Portuguese Journal of Gastroenterology

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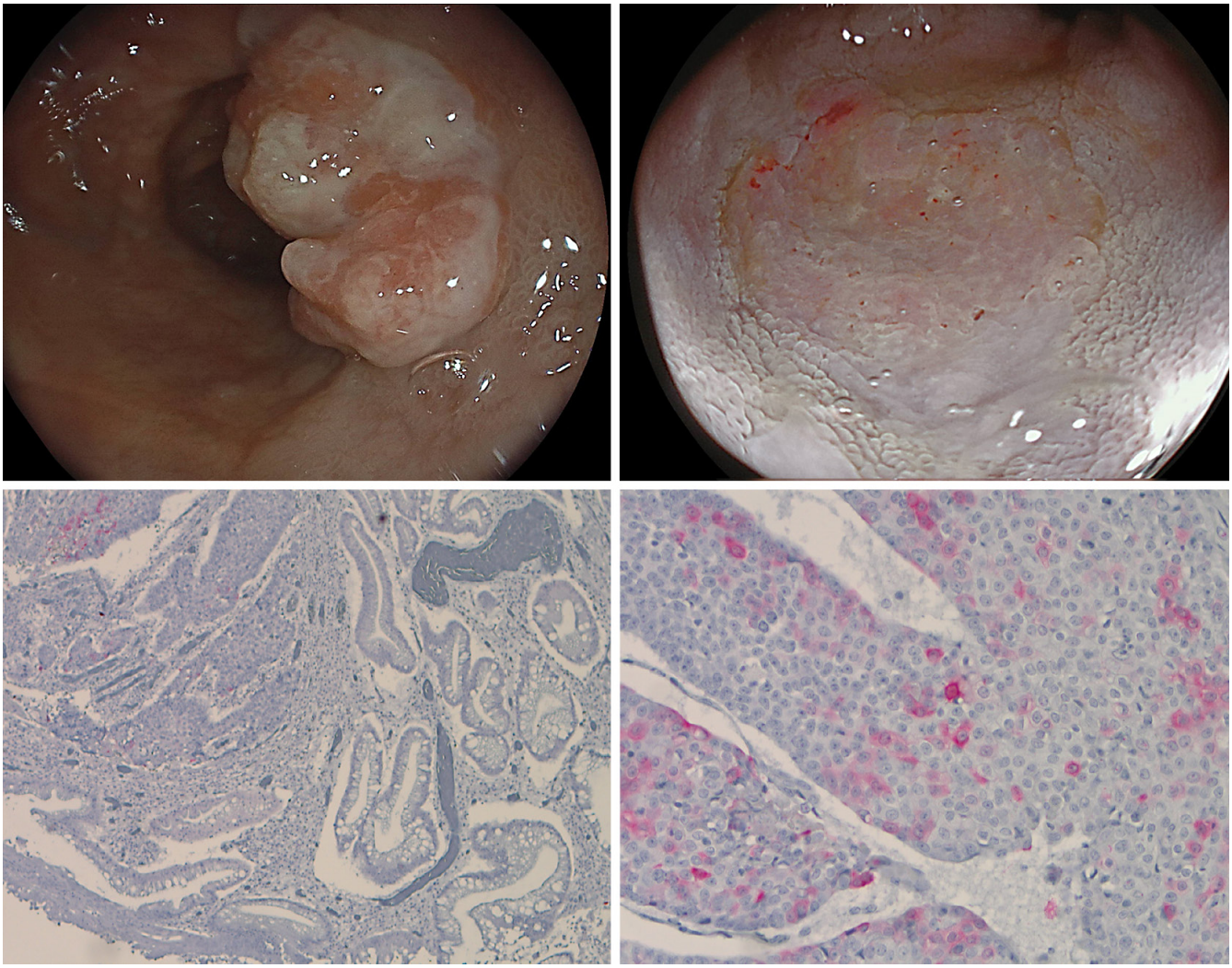

Highlights in this issue:

Review article: Familial and Hereditary Gastric Cancer Risk

Research article: Side versus forward viewing endoscope for ECRP in Billroth II

Research articles: Clinical and Economical Impact of Inflammatory Bowel Diseases and of Short Bowel Syndrome

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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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Cover illustration
A squamous cell carcinoma and an adenocarcinoma arising in one Barrett's segment.
From Zimmer et al., pp. 316–318.

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Review Article

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Gastric Cancer: A Practical Review on Management of Individuals with Hereditary or Familial Risk for Gastric Cancer

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Keywords
Gastric cancer · High-risk population · Sporadic cancer risk · Familial cancer risk

Abstract
Gastric adenocarcinoma is one of the most frequent and deadly cancers worldwide. However, its incidence is variable, being higher in eastern countries where screening the general population is recommended. On the other hand, in low to intermediate-risk countries, screening the general population may not be cost-effective, and therefore, it is necessary to be aware of high-risk populations that may benefit from adequate screening and surveillance. It is not always easy to identify these individuals, leading to a late diagnosis of gastric adenocarcinoma. In this review, the authors intend to summarize the data required to identify the population at risk of sporadic or familial gastric adenocarcinoma and the beginning of screening and its surveillance, with the final aim of increasing early detection of gastric adenocarcinoma and decreasing morbimortality. The authors highlight the importance to be aware of the several hereditary syndromes and MAPS recommendations and apply screen and surveillance protocols. The high-risk syndromes to gastric adenocarcinoma are gastric adenocarcinoma and proximal polyposis of the stomach, hereditary diffuse gastric cancer, and familial intestinal gastric cancer.

Cancro gástrico: uma revisão prática na abordagem de indivíduos em risco de cancro gástrico hereditário ou familiar

Palavras Chave
Cancro gástrico · População de alto risco · Risco cancro esporádico · Risco de cancro familiar

Resumo
O adenocarcinoma gástrico é um dos cancros mais frequentes e mortais em todo o mundo. No entanto, a sua incidência é variável, sendo maior nos países orientais, onde o rastreio da população geral está recomendado. Por outro lado, nos países de risco baixo a intermediário, o rastreio da população geral pode não ser custo-efetivo e, portanto, é necessário conhecer quais são as populações de alto risco que podem beneficiar de rastreio e

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vigilância adequados. Porém, nem sempre é fácil identificar esses indivíduos levando a um diagnóstico tardio de adenocarcinoma gástrico. Nesta revisão, os autores pretendem resumir a informação necessária à identificação da população em risco de adenocarcinoma gástrico esporádico ou familiar e o início do rastreio e sua vigilância, com o objetivo final de otimizar a deteção precoce do adenocarcinoma gástrico e diminuir a morbimortalidade. Os autores salientam a importância de conhecer as diversas síndromes hereditárias e recomendações MAPS e aplicar protocolos de rastreio e vigilância. As síndromes de maior risco para adenocarcinoma gástrico são GAPPS, HDGC e FIGC.

Introduction

Gastric adenocarcinoma is the fifth most common and fourth most mortal cancer worldwide [1]. Its high mortality can be explained by the absence of screening and early-diagnosis strategies, resulting in the diagnosis of gastric cancer (GC) at an advanced stage.

Currently, screening for gastric adenocarcinoma in the opposite, in low to intermediate-risk countries (i.e., Western countries), is only recommended for high-risk groups (e.g., extensive preneoplastic conditions, history of GC in a first-degree relative, genetic syndromes associated with GC risk) [2]. Classically, it is usual to aggregate Western countries in GC risk, but it is important to clarify that it differs between the countries, and so it is essential to adjust screening and/or clinical investigation accordingly to the specific country's risk (shown in Fig. 1).

Most cases of gastric adenocarcinoma are sporadic, with a minority of cases (10%) occurring in a context of familial aggregation or heritable syndromes [3]. GC can be classified into several subtypes depending on the classification, being the mostly used Lauren or WHO classifications. Lauren's classification was established in 1965 and specifically subdivided the gastric adenocarcinoma into intestinal (53%), diffuse (33%), or indeterminate histologic type (14%) [4]. The indeterminate type may correspond to other subtypes according to WHO classification. Despite its simplicity, Lauren's classification is useful to guide the investigation of affected or familial individuals with gastric adenocarcinoma.

Sporadic adenocarcinoma is generally of the intestinal type, associated with *Helicobacter pylori* infection, and corresponds to the last stage of the Correa cascade, which represents the progression of precancerous conditions, although family aggregation exists also in this GC subtype. On the other hand, diffuse adenocarcinoma is less frequent and, as it may be associated with a genetic disorder (hereditary diffuse gastric cancer; HDGC), this condition should be carefully evaluated.

High-risk population includes individuals with heritable syndromes associated with GC and individuals with risk factors for sporadic GC (mainly extensive precancerous conditions associated with *H. pylori*). The lack of gastric adenocarcinoma screening in the general population in low to intermediate-risk countries is associated with the lack of firm evidence of cost-effectiveness, although it is important to identify individuals with a higher risk of GC that may benefit from screening/surveillance.

The scarcity of literature on this topic led to this review. We intend to summarize (i) diagnostic criteria of heritable syndromes associated to GC, (ii) risk factors for sporadic GC, (iii) timing to start screening, and (iv) surveillance of high-risk population. Methods of detection, surveillance, and prophylactic or therapeutic interventions will not be discussed in this review.

Methods

A narrative non-systematic review was performed based on an electronic search through the medical literature using PubMed. The keywords "Heritable Gastric Cancer," "Familial gastric cancer," "Sporadic cancer," "Lynch syndrome," "Li-Fraumeni syndrome," "Gastrointestinal polyposis syndromes," "Gastric Adenocarcinoma and Proximal Polyposis of the Stomach," "Hereditary diffuse gastric cancer," and "Familial intestinal gastric cancer" were used. No publication date restrictions were imposed, but guidelines and systematic reviews in the past 10 years from gastroenterology, endoscopy, oncology, genetics, and histopathology were preferred. When more than one guideline concerning the same subject was available, the most updated one was selected. Only articles published in English were considered. The majority of articles refer to European or North American studies. However, Asian articles were punctually included if relevant to the manuscript.

Hereditary Cancer

Familial aggregation of gastric adenocarcinoma can occur in up to 10% of the patients, but a deleterious genetic variant is only identifiable in about 1–3% of cases [3]. Familial/hereditary GC may be part of a genetic syndrome involving multiple organs or be exclusive to the stomach.

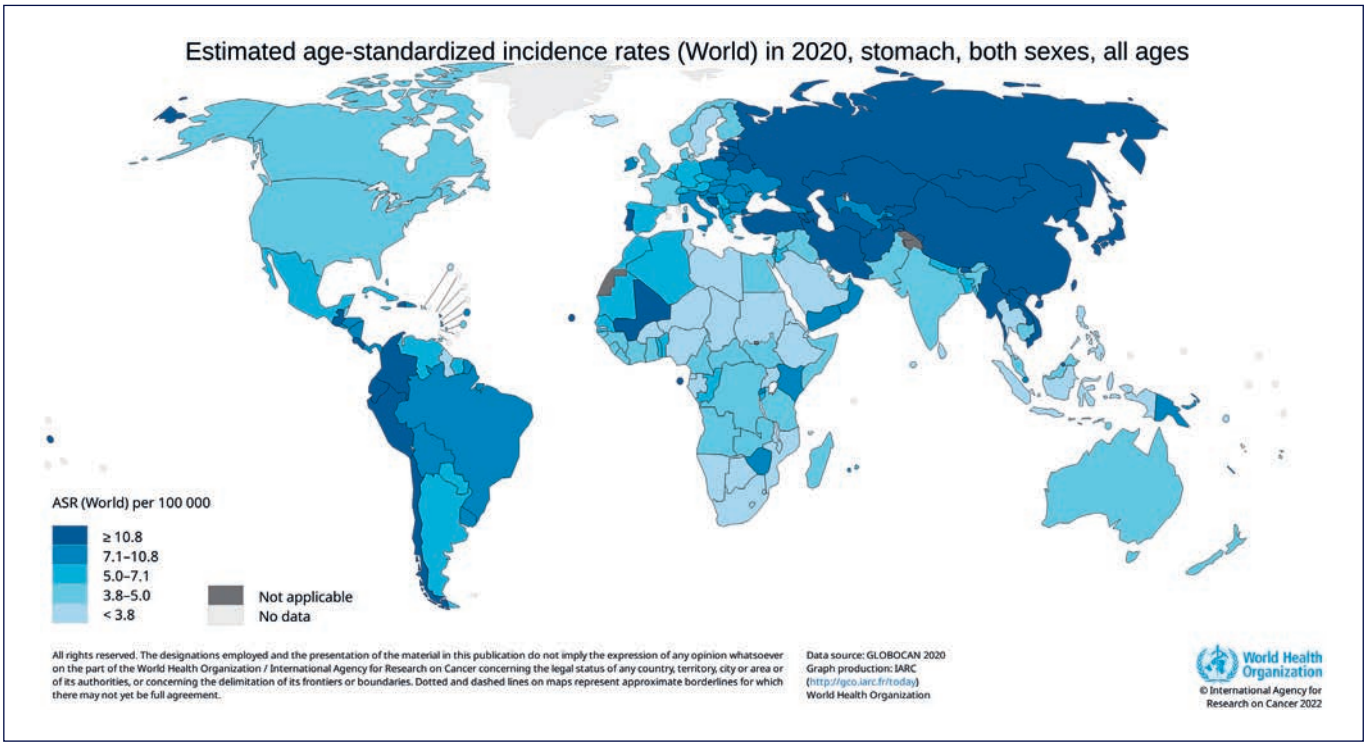

Fig. 1. Global incidence rate of GC in 2020.

Familial aggregation is defined through a high prevalence of GC among first-degree relatives (siblings, parents, and children). Indeed, the existence of a first-degree relative with GC confers an increased risk (OR 2–10) of the disease [5].

However, it is important to clarify that familial GC aggregation may be linked to shared environmental and lifestyle factors, thereafter increasing the incidence of cancer in a genetically susceptible family [6]. In fact, first-degree relatives have a higher prevalence of *H. pylori* infection, atrophy, and intestinal metaplasia [7]. This finding validates the recommendation to perform esophagogastroduodenoscopy (EGD) every 3 years in individuals with precancerous conditions (non-extensive) and a family history (1st degree relatives) of GC, and every 1–2 years in patients with a family history of GC and extensive precancerous conditions according to MAPS II [8]. On the other hand, the risk of GC in second-degree relatives is lower [6] and, therefore, there is no indication for screening these individuals [8].

In the initial approach of a familial aggregation of gastric adenocarcinoma, certain topics must be assessed to recognize patients at high risk of hereditary gastric adenocarcinoma: histological type, presence of gastrointestinal polyposis and extra-gastric neoplasms, a detailed family tree of affected family members, and any known inherited mutation/disease in the family (shown in Fig. 2). These elements are essential in the evaluation of the criteria defined to motivate further risk assessment of heritable GC (shown in Fig. 3) [9]. Briefly, these include two or more relatives with the same cancer; cancer in at least two generations; cancer diagnosed at a young age; multiple neoplasia in the same individual; a family with an unusual cancer pattern; and cancer associated with a known heritable syndrome.

Hereditary causes are rare but multiple and, although the diagnoses are mostly clinical, some can be confirmed through genetic tests. Hereditary GC can be included in polyposis and nonpolyposis syndromes. The polyposis syndrome with the highest risk is gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and those without polyposis are HDGC and familial intestinal gastric cancer (FIGC).

In this section, the main different causes will be discussed with a resume of diagnostic criteria, screening initiation, and surveillance (shown in Table 1, adapted from [10–12]). Prophylactic or therapeutic endoscopic or surgical interventions will not be thoroughly discussed. Ad-

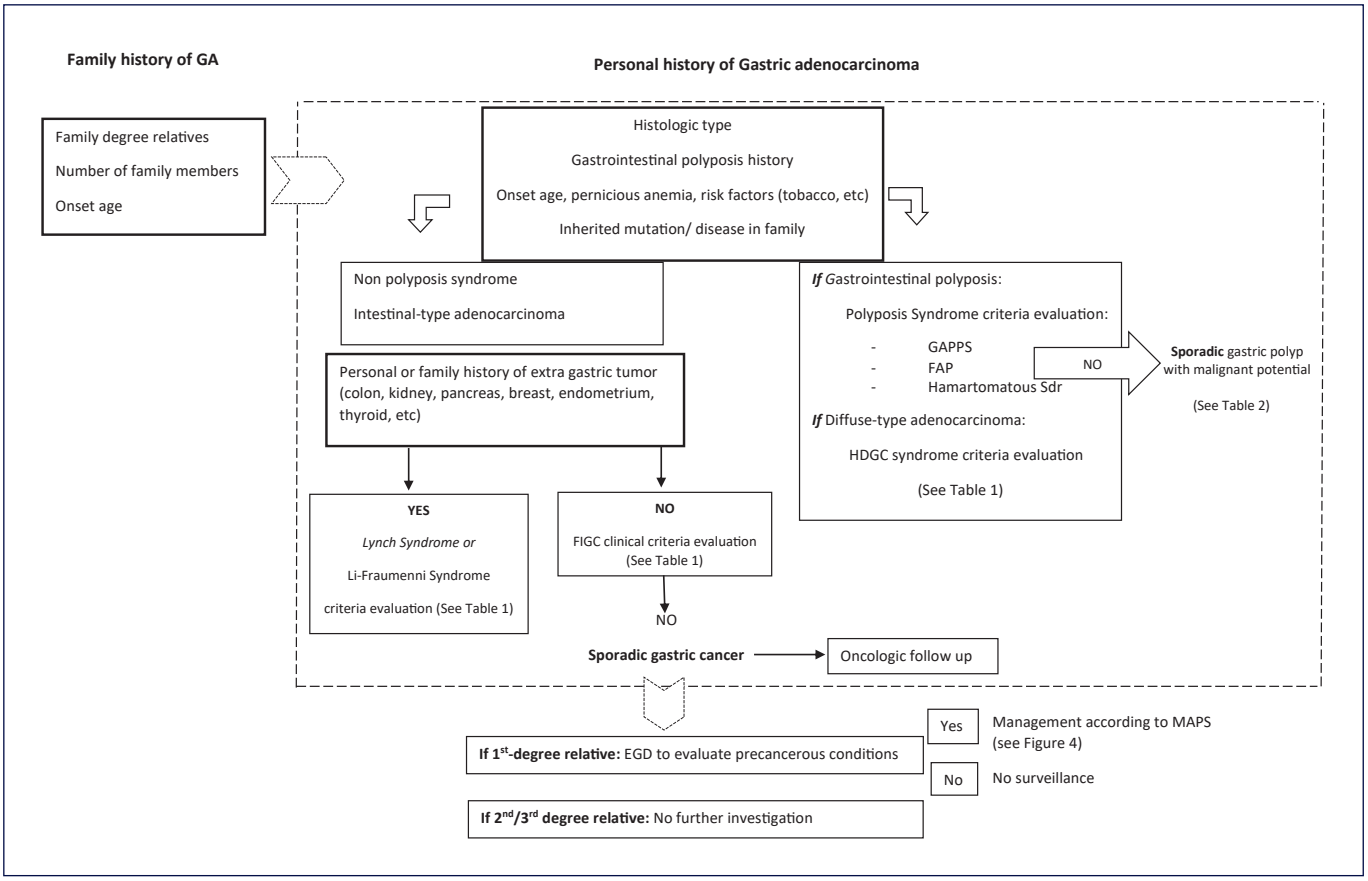

Fig. 2. Initial approach to a patient with personal or family history of GC.

Referral to a cancer geneticist in the presence of at least one
Individual criteria
Gastric cancer before age 40
Gastric cancer before age 50 who had one 1st or 2nd degree relative affected with gastric cancer
Gastric cancer at any age who had 2 or more 1st or 2nd degree relative affected with gastric cancer
Gastric cancer and breast cancer with one diagnosis before age 50
Gastric cancer at any age and a family history of breast cancer in a 1st or 2nd degree relative diagnosed before age 50
Gastric cancer at any age and a family history of juvenile polyps or gastrointestinal polyposis
Gastric cancer at any age and a family history of cancers associated with Lynch syndrome
Familial criteria
Known mutation in a gastric cancer susceptibility gene in a close relative
Gastric cancer in one 1st or 2nd degree relative who was diagnosed before age 40
Gastric cancer in two 1st or 2nd degree relatives with one diagnosis before age 50
Gastric cancer in three 1st or 2nd degree relatives independent of age, or
Gastric cancer and breast cancer in one patient with one diagnosis before age 50, juvenile polyps, or gastrointestinal polyposis in a close relative

Fig. 3. Criteria for further risk evaluation for high-risk syndromes associated to GC (adapted from [9]).

ditionally, other rarer hereditary syndromes associated with GC (ataxia-telangiectasia, Bloom syndrome, hereditary breast and ovarian cancer syndrome, and xeroderma pigmentosum) will not be described due to the lack of information that supports recommendations on screening and surveillance [9].

Polyposis Syndromes

Hamartomatous Syndromes

The presence of hamartoma polyps in the digestive tract should raise the clinical suspicion of a genetic syndrome and, therefore, there is an indication for genetic study. Hamartomatous syndromes include Peutz-Jeghers syndrome, juvenile polyposis syndrome (JPS), and Cowden syndrome.

Peutz-Jeghers syndrome is characterized by perioral hyperpigmentation and hamartomatous polyps [13] and is mostly associated with *STK11/LKB1* tumour suppressor gene variants [14]. Although most polyps are located in the small bowel (60–90%), 15–30% are located in the stomach [14]. The risk of gastric adenocarcinoma is 29% at 15–64 years of age, with an average diagnosis between 30 and 40 years of age [15]. Screening should start at 8 years of age and, in the absence of lesions, repeated at 18 years of age. Surveillance depends on phenotype and should be performed every 1–3 years [10].

JPS is diagnosed in the presence of at least one hamartomatous polyp in the stomach [11], and in 40–60% of the cases there is a deleterious variant in the *SMAD4* or *BMPR1A* genes [16]. The gastric phenotype is normally associated with variants in the *SMAD4* gene [16], and the risk of extracolonic cancer is difficult to assess, ranging from 20% to 60%, including GC [17]. The current recommendation is to start screening in *SMAD4* variant carriers at 18 years of age and in *BMPR1A* variant carriers at 25 years of age. Surveillance should be performed every 1–3 years according to phenotype [10].

Cowden's syndrome is characterized by the existence of several neoplasms dispersed through multiple organs and, concerning the stomach, gastric hamartomas associated with variants in the *PTEN* gene. The risk of gastric adenocarcinoma is higher, but its incidence is unknown [18]. GC screening and surveillance in these individuals is not consensual. Older guidelines recommended screening at 15 years of age and surveillance every 2–3 years [11]; however, more recent NCCN updates no longer recommend EGD due to lack of evidence [19].

Adenomatous Syndromes

Familial adenomatous polyposis (FAP) is mostly a colorectal disease, associated with an autosomal dominant mode of transmission and variants in the *APC* gene, which can be classified as classic or attenuated, according to the number of colorectal adenomas. However, gastric polyps may occur in more than 60% of the patients [20], with different malignant risk.

Most gastric polyps associated with FAP are fundic gland polyps that may present with low-grade dysplasia in up to 40% of the cases [21], with high-grade dysplasia (HGD) and malignant transformation being rare [22, 23]. However, it should be recognized that sporadic fundic gland polyps associated with proton-pump inhibitor can also occur in FAP, and these hardly harbour dysplasia [18].

Up to 20% of polyps correspond to adenomas, encompassing foveolar-type adenomas (85%), pyloric gland adenoma (15%), and intestinal-type adenoma (1–2%), with a corresponding increased risk of malignancy [21, 22]. Foveolar-type adenomas are rare in an absolute matter being the majority associated with *APC* variants and appearing as an isolated sporadic lesion within normal mucosa and, thus, a low progression risk. Pyloric gland adenomas, which are also rare and associated with normal mucosa, present HGD and adenocarcinoma foci at a higher frequency (10–15%). In contrast, intestinal-type adenomas are highly associated with advanced lesions (HGD or adenocarcinoma), intestinal metaplasia, gastritis, and also synchronous adenocarcinoma. This may be explained by other risk factors than *APC* variants, such as *H. pylori* infection. These facts elucidate its lower frequency but high malignancy risk.

The risk of GC in FAP in Western countries is low and was previously described as comparable to the risk of sporadic fundic gland polyps [23]. However, recent case series discovered advanced gastric lesions (including adenocarcinoma) in extensive areas of sporadic fundic gland polyps [24, 25]. This fact may lead to the creation of specific protocols for screening and surveillance of GC in this population, which currently are lacking.

On the other hand, the risk of duodenal adenocarcinoma is known to be highly associated to duodenal polyposis and, therefore, is recommended starting screening at 25 years of age and surveillance according to Spigelman's classification. Consequently, this is an opportunity to surveille gastric mucosa in an attempt to early detection of GC and precursors lesions, as recommended in the ESGE guideline [10].

Table 1. Summary of diagnostic criteria and management of hereditable syndromes associated with gastric cancer (GC) risk

	Gene	GC risk	Diagnostic criteria	Initial screening age	Surveillance
Polyposis syndromes					
Adenomatous					
Familial adenomatous polyposis (FAP)	*APC* promotor IA	4–7% (Asian population) Not increased in Western countries	ACG guidelines: • At least 10 cumulative colorectal adenomas • History of adenomas and FAP-type extracolonic manifestations* • Family history of one of the adenomatous polyposis syndromes	EGD: 25 years of age	EGD: According to Spigelman score
MUTYH-associated polyposis	*MUTYH*	2% (F) to 5% (M)	>10 colorectal adenomas	EGD: 35 years of age	EGD: According to Spigelman score
Hamartomatous					
PJS	*STK11/LKB1*	29% at 15–64 years	WHO criteria: • At least three Peutz-Jeghers polyps • Any number of Peutz-Jeghers polyps with a family history of PJS • Characteristic, prominent mucocutaneous pigmentation with a family history of PJS • Any number of Peutz-Jeghers polyps and characteristic, prominent mucocutaneous pigmentation	EGD: 8 years of age Repeated at 18 years of age	EGD every 1–3 years if polyps found
JPS	*SMAD4* (*BMPR1A*)	10–30%	WHO criteria: • More than three to five juvenile polyps of the colorectum • Juvenile polyps throughout the gastrointestinal tract • Any number of juvenile polyps with a family history of juvenile polyposis	*SMAD4* EGD: 18 years of age *BMPR1A* EGD: 25 years of age	EGD every 1–3 years Management case-by-case
Cowden syndrome	*PTEN*	Rare	ACG guidelines: • Individuals with multiple gastrointestinal hamartomas or ganglioneuromas should be evaluated for Cowden syndrome and related conditions	Not recommended [19] EGD: 15 years of age [11]	Not recommended [19] EGD every 2–3 years If duodenal polyps ECG according to Spigelman score [11]
Fundic glands polyps (FGP)					
GAPPS	*APC* promotor IB	13%	Essential criteria: • Proximal polyposis with antral sparing. • No evidence of colorectal or duodenal polyposis • >100 polyps carpeting the proximal stomach in the index patient or >30 polyps in a first-degree relative of another patient • predominantly FGPs and/or fundic gland-like polyps • Proband or relative with either dysplastic FGPs or GC	Prophylactic gastrectomy in probands (?) EGD in first-degree relatives (age?)	ECG surveillance case-by-case

Table 1 (continued)

	Gene	GC risk	Diagnostic criteria	Initial screening age	Surveillance
Nonpolyposis syndromes					
Intestinal type					
Lynch syndrome	*MSH2, MLH1, MSH6, PMS2, EPCAM*	13% Global (10%, 9%, 7%, 0%, 0%)	Amsterdam criteria II: • HNPCC-associated cancer† in three or more relatives. • One being a first-degree relative of the other two. • Two or more successive generations affected • HNPCC-associated cancer <50 years in one or more patients • Exclusion of FAP Revised Bethesda criteria: • CRC at age <50 years • Synchronous, metachronous colorectal or other HNPCC-associated tumour‡ regardless of age • CRC with MSI histology§ at age <60 years • CRC in one or more first-degree relatives with a Lynch syndrome-related tumour, with one of the cancers diagnosed at age <50 years • CRC in two or more first-degree or second-degree relatives with Lynch syndrome-related tumours, regardless of age Universal screening for all CRCs and endometrial cancers Computational predictive models: • PREMM Model >5%	EGD: 30–35 years of age	EGD every 2–3 years according to phenotype
Li-Fraumeni syndrome (LFS)	*TP53*	2–5%	Revised Chompret criteria: • LFS tumour¶ at age <46 years and at least one first-degree or second-degree relative with LFS tumour (except breast cancer if the proband has breast cancer) at age <56 years or multiple tumours • Multiple tumours (except breast cancer), two of which belonged to the LFS tumour spectrum and the first of which occurred at age <46 years • Adrenocortical carcinoma or choroid plexus tumour	Disagreement EGD: 25 years of age [19] Not recommended [34]	Disagreement EGD every 2–5 years [19] Not recommended [34]
FIGC	Unknown – probable polygenic cause	66%	IGCLC criteria in high-incidence countries: • Intestinal GC in three or more relatives • One being a first-degree relative of the other two • Two or more successive generations affected • Intestinal GC at age <50 years in one or more patients • Exclusion of gastric polyposis IGCLC criteria in low-incidence countries: • Intestinal GC in two or more first-degree relatives • Intestinal GC in second-degree relatives, one diagnosed at age <50 years • Intestinal GC in three or more relatives at any age Proposal of new criteria: • GC in two or more relatives at any age • At least one intestinal GC	EGD: 40 years of age or 5 years before the youngest case	EGD every 5 years

Table 1 (continued)

	Gene	GC risk	Diagnostic criteria	Initial screening age	Surveillance
Diffuse type					
Hereditary diffuse gastric cancer (HDGC)	*CDH1* *CTNNA1*	Clinical criteria 2015: 33% (F) to 42% (M)	IGCLC Family criteria (first and second relatives): • At least two cases of GC in family regardless of age, with at least one diffuse GC • At least one case of diffuse GC at any age and one or more cases of LBC at age <70 years in different family members • At least two cases of LBC in family members aged <50 years IGCLC Individual criteria: • Diffuse GC at age <50 years • Diffuse GC at any age in individuals of Maori ethnicity • Diffuse GC at any age in individuals with a personal or family history (first degree) of cleft lip/cleft palate • History of diffuse GC and LBC, both diagnosed at age <70 years • Bilateral LBC, diagnosed at age <70 years • Gastric in-situ signet-ring cells and/or pagetoid spread of signet-ring cells in individuals aged <50 years	• *CDH1* pathogenic: prophylactic gastrectomy at 20–30 years • *CDH1* variant uncertain significance or *CTNNA1* or HDGC-like: -Probands: surveillance at diagnosis (Cambridge protocol) -First-degree relatives: 40 years or 10 years before youngest case	Annually in first 2 years and then every 2 years according to phenotype (Cambridge protocol)

ACG, American College of Gastroenterologists; CRC, colorectal cancer; EGD, esophagogastroduodenoscopy F, Female; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; HNPCC, hereditary nonpolyposis colorectal cancer; IGCLC, International Gastric Cancer Linkage Consortium; LBC, lobular breast cancer; M, male; MSI, microsatellite instability; WHO, World Health Organization; PJS, Peutz-Jeghers syndrome; JPS, juvenile polyposis syndrome. * Duodenal/ampullary adenomas, desmoid tumours (abdominal > peripheral), papillary thyroid carcinoma, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, and osteomas. † HNPCC-associated cancers include CRC, endometrial cancer, small-bowel cancer, and ureteral or renal pelvis cancer. ‡ HNPCC-related tumours include colorectal tumour, endometrial tumour, stomach tumour, ovarian tumour, pancreatic tumour, small-bowel tumour, ureteral or renal pelvis tumour, biliary tract tumour, brain tumour (usually glioblastoma), sebaceous gland adenoma, and keratoacanthoma. § Tumour-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous and signet-ring cell features, and medullary growth pattern. ¶ Soft tissue sarcoma, osteosarcoma, brain tumour, premenopausal breast cancer, adrenocortical carcinoma, leukaemia, and lung bronchoalveolar cancer.

MUTYH-associated polyposis is an autosomal recessive syndrome associated with biallelic variants in the *MUTYH* gene. This syndrome also has an increased risk of duodenal (4%) [21] and GC (2–5%) [12], thus an EGD should be performed at 35 years of age and then maintained similarly to FAP [10].

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

GAPPS is a recently described gastric polyposis syndrome characterized by an excess of fundic gland polyps that affects the fundus and gastric body, sparing the antrum and small curvature, and no colorectal phenotype. Its diagnosis is clinical and must meet specific criteria (shown in Table 1) [26]. It is an autosomal dominant hereditary disease with incomplete penetrance secondary to variants in the promoter IB of the *APC* gene [27]. This syndrome has a high risk (13%) [26] of intestinal-type gastric adenocarcinoma and HGD, unlike other GC associated polyposis, like FAP and fundic gland polyps [28].

The natural history of GAPPS is variable, and additional mutations can arise that lead to malignant transformation and earlier progression. Thus, affected patients should initiate screening (as their first-degree family members) and endoscopic surveillance. However, there are still no clear recommendations in this issue [26]. There are case-reports where dysplastic, or even neoplastic, lesions are undistinguished within polypoid carpet in patients who present with metastatic disease. This fact may support the recommendation for prophylactic total gastrectomy [28].

Nonpolyposis Syndromes

Lynch Syndrome

Lynch syndrome is the most common cause of heritable gastrointestinal cancer and is an autosomal dominant syndrome linked to germline variants in one of the DNA mismatch repair (MMR) genes (*MSH2*, *MSH6*, *MLH1*, P*MS2*) or exonic deletions in the *EPCAM* gene [29]. Diagnosis of Lynch syndrome can be difficult, so there are different methods to support the diagnostic approach. These include the Amsterdam II criteria (family related clinical criteria; sensitivity 22%, specificity 98%), the Bethesda criteria (individual clinicopathologic criteria; sensitivity 82%, specificity 77%) and, finally, computational predictive models (MMRpredict, MMRpro, and PREMM) (shown in Table 1). The latter can be used when Lynch syndrome is suspected and is impossible to confirm the criteria (dead or distant relatives, etc.). The PREMM model is more practical and applicable to the general population, with higher sensitivity but lower specificity (90% and 67%, respectively). A probability greater than 5% means that the patient is admissible for genetic testing [29].

The lifetime risk of GC in Lynch Syndrome patients remains not deeply studied. An old Finnish study referred to a 13% lifetime risk [30], but a more recent Dutch study reported a lower relative risk (3.4 incidence ratio) [31]. Also, it demonstrated a higher risk in males (8%) compared to females (5.3%) [31]. Since the intestinal type is the most frequent, there is a possibility of surveillance; however, there is a lack of data for robust recommendations [29]. A recent retrospective study has found that patients with MMR deleterious variants have a high prevalence of precursor conditions (HP infection in 58.3%, intestinal metaplasia in 38.2%, and multifocal atrophy in 33.6%). (Raquel Ortigão et al., Eur J Gastroenterol Hepatol, in press).

Thus, it is currently recommended to screen patients with Lynch syndrome or MMR deleterious variants with EGD at 30–35 years of age with biopsies for screening for *H. Pylori* and eradication, if present. Surveillance should be performed every 2–3 years according to individual risk, i.e., family history of gastric adenocarcinoma and/or presence of precancerous conditions [29].

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is an autosomal dominant disease characterized by multiorgan neoplasms associated with deleterious germline variants in *TP53* [32]. The risk of GC in these patients does not seem to be completely determined, with older studies showing a high prevalence (26%) [33], while more recent ones showed a non-superior risk in this population compared to the general population [34].

Thus, the recommendations are discordant regarding screening and surveillance of gastric cancer. NCCN 2022 update recommends surveillance at 25 years of age or 5 years before the earliest GC in the family and to be repeated every 2–5 years [19]; on the other hand, the UK 2021 consensus recommends *H. pylori* testing and eradication, if required, but does not recommend EGD for surveillance, due to lack of evidence [35].

Hereditary Diffuse Gastric Cancer

HDGC is a rare autosomal dominant syndrome defined by the presence of, at least, one diffuse GC plus lobular breast cancer associated with *CDH1* or *CTNNA1* germinative variants [36]. Additionally, some families have an isolated phenotype of lobular breast cancer, designated as hereditary lobular breast cancer, while others fulfil clinical criteria but do not carry a genetic variant, known as HDGC-like.

In 2020, the International Gastric Cancer Linkage Consortium (IGCLC) updated the practice guidelines on clinical criteria for genetic testing (shown in Table 1) [18]. Each subgroup is assigned a different risk of GC, and therefore a different therapeutic approach and surveillance.

Patients and families with HDGC-*CDH1* should undergo prophylactic total gastrectomy after excluding more advanced lesions on endoscopy at the time of diagnosis. In those who have decided to undergo endoscopic surveillance and in hereditary lobular breast cancer, EGD must be performed annually according to the Cambridge protocol.

In patients with *CTNNA1* variants, *CDH1* variants of uncertain significance, or HDGC-like, EGD should be performed annually in the first 2 years and then the interval may increase according to the features. In first-degree relatives, surveillance should be started at 40 years of age or 10 years before the youngest case.

Familial Intestinal Gastric Cancer

FIGC is an autosomal dominant syndrome [37], which remains genetically unexplained but is postulated to be a polygenic syndrome [38]. Diagnosis is clinical and based on GC incidence [38]. In high-incidence countries, the diagnosis respects the Amsterdam criteria, similar to Lynch syndrome, and in low to intermediate-incidence countries the criteria are intestinal GC in two or more

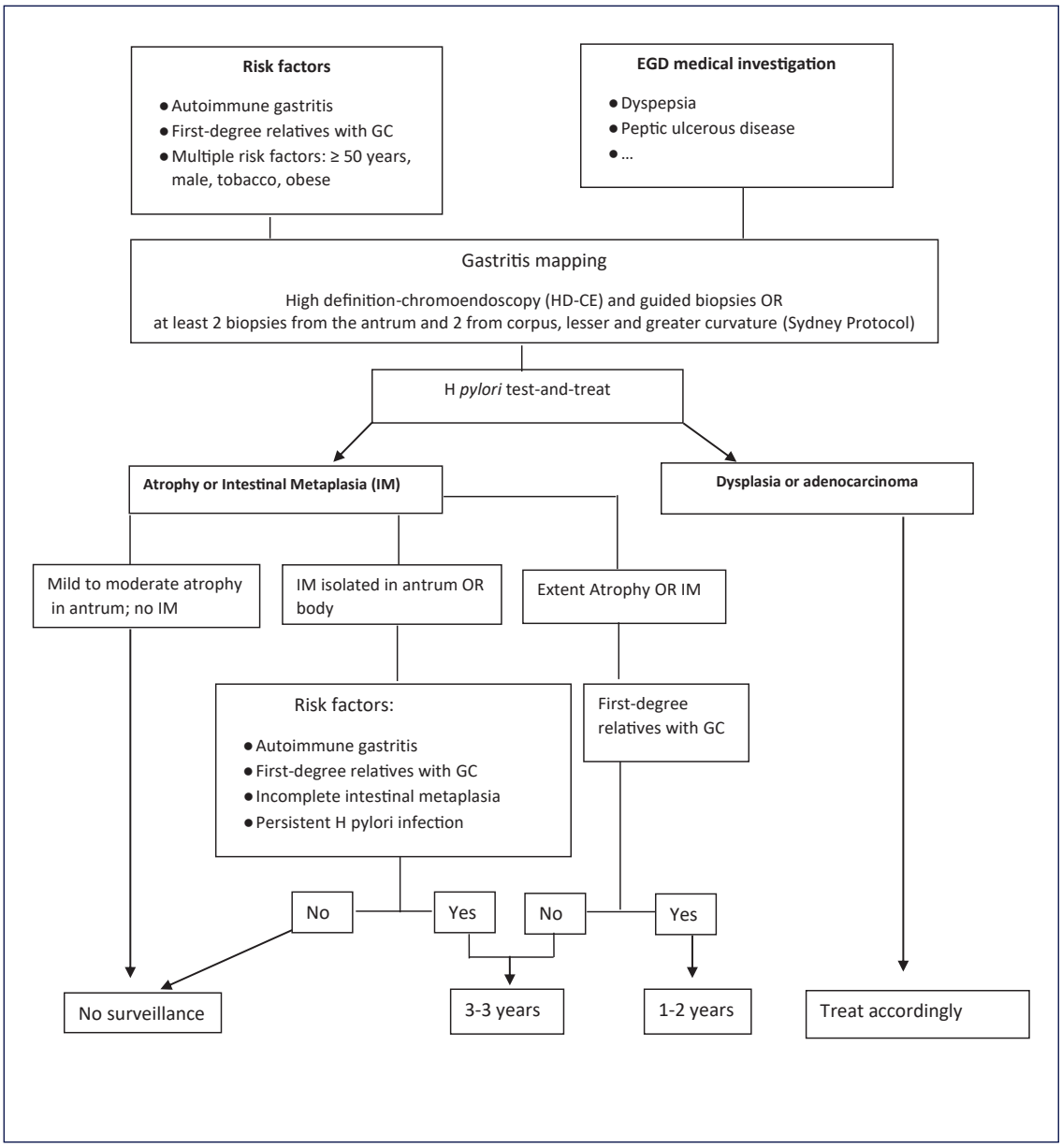

Fig. 4. Sporadic gastric cancer (GC) screening and management of precancerous conditions.

first-degree relatives; intestinal GC in second-degree relatives, one diagnosed at age <50 years; and intestinal GC in three or more relatives at any age (shown in Table 1). There are only a few general recommendations such as starting surveillance at 40 years of age or 5 years before the youngest case, *H. pylori* test-and-treat [39] and every 5 years thereafter [40].

Family History without Heritable Cancer Criteria

So far, recommendations for screening and surveillance of patients with clinical and/or genetic criteria for hereditary syndromes associated with GC have been described. However, with the increase in the incidence of GC, there are more and more individuals with a family history of GC without hereditary criteria, that is, patients with only one relative with GC.

Table 2. Sporadic gastric polyps' characteristics associated to gastric adenocarcinoma and their management

Gastric polyp	Main cause	Typical characteristics	High-risk characteristics	Gastric cancer risk	Management*
Fundic gland polyps	+++ PPI [FAP see Table 2]	• Fundus and gastric body location • Small size (<10 mm) • Translucent and glossy appearance	• Dysplasia • >10 mm size • Antrum location • Ulceration • Unusual appearance	<1%	• Remove when atypical characteristics • Manage PPI reduction dose/suspension • Reevaluation 12 months • Surveillance according to MAPS II
Hyperplastic polyps	Chronic gastritis: +++ *H. pylori* Autoimmune gastritis [GAPPS see Table 2]	• Solitary • Sessile or pedunculated with an eroded surface • Antrum	• >10 mm • Fundus and body	1.5–8%	• Remove >5 mm • Test-and-treat *H. pylori* • Reevaluation 12 months • Surveillance according to MAPS II[#]
Gastric adenomas - Pyloric gland adenomas - Foveolar adenomas - Oxyntic gland adenomas	Atrophy and intestinal metaplasia [FAP see Table 2]	• Solitary • Well delineated often eroded	• >20 mm • Villous	34%	• Remove • Surveillance according to MAPS II[#]

* Biopsies in the surrounding area to evaluate background mucosa. [#] High risk of synchronous and/or metachronous lesions.

Concerning this issue, there are no clear recommendations regarding GC screening in family relatives. What is known, as discussed below, is that the existence of a first-degree relative with GC confers an increased risk of GC [5] and a higher prevalence of *H. pylori* infection, atrophy, and intestinal metaplasia [7]. On the contrary, the risk of GC in second-degree relatives is lower [6].

Despite low evidence, the British Society of Gastroenterology Guidelines suggests that endoscopic screening should be considered in individuals older than 50 years of age with a family history [41]. Additionally, in MAPS II, the existence of familial GC modifies the follow-up of precursor lesions [8].

Thus, there may be a proposal for EGD at age 50 years of age (or before if early-onset in a family relative) in individuals with GC in first-degree relatives (but not in second-degree) to evaluate precursor conditions and/or *H. pylori* infection. If present, management according to MAPS II is recommended; if absent, no further screening is recommended [41].

Sporadic Cancer

As discussed above, the existence of hereditary syndromes and familial risk is responsible for an elevated cancer risk compared to the general population and, therefore, an earlier screening and laborious surveillance is recommended. However, most cancers are sporadic, which increased difficulties in identifying high-risk patients who may benefit from a screening.

The major risk factor associated with sporadic GC is the existence of precancerous conditions (gastric atrophy and intestinal metaplasia), which are mainly caused by chronic *H. pylori* infection. The onset and management of precancerous conditions and their risk factors are elucidated in MAPS II recommendations [8] and summarized in Figure 4.

Other risk factors are autoimmune gastritis; a minority of sporadic gastric polyps; and sociodemographic risk factors. Autoimmune gastritis is a chronic disease with malignant potential for adenocarcinoma or neuroendocrine tumours (OR 2.18 and 11.4, respectively) [42]. A meta-analysis calculated a relative risk of GC of 6.8 and an annual incidence/person of 0.27% [43]. It is recommended to perform an EGD at diagnosis and then every 5 years for GC risk [8].

A minority of sporadic gastric polyps have a malignant potential (even being low) to cause gastric adenocarcinoma. This includes fundic gland polyps, hyperplastic and adenomas; setting aside inflammatory fibroid polyps, which have no malignant potential [44], and sporadic hamartomas that are extremely rare to support data. The main cause and features of the different sporadic gastric

polyps associated with gastric adenocarcinoma and their management are summarized in Table 2 [44–46]. In general practice, biopsies should be performed according to the Sydney protocol to determinate surveillance (independently of polyp histology) and in the surrounding area to detect precancerous conditions or adenocarcinoma [45].

Other risk factors associated with GC risk are age, gender, ethnicity, smoking, and history of gastric surgery for benign disease. The risk of GC appears to be increased after 45 years of age [47, 48], in non-Caucasian individuals [49–51] and in individuals with previous gastric surgery (more than 30 years ago) [52]. However, all of them can be related to *H. pylori* infection chronicity. Additionally, men and current smokers are also at higher risk (1.3–3 times and OR 1.45, respectively) [49, 53, 54]. Despite low evidence, endoscopic screening should be considered in individuals older than 50 years with multiple risk factors for gastric adenocarcinoma, especially in those with family history [41].

Conclusion

GC remains one of the most prevalent and deadly cancers worldwide, but its screening in the general population is only effective in countries with high incidence. In countries with low to intermediate risk of gastric adenocarcinoma, screening is only cost-effective in high-risk populations. High-risk population includes sporadic precancerous conditions (intestinal metaplasia or atrophy) and several genetic syndromes with different risk to gastric adenocarcinoma, being the highest risk attributable to GAAPS, HDGC, and FIGC.

The management of these patients is hampered by the overlap of genetic and environmental risk factors, which by working synergistically may increase the risk of gastric adenocarcinoma. To conclude, clinicians should recognize high-risk patients, and although hereditary adenocarcinoma is rare, that possibility must be considered and the diagnostic criteria applied. However, the lifetime risk of gastric adenocarcinoma differs, and so screening and surveillance protocols may be adapted to local conditions.

Key Points

- Importance of a complete personal and family history of gastric (and extra-gastric) cancer.
- Awareness of heritable syndromes with GC risk.
- All individuals with precancerous conditions and/or heritable syndromes should be tested-and-treated to *H. pylori*, especially in high prevalence countries.
- Interaction between environmental factors and heritable syndromes, especially *H. pylori* infection.
- Importance of family history (and others risk factors) in management of precancerous conditions.

Statement of Ethics

Ethical review and approval was not required as the study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors contributed to the concept and design of the article. Marisa Linhares performed the literature review and wrote the manuscript. All the authors critically reviewed and approved the final version to be published.

Data Availability Statement

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

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.

2 Areia M, Dinis-Ribeiro M, Rocha Gonçalves F. Cost-utility analysis of endoscopic surveillance of patients with gastric premalignant conditions. Helicobacter. 2014;19(6):425–36.

3 Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol. 2015;16(2):e60–70.

4 Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
5 Yaghoobi M, Bijarchi R, Narod SA. Family history and the risk of gastric cancer. Br J Cancer. 2010;102(2):237–42.
6 Safaee A, Moghimi-Dehkordi B, Fatemi SR, Maserat E, Zali MR. Family history of cancer and risk of gastric cancer in Iran. Asian Pacific J Cancer Prev. 2011;12(11):3117–20.
7 Rokkas T, Sechopoulos P, Pistiolas D, Margantinis G, Koukoulis G. Helicobacter pylori infection and gastric histology in first-degree relatives of gastric cancer patients: aA meta-analysis. Eur J Gastroenterol Hepatol. 2010; 22(9):1128–33.
8 Pimentel-Nunes P, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019; 51(4):365–88.
9 NCCN Clinical Practice Guidelines. Gastric cancer. 2022.
10 Van Leerdam ME, Roos VH, Van Hooft JE, Dekker E, Jover R, Kaminski MF, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) gGuideline. Endoscopy. 2019; 51(9):877–95.
11 Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62; quiz 263.
12 Gullo I, van der Post RS, Carneiro F. Recent advances in the pathology of heritable gastric cancer syndromes. Histopathology. 2021; 78(1):125–47.
13 Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044–58.
14 Utsunomiya J, Gocho H, Miyanaga T, Hamaguchi E, Kashimure A. Peutz-Jeghers syndrome: its natural course and management. Johns Hopkins Med J. 1975;136(2):71–82.
15 Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000; 119(6):1447–53.
16 Latchford AR, Neale K, Phillips RKS, Clark SK. Juvenile polyposis syndrome: a study of genotype, phenotype, and long-term outcome. Dis Colon Rectum. 2012;55(10):1038–43.
17 Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998;5(8): 751–6.
18 Blair VR, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020;21(8): e386–97.
19 NCCN Clinical Practice Guidelines. Genetic/Familial high-risk assessment: breast, ovarian, and pancreatic. 2022.
20 Lynch HT, Smyrk T, McGinn T, Lanspa S, Cavalieri J, Lynch J, et al. Attenuated familial adenomatous polyposis (AFAP). A phenotypically and genotypically distinctive variant of FAP. Cancer. 1995;76(12):2427–33.
21 Brosens LAA, Wood LD, Offerhaus GJ, Arnold CA, Lam-Himlin D, Giardiello FM, et al. Pathology and genetics of syndromic gastric polyps. Int J Surg Pathol. 2016;24(3):185–99.
22 Wood LD, Salaria SN, Cruise MW, Giardiello FM, Montgomery EA. Upper GI tract lesions in familial adenomatous polyposis (FAP): enrichment of pyloric gland adenomas and other gastric and duodenal neoplasms. Am J Surg Pathol. 2014;38(3):389–93.
23 Arnason T, Liang WY, Alfaro E, Kelly P, Chung DC, Odze RD, et al. Morphology and natural history of familial adenomatous polyposis-associated dysplastic fundic gland polyps. Histopathology. 2014;65(3):353–62.
24 Leone PJ, Mankaney G, Sarvapelli S, Abushamma S, Lopez R, Cruise M, et al. Endoscopic and histologic features associated with gastric cancer in familial adenomatous polyposis. Gastrointest Endosc [Internet]. 2019;89(5): 961–8.
25 Walton SJ, Frayling IM, Clark SK, Latchford A. Gastric tumours in FAP. Fam Cancer. 2017;16(3):363–9.
26 Worthley DL, Phillips KD, Wayte N, Schrader KA, Healey S, Kaurah P, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): aA new autosomal dominant syndrome. Gut. 2012;61(5):774–9.
27 Mitsui Y, Yokoyama R, Fujimoto S, Kagemoto K, Kitamura S, Okamoto K, et al. First report of an Asian family with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) revealed with the germline mutation of the APC exon 1B promoter region. Gastric Cancer. 2018;21(6):1058–63.
28 Rudloff U. Gastric adenocarcinoma and proximal polyposis of the stomach: dDiagnosis and clinical perspectives. Clin Exp Gastroenterol. 2018;11:447–59.
29 Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of lynch syndrome: aA consensus statement by the us multi-society task force on colorectal cancer. Gastroenterology [Internet]. 2014;147(2): 502–26.
30 Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, De La Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. 1999;81(2):214–8.
31 Capelle LG, Van Grieken NCT, Lingsma HF, Steyerberg EW, Klokman WJ, Bruno MJ, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in The Netherlands. Gastroenterology. 2010;138(2): 487–92.
32 Amadou A, Achatz MIW, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol. 2018;30(1):23–9.
33 Masciari S, Dewanwala A, Stoffel EM, Lauwers GY, Zheng H, Achatz MI, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. Genet Med. 2011;13(7):651–7.
34 Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol. 2015;33(21): 2345–52.
35 Hanson H, Brady AF, Crawford G, Eeles RA, Gibson S, Jorgensen M, et al. UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants. J Med Genet. 2021;58(2):135–9.
36 Hansford S, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. JAMA Oncol. 2015;1(1):23–32.
37 Caldas C, Carneiro F, Lynch HT, Yokota J, Wiesner GL, Powell SM, et al. Familial gastric cancer: overview and guidelines for management. J Med Genet. 1999;36(12):873–80.
38 Carvalho J, Oliveira P, Senz J, São José C, Hansford S, Teles SP, et al. Redefinition of familial intestinal gastric cancer: clinical and genetic perspectives. J Med Genet. 2021; 58(1):1–11.
39 Kluijt I, Sijmons RH, Hoogerbrugge N, Plukker JT, De Jong D, Van Krieken JH, et al. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. Fam Cancer. 2012;11(3):363–9.
40 Chung SJ, Park MJ, Kang SJ, Kang HY, Chung GE, Kim SG, et al. Effect of annual endoscopic screening on clinicopathologic characteristics and treatment modality of gastric cancer in a high-incidence region of Korea. Int J Cancer. 2012;131(10):2376–84.
41 Banks M, Graham D, Jansen M, Gotoda T, Coda S, Di Pietro M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut. 2019;68(9):1545–75.
42 Murphy G, Dawsey SM, Engels EA, Ricker W, Parsons R, Etemadi A, et al. Cancer risk after pernicious anemia in the US elderly population. Clin Gastroenterol Hepatol [Internet]. 2015;13(13):2282–9.e1-4.
43 Vannella L, Lahner E, Osborn J, Annibale B. Systematic review: gastric cancer incidence in pernicious anaemia. Aliment Pharmacol Ther. 2013;37(4):375–82.

44 Islam RS, Patel NC, Lam-Himlin D, Nguyen CC. Gastric polyps: a review of clinical, endoscopic, and histopathologic features and management decisions. Gastroenterol Hepatol. 2013;9(10):640–51.
45 Castro R, Pimentel-Nunes P, Dinis-Ribeiro M. Evaluation and management of gastric epithelial polyps. Best Pract Res Clin Gastroenterol. 2017;31(4):381–7.
46 Okamoto Y, Kanzaki H, Tanaka T, Sakae H, Abe M, Iwamuro M, et al. Gastric adenoma: a high incidence rate of developing carcinoma and risk of metachronous gastric cancer according to long-term follow-up. Digestion. 2021;102(6):878–86.
47 de Vries AC, van Grieken NCT, Looman CWN, Casparie MK, de Vries E, Meijer GA, et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide Cohort Study in The Netherlands. Gastroenterology. 2008;134(4):945–52.
48 Leung WK, Lin SR, Ching JYL, To KF, Ng EKW, Chan FKL, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. Gut. 2004;53(9):1244–9.
49 Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006 Mar–Apr;56(2):106–30.
50 Ali R, Barnes I, Cairns BJ, Finlayson AE, Bhala N, Mallath M, et al. Incidence of gastrointestinal cancers by ethnic group in England, 2001–2007. Gut. 2013;62(12):1692–3.
51 Dong E, Duan L, Wu BU. Racial and ethnic minorities at increased risk for gastric cancer in a regional US population study. Clin Gastroenterol Hepatol. 2017;15(4):511–7.
52 Lagergren J, Lindam A, Mason RM. Gastric stump cancer after distal gastrectomy for benign gastric ulcer in a population-based study. Int J Cancer. 2012;131(6):1048–52.
53 Pérez-Rodríguez M, Partida-Rodríguez O, Camorlinga-Ponce M, Flores-Luna L, Lazcano E, Gómez A, et al. Polymorphisms in HLA-DQ genes, together with age, sex, and *Helicobacter pylori* infection, as potential biomarkers for the early diagnosis of gastric cancer. Helicobacter. 2017;22(1):e12326–10.
54 Morais S, Rodrigues S, Amorim L, Peleteiro B, Lunet N. Tobacco smoking and intestinal metaplasia: systematic review and meta-analysis. Dig Liver Dis. 2014;46(11):1031–7.

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Side-Viewing Duodenoscope versus Forward-Viewing Gastroscope for Endoscopic Retrograde Cholangiopancreatography in Billroth II Gastrectomy Patients

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Keywords

Endoscopic retrograde cholangiopancreatography · Billroth II operation · Gastroscope · Duodenoscope

Abstract

Introduction: Endoscopic retrograde cholangiopancreatography (ERCP) in patients with Billroth II gastrectomy is still a challenging procedure. The optimal approach, namely the type of endoscope and sphincter management, has yet to be defined. ***Aim:*** To compare the efficacy and safety of forward-viewing gastroscope and the side-viewing duodenoscope in ERCP of patients with Billroth II gastrectomy. ***Methods:*** We conducted a retrospective, single-center cohort study of consecutive patients with Billroth II gastrectomy submitted to ERCP in an expert center for ERCP between 2005 and 2021. The outcomes assessed were: papilla identification, deep biliary cannulation, and adverse events (AEs). Multivariate analysis was performed to evaluate potential associations and predictors of the main outcomes. ***Results:*** We included 83 patients with a median age of 73 (IQR 65–81) years. ERCP was performed using side-viewing duodenoscope in 52 and forward-viewing gastroscope in 31 patients. Patients' characteristics were similar in the two groups. The global rate of papilla identification was 66% ($n = 55$). The rate of deep cannulation was 58% considering all patients and 87% in the subgroup of patients in which the papilla major was identified. Cannulation was performed with standard methods in 65% of cases and with needle-knife fistulotomy in 35%. AEs occurred in 4 patients. There was no difference between duodenoscope and gastroscope in papilla identification (64% [95% CI: 51–77] vs. 71% [55–87]). Although not statistically significant, duodenoscope had a lower deep cannulation rate when considering all patients (52% [15–39] vs. 68% [7–35]) and a higher AEs rate (8% [1–15] vs. 0% [0–1]). In a multivariate analysis, the use of gastroscope significantly increased the deep cannulation rate (OR = 152.62 [2.5–9,283.6]). ***Conclusion:*** This study demonstrates that forward-viewing gastroscope is at least as effective and safe as side-viewing duodenoscope for ERCP in patients with Billroth II gastrectomy. Moreover, our study showed that gastroscope is an independent predictor of successful cannulation.

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Colangiopancreatografia retrógrada endoscópica em doentes com gastrectomia com reconstrução Billroth II: duodenoscópio ou gastroscópio de visão frontal?

Palavras Chave
Colangiopancreatografia retrógrada endoscópica · Cirurgia Billroth II · Gastroscópio · Duodenoscópio

Resumo
Introdução: Colangiopancreatografia retrógrada endoscópica (CPRE) em doentes submetidos previamente a gastrectomia com reconstrução Billroth II é ainda um exame desafiante. A melhor abordagem, nomeadamente o tipo de endoscópio e a técnica de canulação biliar, ainda não está definida. ***Objectivo:*** Comparar a eficácia e segurança do gastroscópio de visão frontal e do duodenoscópio de visão lateral na CPRE de doentes com gastrectomia com reconstrução Billroth II. ***Métodos:*** Conduzimos um estudo de coorte retrospectivo e unicêntrico que incluiu consecutivamente doentes com gastrectomia com reconstrução Billroth II submetidos a CPRE num centro de referência para CPRE entre 2005 e 2021. Os outcomes avaliados foram: identificação da papila, canulação biliar profunda e efeitos adversos (EAs). Regressão logística foi realizada para avaliar possíveis associações e preditores dos outcomes. ***Resultados:*** Incluímos 83 doentes com uma idade mediana de 73 (IIQ 65–81) anos. A CPRE foi realizada usando duodenoscópio em 52 doentes e usando o gastroscópio de visão frontal em 31 doentes. As características dos doentes foram semelhantes entre os dois grupos. A taxa global de identificação da papila foi de 66% (n = 55). A taxa de canulação profunda foi de 58% considerando todos os doentes e de 87% considerando apenas o subgrupo de doentes nos quais a papila major foi identificada. A canulação foi realizada usando métodos convencionais em 65% e usando fistulotomia com faca em 35% dos doentes. EAs ocorreram em 4 doentes. Não houve diferenças entre duodenoscópio e gastroscópio relativamente à identificação da papila [64% (95% CI: 51–77) vs 71% (55–87)]. Apesar de estatisticamente não significativo, o uso de duodenoscópio teve uma menor taxa de canulação profunda quando considerados todos os doentes [52% (15–39) vs 68% (7–35)] e uma maior taxa de EAs [8% (1–15) vs 0% (0–1)]. Na regressão logística, o uso de gastroscópio significativamente aumentou a taxa de canulação profunda [OR = 152.62 (2.5–9,283.6)]. ***Conclusão:*** Este estudo demonstra que o uso de gastroscópio de visão frontal é pelo menos igualmente eficaz e seguro ao duodenoscópio na CPRE de doentes com gastrectomia com reconstrução Billroth II. Para além disso, o nosso estudo demonstrou que o uso de gastroscópio é um predictor independente para canulação.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) in patients with Billroth II gastrectomy is still a challenging procedure due to altered anatomy, even among experienced endoscopists. ERCP in patients with Billroth II gastrectomy is technically more demanding, with ERCP failures associated with afferent loop intubation, papilla identification, deep biliary cannulation in an inverted papilla, and performance of sphincterotomy [1–4]. Moreover, it presents more risks than ERCP performed in patients with normal anatomy, with perforation rates of up to 2.8% [1].

Different endoscopes may be used, including side-viewing duodenoscope, forward-viewing gastroscope (with or without cap-fitting) [4, 5], balloon-assisted enteroscope [6, 7], colonoscope [8], and anterior oblique-viewing endoscope [9]. While papilla identification and cannulation are thought to be easier with side-viewing duodenoscope; afferent loop intubation and reaching the papilla are easier with forward-viewing gastroscope with lower risk of perforation [1, 4, 10]. Regarding cannulation, different cannulation techniques have been described: standard cannulas, conventional sphincterotome [3, 8, 11], needle-knife [8, 11], and rotatable or dedicated inverted sphincterotome [11, 12]. However, the optimal approach, namely the type of endoscope and sphincter management, has yet to be defined. Indeed, comparative studies are scarce [10, 11] and the majority of the studies published are retrospective, without prospective databases, and single arm [1, 3, 4, 7, 12].

Therefore, we aim to compare the efficacy and safety, as well as their determinants, of performing ERCP using forward-viewing gastroscope versus duodenoscope in patients with Billroth II gastrectomy.

Methods

Study Design, Setting, and Selection of Participants

We conducted a retrospective, single-center cohort study including all consecutive patients with Billroth II gastrectomy and

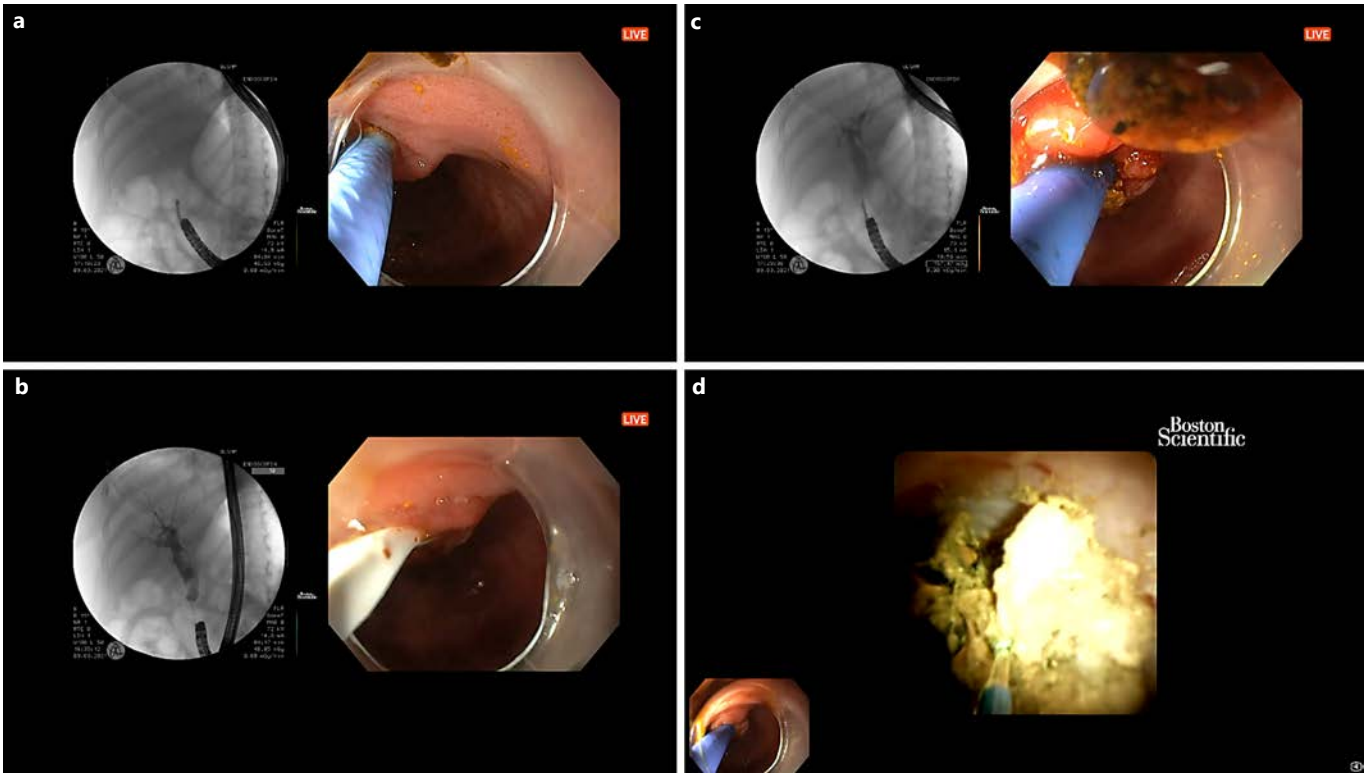

Fig. 1. Endoscopic retrograde cholangiopancreatography performed with a forward-viewing gastroscope with cap. **a** Cannulation. **b** Stone extraction. **c** Cholangiogram. **d** Cholangioscopy-guided laser lithotripsy.

native papilla submitted to ERCP between January 2005 and March 2021 at Hospital Santa Luzia, ULSAM, Viana do Castelo, Portugal; a hospital affiliated with the School of Medicine, University of Minho, a referral center for advanced biliopancreatic endoscopy. We included only ERCP for management of biliary disease.

ERCP Procedures

Written informed consent was obtained from all patients. ERCPs were performed by two experienced endoscopists (L.L. and J.R.) who each performed ≥300 ERCPs annually for the past 15 years. All ERCPs were performed under deep sedation/general anesthesia with propofol (by an anesthesiologist). ERCP was always started with the patient in the prone position. If intubation of the afferent loop was not feasible, the patient was turned to left lateral decubitus, to facilitate entering the afferent loop. The afferent loop intubation was confirmed by the presence of bile and by the endoscope position on fluoroscopy. The afferent loop was intubated with minimal air/CO_2 insufflation, and most papillae were located at the 10- or 11-o'clock position. Deep cannulation was initially attempted using a standard straight catheter (Triple Lumen ERCP cannula, Tapered Tip 5.5 Fr; Boston Scientific, Natick, MA, USA), attempting to insert the catheter gently into the bile duct; if deep insertion was not feasible, after minimal insertion of the catheter in the ampulla (1–2 mm), the guidewire was carefully advanced into the common biliary duct (CBD) under fluoroscopy. Pushing the catheter against the duodenal wall at the 9- to 10-o'clock position or changing the position of the tip of the endoscope led the tip of the catheter to the correct access to the CBD. We used a 0.035-inch hydrophilic guide wire (Jagwire; Boston Scientific). If deep cannulation was not achieved, needle-knife fistulotomy (NKF) was performed as a second-line approach, using an Olympus KD-11Q, Olympus Corporation, Melville, NY, USA). After successful biliary cannulation, if sphincterotomy was indicated, a 5-cm plastic biliary stent was inserted, and an NKF was performed in the 5-o'clock direction over the plastic biliary stent placed along the bile duct. Once the ERCP was completed, all patients were admitted to the inpatient area of the hospital and observed for 24 h, before discharge. When deep cannulation of the bile duct was unsuccessful after NKF, a second ERCP was scheduled in less than a week.

All procedures were performed using a forward-viewing gastroscope or a duodenoscope (Olympus TJF 160 VR, GIF-Q165, GIF-1TH190; Olympus Corporation). Between 2005 and 2015 all ERCPs were performed exclusively with a side-viewing duodenoscope. Taking into account new-evidence-based literature [13, 14] and practice experience, after 2015 all ERCP procedures were always performed using a forward-viewing gastroscope (Fig. 1). All ERCPs performed with a forward-viewing were initially attempted without a cap (Transparent cap Olympus D-201-11804); a cap was attached to the tip of the forward-viewing gastroscope only in cases where cannulation was unsuccessful. In case of failure with either duodenoscope (2005–2015) or gastroscope (2015–2021), there was no attempt to perform ERCP with another endoscope.

Table 1. Patient characteristics and ERCP data according to endoscope type

	All ($n = 83$)	Side-viewing duodenoscope ($n = 52$)	Forward-viewing gastroscope ($n = 31$)	p
Age, years (IQR)	73 (65–81)	74 (65–83)	73 (67–79)	0.992
Male, *n* (%)	56 (68)	36 (69)	20 (65)	0.809
ERCP indications, *n* (%)				0.061
Choledocholithiasis	34 (41)	18 (35)	16 (52)	
Biliary stenosis	31 (37)	19 (37)	12 (39)	
Unspecific dilation of biliary tract	11 (13)	10 (19)	1 (3)	
Biliary leak	2 (2)	2 (4)	0 (0)	
Papilla identification, *n* (%)	55 (66)	33 (64)	22 (71)	0.632
Main reasons for failed papilla identification, *n* (%)				0.619
Acute angulation of the anastomosis	12 (43)	7 (37)	5 (56)	
Long afferent loop	11 (33)	8 (42)	3 (33)	
Food debris	2 (7)	2 (11)	0 (0)	
Papilla not identified	2 (7)	1 (5)	1 (11)	
Deep cannulation, *n* (%)	48 (57)	27 (52)	21 (68)	0.176
Method of cannulation, *n* (%)				0.769
Standard methods	31(65)	18 (67)	13 (62)	
Fistulotomy	17 (35)	9 (33)	8 (38)	
Sphincterotomy	27 (33)	16 (31)	11 (36)	0.809
Plastic/metal stent, *n* (%)	28/4 (39)	13/1 (27)	15/3 (58)	0.006
Cholangioscopy, *n* (%)	3 (4)	0 (0)	3 (10)	0.049
ERCP diagnosis, *n* (%)				0.173
Choledocholithiasis	21(25)	9 (17)	12 (39)	
Malignant stenosis	17 (20)	9 (17)	8 (26)	
Unexplained biliary dilatation	4 (5)	4 (8)	0 (0)	
Benign stenosis	2 (2)	1 (2)	1 (3)	
Complications, *n* (%)				0.147
Perforation	3 (4)	3 (6)	0 (0)	
Hemorrhage	1 (1)	1 (2)	0 (0)	

Data Collection, Variables and Outcomes

Data was collected from a dedicated prospectively maintained database. Data on demographic variables, year of the procedure, ERCP indication and diagnosis, type of endoscope, biliary access technique, therapeutic interventions, complications and its management were extracted from the database. The complications were reported by severity and time of occurrence (intra-procedural, early [within 14 days of follow-up] and late [after 14 days of follow-up]) according to ASGE lexicon's severity grading system [15]. The two primary outcomes evaluated were: (1) success rate of papilla major identification and (2) deep biliary cannulation. The success rate of biliary cannulation is presented for all patients (intention-to-treat), as well as for the subgroup of patients in which the papilla major was identified. The secondary outcomes were: (3) rate of ERCP-related adverse events and (4) evaluation of reasons for not identifying the papilla major. The ERCP-related adverse events are presented for all patients (intention-to-treat) as well as for the subgroup of patients in which the papilla major was identified.

Statistical Analysis

Descriptive statistics included mean and standard deviation or median and interquartile range (IQR) for quantitative variables and proportions for categorical variables. The differences in baseline characteristics between the two endoscope groups was assessed using the Student t test for age and the χ^2 test (with Bonferroni adjustment for multiple comparisons) for categorical variables. The association between endoscope and quantitative variables was analyzed using the t test or the corresponding non-parametric test. The association between endoscope and categorical variables was analyzed with the χ^2 test (with Bonferroni adjustment for multiple comparisons). Multiple logistic regressions were performed to evaluate predictors of the main outcomes. In the multivariable regression model, we included variables that physi-

Table 2. Potential factors affecting papilla cannulation: multivariate analysis

	OR (95% CI)	*p* value
Year of ERCP	0.55 (0.32–0.97)	0.4
ERCP indication	3.21 (0.24–42.4)	0.88
Endoscope	152.62 (2.51–9 283.56)	0.02

ologically could be associated with the outcome or variables with a *p* value less than 0.25 in simple regression model. The 95% CIs were calculated and used to compare the results between endoscope groups. A *p* value of <0.05 was considered statistically significant.

Results

Patient Characteristics and ERCP Indications

We included 83 patients with a median age of 73 (IQR 65–81) years; 68% of them were male. The main indications for ERCP were choledocholithiasis (41%), biliary stenosis (37%), unspecific dilation of biliary tract (13%), and biliary leak (2%). ERCP was performed using a side-viewing duodenoscope in 52 patients and a forward-viewing therapeutic gastroscope in 31 patients. There were no differences between endoscope groups regarding patient characteristics (duodenoscope vs. gastroscope: age, 74 [IQR 65–83] vs. 73 [IQR 67–79] years, $p = 0.992$; male, 69 vs. 65%, $p = 0.809$) (Table 1).

Primary Outcomes

Access to the papilla was achieved in 66% of patients ($n = 55$), of which 93% ($n = 51$) in the first ERCP. The rate of deep cannulation was 58% (48/83) in all patients (intention-to-treat analysis) and 87% (48/55) in the subgroup of patients in which the papilla major was identified, with 88% ($n = 42$) cannulated at the first ERCP. Cannulation was achieved using standard methods in 65% ($n = 31$) of cases (with sphincterotomy performed in 27 patients) or with NKF in 35% ($n = 17$) of cases. Cholangioscopy with the Spyglass system was performed in 3 cases, of which 2 underwent cholangioscopy-guided laser lithotripsy. Of the patients that underwent papilla cannulation, a biliary stent was inserted after cannulation in 66% ($n = 32$) when indicated (plastic stent in 28 and metallic stent in 4) (Table 1).

There was no difference between side-viewing duodenoscope and forward-viewing gastroscope in papilla identification rate (64% [95% CI: 51–77] vs. 71% [55–87], $p = 0.632$). Although not statistically significant, side-viewing duodenoscope had a lower deep cannulation rate than forward-viewing gastroscope when considering all patients (52% [15–39] vs. 68% [7–35], $p = 0.176$) and when considering only the subgroup of patients in which the papilla major was identified (82% [72–92] vs. 95% [89–100], $p = 0.223$).

Secondary Outcomes

Adverse events occurred in 4 patients: 3 perforations in the anastomosis (all intra-procedural and severe) and 1 hemorrhage (intra-procedural and moderate) (Table 1).

When considering all patients, duodenoscope had a higher adverse events rate (8% [1–15] vs. 0% [0–0.5], $p = 0.147$) namely perforation ($p = 1.0$) and hemorrhage rate ($p = 1.0$), though not statistically significant. Likewise, when considering only the subgroup of patients in which the papilla major was identified and biliary cannulation attempted, duodenoscope had a higher adverse events rate (9% [0–18] vs. 0% [0–1], $p = 0.208$), though not statistically significant.

There was failure to identify the papilla in 34% of cases ($n = 28$) due to (i) acute angulation of the anastomosis in 43% ($n = 12$); (ii) long afferent loop in 39% ($n = 11$) of cases; (iii) food debris in 7% ($n = 2$); (iv) papilla not identified despite afferent loop exploration in 7% ($n = 2$); and (v) anesthesia-related complication in 4% of cases ($n = 1$).

Multiple Logistic Regression

There was no significant time trend regarding papilla identification ($p = 0.256$), deep cannulation ($p = 0.779$) and adverse events ($p = 0.962$). In a univariate analysis, there was no significant interaction between time of ERCP and type of endoscope used regarding papilla identification ($p = 0.763$), deep cannulation ($p = 0.16$) and adverse events ($p = 0.763$). In a multivariate analysis, the use of gastroscope significantly increased the cannulation rate [OR = 152.62 (95% CI = 2.5–9,283.6), $p = 0.02$] when controlling for year of ERCP and ERCP indication (Table 2). However, the type of endoscope was not associated with papilla identification or with risk of perforation (Tables 3, 4).

Discussion

ERCP in patients with Billroth II gastrectomy has various challenges that have to be overcome. Firstly, recognition and intubation of the afferent loop, sometimes ham-

Table 3. Potential factors affecting papilla identification: multivariate analysis

	OR (95% CI)	*p* value
Year of ERCP	1.07 (0.91–1.27)	0.41
ERCP indication	1.54 (0.52–4.55)	0.99
Endoscope	1.01 (0.19–5.25)	0.99

Table 4. Potential factors affecting perforation: multivariate analysis

	OR (95% CI)	*p* value
Year of ERCP	1.22 (0.79–1.87)	0.36
Endoscope	0.001 (0.001–1.0)	0.99
Cannulation	5.68 (0.44–74.01)	0.19
Sphincterotomy	0.001 (0.001–1.0)	0.99

pered by acute angulation of the anastomosis. Then, progression on the afferent loop and papilla identification can also be hampered because of angulations, adhesions or long afferent loop. After reaching the papilla, cannulation maneuvers have to be adapted to the inverted position of the endoscope. Therefore, ERCP in patients with Billroth II gastrectomy is still a challenging procedure [2, 16].

Although the side-viewing duodenoscope is the most commonly used endoscope for ERCP in Billroth II gastrectomy patients, forward-viewing gastroscope has been increasingly used. However, each endoscope has its advantages and drawbacks. While papilla identification and cannulation are thought to be easier with side-viewing duodenoscope due to its elevator and large working channel; afferent loop intubation and reaching the papilla are easier with forward-viewing gastroscope with consequently lower risk of perforation [1, 2, 4, 10]. Although the choice of endoscope has been a matter of controversy, there is still lack of comparative studies regarding ERCP in patients with Billroth II gastrectomy. Indeed, Park and Song [1] conducted a recent systematic review showing that there is only 1 retrospective and 1 prospective comparative study about the choice of endoscope [10, 17]. Besides these two comparative studies, 3 retrospective cohorts have been published reporting the use of forward- and side-viewing endoscope in ERCP in patients with Billroth II gastrectomy [3, 8, 18]. In this systematic review, the overall rate of papilla cannulation was 87.9%, and the overall rate of adverse events rate was 7.3%. When analyzed by endoscope, the success rate of papilla cannulation was 95.3% for side-viewing endoscope and 95.2% for forward-viewing endoscope. Moreover, the authors demonstrated that the rate of perforation was slightly higher in side-viewing endoscope (3.6%) compared with forward-viewing endoscope (1.7%) [1]. Likewise, we found that the use of forward-viewing gastroscope significantly increased the deep cannulation rate in a multivariate analysis. Although the type of endoscope was not associated with the risk of perforation in a multivariate analysis, the risk of perforation was higher with side-viewing duodenoscope (6%) compared with forward-viewing gastroscope (0%). Recently, Nennstiel et al. [19] published the daily clinical management of patients with altered anatomy and the need of biliary intervention in four tertiary endoscopic centers in Munich. In 33 patients with Billroth II that underwent ERCP with gastroscope, the success rate (defined as reaching the papilla with successful cannulation) was 79%, with 71% of cases with unsuccessful papilla identification and 29% with unsuccessful papilla cannulation. In 72 patients with Billroth II that underwent ERCP with duodenoscope, the success rate was 86%, with 50% of cases with unsuccessful papilla identification and 50% with unsuccessful papilla cannulation [19].

In our study, the favorable results of forward-viewing gastroscope in comparison to the side-viewing duodenoscope can result from the fact that we used a therapeutic gastroscope with an extra-large channel associated sometimes with a transparent cap fitted to the distal end, facilitating not only afferent loop intubation and progression due to its flexibility and good visual field, but also deep cannulation due to its large working channel and use of cap. Recently, two retrospective cohorts of 18 and 46 patients with Billroth II gastrectomy that underwent ERCP using therapeutic double-channel gastroscope reported afferent loop intubation of 83% and papilla cannulation of 100% [20, 21].

This study has some limitations. It is a single-center retrospective cohort with no randomized allocation of the type of endoscope which can lead to bias. Another possible limitation is the sample size, which can influence the effect size, especially in the subgroup analysis. Indeed, the non-statistically significant lower adverse events rate with the forward-viewing gastroscope may traduce the small sample size. However, the majority of the studies published to date have smaller sample sizes [7, 8, 10, 11, 19–21]. Moreover, this study was performed in a tertiary referral center with expertise in ERCP, which could have positively impacted the results, stressing the need to refer

these patients to expert centers. In our study, before 2015, all ERCPs were performed with a side-viewing duodenoscope and after 2015, all ERCP were performed with a forward-viewing gastroscope. This change of type of endoscope in 2015 resulted from a discretionary decision of the endoscopy team and evidence-based literature [13] in order to improve the safety of the intubation of the afferent limb. Therefore, we conducted a multivariate analysis that excluded any significant impact of time on papilla identification, deep cannulation, or adverse events suggesting that the favorable results of forward-viewing gastroscope were not due to experience of the endoscopist but rather due to the type of endoscope used.

Besides the side-viewing duodenoscope and forward-viewing gastroscope (with or without cap-fitting), other endoscopes and techniques have been studied in surgically altered anatomy according to centers experience and technique availability, namely balloon-assisted enteroscope [6, 7], colonoscope [8], anterior oblique-viewing endoscope [9], endoscopic ultrasonography-guided transhepatic antegrade interventions [22], and underwater cap-assisted ERCP [23]. Future comparative studies are warranted.

Although Billroth II anatomy will become less frequent, we will encounter these patients in our endoscopic practice, and we will have to face the challenges to safely and successfully perform ERCP [2]. Current data and this study demonstrate that therapeutic forward-viewing gastroscope with cap-fitting, when necessary, is at least as effective and as safe as side-viewing duodenoscope for ERCP in patients with Billroth II gastrectomy. However, future multi-center randomized trials with large sample size are needed to validate these results and to define the optimal endoscopic approach.

Statement of Ethics

The study was approved by the Ethical Committee of Hospital Santa Luzia, Unidade Local de Saúde Alto Minho, Viana do Castelo, Portugal.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Carlos Borges Chaves, João Sousa, Tarcísio Araújo, João Fernandes, Luís Lopes – data collection; Inês Marques de Sá – data analysis and drafting the manuscript; Tarcísio Araújo, Jorge Canena, Luís Lopes – review of the article.

Data Availability Statement

Data available on request.

References

1 Park TY, Song TJ. Recent advances in endoscopic retrograde cholangiopancreatography in Billroth II gastrectomy patients: a systematic review. World J Gastroenterol. 2019;25:3091–107.
2 Easler JJ, Sherman S. Cap-assisted pancreaticobiliary endoscopy in Billroth II anatomy: ERCP "through the looking glass. Gastrointest Endosc. 2016;83:1202–4.
3 Bove V, Tringali A, Familiari P, Gigante G, Boškoski I, Perri V, et al. ERCP in patients with prior Billroth II gastrectomy: report of 30 years' experience. Endoscopy. 2015;47:611–6.
4 Park TY, Kang JS, Song TJ, Lee SS, Lee H, Choi JS, et al. Outcomes of ERCP in Billroth II gastrectomy patients. Gastrointest Endosc. 2016;83:1193–201.
5 Park CH, Lee WS, Joo YE, Kim HS, Choi SK, Rew JS. Cap-assisted ERCP in patients with a Billroth II gastrectomy. Gastrointest Endosc. 2007;66:612–5.
6 Chu YC, Su SJ, Yang CC, Yeh YH, Chen CH, Yueh SK. ERCP plus papillotomy by use of double- balloon enteroscopy after Billroth II gastrectomy. Gastrointest Endosc. 2007;66:1234–6.
7 Itoi T, Ishii K, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, et al. Single-balloon enteroscopy-assisted ERCP in patients with Billroth II gastrectomy or Roux-en-Y anastomosis (with video). Am J Gastroenterol. 2010;105:93–9.
8 Wang F, Xu B, Li Q, Zhang X, Jiang G, Ge X, et al. Endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy: one single center's experience. Medicine. 2016;95:e5743.
9 Law NM, Freeman ML. ERCP by using a prototype oblique-viewing endoscope in patients with surgically altered anatomy. Gastrointest Endosc. 2004;59:724–8.
10 Kim MH, Lee SK, Lee MH, Myung SJ, Yoo BM, Seo DW, et al. Endoscopic retrograde cholangiopancreatography and needle-knife sphincterotomy in patients with Billroth II gastrectomy: a comparative study of the forward-viewing endoscope and the side-viewing duodenoscope. Endoscopy. 1997;29:82–5.
11 Coşkun O, Ödemiş B. A comparative study of side-viewing duodenoscope and forward-viewing gastroscope to perform endoscopic retrograde cholangiopancreatography in patients with Billroth II gastrectomy. Surg Endosc. 2021;35:4222–30.

12 Kim GH, Kang DH, Song GA, Heo J, Park CH, Ha TI, et al. Endoscopic removal of bile-duct stones by using a rotatable papillotome and a large-balloon dilator in patients with a Billroth II gastrectomy (with video). Gastrointest Endosc. 2008;67:1134–8.
13 Ki HS, Park CH, Jun CH, Park SY, Kim HS, Choi SK, et al. Feasibility of cap-assisted endoscopic retrograde cholangiopancreatography in patients with altered gastrointestinal anatomy. Gut Liver. 2015;9:109–12.
14 Jang JS, Lee S, Lee HS, Yeon MH, Han J-H, Yoon SM, et al. Efficacy and safety of endoscopic papillary balloon dilation using cap-fitted forward-viewing endoscope in patients who underwent Billroth II gastrectomy. Clin Endosc. 2015;48:421–7.
15 Cotton PB, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc. 2010; 71:446–54.
16 Pribadi RR, Rani AA, Abdullah M. Challenges of endoscopic retrograde cholangiopancreatography in patients with Billroth II gastrointestinal anatomy: a review article. J Dig Dis. 2019;20:631–5.
17 Kawamura T, Mandai K, Uno K, Yasuda K. Does single-balloon enteroscopy contribute to successful endoscopic retrograde cholangiopancreatography in patients with surgically altered gastrointestinal anatomy? ISRN Gastroenterol. 2013;2013:214958.
18 Itoi T, Ishii K, Itokawa F, Kurihara T, Sofuni A. Large balloon papillary dilation for removal of bile duct stones in patients who have undergone a billroth ii gastrectomy. Dig Endosc. 2010;22:S98–102.
19 Nennstiel S, Freivogel K, Faber A, Schlag C, Haller B, Blöchinger M, et al. Endoscopic and percutaneous biliary interventions in patients with altered upper gastrointestinal anatomy: the Munich Multicenter Experience. Surg Endosc. 2021;35(12):6853–64.
20 Wang S, Liu W, Sun S, Wang G, Liu X, Ge N, et al. Clinical evaluation of double-channel gastroscope for endoscopic retrograde cholangiopancreatography in patients with Billroth II gastrectomy. Prz Gastroenterol. 2016; 11:163–9.
21 Yao W, Huang Y, Chang H, Li K, Huang X. Endoscopic retrograde cholangiopancreatography using a dual-lumen endogastroscope for patients with Billroth II gastrectomy. Gastroenterol Res Pract. 2013;2013:146867.
22 Itoi T, Sofuni A, Tsuchiya T, Ijima M, Iwashita T. Endoscopic ultrasonography-guided transhepatic antegrade stone removal in patients with surgically altered anatomy: case series and technical review (with videos). J Hepatobiliary Pancreat Sci. 2014;21(12):E86–93.
23 Fugazza A, Anderloni A, Paduano D, Badalamenti M, Maselli R, Carrara S, et al. Underwater cap-assisted endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy: a pilot study. Endoscopy. 2021;53(9):927–31.

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The Impact of Donor Risk Index, Recipients' and Operative Characteristics on Post Liver Transplant One-Year Graft Failure: A Cohort Analysis

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Organ donor · Liver · Transplantation

Abstract

Background and Aims: The donor risk index (DRI) quantifies donor-related characteristics potentially associated with increased risk of early graft failure. We aimed to assess the impact of the DRI, recipient and perioperative factors on post liver transplant (LT) outcomes. ***Methods:*** This was a single-center retrospective cohort study including all adult (≥18 years) patients who underwent LT from 01/2019 to 12/2019 at Curry Cabral Hospital, Lisbon, Portugal. Primary endpoint was 1-year graft failure post LT. Associations were studied with logistic regression. ***Results:*** A total of 131 cadaveric donor LT procedures were performed in 116 recipients. Recipients' median (IQR) age was 57 (47–64) years and 101/131 (77.1%) were males. Cirrhosis was the underlying etiology in 95/131 (81.2%) transplants. Based on 8 predefined donors' characteristics, median (IQR) DRI was 1.96 (1.67–2.16). Following adjustment for MELDNa score pre LT and SOFA score (adjusted odds ratio [aOR], 95% confidence interval [CI] = 0.91 [0.56–1.47]) or lactate (aOR [95% CI] = 2.76 [0.71–10.7]) upon intensive care unit (ICU) admission post LT, DRI was not associated with 1-year graft failure. However, higher SOFA score (aOR [95% CI] = 1.20 [1.05–1.37]) or lactate (aOR [95% CI] = 1.27 [1.10–1.46]) upon ICU admission post LT were independently associated with higher odds of 1-year graft failure. ***Conclusions:*** In a recent cohort of patients who underwent LT, DRI, despite being high, was not associated with 1-year graft failure, but SOFA score or lactate upon ICU admission post LT were.

O impacto do índice de risco do dador e de características relacionadas com os receptores e cirurgia na falência do enxerto um ano após transplante hepático: um estudo coorte

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Resumo

Introdução: O índice de risco do dador (DRI) quantifica as características relacionadas com o dador potencialmente associadas com risco acrescido de falência precoce do enxerto. Procurou-se avaliar o impacto do DRI e factores relacionados com os receptores e cirurgia nos resultados clínicos após transplante hepático (LT). ***Materiais e Métodos:*** Estudo coorte retrospectivo de centro único incluindo todos os doentes adultos (≥18 anos) que receberam LT entre 01/2019 e 12/2019 no Hospital Curry Cabral, Lisboa, Portugal. O endpoint primário foi a falência do enxerto após um ano do LT. As associações foram estudadas com regressão logística. ***Resultados:*** Um total de 131 transplantes de dadores cadavéricos foram realizados em 116 receptores. A idade mediana (IQR) destes foi 57 (47–64) anos e 101/131 (77.1%) eram homens. A cirrose foi a etiologia subjacente em 95/131 (81.2%) transplantes. Com base nas 8 características dos dadores predefinidas, o DRI mediano (IQR) foi 1.96 (1.67–2.16). Após ajuste para o score MELDNa pre LT e o score SOFA (odds ratio ajustado [aOR], intervalo de confiança 95% [CI] = 0.91 [0.56–1.47]) ou o lactato (aOR [95% CI] = 2.76 [0.71–10.7]) após admissão na unidade de cuidados intensivos (ICU) pós LT, o DRI não se associou com a falência do enxerto um ano depois do LT. Contudo, um maior score SOFA (aOR [95% CI] = 1.20 [1.05–1.37]) ou lactato (aOR [95% CI] = 1.27 [1.10–1.46]) após admissão na ICU depois do LT associaram-se independentemente com a falência do enxerto um ano depois do LT. ***Conclusões:*** Num coorte recente de doentes submetidos a LT, o DRI, apesar de alto, não se associou com a falência precoce do enxerto precoce. Contudo, o score SOFA ou lactato após admissão na ICU depois do LT associaram-se com a falência precoce do enxerto.

Introduction

The liver allocation policy based on the Model for End-Stage Liver Disease (MELD) score, more recently with the added component of serum sodium (MELDNa), prioritizes the sicker patients for liver transplant (LT) [1]. That approach has reduced patients' overall mortality on the LT waitlist for more than a decade [2].

The donor risk index (DRI) was developed more than a decade ago to quantify donor-related characteristics that could be associated with increased risk of 1-year graft failure [3]. DRI has offered the possibility to classify organs as high or low risk and has enabled comparisons of transplant practices with such different organs [4, 5]. However, DRI and the several similar models that have been developed afterwards have generally yielded low discriminative or predictive values for post LT outcomes [6].

Perioperative related factors have also been associated with post LT outcomes [7, 8]. However, while recipient- or donor-related factors may be known in advance to allow clinicians to better match LT recipients and donors, perioperative factors are not. Therefore, perioperative factors remain a distinct and difficult to account for component of complex rules intended to predict post LT outcomes.

Accordingly, the objectives of this study were as follows: (1) to assess the impact of DRI on post LT outcomes in a recent cohort of patients; (2) to evaluate the differential impact of recipient, donor, and perioperative factors on post LT outcomes.

Materials and Methods

This study was approved by the Central Lisbon University Hospital Center (CLUHC) ethics committee (reference number INV_185) and informed consent was waived. The study protocol and conduct abided by the principles of the Declaration of Helsinki [9]. The study reporting followed the STROBE guideline [10].

Design, Setting, and Participants

This was a single-center retrospective cohort study including all adult (≥18 years) patients who underwent LT from January 2019 to December 2019 at Curry Cabral Hospital (CCH), CLUHC. Patients who underwent living-donor LT were excluded from the final analysis (online suppl Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000524421).

Operational Definitions and Endpoints

The CCH has performed 2,257 adult LT procedures from January 1992 to December 2019. Listing criteria and peri-LT management, including immunosuppression (online suppl. Table S1), have been in accordance with specific international guidelines [1, 11]. Following LT, all patients are admitted to an intensive care unit (ICU) specialized in LT care and when deemed clinically stable transferred to a specialized ward.

The following data were collected about LT recipients: age, sex, etiology of liver disease, presence of hepatocellular carcinoma (HCC), cause of LT, LT priority, patient location prior to LT, laboratory-based MELDNa prior to LT, and sequential organ failure assessment (SOFA) score and laboratory parameters on ICU admission post LT. The following data were collected about LT procedures: retransplantation status, time of operation (hours), vena cava and biliary anastomosis surgical technique, type and number of blood components transfused, result of blood cultures, and the type of immunosuppression used for induction.

Table 1. Characteristics (*n* (%) or median (IQR)) of recipients stratified by graft survival status at 1 year post LT (*n* = 131)

Characteristics	Total (*n* = 131)	Graft viable (*n* = 103)	Graft failure (*n* = 28)	*p* value
Age, years	57 (47–64)	57 (47–64)	57 (46–64)	0.74
Male sex	101 (77.1%)	77 (74.8%)	24 (85.7%)	0.31
Etiology (*n* = 117)				0.40
Cirrhosis	95 (81.2%)	75 (84.3%)	20 (71.4%)	
ALF	7 (6.0%)	5 (5.6%)	2 (7.1%)	
Other	15 (12.8%)	9 (10.1%)	6 (21.4%)	
HCC (*n* = 117)	45 (38.5%)	37 (41.6%)	8 (28.6%)	0.22
Pre LT status (*n* = 117)				0.29
At home	81 (69.2%)	62 (69.7%)	19 (67.9%)	
At ward	16 (13.7%)	14 (15.7%)	2 (7.1%)	
At ICU	20 (17.1%)	13 (14.6%)	7 (25.0%)	
Urgent LT (*n* = 117)	36 (30.8%)	27 (30.3%)	9 (32.1%)	0.86
Retransplant	34 (26.0%)	26 (25.2%)	8 (28.6%)	0.72
Pre LT MELDNa (*n* = 117)	15 (10–21)	13 (10–21)	18 (10–27)	0.19

IQR, interquartile range; ALF, acute liver failure; HCC, hepatocellular carcinoma; LT, liver transplant; MELDNa, Model for End-stage Liver Disease Sodium score.

Under Portuguese law, all individuals are potential donors of organs unless they specifically opt out in a mandatory and private national registry. Donation procedures are controlled nationally by the Portuguese Institute of Blood and Transplantation.

The DRI was calculated based on the 8 donor-related components derived in the original study: age (years), height (cm), race (white, African descendent, or other), cause of death (trauma, stroke, anoxia, or other), donor following cardiac death, partial or split graft, location of organ sharing (local, regional, or national), and cold ischemia time (CIT; hours) [3]. Additionally, sex, warm ischemia time (WIT), and the type of organ preservation fluid were also retrieved for donors. According to the original study, 1-year graft survival rates varied substantially with the DRI, for example: 85.0% for a DRI of 1.0–1.1, 79.7% for a DRI of 1.4–1.5, or 75.6% for a DRI of 1.8–2.0 [3]. The balance of risk score was also computed, as previously described, for comparative analysis with the DRI [12].

The primary endpoint was graft failure at 1 year following index LT as described elsewhere [3]. The secondary endpoint was index hospital length of stay (LOS).

Statistical Analysis

Continuous variables were described as median and interquartile range (IQR) and categorical variables were described as frequency (*n*) and proportion (%). Univariate comparisons were done using Mann-Whitney or Kruskal-Wallis tests for continuous variables or χ^2 test for categorical variables. Survival was plotted using Kaplan-Meier curves. Multivariable analysis was performed using logistic or linear regression following automated multiple imputation (5 iterations) due to the level of missing data (7.8% across all values in the dataset). Clinical and statistical ($p < 0.10$ on univariate analysis) covariates were included, and final models were obtained following a stepwise backward selection of covariables. The significance level considered was $\alpha = 0.05$ (2-tailed).

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of LT Recipients

A total of 131 cadaveric donor LT procedures were performed in 116 recipients in 2019 (online suppl. Fig. S1). Recipients' median (IQR) age was 57 (47–64) years and 101/131 (77.1%) were males. Cirrhosis (and its complications) was the underlying liver disease in 95/131 (81.2%) transplants. HCC was the cause for LT in 45 (38.5%) cases. Urgent (patient acutely decompensated in the ward or ICU pre transplant) LT was performed in 36/117 (30.8%) patients. The index LT considered was for retransplantation in 34/131 (26.0%) procedures. Median (IQR) MELDNa score pre LT was 15 (10–21). All characteristics of LT recipients are depicted in Table 1.

Characteristics of LT Donors

Median (IQR) age of donors was 64 (50–74) years (61/129 [47.3%] aged ≥65 years), and 71/129 (55.0%) were males. Stroke was the cause of death in 88/131 (67.2%) donors. Only 2/131 (1.5%) donors had primarily cardiac death. No partial or split grafts were used. Organs from a region outside of Lisbon were used in 56/131

Table 2. Characteristics (*n* (%) or median (IQR)) of donors stratified by graft survival status at 1 year post LT (*n* = 131).

Characteristics	Total (*n* =131)	Graft viable (*n* = 103)	Graft failure (*n* = 28)	*p* value
Age, years (*n* = 129)	64 (50–74)	65 (49–76)	68 (53–74)	0.55
Male sex (*n* = 129)	71 (55.0%)	54 (53.5%)	17 (60.7%)	0.50
Height, cm (*n* = 109)	165 (160–172)	165 (170–175)	165 (160–170)	0.69
Etnic origin				0.79
Caucasian	108 (82.4%)	86 (83.5%)	22 (78.6%)	
African	3 (2.3%)	2 (1.9%)	1 (3.6%)	
Other	20 (15.3%)	15 (14.6%)	5 (17.9%)	
Cause of death				0.74
Trauma	19 (14.5%)	16 (15.5%)	3 (10.7%)	
Stroke	88 (67.2%)	67 (65.0%)	21 (75.0%)	
Anoxia	9 (6.9%)	7 (6.8%)	2 (7.1%)	
Other	15 (11.5%)	13 (12.6%)	2 (7.1%)	
Donor of cardiac death	2 (1.5%)	1 (1.0%)	1 (3.6%)	0.38
Partial/split graft	0	0	0	NA
Organ sharing				0.51
Local	19 (14.5%)	15 (14.6%)	4 (14.2%)	
Regional	56 (42.7%)	42 (40.8%)	14 (50.0%)	
National	56 (42.7%)	46 (44.7%)	10 (35.7%)	
CIT, h (*n* = 125)	7.0 (6.5–8.0)	7.0 (6.0–8.0)	7.0 (7.0–8.0)	0.56
WIT, h (*n* = 130)	0.67 (0.58–0.75)	0.58 (0.58–0.75)	0.67 (0.58–0.75)	0.20
DRI (*n* = 103)	1.96 (1.67–2.16)	1.96 (1.65–2.16)	1.98 (1.70–2.44)	0.48

IQR, interquartile range; CIT, cold ischemia time; WIT, warm ischemia time; DRI, donor risk index.

(42.7%) transplants, with only one coming from outside of Portugal (Spain). Median (IQR) CIT and WIT were 7.0 (6.5–8.0) and 0.67 (0.58–0.75) hours, respectively. Celsior® fluid was used for organ preservation in 130/131 (99.2%) organs (the other used was Belzer® fluid). No organs were subjected to normo- or hypothermic automatic perfusion before implantation.

Taking into account the 8 donors' characteristics defined previously, median (IQR) overall DRI was 1.96 (1.67–2.16). Median DRI was similar between patients with a viable graft over 1 year following index LT and others (1.96 vs. 1.98; $p = 0.48$). Furthermore, median DRI was also similar between patients retransplanted over 1 year and others (1.96 vs. 1.96; $p = 0.83$). All characteristics of LT donors are depicted in Table 2.

Perioperative Characteristics

Median (IQR) time of LT procedure was 5.0 (4.0–5.5) hours. Vena cava piggyback technique was performed in 123/131 (93.9%) patients. A duct-to-duct biliary anastomosis was used in 122/131 (93.1%) cases. A median (IQR) of 2 (0–5) units of red blood cells and 10 (0–18) units of fresh frozen plasma were required in the operating room. Bacteremia was identified in the blood collected in the operating room in 8 (6.8%) patients. Upon ICU admission following surgery, median (IQR) lactate and SOFA score were 4.2 (3.0–6.1) mmol/L and 7 (4–10), respectively. Early immunosuppression regimen included induction with basiliximab in 73/117 (62.4%) patients. All perioperative characteristics are depicted in Table 3.

Clinical Outcomes

Among 116 patients who underwent LT during 2019 at CCH, 15 (12.9%) required retransplantation and 103 (88.8%) were alive within 1 year of index LT (online suppl Fig. S2). None of these patients who underwent retransplantation died up to year following index LT. Therefore, graft survival at 1 year following index LT was 78.6% (103/131). The causes of retransplantation within 1 year of index LT were as follows: hepatic artery thrombosis in 8 patients, stenosis of the biliary anastomosis in 4, intrahepatic abscesses in 1, primary non-function in 1, and piggyback syndrome in another one. The causes of mortality within 1 year of index LT were as follows: hemorrhagic shock in 6 patients, liver-related multiorgan failure in 3, septic shock in 2, and stroke in 2. Overall, median (IQR) hospital LOS was 22 (13–37) days.

Table 3. Perioperative characteristics (*n* (%) or median (IQR)) stratified by graft survival status at 1 year post LT (*n* = 131)

Characteristics	Total (*n* = 131)	Graft viable (*n* = 103)	Graft failure (*n* = 28)	*p* value
Duration of operation, h (*n* = 130)	5.0 (4.0–5.5)	5.0 (4.0–5.0)	5.0 (4.5–6.0)	0.024
Vena cava surgical technique				0.99
Piggyback	123 (93.9%)	96 (93.2%)	27 (96.4%)	
Classical	8 (6.1%)	7 (6.8%)	1 (3.6%)	
Biliary anastomosis				0.11
Duct-to-duct with T tube	22 (16.8%)	18 (17.5%)	4 (14.3%)	
Duct-to-duct without T tube	100 (76.3%)	77 (74.8%)	23 (82.1%)	
Hepatico-jejunostomy	8 (6.1%)	8 (7.8%)	0 (0%)	
Other	1 (0.8%)	0 (0%)	1 (3.6%)	
Transfusions (*n* = 112)	12 (1–25)	11 (1–25)	15 (1–37)	0.20
RBC	2 (0–5)	2 (0–4)	3 (0–7)	
FFP	10 (0–18)	9 (0–17)	11 (0–28)	
Bacteremia from blood in OR (*n* = 117)	8 (6.8%)	5 (5.6%)	3 (10.7%)	0.40
Lactate on ICU admission, mmol/L (*n* = 117)	4.2 (3.0–6.1)	4.0 (2.8–5.5)	5.9 (3.9–9.9)	0.001
SOFA on ICU admission (*n* = 117)	7 (4–10)	6 (4–9)	10 (6–14)	0.009
Early immunosuppression (*n* = 117)				0.26
Steroids + tacrolimus	44 (37.6%)	36 (40.4%)	8 (28.6%)	
Steroids + Basiliximab + tacrolimus	73 (62.4%)	53 (59.6%)	20 (71.4%)	

IQR, interquartile range; RBC, red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; OR, operating room.

Table 4. Study of associations of covariates with graft failure at 1 year post index LT by multivariate logistic regression

Characteristics	OR (95% CI)	aOR (95% CI)	Adjusted *p* value
Model 1			
DRI	1.73 (0.46–6.73)	0.91 (0.56–1.47)	0.69
Pre LT MELDNa	1.03 (0.99–1.08)	0.99 (0.94–1.05)	0.78
SOFA on ICU admission	1.17 (1.05–1.29)	1.20 (1.05–1.37)	0.007
Model 2			
DRI	1.73 (0.46–6.73)	2.76 (0.71–10.7)	0.14
Pre LT MELDNa	1.03 (0.99–1.08)	1.02 (0.97–1.07)	0.52
Lactate on ICU admission (mmol/L)	1.17 (1.05–1.29)	1.27 (1.10–1.46)	0.001

Total *N* patients following multiple imputation (5 iterations) = 131; *N* events of retransplant or death at 1 year post LT = 28; c-statistic (95% CI) model 1 = 0.70 (0.57–0.82) and model 2 = 0.72 (0.60–0.83). OR, odds ratio; aOR: adjusted odds ratio; 95% CI, 95% confidence interval; DRI, donor risk index; LT, liver transplant; MELDNa, Model for End-stage Liver Disease Sodium score; SOFA, Sequential Organ Failure Assessment score; ICU, intensive care unit.

The Adjusted Association of DRI with Endpoints

Using logistic regression, following adjustment for pre LT (MELDNa score) and perioperative (SOFA score or lactate on ICU admission) characteristics, DRI was not associated with 1-year graft failure (Table 4: adjusted odds ratio [aOR] and 95% confidence interval [CI] = 0.91 [0.56–1.47] for model one [$p = 0.69$] or 2.76 [0.71–10.7] for model 2 [$p = 0.14$]). In fact, only higher SOFA score (aOR [95% CI] = 1.20 [1.05–1.37]; $p = 0.007$) or lactate (aOR [95% CI] = 1.27 [1.10–1.46]; $p = 0.001$) on ICU admission were independently associated with higher odds of 1-year graft failure. Furthermore, the discriminative

ability of both models was reasonably good (c-statistic [95% CI] = 0.70 [0.57–0.82] for model one and 0.72 [0.60–0.83] for model 2).

Using logistic regression, both on unadjusted (OR [95% CI] = 1.08 [1.00–1.17]; $p = 0.005$) and adjusted (for SOFA score: aOR [95% CI] = 0.99 [0.89–1.10]; $p = 0.88$) analyses, the balance of risk score (includes donor and recipient's characteristics) was also not associated with 1-year graft failure.

Using linear regression, both on unadjusted (regression coefficient [95% CI] = 2.18 [−8.49 to 12.84]) and adjusted (for MELDNa and SOFA scores: regression coefficient [95% CI] = 1.82 [−9.10 to 12.74]) analyses, DRI was not associated with hospital LOS.

Discussion

Key Results and Comparisons with Previous Literature

In a recent Portuguese cohort of patients who underwent cadaveric donor LT, median DRI was as high as 1.96, but it was not associated with graft failure at 1 year post index LT. In fact, only perioperative characteristics, such as SOFA score or lactate on ICU admission post index LT, were independently associated with 1-year graft failure.

Over the past few decades, reports have documented that given the scarcity of organs and the increasing competence in performing LT internationally, centers have been accepting more frequently extended criteria donors with good post LT outcomes [1, 13, 14]. In our cohort, 47.3% of all donors were ≥65 years old, a unique criterium often used to define marginal donors [1]. Therefore, we were expecting to find a high median DRI (1.96). Fortunately, this did not apparently translate into poorer post LT outcomes, namely the 1-year graft survival. The fact that our LT program has been running for >25 years and currently with >100 procedures performed annually may help to explain the increasing competence in using and taking advantage of such marginal donors at CCH [13]. However, we still observed a retransplantation rate of 12.9% within 1 year post index LT, which signals a window of opportunity for potential improving graft's longevity, especially in terms of prevention and treatment of the hepatic artery thrombosis.

Several studies have tried to evaluate the impact of recipient or perioperative factors on post LT outcomes besides donor characteristics [7, 8, 15–19]. In our cohort, among pre LT, operative, or early post LT characteristics, only higher SOFA score or lactate on ICU admission following index LT were independently associated with higher odds of 1-year graft failure.

SOFA score has been widely used to quantify organ failure severity in general critically ill patients [20]. Therefore, we would expect SOFA score to capture the severity of illness in patients who underwent a complex transplant procedure, often with aggressive ongoing organ support measures. This complexity may result from preoperative clinical instability, surgical complications, or even post reperfusion graft malfunctioning. Much in the same way, lactate is a known good marker of ongoing physiological stress, whether caused by transient hypovolemia or shock [21]. Furthermore, a poorly working liver will not clear lactate appropriately. In fact, worse post LT lactate clearance has been associated with poorer post LT outcomes [18, 19].

Taking into account all of our findings, we should make the following remarks. Firstly, while DRI may be useful to compare specific donors' characteristics, especially for high-risk donors, in our cohort, its prognostic value was poor. However, DRI may be potentially improved by including other relevant donor factors, for example the degree of liver steatosis [6]. Secondly, the overall severity of illness immediately following LT effectively impacted 1-year graft failure. Therefore, understanding, preventing, and timely treating organ failures during and following transplant surgery could be important to improve patients' outcomes.

Limitations

The interpretation of our results should take into account the following limitations. Firstly, this was a single-center retrospective study, therefore it may have been prone to selection bias. Certainly, there are specific features of every LT center. However, the high volume of transplant procedures at CCH and the extensive characterization of both recipients and donors may have helped to mitigate that risk. Secondly, the overall rate of missing values may have interfered with the final modeling performed. However, we think that the multiple imputation strategy used, as per suggested recommendations, may have helped to mitigate that effect [22]. Thirdly, other donors' characteristics may have an impact on the graft quality, for example the degree of liver steatosis or retrieval techniques. Unfortunately, we were unable to collect data on further features that could help to better characterize accepted grafts. Fourthly, based on previous literature, we only analyzed clinical outcomes up to 1 year following index LT. However, it may be of interest to understand if donors' features may impact long-term results, for example at 5 years post LT (criterion of futility of transplant).

Despite these limitations, we think our study adds to the literature dedicated to study the factors that may influence post LT outcomes. In fact, it tries to recognize the multiple factors possibly involved in a complex interconnected way, while highlighting the relevance of the overall severity of illness immediately upon LT. In future studies, to further characterize what happens in the operating room during LT, for example the number and severity of ensuing organ failures, may shed some additional light on the prognosis of LT recipients.

Conclusions

In a recent Portuguese cohort of patients who underwent LT, DRI was high. While DRI was not associated with 1-year graft failure, SOFA score or lactate on ICU admission post LT were.

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Statement of Ethics

This study was approved by the Central Lisbon University Hospital Center (CLUHC) ethics committee (reference number INV_185).

Conflicts of Interest and Source of Funding

None for all authors.

Author Contributions

F.S.C. and L.B. conceived the idea and wrote the protocol. F.S.C., L.B., and A.M. retrieved the data. F.S.C. performed the statistical analysis and wrote the manuscript. All authors provided content expertise and revised and approved the final manuscript.

Data Availability Statement

Due to confidentiality rules, data used in this study will not be publicly available.

References

1 European Association for the Study of the Liver. EASL clinical practice guidelines: liver transplantation. J Hepatol. 2016;64(2):433–85.
2 Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124(1):91–6.
3 Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant. 2006;6(4):783–90.
4 Blok JJ, Braat AE, Adam R, Burroughs AK, Putter H, Kooreman NG, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. Liver Transpl. 2012;18(1):112–9.
5 Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am J Transplant. 2012;12(10):2789–96.
6 Flores A, Asrani SK. The donor risk index: a decade of experience. Liver Transpl. 2017;23(9):1216–25.
7 Schoening W, Helbig M, Buescher N, Andreou A, Schmitz V, Bahra M, et al. Eurotransplant donor-risk-index and recipient factors: influence on long-term outcome after liver transplantation: a large single-center experience. Clin Transplant. 2016;30(5):508–17.
8 Blok JJ, Putter H, Rogiers X, van Hoek B, Samuel U, Ringers J, et al. Combined effect of donor and recipient risk on outcome after liver transplantation: research of the Eurotransplant database. Liver Transpl. 2015;21(12):1486–93.
9 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.
10 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–7.
11 Charlton M, Levitsky J, Aqel B, O'Grady J, Hemibach J, Rinella M, et al. International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients. Transplantation. 2018;102(5):727–43.
12 Martínez JA, Pacheco S, Bachler JP, Jarufe N, Briceño E, Guerra JF, et al. Accuracy of the BAR score in the prediction of survival after liver transplantation. Ann Hepatol. 2019;18(2):386–92.
13 Ozhathil DK, Li YF, Smith JK, Tseng JF, Saidi RF, Bozorgzadeh A, et al. Impact of center volume on outcomes of increased-risk liver transplants. Liver Transpl. 2011;17(10):1191–9.
14 Zhang T, Dunson J, Kanwal F, Galvan NTN, Vierling JM, O'Mahony C, et al. Trends in outcomes for marginal allografts in liver transplant. JAMA Surg. 2020;155(10):926–32.
15 Schrem H, Klußmann A, Focken M, Emmanouilidis N, Oldhafer F, Klempnauer J, et al. Post-operative hemorrhage after liver transplantation: risk factors and long-term outcome. Ann Transplant. 2016;21:46–55.
16 Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am J Transplant. 2008;8(12):2537–46.

17 Karvellas CJ, Bagshaw SM. Advances in management and prognostication in critically ill cirrhotic patients. Curr Opin Crit Care. 2014;20(2):210–7.
18 Takahashi K, Jafri SR, Safwan M, Abouljoud MS, Nagai S. Peri-transplant lactate levels and delayed lactate clearance as predictive factors for poor outcomes after liver transplantation: a propensity score-matched study. Clin Transplant. 2019;33(7):e13613.
19 Kim S, Zerillo J, Tabrizian P, Wax D, Lin HM, Evans A, et al. Postoperative meld-lactate and isolated lactate values as outcome predictors following orthotopic liver transplantation. Shock. 2017;48(1):36–42.
20 Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754–8.
21 Bakker J, de Lima AP. Increased blood lacate levels: an important warning signal in surgical practice. Crit Care. 2004;8(2):96–8.
22 Pedersen AB, Mikkelsen EM, Cronin-Fenton D, Kristensen NR, Pham TM, Pedersen L, et al. Missing data and multiple imputation in clinical epidemiological research. Clin Epidemiol. 2017;9:157–66.

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Burden of Disease and Cost of Illness of Inflammatory Bowel Diseases in Portugal

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Keywords
Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Burden of disease · Cost of illness

Abstract
Background: Inflammatory bowel diseases' (IBD) increasing incidence and prevalence place a heavy health and economic burden on society. ***Objectives:*** This study assesses the burden and cost of IBD in Portugal to support the definition of health policies, resource allocation, and patient care. ***Methods:*** The burden of disease was expressed using disability-adjusted life years (DALY). Costs were estimated considering the societal perspective, using a prevalence-based model and prices established by law. An expert panel composed of 5 expert Portuguese gastroenterologists and a patient-reported study were conducted to support the cost analysis and fill in information gaps. ***Results:*** In Portugal, with a prevalence of 24,069 IBD patients and an incidence of 15/100,000, the burden of disease was estimated at 6,067 DALYs: 507 resulting from premature deaths and 5,560 from disability. Total cost was estimated at EUR 146 million per year, with direct costs representing 59%. Average yearly cost per IBD patient is EUR 6,075, where 60% is related to Crohn's disease and 40% to ulcerative colitis (UC). ***Conclusion:*** This study estimates the annual health burden and cost of IBD in Portugal, thus generating information with the intent to raise awareness of the need to advance health policies as well as better clinical and economic decisions in this pathology.

Custo e carga das doenças inflamatórias intestinais em Portual

Palavras Chave
Doença inflamatória intestinal · Colite ulcerosa · Doença de Crohn · Carga da doença · Custo da doença

Resumo
Contexto: A crescente incidência e prevalência das Doenças Inflamatórias Intestinais (DII) representam um pesado fardo para a saúde e economia na sociedade. ***Objetivos:*** Este estudo avalia o custo e a carga da DII em Portugal, com o objetivo de suportar a definição de políticas de saúde, alocação de recursos e cuidados com o doente.

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Métodos: A carga da doença foi calculada utilizando anos de vida ajustados à incapacidade (DALY). Os custos foram estimados tendo em conta a perspetiva da sociedade, utilizando um modelo baseado na prevalência e preços estabelecidos por lei. Foi realizado um painel de peritos, composto por 5 gastroenterologistas portugueses, assim como um estudo de mercado a doentes, de forma a suportar a análise de custos e colmatar lacunas de informação. ***Resultados:*** Em Portugal, com uma prevalência de 24,069 doentes e uma incidência de 15/100,000, o peso das DII foi estimado em 6.067 DALYs: 507 dos quais resultantes de mortes prematuras e 5.560 de incapacidade. O custo total foi estimado em 146 milhões de euros por ano, com os custos diretos a representarem 59% do total. O custo médio anual por doente de DII é de 6.075 EUR, onde 60% está relacionado com Doença de Crohn (DC) e 40% com Colite Ulcerosa. ***Conclusão:*** Este estudo estima os encargos anuais para a saúde e o custo da DII em Portugal, gerando informação relevante, com o intuito de alertar para a necessidade de uma evolução nas políticas de saúde, assim como como suportar melhores decisões clínicas e económicas nesta patologia.

Introduction

Inflammatory bowel disease (IBD) encompasses two chronic inflammatory conditions: ulcerative colitis (UC) and Crohn's disease (CD) [1]. UC is a lifelong disease described by continuous mucosal inflammation involving the rectum and a variable extent of the colon. In CD, the terminal ileum and/or proximal colon are affected in the majority of cases, though the disease may co-exist in other locations [2–4].

Available medical and surgical therapies are more focused in managing the disease symptoms than in a curative result [5, 6]. Although IBD etiology is still clouded, the incidence has been increasing in newly industrialized countries that have become more westernized, with IBD estimated to affect up to 0.8% of the general western population [7–11]. Characterized as a chronic disease with an early onset, low mortality rates and high morbidity, IBD patients require continuous medical assistance, thus creating a considerable healthcare and economic burden [12, 13]. In addition, surgical hospitalizations and the rising utilization of biologic drugs are increasing the cost of treatment for a disease that is continuously increasing its prevalence, exacerbating the burden on the healthcare system. However, while more expensive than conventional therapies, biologic agents are successfully being used to induce remission in patients with moderate and severe forms and unresponsive to conventional therapies, confirming that those are effective alternatives that remarkably improve the overall quality of life [14, 15]. The annual healthcare burden in Europe is estimated to range between 4.5 and 5.6 billion euros, with global disability-adjusted life years (DALYs) of 1,849,068 reported in the Global Burden of Disease study (GBD) [16–18].

The combination of reduced quality of life and a lifelong need for medical care places a burden on both patients and caregivers, particularly since onset occurs during the most economically productive phase of the patient's life [19–21]. Both UC and CD entail recurring hospitalizations, commuting for appointments and exams, a reduction in work availability and restrictions in time off work. Indirect costs also play a sizable role in the burden of disease [12, 19]. As a result, reports show indirect costs make up almost 50% of the total cost of IBD [17].

To effectively define health policies, improve resource allocation and align patient care health policies for IBD, there is a need to generate data and evidence for this disease. This study aimed to estimate the values associated with the annual health burden and cost of IBD in Portugal.

Materials and Methods

Burden of Disease

The burden of disease was assessed by considering the impact in terms of DALY, a metric adopted by WHO which measures the years of healthy life lost due to disease or premature death. As IBD is a chronic disease, the best suited model to estimate the burden of disease is a prevalence-based model. The most conservative forecast methodology in the paper by Santiago et al. was used to estimate prevalence [22]. DALY is given by, DALY = YLL + YLD, where two time-based indicators are included: years of life lost (YLL), which measures premature mortality due to the disease; and years lost due to disability (YLD), measuring the number of years patients live with disability due to the disease [23–28]. Further details on the methodology used for DALY calculations can be found in the online supplementary Appendix A (for all online suppl. material, see www.karger.com/doi/10.1159/000525206).

Cost of Illness

The cost of IBD was estimated considering the societal perspective to assess the economic impact on the NHS, social security, patients, and caretakers. A prevalence-based model was also used, in which direct costs were estimated for both the NHS and patients in Portugal, alongside indirect costs that could impact other stakeholders. This methodology is commonly used for raising awareness among policy-makers [29]. Both direct healthcare and non-

Table 1. Established price according to type of transport situation and vehicle used

Transport situation	Units	Ambulance	Private vehicle
Not in same district	Price per kilometer in EUR	EUR 0.51	EUR 0.35
Same district	Fixed price in EUR	EUR 7.5	EUR 10

Table 2. Expert panel composition with expert name, hospital, and region of work

Expert	Hospital	Region
Dr. Cristina Chagas	Centro Hospitalar Lisboa Ocidental – Hospital Egas Moniz	Lisbon
Prof. Fernando Magro	Centro Hospitalar São João – Hospital São João	Porto
Dr. Francisco Portela	Centro Hospitalar e Universitário de Coimbra – CHUC	Coimbra
Dr. Luís Correia	Centro Hospitalar Universitário Lisboa Norte – CHULN	Lisbon
Dr. Paula Lago	Centro Hospitalar Universitário do Porto – Hospital de Santo António	Porto

healthcare costs were considered in this analysis. The first entails medical appointments, emergency visits, hospitalizations, surgeries, laboratory tests and exams, drug usage, and administration, and the latter is solely comprised of patient transportation to and from the hospital according to the vehicle used by the patient (see Table 1) [30].

Labor earnings lost due to adverse health disorders are quantified in an indirect cost analysis. Indirect costs are not limited to lost earnings and productivity of patients but also include those of caretakers that assist patients. Costs estimated impact companies where patients are less effective and social ecurity, which assumes the costs of early retirement, sick leave, and work absences by either patients or caretakers.

All costs were calculated separately for UC and CD, except for premature death figures in indirect costs. Further details on the methodology used for cost calculations can be found in the online supplementary Appendix B.

In order to quantify hospital production for IBD patients, the NHS hospital Diagnosis-related group (DRG) database from 2016 was analyzed, since it was the most up-to-date and complete data available, regarding all patients diagnosed with the International Classification of Diseases (ICD-9) codes related to both diseases (555.x for CD and 556.x for UC). All codes used can be found in detail in the online supplementary Appendix C.

Drug costs were analyzed using the consumption of IBD-related molecules in 2019 in both retail and hospital scope. The data sources used were IQVIA's EHN database (National Hospital Study) for public hospital's consumption at purchase price and IQVIA's ICH database (Consumer Health Index) for retail consumption at public selling price. Both databases have national coverage.

A local expert panel, Table 2, composed by 5 Portuguese gastroenterologists' experts from different hospitals and regions, met for a meeting on December 16, 2019. This panel assisted in filling gaps of information, as described in each section, in order to calculate costs. The panel followed a two-round modified Delphi methodology, where a first round consisted of sending a questionnaire to the experts, followed by a second round of live discussion. Data collected was not extrapolated since the experts' view was considered as a representation of the national clinical reality.

To support the cost analysis, an anonymized patient-reported study was conducted online with 370 Portuguese IBD patients. This study was conducted in January 2020 by the Portuguese Association of Inflammatory Bowel Disease (APDI), collecting data from its associates considering a retrospective period ranging between 1 week and 1 year, depending on the type of question. Patients were stratified geographically (NUTS II) and by age. A study error margin of 5% at a 95% confidence level was found [30–36].

Results

Burden of Disease

The IBD population in Portugal is estimated to be 24,069 patients. Considering the diseases' split published, 11,866 of these are estimated to have UC and 12,203 have CD [22, 25, 26]. Considering this prevalence, 6,067 DALYs were estimated to be lost in Portugal due to IBD. This result reflects a total of 507 YLLs and a total of 5,560 YLDs in the Portuguese population. The low value of YLL is a consequence of (1) 133 deaths, calculated using published mortality ratios of 1.19 and 1.38 for UC and CD, respectively [24], and (2) the general population's average remaining life expectancy of 3.8 years, which was obtained by subtracting the median age of death from NHS 2016 data, 77.0 years, from the average life expectancy in statistical national data of 2018, 80.8 years. On the other hand, the value of YLD was calculated by multiplying the reported prevalence, 232/100,000, by the disability weight stated in the GBD 2017 of 0.231 [18, 22].

Table 3. IBD direct and indirect costs by category

	UC, average cost per patient/year	CD, average cost per patient/year	IBD, average cost per patient/year	Total costs
Medical hospitalization	EUR 66	EUR 88	EUR 77	EUR 1,865,213
Surgery	EUR 35	EUR 57	EUR 46	EUR 1,104,254
Gastroenterology HCP visits	EUR 215	EUR 303	EUR 260	EUR 6,254,611
Other specialty HCP visits	EUR 45	EUR 77	EUR 61	EUR 1,472,590
Emergency visits	EUR 144	EUR 161	EUR 153	EUR 3,677,619
Laboratory tests and exams	EUR 206	EUR 189	EUR 197	EUR 4,742,263
Pharmacologic treatment	EUR 2,336	EUR 2,817	EUR 2,580	EUR 62,101,183
Total direct healthcare	EUR 3,047	EUR 3,693	EUR 3,374	EUR 81,217,733
Direct nonhealthcare (transport)	EUR 198	EUR 267	EUR 233	EUR 5,616,278
Total direct costs	EUR 3,245	EUR 3,960	EUR 3,608	EUR 86,834,011
Patient work absence	EUR 574	EUR 1,114	EUR 845	EUR 20,404,544
Caretakers work absence	EUR 98	EUR 61	EUR 79	EUR 1,907,243
Presentism	EUR 798	EUR 779	EUR 788	EUR 18,977,772
Premature death	–	–	EUR 71	EUR 1,709,981
Early retirement	EUR 251	EUR 1,105	EUR 684	EUR 16,459,530
Total indirect costs	EUR 1,772	EUR 3,129	EUR 2,468	EUR 59,459,070
Total costs	EUR 5,037	EUR 7,090	EUR 6,075	EUR 146,293,081

Although not all patients display costs in all categories, in order to obtain the average cost per patient, a direct calculation was performed by dividing the total cost of the category by all patients. UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; HCP, health care professional.

For UC, the YLL yielded was 222 as there were 123 deaths in 2016 and the remaining life expectancy was 1.8 years. In turn, for CD, the YLL yielded was 1,117 as the number of deaths was 143 with 7.8 years of remaining life expectancy. On the other hand, the YLD for UC and CD was 2,741 and 2,819, respectively.

Cost of Illness

The total annual cost associated with IBD patients in Portugal was estimated to be EUR 146,293, 081, with an average annual cost of EUR 6,075 per patient. This value is divided into EUR 86,834,011 direct costs and EUR 59,459,070 indirect costs. All IBD-related costs are summarized in Table 3, with the respective split between UC and CD. Although not all patients display costs in all categories, in order to obtain the average cost per patient, a direct calculation was performed by dividing the total cost of the category by all patients.

Direct Healthcare Cost

From the NHS 2016 database, 1,455 IBD patients were considered, using the ICD-9 UC and CD specific codes, which accounted for 2,420 episodes and 11,989 procedures. Regarding demography, 82% of patients were under 65 years old, 51% were female, and 42% had their address of residence in either Lisbon or Porto (see Table 4). Medical direct costs resulted in a total of EUR 81,217,733, with an average cost of EUR 3,374 per patient.

Medical Hospitalizations

Of the 2,420 episodes registered, 2,148 were recorded as medical episodes. The average cost of a medical episode was EUR 868, meaning a total cost of EUR 1,865,213, with an average of EUR 77.50 per patient.

Surgery

272 episodes out of the 2,420 were registered in our patient data pool as surgical episodes, resulting in an average cost of EUR 4,060 per episode, meaning a total cost of EUR 1,104,254, with an average of EUR 45.90 per patient.

Gastroenterology (HCP) Visits

The 2,420 episodes included were distributed by hospital category, resulting in a price per appointment of EUR 60.20 for UC and EUR 58.10 for CD. With these and the estimate of a total of 94,661 visits (an average of 3.9 per patient – see Table 5), the total cost was calculated to be EUR 6,113,269, with an average of EUR 254 per patient.

Table 4. Key statistics and demographics of the population selected with ICD-9 codes from the National Health Service hospital 2016 database

	UC	CD	IBD
DRG database statistic, *n* (%)			
Patients	523 (36)	932 (64)	1,455
Episodes	774 (32)	1,646 (68)	2,420
Procedures	4,567 (38)	7,422 (62)	11,989
Gender split, *n* (%)			
Male	275 (53)	434 (47)	709 (49)
Female	248 (47)	498 (53)	746 (53)
Age group split, *n* (%)			
≤25 years	104 (32)	233 (68)	327 (22)
26–44 years	147 (29)	358 (71)	505 (35)
45–64 years	136 (38)	225 (62)	361 (25)
65–84 years	117 (50)	116 (50)	233 (16)
≥85 years	19 (66)	10 (34)	29 (2)
Distribution by residence district of patient, *n* (%)			
Lisbon	136 (40)	202 (60)	338 (23)
Porto	73 (27)	197 (73)	270 (19)
Setubal	45 (30)	104 (70)	149 (10)
Braga	35 (34)	69 (66)	104 (7)
Other	234 (39)	360 (61)	594 (41)

UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; DRG, diagnosis related group.

Table 5. Number of Health Care Professional visits, emergencies, and exams & laboratory tests per disease and disease stage

	UC	CD
Gastroenterology (HCP) visits		
Mild disease	96% patients; 1.9 appointments	97% patients; 2.1 appointments
Moderate disease	98% patients; 4.4 appointments	99% patients; 4.6 appointments
Severe disease	100% patients; 7.4 appointments	100% patients; 7.6 appointments
Other HCP specialty visits		
Surgery	6% patients; 1.3 appointments	26% patients; 1.8 appointments
Rheumatology	18% patients; 1.5 appointments	20% patients; 1.5 appointments
Infectiology/immunomodulation	27% patients; 1.1 appointments	33% patients; 1.1 appointments
Dermatology	6% patients; 1.3 appointments	9% patients; 1.5 appointments
Other	5% patients; 1.0 appointments	9% patients; 1.0 appointments
Emergency visits		
Mild disease	6% patients; 1.0 appointments	8% patients; 1.0 appointments
Moderate disease	24% patients; 1.5 appointments	43% patients; 1.4 appointments
Severe disease	73% patients; 2.2 appointments	79% patients; 2.2 appointments
Exams and laboratory tests		
Colonoscopy	0.7 exams per patient	0.5 exams per patient
Endoscopy	0.1 exams per patient	0.3 exams per patient
Magnetic resonance imaging	0.02 exams per patient	0.4 exams per patient
X-ray	0.1 exams per patient	0.2 exams per patient
Ultrasounds	0.1 exams per patient	0.3 exams per patient
Computed tomography	0.1 exams per patient	0.2 exams per patient
Blood tests	1.0 exams per patient	1.0 exams per patient
Faecal tests	1.0 exams per patient	0.9 exams per patient
Sigmoidoscopy	1.3 exams per patient	0.0 exams per patient

UC, ulcerative colitis; CD, Crohn's disease; HCP, Health Care Professional.

Other HCP Specialty Visits

A total of 25,048 appointments were estimated (an average of 1.0 per patient – see Table 5), and with the same indexed hospital visit price, the total cost was estimated to be EUR 1,613,932, with an average cost of EUR 67.10 per patient.

Emergency Visits

The weighted emergency price was estimated to be EUR 57.70 for UC and EUR 56.60 for CD. While a total of 53,639 emergencies were calculated, 1,198 were already being costed via hospitalization or surgery as this emergency resulted in an inpatient episode, hence only 52,441 emergencies (2.2 emergencies per patient – see Table 5) were costed in this category. Total cost was EUR 3,677,619, with an average cost of EUR 152.80 per patient.

Exams and Laboratory Tests

A total of 99,929 exams were estimated in this category, considering the number of patients and the number of exams per patient (see Table 5). Considering user charge exemptions, a total cost of EUR 4,742,263 was calculated, with an average cost of EUR 197 per patient.

Pharmacologic Treatment

The cost was estimated to be EUR 62,101,183, with EUR 14,995,671 resulting from retail and EUR 46,697,462 from hospital drug consumption. For retail, the split between UC and CD was EUR 11,313,646 and EUR 3,682,025, respectively. This high discrepancy is mainly due to mesalazine (EUR 10,118,105), which is used with considerably greater frequency in UC in comparison with CD. Although the evidence of the effectiveness of mesalazine in CD is very low, the expert panel validated its use in residual cases. In contrast, costs of hospital consumption for UC and CD were EUR 15,295,110 and EUR 31,402,352, respectively. Here, the most decisive parameter is the cost of biologic drugs: 36% of its usage is in UC, while 64% is in CD, shifting the cost weight to CD. Here, certolizumab is referred as being used off-label by the expert panel in a residual number of cases. Immunomodulators administration cost is estimated to be EUR 408,050, with EUR 124,849 for UC and EUR 283,200 for CD. Cost split by molecule in both retail and hospital environment can be found in the online supplementary Appendix D.

Direct Nonhealthcare Cost

It was estimated that 85% of IBD episodes registered, occurred in a hospital within the patient's district of residence. This resulted in a total transportation cost of EUR 5,616,278, with an average cost of EUR 233.30 per patient.

Patient Out-Of-Pocket Costs

Considering all dimensions where out-of-pocket expenses are present, costs allocated to patients sum up a total of EUR 12,030,257 per year, with an annual average cost of EUR 499 per patient. These costs are included as a subset of direct costs, representing 14% of them.

The patient reported study returned an average of 10% of UC patients and 25% of CD patients that were exempt from medical taxes. As such, the total out-of-pocket cost for HCP visits was determined to be EUR 680,141, with EUR 293,693 for UC and EUR 386,449 for CD. Emergency visits resulted in a slightly higher cost, with a total of EUR 683,595, of which EUR 344,457 were for UC and EUR 339,138 for CD. Exams and laboratory tests out-of-pocket cost amounted to a total of EUR 357,892 for UC and EUR 300,873 for CD.

By considering the reimbursement rates established for each drug, approximately 30% of retail drugs cost was supported by the patients, representing EUR 4,493,975 in co-payments: EUR 3,472,175 for UC and EUR 1,021,800 for CD. Also, according to the patient-reported study, only 3% of emergency visits and HCP visits travels were made by ambulance. Hence, most transportation costs are allocated to patients: EUR 5,513,781 – being EUR 2,336,737 for UC and EUR 3,166,809 for CD.

Indirect Costs

Total costs were estimated at EUR 59,459,070, with an average cost of EUR 2,468 per patient.

Patient Work Absences

A total of 355,539 days were lost due to IBD in 1 year. This number of days lost was estimated by integrating the following four categories:

1. Inpatient time – a total of 0.7 days per patient were registered in the NHS 2016 database;
2. Appointment time – considering 0.5 days lost per appointment, a total of 3.6 days per patient were determined to be associated with medical appointments and emergency visits;
3. Daycare facilities time – following the same assumption of 0.5 days lost per session of day hospital, 0.4 days per patient were calculated;
4. Sick leave – the patient study recorded 10 days per patient lost yearly as sick leave.

These values computed with the employment rate of IBD patients registered in the patient study, 78.2%, and

considering the national daily wage from 2019, correspond to a total cost of EUR 20,404,544, with an average cost of EUR 845.10 per patient. This cost is attributed not only to social security through inpatient time and sick leave but also to either patients or employers since medical appointments and therapy sessions in day care hospital are usually not eligible for sick leave.

Caretaker Work Absences

Patient study responses showed that an average of 34% of patients is accompanied by a caretaker, a cost that is supported by social security, patients' caregivers, and/or employers. An employment rate of 74% for caretakers and an average of 4.3 days used by the caretaker were also obtained. This yielded a total of 26,055 days, which caretakers lost accompanying patients for IBD-related events, which multiplied by the daily wage resulted in a total cost of EUR 1,907,243, with an average of EUR 79.20 per patient.

Presenteeism

Portuguese IBD patients work an average of 38.3 h per week and the average number of hours lost due to IBD is 2.4 h, thus estimating a 94% efficiency rate when compared to a healthy co-worker. Assuming a total of 220 working days in a year, the patients lost a total of 259,253 days (average of 13.8 days per patient), that amounts to a total cost of EUR 18,977,772, with an average cost of EUR 788.50 per patient. With these costs solely affecting employers, presenteeism is one of the highest indirect costs.

Premature Death

The median age of death for IBD patients reported in the NHS 2016 database was 77.0 years, which differed by 3.8 years from the 80.8 national average life expectancy reported. This number of years lost multiplied by the number of deaths and the average national income per capita resulted in a total cost of EUR 1,709,981, with an average of EUR 71 per patient, a loss supported by social security.

Early Retirement

The number of retirements related to IBD was obtained through the patient study, as well as their average age of retirement – 55 years for UC and 49 years for CD. This data was then compared to the national average age of retirement, which returned a total of 4,881 years lost due to early retirement. Applying the average national income per capita, a total cost of EUR 16,459,530 was estimated, with an average of EUR 683.80 per patient. Like premature death, early retirement costs are supported by social security.

Discussion/Conclusion

This study allowed us to accomplish the proposed main objectives by successfully providing evidence of both the burden and cost of IBD in Portugal, which will allow the filling of an existing information gap at a national level. Considering disease burden, most of the impact of the DALYs lost comes from YLD, which represented 92%, mainly due to the high prevalence of the disease and the early age of onset. On the other hand, the notably small number of deaths and median age of death reported leads to a low YLL, accounting for 8% of total DALYs.

Yet, when comparing the calculated DALYs against the GBD 2017 for Portugal, 4,051, split as 3,029 YLL and 1,022 YLD, there is a significant mismatch not only between final values, but also by split tendency. Being diseases with low reported mortality rates and high overall survival, IBD's YLD was expected to be significantly higher than YLL. Furthermore, the GBD reported prevalence (6,657) and incidence (4,113) are not in agreement with the values reported in other literature [22, 25, 26]. As such, the DALYs calculated in this report are considered to represent more accurately the current reality in Portugal. Regarding the cost of illness, direct costs of IBD in Portugal represent 59% of the total, while indirect costs, a section usually underrepresented in these kinds of analyses, play a crucial role in IBD.

The major cost driver in direct costs is pharmacological treatment, which accounts for 42% of total costs. This is by far the most relevant category, greatly heightened by the use of biologic drugs. Inevitably, as studies keep providing evidence of the efficacy of biologics with better outcomes, the costs associated with this therapeutic remain significant. Nonetheless, the erosion observed in originators' prices in the last years, allied to a progressively increasing number of available biosimilars, can mitigate the costs allocated to these therapies in the near future [14, 37]. With the increasing uptake of biosimilar agents at a significantly lower price than the originators, pharmacological costs could be heavily mitigated in the future years [38]. However, with the prediction of a 4–6 fold increase in the prevalence of IBD until 2030 and the major role that biologics play in the treatment of IBD, it is still expected that pharmacological treatment remains

Table 6. Two-way sensitivity analysis, comparing different sources of mortality

	YLL		DALY	
Age of death	133 deaths	29 deaths	133 deaths	29 deaths
77.00	507	110	6,067	5,670

Comparison of median age of death, average age of death, age of death adjusted, and age of death from the Global Burden of Disease Study, 133 deaths, with the number of deaths calculated from the published mortality rate and number of deaths from NHS 2016 data, 29 deaths. YLL, years of life lost; DALY, disability-adjusted life year.

the highest cost impact in the next years [22]. Nevertheless, there is clear published evidence that anti-TNF biologics are effective in reducing the odds of hospitalization by nearly 50%, as well as preventing surgery in 33–77% of cases [39]. These outcomes can clearly encourage the use of these drugs, originating savings for the NHS as well as improving patients' quality of life.

In addition, direct costs calculated in this study are slightly lower than those reported for Portugal in 2004, in which they estimated direct costs per patient to be EUR 3,732 (updated to 2019 prices). Despite being a cohort study with 1,321 patients, the patient pool in Portugal consisted of only 21 patients. Moreover, it did not make any analysis concerning indirect costs, hence the need to evaluate this significant component of the IBD cost [40]. Nonetheless, direct costs are still below what is shown in literature in other countries. In the Netherlands, it is reported that IBD costs EUR 4,866 per patient per year and in the USA, USD 18,637 [41]. Despite these results, data comparison between countries in cost estimation should be interpreted with caution, considering the potential mismatch between methodologies as well as the different cost items considered.

Regarding out-of-pocket costs, the burden for IBD patients is 14% of total direct costs. Even though the Portuguese healthcare system is tendentially charge-free, this share must not be underrated, especially considering that 54% of this value is allocated to user charges and drug copayments.

Indirect costs account for 41% of IBD's total cost. Here, the weight is mainly divided between patient work absences, presenteeism, and early retirement. The latter shows that even with a small percentage of early retirements due to IBD-related causes, the impact is still considerable, resulting in a EUR 16,459,530 loss. Interestingly, the costs of patient work absences showed very similar values to those associated with presenteeism. This demonstrates that IBD does not manifest its impact only at isolated timepoints but rather that it is present in the everyday lives of patients, significantly reducing their quality of life. Since there is a significant information gap in the literature regarding indirect costs in IBD, cross-checking these results with other studies is limited.

As both direct and indirect costs play an important role in IBD management, it is important to generate evidence that can support policymakers in allocating resources efficiently. Impact analysis and research must be performed to reduce hospitalization and pharmacological costs, as these results can trigger patient-focused policies and reduce the economic impact of the key cost-drivers.

It is essential to discuss the relationship between the burden of disease and its cost, especially when discussing a clinical condition with an increasing incidence rate in an aging population as it is in Portugal. The cost of a DALY due to IBD is EUR 24,112, which is higher than the EUR 10,999 reported for hemophilia A, the EUR 6,339 reported for atrial fibrillation, or the EUR 15,262 reported for schizophrenia in Portugal [42–44].

This study presents some limitations worth discussing, namely the unavailability of structured data for IBD specifically. The most up-to-date data was used in every possible scenario, requiring an integration of data from different years. Additionally, there are no direct ICD9/10 codes for IBD, hence when using 555.x for CD and 556.x for UC, there is an inherent bias introduced since these may also encompass other conditions. In addition, disease codification errors in the DRG database can occur due to diagnosis misinterpretation of the codifying physicians. Another limitation is that, despite estimating the burden and cost of IBD, we do not account for nonclassified/indeterminate colitis. The NHS hospital DRG database does not include an extensive clinical dataset, which could be used for a more precise clinical characterization of the IBD population and to assess risk groups and additional costs. Also, costs inherent to the use of private hospitals' admission, surgeries, and drugs were not estimated. In addition to this, in order to better man-

age the disease, it is common practice among IBD patients to adjust their diet and to seek alternative medicine, which are both not included in the cost analysis.

Regarding the use of prednisolone in retail, there was no way of splitting the consumption allocated to IBD and so a conservative approach was followed, with this molecule not being included in the cost quantification. Regarding IBD mortality, the NHS 2016 data reported 29 deaths. When comparing this value to the published 1.29 mortality rate, a high degree of discrepancy is observed. Taking this into consideration, a two-way sensitivity analysis, summarized in Table 6, was performed to assess the impact of using different variables regarding mortality. Noticeably, despite the parameters chosen, no inversion of tendency is observed, maintaining a YLL value significantly lower than the YLD.

Finally, the IBD pediatric population is not differentiated. All assumptions consider the whole IBD population, characterized by remission, active disease, and disease stages.

In conclusion, as the need to generate further data and evidence regarding IBD arises, this study provides the first comprehensive insight at a national level considering all the dimensions of disease burden. These results will raise social-economic awareness of IBD, allowing for the definition of disease management strategies and support prioritization on resource allocation, especially considering the availability of new treatment approaches. Moreover, this study will set the basis for the thorough assessment of the real burden of IBD in the Portuguese healthcare system and society overall.

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Statement of Ethics

The authors declare that no patient data appear in this article. All data analyzed was anonymous.

Conflict of Interest Statement

Fernando Magro, Francisco Portela, Paula Lago, Cristina Chagas, and Luis Correia received honoraria from Janssen for participation in expert panel. Bernardo Rodrigues is an employee of Janssen Portugal. Francisco Moreira, Fábio Pereira, and Hugo Pedrosa are employees of IQVIA Portugal and were contracted by Janssen Portugal for the development of this article.

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Author Contributions

Fernando Magro, Francisco Portela, Paula Lago, Cristina Chagas, and Luis Correia participated in the expert panel, providing insights as subject experts and reviewed the final article. Bernardo Rodrigues was responsible for the expert panel moderation and article revision. Francisco Moreira, Fábio Pereira, and Hugo Pedrosa were responsible for the expert panel moderation, data collection, and analysis, as well as article development.

Data Availability Statement

Data used for this study relies on the usage of two main data sources that were used throughout the study to support the quantification of the Burden and cost of Inflammatory Bowel Disease: NHS 2016 DRG dataset and the 2019 drug hospital and retail datasets of IQVIA Consulting. These datasets are not publicly available and were acquired for the development of this study. Data used is presented aggregately in this paper. Other public data sources used in the development of this study are disclosed in the bibliography section.

References

1 Sparkes A. Harrison's principles of internal medicine, companion handbook. J Feline Med Surg. 1999 Dec 24;1(4):viii.
2 Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO Guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis. 2020 Jan 1;14(1):4–22.
3 Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017 Jun 1;11(6):649–70.
4 Portela F, Dias CC, Caldeira P, Cravo M, Deus J, Gonçalves R, et al. The who-when-why triangle of complementary and alternative medicine use among Portuguese IBD patients. Dig Liver Dis. 2017 Apr;49(4):388–96.
5 Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn''s disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. Am J Gastroenterol. 2004 Jan;99(1):91–6.
6 Kawalec P. Indirect costs of inflammatory bowel diseases: Crohn's disease and ulcerative colitis. A systematic review. Arch Med Sci. 2016;2:295–302.

7 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1): 46–54.e42; quiz e30.
8 Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017 Dec;390(10114):2769–78.
9 Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology. 2017 Jan; 152(2):313–21.e2.
10 Kaplan GG, Ng SC. Globalisation of inflammatory bowel disease: perspectives from the evolution of inflammatory bowel disease in the UK and China. Lancet Gastroenterol Hepatol. 2016 Dec;1(4):307–16.
11 Bassi A, Dodd S, Williamson P, Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut. 2004 Oct 1;53(10):1471–8.
12 Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015 Dec 1;12(12):720–7.
13 Stone CD. The economic burden of inflammatory bowel disease: clear problem, unclear solution. Dig Dis Sci. 2012 Dec 20;57(12): 3042–4.
14 Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. Therap Adv Gastroenterol. 2015 Mar 11;8(2): 66–82.
15 Pillai N, Dusheiko M, Burnand B, Pittet V. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. PLoS One. 2017 Oct 3;12(10): e0185500.
16 Burisch J, Jess T, Martinato M, Lakatos PL; ECCO-EpiCom. The burden of inflammatory bowel disease in Europe. J Crohns Colitis. 2013;7(4):322–37.
17 Dias CC, Santiago M, Correia L, Portela F, Ministro P, Lago P, et al. Hospitalization trends of the inflammatory bowel disease landscape: a nationwide overview of 16 years. Dig Liver Dis. 2019;51(7):952–60.
18 James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov; 392(10159):1789–858.
19 Kostić M, Djakovic L, Šujić R, Godman B, Janković SM. Inflammatory bowel diseases (Crohn´s disease and ulcerative colitis): cost of treatment in Serbia and the implications. Appl Health Econ Health Policy. 2017 Feb 1; 15(1):85–93.
20 Petryszyn PW, Witczak I. Costs in inflammatory bowel diseases. Prz Gastroenterol. 2016; 11:6–13.
21 Magro F, Portela F, Lago P, Deus J, Cotter J, Cremers I, et al. Inflammatory bowel disease: a patient's and caregiver's perspective. Dig Dis Sci. 2009 Dec 9;54(12):2671–9.
22 Santiago M, Magro F, Correia L, Portela F, Ministro P, Lago P, et al. What forecasting the prevalence of inflammatory bowel disease may tell us about its evolution on a national scale. Therap Adv Gastroenterol. 2019 Jan 21; 12:175628481986004.
23 Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. Bull World Health Organ. 1994; 72(3):429–45.
24 Bewtra M, Kaiser LM, TenHave T, Lewis JD. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. Inflamm Bowel Dis. 2013 Mar;19(3):599–613.
25 Portela F, Magro F, Lago P, Cotter J, Cremers I, de Deus J, et al. Ulcerative colitis in a Southern European country: a national perspective. Inflamm Bowel Dis. 2010 May;16(5):822–9.
26 Magro F, Portela F, Lago P, de Deus JR, Vieira A, Peixe P, et al. Crohn's disease in a southern European country: montreal classification and clinical activity. Inflamm Bowel Dis. 2009 Sep;15(9):1343–50.
27 Azevedo LF, Magro F, Portela F, Lago P, Deus J, Cotter J, et al. Estimating the prevalence of inflammatory bowel disease in Portugal using a pharmaco-epidemiological approach. Pharmacoepidemiol Drug Saf. 2010 May;19(5): 499–510.
28 Department of Health Statistics and Information Systems WHO G. WHO methods and data sources for global burden of disease estimates 2000–-2011. Geneva; 2013 Nov.
29 Tarricone R. Cost-of-illness analysis: what room in health economics? Health Policy. 2006 Jun 1;77(1):51–63.
30 Ministério da Saúde. Despacho n.o 7702-A/2012. Diário da República; 2012 Jun 4. p. 20410.
31 Ministério da Saúde. Portaria n.o 254/2018. Diário da República; 2018 Sep 7. p. 4497.
32 ACSS. Circular Normativa 15/2019/DPS/ACSS. ACSS; 2019 Nov 7. p. 11–275.
33 da República Diário. Decreto-Lei n.o 113/2011. Ministério da Saúde; 2011 Nov 29. p. 5108–10.
34 da República Diário. Portaria n.o 64-C/2016. Ministério da Saúde; 2016 Mar 31. p. 76–7.
35 Instituto Nacional de Estatística. Statistics Portugal [Internet]. 2018 [cited 2020 Mar 11]. Available from: https://www.ine.pt/xportal/xmain?xpgid=ine_main&xpid=INE.
36 Infarmed. Infomed [Internet]. 2020 [cited 2020 Mar 11]. Available from: https://extranet.infarmed.pt/INFOMED-fo/.
37 Huoponen S. Costs, effectiveness and cost-effectiveness of biological drugs in the treatment of rheumatoid arthritis and inflammatory bowel diseases [dissertation]. Helsinki, Finland: Helsingin yliopisto; 2019.
38 Benchimol EI, Bernstein CN, Bitton A, Murthy SK, Nguyen GC, Lee K, et al. The impact of inflammatory bowel disease in Canada 2018: a scientific report from the Canadian gastro-intestinal epidemiology consortium to Crohn's and Colitis Canada. J Can Assoc Gastroenterol. 2019 Feb 2;2(Suppl 1):S1–5.
39 Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 2016 Feb 10;45:3–13.
40 Odes S, Vardi H, Friger M, Wolters F, Russel MG, Riis L, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. Gastroenterology. 2006 Sep;131(3):719–28.
41 Park KT, Colletti RB, Rubin DT, Sharma BK, Thompson A, Krueger A. Health insurance paid costs and drivers of costs for patients with Crohn's disease in the United States. Am J Gastroenterol. 2016 Jan;111(1):15–23.
42 Gouveia M, Ascenção R, Fiorentino F, Pascoal J, Costa J, Borges M. The cost and burden of schizophrenia in Portugal in 2015. Int J Clin Neurosci Mental Health. 2018 Jan 22; 4(Suppl 3):S13.
43 Café A, Carvalho M, Crato M, Faria M, Kjollerstrom P, Oliveira C, et al. Haemophilia A: health and economic burden of a rare disease in Portugal. Orphanet J Rare Dis. 2019 Dec 4;14(1):211.
44 Gouveia M, Costa J, Alarcão J, Augusto M, Caldeira D, Pinheiro L, et al. Carga e custo da fibrilhação auricular em Portugal. Revista Portuguesa de Cardiologia. 2015 Jan;34(1): 1–11.

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Clinical, Economic, and Humanistic Impact of Short-Bowel Syndrome/Chronic Intestinal Failure in Portugal (PARENTERAL Study)

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Keywords

Short-bowel syndrome · Chronic intestinal failure · Parenteral nutrition · Cost of illness analysis · Quality of life · Healthcare resource utilization

Abstract

Introduction: This study aimed to assess the clinical, economic, and humanistic impact of short-bowel syndrome/chronic intestinal failure (SBS/CIF) in Portugal. ***Methods:*** This is a retrospective multicenter cohort chart review study, with a cross-sectional component for quality-of-life (QoL) evaluation. Inclusion criteria comprised patients with SBS/CIF, aged ≥1 year, with stable parenteral nutrition (PN). Data collection included patient chart review over a 12-month period and patient/caregiver self-report and SF-36/PedsQL™ questionnaires. Main endpoints comprised clinical and PN characterization, healthcare resource use (HRU), direct costs, and patient QoL. ***Results:*** Thirty-one patients were included (11 adults and 20 children). Patients' mean age (standard deviation [SD]) was 57.9 (14.3) years in adults and 7.5 (5.0) years in children, with a mean time since diagnosis of 10.2 (5.9) and 6.6 (4.2) years, respectively. PN was administered for a mean of 5.2 and 6.6 days/week in adults and children, respectively; home PN occurred in 81.8% of adults and 90.0% of children for a mean of 9.6 and 10.8 months/year, respectively. The mean annual number of hospitalizations was 1.9 and 2.0 which lasted for a mean of 34.0 and 29.4 days in adults and children, respectively. Twenty-one and forty hospitalization episodes were reported in adults and children, respectively, of which 71.4% and 85.0% were due to catheter-related complications. Mean annual direct costs per patient amounted to 47,857.53 EUR in adults and 74,734.50 EUR in children, with PN and hospitalizations as the main cost-drivers. QoL assessment showed a clinically significant impaired physical component in adults and a notable deterioration in the school functioning domain in children. ***Conclusion:*** In Portugal, SBS/CIF patient management is characterized by a substantial therapeutic burden and HRU, translating into high direct costs and a substantial impairment of the adults' physical function and children's school functioning.

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Impacto clínico, económico e social da síndrome do intestino curto/falência intestinal crónica em Portugal (estudo PARENTERAL)

Palavras Chave
Síndrome do intestino curto · Falência intestinal crónica · Nutrição parenteral · Encargo económico da doença · Qualidade de vida · Utilização de recursos de saúde

Resumo
Introdução: Este estudo teve como objetivo avaliar o impacto clínico, económico e social da síndrome do intestino curto/falência intestinal crónica (SIC/FIC) em Portugal. ***Métodos:*** Estudo de coorte retrospectivo e multicêntrico de revisão dos processos clínicos incluindo uma componente transversal para avaliação da qualidade de vida (QV). Os critérios de elegibilidade incluíram doentes com SIC/FIC, idade ≥1 ano, em nutrição parenteral (NP) e clinicamente estáveis. A recolha de dados incluiu a revisão dos processos clínicos ao longo de um período de 12 meses e a aplicação de questionários auto-administrados a doentes e cuidadores e de questionários de QV (SF-36/PedsQL™). Os indicadores principais foram a caracterização clínica e da NP, a utilização de recursos de saúde, custos diretos e QV dos doentes. ***Resultados:*** Foram incluídos 31 doentes (11 adultos e 20 crianças). A idade média (desvio padrão: DP) foi de 57.9 (14.3) anos nos adultos e de 7.5 (5.0) nas crianças com um tempo médio desde o diagnóstico de 10.2 (5.9) e 6.6 (4.2) anos, respetivamente. A NP foi administrada durante uma média de 5.2 e 6.6 dias por semana, em adultos e crianças respetivamente, em 81.8% e 90.0% dos adultos/crianças foi feita em casa durante uma média de 9.6 ou 10.8 meses por ano, respetivamente. O número médio anual de hospitalizações foi de 1.9 (1.6) e 2.0 (1.5) com uma duração média de 34.0 (47.4) e 29.4 (32.3) dias, em adultos e crianças, respetivamente. Foram reportados 21 e 40 episódios de hospitalização em adultos/crianças, dos quais 71.4% e 85.0% foram devido a complicações relacionadas ao uso de cateter. Os custos diretos anuais médios por doente ascenderam a 47,857.53 EUR nos adultos e a 74,734.50 EUR nas crianças, sendo que os maiores responsáveis foram a NP e as hospitalizações. A avaliação da QV mostrou um comprometimento clinicamente significativo da componente física nos adultos e uma deterioração relevante da dimensão escolar nas crianças. ***Conclusões:*** A gestão dos doentes com SIC/FIC em Portugal é caracterizada por uma sobrecarga substancial a nível terapêutico e de utilização de recursos de saúde, o que se traduz em elevados custos diretos e comprometimento substancial da componente física nos adultos e do desempenho escolar nas crianças.

Introduction

Short-bowel syndrome (SBS) is a rare disease, with an estimated European prevalence of 1–9 cases per 100,000 inhabitants, which arises from a context of extensive bowel resection, congenital defects, or underlying disease, leading to the loss of absorptive intestinal surface [1, 2]. Generally, SBS is defined as small bowel length of less than 200 cm, with residual small bowel of less than 10 cm in children or 20 cm in adults known as ultra-SBS. However, the absorptive limitations reflect not only the extent of the residual small bowel length but also the anatomy, functionality, and adaptative potential of the remaining intestine and patient clinical condition [2–6]. Home parenteral nutrition (HPN) represents the standard-of-care and life-sustaining therapy in patients with SBS and chronic intestinal failure (SBS/CIF) [7, 8].

Treatment-related complications are reported to account for around 14% of the total of deaths in patients with CIF [9]. Long-term HPN complications include central venous catheter (CVC) problems, particular catheter-related blood stream infections (CRBSIs) responsible for over 70.0% of hospitalizations in HPN patients, and metabolic complications, of which intestinal failure-associated liver disease remains a major cause of patient morbidity and mortality [8, 10, 11]. Albeit the benefits in patient longevity and nutritional status, HPN is associated with quality-of-life (QoL) deterioration [12, 13], with SBS/CIF patients showing lower QoL scores when compared to the general population and other chronic diseases [14].

Costs associated with long-term HPN are not negligible and tend to increase with extension of patient longevity. Although HPN costs are counterbalanced by its life-sustaining nature, economic impact in the healthcare system reflects direct costs associated with PN, medical consultations, laboratory monitoring, home support, and hospitalizations due to treatment-related complications. Additionally, non-healthcare costs and indirect costs, due to productivity loss, also contribute to the overall economic burden [13].

In Portugal, a country with 10 million inhabitants, there is a clear absence of national evidence regarding the real-world context of SBS/CIF patients, and to date, no national study unveiled the multidimensional impact of

SBS/CIF. As such, we conducted the PARENTERAL study (ImPActo da SíndRomE do INTEstino Curto em PoRtugAL) with the aim to characterize the clinical, economic, and humanistic impact of SBS/CIF in Portugal.

Materials and Methods

Study Design and Setting

The PARENTERAL study was a nationwide chart review study, with an observational retrospective cohort design and a cross-sectional component to evaluate SBS/CIF patients' QoL. Investigation center enrollment followed the initial contact with the Portuguese Association of Enteral and Parenteral Nutrition (APNEP) to identify the hospital centers treating SBS/CIF patients.

Study Population

Patient eligibility was assessed according to the following inclusion criteria: patients diagnosed with SBS/CIF; age ≥1 year-old; home- or hospital-based PN considered stable, defined as under PN for a period ≥6 months; no previous treatment with teduglutide or any other growth hormone. Pregnant or breastfeeding women, patients diagnosed with active malignant disease, or history of gastrointestinal cancer on the past 5 years were excluded. Additionally, patients or caregivers unwilling or unable to provide informed consent were not eligible for study participation.

Eligible patients or respective caregivers were invited to participate by their attending physician during follow-up visit. The overall recruitment period ranged from March 2018 to September 2019.

Data Collection and Variables

Data were collected through three main instruments: clinical case report form; self-report patient questionnaire; and QoL measurement instruments. After obtaining written informed consent, clinical case report form was filled by the investigator and captured electronic health record data regarding patient demographics and SBS/CIF clinical characterization, therapeutic management (PN support and pharmacological treatment) and healthcare resource use (HRU) (including medical consultations and consultations with other healthcare professionals, home visits, emergency department [ED] episodes, hospitalizations, laboratory and imaging exams, surgeries) collected from chart review over a 12-month observation period.

The patient questionnaire was handed by the investigator during patient follow-up visit and, whenever possible, self-administered or in the applicable cases, by the parent/caregiver. Self-reported data included SBS/CIF-related symptomatology and healthcare- and non-healthcare-related costs, including healthcare products, private healthcare and insurance, transportation, home adaptations, medical devices, and home care. A 6-month recall period was selected to address and minimize the potential of recall bias, chosen according to the available literature evidence regarding recall period length in healthcare surveys and investigators advice [15, 16].

QoL assessment included the Portuguese versions of the Short Form-36 version 2 (SF-36v2) and Pediatric Quality of Life Inventory version 4.0 (PedsQL™) for adult and pediatric SBS/CIF patients, respectively, both with a 1-month recall period. Both generic instruments were chosen due to validation in Portuguese population and availability of normative data that would allow comparison of QoL scores with the general population or other chronic illnesses [17–19]. As in the self-report questionnaire, instruments were handed to patients by the investigator during follow-up visit and, whenever possible, self-administered.

Healthcare and Non-Healthcare Cost Estimation

Cost analysis focused on direct costs (healthcare and non-healthcare costs), namely, on expenditures supported by the Portuguese National Health System (NHS), patients, and caregivers. Cost estimation included two major steps: identification and classification of cost items; measurement and valuation, i.e., attributing a monetary value to each item. Cost item and cost source are detailed in online supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000526059). PN support costs included acquisition cost for commercially premixed ready-to-use PN admixture and tailored PN admixtures formulation (PN bags, formulation nutrients, and supplements).

Data from electronic medical prescriptions regarding inpatient and outpatient pharmacological treatment were retrieved, and costs estimated based on unit prices reported by public NHS hospital tenders and, for retail medication, selling prices in the national medicines database [20, 21]. Healthcare products costs, namely, consumables, were estimated according to available tender documents and retail prices.

Unit costs of healthcare resources, including consultations with other healthcare professionals, home visits, ED episodes, surgeries, and laboratory and imaging exams, were retrieved from national diagnostic-related group tariffs [22, 23]. Hospitalization costs were estimated based on patient's length of stay (LoS) per specific hospital clinical unit. Average daily costs of hospital stay and medical visit costs, per medical specialty, were retrieved from the analytical elements national database [24].

Out-of-pocket expenses, i.e., nonrefundable healthcare costs directly paid by patients and/or caregivers, were reported by patients and included private insurance, private healthcare, formal home care, medical devices and required home adaptations. Patient costs with transportation were estimated by proxy, considering the unit cost per km in the national tariff for nonurgent patient transportation and travel burden data reported by patients [25].

Statistical Analysis

Study population was described according to demographic and clinical characteristics, through measures of central tendency (mean) and dispersion (standard deviation [SD]) of continuous variables and by absolute and relative frequencies of categorical variables. Cost-related outcomes were estimated through the product of cost item number, frequency, duration, collected from the instruments, and the unitary cost, obtained from official national sources.

Total costs were estimated by a Poisson regression model as a mean annual cost per patient. The mean number of patient monthly travels to the hospital and the respective monthly traveled distance (kilometer) were also estimated by a Poisson regression model. The assumption of cost and utilization homogeneities over the year was used to express annualized costs. Costs were annualized assuming constant use of resources, except for one-off acquisition costs (medical devices and home adaptations), and standardized using the 2019 consumer price index.

Table 1. Study population demographic and clinical characteristics

	Adults (*n* = 11)	Children (*n* = 20)	Total (*n* = 31)
Age, years, mean±SD (range)	57.9±15.3 (39.5–91.3)	7.5±5.0 (1.3–19.2)	25.4±26.4 (1.3–91.3)
Female sex, *n* (%)	6 (54.6)	10 (50.0)	16 (51.6)
Weight, mean ± SD (range)	61.2±10.7 (42.0–79.0)	20.9±13.8 (9.0–65.0)	35.2±23.3 (9.0–79.0)
BMI, mean ± SD (range)	24.2±3.2 (18.7–29.4)	–	–
BMI: 18.5–24.9, *n* (%)	5 (55.7)	–	–
BMI: 25.0–29.9, *n* (%)	4 (44.4)	–	–
Time since SBS/CIF diagnosis, years, mean±SD (range)	10.2±5.9 (1.4–22.4)	6.6±4.2 (0.9–18.1)	7.9±5.1 (0.9–22.4)
Disease classification, *n* (%)			
SBS†	5 (45.5)	12 (60.0)	17 (54.8)
Ultra-SBS†	4 (36.4)	8 (40.0)	12 (38.7)
Functional SBS*	2 (18.4)	–	2 (6.5)

SBS/CIF, short-bowel syndrome/chronic intestinal failure; SD, standard deviation. † Classification according to 2016 ESPEN definitions: SBS – remnant bowel <200 cm; ultra-SBS – remnant bowel <20 cm for adults and <10 cm for children [9]. * As defined by Pironi et al. [4].

QoL assessed by the SF-36v2 score as well as the PedsQL™ was summarized by the calculation of the mean and SD of their main domains and summary or total scores. No data imputation was performed. All statistical analysis adopted a 5% significance level, and whenever applicable, 95% confidence intervals (CIs) were reported. Statistical analysis was performed with the statistical software R 4® [26].

Results

Population Characterization

A total of eight hospital centers nationwide were approached, of which six accepted to participate in the study. In the participating centers, 41 patients were assessed by investigators for study eligibility, of which 10 were not eligible for study participation. As such, the study population comprised 31 patients, namely, 11 adult and 20 pediatric SBS/CIF patients (online suppl. Fig. S1).

The patient characteristics are presented in Table 1. Patient mean (SD) age was 57.9 (15.3) and 7.5 (5.0) years in the adult and children cohort, respectively, with an even sex distribution.

In the adult cohort, the mean time since diagnosis was 10.2 (5.9) years. All the patients presented CIF, most with bowel length reduction classified as SBS (45.5%) and ultra-SBS (36.4%). The remaining patients (18.4%), despite not having major intestinal resections, had a significant reduction on the gut function. Comparatively, a mean of 6.6 (4.2) years since SBS/CIF diagnosis was reported in the pediatric cohort, with 60.0% of patients classified as SBS and 40.0% with ultra-SBS.

SBS/CIF Clinical Impact

Regarding nutritional support, except for 1 pediatric patient, all patients had oral caloric intake. Enteral nutrition was given in four children, with feeding via surgical gastrostomy (*n* = 2), percutaneous endoscopic gastrostomy (*n* = 1), or nasogastric tube (*n* = 1).

Four adults and three children had at least one type of ostomy, of which jejunostomy was the most common (*n* = 4). No enterocutaneous fistula was reported among included patients. Overall, 66.6% of patients reported at least one SBS/CIF-related symptom over the previous 6-month period, including diarrhea (46.7%), fatigue/weakness (36.7%), flatulence (33.3%), nausea/vomiting (30.0%), and abdominal pain (26.7%).

Table 2 summarizes PN support characteristics. PN support spanned for years, with a mean of 9.2 (7.0) years in adults and 6.6 (4.2) years in children since treatment initiation. The average weekly PN frequency was 5.2 (1.5) and 6.6 (0.9) administration days in adults and children, respectively. Regarding the European Society for Clinical Nutrition and Metabolism (ESPEN) clinical classification of PN volume requirements [4], more than half of patients (58.1%) were categorized as PN2 with daily volume ranging from 1,001 to 2,000 mL.

Considering the PN administration setting, 81.8% of adults and 90.0% of children were on HPN during a mean of 9.6 (3.5) and 10.8 (1.3) months over the 12-month observation period, respectively. Nevertheless, 54.5% of adults and 60.0% of children had inpatient PN administration at least once during the observation period, lasting an average of 4.0 (3.5) and 1.8 (1.0) months. Most of the patients (83.9%) were being treated for prevention of

Table 2. PN support characterization

	Adults (*n* = 11)	Children (*n* = 20)	Total (*n* = 31)
Time since start of PN, years, mean ± SD (range)	9.2±7.0 (1.1–22.4)	6.6±4.2 (0.9–18.1)	7.5±5.4 (0.9–22.4)
Administration days/week, mean ± SD	5.2±1.5	6.6±0.9	6.1±1.3
Calories/bag, kcal, mean ± SD (range)	1,452.8±326.0 (740.0–1,800.0)	1,241.0±557.5 (450.0–2,810.0)	1,316.2±492.8 (450.0–2,810.0)
Volume/bag, mL, mean ± SD (range)	1,300.6±275.4 (625.0–1,500.0)	1,709.4±893.0 (502.0–3,634.0)	1,564.3±754.9 (502.0–3,634.0)
PN requirements, mL/day, *n* (%)*			
PN 1 (≤1,000)	3 (27.3)	5 (25.0)	8 (25.8)
PN 2 (1,001–2,000)	8 (72.7)	10 (50.0)	18 (58.1)
PN 3 (2,001–3,000)	0	2 (10.0)	2 (6.4)
PN 4 (>3,000)	0	3 (15.0)	3 (9.7)
Patients with at least one PN administration, *n* (%)			
Home	9 (81.8)	18 (90.0)	27 (87.1)
Hospital			
Inpatient setting	6 (54.5)	12 (60.0)	18 (58.1)
Outpatient setting	2 (18.2)	2 (10.0)	4 (12.9)
Time per PN setting, months, mean ± SD (range)			
Home	9.6±3.5 (1.3–12.0)	10.8±1.3 (8.0–12.0)	10.4±2.3 (1.2–12.0)
Hospital			
Inpatient setting	4.0±3.5 (2.0–10.6)	1.8±1.0 (0.9–4.0)	2.6±2.3 (0.9–10.6)
Outpatient setting	10.8±1.7 (9.6–12.0)	11.4±0.9 (10.8–12.0)	11.1±1.2 (9.6–12.0)

PN, parenteral nutrition; SD, standard deviation. * According to revised ESPEN classification of energy and volume requirements (Pironi et al. [4]).

catheter-related complications, including the use of taurolidine (adults – 9.1%; children – 68.8%), heparin (adults – 90.9%; children – 25.0%), or both (children – 6.3%).

SBS/CIF Economic Impact

Table 3 presents HRU for SBS/CIF management. During the observation period, an annual average of 8.7 (5.1) and 10.2 (5.3) medical consultations were reported in adults and children, respectively. Patient follow-up with other healthcare professionals accounted for an average of 37.8 (63.6) consultations in adults and 29.8 (85.3) in children during the 1-year period, mainly nursing and nutrition.

Home visit frequency differed widely between patient cohorts. In the adult cohort, only 18.2% of patients required domiciliary visits, although with a significant resource use considering an annual average of 45.5 (101.1) visits. Comparatively, almost half of pediatric patients (40.0%) had at least one home visit during study period, with an average of 4.6 (10.2) visits.

ED episodes were more frequent in pediatric patients (85.0%), with an average of 3.0 (2.5) episodes. Considering hospitalizations, 77.4% of patients had at least one episode related to SBS/CIF. Globally, there were no major differences in the number of episodes and LoS between patient cohorts, with an average of 2.0 (1.5) episodes, and an overall LoS of 31.0 (37.6) days observed during the 12-month period.

Of a total of 61 hospitalization episodes, 21 in adults and 40 in children, 71.4% and 85.0%, were motivated by catheter-related complications, respectively, of which CRBSI constituted the major driver for hospital admission (adults – 19.0%; children – 52.5%). Other catheter-related complications included local CVC infection, mechanical complications, and venous thrombosis, with no major difference between patient cohorts. Admissions due to metabolic complications were residual in both patient cohorts. LoS per hospitalization episode reason is detailed in online supplementary Table S2.

Although the negligible number of surgeries performed during the observation period (*n* = 7), the majority were associated with catheter-related complications (*n* = 5), namely, CVC replacements. Only 23.3% (*n* = 7) of patients reported having resorted to private healthcare, of which 6 were pediatric patients with an average annual number of 2.1 (4.8) private healthcare consultations.

An annual average cost per patient (95% CI) of EUR 65,197.50 (95% CI: 65,017.68–65,287.45) was estimated, namely, EUR 47,857.53 (47,728.43; 47,986.99) in adults and EUR 74,734.49 (74,614.77–74,854.40) in children. Figure 1 presents the distribution of costs in each patient cohort per main cost item categories. The annual average

Table 3. Health resource use during the 12-month review period

Healthcare resource	Adults (*n* = 11)	Children (*n* = 20)	Total (*n* = 31)
Medical consultations, mean ± SD	8.7±5.1	10.2±5.3	9.7±5.2
Consultations with other healthcare professionals, *n* (%)	10 (90.0)	18 (90.0)	28 (90.3)
Annual number, mean ± SD	37.8±63.6	29.8±85.3	32.9±76.7
Nursing	14.4±31.3	23.6±80.7	20.3±66.8
Nutrition	23.5±61.4	2.1±4.3	9.7±37.1
Psychology	–	0.9±2.8	0.6±2.3
Home visits, *n* (%)	2 (18.2)	8 (40.0)	10 (32.3)
Annual number, mean ± SD	45.5±101.1	4.6±10.2	19.1±62.2
Surgeries, *n* (%)	2 (18.2)	4 (20.0)	6 (19.4)
Annual number, mean ± SD	0.2±0.4	0.4±0.8	0.3±0.7
ED episodes, *n* (%)	4 (36.4)	17 (85.0)	21 (67.7)
Annual number, mean ± SD	0.9±1.4	3.0±2.5	2.2±2.3
Hospitalization episodes, *n* (%)	8 (72.7)	16 (80.0)	24 (77.4)
Annual number, mean ± SD	1.9±1.6	2.0±1.5	2.0±1.5
Annual LoS (days), mean ± SD	34.0±47.4	29.4±32.3	31.0±37.6
Admission reasons, *n* (%)	*N* = 21	*N* = 40	*N* = 61
Catheter-related complications	15 (71.4)	34 (85.0)	49 (80.3)
CRBSI	4 (19.0)	21 (52.5)	25 (41.0)
Local CVC infection	6 (28.6)	7 (17.5)	13 (21.3)
Catheter mechanical complications	4 (19.0)	5 (12.5)	9 (14.8)
Venous thrombosis	1 (4.8)	1 (2.5)	2 (3.3)
Metabolic complications	1 (4.8)	1 (2.5)	2 (3.3)
Lactic acidosis	1 (4.8)	–	1 (1.6)
Dehydration	–	1 (2.5)	1 (1.6)
Other	5 (23.8)*	5 (12.5)†	10 (16.3)

CRBSI, catheter-related blood stream infection; CVC, central venous catheter; ED, emergency department; LoS, length of stay; SD, standard deviation. * Includes nutritional support (*n* = 2) and fever (*n* = 3). † Includes stoma infection (*n* = 2), low digestive hemorrhage (*n* = 1), and pyelonephritis (*n* = 2).

cost per item category is detailed in online supplementary Table S3.

In both cohorts, the main cost-drivers were PN support and HRU, of which hospitalization episodes constituted the major resource. Direct costs associated with PN support amounted to over half (57.3%) of the overall annual cost in the children cohort. HRU costs were higher in adult patients (43.7%), with hospitalization episodes and consultations with other healthcare professionals ascending to more than 80.0% of HRU total cost. For children, HRU constituted 34.3% of the overall annual costs, notably with over half of resource costs associated with hospitalizations (61.2%). Costs related to pharmacological treatment were more substantial in the adult patient cohort, amounting to 18.1% of the annual costs in comparison to just 3.7% in children.

Out-of-pocket costs were residual counting for 2.7% and 4.6% of the overall annual costs in adult and children cohort, respectively. Transportation costs represented 90.0% of the out-of-pocket annual expenses, which is not surprising when considering self-reported travel burden. Patients went to the hospital on average (95% CI) 9.5 times/month (8.4; 10.8), with a higher frequency in children (4.5 times [8.4; 10.8]) when compared to adult patients (3.2 times [2.3; 4.5]).

SBS/CIF Humanistic Impact

Adult Cohort (SF-36v2)

All adult patients filled the SF-36v2 questionnaire. Table 4 summarizes the average raw scores per QoL domain and compares with the Portuguese population norm reported by Ferreira et al. [18]. Globally, SBS/CIF adult patients scored below in every dimension in comparison to the Portuguese general population, with the largest differences found in the physical functioning, role physical, role emotional, and social functioning domains.

PCS and MCS standardized scores, based on Portuguese norm data, are presented in the boxplot (Fig. 2).

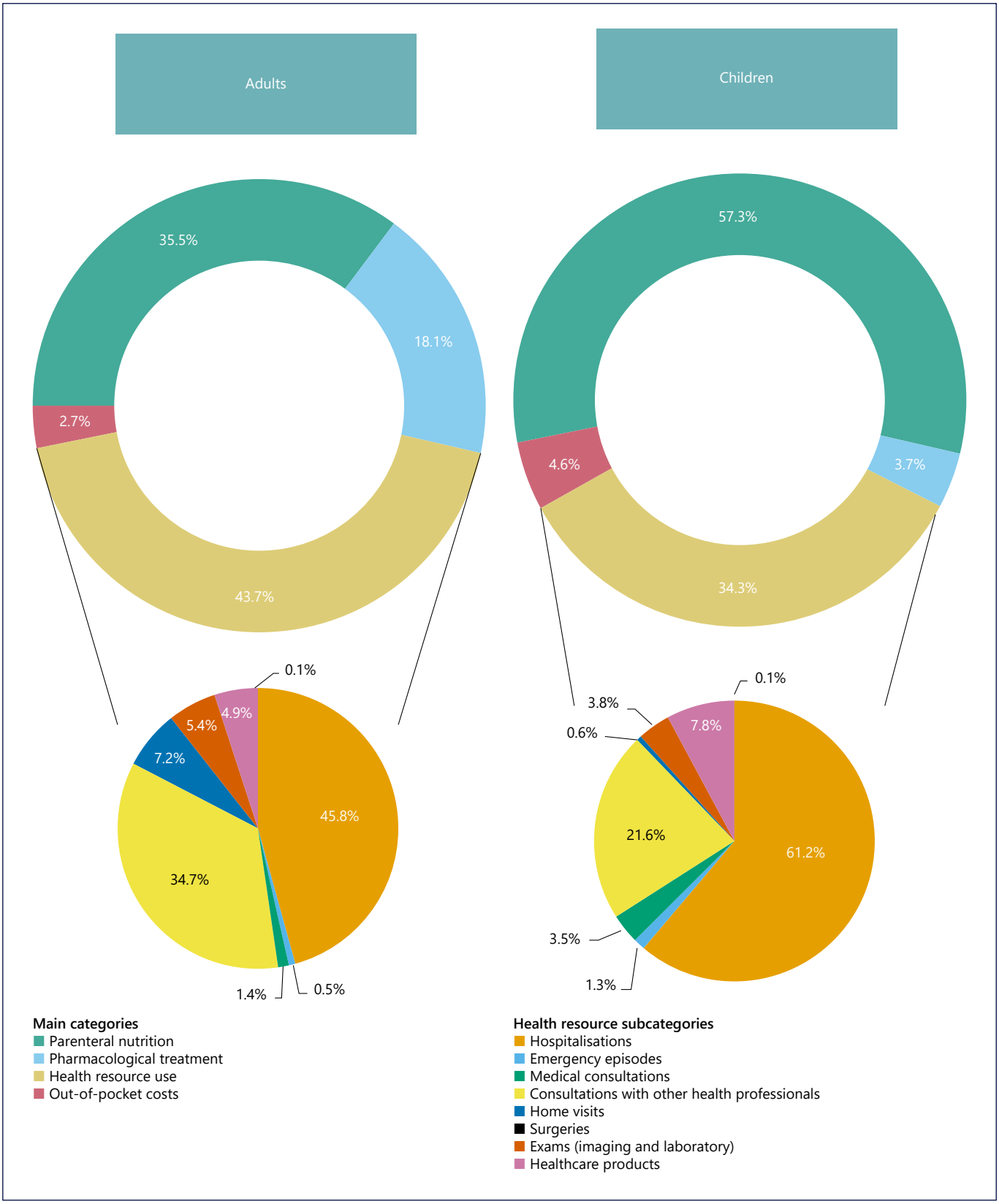

Fig. 1. Distribution of annual average cost per SBS/CIF patient according to the cost item category.

Table 4. QoL assessment in SBS/CIF patients

Instrument	Dimensions, mean score ± SD	Adults (n = 11)		Portuguese adult norm (n = 1,500) [18]		
SF-36v2	Physical functioning	62.3±30.0		80.2±24.7		
	Role physical	61.9±34.1		78.4±25.6		
	Bodily pain	62.4±33.6		71.4±24.3		
	General health	49.8±29.1		59.6±15.4		
	Vitality	56.9±25.1		63.0±23.1		
	Social functioning	65.9±28.0		80.0±23.4		
	Role emotional	62.1±35.2		79.8±24.7		
	Mental health	68.5±23.9		73.0±23.3		
Instrument	Dimension mean score ± SD	Children (n = 13)	Parent's proxy (n = 19)	Portuguese children norm		
				children		parent proxy
				8–12 years (n = 381) [17]	5–12 years (n = 179) [19]*	5–12 years (n = 97) [19]*
PedsQL™	Psychosocial health	71.1±10.8	73.6±12.2	78.2±12.9	74.5±12.8	69.6±15.2
	Emotional functioning	72.1±12.9	74.5±15.7	73.3±16.7	71.8±17.4	65.8±18.4
	Social functioning	79.6±19.9	78.5±17.7	84.6±15.1	79.1±16.8	75.9±20.8
	School functioning	57.5±18.1	58.1±15.8	78.2±15.9	72.6±16.2	65.9±18.2
	Physical functioning	77.4±13.9	67.4±24.8	83.5±14.8	77.8±19.1	68.7±22.4
	Total score	73.3±11.0	71.3±17.3	79.8±12.1	75.6±13.5	69.0±16.4

PedsQL, Pediatric Quality of Life Inventory; SF-36v2, Short Form-36 version 2. * Reported the average weighted scores for the overall population, considering published stratified norm data per children age-group (5–7 years and 8–12 years).

PCS average (SD) score was 45.8 (11.1), i.e., was three SD or t-scores points below norm, which translates into a clinically significant impaired physical function compared to the Portuguese general population. On the other hand, the MCS mean score was 47.7 (8.9), which although being below the Portuguese norm is still considered within the average function interval.

Children Cohort (PedsQL™ 4.0)

Self-report version (n = 14) and proxy version (n = 20) response rates was 92.9% and 95.0%, respectively. The average score per PedsQL™ domain and the Portuguese norm scores from two national studies [17, 19] are reported in Table 4.

The average total score in SBS/CIF children was slightly lower in comparison to the Portuguese norm, with a substantial deterioration in the school functioning domain. In fact, considering stratified data per healthy and chronically ill children (diabetes and spina bifida) reported by Ferreira et al. [19], presented in online supplementary Table S4, average scores in every dimension were lower in SBS/CIF children when compared to the healthy population norm. In line with overall population, school functioning scores were consistently lower even when compared to children with other chronic diseases. In comparison to the Portuguese parent proxy norm, SBS/CIF average scores were higher, except for the school functioning domain.

Discussion/Conclusion

SBS/CIF constitutes a rare, chronic, and debilitating disease, characterized by a complex management and requiring a tailored, multidisciplinary, and comprehensive care. The absence of national evidence regarding the real-world context of SBS/CIF undermines disease awareness within the clinical community, regulators, and overall society, which reflects directly in the lack of health strategies and policies to address patient's needs. The PARENTERAL study findings fill the current evidence gap by revealing the overall impact of SBS/CIF in Portugal, with a notable clinical, economic, and humanistic impact.

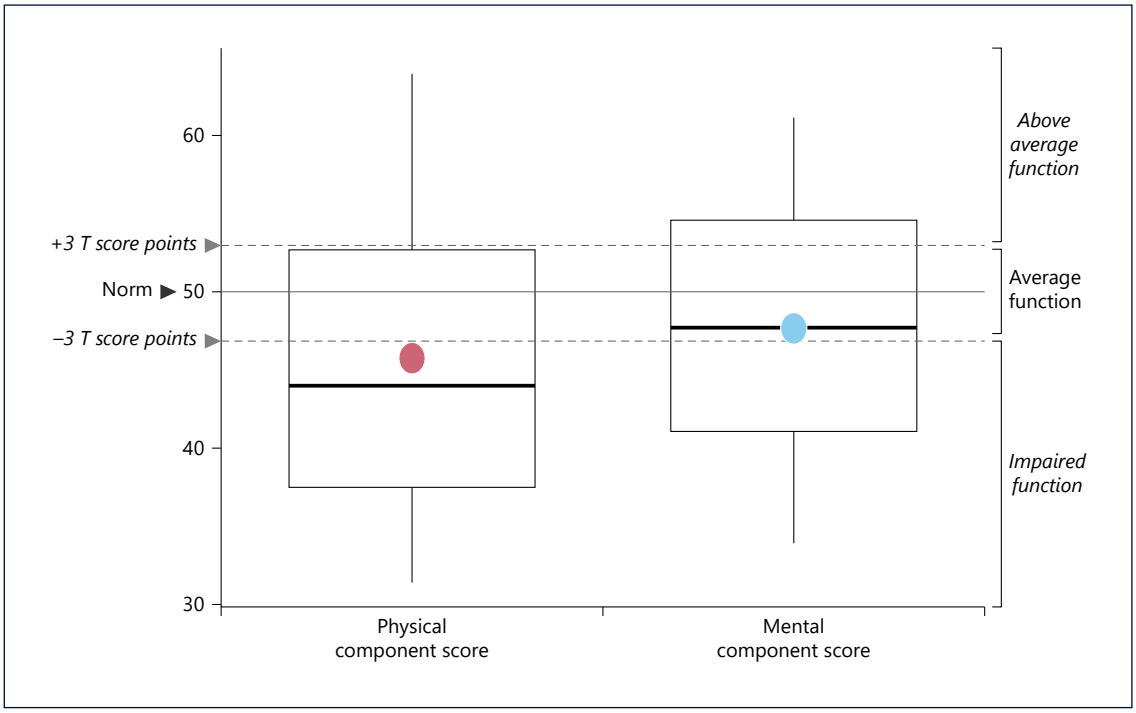

Fig. 2. Standardized physical and mental component scores of the SF-36v2 in SBS/CIF adult patients. Dots represent the mean estimate.

The clinical impact related to the PN support burden in Portugal was high, with only one PN free day per week. Although HPN was the major setting, non-negligible 13% of patients (n = 4) were treated almost exclusively in a hospital outpatient setting during the 12-month observation period.

One of the major study findings was the substantial HRU in SBS/CIF patients. SBS/CIF-related hospitalizations were notoriously frequent, with 77.4% of patients with at least one episode during the study period. An annual average per patient of two admissions and 31 days of LoS was estimated, which in practical terms translates into 1 month of hospitalization per year. This is consistent with the findings of a recently published retrospective cohort study in Danish SBS/CIF patients over a 46-year study period, which estimated an admission incidence of 2.5 episodes per year [27].

Catheter-related complications, mainly CRBSI, were responsible for over 80% of hospitalization episodes, which is in accordance with available literature evidence stating that CRBSIs remain to date the major limitation in long-term HPN, as a major source of morbidity and mortality in PN patients [10, 11]. Our study shows a significant economic impact associated with SBS/CIF management, with direct costs amounting to an overall annual average of EUR 65,000 per patient, namely, EUR 47,800 in adults and EUR 74,700 in children. PN support was the major cost-driver, and this difference may reflect different acquisition costs between commercialized and tailored PN used in the management of adult and pediatric patients, respectively. HRU was the second main cost-driver of which hospitalizations were the main source of financial burden, accounting for 46% of HRU costs in adults and 61% in children, followed by consultations with other healthcare professionals. These findings clearly show SBS/CIF burden in the NHS related to PN support complication management and SBS/CIF patient follow-up.

Although residual, it still should be mentioned that out-of-pocket costs are not refundable by the NHS, with patients having to support these costs many times required to manage the condition. In the children cohort, an annual average out-of-pocket cost of EUR 3,472.57 was estimated. Considering the last updated data (2014) regarding the average net annual household income (EUR 23.635) [28], out-of-pocket expenses in SBS/CIF pediatric management are estimated to account for over 15% of the average annual household income of a Portuguese family.

Evidence regarding economic impact of SBS/CIF management remains scarce. Results of a recent systematic literature review focused specifically on the costs of HPN program revealed the clinical and methodological heterogeneity between published studies which limits comparability with our findings [29].

A retrospective cost analysis performed by Canovai et al. [30] aimed to assess total annual costs in a cohort of stable and long-term intestinal failure adult patients, of which 59% diagnosed with SBS. With a median HPN duration of 5.3 years, costs stabilized by year five of PN support with an average annual cost per patient of EUR 68,278, with no significant variation between disease conditions [30]. In a prospective cohort study including nine Dutch children, with data collected since SBS/CIF diagnosis, the average annual cost of the patients who maintained PN with a follow-up ≥4 years was EUR 76.700, which is aligned with our findings [31].

QoL assessment in adult patients showed a clinically significant impaired physical component compared to the general population. Previous research in an SBS/CIF Swedish patient cohort revealed significant lower PCS when compared not only the population norm but also to patients with IBD. Although Crohn's disease was the major primary cause of SBS in this cohort (85%), patient demographics and time on PN support were consistent with our population characteristics [14].

Considering the pediatric cohort, PedsQL™ average scores were slightly lower in comparison to the overall Portuguese norm. Deterioration was substantial in the school functioning domain, even when compared to children with other chronic diseases, reflecting the major impact of school absenteeism in SBS/CIF pediatric patients due to the high disease management burden for patients and caregivers. In fact, the impact of SBS/CIF in school functionality has also been previously reported elsewhere [32].

Particularly in children, the slight deterioration of QoL when compared to the Portuguese norm might be surprising due to the high burden that SBS/CIF imposes. However, this may reflect adjustment and coping mechanisms, a phenomenon well described in chronic patient populations [33].

To our knowledge, the PARENTERAL study is the first study conducted to characterize comprehensively SBS/CIF impact in Portugal, which translates into a major national investigation milestone. This study is indeed very important since there are no designated specialized centers on SBS/CIF management.

Although study sample is small, rarity of this disease on a global scale should be accounted. A recent multicentric national study aimed to determine the prevalence of pediatric CIF in Portugal, in which a total of 51 children/adolescents were identified, including 38 patients with SBS/CIF diagnosis [34]. As such, it is estimated that the current study included over half of the national SBS/CIF pediatric population.

Despite the strengths of this study, some limitations should be mentioned. First, the refusal to participate by two centers and the retrospective nature of the study design and chart review data collection. Due to the absence of centralized national patient registry, data validity in this retrospective analysis was dependent on accurate medical records.

Second, cost estimation focused solely on direct costs, not accounting for indirect costs associated with patient and caregiver productivity loss. It is reasonable to assume that these costs may be significant considering the debilitating nature of this condition and the pressure exerted on caregivers. Nevertheless, as mentioned by the authors of the previously mentioned SLR, no current study included productivity losses [29].

Lastly, although formal home care costs were not reported by patients, cost of informal caregiving may have a significant impact. At the time of study protocol development, no national decree regulated informal care, with the informal caregiver statute decreed only in 2019 [35] and subsidy conditions established in 2020 [36].

In conclusion, the PARENTERAL study revealed the wide-ranging impact of SBS/CIF in Portugal. The life-sustaining nature of PN support is offset by the high treatment burden and HRU associated with patient management and follow-up, with a notorious emphasis on incidence of admissions due to catheter-related complications, translating into high costs for the healthcare system and patient QoL deterioration. Although PN support remains the main standard-of-care in SBS/CIF, disease-modifying treatments have emerged and recently been made available in Portugal, which might avert the long-term impact of SBS/CIF.

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Statement of Ethics

This study was conducted according to the gold standard of ethical recommendations, namely, the last update of the Helsinki Declaration and International Guidelines for Ethical Review of Epidemiological Studies. After invitation by the investigator, patients, and when applicable, parents/caregivers provided written informed consent for study participation. Study protocol was approved by the National Committee for Data Protection and local Ethics Committee of each participating investigation center.

Conflict of Interest Statement

R.S., P.G., A.R., M.C., R.F., J.F., E.L., A.O., and M.D.S. declare to have received a fee for participation in steering committees, organized by Exigo Consultores on behalf of the funding institution, conducted for study protocol development. E.L. declares to have received a webinar speaker fee from Takeda. A.R. declares to have received a financial support for attending a meeting from Takeda. J.F. declares to have received a consulting fee and support for attending meetings from Takeda. M.V.G., D.R., and V.A. were employees of Exigo Consultores at the time of the study, which was the Clinical Research Organization hired and paid for the development, implementation, execution, and medical writing, and did not receive any direct individual payment or fee from Takeda.

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Author Contributions

R.S., P.G., A.R., M.C., R.F., J.F., E.L., A.O., and M.D.S. contributed to the study conception and design, data acquisition and interpretation, revision, and final approval of the manuscript. M.V.G. and D.R. contributed to the study conception and design, data interpretation, revision, and final approval of the manuscript. V.A. contributed to the study conception and design, data analysis and interpretation, revision, and final approval of the manuscript.

Data Availability Statement

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

References

1 Orphanet. Short bowel syndrome. 2021. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en& Expert=104008 (accessed December, 2021).
2 Pironi L, Sasdelli AS, Pazzeschi C. Chapter 2: short bowel syndrome (SBS) – classification, underlying causes, and global footprint. In: Corrigan ML, Roberts K, Steiger E, editors. Adult short bowel syndrome. Cambridge, MA: Academic Press; 2019. p. 17–25.
3 Nightingale J, Woodward JM. Small Bowel and Nutrition Committee of the British Society of Gastroenterology; Nutrition Committee of the British Society of G. Guidelines for management of patients with a short bowel. Gut. 2006;55(Suppl 4):iv1–iv12.
4 Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015 Apr;34(2):171–80.
5 Bielawska B, Allard JP. Parenteral nutrition and intestinal failure. Nutrients. 2017;9(5):466.
6 Goulet O, Abi Nader E, Pigneur B, Lambe C. Short bowel syndrome as the leading cause of intestinal failure in early life: some insights into the management. Pediatr Gastroenterol Hepatol Nutr. 2019;22(4):303–29.
7 Hill S, Ksiazyk J, Prell C, Tabbers M; ESPGHAN/ESPEN/ESPR/CSPEN Working Group On Pediatric Parenteral Nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: home parenteral nutrition. Clin Nutr. 2018;37(6 Pt B): 2401–8.
8 Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S, et al. ESPEN guideline on home parenteral nutrition. Clin Nutr. 2020 Jun;39(6):1645–66.
9 Pironi L, Steiger E, Brandt C, Joly F, Wanten G, Chambrier C, et al. Home parenteral nutrition provision modalities for chronic intestinal failure in adult patients: an international survey. Clin Nutr. 2020 Feb;39(2):585–91.
10 Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016 Apr;35(2):247–307.
11 Hartman C, Shamir R, Simchowitz V, Lohner S, Cai W, Decsi T, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: complications. Clin Nutr. 2018 Dec;37(6 Pt B):2418–29.
12 Baxter JP, Fayers PM, McKinlay AW. A review of the quality of life of adult patients treated with long-term parenteral nutrition. Clin Nutr. 2006 Aug;25(4):543–53.
13 Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. JPEN J Parenter Enter Nutr. 2014 May;38(1 Suppl):32s–7s.
14 Kalaitzakis E, Carlsson E, Josefsson A, Bosaeus I. Quality of life in short-bowel syndrome: impact of fatigue and gastrointestinal symptoms. Scand J Gastroenterol. 2008;43(9): 1057–65.
15 Ritter PL, Stewart AL, Kaymaz H, Sobel DS, Block DA, Lorig KR. Self-reports of health care utilization compared to provider records. J Clin Epidemiol. 2001 Feb;54(2):136–41.
16 Kjellsson G, Clarke P, Gerdtham UG. Forgetting to remember or remembering to forget: a study of the recall period length in health care survey questions. J Health Econom. 2014 May;35:34–46.
17 Lima L, Guerra MP, de Lemos MS. Adaptação da escala genérica do Inventário Pediátrico de Qualidade de Vida: Pediatric Quality Life Inventory 4.0 – PedsQL, a uma população portuguesa. Rev Port Saúde Pública. 2009;83–96.
18 Ferreira PL, Noronha Ferreira L, Nobre Pereira L. Medidas sumário física e mental de estado de saúde para a população portuguesa. Revista Portuguesa de Saúde Pública. 2012; 30(2):163–71.
19 Ferreira PL, Baltazar CF, Cavalheiro L, Cabri J, Goncalves RS. Reliability and validity of PedsQL for Portuguese children aged 5–7 and 8–12 years. Health Qual Life Outcom. 2014 Sep 11;12:122.
20 Instituto dos Mercados Públicos dIedC, I.P. (IMPIC). base: public contracts online. 2019.
21 Nathional Authority for Medicament and Health Products IPI. Infomed: national medicines database. 2019.

22 Diário da República. Decree no 207/2017, 11th July. Diário da República n.º 132/2017, Série I de 2017-07-11. Lisbon, Portugal: Health Ministry; 2017.
23 Diário da República. Decree no 254/2018, 7th September. Diário da República no 173/2018, Série I de 2018-09-07. Lisbon, Portugal: Health Ministry; 2018.
24 Central Administration of the Health System IP. Analyitical elements database (BDEA). 2012. Available from: http://www.acss.min-saude.pt/bdea/.
25 Diário da República. Legal order no. 7702-A/2012, Diário da República no 108/2012, 1º Suplemento, Série II de 2012-06-04. Lisbon, Portugal: Health Ministry; 2012.
26 R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. Available from: https://wwwR-projectorg.
27 Fuglsang KA, Brandt CF, Scheike T, Jeppesen PB. Hospitalizations in patients with nonmalignant short-bowel syndrome receiving home parenteral support. Nutr Clin Pract. 2020 Oct;35:894–902.
28 Instituto Nacional de Estatística. Inquérito às Despesas das Famílias: 2015–2016. Lisboa, Portugal: INE; 2017.
29 Arhip L, Serrano-Moreno C, Romero I, Camblor M, Cuerda C. The economic costs of home parenteral nutrition: systematic review of partial and full economic evaluations. Clin Nutr. 2021;40(2):339–49.
30 Canovai E, Ceulemans LJ, Peers G, De Pourcq L, Pijpops M, De Hertogh G, et al. Cost analysis of chronic intestinal failure. Clin Nutr. 2019 Aug;38(4):1729–36.
31 Olieman JF, Poley MJ, Gischler SJ, Penning C, Escher JC, van den Hoonaard TL, et al. Interdisciplinary management of infantile short bowel syndrome: resource consumption, growth, and nutrition. J Pediatr Surg. 2010 Mar;45(3):490–8.
32 Sanchez SE, McAteer JP, Goldin AB, Horslen S, Huebner CE, Javid PJ. Health-related quality of life in children with intestinal failure. J Pediatr Gastroenterol Nutr. 2013 Sep;57(3):330–4.
33 White K, Issac MS, Kamoun C, Leygues J, Cohn S. The THRIVE model: a framework and review of internal and external predictors of coping with chronic illness. Health Psychol Open. 2018;5(2):2055102918793552.
34 Antunes H, Nóbrega S, Correia M, Campos AP, Silva R, Guerra P, et al. Portuguese prevalence of pediatric chronic intestinal failure. J Pediatr Gastroenterol Nutr. 2020;70(4):e85.
35 Diário da República. Law no 100/2019, Diário da República no 171/2019, Série I de 2019-09-06. Lisbon, Portugal: Health Ministry; 2019.
36 Diário da República. Decree no 64/2020, Diário da República no 49/2020, Série I de 2020-03-10. Lisbon, Portugal: Health Ministry; 2020.

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Primary Diffuse Large B-Cell Lymphoma of the Rectum in a Non-Immunosuppressed Patient with Ulcerative Colitis

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Keywords
Diffuse large B-cell lymphoma · Ulcerative colitis · Epstein-Barr virus

Abstract
Introduction: The incidence of primary colorectal lymphoma in the gastrointestinal tract is very low, the rectum being infrequently affected. The development of this entity in inflammatory bowel disease patients usually occurs in a context of immunosuppression-based therapy, with only a few case reports describing its development in patients presenting no known risk factors. Moreover, the clinical presentation of primary colorectal lymphomas may be difficult to distinguish from an acute flare of ulcerative colitis (UC). ***Case Presentation:*** We present a case of non-Hodgkin lymphoma of the rectum in a 42-year-old male with a 7-year history of UC and no previous exposure to immunomodulatory agents. He presented with a history of mucous diarrhoea, tenesmus, proctalgia and weight loss, refractory to optimized therapy. A lower gastrointestinal endoscopy was performed revealing a circumferential ulcerated lesion of the rectum, from which histopathological analysis established the diagnosis of a non-Hodgkin diffuse large B-cell lymphoma (DLBCL). ***Discussion/Conclusion:*** The present case suggests the existence of alternative mechanisms for the development of DLBCL in UC patients. The clinical presentation mimicking an acute flare of UC posed a diagnostic challenge, highlighting the complexity behind the management of UC patients.

Linfoma difuso de grandes células B primário do reto em doente com colite ulcerosa sem terapêutica imunossupressora

Palavras Chave
Linfoma difuso de grandes células B · Colite ulcerosa · Vírus Epstein-Barr

Resumo
Introdução: O linfoma não *Hodgkin* (LNH) difuso de grandes células B (DGCB) colorretal primário é uma entidade rara, estando a sua associação com a colite ulcerosa (CU) relacionada com a exposição a imunomoduladores. Apresentamos uma forma particularmente rara de LN-

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HDGCB primário, com atingimento do reto em doente com proctite ulcerosa sem história de imunossupressores, cuja apresentação simula agudização da CU. ***Descrição do caso clínico:*** Homem de 42 anos, com diagnóstico de proctite ulcerosa desde 2014, e sem história de terapêutica imunossupressora. Inicia quadro de diarreia com muco, proctalgia intensa, tenesmo e perda ponderal (10% em 2 meses), sem melhoria após otimização da terapêutica. Realiza colonoscopia que revela lesão ulcerada e circunferencial a nível do reto, condicionando estenose luminal, cujas biopsias revelaram LNHDGCB. ***Discussão/Conclusão:*** O presente caso sugere a existência de mecanismos fisiopatológicos alternativos à terapêutica imunossupressora para o desenvolvimento de LNH em doentes com CU. A apresentação clínica sugestiva de agudização da CU, constituiu um verdadeiro desafio diagnóstico, fazendo realçar a complexidade da abordagem destes doentes.

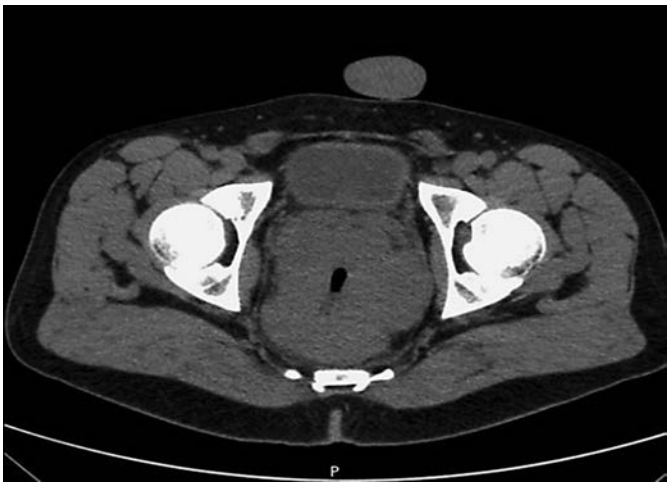


Fig. 1. Abdominal CT scan showing circumferential stricturing lesion located at the lower/mid rectum with associated wall thickening.

Introduction

Primary colorectal lymphoma is a very rare condition, accounting for 0.2% of all colorectal malignancies [1–3]. Its association with ulcerative colitis (UC) is mainly related to the use of immunomodulators, which dictate a definite increase in risk of lymphoproliferative disorders (LDs). In the absence of immunosuppressive therapy, the risk of LD in inflammatory bowel disease (IBD) patients seems to be similar to that of the general population [4]. Herein we describe a case of a particularly rare form of diffuse large B-cell lymphoma (DLBCL), with rectal involvement, in a patient with ulcerative proctitis with no history of immunomodulator exposure. The disease presentation simulated an acute flare of the patient's chronic disease.

Case Report

We present the case of a 42-year-old male with a 7-year history of ulcerative proctitis treated with topical mesalamine (suppository 1 g/day) and no previous exposure to immunomodulatory agents or corticosteroids. His medical history was uneventful. He had a family history of IBD but no history of neoplasia or LD. In the last colonoscopy, performed in March 2019, the patient was in endoscopic remission (Mayo subscore 0).

In September 2020 the patient developed diarrhoea with 3–4 bowel movements per day, the stools consisting of watery fluids and mucus, without blood. Three months later, symptoms persisted despite intensive topical and oral treatment with mesalamine (suppository 1 g/day + oral mesalamine 4.5 g/day). At this time, the patient also complained of severe rectal pain, tenesmus and weight loss (10% in 2 months). He denied fever, fatigue or night sweats. Topical budesonide was prescribed without improvement. Oral prednisolone was then started, and colonoscopy performed, revealing a suspicious rectal lesion. The patient was admitted to the hospital to proceed with the investigation and for pain management.

At admission, the patient complained of severe rectal pain, only controlled with tramadol perfusion. On physical examination, the patient was haemodynamically stable and had no fever. There were no enlarged palpable lymph nodes. Abdominal examination did not show any signs of tenderness or palpable masses, but on rectal examination, a palpable firm mass was detected. Blood tests revealed a slightly elevated C-reactive protein (1.17 mg/dL) with normal white blood cell count (10.9×10^9/L). Abdominal X-ray was normal. An urgent computed tomography (CT) revealed the presence of a circumferential lesion located at the lower/mid rectum with associated wall thickening. Significant luminal narrowing was also described (Fig. 1). A pelvic magnetic resonance imaging (MRI) was further conducted, showing a concentric circumferential rectal wall thickening with ulceration beginning at 3 cm from the anal verge and extending longitudinally along 12 cm. This mass invaded the mesorectal fascia and the right sphincter complex, having a defined cleavage plane with the prostate and bladder. Regional lymph node involvement was observed (Fig. 2).

Complementary laboratory studies were obtained; namely, tests for sexually transmitted diseases, including human immunodeficiency virus (HIV) types 1 and 2, herpes simplex virus (HSV) type 2, *Chlamydia trachomatis* and *Treponema pallidum*, were negative; serology for HSV type 1 and *Cytomegalovirus* revealed the presence of specific IgG antibodies; serological marker for hepatitis C virus (HCV) was negative and hepatitis B surface antibody was detected for hepatitis B virus (HBV). Evaluation of the Epstein-Barr virus (EBV)-specific antibody profile revealed positivity for IgG with equivocal IgM. The viral load measurement was fur-

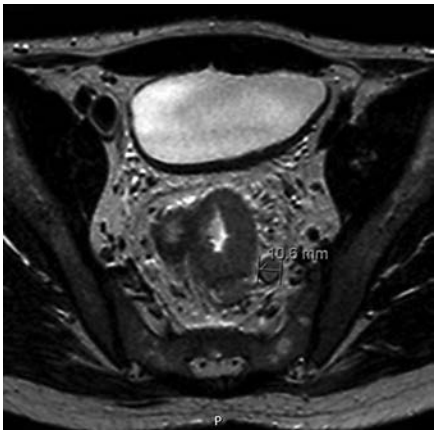


Fig. 2. Pelvic MRI confirmed the presence of rectal wall thickening with ulceration extending from 3 to 12 cm above the anal verge. Regional lymph node involvement was also observed.

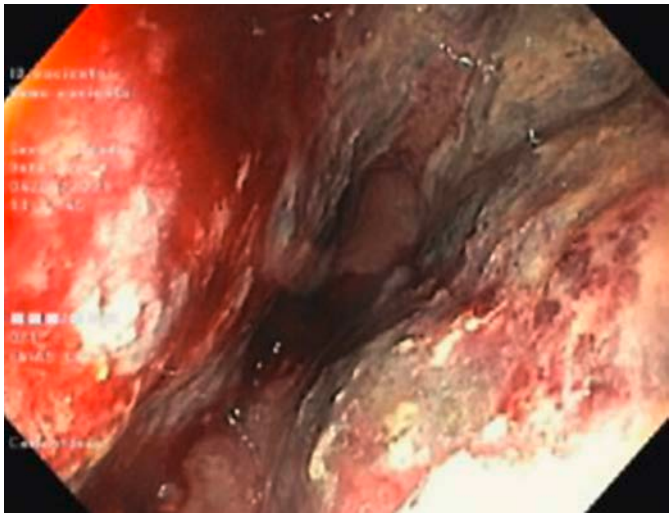


Fig. 3. Colonoscopy showing circumferential and extensively ulcerated lesion of the rectum, with associated stenosis.

ther added to the study, confirming the presence of an acute infection (5,972 copies/mL).

A lower gastrointestinal (GI) endoscopy was performed, revealing a circumferential lesion extending continuously from 12 cm above the anal verge to the dentate line, with associated stenosis. The lesion was extensively ulcerated with some areas covered with grey necrotic tissue (Fig. 3). The histopathological analysis of the rectal biopsies revealed lymphocyte infiltration in all layers of the rectal wall (Fig. 4a). In the immunohistochemical staining, cells were immunoreactive for CD20, CD10, bcl-6 and c-myc; the Ki67 immunohistochemical stain depicted 100% proliferative index (Fig. 4b). Detection of EBV by in situ hybridization to EBV-encoded RNA was also positive (Fig. 4c). Fluorescence in situ hybridization analysis revealed positive C-MYC gene rearrangement in 80% of analysed nuclei. Based on these findings, the diagnosis of a high-grade non-Hodgkin lymphoma (NHL) – DLBCL type was considered. After a lymphoma-negative bone marrow biopsy infiltration and negative neck and thorax CT scan, needed to complete adequate staging, the final diagnosis of primary rectal NHL DLBCL stage IV was established, and chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and high-dose methotrexate was started. Colonoscopy evaluation after 6 cycles of chemotherapy revealed complete endoscopic remission (Fig. 5). In the last follow-up visit (November 2021), 4 months after treatment, the patient remains in complete remission, for both the NHL DLBCL and UC.

Discussion/Conclusion

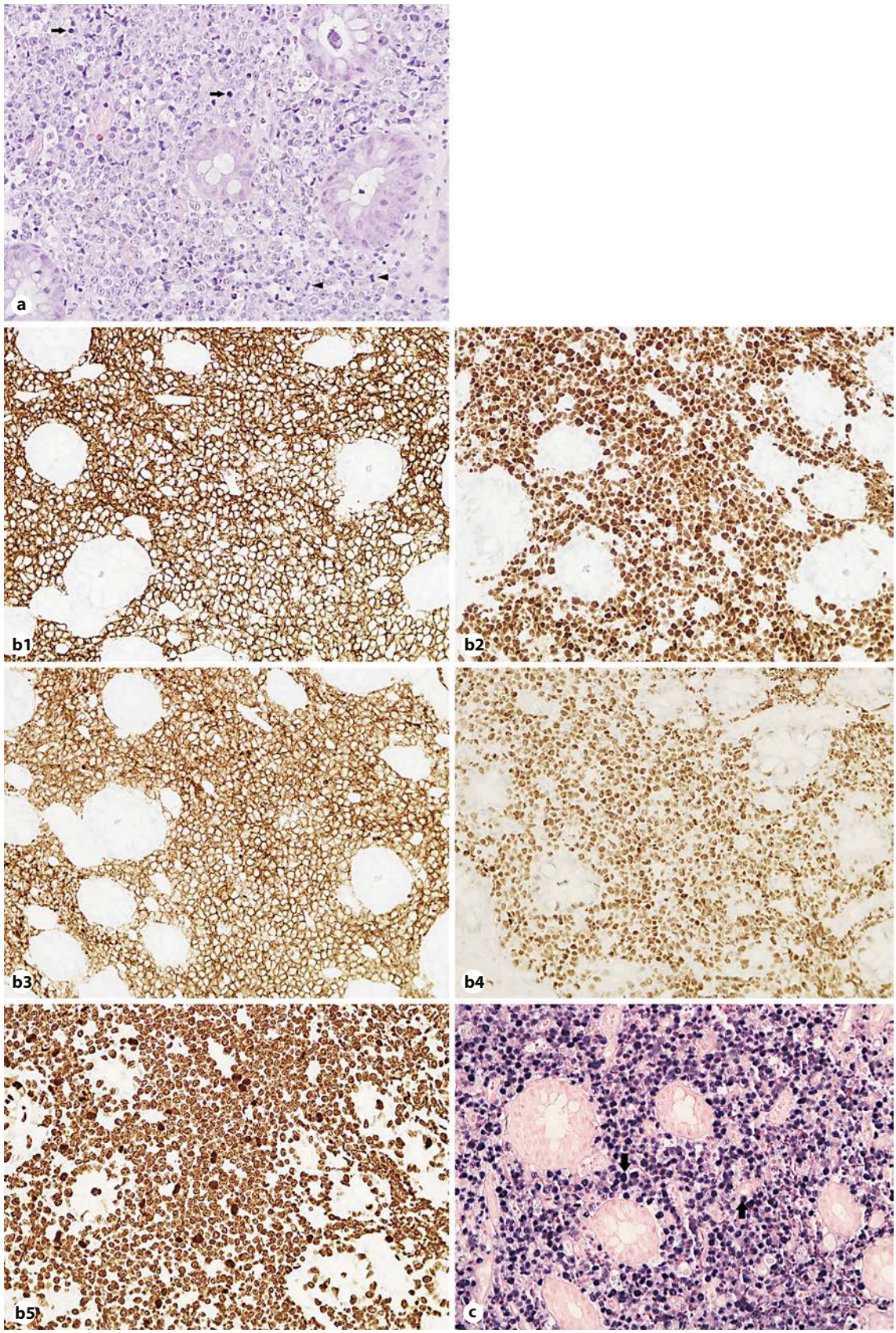
The GI tract is the major site of extranodal NHL and accounts for 30–40% of all cases [2]. While secondary GI involvement is relatively common, primary GI lymphomas are rare, representing only 1–4% of malignancies arising in the GI tract [3, 5]. They are generally defined as lymphomas that predominantly involve any section of the GI tract, in the absence of evidence of systemic disease [6]. They have unique clinical aspects and management considerations [2].

The most common site of primary GI lymphomas is the stomach (50–60%), followed by the small intestine (20–30%) [5, 7]. Involvement of the colon is rare (10–20%), with the cecum being the segment most commonly affected. Primary rectal lymphoma is the rarest location of lymphomas, accounting for 0.05% of all primary rectal malignancies [8].

Primary colorectal lymphomas have a male predominance, with men being twice more often affected than women. It usually occurs in the sixth to seventh decade and presents with abdominal pain, weight loss or changing in bowel habits [2, 3]. Less frequently described symptoms include lower GI bleeding (20% of patients) and obstruction, which occurs less often than in colorectal adenocarcinoma [3, 7].

Among the different histological subtypes of primary colorectal lymphomas, DLBCL is the most common [5, 7, 9], being generally aggressive. Thus, prognosis is poor with a 5-year survival rate of 27–33% [10].

Specific risk factors for primary colorectal lymphomas are largely unknown. However, it is generally assumed that the established risk factors for NHL will also increase the risk for primary colorectal lymphoma. Viral infections (namely HIV, HCV, HBV and EBV), immunosuppressive medications, organ transplantation, family history of lymphoma and personal history of chemo- and/or



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radiotherapy are the main risk factors described in the literature [2]. Some chronic systemic diseases such as autoimmune and immunodeficiency disorders are intrinsically associated with an increased risk of LDs [2, 4]. Contrarily, according to some studies, IBD on its own does not seem to increase the risk for primary colorectal lymphoma [4, 11]. However, when IBD patients are exposed to immunosuppressive therapy, the risk increases significantly. Thiopurines and, to a lesser extent, anti-tumour necrosis factor agents are the drugs associated with excess risk of lymphomas [11]. This LD is often EBV-associated. While the virus promotes malignant transformation, immunosuppressive therapy inhibits the immune system´s ability to detect and clear malignant cells [4]. In fact, in the CESAME cohort, the risk of LD was highest in those exposed to thiopurines, with a four- to sixfold increase in risk, and 46% of cases were EBV positive [4, 11].

In the present case, however, primary rectal DLBCL developed in the absence of previous or current immunomodulatory therapy for the treatment of UC. Although being extremely rare, similar cases have been reported in the literature [10, 12, 13], raising the hypothesis of alternative mechanisms contributing to the development of DLBCL in UC patients [10]. One of the possible mechanisms is overstimulation of the immune system secondary to chronic colorectal inflammation. In fact, previous studies have suggested that extensive or long-standing IBD seems to be associated with the development of lymphomas in IBD patients, with the mean time between the diagnosis of UC and lymphoma being 12 years [10, 14]. Moreover, lymphoma usually develops in areas affected by intense inflammation.

The underlying possible mechanism is chronic inflammation leading to clonal lymphocyte activation and subsequent proliferation. The maintained lymphocyte stimulation increases the possibility of mutations with consequent development of malignant lymphoma [14]. Additionally, EBV infection may also play a role in the development of lymphoma in long-standing IBD patients, even in the absence of immunosuppressive therapy. Thus, chronic local inflammation may induce a localized immunodepression, favouring the clonal proliferation of EBV-infected B cells [4, 15].

In our case, although the DLBCL developed in a time interval (7 years) that was shorter than that usually reported in the literature, chronic local inflammation may have triggered clonal proliferation of EBV-positive lymphocytes. Although the previous status of EBV infection of our patient is not known, the most probable scenario is the reactivation of a latent EBV infection. Critical association of EBV-associated lymphoproliferative diseases with viral latency and contribution of specific latent antigens to B-cell transformation has been described [16].

In the present case, the clinical presentation mimicking an acute flare of UC and the absence of rectal mucosal lesions in the endoscopic evaluation performed 1 year before posed a diagnostic challenge, highlighting the complexity behind the management of UC patients. This case report emphasizes that, although being rare, the occurrence of colorectal lymphoma should be taken into consideration in UC patients presenting with refractory disease, even when there is no history of previous exposure to immunomodulatory agents, to ensure proper diagnosis and treatment.

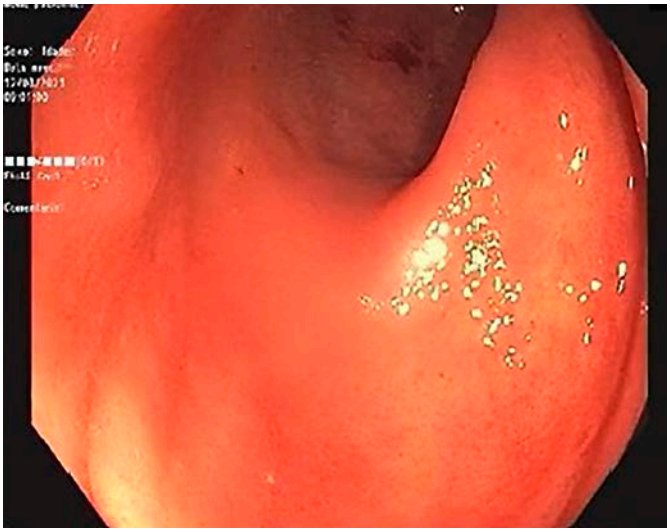

Fig. 5. Complete endoscopic remission after treatment.

Fig. 4. Rectal biopsies. **a** Infiltration of the rectal wall by lymphoid cells, where mitotic figures (arrowheads) and apoptotic cells (arrows) are easily recognized. Haematoxylin and eosin stain. Magnification ×400. **b1–5** Immunohistochemical examination: atypical lymphocytes are CD20, CD10, bcl-6 and c-myc positive with Ki67 immunohistochemical stain depicting 100% proliferative index. **c** Detection of EBV by in situ hybridization to EBV-encoded RNA was positive (blue staining) in the tumor cell nuclei (arrows). Magnification ×400.

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Statement of Ethics

All rules of the local Ethics Committee (Comissão de Ética do Centro Hospitalar Universitário de Lisboa Norte/Centro Académico de Medicina de Lisboa) were followed, preserving patient identity and confidentiality. Informed consent was obtained from the patient for the publication of his case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.S. conceptualized and wrote the original draft. S.B., S.M., and L.C. revised the manuscript critically. All the authors read and approved the final paper.

References

1 Hangge PT, Calderon E, Habermann EB, Glasgow AE, Mishra N. Primary colorectal lymphoma: institutional experience and review of a national database. Dis Colon Rectum. 2019 Oct;62(10):1167–76.
2 Gay ND, Chen A, Okada CY. Colorectal lymphoma: a review. Clin Colon Rectal Surg. 2018 Sep;31(5):309–16.
3 Ghimire P, Wu GY, Zhu L. Primary gastrointestinal lymphoma. World J Gastroenterol. 2011 Feb;17(6):697–707.
4 Sokol H, Beaugerie L, Maynadié M, Laharie D, Dupas JL, Flourié B, et al.; CESAME Study Group. Excess primary intestinal lymphoproliferative disorders in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2012 Nov;18(11):2063–71.
5 Stanojevic GZ, Nestorovic MD, Brankovic BR, Stojanovic MP, Jovanovic MM, Radojkovic MD. Primary colorectal lymphoma: an overview. World J Gastrointest Oncol. 2011 Jan;3(1):14–8.
6 Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg. 1961 Jul;49:80–9.
7 Quayle FJ, Lowney JK. Colorectal lymphoma. Clin Colon Rectal Surg. 2006 May;19(2):49–53.
8 Jiang C, Gu L, Luo M, Xu Q, Zhou H. Primary rectal lymphoma: a case report and literature review. Oncol Lett. 2015 Jul;10(1):43–4.
9 Chen Y, Chen Y, Chen S, Wu L, Xu L, Lian G, et al. Primary gastrointestinal lymphoma: a retrospective multicenter clinical study of 415 cases in Chinese province of Guangdong and a systematic review containing 5,075 Chinese patients. Medicine. 2015 Nov;94(47):e2119.
10 Mansour R, Beattie M, Miller J, Haus C. Diffuse large B-cell lymphoma mimicking an ulcerative colitis flare. ACG Case Rep J. 2019 Mar;6(3):1–3.
11 Subramaniam K, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: a review. J Gastroenterol Hepatol. 2013 Jan;28(1):24–30.
12 Suzuki T, Iwamoto K, Nozaki R, Saiki Y, Tanaka M, Fukunaga M, et al. Diffuse large B-cell lymphoma originating from the rectum and diagnosed after rectal perforation during the treatment of ulcerative colitis: a case report. BMC Surg. 2021 Jan 21;21(1):50.
13 Marín García D, Cárdenas Lafuente F, Utrilla Ayala Mdel C, Galán Jurado MV, Jiménez Martín JJ, García Ordóñez MA. Linfoma de tipo B difuso de células grandes primario rectal que simula un adenocarcinoma de recto [Primary diffuse large B-cell lymphoma of the rectum simulating a rectal adenocarcinoma]. Gastroenterol Hepatol. 2010 Feb;33(2):92–8.
14 Watanabe N, Sugimoto N, Matsushita A, Maeda A, Nagai K, Hanioka K, et al. Association of intestinal malignant lymphoma and ulcerative colitis. Intern Med. 2003 Dec;42(12):1183–7.
15 Copie-Bergman C, Niedobitek G, Mangham DC, Selves J, Baloch K, Diss TC, et al. Epstein-Barr virus in B-cell lymphomas associated with chronic suppurative inflammation. J Pathol. 1997 Nov;183(3):287–92.
16 Saha A, Robertson ES. Epstein-Barr virus-associated B-cell lymphomas: pathogenesis and clinical outcomes. Clin Cancer Res. 2011 May;17(10):3056–63.

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Testicular Seminoma Presenting as Gastrointestinal Bleeding: A Rare Cause of Metastatic Disease in the Stomach

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Keywords
Testicular seminoma · Gastric metastases · Gastrointestinal bleeding

Abstract
Introduction: Gastric metastases are quite infrequent. When arising from testicular germ cell tumors, gastric metastases are usually associated with nonseminomas. ***Case Report:*** A 45-year-old man presented with upper gastrointestinal bleeding, severe anemia, and elevated lactate dehydrogenase. Endoscopy revealed three atypical-looking gastric ulcers. Abdominal computed tomography showed an extensive heterogeneous retroperitoneal mass and a smaller one in the pelvis. Biopsies of both the ulcers and the retroperitoneal mass revealed a highly proliferative neoplasia of unknown origin. While the diagnostic work up was taking place, the patient complained of a testicular mass which was resected, after suspicious findings in the ultrasound. Histopathologic findings revealed a testicular seminoma. Revision of previous biopsies was compatible with metastatic seminoma to the stomach and the retroperitoneum. ***Discussion/Conclusion:*** Gastric metastasis arising from testicular seminoma is quite infrequent and usually diagnosed after the primary tumor is known. We report a rare case of a testicular seminoma presenting as upper gastrointestinal bleeding due to gastric metastases. This case highlights the importance of detailed anamnesis and physical examination in the differential diagnosis of atypical gastric ulcers with initial inconclusive work up and emphasizes an unusual manifestation of a germ cell malignancy.

Manifestação inaugural de seminoma testicular como hemorragia digestiva: uma causa rara de metastização gástrica

Palavras-chave
Seminoma testicular · Metastização gástrica · Hemorragia digestiva

Resumo
Introdução: As metástases gástricas são bastante infrequentes. Quando são secundárias a tumores testiculares, geralmente as metástases gástricas associam-se a não-seminomas. ***Caso Clínico:*** Um homem de 45 anos recorreu ao serviço de urgência por quadro de hemorragia digestiva alta, tendo-se detetado uma anemia grave e elevação da lactato desidrogenase. A endoscopia revelou

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três úlceras gástricas de aspeto atípico. A tomografia computorizada abdominal mostrou uma extensa massa heterogénea retroperitoneal e outra de menores dimensões na cavidade pélvica. Foram realizadas biópsias das úlceras gástricas e da massa retroperitoneal, sendo compatíveis com uma neoplasia altamente proliferativa de origem indeterminada. Durante a investigação etiológica, o doente referiu a deteção de uma massa testicular. Esta foi ressecada após a realização de ecografia com achados suspeitos. A histologia fez o diagnóstico de um seminoma testicular. A revisão das biópsias prévias foi compatível com metastização gástrica e retroperitoneal do seminoma. ***Discussão/Conclusão:*** A metastização gástrica com origem em seminomas do testículo é infrequente e geralmente é detetada após o diagnóstico do tumor primário. Apresenta-se um caso raro de manifestação inaugural de um seminoma testicular como hemorragia digestiva alta devido a metástases gástricas. Este caso evidencia a importância de uma anamnese e um exame objetivo detalhados no diagnóstico diferencial de úlceras gástricas atípicas com investigação inicial negativa, salientando também uma manifestação infrequente de uma neoplasia de células germinativas.

Introduction

Gastric metastases from solid primary malignancies are rare findings, usually diagnosed in a setting of a known advanced primary tumor, more frequently lung and breast cancers [1]. They present more often as solitary lesions with submucosal endoscopic appearance [2]. Metastases in the gastric mucosa are even rarer, with a reported incidence of 0.2–0.7% among patients with nonhematologic malignancies in postmortem studies [3].

Testicular germ cell tumors metastasize to the gastrointestinal tract in about 5% of cases, most of these evolving in the small intestine and manifesting as bowel obstruction or, less frequently, as gastrointestinal bleeding [4]. They are classified as seminomas and nonseminomas. Seminomas are the least likely testicular tumor to metastasize to the gastrointestinal tract, with an incidence of 1% in a 486-post-mortem-cases study [4]. We report a rare case of a previously undiagnosed testicular seminoma presenting as upper gastrointestinal bleeding due to multiple metastases to the gastric mucosa.

Case Report

A 45-year-old man without past medical history was admitted to the emergency room with weight loss (11% of total body weight in 2 months), asthenia, and fever, followed by melaena. The initial work up revealed a severe normocytic normochromic anemia (hemoglobin at 4.1 g/dL, normal range [NR]: 13.0–17.7) and markedly elevated lactate dehydrogenase (2,231 U/L, NR: 100–247). Upper endoscopy showed three atypical-looking ulcers in the greater curvature of the gastric body, one of which with a visible vessel successfully submitted to endoscopic hemostasis with two through-the-scope clips after diluted adrenalin injection (1:10,000) in and around the ulcer base (shown in Fig. 1). Biopsies of the ulcers were performed. Abdominal computed tomography revealed an extensive heterogeneous retroperitoneal mass with a diameter of 15 cm, causing inferior vena cava stenosis, and a right pelvic mass with a diameter of 10 cm (shown in Fig. 2). The laboratory evaluation was notable for neuron-specific enolase of 168.5 ng/mL (NR: < 12.5). Prostate-specific antigen, carcinoembryonic antigen, alpha-fetoprotein, cancer antigens 19-9 and 72-4, immunoglobulin levels, protein

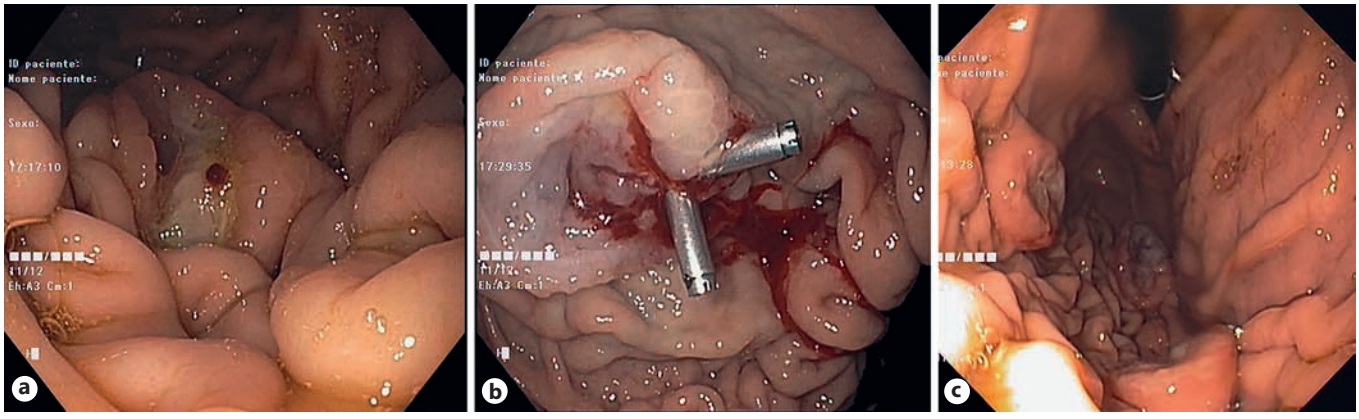

Fig. 1. Atypical "volcano-like" gastric ulcers. **a**, **b** One of the ulcers with a visible vessel that was submitted to endoscopic hemostasis. **c** Four-week re-evaluation with repeated biopsies.

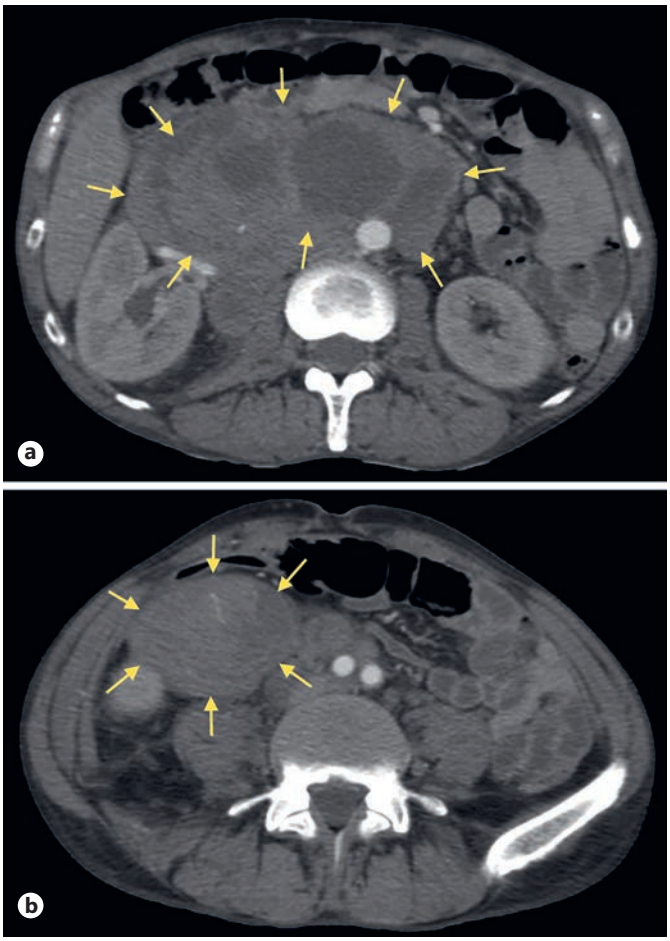

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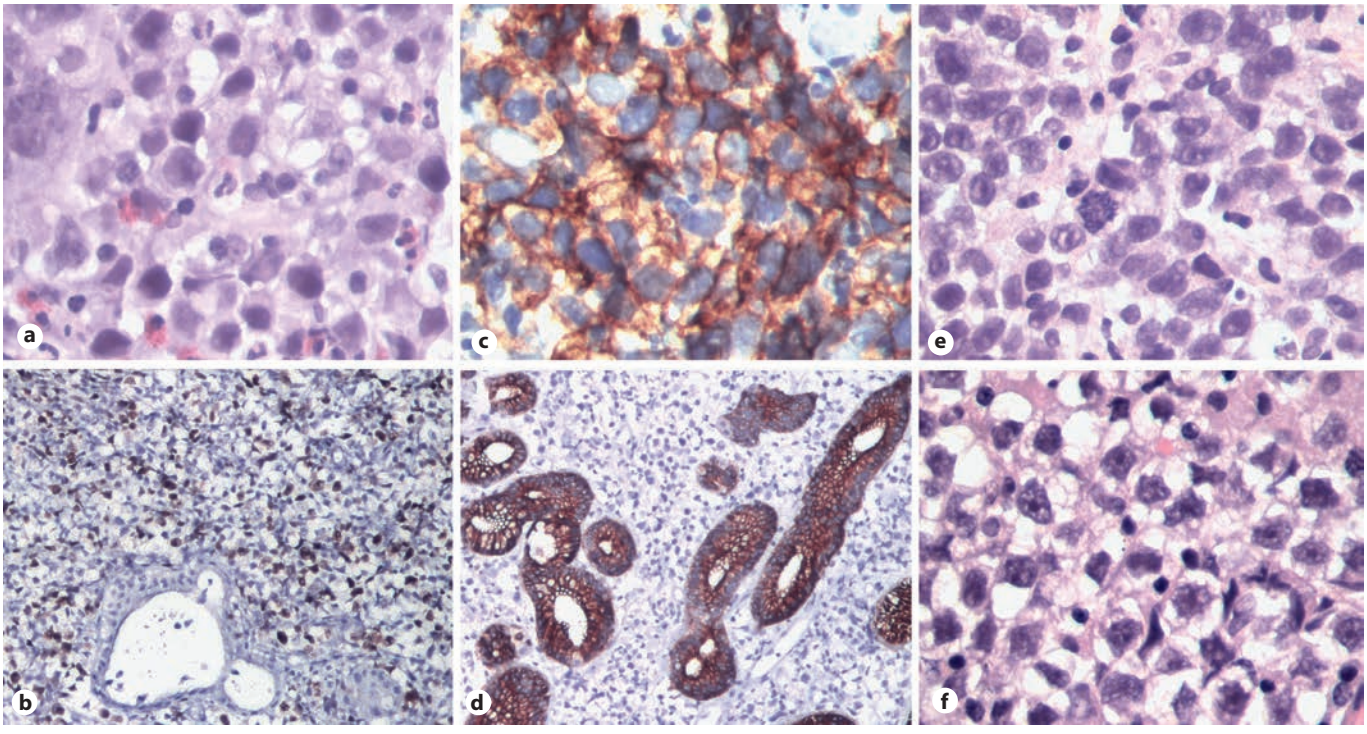
Fig. 2. Abdominal computed tomography findings. **a** An extensive heterogeneous retroperitoneal mass with a diameter of 15 cm. **b** A right pelvic mass with a diameter of 10 cm.

Fig. 3. Histologic findings: gastric biopsies revealing large cells with big hyperchromatic nuclei and prominent nucleoli, independent from the gastric glandular component (**a**, hematoxylin and eosin, ×400), with high proliferation index (Ki-67, **b**, ×100), positivity for CD117 (**c**, ×400), and negativity for cytokeratins (**d**, ×100). Identical findings in the retroperitoneal mass biopsy (**e**, ×400) and in the testicular tumor specimen (**f**, ×400).



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electrophoresis, immunophenotyping of peripheral blood and human immunodeficiency virus serology were negative. Gastric ulcers' biopsies revealed a highly proliferative neoplasia of unknown origin, dissociated from the gastric glandular component, with immunohistochemical positivity for cluster of differentiation (CD) 56, CD117, CD68, CD10, and CD99 and negativity for cytokeratins, CD3, CD5, CD20, CD23, B-cell lymphoma 2, B-cell lymphoma 6, cyclin D1, melan-A, myeloperoxidase, and neuroendocrine markers (shown in Fig. 3a–d). The retroperitoneal mass biopsy showed an undifferentiated neoplastic proliferation with similar histologic findings and immunohistochemical profile (shown in Fig. 3e). The remaining study performed over the following weeks was unremarkable, including head, neck, chest, and lumbar/dorsal spine computed tomography; prostatic ultrasound; and colonoscopy. One month after the initial presentation, upper endoscopy was repeated under deep sedation. Similar findings were observed (shown in Fig. 1), and multiple biopsies of the ulcers were taken. At this point, the patient complained of an enlarged right hemiscrotum suggestive of a testicular tumor in testicular ultrasound. A radical orchiectomy was performed. Histopathologic findings were compatible with a pure testicular seminoma (shown in Fig. 3f), with tunica albuginea and spermatic cord invasion. Revision of both gastric and retroperitoneal biopsies was compatible with metastatic seminoma. Further laboratory study revealed an elevated β-human chorionic gonadotropin (29.4 IU/L, NR: < 0.5) and persistently normal alpha-fetoprotein. With an IIIC stage (T3N3M1bS2) [5], the patient underwent chemotherapy with bleomycin, etoposide, and platinum. Because of an incomplete response of the retroperitoneal mass, not resectable due to vascular adherences, the patient is undergoing radiotherapy. There was no hemorrhagic recurrence.

Discussion/Conclusion

Metastatic involvement of the stomach arising from testicular germ cell tumors is rare and usually detected after the primary tumor is diagnosed [1]. We report a case in which the first presentation was gastrointestinal bleeding arising from gastric metastases. The multiplicity of gastric lesions with mucosal involvement, suggesting a hematogenous route, is an even rarer finding [3].

Contrary to our case, most germ cell tumors with gastric metastasis have a nonseminoma component [6]. There are few reported cases of pure seminoma presenting at diagnosis with gastric metastases, both with and without macroscopic retroperitoneal ganglia involvement [7–9]. Most of these cases report a single gastric metastasis and some are associated with other visceral organ metastases, unlike our patient.

This case highlights the importance of the differential diagnosis of malignant gastric ulcers. The hypothesis of a germ cell tumor should be considered in cases where biopsies reveal a poorly differentiated neoplasm, particularly in young men with severe anemia. In our particular case, since a retroperitoneal mass was diagnosed at admission, a germ cell tumor should have been considered earlier in the diagnostic work up. The marked elevation of lactate dehydrogenase was in accordance with this hypothesis. Direct questioning about scrotal swelling, genital examination, dosing of the tumor marker β-human chorionic gonadotropin, and a low threshold for the performance of a testicular ultrasound would have been crucial for a prompter diagnosis. In addition, an early second opinion from a more specialized pathologist would have been appropriate.

A prompt diagnosis is of particular importance in the setting of a testicular seminoma, in which the presence of metastatic disease does not preclude a curative approach. In fact, all seminomas are categorized as having good or intermediate prognosis. In our case, the presence of nonpulmonary visceral metastases warrants an intermediate prognosis, with 88% 5-year survival rate [10]. However, lactate dehydrogenase elevation was recently redefined as an independent adverse prognostic marker [10], and there are insufficient data to predict the outcome in the infrequent scenario of gastric involvement by metastatic disease.

In conclusion, we report a rare initial presentation of testicular seminoma as gastrointestinal bleeding due to gastric metastases, emphasizing one of the unusual manifestations of germ cell malignancies and highlighting the importance of detailed anamnesis and physical examination in the differential diagnosis of atypical gastric ulcers.

Statement of Ethics

All procedures performed were in accordance with both the ethical standards of the Institutional Research Committee and the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report, including images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Analysis of the case and reviewing of the literature: Maria Azevedo Silva, Carina Leal, and André Ruge; drafting of the article: Maria Azevedo Silva; critical revision of the article for important intellectual content: Alexandra Fernandes and Maria Fernanda Cunha; and final approval of the article: Helena Vasconcelos.

References

1 De Palma GD, Masone S, Rega M, Simeoli I, Donisi M, Addeo P, et al. Metastatic tumors to the stomach: clinical and endoscopic features. World J Gastroenterol. 2006 Dec; 12(45):7326–8.
2 Kim GH, Ahn JY, Jung HY, Park YS, Kim MJ, Choi KD, et al. Clinical and endoscopic features of metastatic tumors in the stomach. Gut Liver. 2015 Sep;9(5):615–22.
3 Green LK. Hematogenous metastases to the stomach. A review of 67 cases. Cancer. 1990 Apr;65(7):15962–600.
4 Chait MM, Kurtz RC, Hajdu SI. Gastrointestinal tract metastasis in patients with germ-cell tumor of the testis. Am J Dig Dis. 1978 Oct;23(10):925–8.
5 Amin MB, Edge SB, Greene FL. AJCC cancer staging manual. 8th ed. Springer International Publishing; 2017.
6 Lauro S, Righini R, Onesti CE, Pucci E, Bramini A, Marchetti P. Gastric metastases from testicular cancer: case report and review of literature. J Gastrointest Cancer. 2014 Dec; 45(Suppl 1):22–4.
7 Pollheimer VS, Gurakuqi GC, Pollheimer MJ, Beham-Schmid C, Langner C. Testicular seminoma presenting with gastric metastasis. Gastrointest Endosc. 2008 Apr;67(4):726–7; discussion 727.
8 McLaren A, Baxter MA, Katbeh T, Lynch V, Fullarton G, White J. Metastatic seminoma with isolated gastric metastases: a case report. Scott Med J. 2019 Nov;64(4):133–7.
9 Yuan R, Zhou C, Meneghetti V, Lavoie JM, Kollmannsberger C, Wang G. Seminoma presenting as a solitary metastasis in gastric mucosa with regressed testicular mass. Urol Case Rep. 2020 Dec;29:101083.
10 Beyer J, Collette L, Sauvé N, Daugaard G, Feldman DR, Tandstad T, et al. Survival and new prognosticators in metastatic seminoma: results from the IGCCCG-update consortium. J Clin Oncol. 2021 May;39(14):1553–62.

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Endoscopic Snapshot

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Two Cancers in One Barrett's Segment: First Report of Concurrent Squamous Cell Carcinoma and Adenocarcinoma

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Keywords
Esophageal cancer · Barrett esophagus · Endoscopy

Duas neoplasias num segmento de Barrett: primeiro relato de carcinoma espinocelular e adenocarcinoma concomitantes

Palavras Chave
Esófago de Barrett · Endoscopia · Neoplasia de esófago

A 70-year-old male patient underwent his first upper endoscopy for anemia work-up. Beyond a 3-cm hiatal hernia, an endoscopic diagnosis of Barrett's esophagus (Prague classification C3M4) was entertained, as illustrated by a tongue at 3 o'clock on blue laser imaging (Fig. 1a). However, at the gastroesophageal junction an estimated 20-mm nodular, superficially ulcerated lesion emerged (Fig. 1b), likewise visualized on linked color imaging (LCI) after intra-hernial retroflexion (Fig. 1c). Given this presumed malignant complication, full-scale assessment of the Barrett's esophagus was warranted, including acetic acid spraying. In combination with LCI, another 8-mm utterly flat lesion emerged at 6 o'clock with an irregular vessel and surface pattern, highly suggestive of early cancer as a second lesion (Fig. 1d). Pathology of endoscopic biopsies confirmed specialized intestinal metaplasia and, more intriguingly, indicated a well-differentiated adenocarcinoma (AC) for the flat lesion (Fig. 2a) and a poorly differentiated squamous cell carcinoma (SCC) for the nodular lesion (Fig. 2b). Cross-sectional and EUS staging indicated T1/2N+ stage. Notwithstanding, due to advanced chronic obstructive pulmonary disease (GOLD IIIB with long-term oxygen therapy), the patient underwent upfront esophagectomy without significant complications after pulmonary prehabilitation. Final surgical pathology indicated pT1a, pN0(0/27), G1 for the AC and pT1b, pN1(2/27), G3 for the SCC (furthermore: L0, V0, Pn0, R0 each).

Barrett´s esophagus is a well-acknowledged risk factor for esophageal AC formation; however, singular cases of

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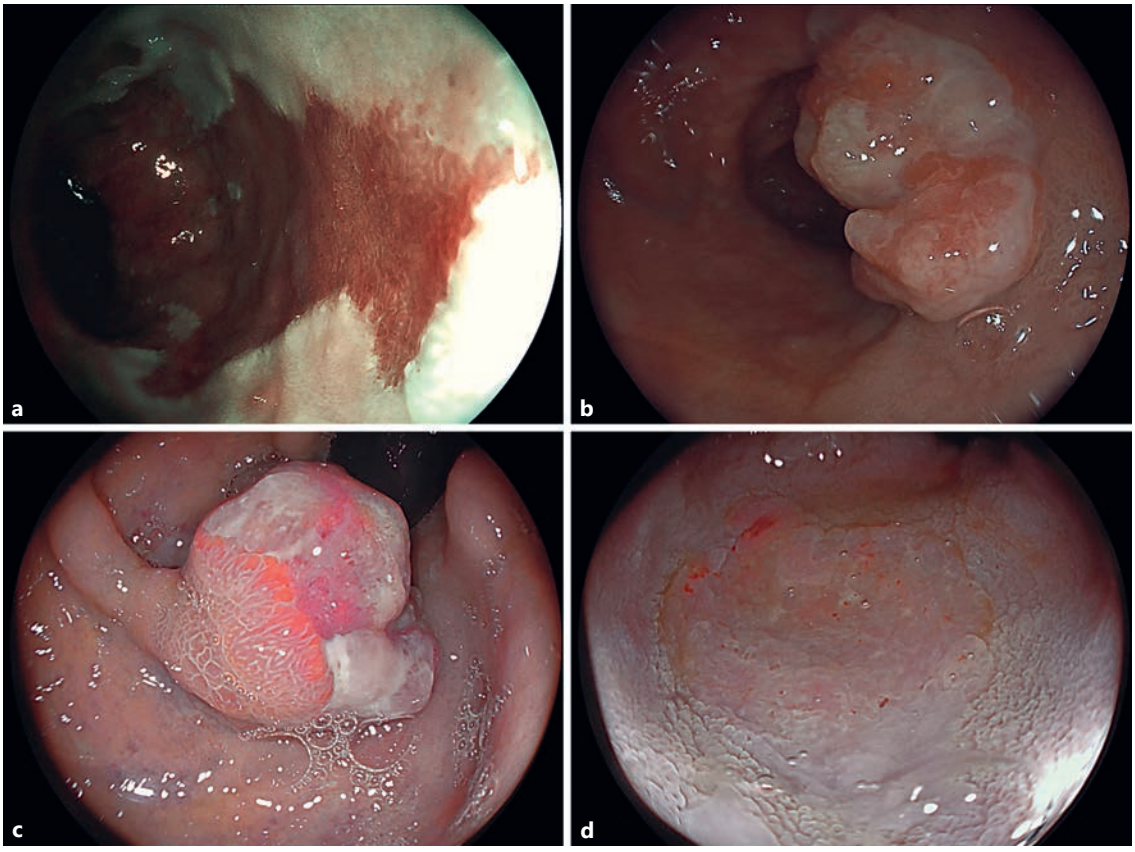

Fig. 1. a Blue laser imaging of a Prague C3M4 Barrett's esophagus with a tongue highlighted at 3 o'clock. **b** An estimated 20-mm nodular ulcerated lesion emerged at the gastroesophageal junction (**c**) as replicated on retroflexed LCI visualization. **d** LCI after acetic acid spraying in the distal esophagus highlighted another 8-mm flat lesion with an irregular vessel and surface pattern consistent with early cancer.

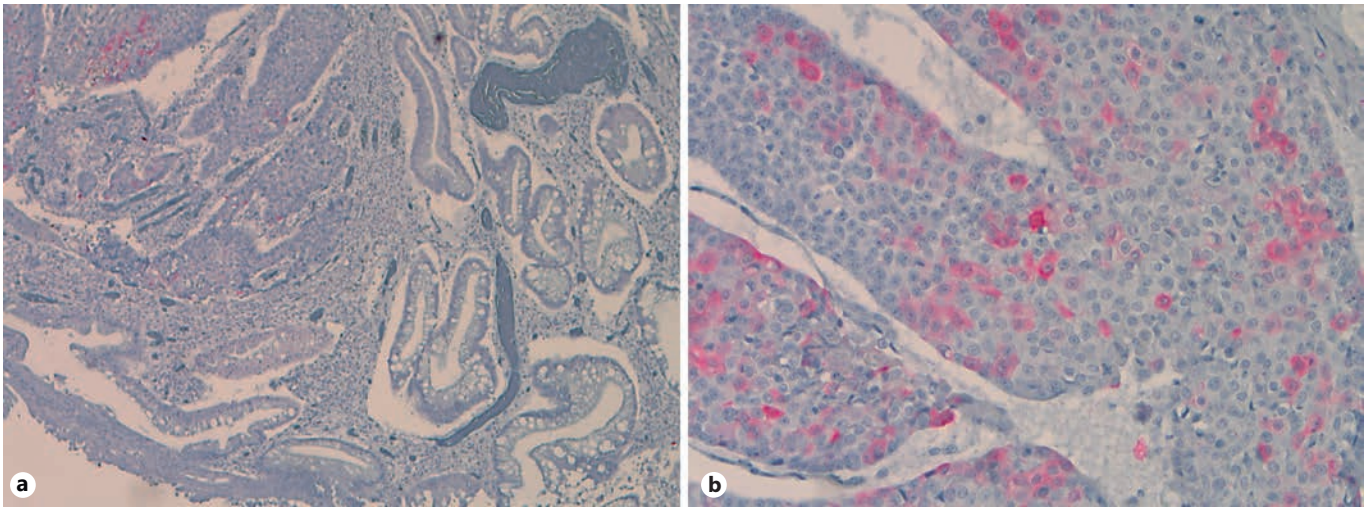

Fig. 2. Immunohistochemistries for cytokeratin (CK) 5/6 with negative staining of the AC (**a**) and positive results in the SCC (**b**).

SCC arising in Barrett's esophagus and/or collision tumor comprising SCC and AC elements have been documented in the literature, pointing to ambivalent carcinogenic field effects [1–3]. Concurrent SCC and Barrett's carcinoma has occasionally been reported in Barrett's esophagus before, however, to the best of our knowledge, not with the Barrett's segment itself [4–6]. Of interest, the patient had a mixed risk profile, including obesity and metabolic syndrome (Barrett's) and heavy smoking (SCC). The distinct molecular mechanisms for a presumed field cancerization within a Barrett's esophagus, which has been discussed in the literature, however, remain elusive.

Statement of Ethics

The patient gave 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

No funding was involved in this work.

Author Contributions

V.Z. – clinical care, drafting and finalization of manuscript; B.B. – pathology care, finalization of manuscript; M.M. – pathology care, finalization of manuscript; M.G. – surgical care, finalization of manuscript.

Data Availability Statement

Not applicable (clinical routine case).

References

1 Streppel MM, Siersema PD, de Leng WW, Morsink FH, Vleggaar FP, Maitra A, et al. Squamous cell carcinoma in Barrett's esophagus: field effect versus metastasis. Dis Esophagus. 2012;25(7):630–7.
2 Takeuchi A, Hatta W, Koike T, Saito M, Jin X, Asanuma K, et al. A primary Barrett's adenocarcinoma with a squamous cell carcinoma component. Intern Med. 2019;58(17):2467–72.
3 Mishima Y, Amano Y, Yuki T, Kusunoki R, Oka A, Uno G, et al. A rare case of Barrett's adenocarcinoma including squamous cell carcinoma component. Clin J Gastroenterol. 2011;4(1):5–9.
4 Yamazaki T, Iwaya Y, Iwaya M, Watanabe T, Seki A, Ochi Y, et al. A case of simultaneous esophageal squamous cell carcinoma and Barrett's adenocarcinoma. Clin J Gastroenterol. 2016;9(4):222–7.
5 Kobayashi T, Shiozaki A, Fujiwara H, Konishi H, Arita T, Kosuga T, et al. A case of synchronous multiple esophageal cancers composed of squamous cell carcinoma and Barrett's adenocarcinoma. Gan To Kagaku Ryoho. 2015;42(12):1890–2.
6 Maleki I, Shekarriz R, Nosrati A, Orang E. Simultaneous esophageal squamous cell carcinoma and adenocarcinoma: a case report. Middle East J Dig Dis. 2015;7(4):257–60.

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Endoscopic Snapshot

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Difficult Intragastric Balloon Retrieval: A Different Technique

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Keywords
Balloon dilatation · Bariatric endoscopy · Intragastric balloon

Remoção difícil de balão intragástrico: uma técnica diferente

Palavras Chave
Balão intragástrico · Endoscopia bariátrica · Dilatação por balão

Intragastric balloon is a temporary nonsurgical treatment for weight loss [1, 2]. The standard routine for its removal consists of: (i) puncturing with a needle held in the aspirator; (ii) pushing the needle inside the balloon, leaving the catheter inside; (iii) connecting the catheter to a vacuum drainage device, and then aspiring the entire balloon content; (iv) removing the collapsed balloon with a wire grasper. We hereby present a difficult intragastric balloon retrieval using a different technique.

A 39-year-old woman, with no significant medical history but obesity, was referred to our center after an unsuccessful Bioenteric Intragastric Balloon (BIB) retrieval. The balloon had been placed 5 months earlier and since then the patient had lost 8 Kg. On the first retrieval attempt, the aspiration of the BIB content with a standard BIB kit (Apollo Endosurgery, consisting of a wire grasper removal instrument and a needle aspirator) had not resulted in its full collapse. Therefore, the balloon could not be removed, as it did not pass the esophago-gastric junction. At our unit, under propofol sedation, a second attempt to fully aspirate the balloon with the same system was ineffective, as the surface of the balloon was pliable (Fig. 1). While mobilizing the BIB with the two-prong grasper device, a small hole was accidentally made (Fig. 2a); this allowed the needle to be inserted and the suctioning of some fluid. However, it was not possible to fully aspirate the balloon. Therefore, to promote passive emptying, we decided to enlarge the hole with a through-the-scope balloon dilator (18/19/20 mm, EndoFlex® Ref. 34118PRO; Fig. 2b, c). This allowed the volume of the balloon to be reduced, which was then gently retrieved with

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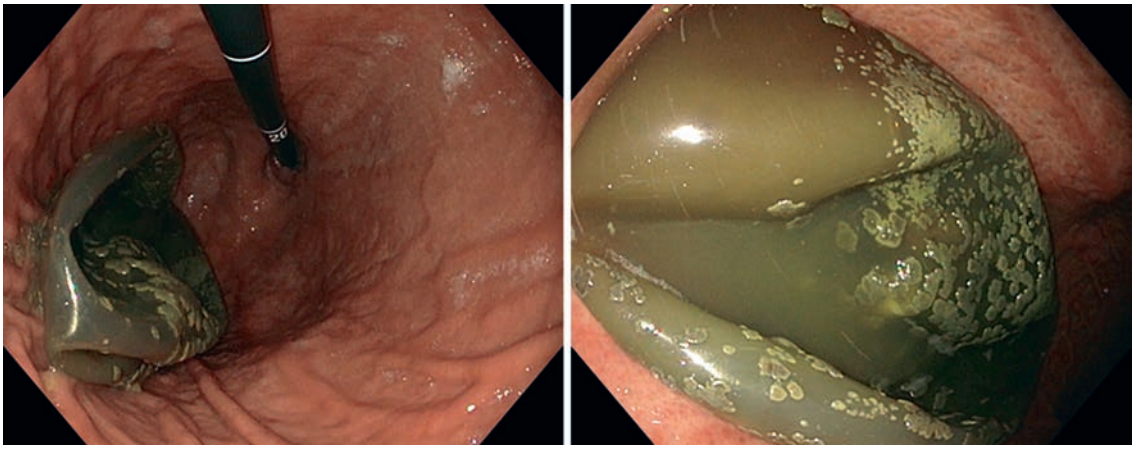

Fig. 1. BIB partially deflated in the gastric lumen (note the absence of sharp folds).

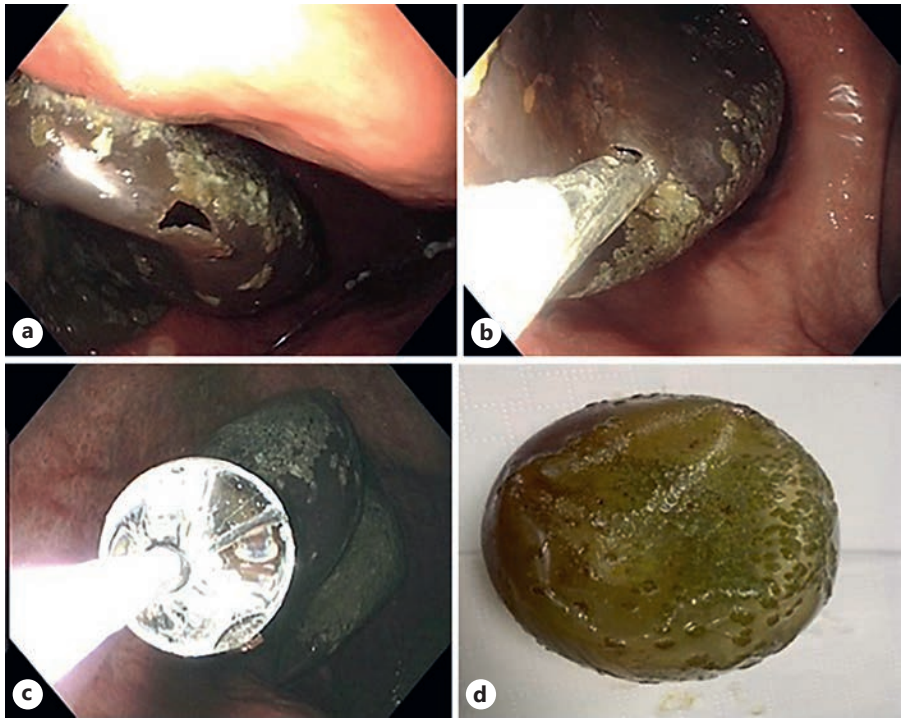

Fig. 2. New retrieval technique. **a** Hole in the intragastric balloon by a two-prong grasper device. **b** Through-the-scope (TTS) balloon through the hole in the intragastric balloon. **c** TTS balloon dilation. **d** Balloon retrieval.

the two-prong grasper (Fig. 2d). Re-examination of the stomach and esophagus was unremarkable, and the women was asymptomatic afterwards. Balloon retrieval may be a challenging task, especially when it is maintained longer than the recommended 6 months [3]. Some non-standard retrieval techniques have already been described, such as the use of a larger needle with a stronger suction device, the use of a snare around the end of the endoscope, or spraying vegetable oil over the balloon to ease balloon passage [4]. A procedure identical to ours was described by a Canadian group, who used a through-the-scope balloon dilator to allow intragastric balloon decompression. The balloon was then removed through an overtube, using a snare [5].

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

M.M.E., A.C.G., and R.P. were involved in the endoscopic procedure and in manuscript drafting. J.C. and E.A. were involved in manuscript drafting and critical revision. T.F. reviewed the manuscript and gave final approval. All authors approved the final version.

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.

References

1 Usuy E, Silva M, dos Passos Galvão Neto M, Grecco E, Ferreira de Souza T, de Quadros LG. Antibiotics to prevent relapse of adjustable gastric balloon hyperinflation: feasible for balloon maintenance? GE Port J Gastroenterol. 2021;28:52–5.

2 Ribeiro da Silva J, Proença L, Rodrigues A, Pinho R, Ponte A, Rodrigues J, et al. Intragastric balloon for obesity treatment: safety, tolerance, and efficacy. GE Port J Gastroenterol. 2018;25(5):236–42.

3 Dib J Jr, Bandres D. Retrieval of intragastric balloon used to treat obesity. Endoscopy. 2010;42(7):608.

4 Neto G, Campos J, Ferraz A, Dib R, Ferreira F, Moon R, et al. An alternative approach to intragastric balloon retrieval. Endoscopy. 2016;48 Suppl 1 UCTN:E73.

5 Falk V, Eccles JK, Karmali S, Sultanian R. Intragastric balloon removal: puncture, dilate, deflate. J Can Assoc Gastroenterol. 2018; 1(Suppl 2):449–50.

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Images in Gastroenterology and Hepatology

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Peribiliary Cyst: An Unusual Mimicker of Cystic Liver Lesions

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Keywords
Peribiliary cyst · Intraductal papillary neoplasm of the bile duct · Cystic liver lesion

Cisto peribiliary: um imitador incomum de lesões hepáticas císticas

Palavras Chave
Cisto peribiliary · Neoplasia papilar intraductal do ducto biliar · Lesão hepática cística

A 51-year-old man presented with chronic right subcostal pain and liver mass discovered by ultrasound. There were no significant findings on physical examination. He did not have any clinical features of chronic liver disease, including history, physical examination, and laboratory results. His viral hepatitis panels were unremarkable. His liver function tests were within normal limits, except for alkaline phosphatase at 154 IU/L (42–121), aspartate transaminase at 384 IU/L (12–32), and alanine aminotransferase at 170 IU/L (4–36). The carbohydrate antigen (CA19-9) level was at 33.1 (0–37) IU/L. He underwent computed tomography of the abdomen that revealed cystic lesions at the left hepatic duct, and magnetic resonance cholangiopancreatography revealed several side-by-side cysts with upstream dilatation of the adjacent bile duct (Fig. 1). Owing to the high prevalence of bile duct tumors, intraductal papillary neoplasms of the bile duct (IPNB), in our region, the patient was advised to have an endoscopic examination of the bile duct. Endoscopic retrograde cholangiopancreatography was performed to be a route for peroral cholangioscopy, but the procedure was unable to be performed due to a failure of cannulation into the common bile duct. Since the possibility of bile duct tumor was not fully eliminated, the patient therefore opted for a surgical resection rather than observation or re-endoscopic retrograde cholangiopancreatography. During the left hepatectomy operation, intraoperative ultrasound was performed, revealing several side-by-side simple cystic lesions near the bile duct of segment 2 of the liver (Fig. 2a). After finishing the operation, we performed cholangioscopy of the surgical specimen, to evaluate the mucosa and status of bile duct communication, using a cholangioscope (Olympus;

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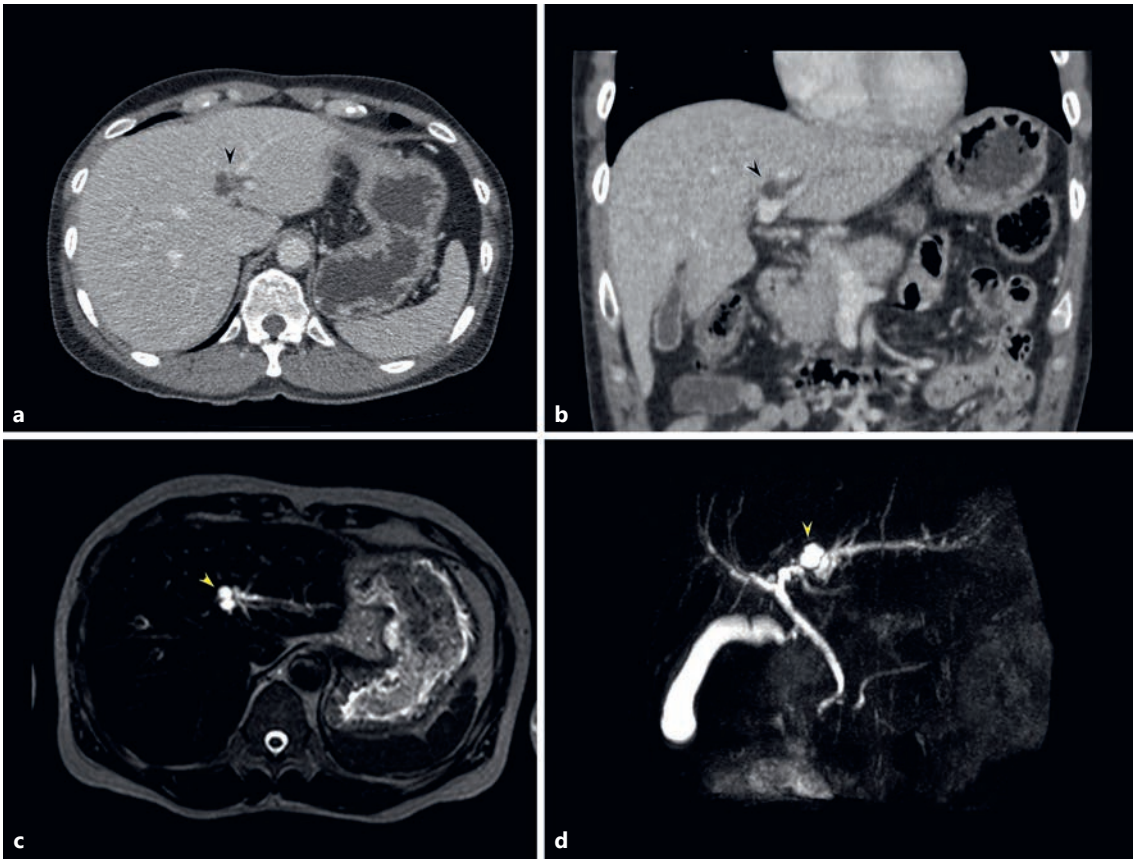


Fig. 1. Preoperative imaging of the patient. **a**, **b** CT scan revealed cystic lesions at LHD (black arrowhead). **c**, **d** MRCP revealed several side-by-side cystic lesions (yellow arrowhead) with upstream dilatation of the adjacent bile duct. CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography.

CHF type V: 4.9 mm). We found the normal mucosa of the biliary tract and external compression at the bile duct side wall without a bile duct communicated lesion (Fig. 2b, c). The surgical specimen revealed multiple varying-in-size simple cystic lesions lying near the bile duct segment 2 of the liver (Fig. 2d). The postoperative course was uneventful.

Peribiliary cysts are one of the most recently described entities of liver lesions. These cysts are variable in size, with variable numbers coursing along the hepatic hilum and intrahepatic large bile duct, situated externally to the bile duct wall, and not communicating with the biliary lumen. The intrahepatic location is the most frequent type. Although these cysts are benign, they can frequently cause symptoms and occasionally cause biliary obstruction, leading to cholangitis [1]. Despite the presence of the typical features of diagnosis as a linear collection of numerous small simple cysts paralleling the portal and biliary structures (Fig. 3a, b), there have been a number of misdiagnoses and the occurrence of therapeutic misadventures [1]. Although peribiliary cysts have been extensively described by their unique radiologic findings, their real surgical specimens and cholangioscopic findings demonstrating patho-radiologic correlation are rarely to be found. The differential diagnosis of multicystic lesions of the liver ranges from benign lesions with no clinical significance to malignancies which are potentially lethal [2]. Hereafter, we compare the typical features of cross-sectional imaging of our patients, among the diseases with multiple-cystic-lesion appearances; these should be differentiated from peribiliary cysts, including polycystic liver disease, Von-Meyenberg complex, Caroli disease, and IPNB (Fig. 3c–j). The last one, IPNB, is also a notable mimicker of cystic liver lesion through unique progression and various morphologies [3].

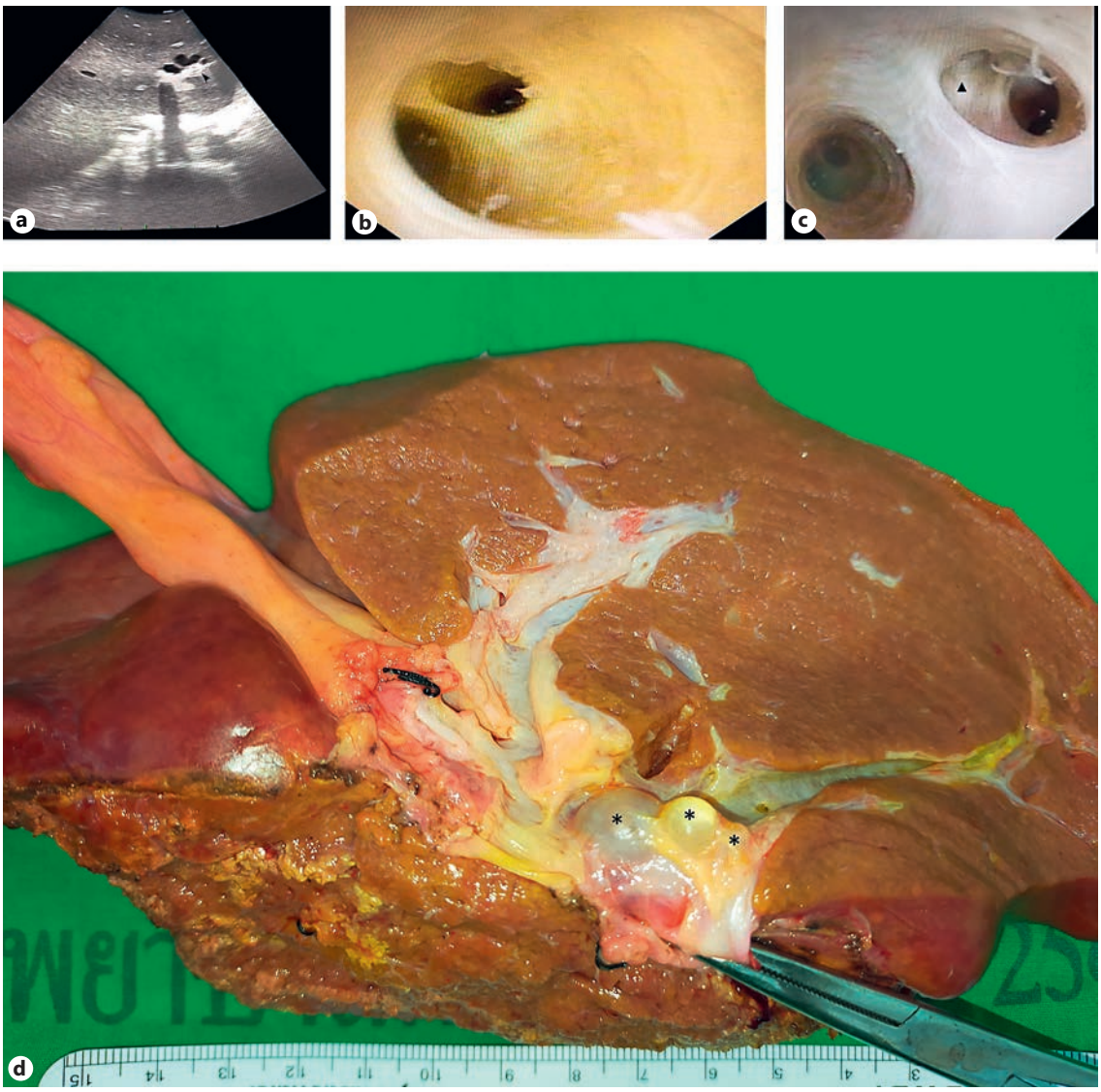
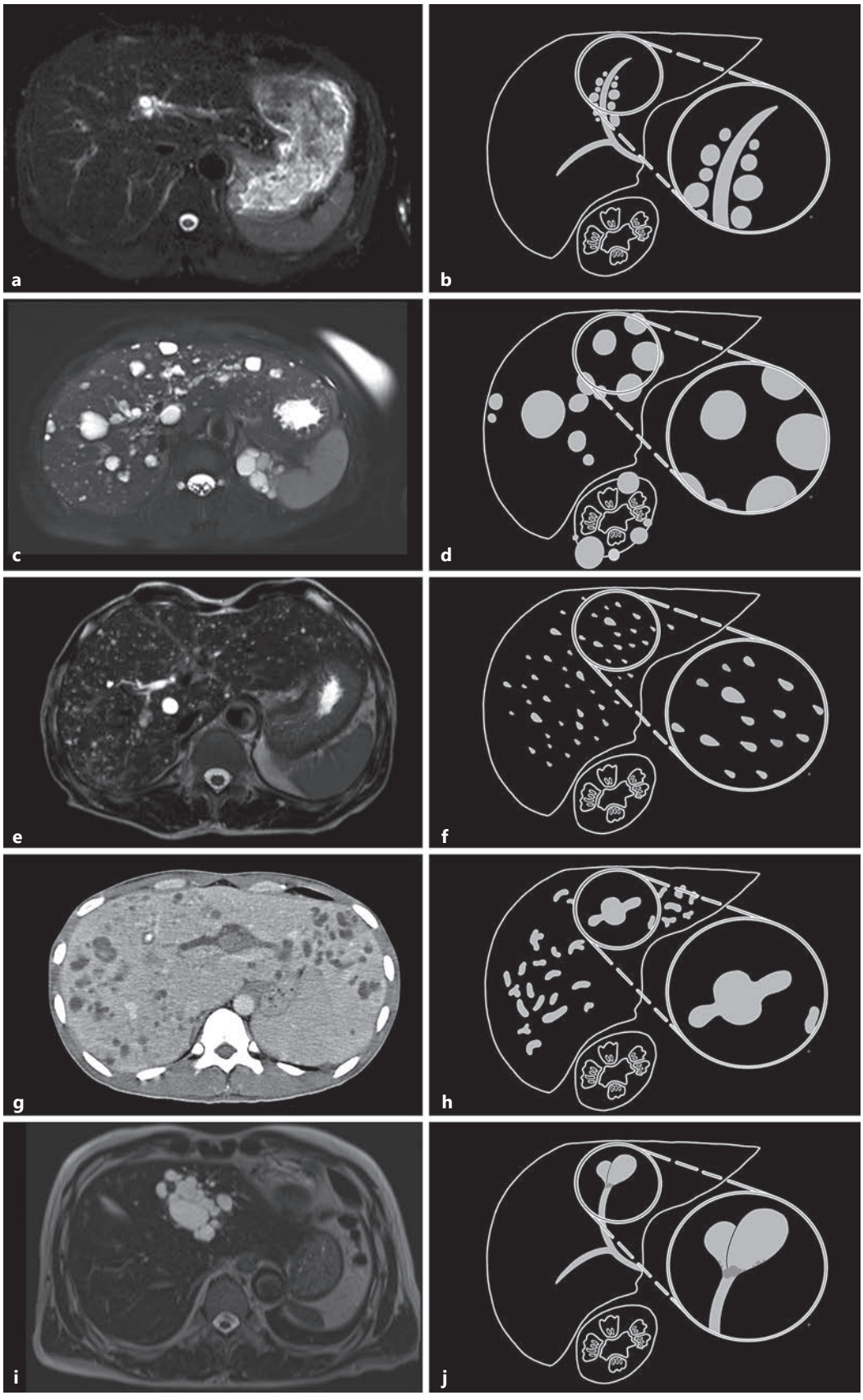


Fig. 2. Intraoperative findings. **a** IOUS showed several side-by-side simple cystic lesions near the bile duct of segment 2 of the liver. **b**, **c** Intraoperative choledochoscopy revealed normal mucosa of the biliary tract. The external compression was noted at the bile duct wall (triangle) without bile duct-lesion communication. **d** Surgical specimen revealed multiple varying-in-size simple cystic lesions (asterisk) lying near the bile duct of segment 2 of the liver. IOUS, intraoperative ultrasound.

Fig. 3. Comparison of typical features of cross-sectional imaging (**a**, **c**, **e**, **g**, **i**) and illustrated diagram (**b**, **d**, **f**, **h**, **j**) among diseases with multiple-cystic-lesion appearance. **a**, **b** Peribiliary cysts; multiple small simple cysts alongside the bile duct without bile duct communication. **c**, **d** Polycystic liver disease; innumerable varying-in-size simple cysts scattered around the liver and often kidneys. **e**, **f** Von-Meyenberg complex (also known as biliary hamartomas); multiple small irregular varying-in-size cysts scattering around the liver. **g**, **h** Caroli disease; diffuse, mostly saccular, and fusiform dilatation of the intrahepatic bile duct, with a "central-dot" sign. **i**, **j** IPNB; localized marked cystic dilatation of the bile duct with usually identifiable intraluminal lesions.

(For figure see next page.)



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Statement of Ethics

This study was approved by the Institutional Review Board, Office of Human Research Ethics, Khon Kaen University (HE641665). Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Arada Wongwattanachai: project development, data collection, diagram illustration, and manuscript drafting. Vor Luvira: project development, data collection, image preparation, and manuscript writing. Chawalit Pairojkul: project development, data collection, image preparation, and manuscript editing.

Data Availability Statement

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

References

1 Bazerbachi F, Haffar S, Sugihara T, Mounajjed TM, Takahashi N, Murad MH, et al. Peribiliary cysts: a systematic review and proposal of a classification framework. BMJ Open Gastroenterol. 2018;5(1):e000204.
2 Borhani AA, Wiant A, Heller MT. Cystic hepatic lesions: a review and an algorithmic approach. Am J Roentgenol. 2014;203(6):1192–204.
3 Luvira V. Progression of intraductal papillary neoplasm of the bile duct (IPNB): A proposed model through the observation of patients with non-resected tumors. Ann Hepatol. 2021;23:100299.

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INFORMAÇÕES ESSENCIAIS COMPATIVEIS COM O RESUMO DAS CARACTERISTICAS DO MEDICAMENTO. DENOMINAÇÃO DO MEDICAMENTO: Dioralyte, pó para solução oral. **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA: Substâncias activas** g/saqueta: Glicose 3,56; Cloreto de sódio 0,47; Cloreto de potássio 0,30; Citrato dissódico 0,53. **INDICAÇÕES TERAPÊUTICAS:** Correcção da perda de líquidos e electrólitos nos lactentes, crianças e adultos. Tratamento da diarreia aquosa de várias etiologias, incluindo as gastrenterites, em todos os grupos etários. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Cada saqueta deve ser sempre dissolvida em 200 ml de água. O volume de Dioralyte reconstituído a tomar deve ser decidido pelo médico assistente, tendo em consideração o peso do doente e o estado e gravidade da situação. Um princípio básico no tratamento da diarreia é a substituição da perda de líquidos e a manutenção de uma ingestão de líquidos suficiente para repor a sua perda nas fezes. A ingestão diária deve ser baseada num volume de 150 ml/Kg de peso nos lactentes e 20–40 ml/Kg de peso nos adultos e crianças. Uma aproximação razoável é a seguinte: -lactentes – 1 a 1,5 vezes o volume alimentar habitual, - crianças – 1 ou 2 saquetas após cada dejecção diarreica, - adultos – 1 ou 2 saquetas após cada dejecção diarreica. Inicialmente, podem ser necessárias maiores quantidades de Dioralyte para assegurar uma reposição precoce do equilíbrio hidro-electrolítico. Nos estadios iniciais do tratamento da diarreia, todos os alimentos, incluindo o leite de vaca e o leite artificial, devem ser interrompidos. Não se deve no entanto interromper o aleitamento materno. Nas crianças amamentadas sugere-se que se dê à criança o mesmo volume de Dioralyte do que o da alimentação normal, seguindo-se o aleitamento. Pode ser necessário, durante este período, a expressão do leite residual da mama. Após 24-48 horas, quando os sintomas desaparecerem, a dieta normal deve ser retomada gradualmente para evitar o agravamento da situação. O regime sugerido para o tratamento da diarreia infantil grave baseado no peso corporal em Kg é apresentado no quadro anterior. Quando a diarreia é acompanhada de vómitos, sugere-se ingestão frequente de pequenas quantidades de Dioralyte. No entanto, é importante que seja tomado o volume total necessário de Dioralyte. Quando o funcionamento dos rins é normal torna-se difícil superhidratar por via oral e quando existem dúvidas acerca da dosagem correcta, mais vale tomar a mais do que a menos. **CONTRA-INDICAÇÕES:** Não se conhecem contra-indicações ao Dioralyte. No entanto, existem algumas situações em que o tratamento com Dioralyte é inapropriado, tais como por exemplo, situações de oclusão intestinal requerendo intervenção cirúrgica, ou em caso de vomitos persistentes e desidratação grave ou diarreia infantil grave em que será necessária uma terapêutica por via intravenosa. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** O Dioralyte só deve ser reconstituído com água. Cada saqueta deve ser sempre reconstituída em 200 ml de água. Uma solução mais fraca do que a recomendada não contem a concentração óptima de glicose e electrólitos e uma solução mais forte do que a recomendada pode provocar desequilíbrio electrolítico. Se a diarreia não melhorar rapidamente, os doentes deverão ser reavaliados. Nos idosos, a administração de soluções contendo glucose e electrólitos deve ser cuidadosa em caso de alterações renais ou hepáticas graves ou em outras situações em que o balanço electrolítico normal se encontre alterado. Nos lactentes, deve interromper-se durante 24 horas a alimentação com leite de vaca ou leite artificial, que deverão ser reintroduzidos gradualmente quando a diarreia tiver diminuído. Não se deve interromper o aleitamento materno. **EFEITOS INDESEJÁVEIS:** Podem ocorrer náuseas ou vómitos após a administração da solução, em particular quando esta é ingerida com demasiada rapidez. Estão também descritos casos isolados de desconforto abdominal e de obstipação.Data da revisão do texto: Janeiro de 2004. **TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO:** KORANGI - Produtos Farmacêuticos, Lda. Medicamento não sujeito a receita médica. **Para mais informações contactar o Titular da Autorização de Introdução no Mercado**

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