]. In this case, the patient presented with peripheral edema. It is unclear if the level of portal hypertension is correlated with the severity of PoPH [23]. The treatment includes general measures, such as diuretics, which can reduce volume overload, and specific treatment for PAH, such as endothelin receptor antagonists (caution is advised due to hepatic impairment), phosphodiesterase subtype-5 inhibitors, and prostacyclin analogues [22, 23]. Our patient was intolerant to beta-blockers, but even if this was not the case, withdrawal of beta-blocker therapy (in the context of

esophageal varices) may help to increase cardiac output and thereby help exertional dyspnoea [22, 23]. Cohort studies have demonstrated that patients with PoPH have a worse prognosis compared with patients with idiopathic PH [23].

The initial management of PSVD includes treatment of underlying conditions. Complications of PHT should be treated according to cirrhosis recommendations. Patients should be screened regularly for varices and adequate prophylaxis of variceal bleeding with endoscopic band ligation/beta-blockers should be implemented. The indications for transjugular intrahepatic portosystemic shunts and transplantation are the same as for cirrhosis [5, 7].

PVT, a frequent complication (13–45%) during follow-up [7] (increased incidence if history of bleeding and HIV infection) [4], is an indicator of worse prognosis [5]. Anticoagulation is reserved for prothrombotic disorders or PVT [4, 5, 7].

Long-term outcome in PSVD is better than in cirrhosis, given the relatively preserved hepatocellular function [4, 7]. Despite higher frequency of variceal bleeding, mortality is lower than in cirrhosis [4]. In conclusion, this case illustrates the uncommonly reported association between PSVD and PoPH and the importance cardiopulmonary and HH study with TJLB to confirm both.

Acknowledgment

There were no sources of funding or financial disclosures for this manuscript.

Statement of Ethics

The authors declare that all ethical procedures and standards were followed. The patient gave consent to the publication of the case report and accompanying images. Ethical approval was not needed according to local laws.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors do not have any financial disclosures to report.

Author Contributions

All authors fulfilled criteria of ICMJE for authorship: acquisition, analysis, or interpretation of data for the work; drafting the work or 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.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2025;32:61–66
DOI: 10.1159/000539226

Received: January 26, 2024
Accepted: April 29, 2024
Published online: June 18, 2024

Navigating Challenges in a Case of Unusual Hepatic and Pulmonar Sarcoidosis: A Comprehensive Clinical Journey

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Keywords
Gastrointestinal sarcoidosis · Liver granuloma · Hepatic sarcoidosis · Pulmonar sarcoidosis

Abstract
Introduction: Sarcoidosis, a systemic granulomatous disorder with uncertain etiology, commonly involves the lungs and, to a lesser extent, the liver. ***Case Presentation:*** A previously healthy 35-year-old Congolese female was admitted with a 7-month history of jaundice, itching, and weight loss. Despite markedly mixed hepatitis of a cholestatic pattern of liver injury, liver function tests remained normal in admission laboratory work. Enlarged ethiological study was negative for infections, autoimmunity, heavy metal poisoning, and metabolic diseases. Imaging aligned with compatible biopsy histology led to the diagnosis of hepatic and pulmonary sarcoidosis with vanishing bile duct syndrome. Despite initial treatment with ursodeoxycholic acid and corticosteroid therapy, the patient exhibited an unexpected exacerbation of liver enzymes, prompting a careful consideration of second-line interventions. Following discussion with a tertiary center and a comprehensive review of the literature, it was determined not to intensify therapy due to an inadequate response. Recognizing the persistent challenge of managing advanced cases and the potential progressive course of the disease, the patient was referred to a tertiary transplant center. Currently, she is under outpatient follow-up, clinical and analytically stable with no targeted therapy. ***Conclusion:*** This case report details a rare presentation of hepatic sarcoidosis with an unusual laboratory pattern, emphasizing diagnostic and management challenges in recognizing atypical presentations of hepatic sarcoidosis. The complexity of managing advanced cases warrants a multidisciplinary approach and the limited literature on this subject emphasizes the urgency for a more comprehensive understanding of sarcoidosis to improve diagnostic accuracy and refine therapeutic approaches.

Resolução de desafios num caso atípico de sarcoidose hepática e pulmonar

Palavras Chave
Sarcoidose gastrointestinal · Granuloma hepático · Sarcoidose hepática · Sarcoidose pulmonar

Resumo
Introdução: A sarcoidose é uma doença granulomatosa sistémica, de etiologia não totalmente esclarecida, que afeta frequentemente os pulmões e, menos comumente,

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o fígado. ***Caso clínico:*** Mulher de 35 anos, Congolesa, previamente saudável, admitida por história de icterícia e prurido com 7 meses de evolução. Analiticamente com hepatite de padrão colestático, sem alteração das provas de função hepática. Estudo etiológico alargado negativo para infeções, doenças de autoimunidade, intoxicação por metais pesados e doenças metabólicas. Os achados imagiológicos, em conjunto com histologia de biópsia hepática, o diagnóstico de sarcoidose hepática e pulmonar associada a *vanishing bile duct syndrome* foi assumido. Realizado *trial* inicial de corticoterapia em associação com ácido ursodesoxicólico, com agravamento das enzimas hepáticas. Após revisão da literatura e discussão com centro hospitalar terciário, optou-se por não escalar terapêutica. Reconhecendo provável otimização terapêutica difícil e curso progressivo da doença, a doente foi encaminhada para um centro terciário de transplantação hepática. Atualmente, a doente mantém seguimento em consulta, sem terapêutica dirigida, estável do ponto de vista clínico e analítico. ***Conclusão:*** Os autores apresentam um caso raro de sarcoidose hepática com um padrão laboratorial incomum, enfatizando os desafios diagnósticos e terapêuticos nas apresentações atípicas desta doença. A complexidade destes quadros clínicos avançados requer uma abordagem clínica multidisciplinar. A paucidade de literatura atual enfatiza a necessidade de uma melhor compreensão da sarcoidose, para aprimorar o diagnóstico e a abordagem terapêutica nestes doentes.

Introduction

Sarcoidosis is a systemic condition characterized by the presence of noncaseating granulomas, and its exact cause remains unknown. Among the various organs it can affect, the liver stands out as one of the most commonly involved [1, 2].

The clinical presentation of hepatic involvement in sarcoidosis can exhibit a broad spectrum, ranging from asymptomatic cases to severe complications and cirrhosis, potentially necessitating liver transplantation. In hepatic sarcoidosis, the majority of patients display mild cholestasis. Elevation in AST and ALT are lesson common.

The authors present a case of Hepatic Sarcoidosis (HS) with an unusual laboratory pattern, characterized by a pronounced elevation on liver enzymes. This case sheds light on the intricate challenges associated with diagnosis and management.

Case Presentation

A previously healthy 35-year-old Congolese female was admitted to the Gastroenterology ward with a 7-month history of progressive jaundice and pruritus. Seven months prior, she had sought emergency care in Congo due to sudden dyspnea, vomiting, and decreased visual acuity, suspected to be related to poisoning. During her hospital stay, she developed generalized mucocutaneous jaundice and abdominal pain. She denied the use of medication, herbal supplements, alcohol or recreational drugs, prior blood transfusions and her family history was unremarkable. Following an inconclusive initial study, she was discharged on cholestyramine and a statin due to severe hypercholesterolemia. Over the next 7 months, she experienced a 15 kg weight loss (21% of the previous body weight), hair loss and worsening jaundice and pruritus, for which she sought medical care at our institution. Notably, upon presentation, she exhibited neither vomiting nor reported any visual or respiratory symptoms.

Upon physical examination, she exhibited generalized mucocutaneous jaundice and multiple yellowish scaly patches, primarily around the eyelids, consistent with xanthomas. No chronic liver-related signs, ascites, splenomegaly, or other relevant findings were noted.

Admission laboratory work revealed a cholestatic pattern of liver injury, with elevated total and direct bilirubin levels (16.4 mg/dL and 13.1 mg/dL, respectively), gamma-glutamyl-transpeptidase (GGT: 481 U/L), and alkaline phosphatase (ALP: 1,093 U/L). Liver transaminases were also elevated, 3–4 times the upper limit of normal (aspartate aminotransferase [AST] 141 U/L, alanine transaminase [ALT] 179 U/L). These abnormalities were associated with low 25-hydroxyvitamin D (7 U/L – normal range: 30–100 U/L) and severe hypercholesterolemia (total cholesterol 735 mg/dL, high-density lipoprotein 165 mg/dL, low-density-lipoprotein 55 mg/dL, triglycerides 299 mg/dL). Notably, liver function tests were within the normal range.

Abdominal ultrasound, contrasted tomography, and magnetic resonance cholangiopancreatography revealed mild hepatomegaly with a homogeneous liver and no other significant findings. Comprehensive study results were negative for infections, autoimmunity, heavy metal poisoning, metabolic diseases, and plasma cell dyscrasia (shown in Table 1). Despite the absence of respiratory symptoms, angiotensin-converting enzyme was elevated (200.7 U/L – normal range: 20–70 U/L). In this context, a chest radiological study was performed, revealing mediastinal and peribronchial adenopathies and a diffuse interstitial densification pattern in lung bases on computed tomography (shown in Fig. 1). Additionally, bronchoscopy identified whitish micronodules on the left lateral wall of the trachea and left main bronchus, with biopsies confirming non-caseating epithelioid granulomas. Immunophenotyping of bronchoalveolar lavage showed a $CD4^+/CD8^+$ lymphocyte ratio greater than 3.5. A liver biopsy was then performed (shown in Fig. 2), revealing multiple epithelioid granulomas located periportally and in the lobular areas, without necrosis. The histochemical study showed no evidence of microorganisms, including acid-fast bacilli (Ziehl-Nielsen) or fungal structures (PAS and

Table 1. Comprehensive etiological study

Hepatotropic vírus (HAV; HBV, HCV, HEV), HIV 1 and 2; CMV; EBV; HSV serologies	Negative
Serum iron; ferritin; TIBC; transferrin	Normal range
Microbiologic study (IGRA, blood, and stool cultures)	Negative
IgA; IgG; IgM; IgG4	Normal range
Alpha-1 antitrypsin	Normal range
ANCA; ANA; AMA; ASMA; anti-PR3; anti-MPO; anti-gp210; anti-sp100; anti-LKM-1; anti-F-actin; anti-LC1; anti-SLA; anti-TGA	Negative
Serum ceruloplasmin; Cu^{2+} (urine 24 h); Cu^{2+} (biological samples)	Normal range
Heavy metal measurement (zinc, mercury, arsenic, lead)	Negative

ANCA, anti-neutrophil cytoplasm antibodies; ANA, antinuclear antibody; AMA, antimitochondrial antibodies; anti-LC1, antibodies to liver cytosol antigen type 1; anti-LKM-1, anti-liver kidney microsomal type 1 antibody; anti-SLA, anti-soluble liver antigen antibody; ASMA, anti-smooth muscle antibody; anti-PR3, anti-proteinase 3 antineutrophil cytoplasmic antibody; anti-MPO, antibodies directed against myeloperoxidase; anti-TGA, anti-transglutaminase antibody; CMV, cytomegalovirus; Cu^{2+}, cupper; EBV, Epstein-Barr virus; HAV, Hepatitis A vírus; HBV, Hepatitis B vírus, HCV, Hepatitis C virus, HEV, Hepatitis E vírus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; Ig, immunoglobulin; IGRA, interferon-gamma release assays; TIBC, total iron-binding capacity.

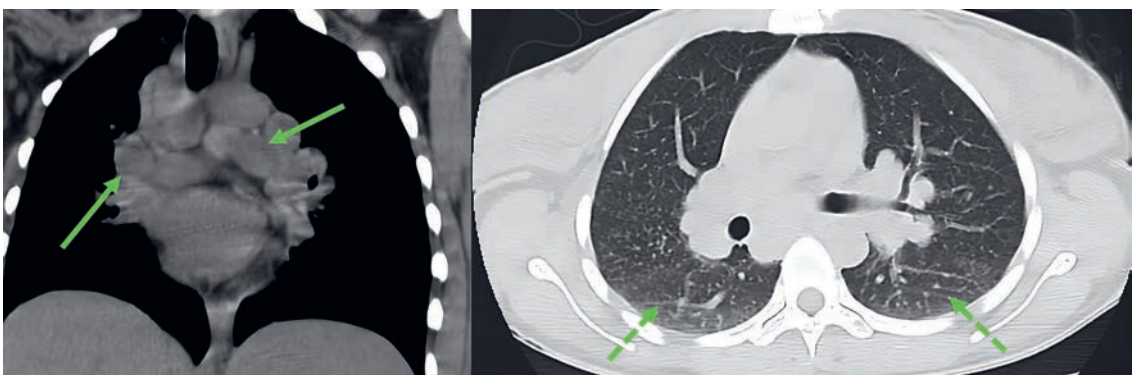

Fig. 1. Thoracic computed tomography revealing multiple mediastinal and peribronchial adenopathies and diffuse interstitial densification pattern at the lung bases (see arrows).

Grocott); there was an absence of hyaline globule deposits, hemosiderin (Perls), and copper (rhodanine). In the immunohistochemical study, rare bile ducts were observed, and periportal hepatocytes exhibited an intermediate cell phenotype, suggesting chronic cholestasis. These findings were suggestive of HS.

Mycobacterium tuberculosis work-up was negative, and the hepatic granuloma etiological study was negative for *syphilis*, *toxoplasmosis*, r*ubella*, *leptospirosis*, *Q fever*, *Schistosom*a, *brucella*, *leishmaniasis* and *histoplasmosis*. A diagnosis of hepatic and pulmonary sarcoidosis with vanishing bile duct syndrome, hypothetically related to a toxic trigger, was assumed.

Itching was managed symptomatically with escalating doses of hydroxyzine (up to 25 mg four times daily), ursodeoxycholic acid (UDCA; up to 15 mg/kg daily), cholestyramine (up to 4 g twice daily), and naltrexone (up to 50 mg daily). Targeted therapy with gradually increasing doses of prednisolone (0.5 mg/kg to 0.8 mg/kg maximum) was added to UDCA. The patient demonstrated slightly improvement in hyperbilirubinemia throughout the hospitalization, but it is noteworthy that this trend was already observed before the initiation of corticosteroid therapy. Hepatic encephalopathy was absent, and coagulation remained consistently normal. However, there was no significant improvement in ALP (809 U/L before

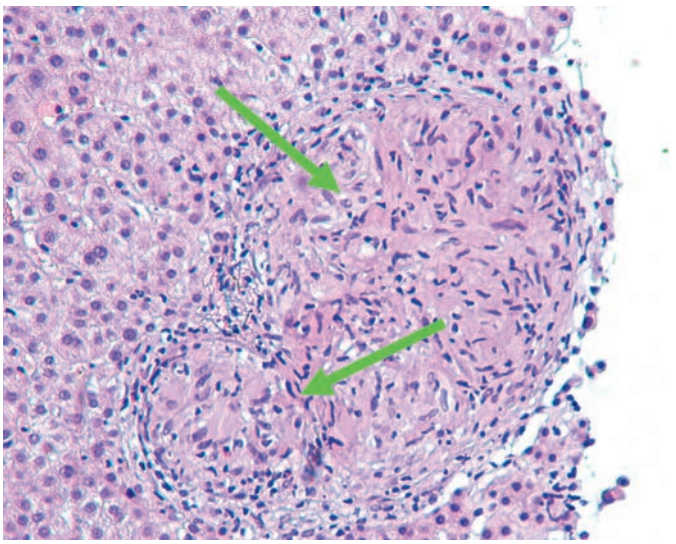

Fig. 2. Liver biopsy revealing multiple epithelioid granulomas located periportally and in the lobular areas, without necrosis (see arrows) immunohistochemical study revealing rare bile ducts, and periportal hepatocytes with an intermediate cell phenotype, suggesting chronic cholestasis.

therapy; 715 U/L on day 12 of corticosteroid), and transaminases exhibited a worsening trend during hospitalization (AST: 200 U/L before corticosteroid; 289 U/L on day 7 of corticosteroid; 236 U/L on day 14, and ALT: 232 U/L before corticosteroid and 411 U/L on day 12 of corticosteroid). Despite the lack of improvement, a decision was made on day 12 of corticosteroid therapy to escalate the dose from 25 (0.5 mg/kg) to 40 mg/day (0.8 mg/kg), resulting in a further exacerbation of transaminase levels (see online suppl. Fig. 1 at https://doi.org/10.1159/000539226). Faced with this deterioration, the corticosteroid was subsequently tapered and ultimately discontinued, leading to an improvement in the cytolysis pattern to the initial ranges. MELD score was 16 points.

Acknowledging the potential resistance to corticosteroid therapy, the medical team considered the prospect of second-line intervention. Following discussion with a tertiary center and a comprehensive review of the literature, it was determined not to intensify the current therapy. Recognizing the hypothetical progressive course of the disease, the patient was referred to a tertiary transplant center.

At 12-month outpatient follow-up, the laboratory values and pulmonary findings remain stable. In addition to UDCA, she is currently under medication for pruritus, including optimal doses of naltrexone, hydroxyzine, and cholestyramine with a satisfactory response.

Discussion

Sarcoidosis, a condition of uncertain etiology, manifests as a granulomatous inflammation primarily affecting the lungs and, to a lesser extent, the lymphoid system. Among the organs involved, the liver ranks as the third most commonly affected organ, observed in approximately 50–65% of cases [1, 2]. This systemic disorder is characterized by non-caseating epithelioid granulomas, leading to disruption of normal tissue architecture and histology [3].

The diagnosis of hepatic sarcoidosis requires a compatible biopsy histology. It is crucial to exclude alternative causes of hepatic granulomas, such as primary biliary cholangitis (PBC), infectious diseases, drug reactions, and malignancies. Notably, up to 36% of granulomas may have an unknown etiology [3, 4]. In our case, differential diagnosis was even more challenging, as endemic infectious agents of Central Africa had to be excluded.

While liver involvement is common in sarcoidosis, it frequently remains asymptomatic and undiagnosed [5]. Clinical signs and symptoms become apparent in only 5–30% of individuals with hepatic involvement [3]. Approximately 15% of patients may experience pruritus due to chronic cholestasis, and abdominal pain has been reported in the same proportion [6]. Jaundice is rare, occurring in less than 5%, while fatigue is a common symptom in hepatic sarcoidosis [6, 7].

Despite being mostly benign, hepatic sarcoidosis can lead to severe complications, including severe cholestatic jaundice, portal hypertension, Budd-Chiari syndrome and cirrhosis, ultimately progressing to end-stage liver disease [5]. Abnormalities in liver tests are observed in 20–40% of cases, typically manifesting as a cholestatic pattern [8]. Elevated ALP, GGT, bilirubin (usually <5 mg/L), and slightly increased aminotransferase levels are the typical laboratory findings [8]. Elevations in AST and ALT are less common, generally remaining less than twice the upper normal limits and less severe than ALP and GGT elevations [9]. In our patient, however, a departure from the conventional pattern was observed, with a pronounced elevation of AST and ALT that exceeded the commonly observed levels in hepatic sarcoidosis. This unusual laboratory profile accentuates the heterogeneity of hepatic sarcoidosis presentations. Notably, in our case, the diagnosis was corroborated by pulmonary findings.

Hepatic sarcoidosis is distinguishable from other granulomatous disorders by the location and distribution of granulomas [10]. In sarcoidosis, the classic granuloma is predominantly situated in the portal triads, characterized by a cluster of large epithelioid cells, often accompanied by multinucleated giant cells [11]. It is worth noting that chronic intrahepatic sarcoidosis can present in a manner that mimics PBC and primary sclerosing cholangitis, and these conditions can coexist. The chronic intrahepatic cholestasis observed in sarcoidosis appears to result from progressive destruction of the bile ducts by portal and

periportal granulomas. This differs from PBC and primary sclerosing cholangitis, where nonsuppurative bile duct destruction is responsible for cholestasis, and the granulomas in PBC are secondary to duct damage [3]. Histology also plays a role in differentiating between liver sarcoidosis and drug-induced liver injury (DILI). In DILI, granulomatous hepatitis is characterized by small intralobular granulomas with periportal inflammation [12].

Data for the management of liver sarcoidosis are primarily derived from small trials and case reports. Treatment is warranted in patients with symptomatic liver disease, cholestasis, or those at risk for hepatic complications [13].

Glucocorticoids are classically administered as first-line therapy, but large controlled studies conducted to date do not support the efficacy and long-term benefits of glucocorticoids and other immunosuppressive agents [14, 15]. While steroid treatment can effectively alleviate clinical symptoms, lower liver enzyme levels, and reduce hepatomegaly, such interventions may not alter the natural course of the disease [9, 16, 17]. Notably, although a majority of patients exhibited biochemical improvement with corticosteroid therapy, with some cohorts reporting normalization of ALP and significant reduction in transaminases in almost 50% of cases, Kennedy et al. [16, 17] found that 12.5% showed no biochemical response and 8% (3/24) progressed to cirrhosis despite biochemical. In our case, it is noteworthy that, to the best of our knowledge, is the first case documented in the literature where the patient experienced an unexpected worsening of transaminase levels and ALP, highlighting the uncertainties about the optimal management of hepatic sarcoidosis, particularly in the setting of an unusual biochemical profile.

Another first-line option described in the literature for hepatic sarcoidosis is UDCA. Data demonstrate improvements in liver tests with the use of UDCA, although there is currently no evidence supporting its impact on long-term prognosis [7]. In contrast to the findings in a small study where UDCA demonstrated superiority to prednisone in ameliorating cytolysis syndrome, pruritus, and fatigue [18], such clear benefits were not evident in our scenario. The UDCA safety profile was also taken into account.

Second- and third-line treatments should be reserved for cases where there is a deterioration in the disease course, taking into consideration the potential hepatotoxicity and side effects. In our case, the patient has achieved a laboratory plateau, influencing our decision to watch-and-wait. Also, pruritus, the most severe complaint, has gradually receded. Despite the reported success of medications such as cyclosporine, cyclophosphamide, azathioprine, methotrexate, thalidomide, pentoxifylline, and infliximab in other cases, the limited supporting evidence regarding their efficacy and safety has led us to uphold the current treatment strategy [7, 17].

In spite of therapeutic interventions, a considerable number of patients with sarcoidosis progress to a chronic and progressive form, with 10–20% experiencing long-term complications and a mortality rate estimated at 6–7% [19]. Notably, the challenges persist even with advanced treatments, prompting consideration of liver transplantation as last resort. Posttransplant survival rates for HS patients, with 1-year and 5-year survival rates at 78% and 61%, respectively, are less favorable compared to other cholestatic liver diseases [20].

This case serves as a poignant reminder of the intricate nature of sarcoidosis and its treatment. The rarity of published data underscores the pressing need for a more comprehensive understanding of sarcoidosis to enhance diagnostic accuracy and refine therapeutic approaches.

Statement of Ethics

Ethical approval was not required for this study due to the retrospective design of the study, in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The project was subjected to the standards of good clinical practice and always complied with the ethical precepts of the Helsinki Declaration.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

André Ruge Gonçalves wrote the manuscript. Diogo Simas, Plácido Gomes, Carina Leal, Catarina Atalaia-Martins, and Helena Vasconcelos revised the paper critically for important intellectual content. Catarina Atalaia-Martins and Carina Leal participated in patient management during hospitalization. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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GE – Portuguese Journal of Gastroenterology

Methods Article

GE Port J Gastroenterol 2025;32:67–74
DOI: 10.1159/000539455

Received: January 16, 2024
Accepted: May 16, 2024
Published online: July 24, 2024

Implementation of a Microbiological Surveillance Protocol in a Portuguese Tertiary Care Academic Endoscopy Unit

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Keywords
Microbiological surveillance · Protocol · Endoscopy · Endoscope reprocessing

Abstract

Introduction: International societies recommend microbiological surveillance of endoscopes to reduce the incidence of endoscope-associated infections, particularly for duodenoscopes. However, surveillance protocols are not internationally standardized, both regarding sample collection, processing, and culture. This study aims to provide a framework protocol encompassing the experience of a tertiary large volume endoscopy center and the microbiology laboratory for collecting and culturing of endoscope samples for microbiological surveillance. ***Methods:*** A sample collection and processing protocol was designed as a result of a cooperation between the Endoscopy Center of the Gastroenterology Department and the Microbiology Laboratory of the Department of Clinical Pathology. This protocol reflects international recommendations in this topic and the human and technological resources of the involved departments. ***Results:*** The established protocol for collecting samples varies according to the type and model of endoscope. The specimens are collected as sterile saline liquid samples, as well as swabs (with and without transport media). Together with the collection of samples from the endoscope, samples from the final rinse water as well as the water bottle are also collected. For duodenoscopes and curvilinear echoendoscopes, we perform microbiological surveillance every 3 months; for gastroscopes and colonoscopes, at least, once a year; and for specific endoscopes, such as the pediatric or dual-channel therapeutic endoscopes, enteroscopes, or radial echoendoscopes, every 6 months. ***Conclusion:*** Endoscopy units should have detailed protocols for microbiological surveillance of endoscopes. These protocols should be drawn up by a multidisciplinary team that includes endoscopy nurses, gastroenterologists, microbiologists, and the antimicrobial stewardship team, following international recommendations, adapted to each institution resources.

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Implementação de Protocolo de Vigilância Microbiológica numa Unidade Terciária de Endoscopia Portuguesa

Palavras Chave
Vigilância microscópica · Protocolo · Endoscopia · Reprocessamento endoscópico

Resumo
Introdução: As sociedades científicas internacionais recomendam a vigilância microbiológica para reduzir a incidência de infeções associadas aos endoscópios, particularmente dos duodenoscópios. Contudo, não existe uma padronização internacional dos protocolos de vigilância microbiológica, tanto no que diz respeito à colheita, quanto à cultura e análise das amostras. Este estudo tem como objetivo estabelecer um protocolo com base na experiência de um centro terciário de endoscopia digestiva e do laboratório de microbiologia para a colheita e cultura de amostras de endoscópios para vigilância microbiológica. ***Métodos:*** Foi elaborado um protocolo de colheita e processamento de amostras como resultado da cooperação entre a Unidade de Endoscopia e o Laboratório de Microbiologia do Departamento de Patologia Clínica de um hospital terciário. Este protocolo reflete as recomendações internacionais nesta área, assim como os recursos humanos e tecnológicos necessários à sua implementação. ***Resultados:*** O protocolo estabelecido para a colheita de amostras varia de acordo com o tipo e modelo do endoscópio. São colhidas amostras líquidas em meio salino estéril, bem como zaragatoas (com e sem meio de transporte). Simultaneamente, são colhidas amostras da água do enxaguamento final e do copo de água. Para duodenoscópios e ecoendoscópios curvilíneos, foi realizada uma vigilância trimestral; para gastroscópios e colonoscópios, essa vigilância foi realizada, pelo menos, anualmente; para endoscópios específicos, como endoscópios pediátricos ou terapêuticos de duplo canal, enteroscópios ou ecoendoscópios radiais, foi realizada uma vigilância semestral. ***Conclusão:*** As unidades de endoscopia devem estabelecer protocolos detalhados de vigilância microbiológica dos endoscópios. Estes protocolos deverão ser elaborados por uma equipa multidisciplinar que inclua enfermeiros de endoscopia digestiva, gastroenterologistas, microbiologistas e a equipa responsável pela gestão de antimicrobianos, seguindo as recomendações internacionais, adaptadas aos recursos de cada instituição.

Introduction

Historically, endoscope-associated infection was deemed to be very rare and the majority of documented cases were believed to be caused by noncompliance with guidelines [1, 2]. Recently, infection risk associated with contaminated, patient-ready flexible endoscopes has been reappraised [3] and several outbreaks of multidrug-resistant organisms have been particularly concerning [1].

A key recommendation is from scientific societies for reducing infection transmission risk focus in the culture of patient-ready endoscopes to detect contamination with organisms of concern [1, 4]. In fact, microbiological surveillance is a tool that we can use to monitor and adapt reprocessing protocols and a quality control measure for this process [2, 5–7], which allows us to identify endoscopes with persistent contamination, despite their reprocessing [8].

Microbiological surveillance can also alert to possible defects in endoscopes and washer-disinfectors, so that endoscopy units can react at an early stage [9]. However, to implement an endoscope microbiological surveillance program, there is a need for specialized human and technical resources, both for sample collection and specimen culture and analysis [8]. Moreover, we must also consider the impact on procedure costs and environmental footprint. All these factors must be taken into account when developing microbiological surveillance protocols in endoscopy units, for them to be feasible in clinical practice.

Protocols for endoscope microbiological surveillance are established in several countries but lack standardization [4, 9]. There are significant variations in the timing and methods of sampling, the number of channels checked, the type of sampling solution used, the microbiological methods used (e.g., filtration vs. centrifugation), and the interpretation of the results [9]. The aim of this report was to summarize the critical aspects of the microbiological surveillance protocol drawn up by the Gastroenterology and the Clinical Pathology Departments in a Portuguese tertiary care academic Hospital.

Methods/Design

Microbiological Surveillance Protocol

The protocol resulted from a multidisciplinary partnership taking into account current scientific societies guidelines and the existing technical and human resources available in our hospital. Decisions were made regarding the frequency, sampling and

GE Port J Gastroenterol 2025;32:67–74
DOI: 10.1159/000539455

Table 1. Microbiological surveillance request template

Microbiological surveillance				
Endoscope identification	Model: Serial number:	Harvest date: ____/_____/_____ Harvest time: ____:____		
Responsible for the harvest Research to be carried out	• Bacteriological examination • Legionella research • Mycobacteria research			
Identification of samples to be sent	Liquid samples	Labeling	Sent	Results
	1. Final rinse water from the AER (100 mL) AER identification:	ESN – 1		
	2. 2A. Water container (100 mL)	ESN – 2A		
	2B. Lid tube (100 mL)	ESN – 2B		
	3. Suction, air/water, and working channel (100 mL)	ESN – 3		
	4. Elevator channel (5 mL)	ESN – 4		
	5. Auxiliary water channel (5 mL)	ESN – 5		
	Swabs			
	Z1. Swab in transport media to suction cylinder, air/water cylinder, and working channel	ESN – Z1		
	Z2. Swab in transport media to elevator mechanism/recess	ESN – Z2		
	Z3. Swab without transport media to suction cylinder, air/water cylinder, and working channel	ESN – Z3		
	Z4. Swab without transport media to elevator mechanism/recess	ESN – Z4		
Total samples sent	Liquid samples: _____ Swabs: _____			

AER, automatic endoscope reprocessor; ESN, endoscope serial number.

GE Port J Gastroenterol 2025;32:67–74
DOI: 10.1159/000539455

Table 2. Samples taken according to type and model of endoscope

	Duodenoscope	Curvilinear echoendoscope	Radial echoendoscope	Pediatric endoscope	Pediatric colonoscope	Therapeutic endoscope	Enteroscope	Gastroscope	Colonoscope
Liquid samples									
Aspiration channel	X	X	X	X	X	X	X	X	X
Air/water channel	X	X	X	X	X	X	X	X	X
Working channel	X	X	X	X	X	X	X	X	X
Elevator channel	X (only in models TJF-Q160 and TJF-145)	X	___	___	___	___	___	___	___
Auxiliary water channel	___	___	___	___	X	X	___	X (except models GIF-Q180 and GIF-Q165)	X
Balloon channel	___	___	___	___	___	___	X (Fujifilm only)	___	___
Final rinse water	X	X	X	X	X	X	X	X	X
Water bottle	X	X	X	X	X	X	X	X	X
Swabs									
Aspiration cylinder	X	X	X	X	X	X	X	X	X
Air/water cylinder	X	X	X	X	X	X	X	X	X
Working channel	X	X	X	X	X	X	X	X	X
Elevator mechanism/ recess	X	X	___	___	___	___	___	___	___
Distal end	___	___	X	X	X	X	X	X	X
Type/model of endoscope in the unit	Olympus (TJF-Q190V; TJF-Q180V; TJF-160; TJF-145)	Olympus (UCT-180), Pentax (EG-3870OUTK)	Olympus (GF-UE 190)	Olympus (GIF-H190 N; GIF-XP160)	Olympus (PCF-H190TL)	Olympus (GIF-2TH180; GIF-2T160)	Olympus (SIF-180), Fujifilm (EN-580T)	Olympus (GIF-EZ1500; GIF-1100; GIF-HQ190; GIF-H190; GIF-Q180; GIF-Q165)	Olympus (CF-EZ1500; CF-HQ1100DL; CF-H190L; CF-Q180AL)

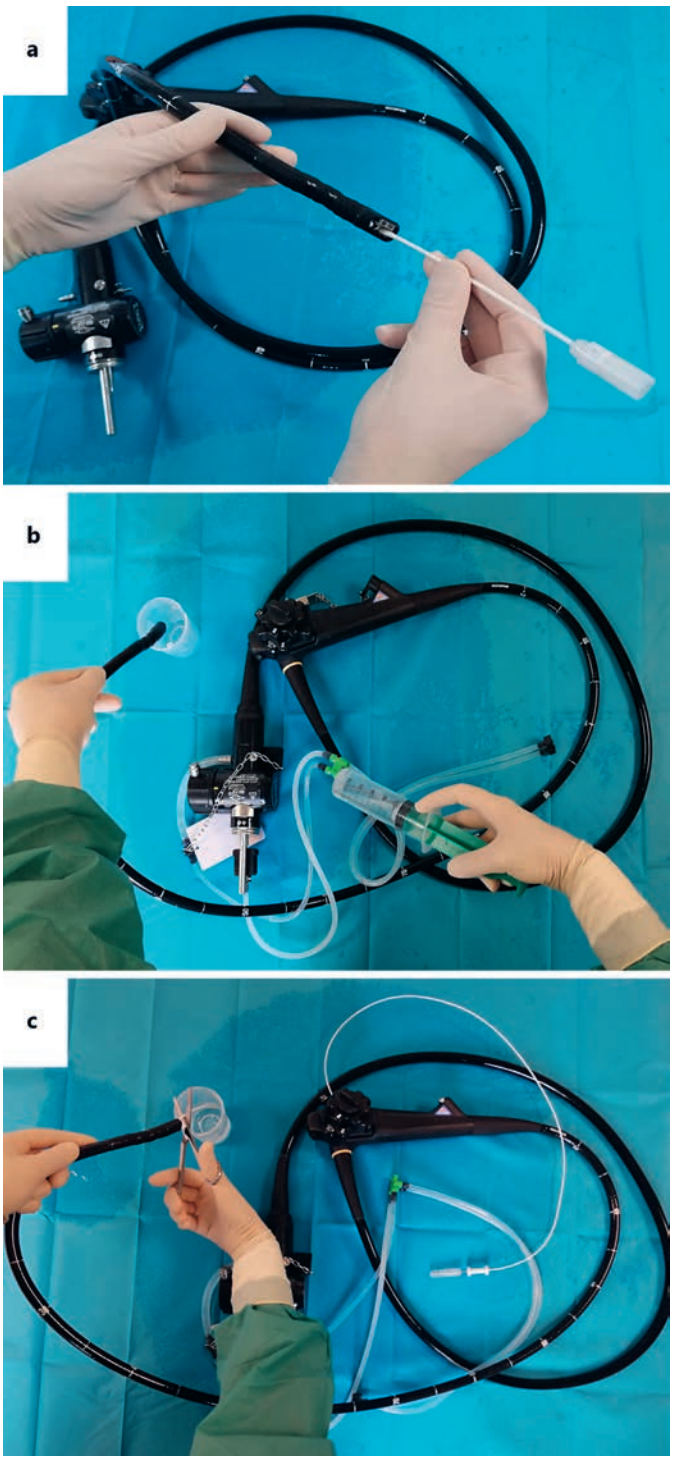

Fig. 1. Collection of microbiological samples. **a** Swab from the elevator recess from duodenoscope/echoendoscope (or from the distal end in the case of endoscopes that do not have an elevator). **b** Liquid sample from the aspiration, air/water, and working channel. **c** "Flush-brush-flush" method.

culture methods and analysis. A microbiology request form was drawn up, accounting for the specificities of these samples (Table 1).

Sample Collection

The sample collection methods depend on endoscope type and model (Table 2). The collected samples are sterile saline liquid samples, as well as swabs (with and without transport media). No neutralizing substances were used, and the samples were transported to the local laboratory within a 30 min timeframe. Liquid samples are taken from the suction, air/water and biopsy channels of the endoscope, regardless the type and model. Then, depending on the presence of other channels, additional samples are obtained, such as from the elevator channel for duodenoscopes and curvilinear echoendoscopes, as well as from the auxiliary water channel in endoscopes that include this channel (colonoscope, gastroscope, pediatric colonoscope, or therapeutic endoscope) and balloon channel in the enteroscope (depending on the endoscope manufacturer). Additionally, samples of the final rinse water and from the water bottle are also collected.

Regarding swabs, samples are collected from the suction and air/water cylinder and biopsy channel of all endoscopes. For endoscopes that include an elevator channel, an additional specimen is taken from the elevator mechanism and from the elevator recess. For other endoscope types, this is replaced by a sample from the external distal end of the endoscope. These samples are collected in duplicate swabs (with and without transport media).

For effective detection of microbial contamination in patient-ready endoscopes, an aseptic technique is used. First, a 100 mL sample of the final rinse water from the automatic endoscope reprocessor (AER) machine is taken. Then, from the water bottle used in the endoscopic procedure, two samples are taken: one directly from the water in the container (100 mL) and the other by irrigating sterile saline through the line of the tube lid (100 mL). These samples are placed in separate containers.

For endoscopes, swabs and liquid samples are collected. Swabs are soaked in sterile saline and only then, the sample is obtained from the suction aspiration cylinder, air/water cylinder, working channel, and elevator mechanism/recess in the case of duodenoscopes and linear echoendoscopes or from the distal end in the case of endoscopes that do not have an elevator mechanism (Fig. 1a). This is done for both swabs with and without transport media. The swab of the suction cylinder, air/water cylinder, and working channel is different from the swab of the elevator mechanism/recess or distal end of the endoscope, so that, in the event of a positive microbiological test, we can identify the microbiological contamination origin. For the liquid samples, 100 mL specimens of sterile saline from the suction channel, air/water channel, and working channel are taken using sterile connectors (Fig. 1b). Halfway through sample collection (after collecting 50 mL), we insert a previously sterilized brush through the suction channel and the working channel and cut the brush to be sent for analysis, together with the liquid sample, in order to improve sensitivity ("flush-brush-flush" method – Fig. 1c). The brush follows a sterilization process with ethylene oxide, as previously described by Ji et al. [10]. This sample is placed in a sterile container.

Table 3. Microbiological timetable surveillance

Microbiological frequency surveillance			
type/endoscope model	every 3 months	every 6 months	annually
Duodenoscope	X	___	___
Curvilinear echoendoscope	X	___	___
Radial echoendoscope	___	X	___
Pediatric endoscope	___	X	___
Pediatric colonoscope	___	X	___
Therapeutic endoscope	___	X	___
Enteroscope	___	X	___
Gastroscope	___	___	X
Colonoscope	___	___	X

In the case of duodenoscopes or echoendoscopes with an elevator channel, or endoscopes with an auxiliary water channel, a 5 mL sample of sterile saline is irrigated through these channels, and it is sent for culture. These samples are placed in different containers.

The sample collection protocol for the duodenoscope is reported in the online supplementary material 1 (for all online suppl. material, see https://doi.org/10.1159/000539455). For other types of endoscopes, the protocol must be altered depending on the presence of other channels, such as the auxiliary water channel or balloon channel.

Microbiology Specimen Processing

The samples are processed immediately on arrival at the laboratory. In order to improve microbial recovery, samples with an optimum volume of 100 mL, as well as all samples over 5 mL, are previously concentrated by centrifugation for 15 min at 3,000 rpm. Subsequently, the samples are inoculated into a set of culture media suitable for the growth of the microorganisms to be assessed.

For the bacteriological test, 0.1 mL of each sample is inoculated using the 3-quadrant streak method onto Blood Agar (BioMérieux, Marcy-l'Étoile, France), and incubated at 35° in a CO_2 atmosphere for 5 days. For the detection of Legionella species, 0.1 mL of each sample is inoculated using the 3-quadrant streak method onto Buffered Charcoal Yeast Extract (BCYE; Oxoid, Madrid, Spain) and Glycine Vancomycin Polymyxin Cicloheximide (GVPC; Oxoid, Madrid, Spain) media and incubated at 35° in a CO_2 atmosphere for 10 days. For the recovery of mycobacteria, 0.5 mL are inoculated into Mycobacteria Growth Indicator Tube (MGIT; Becton Dickinson, NJ, USA), with Middlebrook 7H9 broth, and incubated and monitored for 42 days using the BD BACTEC MGIT 960 system (Becton Dickinson, New Jersey, USA).

Bacteriological and Legionella testing of swab with transport medium samples is carried out by direct inoculation into the culture media and incubation conditions described above. To improve mycobacteriological recovery, the swabs without transport media for this test are previously embedded in MGIT and incubated at 35°C for 24 h, after which the MGIT is incubated under the conditions described for the liquid samples.

Frequency of Surveillance

The timing and frequency for microbiological surveillance are determined by the type of endoscope (Table 3). Endoscopes that include an elevator channel are sampled every 3 months. For specific endoscopes, such as radial echoendoscopes, pediatric endoscopes/colonoscopes and therapeutic (dual channel) endoscopes, we collect samples every 6 months and, for gastroscopes and colonoscopes, annual surveillance is performed.

Timing of Sample Collection

Due to the personnel's working hours, our protocol includes collecting samples within four to 6 h after reprocessing.

Results Report

As the microbiological control is performed under sterile conditions, any microbial growth is valued. In the presence of microbial growth, most of the species are identified using mass spectrometry on the VITEK® MS automated system (BioMérieux, Marcy-l'Étoile, France), based on MALDI-TOF (Matrix Assisted Laser Ionisation Time-of-Flight) technology. Mycobacteria are identified by molecular biology using GenoType Mycobacterium CM/AS (Hain Lifescience, Nehren, Germany), based on the PCR reaction and detection by DNA-strips reverse hybridization and an enzymatic staining reaction.

Discussion

The aim of microbiological surveillance was to ensure the quality of endoscope reprocessing, to identify deficiencies at an early stage and to provide information about possible risks [9]. The European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) provide guidance on how to

perform endoscope microbiological surveillance, namely regarding frequency, sampling, sample volume, and culture, for either manual or automated reprocessing. If reprocessing is carried out automatically, the endoscope must be analyzed at the same time as the AER and the water bottle used in the procedure, in order to identify the source of the infection, in the event of a positive microbiological control [5, 11]. The ESGE/ESGENA guidelines recommend implementing microbiological surveillance on all endoscopes [5], while the US Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the American Society for Microbiology (ASM) recommend it only for duodenoscopes [8].

The microbiological surveillance protocols used in different institutions differ in the methods of sampling, number of sampled channels, type and volume of sampling solutions and culture methods [1]. Considering the different guidelines and taking into account the resources available in our institution, we developed a protocol that could be implemented in our hospital, respecting its routines and taking into consideration sustainability issues.

In order to reduce the number of liquid samples from each endoscope, it was decided to combine certain samples in the same container, taking care not to interfere with the interpretation and analysis of the results or the corrective actions to be implemented, in the case of a positive control. Indeed, samples from different locations were combined ensuring that, in case of positive results, the following corrective measures were similar. As such, samples from the suction channel, air/water channel, and working channel were combined in the same container. Samples of additional channels, such as the elevator channel, auxiliary water channel, or balloon channel, are taken into another container, as well as samples from the final rinse water and water bottle in separate containers.

Regarding swabs, we collect samples from the suction cylinder, air/water cylinder, and working channel with the same swab and then use a second swab to sample the elevator mechanism/recess in duodenoscopes and linear echoendoscopes or in the case of other endoscopes, this is replaced by a sample from the distal end of the endoscope. It was decided to replace and not add this sample, in order not to increase the number of swabs needed from each endoscope and, once again, not to invalidate the implementation of the protocol in clinical practice. Therefore, our protocol includes collecting four swabs for each endoscope (two in transport media and two without transport media), in order to meet the laboratory capacities and reduce costs. At our endoscopy unit, we use sterile saline for irrigation through the water pump. Besides avoiding contamination, the use of sterile saline is intended to maintain an optimal environment for electric conductivity when performing polypectomy/mucosectomy. The saline vials are "single-day use"; therefore, they are discarded at the end of each shift. Thus, we opted to not include samples from these vials in our protocol. Nevertheless, for endoscopy units using reusable vials for water instillation through the water pump it would be relevant to include samples both from the vial as well as from the water itself.

For liquid sample collection, we selected the "flush-brush-flush" method. It is recommended by the CDC and was shown to be a more sensitive sampling technique in a Chinese study published in 2021 when compared with the conventional "flush method" (91.8 vs. 81.6% qualification rate) [8, 10]. No debris was found during sample collection.

With respect to sampling frequency, the recommendations are controversial, particularly concerning duodenoscopes. The ESGE/ESGENA guidelines recommend duodenoscope microbiological surveillance to be performed at least every 3 months, while, e.g., the World Gastroenterology Organization, in its recently published guideline, recommends it to be carried out monthly [5, 12]. A joint position statement by several Italian societies recommends monthly monitoring of duodenoscopes or after every sixty procedures [4].

Regarding frequency, and in order to be able to include all endoscopes in the surveillance program, we have chosen to follow the European recommendations, taking samples every 3 months from duodenoscopes and curvilinear echoendoscopes, and, at least, annually for other endoscope types, with specific endoscopes such as pediatric, therapeutic, enteroscopes, and radial echoendoscopes being sampled twice a year. With this frequency, we can conciliate the microbiology laboratory response with the inclusion of all endoscopes in use at our unit in the surveillance program, with the possibility for repeating sampling on endoscopes with positive results, after the implementation of corrective measures.

Our protocol has some limitations. First, our protocol focuses on the timing for sample collection. The Italian multisociety position paper recommends sampling to be performed at least 6 to 12 h after storage, to increase the likelihood of biofilm growth [4]. However, at our institution, we have only been able to collect samples within four to 6 h after reprocessing, due to the working hours of the departments and the professionals involved in sample collection, culture, and analysis. This fact can significantly impact on culture results, and in future studies we plan to

evaluate this variable also taking into account endoscope storage conditions. With respect to the eluent solution used for sample collection, the fact that we do not use a buffered solution may be pointed as another limitation that can impact microorganism recovery and viability. In order to overcome this limitation, the samples are sent to the laboratory immediately after collection because it is known that delays in sample delivery and culturing can negatively interfere with the results.

In conclusion, endoscopy units should have detailed protocols for microbiological surveillance of their endoscopes as this is considered a structural quality indicator, to ensure high reprocessing quality [7]. These protocols should be drawn up by a multidisciplinary team that includes endoscopy nurses, gastroenterologists, microbiologists, and the antimicrobial stewardship team, guided by scientific society's recommendations but adapted to each institution resources. The endoscopy units must establish a strong partnership with the microbiology laboratory and endoscope manufacturers, so that these protocols can be applied in clinical practice to guarantee patient safety.

Statement of Ethics

Not applicable due to the procedural character of the study, not involving patients.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

Funding Sources

No funding sources to be declared.

Author Contributions

C.M.: protocol design, sample collection, bibliographic review, drafting of the manuscript, and critical revision of the manuscript; J.L.: protocol design, sample collection, bibliographic review, and critical revision of the manuscript; T.R.: drafting of the manuscript and critical revision of the manuscript; M.H.G.: microbiological analyses and reports and critical revision of the manuscript; N.G., L.S., A.C., and C.O.: sample collection and critical revision of the manuscript; F.V.B.: protocol design and critical revision of the manuscript; M.M.R.: protocol design, microbiological analyses and critical revision of the manuscript; G.M.: critical revision of the manuscript; S.B.: protocol design, critical revision of the manuscript, and final approval of the manuscript.

Data Availability Statement

Data will be made available upon reasonable request.

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