Portuguese Journal of Gastroenterology

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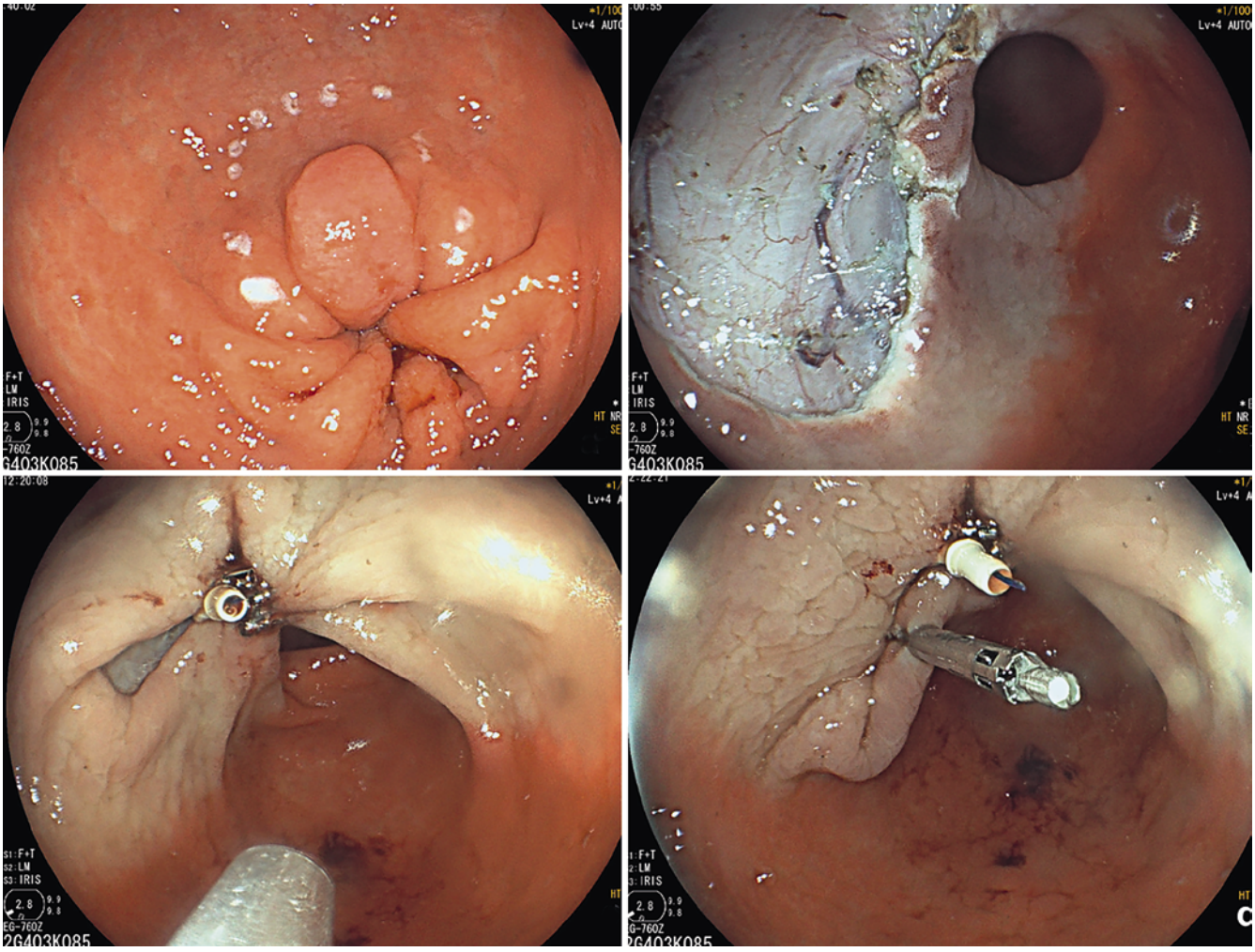
SPED SOCIEDADE PORTUGUESA DE ENDOSCOPIA DIGESTIVA

APEF ASSOCIAÇÃO PORTUGUESA PARA O ESTUDO DO FÍGADO



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Systematic review: Treatment of Hemorrhoidal Disease in Patients with Liver Cirrhosis

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Aims and Scope

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Editorial

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Building Clinical and Research Delivery Networks: A Blue Print for Multidisciplinary Management and Consensus in Wilson Disease

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Keywords
Network · Wilson disease · Multidisciplinary management

Redes de disseminação clínica e de investigação – um diagrama para consensos e abordagem multidisciplinar na Doença de Wilson

Palavras Chave
Redes · Doença de Wilson · Multidisciplinar

Calinas et al. [1] present an overview of the current state of Wilson disease (WD) management in Portugal. Due to the varied clinical presentations of WD, as in many other countries, the management of the condition utilizes a number of different specialities, which do not have consensus on management strategies [2]. Their aim of creating a practical guide, which includes several different specialities to help standardize the approach to management of a very complex condition, must be commended. It will also help, as they state, to raise awareness about WD in Portugal since globally diagnosing this disorder remains a significant challenge in diagnosis and further management.

Their summary of current evidence and reported presentations highlights well the huge variation in WD that is found both clinically and in the literature. Across all three different categories of clinical phenotype that include neurology, hepatology, and psychiatry, there are a plethora of reported symptoms ranging from common to the rarer. This range of symptoms makes creating comprehensive guidance difficult since it is not possible to account for every situation. Historically, consensus guidance was based on case-reports and retrospective work, but more recently there has been a drive towards prospective clinical trials. However, many areas of patient care are still reliant on older data with case series, and many articles still lack sufficient statistical power for conclusive recommendations due to their cohort size. The heterogeneity of WD combined with a limited number of prospective studies makes forming evidence-based recommendations for diagnosis and management challenging due to some areas of uncertainty and controversy. While the authors have presented their findings and advice in a structured and practical way with acknowledgement of limitations, there are some areas which benefit from further discussion.

It is widely accepted that there can be disease progression in WD; this is usually a combination of factors including compliance with medication and incorrect administration of medication [3]. Nevertheless, a minority of patients with hepatic involvement, who despite reported compliance, normal liver function tests and what appears to be adequate chelation treatment still have progression of disease [4]. It is unclear whether the

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disease in these individuals is progressive despite treatment, or, the more likely issue, that the current measures of disease stability are not accurate enough to detect changes that indicate that therapy may need to be altered. This reinforces the need to develop new and more sensitive techniques that might not only detect but predict progression; a candidate for this is accurately measured bioavailable copper levels in the circulation discussed below. Future work must demonstrate correlation of changes in bioavailable copper with disease activity and importantly for patient outcomes. Additionally, in these individuals with disease progression, we must be open-minded and recognize that there may be concurrent disease that is driving disease progression and be on the lookout for this. Guidance being produced should therefore ideally not only assimilate current practice but be adaptable to new possibilities.

One of the key areas of development within the field of WD mentioned above is the measurement of bioavailable copper in the circulation. Current standard tests such as serum copper and caeruloplasmin are known to be poor markers of true bioavailable copper levels. The estimated "non-caeruloplasmin bound copper" is universally accepted as an inaccurate measurement due to the flaw in calculating the amount of copper in caeruloplasmin, leading to a result which is zero or negative in value in almost half of individuals, therefore rendering it clinically un-interpretable. Twenty four-hour urinary copper excretion has been in use for diagnosis and treatment monitoring of WD since the first use of penicillamine in the 1950s and its more widespread use in the 1960s [5]. Additionally, there are data for the use of penicillamine induced urine copper excretion for the diagnosis of WD (penicillamine challenge testing) that was validated in paediatric patients. There has been a significant shift in focus over the last decade to move away from using just the urinary copper excretion in isolation, and moving to pairing it with methods of measuring circulating bioavailable copper. As mentioned by the authors, serum exchangeable copper (CuEXC) and the relative exchangeable copper (REC) were adopted by many different international centres. There are a number of manuscripts describing the use of REC for WD diagnosis [5–7]. In the upcoming European Association for the Study of Liver WD guidelines, REC was recognized as a potentially useful diagnostic tool. However, while there are increasing data on the use of CuEXC and REC in clinical practice with good results, there remain some questions on its use. The CHELATE trial, the first head-to-head trial for WD treatment, was not granted the use of REC as an endpoint in the study, which led to the development and use of a novel method for measuring bioavailable copper that combined

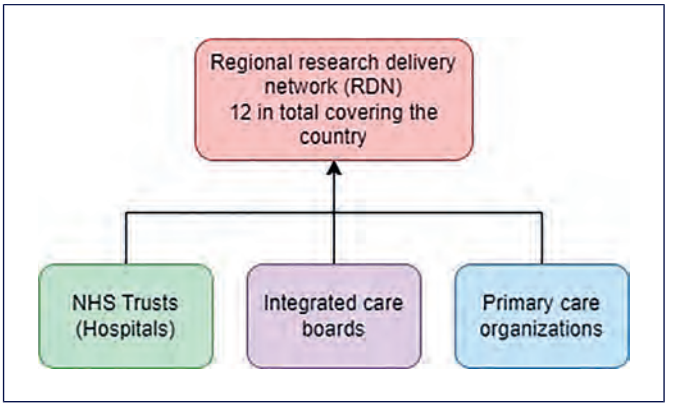

Fig. 1. Twelve NIHR Regional Research Delivery Networks (RDN) are formed from local services across England and encompassing all NHS services including hospitals, integrated care board, and primary care organizations. These same services will also refer patient to trientine centre/WD centres of excellence forming the clinical network. These twelve RDNs are co-ordinated from a single network coordinating centre with overall oversite from the Department of Health and Social Care (DHSC).

liquid chromatography and mass spectroscopy [8]. The underpinnings of this technique were published by Solovyev et al. [9], using inductively coupled plasma spectroscopy to accurately measure copper in chromatographically separated fractions. However, the availability of this equipment and conditions needed for sample processing may limit access to this testing.

An important key issue highlighted in this article is the assortment of specialities who may be involved in the care of WD patients. The authors recognize that there are multiple pathways to enter into care for different presentations of WD, and these can lead to less comprehensive care if there is no communication between specialists. To address this issue of having complex presentations with varied symptoms in patients across a range of ages, the best approach to the diagnosis and management of this condition would be to have dedicated centres with a concentration of expertise and a commitment to a multidisciplinary approach to care. Ideally, this would utilize joint clinics, or if not possible, facilitated communication between personnel that may include clinical biochemists, hepatologists, neurologists, psychiatrists, clinical nurse specialists, and other allied health care professionals. This concept of specialist centres is already in place in many countries, such as the USA and UK, where there is a system of accreditation by patient organizations of "centres of excellence" in WD. In France, there is also an extensive network for WD which links larger and smaller centres across the country, helping to

address diagnostic challenges and access to more specialized care and testing. This has been shown to be highly effective in France, where the assays for CuEXC were developed and utilized in clinical practice for a number of years. In Denmark, all WD is focused in a single centre, which has the necessary expertise.

Networks are an important part of treating a rare disease, both in clinical practice and research. Again, France is exemplary in having a robust clinical network for care and research for WD patients. In England, all public hospitals fall under the umbrella of NHS England and so there is an aspect of collaboration that is unique to this health service. There is ongoing work on central collation and integration of data from across different areas. The ability of the system to allow this may well provide crucial data to the understanding of disease progression. There also exists a WD special interest group which is a subset of the larger liver association (British Association for the Study of the Liver – BASL), helping bring together clinicians including allied health professional, patient organizations, and researchers across a range of specialities. In the wider setting, the UK/NIHR (National Institute for Health and Care Research) research delivery network (RDN) is a body that helps co-ordinate and support studies and is an important key factor in bringing together patients in less commonly seen conditions (Fig 1). It also plays in important role in supporting health care professionals in accessing resources with clinical and administrative support for studies.

The use of these networks in different countries are examples of connecting different health care professionals together to improve the standard of care in a condition that is less commonly seen. It also helps introduce new techniques and access to testing to a wider area. These networks can be a building block to develop a wider international collaborative effort to bring more people together for better care in WD. Hopefully, the generation of this multidisciplinary guideline in Portugal will be the first step in its journey along this same route to bring the latest diagnostics and comprehensive evaluation and testing to bear to achieve best patient outcomes for their population of WD, and for the larger community caring for this disorder.

Conflict of Interest Statement

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Author Contributions

A.A. and J.L.Y. wrote the 1st and 2nd draft. J.L.Y. added the references and figures. M.L.S. and A.A. finalized the manuscript with J.L.Y. A.A. is the overall guarantor for the manuscript and corresponding author.

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Review Article

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Practical and Multidisciplinary Review on Wilson Disease: The Portuguese Perspective

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Keywords
Wilson disease · Diagnosis · Treatment · Monitoring · Adherence

Abstract
Wilson disease (WD) is a genetic disorder of copper metabolism caused by mutations in the ATP7B gene resulting in toxic copper accumulation in several organs. WD can manifest as liver disease, a progressive neurological disorder, a psychiatric illness, or a combination of these. Other clinical manifestations can also occur. Diagnosis is challenging and typically requires a range of biochemical tests, imaging, genetic testing for ATP7B, and/or liver biopsy. WD is treatable with chelating agents, such as D-penicillamine and trientine, and/or zinc salts alongside with dietary copper restriction. Liver transplantation may be indicated in WD patients with severe hepatic disease, and cautiously considered in patients with neurological WD. Treatment success highly depends on patient adherence and treatment persistence. Therefore, effective interventions for improving patient adherence and close monitoring are key for preventing WD progression. In Portugal, there are no reference centers for WD, and patients are dispersed across numerous medical specialists. This review aimed to summarize the most recent and relevant information for the

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diagnosis, treatment, and monitoring of WD in Portugal, as well as possible interventions for stimulating adherence to treatment.

Revisão Prática e Multidisciplinar sobre a Doença de Wilson – Perspectiva portuguesa

Palavras Chave
Doença de Wilson · Diagnóstico · Tratamento · Monitorização · Adesão

Resumo
A doença de Wilson é uma doença genética do metabolismo do cobre, causada por mutações no gene *ATP7B*, que levam à acumulação tóxica de cobre em diversos órgãos. A doença de Wilson pode manifestar-se como doença hepática, perturbação neurológica progressiva, doença psiquiátrica ou como uma combinação destas patologias. Outras manifestações clínicas também podem ocorrer. O diagnóstico é complexo e normalmente requer a combinação de análises bioquímicas, imagiologia, testes genéticos para o gene *ATP7B* e/ou biópsia hepática. A doença de Wilson é tratável com agentes quelantes, como a D-penicilamina e a trientina, e/ou sais de zinco, em conjunto com uma dieta com baixo teor de cobre. O transplante de fígado pode ser indicado em doentes com doença hepática grave, e deve ser cuidadosamente considerado em doentes com manifestações predominantemente neurológicas. O sucesso do tratamento é altamente dependente da adesão do doente e da persistência no tratamento. Portanto, intervenções eficazes para melhorar a adesão do doente ao tratamento, bem como a monitorização rigorosa, são cruciais para prevenir a progressão da doença de Wilson. Em Portugal não existem centros de referência para a doença de Wilson e os doentes encontram-se dispersos por numerosos especialistas médicos. Este artigo de revisão pretende reunir informação recente e relevante para o diagnóstico, tratamento e monitorização da doença de Wilson em Portugal, assim como possíveis intervenções para estimular a adesão ao tratamento.

Introduction

Wilson disease (WD) is an autosomal recessive disorder of copper metabolism, caused by mutations in the *ATP7B* gene, which encodes a transmembrane copper transporting ATPase, leading to copper overload in the liver, brain, and other organs [1–4]. WD can present with a variety of symptoms, making it important for healthcare professionals to maintain a high level of suspicion for early diagnosis [4–7].

Symptoms of WD can manifest at different ages, more commonly observed between the ages of 3 and 55 years old. Liver-related symptoms are more prevalent during childhood and adolescence, while neurological symptoms tend to develop later, usually about a decade after the liver involvement [5, 7, 8].

The global prevalence of WD ranges from 1:29,000 to 1:40,000 individuals, with some variation based on ethnicity [9]. In Spain (mainland), estimated frequencies of affected individuals with WD are reportedly higher, ranging from 1:6,278 to 1:16,540 [10]. Moreover, recent genetic research suggests that the frequency of ATP7B mutations (associated with WD) is higher than the reported clinical prevalence, which could be due to variable clinical presentations, incomplete penetrance, or the influence of modifier genes [11–13].

In Portugal, there are no reference centers for WD, and patients are dispersed across numerous medical specialists. There is also no WD patient association. Data on the distribution, prevalence, genetic variability, and current management of WD in Portugal are not available but are being gathered in a national registry of hepatic diseases. The registry is coordinated by APEF – Portuguese Association for Study of the Liver and is hosted at www.liver.pt.

This review was elaborated by a multidisciplinary team of national medical experts (gastroenterology, internal medicine, neurology, and pediatrics) with large experience in WD. The aim was to summarize important information for the diagnosis, treatment, and monitoring of WD patients in Portugal. It also includes possible interventions for stimulating adherence to treatment. The ultimate goal of this practical review is to promote the adoption of appropriate actions for managing WD patients and to bring awareness on the disease.

Diagnosis

Clinical Manifestations

WD comprehends a wide spectrum of clinical manifestations, including liver disease, progressive neurological disorders, psychiatric symptoms, or a combination of these. Other manifestations involving the eyes, blood, kidneys, and joints can also occur [2, 4–8].

Hepatic symptoms typically manifest during pediatric ages. Liver damage can present in various forms, spanning from asymptomatic abnormalities in liver

biochemistry to severe and life-threatening liver failure [8, 14]. Patients with clinically asymptomatic forms (3–40%) often exhibit hepatomegaly, discretely elevated transaminases, or are identified through family screening [15–17].

Acute hepatitis may develop in up to 25% of patients, presenting with similar symptoms to acute viral hepatitis, such as jaundice and abdominal pain. Up to 20% of patients may present acute liver failure, usually associated with Coombs-negative intravascular hemolysis, coagulopathy, progressive encephalopathy, and renal dysfunction [7, 8, 14].

Chronic presentations of liver impairment encompass chronic hepatitis (10–30%) and cirrhosis (35–60%). Patients may develop cirrhosis-related complications, including ascites, encephalopathy, renal failure, or portal hypertension [14]. Hepatic steatosis can also be observed in up to 80% of biopsies of WD patients [18].

Neurological symptoms typically appear at an older age than hepatic impairment and comprehend a wide spectrum of movement disorders. The most common symptom is dysarthria (46–97%), particularly in the early stages of the disease. Other symptoms include tremor (55%), parkinsonism (12–58%), gait abnormalities/ataxia (28–75%), dysphagia (50%), and chorea (6–30%). Dystonia affecting facial expression and causing involuntary smiling (*risus sardonicus*) is characteristic of WD. In most cases, these symptoms overlap, fluctuate, and can be aggravated by several factors (e.g., stress, emotions, general health conditions, concomitant disorders) [7, 19, 20].

Although most WD patients present with psychiatric symptoms at some stage of the disease, they are present in 10–25% of the patients at diagnosis [7, 21]. In children, it may manifest as a decline in school performance, inappropriate behavior or impulsiveness. In adults, the most common conditions include mood disorders (depressive or bipolar spectrum), behavioral or personality changes (irritability, aggression, and disinhibition), psychotic disorders, sleep disturbances, and subtle cognitive dysfunction [21].

In WD, the most typical ophthalmologic sign is the Kayser-Fleischer ring. This is due to the deposition of excess copper on the inner surface of the cornea in the Descemet membrane. Kayser-Fleischer rings can be detected by optical coherence tomography (preferential method) or slit-lamp examination, which requires an experienced ophthalmologist. These rings are present in almost all patients with neurological symptoms, in 50% of patients with liver manifestations and in 10–30% of asymptomatic patients. In children presenting with liver disease, Kayser-Fleischer rings are usually absent. Additionally, sunflower cataract is a rare but also characteristic sign. Notably, Kayser-Fleischer rings and sunflower cataract are not associated with impaired vision, and they gradually disappear with effective treatment [7, 22].

Other clinical symptoms are less common and result from the multi-organ damage due to copper accumulation. Hematological manifestations may include hemolysis, thrombocytopenia, and leukopenia. Renal abnormalities comprise tubular dysfunction (e.g., renal tubular acidosis, aminoaciduria, Fanconi syndrome) and nephrolithiasis. Cardiac problems include cardiomyopathy, arrhythmias, and autonomic dysfunction. Bone demineralization and endocrinological symptoms, such as infertility or repeated miscarriages, and hypoparathyroidism may be also observed [23].

Diagnostic Testing

Standard Biology

Laboratory testing should begin with biochemical liver tests, blood counts, and coagulation parameters to assess for liver disease and hemolysis. Abnormal hepatic biochemistry is common in WD, but it is not a specific feature. Of note, a normal hepatic workup does not rule out the possibility of liver involvement [6, 7, 24].

Copper Metabolism Tests

Tests of copper metabolism may include serum ceruloplasmin, serum copper, 24-h urinary copper excretion and liver biopsy for histology, histochemistry, and/or copper quantification (Table 1). Low serum ceruloplasmin, usually <10 mg/dL, is indicative of WD. However, intermediate concentrations of ceruloplasmin, ranging from 10 to 20 mg/dL, are often observed in patients [6, 7, 14, 25, 26]. This test should be carefully interpreted, as false positive or negative results can occur due to other physiological and/or pathological conditions [24, 27–30].

Over 90% of serum copper is bound to ceruloplasmin; thus, in WD, serum copper is usually low in proportion to the decrease of this protein in circulation. Only the determination of total serum copper (ceruloplasmin-bound plus non-ceruloplasmin-bound copper [NCC]) is available, which is generally <635 μg/L (<10 μmol/L) in WD [24, 34]. However, this parameter is no longer useful in WD diagnosis.

Urinary copper excretion is negligible in healthy individuals, while in symptomatic WD patients, it is

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Table 1. Tests for diagnosis of WD [24, 25, 31–33]

Tests	Normal	Typical findings	False negatives	False positives
Current tests				
Ceruloplasmin	20–40 mg/mL	<10 mg/mL	Increased in: • pregnancy • use of contraceptives • inflammation Normal value in • 50% of WD patients with highly inflammatory liver involvement • 15–36% of children with WD	Decreased: • until 6–10 months of age • healthy heterozygotes for WD • acute, iatrogenic viral hepatitis • Menkes disease • acquired copper deficiency • malnutrition, cachexia • nephrotic syndrome • aceruloplasminemia
24-h urinary copper	<40 µg/24 h <0.6 µmol/24 h	>100 µg/24 h >1.6 µmol/24 h	Normal: • incomplete or inadequate sample collection • in 16–23% of WD patients (children, asymptomatic)	Increased in: • cholestasis • acute liver failure from any cause • healthy heterozygotes for WD (intermediate rates)
Liver copper	<50 µg/g dry tissue 0.2–0.9 µmol/g dry tissue	>250 µg/g dry tissue >3.3 µmol/g dry tissue	Normal or intermediate value due to heterogeneous copper distribution in patients with WD and: • active liver disease • regeneration nodules	High value in: • cholestasis
Genetic analysis	Sequencing of the entire ATP7B gene Whole-genome sequencing permits assessing all liver disease genes, not just WD			
New tests				
CuEXC	39–73 µg/L 0.62–1.15 µmol/L	>132 µg/L[a] >2.08 µmol/L[a]		
REC	3–8.1%	>18.5%		

CuEXC, serum exchangeable copper; REC, relative exchangeable copper; WD, Wilson disease. [a]In the extrahepatic forms.

typically >100 μg (>1.6 μmol)/24 h. A lower threshold of 40 μg (0.6 μmol)/24 h may indicate WD in asymptomatic individuals or children [6, 7, 25, 31]. When performing this test, written instructions for conducting 24-h urine collections should be provided to the patients together with copper-free containers [6].

The penicillamine challenge test may be helpful in the diagnosis of WD [35]. This test has only been validated in a pediatric population, in which 500 mg of D-penicillamine was administered orally at the beginning and after 12 h during the 24-h urine collection period. A clear differentiation from other liver disorders was found when >1,600 μg copper/24 h (>25 μmol/24 h) was excreted [7, 25, 35].

Serum exchangeable copper (CuEXC) corresponds to the labile fraction of copper in serum. The ratio of CuEXC to total serum copper, called the relative exchangeable copper, is an excellent diagnostic biomarker with a sensitivity and specificity close to 100% for the diagnosis of WD, when its value is >18.5%. This biomarker distinguishes patients with WD from normal individuals, simple heterozygotes and patients with other hepatopathies [32, 36].

CuEXC is shown to be statistically higher in patients with extrahepatic involvement than in patients with hepatic disease; thus, it may be a marker of extrahepatic involvement and severity. A value >132 μg/L (>2.08 μmol/L) was described by some authors and may indicate corneal and brain involvement [37, 38]. CuEXC exhibits promising diagnostic performance and could be determined if available; however, it is not yet accessible in Portugal.

Radioactive copper incorporation is a highly sensitive and specific test for WD; although not commonly available. A ^{64}Cu ratio 24 h/2 h <0.3 and a ^{64}Cu ratio 48 h/2 h <0.395 are diagnostic of WD [39, 40]. New methods for the determination of the main Cu-species in human serum applying mass spectrometry technology are also under development [41].

Liver biopsy is no longer systematically used for establishing a diagnosis of WD; it should be considered on a case-by-case basis [24]. Liver biopsy permits the weighted determination of intrahepatocyte copper and the assessment of the grade of liver injury [6, 31].

Biopsy specimens with adequate size (at least 5 mm in length) for copper estimation by atomic absorption spectroscopy should be sent in a dry condition in a copper-free container [7, 42]. In Portugal, the Toxicology Laboratory of the Faculty of Pharmacy of the University of Porto has proven experience in performing this analysis.

The copper content in the liver of healthy individuals is typically <50 μg/g of dry weight. In WD patients, the copper levels can exceed 250 μg/g of dry liver tissue [43]. Interpreting the results may be challenging due to heterogenous copper deposition in the liver, sampling error, or the presence of other liver disorders, particularly cholestatic conditions and cirrhosis [31, 26].

Histopathological changes in the liver are usually not specific to WD and can vary depending on the disease stage. Early and common changes often involve mild steatosis, observed in up to 80% of biopsies [18]. Histological features classically associated with chronic hepatitis may be present. In later stages, progressive parenchymal damage may evolve into fibrosis and cirrhosis [44]. Histochemical stains (such as rhodamine) for copper typically have poor sensitivity and a negative stain does not exclude the diagnosis of WD [7, 25].

In clinical practice, converting copper units may be useful; for this, find the unit converter at www.convertunits.com/from/grams+Copper/to/molecule.

Imaging

Brain magnetic resonance imaging (MRI) is used for the differential diagnosis of neurological WD and should be performed in all patients, including asymptomatic or with only hepatic manifestations. Additionally, brain MRI serves as a valuable tool for monitoring progression, detecting structural abnormalities or changes in the brain, and predicting outcomes [19]. The recommended brain MRI sequences include 3D (preferable) or 2D FLAIR, axial T1, axial T2, axial DWI, axial T2*, and coronal T2 (optional). Important anatomical areas to focus on include putamen, caudate, globus pallidus, thalamus, mesencephalon, pons, cerebellum, cortex, and subcortical white matter [45–47].

Neuroimaging abnormalities are present in more than 90% of patients with neurological WD, in 40–70% of patients with hepatic WD, and in 20% of presymptomatic patients [47–49]. The most frequent findings include signal changes in the basal ganglia, thalami, pons, and white matter, as well as atrophy. The increased T2 signal in the midbrain, commonly referred to as the "face of the giant panda sign" is considered pathognomonic for WD, although it is present in only 12% of cases [19, 45, 46]. In patients with abnormal neurological findings, sequential imaging examinations may correlate with progression or recovery [7, 50].

Liver ultrasound should be performed in all patients with suspected WD, irrespective of their clinical presentation. Hepatic steatosis is the most common finding,

Table 2. Leipzig score for diagnosis of WD [58]

Typical clinical symptoms and signs	
Kayser-Fleischer rings	
Present	2
Absent	0
Neuropsychiatric symptoms[a]	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>20 mg/dL)	0
10–20 mg/dL	1
<10 mg/dL	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0
Other tests	
Liver copper (in the absence of cholestasis)	
>250 µg (>4 µmol/g dry weight)	2
50–249 µg (0.8–4 µmol/g dry weight)	1
Normal: <50 µg (<0.8 µmol/g dry weight)	−1
Rhodanine-positive granules[b]	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1–2 × ULN	1
>2 × ULN	2
Normal, but >5 × ULN[c] after D-penicillamine[d]	2
Mutation analysis	
On both chromosomes detected	4
On one chromosome detected	1
No mutations detected	0

Assessment of the WD score	
Total score	Evaluation
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

MRI, magnetic resonance imaging; ULN, upper limit of normal. [a]Or typical abnormalities at brain MRI. [b]If no quantitative liver copper available. [c]The cutoff of >1,600 µg copper/24 h is more reliable. [d]Penicillamine challenge test is only validated in children.

reported in 35–88% of patients. Signs suggesting cirrhosis could also be present. Computed tomography or MRI can also show evidence of liver cirrhosis and portal hypertension [6, 51, 52]. Liver ultrasound is the gold standard for screening hepatocellular carcinoma, although the occurrence of hepatobiliary malignancies is rare in WD [53].

Liver stiffness measurement by transient elastography should be performed in all adults at diagnosis. A study by Paternostro et al. [54] suggested that a liver stiffness measurement value ≥9.9 kPa accurately identified cirrhosis in patients with recently diagnosed WD (positive predictive value: 74%, negative predictive value: 100%). Another study reported that a liver stiffness measurement of 8.4 kPa could differentiate advanced fibrosis stages from milder stages [55].

Genetic Testing

The number of known variants in the *ATP7B* gene, which exceeds 900, without a clear clinical relationship, limits the usefulness of genetic tests in routine diagnostics. However, sequencing of the entire *ATP7B* gene is very important to make the diagnosis in asymptomatic patients or in the early phases of disease. Genetic testing is recommended for all patients suspected of having WD and, importantly, for family screening. In Portugal, it may take some time to obtain results, so genetic confirmation should not delay the initiation of treatment [6, 56, 57]. Clinicians should be aware that a genetic diagnosis of WD should always be corroborated with clinical and biochemical findings, and the absence of two pathogenic mutations does not exclude a diagnosis of WD [6].

Diagnostic Strategies

No diagnostic test is per se specific for WD; therefore, a range of tests has to be applied [25]. In symptomatic patients, the diagnosis could be established when Kayser-Fleischer rings are present, serum ceruloplasmin is below the lower limit of normal, and urinary copper excretion is above 100 µg/24 h (>1.6 µmol/24 h) [58]. Otherwise, several additional investigations might be required.

Diagnostic scoring systems and algorithms provide a structured approach to diagnosis. The Leipzig scoring system for general diagnosis combines key laboratory and clinical findings and it is validated in adult and pediatric patients (Table 2) [6, 7, 25, 58–60]. Additionally, several indices based on standard biochemistries can be used to establish the diagnosis and prognosis of acute liver failure due to WD [61, 62].

Algorithms can facilitate diagnosis, but their interpretation should be cautiously performed considering the limitations. Algorithms for diagnosing WD in patients with liver disease and/or neuropsychiatric manifestations, adjusted to the Portuguese medical settings, are presented in Figures 1 and 2, respectively [7].

Family Screening

Within families, the risk of WD among siblings of an index case is 25%; while among the progeny, the risk is 0.5% [63]. Therefore, first-degree relatives should be screened for WD. Family screening should involve a

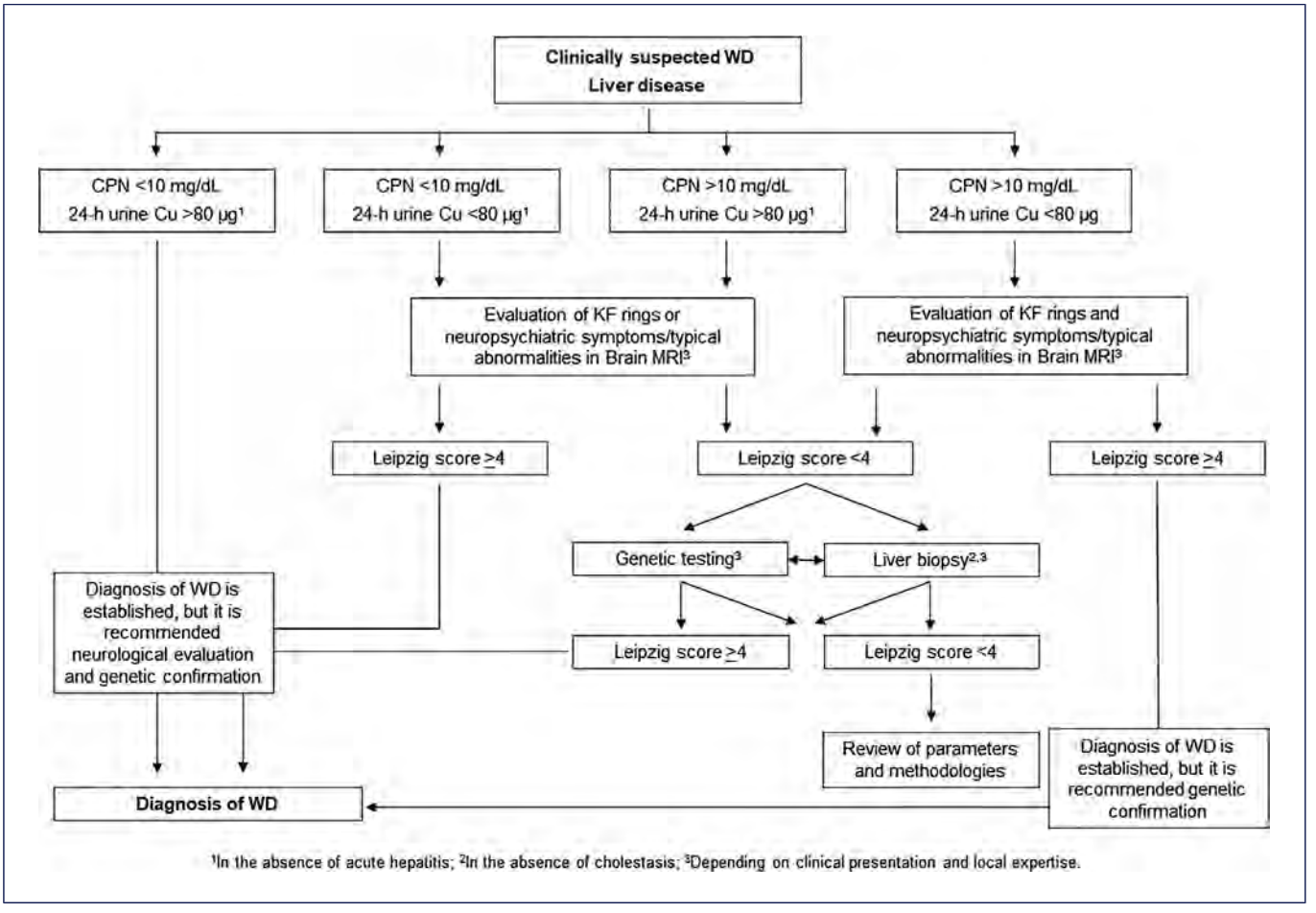

Fig. 1. Algorithm for diagnosing WD in patients with liver disease [7, 58]. CPN, ceruloplasmin; Cu, copper; KF, Kayser-Fleischer; WD, Wilson disease.

clinical examination, routine investigations including standard biology and copper metabolism tests, and genetic testing for familial *ATP7B* mutations. For children of the index case, screening should be performed after they complete 3 years [6, 7, 24].

Treatment

Adults and children aged >3 years old with WD, including asymptomatic patients, should initiate treatment immediately after diagnosis. In children <3 years old, timing to treatment should be individualized according to the degree of organ damage [7, 14].

Currently, lifelong oral pharmacotherapy and dietary copper restriction are recommended to treat WD. Liver transplantation, which corrects the underlying hepatic defect, is also a therapeutic option for WD [7, 64].

Treatment depends on the disease severity and should be driven by the drug safety and efficacy in the individual patient. Initial treatment should include chelating agents and/or zinc salts. Time to observe a clinical response is variable, but liver function tests and neurological symptoms usually begin to improve within 6 months. After a period of sustained clinical and biochemical response, typically at least 2 years, the drugs should be reduced to the lowest effective dose [7, 14].

Pharmacological Treatment

Chelating agents, such as D-penicillamine and trientine, non-specifically bind to copper in the body, facilitating its urinary excretion [65–67]. Trientine also chelates copper in the intestinal tract, thereby preventing its absorption [66–68]. Zinc salts reduce the absorption of copper from the gastrointestinal tract (Table 3) [69, 70, 71].

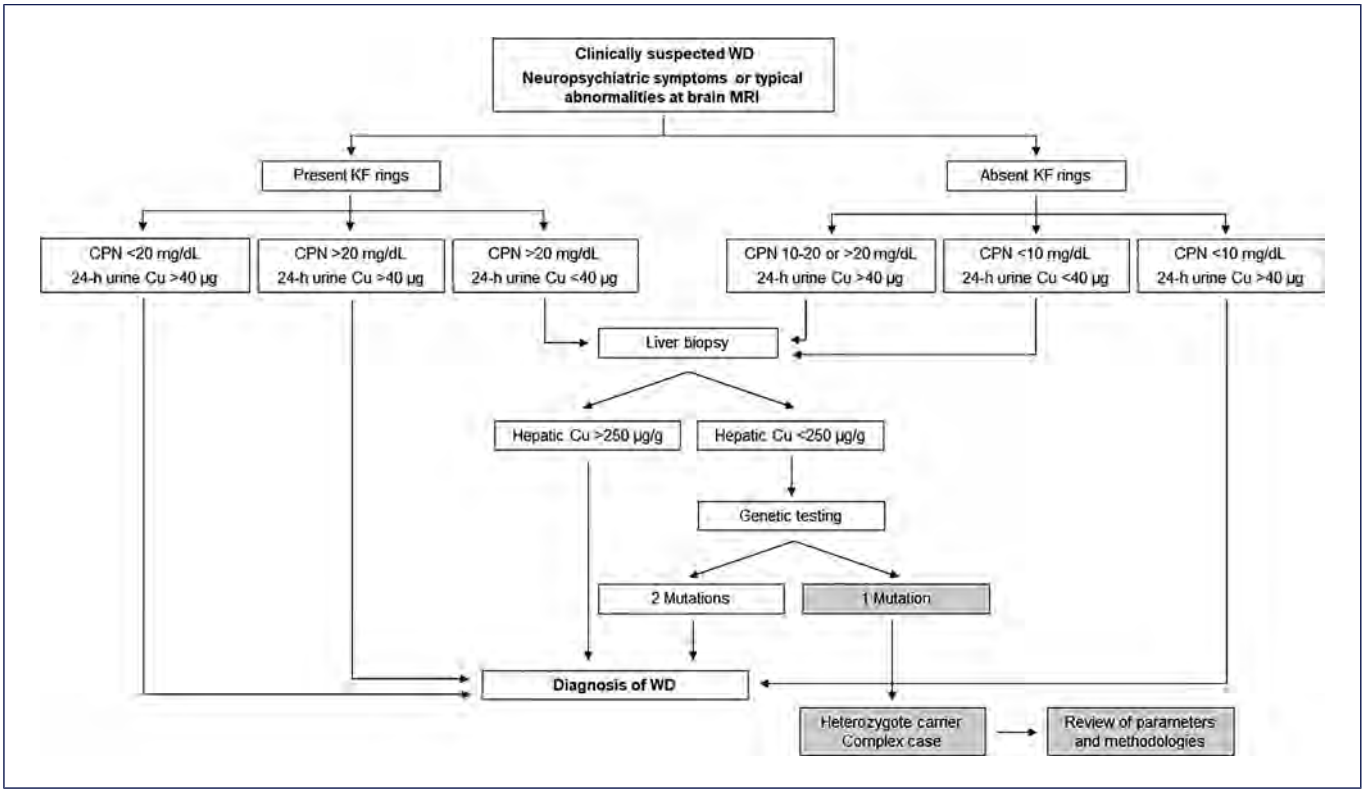

Fig. 2. Algorithm for diagnosing WD in patients with neuropsychiatric manifestations [7, 58]. CPN, ceruloplasmin; Cu, copper; KF, Kayser-Fleischer; WD, Wilson disease.

D-Penicillamine is the most used therapy for WD [6, 14, 25, 72]. Hepatic improvements are observed in patients under D-penicillamine, but its efficacy in neurologic WD is less satisfactory [73, 74].

D-Penicillamine carries numerous adverse effects, which may lead to prompt drug discontinuation in up to 30% of patients [6, 75–77] (Table 3). Paradoxical worsening of neurologic symptoms may occur at the onset of treatment, affecting 10–20% of patients with pre-existing neurological symptoms. This adverse reaction has also been observed with other anti-copper therapies (e.g., trientine, zinc) and can be mitigated by gradually titrating the doses [6, 75–77]. Oral D-penicillamine is rapidly but incompletely absorbed [75].

Trientine is effective for WD with fewer adverse reactions than D-penicillamine (Table 3) [78, 79]. Trientine, in the form of dihydrochloride or tetrahydrochloride salt, is commonly used in patients who are intolerant to D-penicillamine or at increased risk of adverse effects and it is now becoming a preferred treatment for WD [14, 25, 66, 67, 78, 80].

The recently available trientine tetrahydrochloride formulation has demonstrated efficacy comparable to that of the dihydrochloride salt and has shown good tolerability [81, 82]. Trientine tetrahydrochloride has also shown non-inferior efficacy to D-penicillamine when used as oral maintenance therapy in WD [83]. Trientine tetrahydrochloride is characterized by more favorable pharmacokinetics (increased systemic exposure) compared with the dihydrochloride salt, resulting in a reduced pill burden [84, 85]. The tetrahydrochloride form is a more stable salt of trientine that can be stored at room temperature [82].

Zinc is not recommended as a first-line treatment in symptomatic forms but can be used in presymptomatic or asymptomatic forms and for long-term maintenance therapy after optimal decoppering with chelators [24, 70]. Zinc has demonstrated good efficacy in WD, particularly in patients with neurological manifestations and in asymptomatic siblings. However, its effectiveness may be reduced in case of symptomatic liver disease [86]. If zinc is used, careful monitoring of transaminases is necessary [25].

The most common side effect of zinc is gastric irritation (Table 3). Different zinc salts (sulfate, acetate, gluconate) can be used; however, acetate salts are

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Table 3. Available drugs for treatment of WD: dosages and adverse effects [6, 24, 65, 66, 67, 69, 70, 71]

Drug	Initial dose			Maintenance dose (typically after 2 years)	Precautions	Adverse effects	Management of adverse effects
	children	adults without neurological or psychiatric symptoms	adults with neurological or psychiatric symptoms				
D-Penicillamine	Progressively increase dose up to 20 mg/kg/day in 2–4 divided doses	600–2,100 mg/day in 2–4 divided doses	150–300 mg/day, slowly increasing by 150–300 mg/week, to 600–2,100 mg/day in 2–4 divided doses	10–20 mg/kg/day in 2 divided doses in children, 600–1,200 mg/day in adults	Gradual titration of the dose. Administration should be done 1 h before or 3 h after meals[a]. Avoid administration with antacids or iron supplements. Pyridoxine supplementation (25–50 mg/day) is advised, particularly in children, pregnant women, patients with malnutrition and intercurrent illness.	*Early reactions*: hypersensitivity reactions (fever and rash), proteinuria, bone marrow suppression, altered sense of taste or smell, and paradoxical neurological worsening *Late reactions*: lupus-like syndrome, Goodpasture syndrome, elastosis perforans serpiginosa, cutis laxa, and poor wound healing	*Hypersensitivity reactions*: Prednisolone 10–30 mg/day + drug discontinuation. Reintroduction of the drug at low doses followed by gradual increase. D-Penicillamine can be substituted by trientine. *Cytopenia*: Dose reduction or drug discontinuation. Reintroduction of the drug at low doses followed by gradual increase. *Bone marrow suppression*: Immediate drug discontinuation. *Neurological worsening*: Dose reduction followed by gradual increase. Change to trientine or to zinc salts. *Late reactions*: Drug discontinuation and substitution by zinc salts. Corticoids and symptomatic treatment. In some cases, chelating agents could be maintained at low doses. Cryotherapy for cutaneous lesions.
Trientine dihydrochloride	400–1,000 mg/day in 2–4 divided doses	800–1,600 mg/day in 2–4 divided doses	150–200 mg/day, slowly increasing by 150–200 mg/week to 800–1,600 mg/day in 2–4 divided doses	800–1,600 mg/day in 2–4 divided doses	Gradual titration of the dose. Administration should be done 1 h before or 3 h after meals[a]. Avoid administration with antacids or iron supplements.	Nausea, skin rash, anemia, aplastic anemia, sideroblastic anemia, dystonia, tremor, lupus-like syndrome, colitis, duodenitis, paradoxical neurological worsening during initial phase of treatment	
Trientine tetrahydrochloride	225–600 mg/day in 2–4 divided doses	450–975 mg/day in 2–4 divided doses	150–200 mg/day, slowly increasing by 150–200 mg/week to 450–975 mg/day in 2–4 divided doses	450–975 mg/day in 2–4 divided doses	Gradual titration of the dose. Administration should be done 1 h before or 3 h after meals[a]. Avoid administration with antacids or iron supplements.	Nausea, skin rash, pruritus, erythema, urticaria, sideroblastic anemia, iron deficiency anemia, duodenitis, colitis, paradoxical neurological worsening during initial phase of treatment	

Table 3 (continued)

Drug	Initial dose			Maintenance dose (typically after 2 years)	Precautions	Adverse effects	Management of adverse effects
	children	adults without neurological or psychiatric symptoms	adults with neurological or psychiatric symptoms				
Zinc salts	Age <6 years: 25 mg 2× daily Age 6–16 years or <57 kg: 25 mg 3× daily Age >16 years or >57 kg: 50 mg 3× daily	50 mg 3× daily if patient >57 kg	50 mg 3× daily if patient >57 kg	25–50 mg 3× daily	Administration should be done 1 h before or 3 h after meals[a].	Nausea, abdominal pain, gastritis, zinc accumulation, possible changes in immune function, paradoxical neurological worsening (rare), hepatic function impairment	*Gastritis*: Symptomatic treatment. Administration of the first dose between breakfast and lunch. Occasional administration with a protein (e.g., gelatine or ham). *Neurological worsening*: Zinc discontinuation and restart with a chelating agent at low doses. *Hepatic function impairment*: Zinc discontinuation and restart with a chelating agent at low doses.

Dosing for penicillamine, trientine dihydrochloride, trientine tetrahydrochloride, and zinc salts is based on the respective summary of product characteristics [60–64] and on the references [6, 21]. Higher doses of trientine tetrahydrochloride (up to 1,050 mg/day in adults) could be used, without being associated with increased toxicity. [a]Clinicians should assist the patient in planning the drug administration, by elaborating a schedule adapted to the patient routine and lifestyle.

associated with a lower incidence of gastric side effects [7, 14, 25].

Antioxidants, such as vitamin E, vitamin C, N-acetylcysteine, and curcumin, have been proposed as adjunctive treatment. However, no benefit has been definitively proven [7]. When combining treatments, it is important to assess the potential drug interactions. For this, online websites such as https://www.drugs.com/interaction/list/ can be consulted.

Currently, clinical trials are being conducted to investigate the safety and efficacy of adeno-associated virus (AAV) curative gene therapy for WD [87, 88].

Dietary Copper Restriction

Dietary copper restriction is an essential part of the WD treatment, and a low-copper diet is advised in combination with pharmacological treatment, especially during the initial treatment phase or until liver function tests normalize. Foods high in copper, such as liver and shellfish, should be avoided. Patients should avoid consuming water from copper pipes or vessels and preparing food with copper cookware [6, 7, 89, 90]. After the initial treatment phase, the decision to continue dietary copper restriction may be revised taking into consideration the response to treatment, adherence, and impact on quality of life [6]. Seeking guidance from a dietitian experienced in managing WD can be highly beneficial for obtaining personalized advice on dietary copper restriction, meal planning, and suitable alternatives to copper-rich foods [6, 7].

Liver Transplantation

In WD, orthotopic liver transplantation (OLT) should be considered in adult and pediatric patients with acute liver failure, end-stage liver disease, hepatocellular carcinoma, or disease progression, despite adequate chelating therapy [6, 7, 25, 91]. Acute hepatic WD may be present in up to 20% of WD patients with hepatic presentations and can rapidly progress to hepatic failure, often necessitating emergency liver transplantation. It is predominantly observed in young patients and is typically characterized by moderately elevated aminotransferases and high bilirubin to alkaline phosphatase ratio, along with Coombs-negative hemolytic anemia and encephalopathy. Acute hepatic WD may also occur in patients who were previously treated but stopped their medications [6, 25]. Longitudinal assessment with a prognostic scoring system may facilitate the decision to transplant patients. The New Wilson's Index, based on bilirubin, INR, aspartate aminotransferase, white blood cell count, and serum albumin, accurately predicts survival without OLT, indicating a poor prognosis when the score is ≥ 11 [62, 92].

In patients with neurological WD, OLT might be cautiously considered. Results from a recent systematic review encourage OLT in severe neurological patients not responding or getting worse with anti-copper treatment; however, it is still uncertain which patients with neurological impairment benefit most from OLT and when is the optimal timing for OLT [93]. The Unified WD Rating Scale (UWDRS) score is used in the evaluation and selection of neurological patients for transplantation [94].

Monitoring

Patients should be regularly monitored to confirm treatment efficacy, ensure therapy adherence, and early identify adverse effects [7, 25]. The frequency of follow-up clinical examination is variable, depending on the disease severity. In general, a clinical examination should be performed every 15 days for the first 3 months of treatment; every 3 months for the first year; and every 6 months when therapeutic objectives are met. Patients should be also examined at each dose change and when clinically indicated [7, 25].

Follow-up should include clinical assessment, complete blood count, liver function tests, coagulation profile, renal function, bone profile, serum ceruloplasmin, serum copper and urine tests, including 24-h urine copper and urine dipstick [6, 7, 25]. Monitoring of disease progression and neurologic response to treatment could be facilitated by using rating scales, such as the Unified Wilson's Disease Rating Scale [95] and the Global Assessment Scale for Wilson disease [96, 97].

Brain MRI and Kayser-Fleischer rings examination should be done in patients with brain or ocular involvement at baseline, before and during treatment to evaluate response, and in case of any worsening. Fading or disappearance of Kayser-Fleischer rings may be observed in adequately treated patients [7, 22, 25].

Liver stiffness measurement (hepatic elastography [FibroScan®]) and non-invasive biological tests for fibrosis (FibroTest, APRI, etc.) could be repeated to monitor the evolution of fibrosis [54, 98]. Hepatocellular carcinoma screening by a 6-monthly ultrasound should be considered in cirrhotic patients [53].

The biochemical response to treatment should be monitored at least annually by 24-h urine copper output and NCC (Table 4), which is estimated using the following formula: NCC [μg/dL] = total copper [μg/dL] – 3.15 × ceruloplasmin [mg/dL]. Estimated NCC may not accurately reflect real free copper [6, 7, 99, 100]; however, new methods are being developed to directly

Table 4. Biochemical targets for the different treatments of WD [6, 7, 14, 99, 100, 102]

Drug	Treatment initiation	Maintenance treatment				Overtreatment		Treatment failure on chronic therapy		
	24-h urine copper	24-h urine copper, µg/24 h		NCC, µg/dL	AST, ALT	24-h urine copper, µg/24 h	NCC, µg/dL	24-h urine copper µg/24 h[b]	NCC, µg/dL	AST, ALT
		On treatment	Off treatment[a]							
D-Penicillamine	↑	~200–500	12–40	5–15	Trend to normal	<100	<5	>500 (previously in range)	>15	↑
Trientine	↑	~150–500	12–40	5–15	Trend to normal					
Zinc salts	No change, then ↓	~25–75	–	5–15	Trend to normal	<25		>75 (previously in range)	>15	↑

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NCC, non-ceruloplasmin-bound copper. [a]Forty-eight hours off treatment. [b]Persistently increase in 24-h urine copper values.

measure NCC, e.g., using anion exchange chromatography coupled to inductively coupled plasma mass spectrometry [101]. CuEXC could be an alternative as soon as it becomes available in Portugal.

Serum aminotransaminase normalization is a good marker of effective treatment, and it positively correlates with the maintenance of 24-h urine copper excretion (Table 4). Treatment safety should be monitored by checking blood cell counts, iron status, proteinuria, and renal function [6, 7, 14, 25].

Measuring copper indices on treatment can be highly informative, although results must be judged in relation to the drug, drug dose, and stage of treatment. Moreover, results from treatment collections can be misleading in patients who do not adequately adhere to treatment. Therefore, a collection after a 48-h washout period (off treatment) should be considered during maintenance treatment [6, 7].

Adherence to Treatment

Long-term effects of treatment are largely dependent on patient adherence to the treatment recommendations and treatment persistence (continuation in drug use) [103]. Low adherence leads to progressive worsening of the clinical condition, and treatment discontinuation can lead to severe organ injury and even death [104, 105]. In fact, a retrospective study demonstrated that clinical improvement or disease stabilization was noted in almost 98% of persistent patients, whereas clinical worsening was observed in 52% of non-persistent patients [106].

Diverse factors influence patient adherence and persistence, including the phenotypic presentation, disease severity, and the delayed manifestation of symptoms after treatment discontinuation [104, 107]. The treatment duration, posology (e.g., single vs. multiple doses, number of pills), drug characteristics (e.g., pill size), and safety profile, as well as the mode of acquiring the medication (in hospital pharmacy) and associated costs are also important factors [104, 107, 108]. Furthermore, family support is fundamental to stimulate patient adherence and treatment persistence [106].

Treatment adherence can be monitored by direct and indirect methods. Direct methods consist of the determination of hepatic biochemistry, 24-h urine copper on treatment and off treatment, 24-h urine zinc and serum copper, both on treatment, and clinical monitoring using rating scales. Indirect methods include patient/caregiver interview and clinician assessments (e.g., using the Morisky scale), monitoring of medication refills, pill counts, and patient self-evaluation on treatment adherence [109].

Non-adherence could be very challenging and should be suspected in patients with abnormalities or great oscillations on the laboratorial measurements and/or failing to achieve treatment targets, and/or when there is a reappearance of Kayser-Fleischer rings after their previous resolution, an erratic attendance for follow-up appointments and/or irregularity in getting prescription refills [7].

A well-defined treatment plan gradually implemented and adapted to the patient's lifestyle and conditions, with regular clinical and biochemical assessments, and a broadly supportive team-based approach, involving the patient family, are good interventions to improve adherence [7]. The posology of the current treatments still challenges patient adherence; nevertheless, some small studies have reported promising results of a single daily dose for treating WD [110, 111].

Conclusion

WD is a genetic disease of copper metabolism, associated with a multitude of non-specific and highly variable clinical manifestations, which demands a high index of suspicion for prompt diagnosis. A structured approach employing several biochemical tests, imaging, genetic testing for ATP7B and/or liver biopsy is usually considered for the diagnosis of WD. Chelating agents and zinc salts are effective pharmacological options for WD as long as patients adequately adhere and persist on treatment. Liver transplantation is indicated for patients with severe hepatic manifestations and should be cautiously considered in patients with neurological WD. Close monitoring and effective interventions for improving patient adherence to treatment are fundamental for preventing the progression of WD.

In Portugal, there are no reference centers for WD, and patients are followed by various medical specialists. Therefore, the knowledge and adoption of evidence-based actions by clinicians are of utmost importance for the appropriate management of WD patients. Data gathered in the National Registry of Liver Diseases will also shed new light on patients' characterization and current management, potentially serving as a starting point for scientific decisions and collaborations that will ultimately benefit WD patients.

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Conflict of Interest Statement

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Author Contributions

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Data Availability Statement

Original data were not analyzed as the article is based exclusively on published literature.

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Treatment of Hemorrhoidal Disease in Patients with Liver Cirrhosis: A Systematic Review

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Keywords
Hemorrhoidal disease · Liver cirrhosis · Systematic review

Abstract

Introduction: The incidence of hemorrhoidal disease (HD) in cirrhotic patients is similar to that of general population, varying between 21% and 79%. Managing this clinical condition in these patients is challenging, due to the need to differentiate between bleeding originating from hemorrhoids or anorectal varices, and the unique hemostatic balance of each patient, which can lead to a decompensation of liver function and subsequently increase the anesthetic risk. To date, there are no systematic reviews specifically addressing this topic. ***Methods:*** This was a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were retrieved from three electronic databases. Efficacy (symptomatic improvement, patient satisfaction, quality of life improvement, disease recurrence/need for surgery and/or hemorrhoidal prolapse reduction in anoscopy) and safety (reported adverse events) outcomes were evaluated. Data from each study were initially described individually, followed by a comparative analysis for procedures applied in multiple studies. ***Results:*** Six studies were included – 1 randomized clinical trial (RCT), 2 prospective cohort studies, 1 retrospective cohort study, and 2 case series. The considered techniques encompassed rubber band ligation (RBL), injection sclerotherapy (IS) using 3 agents – aluminum potassium sulfate and tannic acid (ALTA), ethanolamine oleate 5% (EAO), or N-butyl-cyanoacrylate, hemorrhoidopexy, and emborrhoid technique. RBL showed great symptomatic improvement and patient satisfaction in 63% and 73% of patients, respectively, and in 90% was associated with one-grade prolapse reduction after only one session. The most frequently reported adverse events included pain (16%) and ulceration/fissure (1–17%). Concerning IS, symptomatic improvement was observed in all patients. Recurrence rates varied with the agent used (EAO: 13% at 12 months; N-butyl-cyanoacrylate: 40% at 12 months; ALTA: 18% at 5 years), and 86.7% of patients exhibited more than one-grade reduction after the initial session. The most frequent adverse event was pain (EAO: 63%; N-butyl-cyanoacrylate: 60%). Stapled hemorrhoidopexy resulted in symptomatic improvement in all patients, although associated with a recurrence rate of 25% within 4 months. With an emborrhoid technique, 80% of the patients showed clinical improvement at a 3-month follow-up, without significant adverse events, at the cost of a 40% recurrence rate. ***Conclusions:*** All the treatment methods assessed in the included studies appear to be effective and safe in cirrhotic patients. This assumption challenges previous concerns regarding significant bleeding after office-based procedures like RBL in this population. Future

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research should prioritize RCT to thoroughly assess the management of HD in these patients, particularly addressing polidocanol foam sclerotherapy, a minimally invasive technique that has previously been shown to be more effective than RBL in the general population and in patients with bleeding disorders.

Tratamento de Doença Hemorroidária em Doentes com Cirrose Hepática: uma Revisão Sistemática

Palavras Chave
Doença hemorroidária · Cirrose hepática · Revisão sistemática

Resumo
Introdução: A incidência da doença hemorroidária em doentes cirróticos é semelhante à da população geral, variando entre 21% e 79%. A abordagem desta patologia nestes doentes constitui um desafio, dada a necessidade de distinguir entre hemorragia hemorroidária ou por rotura de varizes anorretais e o balanço hemostático singular dos doentes cirróticos, que pode acarretar um maior risco anestésico. ***Métodos:*** Revisão sistemática de acordo com *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)*. Os artigos foram selecionados de 3 bases de dados eletrónicas. Foram avaliados parâmetros de eficácia (melhoria sintomática, satisfação do doente, melhoria na qualidade de vida, recorrência da doença/necessidade de cirurgia e/ou redução do prolapso hemorroidário na anuscopia) e segurança (complicações). Os resultados de cada estudo foram descritos individualmente e, sempre que possível, foi posteriormente realizada uma análise comparativa. ***Resultados:*** Seis estudos foram incluídos – 1 ensaio clínico randomizado, 2 estudos de coorte prospetivos, 1 estudo de coorte retrospetivo e 2 séries de casos. As técnicas estudadas incluíram laqueação elástica, escleroterapia com 3 agentes esclerosantes - sulfato de alumínio e potássio e ácido tânico (ALTA), oleato de etanolamina a 5% (EAO) ou N-butil cianoacrilato, hemorroidopexia e embolização. A laqueação elástica demonstrou grande melhoria sintomática e taxa de satisfação em 63% e 73% dos doentes (respetivamente) e associou-se a uma redução de pelo menos 1 grau no prolapso após a primeira sessão em 90%. As complicações mais comuns foram a dor (16%) e ulceração/fissura (1–17%). A escleroterapia provocou uma melhoria sintomática em 100% dos doentes. As taxas de recorrência variaram com o agente (EAO: 13% aos 12 meses; N-butil-cianoacrilato: 40% aos 12 meses; ALTA: 18% aos 5 anos), e 86.7% dos doentes apresentaram uma redução de pelo menos 1 grau no prolapso após a primeira sessão. O evento adverso mais frequente foi a dor (EAO: 63%; N-butil-cianoacrilato: 60%). A hemorroidopexia demonstrou melhoria sintomática em 100% dos doentes, contudo, com uma recorrência de 25% em 4 meses. Com a embolização hemorroidária, 80% dos pacientes mostraram melhoria clínica aos 3 meses, sem registo de eventos adversos major, mas associada a uma taxa de recorrência de 40%. ***Conclusão:*** Todas as técnicas avaliadas parecem ser eficazes e seguras nos doentes cirróticos. Esta premissa vem desafiar o pressuposto de um elevado risco hemorrágico associado aos procedimentos terapêuticos na doença hemorroidária nesta população. Investigações futuras devem priorizar ensaios clínicos randomizados, que incluam técnicas minimamente invasivas, nomeadamente a escleroterapia com polidocanol espumoso, que já demonstrou ser mais eficaz do que a laqueação elástica na população geral e em doentes com distúrbios de coagulação.

Introduction

Hemorrhoidal disease (HD) is a common health problem, whose associated symptoms such as bleeding, pain, prolapsing, and mucus soiling can cause a significant impact on patients' quality of life [1]. Internal HD can be classified into four degrees according to Goligher's classification. Grade I hemorrhoids are non-prolapsing hemorrhoids. In grade II hemorrhoids, prolapse can occur during straining but is spontaneously reduced, while in grade III manual reduction is required. Last, grade IV includes irreducible hemorrhoids [1].

The incidence of HD in cirrhotic patients is similar to that in the general population, ranging from 21% to 79% [2], apparently with no correlation with hepatocellular function or portal hypertension [3]. HD in these patients is challenging for physicians because of the need to discern the bleeding originating from HD or anorectal varices [4]. Also, the unique hemostatic balance of each patient can lead to a decompensation of liver function and subsequently increase the anesthetic risk, due to pharmacokinetic and pharmacodynamic changes [5]. As there is few evidence about HD treatment in cirrhotic patients,

the data regarding the magnitude of adverse events risk in this special population (in comparison with general population) are also scarce [6]. Thus, an individualized assessment is crucial in these patients.

Despite the high prevalence of the disease and demanding therapeutic approach of cirrhotic patients, there are few published articles addressing this issue. Some of the studies point injection sclerotherapy (IS) as a safe and effective procedure, while contraindicating rubber band ligation (RBL) due to the potential risk of post-procedural bleeding [1, 7]. Hemorrhoidectomy is advocated as the preferred approach when bleeding hemorrhoids prove refractory to other approaches [1].

The aim of this study was to carry out a systematic review to assess the efficacy and safety of either office-based or surgical procedures in the management of HD in cirrhotic patients. To our knowledge, there are no published systematic reviews addressing this topic.

Methods

A systematic search of PubMed (Medline), Scopus (Elsevier), and Web of Science (Clarivate Analytics) databases was performed for papers available on October 2, 2023. This study was conducted and reported in accordance with the most recent PRISMA guidelines [8] and is registered in PROSPERO database under the following code: CRD42024489679.

The search was carried out according to the following search query: ((Cirrhosis) or ("chronic liver disease") or ("portal hypertension")) AND ((hemorrhoid) OR (haemorrhoid) OR ("hemorrhoidal disease") OR ("haemorrhoidal disease") OR (sclerotherapy) OR ("rubber band ligation") OR ("Infrared coagulation") OR (cryotherapy) OR ("radiofrequency ablation") OR ("laser therapy") OR ("diathermy") OR ("hemorrhoidectomy") OR ("hemorrhoidopexy") OR ("PPH") OR ("HAL-RAR")) AND NOT ((varices) OR (carcinoma) OR (gastric) OR (scar)).

After duplicates were excluded, all titles and abstracts were screened independently by two authors (S.B.P. and J.O.) for relevance and consideration of further review. Full texts were assessed by both authors for consideration of inclusion. Then, the back-search on the articles' references was conducted, selecting two additional ones not previously captured by our query. In case of disagreement in study inclusion, the author "P.S." performed the review.

Eligible studies included any English language primary research study published between 2003 and 2023, referring to adult patients with liver cirrhosis and reporting office-based or surgical treatments of symptomatic HD, as well as efficacy and/or safety outcomes. Review articles, systematic reviews, single case reports, and meta-analysis were excluded. Studies regarding dietary/lifestyle measures or medical therapies or conducted in pediatric or animal populations were excluded from the analysis.

Data were extracted using a defined spreadsheet and included study design, inclusion criteria, overall number of patients and percentage of those with liver cirrhosis, baseline characteristics of all included patients (age, sex, hemorrhoidal degree according to Goligher's classification, liver cirrhosis etiology and Child-Pugh staging, applied intervention characteristics (pre-procedure preparation, procedure and adjuvant medical treatment post-procedure), follow-up period, and evaluated outcomes. Regarding efficacy outcomes, the variables considered were symptomatic improvement, patient satisfaction, and improvement in quality of life, disease recurrence/need for surgery, and/or hemorrhoidal prolapse reduction in anoscopy. As for safety outcomes, the reported adverse events were analyzed for each intervention, such as bleeding, pain, ulceration, abscess, tenesmus, local edema, and fever. Most of the studies only reported the presence or absence of each post-procedural adverse event, with the exception of Pirolla et al.'s [9] study, where pain was graded according to a scale from 0 to 10 [10], and Awad et al.'s [11] study, where rebleeding was defined as anal bleeding with two separate bowel movements or massive bleeding that required further treatment occurring 1 month after the procedure [12].

The selected studies underwent a quality assessment using either Risk of Bias 2 (RoB-2) tool [13] for randomized clinical trials (RCTs) or Risk Of Bias In Nonrandomized Studies – of Interventions (ROBINS-I) tool [12] for nonrandomized studies. The RoB-2 tool is divided into five potential sources of bias: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. After applying the tool, an overall risk of bias is determined, and the study is classified as *Low risk of bias*, *Some concerns*, and *High risk of bias*. The ROBINS-I tool evaluates studies across seven domains: bias due to confounding, in selection of participants into the study, in classification of interventions, due to deviations from intended interventions, due to missing data, in measurement of outcomes, and in selection of the reported result. A final risk of bias judgment is achieved and categorizes each study as *Low*, *Moderate*, *Serious*, *Critical*, or *No information*.

First, the studies were divided into two groups: office-based procedures and surgical treatments. Within these, data from each study were described individually, focusing on mean values. Subsequently, when multiple studies examined the same procedure, a descriptive comparative analysis was conducted. Meta-analysis was precluded due to the heterogeneity of outcome measures.

The primary objective of this study was to review all the current therapeutic modalities for the management of HD in cirrhotic patients. The secondary objectives were to assess the efficacy and safety of either office-based or surgical procedures in HD management in cirrhotic patients.

Results

A total of 1,659 records were initially identified across *PubMed* (n = 892), *Scopus* (n = 519), *Web of Science* (n = 246), and citation searching (n = 2). Of these, 1,449 remained after duplicate removal. Initially screening based on title and abstract led to the exclusion of 1,424 articles and the remaining 25 were sought for retrieval. Finally, 6 studies met the inclusion criteria. The flowchart

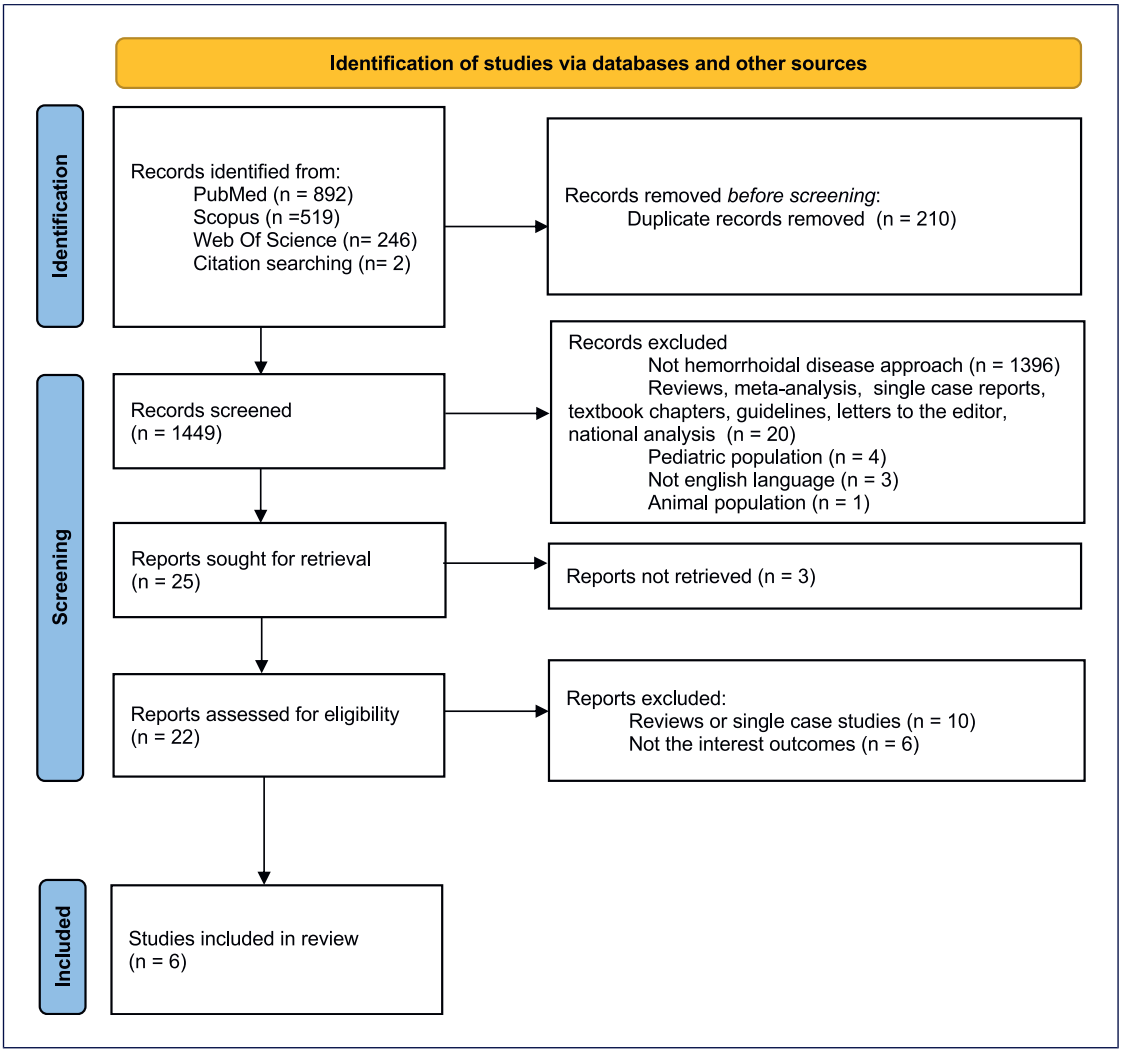

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews that included searches of databases and registers only.

illustrating the process of study selection is described in Figure 1.

Tables 1 and 2 delineate the characteristics of the included studies. Table 3 present the results of risk of bias evaluation. Table 4 refers to efficacy outcomes.

Results of Individual Studies

Office-Based Procedures

Concerning office-based procedures, 3 articles were identified evaluating the use of RBL or IS in the treatment of HD in cirrhotic patients. The first article was an RCT by Awad et al. [11] involving 120 adult patients with liver cirrhosis aiming to compare the efficacy and adverse events of endoscopic band ligation (EBL) versus IS (ethanolamine oleate 5% – EAO – or N-butyl-cyanoacrylate). The participants were randomly allocated into two equal groups, each undergoing one of the specified interventions, followed by a 12-month follow-up period. Both techniques allowed adequate bleeding control – demonstrated by a low rebleeding rate (10% in EBL vs. 13.3% in IS, p = 0.754) – and a decrease in disease recurrence (18.3% in EBL vs. 26.6% in IS, p = 0.530), with no significant difference observed between groups. A reduction of at least one grade in Goligher's grading system was obtained in most cases. There were no significant differences in adverse event rates between EBL and IS, except for pain score and need for analgesia, which were higher in the IS group (1.0 ± 1.9 vs. 2.9 ± 2.1, $p < 0.001$ for pain and 20% vs. 61.6%, $p < 0.001$ for analgesia need). Comparing both sclerosing agents, EOA was associated with a significantly

Table 1. Included studies' design and baseline characteristics regarding all participants

Author (publication year)	Study design, follow-up time	Number of participants			Baseline characteristics (regarding all participants)									
		total	with liver cirrhosis	% with liver cirrhosis	age	sex		hemorrhoidal grade according to Goligher's classification				cirrhosis etiology	Child-Pugh stage of cirrhotic patients	
						female, %	male, %	I	II	III	IV		A	B C
Awad [11] (2012)	RCT, 1 year	120	120	100	Mean + SD RBL group: 48.9 years±10.1 IS group: 46.6 years±3.8	RBL group: 16.6	RBL group: 83.3	RBL: 0	RBL: 27 (45%)	RBL: 31 (51.7%)	RBL: 2 (3.3%)	No description	Mean ± SD	
						IS group: 25	IS group: 75.0	IS: 0	IS: 25 (41.7%)	IS: 34 (56.7%)	IS: 1 (1.7%)		RBL group: 7.8±2.6	
													IS group: 7.9±2.9	
Miyamoto [14] (2015)	Prospective single-arm cohort study, not specified	11	11	100	Mean, 73.5 years	63.6	36.4	0	0	7 (63.6%)	4 (36.4%)	No description	2	8 1
Komporozos [15] (2021)	Prospective single-arm cohort study, 2 years	2,635	57	2.2	Mean, 49.4 years	36.5	63.5	Not specified				No description	0	Number of patients of each stage not specified
Huang [10] (2007)	Case series, 6 months	8	8	100	Mean, 54.8 years	37.5	62.5	Not specified				Hepatitis B – 3	6	2 0
												Hepatitis C – 1		
												Hepatitis B and C – 2		
												Alcoholic – 2		
Pirolla [9] (2017)	Retrospective single-arm cohort study, not specified	22	10	45.5	Median, 58 years	36	64	0	0	22 (100%)	0	Hepatitis B – 5 and hepatitis C – 5	0	0 10
Giurazza [16] (2020)	Case series, 3 months	5	5	100	Mean, 61.6 years	40	60	2 (40%)	0	2 (40%)	1 (20%)	Hepatitis C – 2	3	2 0
												Metabolic – 1		
												Alcoholic – 2		

IS, injection sclerotherapy; RBL, rubber band ligation; SD, standard deviation.

lower rebleeding rate (0.0% vs. 26.7% with cyanoacrylate, $p = 0.010$) but with a higher pain score (3.5 ± 2.0 vs. 2.3 ± 2.1 with cyanoacrylate, $p = 0.025$). Child-Pugh score exhibited a positive correlation with rebleeding, recurrence, and abscess formation, but only in the IS group. Overall patient satisfaction was higher in the EBL group (73.3% vs. 36.6% in the IS group, $p < 0.001$).

A second research by Miyamoto and colleagues [14] investigated the efficacy and safety of ALTA sclerotherapy in the treatment of symptomatic hemorrhoids among 11 liver cirrhotic patients. Three-dimensional power Doppler angiography (3D-PDA) was also performed to evaluate blood flow differences in the hemorrhoidal tissue of these patients. Results showed clinical improvement for all patients. However, after 5 years, 2 cases experienced relapsing of prolapse. Post-procedural adverse events included mild bleeding ($n = 2$) in patients with concomitant hypervascularity in hemorrhoidal tissue in 3D-PDA evaluation, and sustained ascites ($n = 3$). The 3D-PDA tool has shown to predict posttreatment bleeding.

A more recent prospective single-arm cohort study by Komporozos et al. [15] assessed the efficacy and safety of RBL in the treatment of grades II to IV symptomatic internal hemorrhoids. The study enrolled 2,635 patients, including 57 with liver cirrhosis. Cirrhotic patients underwent synchronous multiple ligations in a single session. Follow-up examinations were conducted after 2 months and 2 years. Although RBL exhibited overall symptomatic improvement in the early follow-up period for the majority of cirrhotic patients, the rate of success was significantly lower when compared to non-cirrhotic patients: healing or great improvement in 63.2% (vs. 86.8%, $p < 0.05$), improvement in 22.8% (vs. 8.9%, $p < 0.05$), and treatment failure in 14.0% (vs. 4.3%, $p > 0.05$). The adverse event rate was not significantly different from non-cirrhotic patients, with preventive hospitalization being required in only 4 cirrhotic patients.

Endovascular Nonsurgical Procedures

Through a case series, Giurazza et al. [16] evaluated efficacy and safety of embolization of the superior hemorrhoidal artery using a novel coiling method described as "Spaghetti technique" (consisting of releasing oversized coils in a stretched fashion), in 5 liver cirrhotic patients with chronic anemia due to hemorrhoidal bleeding. All patients required transfusion prior to the intervention. Technical success, defined as the occlusion of all superior hemorrhoidal artery branches above the pubic symphysis, was achieved in all cases. At the 3-month follow-up, 4 patients (80%) mentioned clinical improvement, but there was no improvement in the Goligher grade. Symptomatic recurrence was reported in 2 patients, after 10 and 15 days, leading to a second session. No major adverse events were described. Hemoglobin levels remained stable or increased in all patients.

Surgical Treatment

Two articles were identified that evaluated stapled hemorrhoidopexy in patients with liver cirrhosis. In 2007, Huang and coauthors [10] conducted an analysis of 8 liver cirrhotic patients undergoing stapled hemorrhoidopexy (6 patients categorized as Child-Pugh A and 2 as Child-Pugh B). All patients experienced clinical improvement, although symptom relapse with mild bleeding was reported by 2 patients at 2 and 4 months. As for safety, 25% of the patients described postoperative bleeding during hospitalization, which was managed conservatively. Additional adverse events included fecal impaction (62.5%), dysuria (25%), and urinary retention requiring catheterization (37.5%). Pain was a common adverse event, evaluated using a Visual Analog Scale (VAS) from 0 to 10 at postoperative 6 h (mean 5.5), 24 h (mean 4.3), 7 days (mean 1.8), and 21 days (mean 0.8). Additional assessed outcomes comprised median operation duration (38 min), mean intraoperative blood loss (approximately 111.3 mL), mean time lapse from daily activity (12.3 days), and median length of hospital stay (3 days). Patient's acceptability was also reported, with 62.5% expressing it as good and 37.5% as fair.

A research led by Pirolla et al. [9] investigated the surgical outcomes of the same technique when combined with the application of biological glue in patients with grade III internal hemorrhoids and high risk of bleeding. The study comprised 22 patients, from which 10 had Child-Pugh C cirrhosis. This study focused on assessing only the safety of the procedure, evaluating the presence or absence of bleeding and pain in the postoperative period. Despite the occurrence of postsurgical bleeding in 1 of the 22 patients, none of the cirrhotic patients experienced it. All patients reported pain levels below 3 on a VAS from 0 to 10. Other reported outcomes included a median operation duration of 55 min and a median length of hospital stay of 3 days.

Synthesis Results

Office-Based Procedures

Two selected studies focused on the use of RBL for treating symptomatic hemorrhoids: one by Komporozos et al. [15], which was considered to have a low risk of bias,

Table 2. Included studies' details of intervention and outcomes assessed

Author (publication year)	Intervention			Outcomes assessed
	pre-procedure preparation	procedure	adjuvant medical care post-procedure	
Awad [11] (2012)	Minalax 10 tablets 12 h before endoscopy followed by 3 evacuation bland water enemas every 4 h	Endoscopic RBL (50% of patients) and endoscopic IS (in the other 50%, with either ethanolamine oleate 5% or N-butyl-cyanoacrylate). No anesthesia	Oral lactulose and analgesics ("on demand"). Antibiotics if fever (not specified)	Patient's satisfaction (yes/no), treatment success (symptom free 6 weeks post-procedure), reduction of hemorrhoidal prolapse (according to Goligher grading system), post-procedural complications (rebleeding, pain and need for analgesia, ulcer, abscess, hematocyst, local edema, fever), disease recurrence
Miyamoto [14] (2015)	No description	Sclerotherapy with aluminum potassium sulfate and tannic acid. No anesthesia	No description	Patient's symptoms (prolapse and/or bleeding), symptom relapse, post-procedural Child-Pugh stage, post-procedural complications
Komporozos [15] (2021)	Fleet enema a few hours before and 500 mg metronidazole per os just before the procedure. Previous correction of coagulation parameters (INR<1.6) in cirrhotic patients	RBL. No anesthesia	Oral metronidazole 500 mg 3×/24 h, mild laxatives and common analgesics (″on demand″)	Patient's symptoms (cure or great improvement, improvement, failure – both early and 2-year follow-up results), post-procedural complications (pain, bleeding, tenesmus, thrombosis, ulceration/ fissure, vagotomy, fever, perianal abscess, perianal tissue necrosis), disease recurrence, need for surgery
Huang [10] (2007)	Blood transfusion and fleet enema	Procedure for prolapsed hemorrhoids with mass suture or electrocauterization at the staple line. Under spinal/intravenous general anesthesia	Oral acetaminophen 500 mg 4×/24 h, oral mefenamic acid 250 mg 4×/24 h, oral magnesium oxide 500mgat night, IM meperidine 50 mg (″on demand″)	Intraoperative blood loss and staple-line bleeding, operation duration, length of hospital stay, VAS scores, dosages of nonsteroid anti-inflammatory drugs, additional IM narcotics, time lapse from daily activity, acceptability to patient, symptom relapse, frequency of intermittent urinary catheterization plan and post-procedural complications

Table 2 (continued)

Author (publication year)	Intervention			Outcomes assessed
	pre-procedure preparation	procedure	adjuvant medical care post-procedure	
Pirolla [9] (2017)	None	Procedure for prolapsed hemorrhoids followed by use of biological glue in the staple line. Under general anesthesia	Acetaminophen and tramadol and, if pain bigger than 8, decimal solution of morphine sulfate	Post-procedural bleeding and pain, operation duration, length of hospital stay
Giurazza [16] (2020)	Blood transfusion for all patients	Emborrhoid using ″spaghetti technique″. Under local anesthesia	Anti-inflammatory and oral antibiotics (not specified)	Technical success (occlusion of all superior hemorrhoidal artery branches), clinical improvement (bleeding severity, symptoms and QoL scores), hemoglobin values, post-procedural complications

IM, intramuscular; VAS, Visual Analog Scale.

and the other by Awad and his colleagues [11], assessed as having a high risk of bias. Both studies included data from non-cirrhotic population [15] or non-RBL treatments [11] that were dismissed from this part of synthesis (aside from adverse event rates in the Komporozos study).

The average age (mean + SD) of cirrhotic patients managed with RBL was 64.0 ± 12.5 years in Komporozos's study and 48.9 ± 10.1 years in Awad's article. In both studies, treated patients were predominantly male (from 83.3% to 91.2%). Exclusion criteria included colorectal carcinoma in Komporozos's study and thrombosed hemorrhoids, anal fistulas, or perianal abscesses in Awad's study.

To assess efficacy, the two studies applied different outcome measures. Komporozos et al. [15] divided the patients into 3 groups based on their symptoms at a 2-month follow-up visit: asymptomatic (healing or great improvement) – 63.2%, minimized symptoms (improvement) – 22.8%, or no improvement (failure) – 14%. Meanwhile, Awad and coauthors evaluated efficacy through 3 outcomes: patient satisfaction rate (73.3%), recurrence rate (18.3%), and hemorrhoidal prolapse severity reduction according to Goligher's grading system (90% of the patients developed at least one-grade reduction after the first session).

Adverse events from both studies are summarized in Table 5. Noteworthy, although Komporozos's article does not address specifically the results for the cirrhotic population, these are stated as similar as those in non-cirrhotic. Therefore, the results incorporated in Table 5 include both cirrhotic and non-cirrhotic individuals.

The treatment of symptomatic hemorrhoids through IS was explored in two studies: one by Miyamoto et al. [14], with a low risk of bias, and the other by Awad and coauthors [11], with a high risk of bias. Awad's study included information on non-IS treatments, which were excluded from this synthesis section. In Miyamoto's study, patients had a mean age of 73.5 years and were mostly female (63.6%), while in Awad's article, the mean age was 46.6 ± 3.8 years and the patients were predominantly male (75%).

In the Miyamoto et al. [14] study, exclusion criteria were not specified, while Awad's study excluded patients with thrombosed hemorrhoids, anal fistulas, or perianal abscesses. Miyamoto and colleagues [14] used ALTA as the sclerosing agent, while Awad et al. [11] divided patients into two subgroups using either EAO or N-butyl-cyanoacrylate.

In Miyamoto's study, all patients exhibited symptom improvement, but 2 patients reported disease recurrence after 5 years (18.2%). Awad's study evaluated efficacy outcome by examining patient satisfaction rate (16.7% for EAO vs. 40% for N-butyl-cyanoacrylate), recurrence rate at the 12-month follow-up visit (13.3% for EAO vs. 40% for N-butyl-cyanoacrylate), and reduction in the severity of hemorrhoidal prolapse according to Goligher's grading system (86.7% showed at

Table 3. Risk of bias assessment

Study	Risk of bias (ROBINS-I tool)							
	signaling questions	bias in selection of participants into the study	bias in classification of interventions	bias due to deviations from intended interventions	bias due to missing data	bias in measurement of outcomes	bias in selection of the reported result	overall bias
Giurazza et al. [16]	Low	Low	Low	Low	Low	Low	Low	Low
Huang et al. [10]	Low	Low	Low	Low	Low	Low	Low	Low
Komporozos et al. [15]	Low	Low	Low	Low	Low	Low	Low	Low
Miyamoto et al. [14]	Low	Low	Low	Low	Low	Low	Low	Low
Pirolla et al. [9]	Low	Low	Low	Low	Low	Low	Low	Low

Study	Risk of bias (RoB-2 tool)					
	risk of bias arising from the randomization process	risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	missing outcome data	risk of bias in measurement of the outcome	risk of bias in selection of the reported result	overall risk of bias
Awad et al. [11]	Some concerns	Some concerns	Low	Some concerns	Low	High

ROBINS-I, Risk Of Bias In Non-randomized Studies – of Interventions; RoB-2, Risk of Bias 2.

least a one-grade reduction after the first session). Post-procedure adverse events from both studies are detailed in Table 5.

Endovascular Nonsurgical Procedures

The singular study discussing the emborrhoid technique for treating symptomatic hemorrhoids in cirrhotic patients is authored by Giurazza et al. [16], and it was previously described in this review.

Surgical Treatment

Two of the chosen research studies focused on employing stapled hemorrhoidopexy for treating symptomatic hemorrhoids in cirrhotic patients – one authored by Pirolla et al. [9] and the other by Huang and collaborators [10]; both were assessed as having a low risk of bias. The age of the included patients was 58 years (median) in Pirolla's study and 54.8 years (mean) in Huang's article. In both, most patients were male (from 62.5% to 64%). Pirolla's exclusion criteria were not specified, while Huang's study excluded patients with concomitant anal fissure, abscess, fistula, and/or prominent external component.

Both studies evaluated safety outcomes assessing post-procedural bleeding rate and pain levels. Pirolla's research reported a nil post-procedural bleeding rate, while Huang's article documented a 25% bleeding rate. In Pirolla's study, all patients experienced pain levels below 3 in a VAS score from 0 to 10, although the timeframe for evaluation was unspecified. Conversely, Huang's study assessed pain at four distinct postsurgery intervals (6 h, 24 h, 7 days, and 21 days). During the initial 6 h, the mean VAS score was approximately 5.5, decreasing to about 1.8 at 7 days post-procedure.

Discussion

With regard to office-based procedures, specifically RBL, research on cirrhotic patients indicates that this intervention is effective, achieving cure rates of 63.2%

Table 4. Efficacy outcomes with RBL and IS

			Efficacy			
			symptomatic improvement	disease recurrence	patient satisfaction, %	hemorrhoidal prolapse reduction in anoscopy
Awad et al. [11]	RBL (n = 60)		Not specified	18.3% (at 12 months)	73.3	90% (≥1 grade)
	IS	Ethanolamine oleate 5% (n = 30)	Not specified	13.3% (at 12 months)	16.7	86.7% (≥1 grade)
		N-butyl-cyanoacrylate (n = 30)	Not specified	40% (at 12 months)	40	
		General	Not specified	26.7% (at 12 months)	36.6	
Komporozos et al. [15] (n = 57)	RBL		Great improvement: 63.2%	Not specified	Not specified	
			Improvement: 22.8%			
Miyamoto et al. [14] (n = 11)	IS	Aluminum potassium sulfate and tannic acid	100%	18.2% (at 5 years)	Not specified	

IS, injection sclerotherapy; RBL, rubber band ligation.

[15], closely resembling the approximately 70% cure rates reported in the general population [17]. In the cirrhotic population, this technique has also demonstrated a 12-month recurrence rate of approximately 18.3%, which is notably lower than the 37.5% recurrence rate reported in the HubBLe trial for the general population [18] where there was a need for multiple ligation sessions within the period of 1 year. Concerning safety, the most commonly reported adverse events across the included studies were pain, bleeding, ulceration/fissure, fever, abscess, and local edema – which aligns to those documented in the general population [19]. When assessing adverse event rates in both studies addressing the use of RBL in cirrhotic patients, Awad et al. [11] showed higher adverse event rates than those documented by Komporozos et al. [15]. Several factors could account for this difference, including that adverse event rates were not specifically provided for the cirrhotic population in Komporozos's study, and can possibly be slightly higher, although not significantly different. One of the major differences between the results achieved by the two studies was the post-procedural bleeding rates (2.9% in Komporozos vs. 10.0% in Awad). Although this difference may initially appear to result from the pre-procedural correction of coagulation parameters based on INR in cirrhotic patients in Komporozos's study, recent clinical evidence showed that correcting any coagulopathy or platelets levels before a high bleeding risk procedure in cirrhotic patients does not preclude or reduce the rate of clinically significant procedure-related bleeding [20]. In fact, in most cases, laboratory evaluation of hemostasis for this purpose is not indicated, since the post-procedural bleeding risk cannot be accurately predicted [20]. In summary, when managing liver cirrhotic patients with concomitant HD, RBL proves to be a safe and successful technique, yielding a patient satisfaction rate of 73.3% [11].

When assessing IS as a treatment for HD in cirrhotic patients, the studies included explored the use of three sclerosing agents – ALTA, EAO, and N-butyl-cyanoacrylate. All agents demonstrated clinical improvement, yet with varied recurrence rates. At 12 months, recurrence rates ranged from 13.3% for EAO to 40% for N-butyl-cyanoacrylate, and the 5-year recurrence rate with ALTA was reported at 18.2%. Comparatively, the recurrence rates at 12 months for the general population, when employing polidocanol foam sclerotherapy, vary between 12% [21] and 16% [22], depending on the studied population. This rate does not differ significantly from the documented with the EAO agent in cirrhotic patients. Regarding safety outcomes, the most reported issues include bleeding, ulceration, pain, and ascites. Overall,

Table 5. Adverse events

Adverse events	Awad et al. [11]			Miyamoto et al. [14] IS with ALTA (n = 11)	Komporozos et al. [15] RBL (n = 57)
	IS		RBL (n = 60)		
	EAO (n = 30)	N-Butyl-cyanoacrylate (n = 30)			
Bleeding, %	0	26.7	10	18.2	2.9
Ulceration/fissure, %	13.3	26.7	16.7	–	0.9
Abscess, %	13.3	13.3	11.7	–	0.04
Hematocyst, %	13.3	13.3	3.3	–	–
Local edema, %	0	6.7	6.7	–	–
Fever, %	13.3	20	11.7	–	0.1
Need for analgesia, %	63.3	60	20	–	–
Pain score (mean±SD)	3.5±2	2.3±2.1	1±1.9	–	–
Pain, %	–	–	–	–	16.2
Ascites, %	–	–	–	27.3	–
Serum bilirubin elevation, %	–	–	–	9.1	–
Others, %	–	–	–	–	Tenesmus: 3.5
					Thrombosis: 1.4
					Vagotomy: 0.8
					Perianal tissue necrosis: 0.04

ALTA, aluminum potassium sulfate and tannic acid; EAO, ethanolamine oleate 5%; IS, injection sclerotherapy; RBL, rubber band ligation; SD, standard deviation.

EAO appears to be associated with fewer adverse events compared to N-butyl-cyanoacrylate, with both agents having similar rates of abscesses and hematocyst formation. However, EAO is linked to higher pain levels and a higher need for analgesia, leading to lower satisfaction rates. On the other hand, ALTA sclerotherapy carries a higher bleeding risk than EAO but lower than N-butyl-cyanoacrylate.

IS emerges as an effective approach for treating hemorrhoids in cirrhotic patients, demonstrating recurrence rates comparable to the general population, although with a low patient satisfaction rate of 36.6% [11]. The sclerosing agent must be carefully chosen with EAO being associated with less adverse events, but higher pain levels, N-butyl-cyanoacrylate with higher satisfaction rates but increased recurrence rates, and ALTA with ascites as a potential adverse event. Although the pathophysiological mechanism is not certain, ascites following ALTA treatment might happen due to the inflammatory response that originates after the injection of a sclerosing agent, with a subsequent increased capillary permeability in a susceptible population.

Comparing RBL and IS performed in the cirrhotic population, both techniques demonstrated effectiveness and exhibited similar adverse event rates. However, patient satisfaction rates were higher with RBL, likely attributed to the reduced associated pain [11].

The emborrhoid technique showed a clinical improvement rate of 80% with a reported bleeding relapse of 40%. No major adverse events were documented. However, these findings appear less promising compared with those previously published for generic patients with high surgical risk. In those, a clinical improvement rate of 100% was reported and a recurrence rate and an adverse event rate of, respectively, 14.3% for each were reported [23].

Regarding surgical treatment modalities, namely stapled hemorrhoidopexy, the reviewed studies highlighted this technique as an attractive method for managing HD in cirrhotic patients, due to its relatively brief mean operation duration, short hospitalization period, and reduced time to return to daily activities. Adverse events include post-procedural bleeding, manageable with the application of biological glue (reducing to 0% vs. 25% without glue application), pain (with mean VAS scores ranging from 5.5 at 6 h postoperative to 0.8 at 21 days postoperative), fecal impaction (62.5%), dysuria (25%), and urinary retention needing catheterization (37.5%). Comparing to the general population, bleeding rates are similar (from 0% to 68% in non-cirrhotic population) [24], while rates of fecal impaction (from 1.9% to 6%) [25–29] and urinary retention (from 0 to 22%) [24] are higher.

While it appears to be a favorable method with high patient acceptability (62.5% with good satisfaction), there is symptomatic recurrence at 4 months, in line with the high recurrence rates reported for the general population. This aligns with the general population's high recurrence rates reported in previous studies [30].

This review has some limitations that we should underscore: first, the restricted pool of included studies, which emphasizes the paucity of research on this subject; second, the design of the included articles, with one single RCT assessed with a high risk of bias. Most of the remaining studies are single-arm investigations, valued primarily for their role in hypothesis generation and initial insights, yet generally regarded as weaker in evidence. Furthermore, the heterogeneity observed in both pre-procedural and post-procedural medical therapy, as well as the lack of a standard definition for each in outcome, precluded a comprehensive comparison of techniques. Finally, it is important to refer a major limitation in interpreting and comparing data when directly comparing percentages from different studies, particularly those using different therapies and with small sample sizes (e.g., Komporozos et al. [15] and Miyamoto et al. [14] studies), as this can lead to variability and weak statistical power.

Despite the mentioned drawbacks, this review represents a valuable and pioneering work in this field, aiming to fill the gap in the preexisting literature by thoroughly investigating the efficacy and safety of the available treatment modalities for HD in liver cirrhotic patients. These findings can lead to clinical practice change, as they challenge previous assumptions. Namely, those outlined in guidelines [31–33], regarding the feasibility of some office-based or surgical interventions in cirrhotic patients, such as the perception that RBL was unsuitable for cirrhotic population. Thus, this comprehensive systematic review allows to set up a fundamental framework of evidence-based medicine and provides rationale for future research.

Conclusion

All treatment methods assessed in the included studies appear to be effective and safe for use in patient with liver cirrhosis, although with variations in success rates and adverse event profiles. This challenges previous assumptions, consequently reshaping the paradigm concerning HD management in cirrhotic patients.

Future studies must focus on RCT to thoroughly assess the efficacy and safety of managing HD in cirrhotic patients. Incorporating newer and promising treatment modalities, such as polidocanol foam sclerotherapy, a minimally invasive technique that has already proven to be more effective than RBL in the general population and at least as effective and safe in patients with bleeding disorders, is an imperative research demand in this setting.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.B.P.: contributions to the conception and design of the work; analysis and interpretation of data; reviewing the work critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity were appropriately investigated and resolved. J.O.: acquisition, analysis, and interpretation of data; drafting the work; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions

related to the accuracy or integrity were appropriately investigated and resolved. A.R.: substantial contributions to the conception and design of the work; analysis and interpretation of data; reviewing the work critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity were appropriately investigated and resolved. P.S.: Substantial contributions to the conception and design of the work; analysis and interpretation of data; reviewing the work critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity were appropriately investigated and resolved.

Data Availability Statement

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

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Early-Stage Colon Cancer Surveillance: Pattern and Timing of Recurrence and the Role of 5-Year Surveillance

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Keywords
Colon cancer · Early stage · Recurrence · Surveillance

Abstract

Introduction: Colorectal cancer is the third most prevalent cancer among both men and women with 80% of patients having localized disease enabling curative treatments. Given the low recurrence rate in early-stage disease, there is a growing interest in reviewing follow-up protocols. The aim of this study was to assess the frequency and timing of recurrence in early-stage colon cancer, as well as recurrence patterns. ***Methods:*** The data from all patients with colon adenocarcinoma consecutively treated with surgery at the Instituto Português de Oncologia do Porto, EPE, between January 2013 and December 2016, were retrospectively reviewed. ***Results:*** A total of 1,372 patients with colon cancer were submitted to surgery during the study period. From this group, 51.4% (n = 705) were early-stage colon cancers. Regarding the pathological stage, 3.5% were stage 0, 37.4% were stage I and 59.1% were stage II. The overall recurrence rate was 6.7%. When considering the group of patients without risk factors, the recurrence rate was 5.6%. The majority of recurrences occurred in the first 3 years of follow-up. The recurrence was diagnosed in the majority of patients through carcinoembryonic antigen elevation, followed by imaging exams. The presence of one or more risk factors (high nuclear grade, vascular invasion, extramural venous invasion, and perineural invasion) showed a statistically significant association with recurrence rate. ***Conclusion:*** The recurrence rate was low in early-stage colon cancer, with the majority of recurrences occurring in the first 3 years. Our study results show that surveillance should be tailored according to individual risk factors.

Vigilância do cancro do cólon em estadios iniciais: padrão de recorrência e o papel da vigilância até aos 5 anos

Palavras Chave
Cancro do cólon · Estadio inicial · Recorrência · Vigilância

Resumo

Introdução: O cancro do cólon é o terceiro cancro mais prevalente tanto em mulheres como em homens. Cerca de 80% têm doença localizada ao diagnóstico, permitindo o tratamento curativo. Considerando a baixa taxa de recorrência em doentes com estadios iniciais, existe

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uma necessidade de rever os critérios e protocolos de vigilância. O objetivo do estudo é avaliar a frequência e padrão de recorrência em doentes com cancro do cólon em estadios iniciais. ***Métodos:*** Foram analisados retrospectivamente todos os doentes diagnosticados com adenocarcinoma do cólon tratados com cirurgia no Instituto Português de Oncologia do Porto, EPE, entre Janeiro de 2013 e Dezembro de 2016. ***Resultados:*** Durante este período, foram submetidos a cirurgia um total de 1,372 doentes com diagnóstico de cancro do cólon. Neste grupo, 51.4% (*n* = 705) têm tumores em estadio inicial ao diagnóstico. Considerando o estadio patológico, 3.5% são estadio 0, 37.4% são estadio I e 59.1% estadio II. A taxa de recorrência global foi de 6.7%. Quando analisamos o grupo sem fatores de mau prognóstico, a taxa de recorrência foi de 5.6%. A maioria dos casos de recorrência ocorreu nos primeiros 3 anos de vigilância, sendo que a recorrência foi diagnosticada, na maior parte dos casos, por aumento do CEA, seguido de exames de imagem. A presença de um ou mais fatores de risco (alto grau nuclear, invasão vascular, invasão venosa extramural e invasão perineural) mostrou uma associação estatisticamente significativa com a taxa de recorrência. ***Conclusão:*** Em conclusão, a taxa de recorrência é baixa no cancro do cólon em estadios iniciais, com a maioria dos casos de recorrência a ocorrer nos primeiros 3 anos de vigilância. O presente estudo demonstra a importância da individualização da vigilância em função dos fatores de risco individuais.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both women and men. In general, the lifetime probability of developing CRC is approximately 1 in 23 for men and 1 in 26 for women [1]. Approximately 80% of these patients present with localized disease and the majority undergo curative treatment [2]. Intensive surveillance is routinely recommended for these patients [2–4].

Considering the incidence of this pathology, patients with CRC represent one of the largest groups of cancer survivors, requiring an important number of hospital appointments during follow-up [5]. Between 30 and 50% of all patients treated with localized disease will eventually recur and die of the disease [6]. The goal of intensive follow-up protocols is the early detection of recurrence, in order to provide the possibility of a treatment with curative intent [5, 7].

The risk of recurrence is higher with higher stage disease and 85% of recurrences develop during the first 2.5 years after surgery. Patients who are disease free at 5 years have a recurrence risk of less than 5%. The timing and pattern of recurrence are stage dependent [8].

The majority of surveillance protocols include clinical evaluation, carcinoembryonic antigen measurement, chest-abdominal-pelvic CT scan, as well as colonoscopy every 3–5 years starting 1 year after surgery or earlier if the diagnostic colonoscopy was not complete. The time interval between consultations and exams gradually widens throughout the surveillance [7, 9]. Considering the low recurrence rate in the early stages and the resources required for follow-up in the hospital setting, there has been a growing interest in reviewing follow-up protocols.

The aim of this study was to assess the frequency and timing of recurrences in early-stage colon cancer. Additionally, we aimed to analyze the recurrence patterns and diagnostic approaches as secondary goals.

Materials and Methods

The data from all patients with colon adenocarcinoma consecutively treated with surgery at the Instituto Português de Oncologia do Porto, EPE, between January 2013 and December 2016, were retrospectively reviewed. The enrollment period was chosen to ensure a minimum of 5 years follow-up for all patients.

In our institution, surveillance is conducted during the first 2 years with clinical assessment and tumor marker evaluation every 3–4 months, plus thoraco-abdomino-pelvic CT scans annually. Colonoscopy is performed 1 year after surgery (earlier in cases of incomplete colonoscopy at diagnosis) and 3 years after. After the fifth year of surveillance, the patient is discharged from hospital-level follow-up and transits to monitoring at the primary care center.

Inclusion criteria were adult patients (≥18 years old) submitted to surgery with curative intent, with an early clinical stage colon cancer (defined by the authors as stages 0, I, and II according to AJCC TNM classification), with lesions proximal to 15 cm from the dentate line in colonoscopy and histologic confirmation of adenocarcinoma. Exclusion criteria were stages III and IV at diagnosis, surgery for recurrent disease, genetic syndromes associated with higher risk of colon cancer, extracolonic synchronous tumors, and lack of surveillance data (due to loss of follow-up or death within 30 days of surgery).

Data regarding demographic features, treatments, histologic characteristics of the tumor, follow-up, and disease recurrence were recorded. The descriptive analysis of categorical variables was presented with frequency tables and continuous variables were presented using median and interquartile range (IQR).

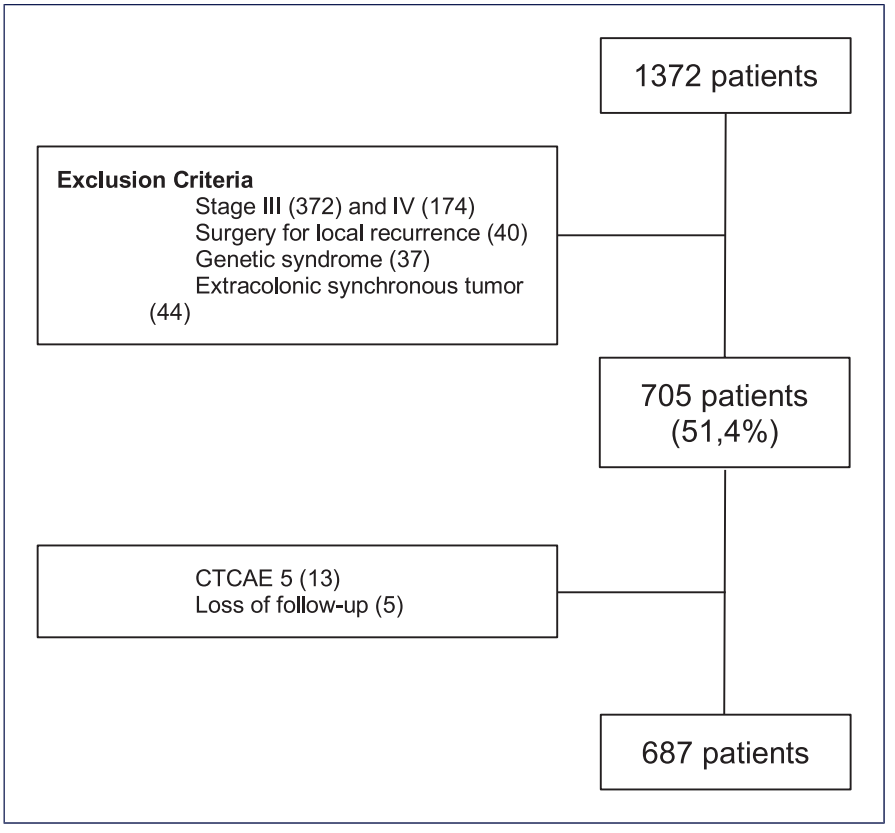

Fig. 1. Distribution of patients applying exclusion criteria.

A univariate analysis was carried out using χ^2 tests in order to test the association between known prognostic factors (independent variables) and the risk of recurrence (dependent variable). The analyzed independent variables were the location of the tumor (right colon defined as lesions proximal to the midpoint of the transverse colon vs. left colon defined as all lesions distal to the midpoint of the transverse colon), surgical approach (open vs. laparoscopic), 30-day surgical morbidity (classified according to the common terminology criteria for adverse events (CTCAE) version 5.0), and histologic characteristics such as pT, nuclear grade, vascular invasion, extramural venous invasion (EMVI), perineural invasion, and a number of lymph nodes retrieved in the surgical specimen (analyzed using both 12 as a cutoff point since it is the guideline-recommended minimum number of lymph nodes to be removed, as well as 19 since it was the median of lymph nodes removed in the surgical specimens in our patient sample). The association between ≥1 prognostic factor (high nuclear grade, vascular invasion, EMVI, or perineural invasion) and risk of recurrence was also tested since these are the major factors used to decide adjuvant chemotherapy indication. Only factors that achieved statistical significance in the univariate analysis were used to build the multivariate analysis model, through a Cox regression model, with hazard ratio (HR) and the respective 95% confidence intervals (95% CI) reported. Survival analysis was performed using Kaplan-Meier's survival curves and life tables. A p value <0.05 was considered statistically significant and statistical analysis was performed using SPSS® version 26.0 software.

Results

A total of 1,372 patients with colon cancer were submitted to surgery during the study period. A total of 546 patients were staged as III or IV and were excluded from the study. Additionally, in 44 patients, synchronous extracolonic cancer was diagnosed and another 37 patients had a genetic syndrome associated with higher risk of colon cancer, excluding all of these patients from this analysis. Of the 705 patients remaining, 5 were lost to follow-up and 13 died within 30 days after surgery (mortality rate 1.8%) (shown in Fig. 1, 2).

Of the 687 patients included, 43.8% (301) corresponded to female patients, with a median age of 68 years old (IQR 15). The characteristics of the surgical treatment are described in Table 1. The majority of patients were submitted to elective surgery (99%; n = 680). The most common approach was laparotomy (73.1%; n = 502) and the most common procedures were right colectomy (43.8%; n = 301) and sigmoidectomy (39.9%; n = 274). The major complication rate, defined as CTCAE 3/4 was 9.5% (n = 65).

Regarding the pathological stage, 3.5% (n = 24) were stage 0, 37.4% (n = 257) were stage I, and 59.1% (n = 406)

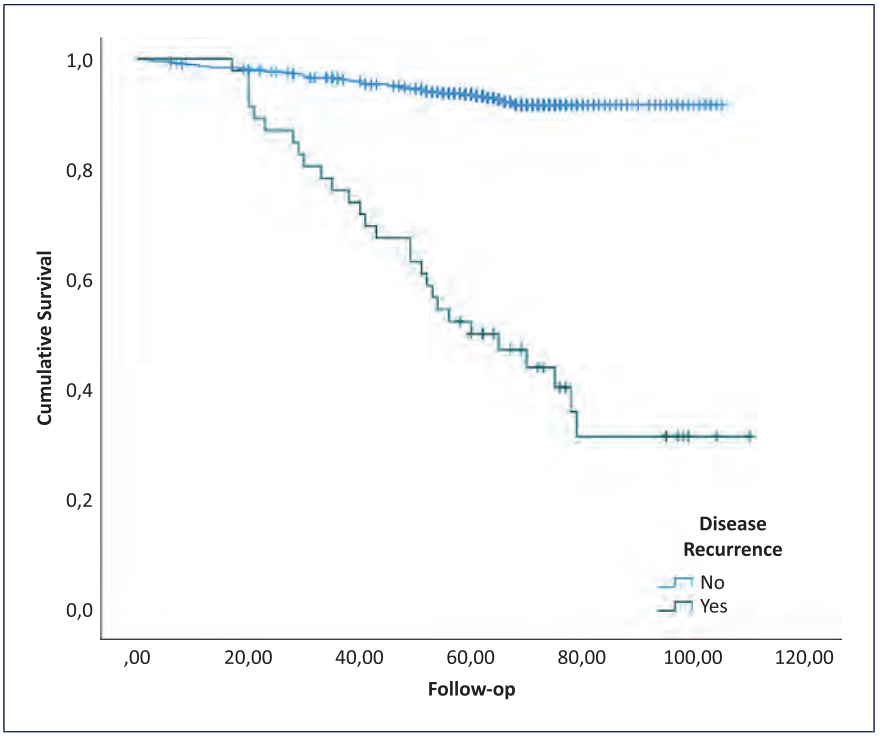

Fig. 2. Overall survival comparing the groups with and without recurrence.

Table 1. Demographic characteristics of the study cohort

Variables	*n* (%)
Type of surgery	
Elective	680 (99)
Urgent	7 (1)
Surgical approach	
Laparotomy	502 (73.1)
Laparoscopy	185 (26.9)
Surgical procedure	
Right hemicolectomy	301 (43.8)
Sigmoidectomy	274 (39.9)
Left hemicolectomy	85 (12.4)
Transverse colectomy	16 (2.3)
Subtotal/total colectomy	11 (1.6%)
Surgical morbidity	
CTCAE 0	563 (82%)
CTCAE 1	5 (0.7%)
CTCAE 2	54 (7.9%)
CTCAE 3	44 (6.4%)
CTCAE 4	21 (3.1%)

were stage II. Within the stage II patients, the majority were stage IIA (53.4%; *n* = 367), followed by stage IIB in 3.8% (*n* = 26) and stage IIC in 1.9% (*n* = 13). All resections were pathologic R0. Considering the grade, 54.1% (*n* = 372) were in grade 1, 33.5% (*n* = 230) in grade 2, and 4.2% (*n* = 29) in grade 3. Examining other histological features, 18.5% (*n* = 127) had vascular invasion, 9.2% (*n* = 63) had EMVI and 10.8% (*n* = 74) had perineural invasion. Ten percent (*n* = 69) of the patients were submitted to adjuvant chemotherapy. The histological characteristics of the surgical specimens are described in Table 2.

The median follow-up time was 62 months (IQR 12). The overall recurrence rate was 6.7% (*n* = 46). When considering the group of patients without risk factors (*n* = 390), the recurrence rate was 5.6% (*n* = 22). The majority of recurrences (73.9%, *n* = 34) occurred in the first 3 years of follow-up, 21.7% (*n* = 10) between the third and fifth years of follow-up and 4.4% (*n* = 2) after the fifth year of follow-up.

Figure 3 enables the observation of survival curves based on the diagnostic stage. It can be noted that stage 0 initially exhibits a better prognosis, but over time, it becomes comparable to stage I. Additionally, stage IIa tends to align more closely with stage I than with other subgroups within stage II.

Considering each stage group, among the patients in stage 0 (*n* = 24), the median follow-up was 61.5 months and no cases of recurrence were observed. The stage I group had 257 patients with a median follow-up time of 62 months. Within this subgroup, a total of 3.9% of

Table 2. Histological descriptive characteristics of the study cohort

Variables	*n* (%)
Pathologic tumor staging (*n* = 687)	
Stage 0	24 (3.5%)
Stage I	257 (37.4)
Stage IIA	367 (53.4)
Stage IIB	26 (3.8)
Stage IIC	13 (1.9)
Tumor grade (*n* = 631)	
1	372 (58.9)
2	230 (36.5)
3	29 (4.6)
Vascular invasion (*n* = 671)	
No	544 (81.1)
Yes	127 (18.9)
EMVI (*n* = 646)	
No	583 (90.2)
Yes	63 (9.8)
Perineural invasion (*n* = 639)	
No	565 (88.4)
Yes	74 (11.6)

Table 3. Characteristics of recurrent disease

Variables	*n* (%)
Pattern of recurrence	
Distant metastasis	33 (71.7)
Loco-regional metastasis	12 (26.1)
Local and distant metastasis	1 (2.2)
Diagnostic method	
CEA elevation	25 (54.3)
Imaging exams	15 (32.6)
Colonoscopy	5 (10.9)
Clinical evaluation	1 (2.25)
Treatment	
Surgical treatment	24 (52.2)
Systemic treatment	13 (28.3)
Supportive care	9 (19.6)

CEA, carcinoembryonic antigen.

patients relapsed (*n* = 10). Among those, 1.6% (*n* = 4) recurred within the first 3 years, 1.9% (*n* = 5) between the third and fifth year of follow-up, and only one after the fifth year. The median time until recurrence was 36 months. The stage II group comprised 406 patients, with a median follow-up of 61.5 months. Within this subgroup, the recurrence rate was 8.9% (*n* = 36). Among them, 7.6% (*n* = 31) recurred within the first 3 years, 1% (*n* = 4) between the third and fifth year of follow-up, and only one after the fifth year. The median time to recurrence was 14.5 months Table 3.

In regards to the pattern of recurrence, 71.7% (*n* = 33) of patients had distant metastasis, 26.1% (*n* = 12) loco-regional disease, and 2.2% (*n* = 1) both local and distant recurrence. The recurrence was diagnosed in the majority of patients through carcinoembryonic antigen elevation (54.3%; *n* = 25), followed by imaging exams in 32.6% (*n* = 15), colonoscopy in 10.9% (*n* = 5), and clinical evaluation in 1 patient (2.25%). Considering the treatment for recurrent disease, 52.2% (*n* = 24) of the patients were submitted to surgical treatment, 28.3% (*n* = 13) to systemic treatment, and 19.6% (*n* = 9) to support care.

An evaluation of prognostic factors for recurrence was made in stages I and II patients (*n* = 663). EMVI, perineural invasion, pT, and the presence of one or more risk factors were statistically significant in the univariate analysis. In the multivariate analysis, the presence of EMVI did not show statistical significance (HR = 1.753, p = 0.194, 95% CI [0.751–4.092]). Conversely, perineural invasion demonstrated a statistically significant association with recurrence (HR = 2.298, p = 0.037, 95% CI [1.052–5.016]). Although the pT stage did not reach statistical significance (p = 0.124), a noticeable relationship was observed between higher pT stages and an increased risk of relapse (shown in Table 4). Upon comparing the overall survival between the group of patients with recurrence and the group that remained recurrence-free, a notable observation is the significantly higher overall survival in the recurrence-free group.

Discussion

The aim of this study was to assess the frequency and timing of recurrences in early-stage colon cancer. In our study sample, the overall recurrence rate was 6.7%, with the majority of patients (73.9%) being diagnosed in the first 3 years of follow-up. We analyzed the recurrence in each stage group, and in stage 0, no cases of recurrence were observed, as was expected according to the literature. In stage I, the relapse rate was 3.9%, and in stage II, the relapse rate was 8.9%. In our cohort, the proportion of early-stage colon cancer was 51.4%, which is higher compared to the 37% reported in the literature, especially considering that our center is a tertiary care facility, where a higher number of advanced cases would be expected

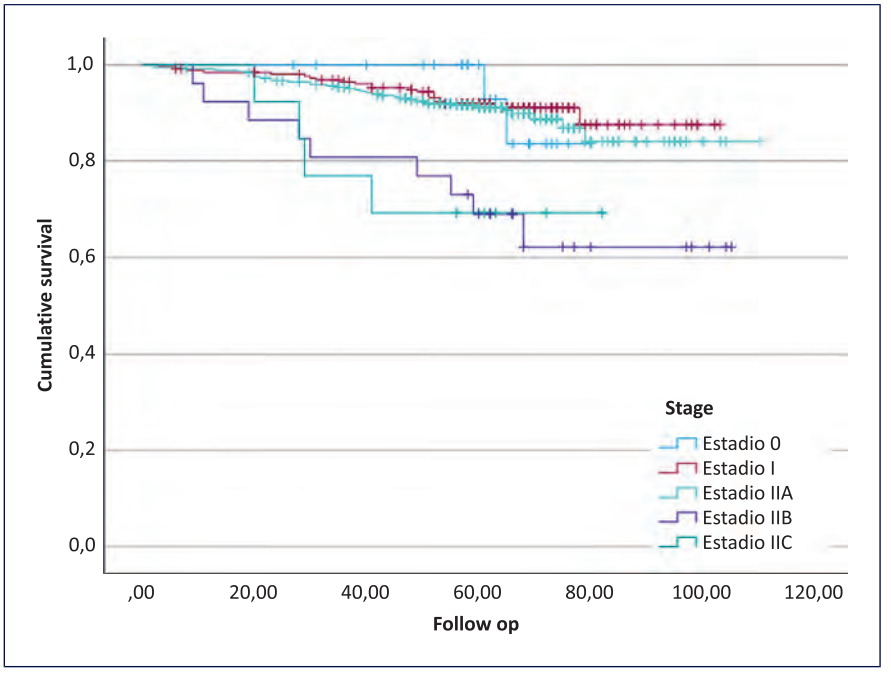

Fig. 3. Overall survival comparing the stages 0, I, and II at diagnosis.

Table 4. Univariate and multivariate analysis of prognostic factors for recurrence

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Surgical approach (open approach)	1.336 (0.649–2.752)	$p = 0.432$		
Tumor localization	1.146 (0.612–2.145)	$p = 0.670$		
Surgical complications	0.539 (0.274–1.057)	$p = 0.072$		
Tumor grade				
1	1	$p = 0.376$		
2	1.850 (0.240–14.238)			
3	2.692 (0.348–20.846)			
Vascular invasion	0.523 (0.270–1.012)	$p = 0.054$		
EMVI	0.394 (0.180–0.863)	$p = 0.020$	1.753 (0.751–4.092)	$p = 0.194$
Perineural invasion	0.378 (0.182–0.783)	$p = 0.009$	2.298 (1.052–5.016)	$p = 0.037$
Mucinous tumor	1.611 (0.704–3.683)	$p = 0.259$		
pT		$p = 0.009$		$p = 0.124$
T1	1		1	
T2	0.168 (0.036–0.775)		0.457 (0.118–1.760)	
T3	0.104 (0.020–0.531)		1.040 (0.379–2.852)	
T4a	0.275 (0.072–1.058)		1.583 (0.342–7.334)	
T4b	0.794 (0.157–4.000)		4.087 (0.832–20.076)	
Number of lymph nodes (>12)	0.835 (0.344–2.024)	$p = 0.689$		
Number of lymph nodes (>19)	0.808 (0.441–1.477)	$p = 0.488$		
≥1 risk factor	2.371 (1.224–4.592)	$p < 0.010$		

CI, confidence interval; HR, hazard ratio; *n*, number.

[10]. In Portugal, there is a national guideline, provided by the Directorate-General of Health, recommending screening based on colonoscopy and fecal blood testing for asymptomatic individuals aged between 50 and 74 years, but there is no nationwide covered program. Some geographical areas are covered by an organized screening program, similar to the scenario in Northern Portugal, which had an annual population coverage of 69% in 2021, and this effective coverage may explain the higher rate of early cases represented in our study [11–13].

Despite the occurrence of local recurrence and distant metastasis following curative surgery remaining a significant concern and being associated with poor prognosis, this high proportion of early cases raises the question of the burden associated with intensive and long-term surveillance in these patients [9]. According to existing literature, the risk of recurrence for stages I to III colon cancer ranges from 30 to 40%, with the occurrence of relapse being dependent on the stage of the disease at diagnosis [9]. In our population, the relapse rate of stage I patients was 3.9%, lower than the 5% described in the literature [5]. Within the stage II subgroup, the relapse rate was 8.9%, as expected higher than in stage I, but still lower than the rates reported in the literature (10–20%) [5]. These low recurrence numbers may question the need for intense surveillance protocols in early-stage colon cancer.

Several recommendations regarding post-treatment surveillance for CRC have been published and endorsed by professional societies. According to NCCN, the surveillance program is, in fact, stage dependent. In stage I patients, there is no need for other exams beyond colonoscopy. In stage II, a more intensive surveillance protocol is advised, with clinical evaluation and tumor seric markers every 3–6 months for the first 2 years and every 6 months between the third and fifth year, as well as a CT scan annually for the first 5 years [8]. Other societies, such as ESMO and ASCO guidelines, suggest similar timings for follow-up exams [5, 14].

While these conventional guidelines advocate for rigorous surveillance, emerging data suggest that less intensive approaches are not inferior. In the "Colofol Randomized Clinical Trial," approximately 2,500 patients with stages II and III colon cancer were studied, and it was found that more or less intensive surveillance had no impact on overall survival [3]. Synder et al. [4] revealed that the difference between the intensity of surveillance did not have an impact on recurrence, resectability of the recurrent disease, and overall survival. Notably, the literature reveals that increased postoperative CRC follow-up, from 2 to 5 examinations over 3 years of post-surgery with 5 years of follow-up, did not yield significant differences in 5-year overall mortality or CRC-specific mortality rates [2]. In a scenario involving a diverse group of patients who could potentially benefit from more intensive surveillance, there is a notable focus on developing strategies better tailored to individual risk levels. Although the high-intensity follow-up group detected CRC-specific recurrences earlier, this did not lead to reduced mortality rates [2–4].

Another important point concerns the timing of recurrence. Our results demonstrated that the vast majority of relapses occur within the first 3 years after surgery (73.9%), with a low percentage occurring between the third and fifth years of follow-up. This difference was even more pronounced in the stage II subgroup, where despite a higher percentage of relapse, these occurred earlier (median time to recurrence of 14.5 months). These findings allow us to infer that the highest risk period lies within the first 3 years of surveillance. These data may lead us to consider the possibility of reducing the hospital follow-up time.

An acknowledgment has also to be made regarding the low rate of adjuvant chemotherapy in this group. This can be explained by the fact that, during the study period, histologic factors were not yet used as criteria for adjuvant treatment (specifically undifferentiated tumor, lymphovascular and perineural invasion, and microsatellite instability) [8].

In our study, factors impacting recurrence in the univariate analysis were EMVI and perineural invasion, stage, and the presence of at least one risk factor. In the multivariate analysis, only perineural invasion was found to be statistically significant. These findings in a group with a low rate of adjuvant chemotherapy allow us to confirm that histologic factors such as lymphovascular and perineural invasion have an impact on the risk of recurrence and should be used to aid in the decision regarding adjuvant treatments, as reported in recent literature [9]. In patients without risk factors, the recurrence rate was 5.6%, increasing to 8.8% in patients with at least one risk factor. Therefore, these adverse prognostic factors may not only be used to guide treatment decisions but also to tailor follow-up programs in patients with early-stage disease. In patients without risk factors for recurrence and with early-stage colon cancer, the risk of recurrence is very low and it is in this group that the decrease in intensity of follow-up could have a significant impact at a hospital level.

Our findings challenge the need for intense surveillance in early-stage patients, as the low recurrence rates observed question the benefits of such protocols, emphasizing the importance of finding a balanced approach considering both clinical needs and economic considerations [2, 9]. They also emphasize the need to develop risk scores that can be used to identify patients who require more intensive surveillance. The future of surveillance seems to be moving toward a more personalized, risk-based approach that takes into account individual patient and disease characteristics.

The study's strengths include having a substantial sample size, being conducted with a group of patients treated in a tertiary center with standardized treatment by experienced teams and using real-world data. The limitations encompass its retrospective design, being conducted in a single center, lack of emergency surgery cases, and the time period not yet encompassing a significant laparoscopy rate.

Conclusion

The recurrence rate is low in early-stage colon cancer, with the majority of recurrences occurring within the first 3 years. Histologic factors have a significant impact on recurrence and may allow a less intense follow-up regimen in these patients. Therefore, these results suggest that long-term follow-up plans should be tailored according to individual risk factors, taking into account multiple disease factors, which may have not only an economic impact but also on the patient's quality of life.

Statement of Ethics

All procedures in this study were in accordance with the ethical standards and with the Helsinki Declaration of 1964. All patients at our institution sign a consent form on admission allowing their data to be used. The Ethics Committee approved the present work. The ethics opinion document has the following identification: Parecer CES. 109/024.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Paula Ferreira Pinto and Mariana Peyroteo: design of the work; acquisition, analysis, interpretation of data; and writing of the manuscript. Catarina Baía, Mariana Marques, and Maria João Cardoso: drafting of the work and acquisition of data. José Flávio Videira and Joaquim Abreu de Sousa: revision of the manuscript and acceptance for publication.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article (and/or) its supplementary materials.

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Research Article

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Real-Time Gastric Juice Analysis in Cirrhotic Patients: Can We Avoid Unrewarding Gastric Biopsies?

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Keywords
Cirrhosis · *H. pylori* · Gastric precancerous lesions · Gastric juice analysis · Ammonia · pH

Abstract
Background: To search for *H. pylori* infection and gastric precancerous lesions in cirrhotic patients is worthwhile when considering the high incidence of peptic ulcers and gastric cancer in these patients. We tested if gastric juice analysis allows to avoid unrewarding gastric biopsies. ***Methods:*** This prospective study enrolled consecutive patients with liver cirrhosis who underwent upper endoscopy with standard gastric biopsies. Real-time gastric juice analysis was performed with a specific device (EndoFaster®) that test ammonium concentration for *H. pylori* diagnosis, and pH values to suspect extensive atrophy/metaplasia involving gastric body mucosa. Sensitivity, specificity, positive predictive value, negative predictive value (NPV), the overall accuracy, and the likelihood ratio were calculated for both *H. pylori* infection and extensive precancerous lesions on gastric mucosa. ***Results:*** A total of 78 cirrhotic patients (males: 55; mean age: 66 ± 12 years) were enrolled. When considering as positive EndoFaster® results when at least one of two (ammonium and pH levels) tests were positive, the NPVs were as high as 89% and 86%, respectively, to rule out *H. pylori* and extensive precancerous lesions on gastric mucosa, with an overall accuracy of 83% and 74%. ***Conclusions:*** This study supports the evidence that real-time gastric juice analysis allows to avoid clinically unrewarding and potentially unsafe gastric biopsies in a definite portion of cirrhotic patients, but more data are needed.

Análise do suco gástrico em tempo real em pacientes cirróticos: podemos evitar biópsias gástricas insatisfatórias?

Palavras Chave
Cirrose · *H. pylori* · Lesões pré-malignas gástricas · Análise do suco gástrico · Amónia · pH

Resumo
Introdução/Objetivo: A pesquisa de infeção *H. pylori* e lesões pré-malignas gástricas em doentes cirróticos é relevante, considerando a elevada incidência de úlceras pépticas e cancro gástrico nesta população. Avaliámos se a análise do suco gástrico permite evitar biópsias gástricas desnecessárias. ***Métodos:*** Estudo prospetivo

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incluindo doentes cirróticos consecutivos submetidos a endoscopia digestiva alta com biópsias gástricas. Foi realizada análise do suco gástrico em tempo real com dispositivo EndoFaster®, que avalia a concentração de amónia para diagnóstico de *H. pylori* e o pH para avaliação de atrofia/metaplasia extensa da mucosa gástrica. Calculámos a sensibilidade, especificidade, valor preditivo positivo (VPP), valor preditivo negativo (VPN), acuidade global e *likelihood ratio* para a infeção por *H. pylori* e lesões gástricas pré-malignas extensas. ***Resultados:*** Foram incluídos 78 doentes cirróticos (sexo masculino: 55; idade média: 66 ± 12 anos). Considerando resultados positivos do EndoFaster® quando pelo menos um dos dois testes (amónia e pH) apresentava valor positivo, os VPNs atingiram 89% e 86% para exclusão de infeção por *H. pylori* e lesões pré-malignas extensas na mucosa gástrica, respetivamente, com uma acuidade global de 83% e 74%. ***Conclusão:*** Este estudo suporta que a análise do suco gástrico em tempo real permite evitar biópsias gástricas clinicamente desnecessárias e potencialmente inseguras numa determinada percentagem de doentes cirróticos. No entanto, são necessários mais dados.

Introduction

Patients with liver cirrhosis have several alterations on the gastroduodenal mucosa that may impair the repair processes following an injury [1, 2]. Indeed, these patients are at higher risk of developing peptic ulcer, despite *H. pylori* prevalence – namely the main factor for peptic ulcer development – is similar to that of controls [2, 3]. Some evidences also suggest that the incidence of gastric cancer is increased in cirrhotic patients [4]. In detail, the risk of developing gastric cancer was fund to be increased by 1.7- and 5-fold in patients <60 years and >75 years old, respectively, and by 2.6-fold cumulatively as compared to the general population [4]. In the large majority of cases, gastric cancer is preceded by precancerous lesions, including extensive atrophy or metaplasia involving both antrum and gastric body mucosa [5], and the intestinal metaplasia is frequently detected on gastric mucosa of cirrhotic patients [6]. Therefore, to search for *H. pylori* infection and precancerous lesions by taking standard biopsies on gastric mucosa during upper endoscopy is worthwhile in these patients. However, clotting impairment due to both platelets and coagulation factors reduction due to liver cirrhosis may potentially increase the risk of bleeding following gastric biopsies [7, 8]. For instance, bleeding complications during percutaneous liver biopsy, central venous cannulation, paracentesis and thoracocentesis procedures, as well as surgical interventions, were reported to occur more frequently in cirrhotic patients than controls [7]. However, taking into account data of 9 studies with 587 cirrhotic patients who underwent gastric biopsies, no major bleeding was observed when platelets count was >45,000/mm^3 and prothrombin activity >45% [8]. Therefore, a biopsy-free test able to suspect or rule out *H. pylori* infection and extensive precancerous lesions in the stomach could be advantageous. By performing a real-time analysis of gastric juice, the current version of EndoFaster® – a device firstly developed on 2005 [9] – is able to accurately discard the presence of *H. pylori* infection and extensive precancerous lesions through measure of ammonium concentration and pH levels, respectively [10]. In detail, a systematic review of several studies showed that when the results of EndoFaster® testing are negative, the negative predictive value (NPV) for excluding *H. pylori* infection and extensive precancerous lesions on gastric mucosa is approaching 100% [10]. In detail, by considering data of 11 studies, the NPV to rule out either *H. pylori* infection or extensive precancerous in the stomach was >96% in all, but two studies showing values of 84.3%–85.4% [10]. However, to our knowledge, no data on the use of EndoFaster® in cirrhotic patients are available. Indeed, the modifications of ammonia content in the gastric juice of cirrhotic patients [11], from one side, and the alterations of gastric acid output [12], in the other, may potentially affect the accuracy of gastric juice analysis with such a device. We therefore designed this study to evaluate the accuracy of gastric juice analysis to rule out *H. pylori* infection and extensive precancerous lesions in patients with liver cirrhosis, aiming to avoid clinically useless and potentially unsafe gastric biopsies in these patients.

Materials and Methods

Study Design and Patients

In this prospective study, consecutive cirrhotic patients who underwent upper endoscopy for any indication in our endoscopy unit were considered for the enrolment. Inclusion criteria were the presence of a documented liver cirrhosis on the basis of clinical findings, abdominal sonogram, laboratory parameters, or liver biopsy and age >18 years. Patients with marked clotting impairment (platelet counts <50,000/mm^3 and/or international normalized ratio (INR) > 1.5) were excluded [8]. Informed consent was obtained for all procedures. In detail, following explanation on the clinical research, patients

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were informed and signed the consent for both procedures (endoscopy with biopsies and real-time gastric juice analysis) and anonymous use of their data for scientific purposes. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Since no experimental drugs were administered, no additional costs or procedures for the patients were required, no identification of patients was allowed, and no funds were received, a formal approval by Investigational Review Boards could be waived.

Endoscopic Procedures

All patients underwent endoscopy and standard biopsy sampling (2 antrum, 1 angulus, and 2 gastric body) of gastric mucosa were performed with standard 5-mm biopsy forceps. After removing the biopsy specimens, we waited for haemostasis to take place. Biopsies were used for histological assessment and to search for *H. pylor*i. The infection was considered present when histological assessment revealed the presence of bacteria together with a feature of chronic active gastritis. Extensive atrophy or intestinal metaplasia were considered present when these histological findings involved both antral and gastric body mucosa, as reported in the RE.GA.IN system and graded according to the OLGA-OLGIM systems [13, 14].

Gastric Juice Analysis

Gastric juice analysis was performed by using EndoFaster® (Manufacturer: NISO Biomed S.r.l, Turin; Italy; Italian distributor: Waldner Tecnologie Medicali, Trento; Italy). The device was provided for 2 months to the endoscopic unit without any adjunctive cost for both hospitals and patients. In detail, the device was interposed between the endoscope and the suction system, so that no adjunctive invasive procedure was required and without any discomfort for the patient [10]. During endoscopy, lumen washing was avoided until the stomach was reached and until 3 mL of gastric juice were aspirated. *H. pylori* diagnosis was based on the determination of ammonium concentration, as a consequence of the urease activity of the bacterium within 60–90 s that is during endoscopy. The device performs in the meantime also H^+ concentration. The infection was considered to be present when the ammonium concentration in gastric juice was >62 ppm, whilst extensive atrophy/metaplasia involving gastric body mucosa was suspected when pH values of were >4.5, as reported elsewhere [15, 16].

Table 1. Demographic and clinical characteristics

Variable	Finding
Male/female	55/23
Age, mean±SD, years	66±12
Cirrhosis aetiology	
Hepatitis C virus	23
Hepatitis B virus	7
Hepatitis C virus + Hepatitis B virus	2
Alcohol	12
Primary Biliary Cholangitis	4
Non-alcoholic steatohepatitis	20
Autoimmune	1
Wilson's disease	1
Cryptogenic	8
Cirrhosis Child-Pugh class	
A	49
B	22
C	7
Upper endoscopy indication	
Portal hypertension evaluation	31
Varices follow-up	36
Melena	3
Anaemia	6
Dyspepsia	2
Ongoing proton pump inhibitor therapy	38
Varices	
Absent	9
Oesophageal	66
Oesophageal plus gastric	3
Congestive gastropathy	
Absent	22
Mild	26
Marked	30
OLGA/OLGIM score	
0	41
I	26
II	6
III	4
IV	1

Statistical Analysis

Frequencies, percentages and means values with standard deviations were calculated for all observations. Sensitivity, specificity, positive predictive value (PPV), NPV, the overall accuracy, and the likelihood ratios were calculated by considering the histology as gold standard for both *H. pylori* infection and extensive precancerous lesion on gastric mucosa. To assess the cumulative impact of gastric juice analysis for clinical practice, the accuracy values were also calculated by combining data of both results of testing, by

Table 2. Accuracy of EndoFaster® for either *H. pylori* infection or extensive precancerous lesions on gastric mucosa

	H. pylori	Precancerous lesions
Sensitivity	65 (46–85)	68 (50–86)
Specificity	75 (63–86)	60 (47–74)
Positive predictive value (PPV)	52 (34–70)	45 (29–61)
Negative predictive value (NPV)	84 (73–94)	80 (68–92)
Accuracy	72 (62–82)	63 (52–74)
Likelihood ratio positive	3	2
Likelihood ratio negative	0.5	0.5

Percentages and their 95% confidence intervals.

considering eventually missed diagnosis when both tests were negative, but histology revealed at least one of the investigated conditions (*H. pylori* and/or precancerous lesions).

Results

Demographic and the main clinical characteristic of the 78 cirrhotic patients enrolled in this study are provided in Table 1. Beyond varices and congestive gastropathy, at upper endoscopy 4 (5.1%) patients had erosive oesophagitis, 1 (1.3%) Barrett's oesophagus, 16 (20.5%) erosive gastritis, 4 (5.1%) gastric ulcer, 8 (8.2%) erosive duodenitis, and 1 (1.3%) duodenal ulcer. No case of bleeding following gastric biopsies occurred. At histology, *H. pylori* infection was diagnosed in 23 (29.5%) patients, whilst extensive atrophy/metaplasia – that is involving antral and gastric body mucosa, irrespective of grade – was present in 23 (29.5%) patients, and a grade III-IV OLGA/OLGIM was overall detected in 5 (6.4%) cases. The values of sensitivity, specificity, PPV, NPV, the overall accuracy, the likelihood ratios positive (LH+) and negative (LH−) for *H. pylori* infection were 65%, 75%, 52%, 84%, 72%, 3, and 0.5, and that for extensive precancerous lesions were 68%, 60%, 45%, 80%, 63%, 2, and 0.5 (Table 2). In detail, NPVs of 84% and 80% were found, respectively, in ruling out *H. pylori* infection and extensive atrophy/metaplasia on gastric mucosa. However, by considering as positive EndoFaster® results when at least one of two tests (ammonium and pH levels) were positive, the NPVs increased to 89% and 86%, respectively. These values indicate that a missed *H. pylori* infection occurred in only 8 cases every 100 patients with negative EndoFaster result for ammonium concentration, and a missed extensive precancerous condition in only 9 cases every 100 patients with normal pH values.

Discussion

The prevalence of gastric and duodenal ulcers has been reported to be 10-fold higher in cirrhotic patients than in controls [17], accounting for a 7.4–16% rate of upper gastrointestinal bleeding, with a 5-fold increased mortality rate in these patients [2]. Data of a meta-analysis showed that *H. pylori* infection significantly increases peptic ulcer risk in these patients, with an estimated odds ratio of 2.70 (95% CI = 1.91–3.82) as compared to controls [18]. Moreover, some studies suggested a potential role of *H. pylori* in causing hepatic encephalopathy by ammonia production in the stomach, although data are largely controversial [19]. On the other hand, the incidence of upper gastrointestinal (oesophageal, gastric, pancreatic) cancers in patients with cirrhosis was reported to be higher as compared to controls [20]. In detail, the incidence of gastric cancer was 2.6-fold increased in these patients as compared to that expected in the general population [4]. Moreover, gastric epithelial cell proliferation is increased in patients with cirrhosis, particularly when congestive gastropathy and *H. pylori* infection were present [21], and intestinal metaplasia is frequently detected in these patients [6, 22]. In detail, the present study showed a prevalence of extensive precancerous lesions on gastric mucosa as high as 30%, with a stage III-IV OLGA/OLGIM present in 6.4% of cases. The latter value is in agreement data of previous Italian studies showing a frequency ranging from 2.3 to 7.8% in routine endoscopic examinations [16]. These

patients deserve scheduled follow-up to detect early neoplastic lesions amenable of endoscopic removal [23]. Some evidences suggest that the endoscopic submucosal dissection is safely performed also in cirrhotic patients, allowing to avoid a more harmful surgical approach [24]. All these observations clearly suggest how it is clinically worthy to exclude the presence of both *H. pylori* infection and precancerous lesions at endoscopy in cirrhotic patients.

This is first study that evaluated the accuracy of real-time gastric juice analysis by EndoFaster® for ruling out both *H. pylori* infection and extensive precancerous lesions on gastric mucosa in patients with cirrhosis. Our data found that when the cumulative results of the test were considered, a NPV of 89% and 86% in excluding *H. pylori* infection and extensive atrophy/metaplasia on gastric mucosa, respectively, were found, indicating an acceptably high precision for these purposes. Indeed, the NPV for *H. pylori* diagnosis we observed was consistent with the 92.3% reported for the ^{13}C-urea breath testing in these patients [25]. Therefore, gastric juice analysis during endoscopy allows to safely avoid useless biopsies on normal appearing gastric mucosa, a procedure particularly advantageous in cirrhotic patients, when considering their clotting impairment [7, 8]. However, a negative EndoFaster® result decreases the post-test probability of finding both *H. pylori* infection and extensive precancerous, but in those situations where the bleeding risk is not prohibitive, biopsies should still be performed. On the other hand, a positive EndoFaster® increases the post-test probability and should lead to performing biopsies, when considering that both PPV and positive likelihood ratio values are not enough elevated.

Although satisfactory, the data of this study would suggest that the EndoFaster® performs less well than what observed in patients without liver cirrhosis. Indeed, data of previous studies found NPV values as high as 96% and 97% for *H. pylori* and precancerous lesions, respectively, in more than 2,000 investigated patients [10]. The reasons of a lower performance of gastric juice analysis in cirrhotic patients remain unclear. The relatively low sample size (N = 78) of cirrhotic patients studied in the present study may have played a role in estimating the EndoFaster® performance. However, the a posteriori calculation of the study's power with an alfa error of 0.05 was 91.3%, by considering a NPV of 86% we computed and the 96% found in non-cirrhotic patients [10]. On the other hand, the levels of ammonium concentrations in gastric juice – that could potentially impair ammonium testing with EndoFaster® – of patients with liver cirrhosis with or without *H. pylori* infection were reported to be very similar to that of matched controls [11]. On the other hand, gastric acid output – that could potentially impair pH evaluation with EndoFaster® irrespective of extensive gastric mucosa atrophy – has been inconsistently reported to be lower, similar or increased compared to controls [26]. Therefore, the findings of present study should be confirmed in further studies.

Conclusions

This study adds evidence that real-time gastric juice analysis might avoid clinically unrewarding and potentially unsafe gastric biopsies in a definite portion of cirrhotic patients, also reducing the environmental impact [27], but more data are needed.

Statement of Ethics

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Sergio Peralta and Angelo Zullo conceived the study. Sergio Peralta, Vincenza Calvaruso, Francesca Di Giorgio, Vincenzo Di Martino, and Ada Maria Florena provided data acquisition; Angelo Zullo analysed data and wrote the manuscript providing critical revision. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data are available following reasonable enquiries directed to the first author, Sergio Peralta.

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Under the Hood: An Easy Method for Lesions Retrieval

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Keywords
Endoscopic submucosal dissection · Retrieval · Capuchon · Gastrointestinal lesion · Specimen

Debaixo do capuz: um método fácil de extração de lesões

Palavras Chave
Disseção endoscópica da submucosa · Extração · Capuz · Gastrointestinal · Espécime

Endoscopic submucosal dissection (ESD) allows for effective resection of large gastrointestinal lesions with minimal risk of recurrence. The goal of ESD is to provide *en bloc* removal of lesions with free margins. Accurate pathological evaluation of the resected specimen is crucial for guiding patient management. In some cases, the dissected specimen is too large, hampering its retrieval through the cardia, upper esophageal sphincter or the anal canal [1]. In other cases, mostly in the colon and duodenum [2], the tissue is soft, and its retrieval can cause specimen fragmentation. Conventional endoscopic nets are useful for small or middle-size specimens but can fragment large specimens. Some other techniques were described. However, most use non-conventional devices not easily available [3, 4].

Tumor extraction through defecation is a simple technique [5] but has limitations, particularly for large lesions requiring deep sedation over several hours. In these cases, immediate retrieval of the specimen is not possible, affecting pathological assessment.

Herein, we describe the "under the hood" technique, using a standard endoscope to overcome this issue. This technique is easy to use and enables the retrieval of large gastrointestinal specimens intact, avoiding fragmentation. The device used is a standard bell-shaped latex tool for foreign body removal (ENDOLINE®HOOD, Prince Medical, Ercuis-France). It has a tip diameter of 8 mm and a distal diameter of 40 mm, is 75 mm long, and is easily attachable to a conventional gastroscope's tip (shown in Fig. 1).

Case Reports

A 60-year-old woman was referred for ESD resection of a large sigmoid colon polyp. Large size and complex morphology made margin delineation and size estimation difficult. After *en bloc* ESD, the specimen could not be passed

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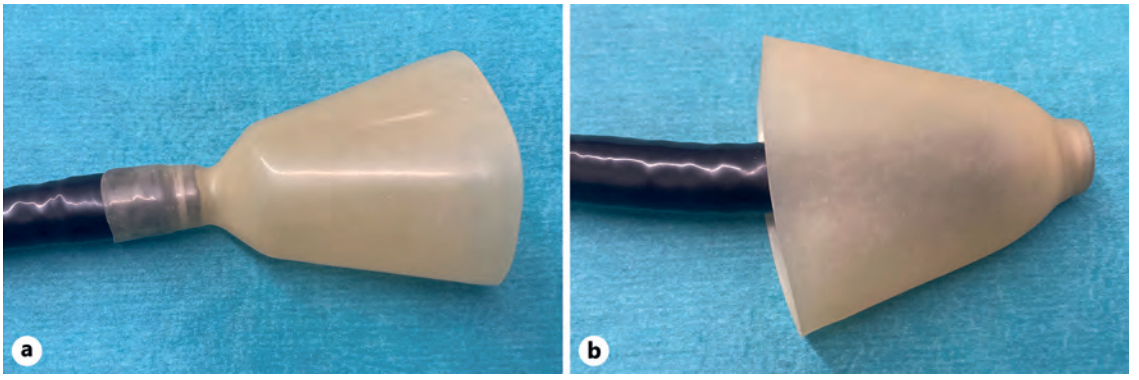

Fig. 1. a ENDOLINE®HOOD: it has a tip diameter of 8 mm, distal diameter of 40 mm, a length of 75 mm and can be easily attached to the tip of a conventional gastroscope. **b** Inverted ENDOLINE®HOOD, the way of intraluminal insertion.

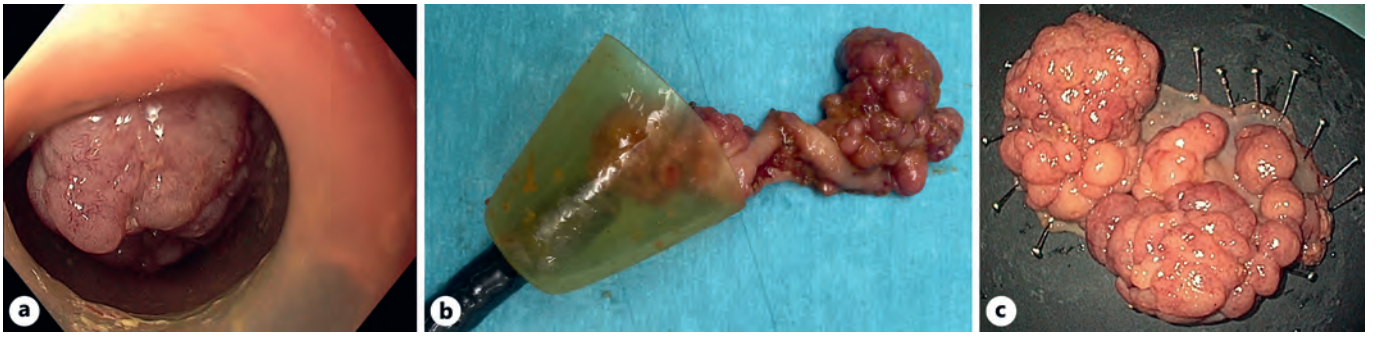

Fig. 2. a Resected specimen being captured into the hood. **b** Specimen retrieved *en bloc*. **c** Colonic specimen was intact and 80 × 35 mm in size.

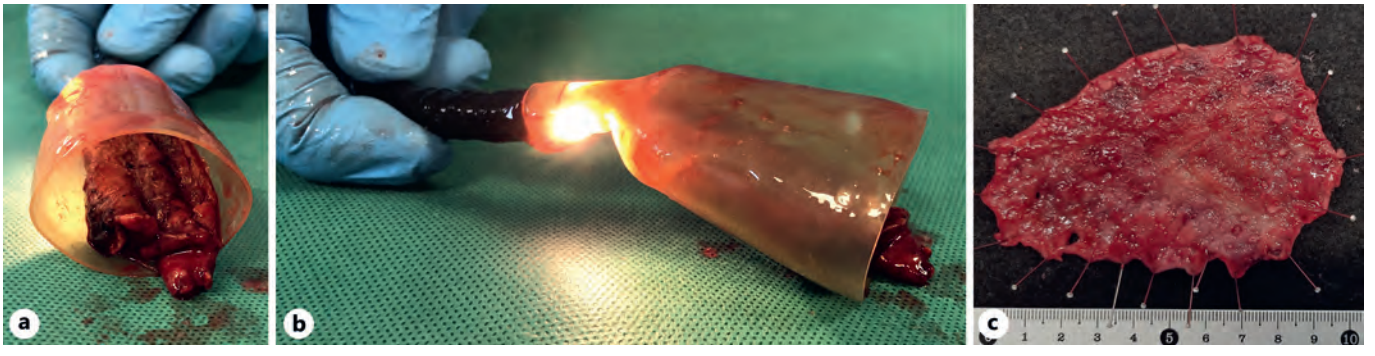

Fig. 3. a Gastric specimen inside the hood. **b** Lateral view of the ENDOLINE®HOOD, demonstrating the good adaptation of the device to the endoscope even with specimen weight. **c** Undamaged gastric specimen 100 × 68 mm in size.

through the anal canal despite several attempts with different conventional nets.

We decided to use the "under the hood" technique. The hood was assembled on the tip of the 9.9 mm endoscope and inserted using lubrification. After pushing the instrument gently into the proximal rectum, the scope was slowly withdrawn to deploy the hood. Then, the specimen was gently suctioned into the hood and withdrawn. The specimen was intact, measuring 80 × 35 mm (shown in Fig. 2). Histopathologic analysis revealed an adenoma with high-grade dysplasia and free margins.

The second case refers to a 68-year-old male patient who was planned for ESD resection of an 8 cm dysplastic flat lesion (Paris 0-IIb) in the proximal gastric body. It was not possible to pass the specimen through the cardia following *en bloc* ESD. After assembling the hood, the scope was inserted into the stomach. Afterward, the scope was withdrawn to deploy the hood, and the specimen was gently captured by suction.

The scope was withdrawn with suction, retrieving a 10 cm specimen (shown in Fig. 3). Histopathologic analysis revealed an adenocarcinoma with free margins.

This technique is effective regardless of specimen size and the diameter of the endoscope's working channel. It utilizes a widely available device in most endoscopy units. However, it is contraindicated for patients with latex allergy. In conclusion, this simple, easy, cheap, and effective approach should be considered for retrieving large upper and lower gastrointestinal specimens.

Statement of Ethics

An informed consent was obtained from patients for publication of the details of their medical case and accompanying images. Ethical approval was not required according to local norms.

Conflict of Interest Statement

No authors report potential conflicts of interest relevant to this manuscript.

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Author Contributions

Execution: Francisco Baldaque-Silva, João Pereira, Leonor Guedes-Novais, and Pedro Antunes. Critically review of manuscript for intellectual content and approval of final submitted draft: Francisco Baldaque-Silva, João Pereira, Leonor Guedes-Novais, Pedro Antunes, Masami Omae, and Henrik Maltzman.

Data Availability Statement

All relevant clinical data of this case report study are included in this article. Further inquiries can be directed to the corresponding author.

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X-Tackling the Path to Closure: Post-Endoscopic Submucosal Dissection Defect Resolution Strategies

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Keywords
Endoscopy · Endoscopic submucosal dissection · Endoscopic suturing · Hemorrhage

X-Tackling: estratégias para encerramento de escaras após disseção endoscópica da submucosa

Palavras Chave
Endoscopia · Disseção endoscópica da submucosa · Sutura endoscópica · Hemorragia

Introduction

Mucosal defect closure after endoscopic submucosal dissection (ESD) may reduce the likelihood of delayed bleeding and perforation [1]. Several devices are currently available for the closure of mucosal defects, including through-the-scope (TTS) and over-the-scope (OTS) clips, and OTS endoscopic suturing devices. However, defect closure can be technically demanding, with TTS clips typically limited to defects up to 20 mm, whereas OTS clips and suturing equipment require endoscope removal for device placement. More recently, the X-Tack Endoscopic HeliX Tacking System™, a novel TTS suturing device, has emerged as a potential tool for overcoming technical issues related to previous closure devices. We present 2 cases of gastric post-ESD defect closure with X-Tack, highlighting the technical challenges and main steps required to achieve high-quality closure without exposed submucosal tissue.

Case 1

A 73-year-old woman with a 15-mm Paris 0-IIb dysplastic lesion of the posterior wall of the antrum was referred for ESD (Fig. 1a). En bloc ESD was performed (Fig. 1b), and the 25-mm mucosal defect was closed with X-Tack in a "Z" pattern (Fig. 1c). However, the placement of the tacks was suboptimal leading to closure of the central part of the scar, leaving two areas of exposed submucosa at the edges. High-quality closure was achieved with the additional placement of four TTS clips at the edges, only possible due to the previously achieved proximity (Fig. 1d).

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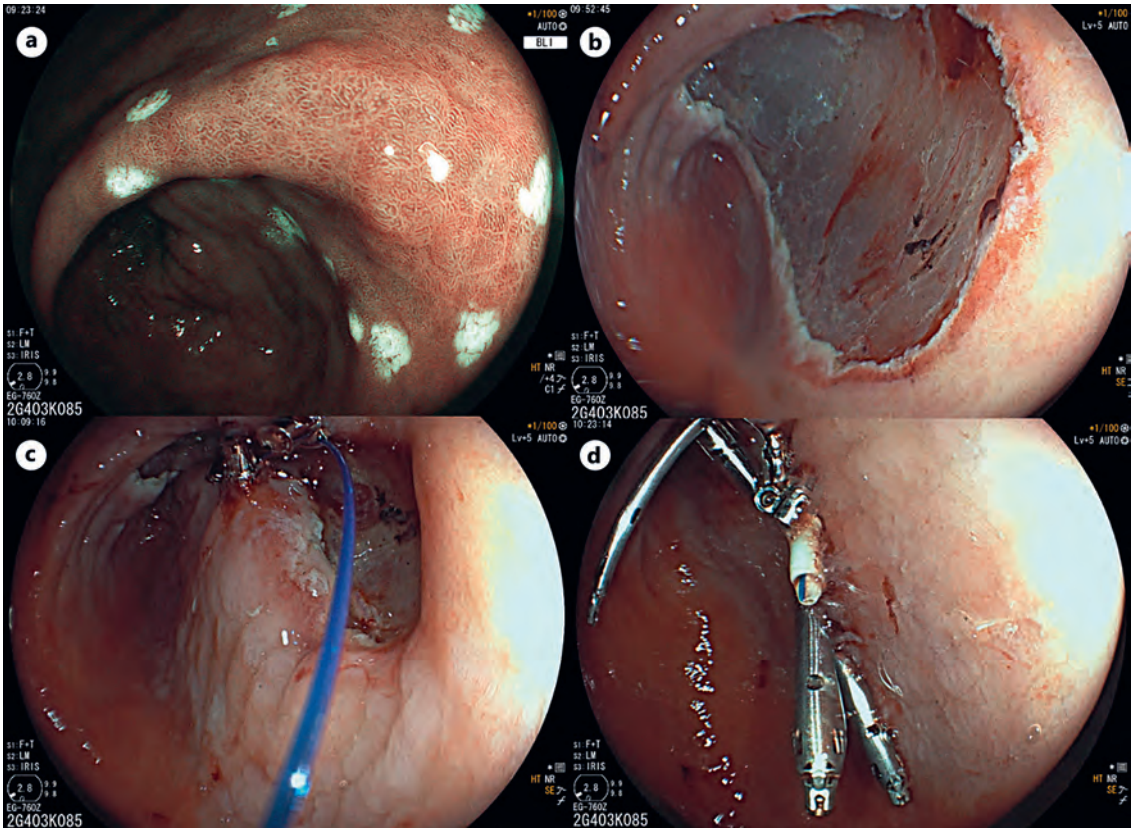

Fig. 1. a 15-mm Paris 0-IIb dysplastic lesion of the posterior wall of the antrum. **b** Post-ESD mucosal defect. **c** Mucosal defect after closure with X-Tack system: visible submucosal tissue at the edges of the defect due to tack suboptimal placement. **d** Complete closure of the defect after placement of TTS clips at both edges.

Case 2

A 55-year-old man was referred for ESD of a 13-mm Paris 0-IIa dysplastic lesion of the lesser curvature of the antrum (Fig. 2a). En bloc ESD was successfully performed (Fig. 2b). The 25-mm mucosal defect was subsequently closed using X-Tack in a "Z" pattern (Fig. 2c and online suppl. Video 1; for all online suppl. material, see https://doi.org/10.1159/000541865). High-quality closure was achieved with additional placement of one TTS clip (Fig. 2d).

Both patients were discharged the following day and presented with no complications at 1-month follow-up. The risk of delayed bleeding post-gastric ESD ranges from 5% to 10% [2]. Routine coagulation of visible vessels at the end of the procedure has been shown to significantly reduce the risk of delayed bleeding [3]. There is currently insufficient evidence to support the routine implementation of additional techniques, such as mucosal closure using suturing devices. Despite limited data, mucosal closure with the new X-Tack device may be considered as a potential add-on to coagulation of visible vessels at the end of gastric ESD especially in patients at higher risk of delayed bleeding, such as those receiving antithrombotic therapy.

The X-Tack comprises four steel helix tacks connected by a 3-0 polypropylene suture, allowing the placement of tacks into adjacent healthy tissue, followed by cinching to hold the suture securely [4]. This method allows the management of sizable and deeper defects where conventional TTS and OTS clips may be insufficient. Studies in porcine models have confirmed the effectiveness of X-Tack in closing mucosal defects ranging from 20 mm to 50 mm [5]. More recently, a multicenter study concluded that the X-Tack provides a practical approach for repairing defects of up to 30 mm [6]. Larger defects may warrant additional sutures or a double-closure technique for optimal quality in up to 25% of cases [6]. Despite a lack of standardized suturing technique, "Z" patterns have been previously reported as more adequate for linear defects rather than for circular or irregular defects [7]. Nonetheless, precise tack placement is paramount to avoiding visible submucosa, precluding high-quality closure

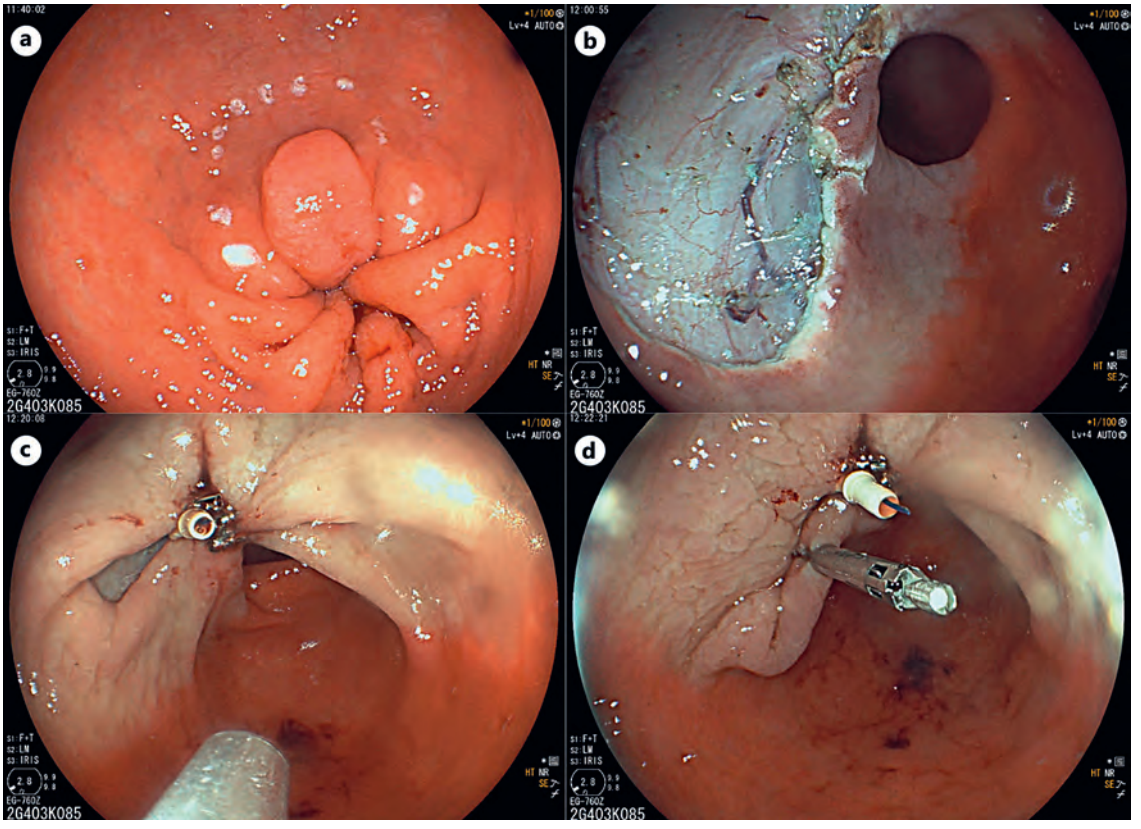

Fig. 2. a 13-mm Paris 0-IIa dysplastic lesion of the lesser curvature of the antrum. **b** Post-ESD mucosal defect. **c** Mucosal defect after closure with X-Tack system. **d** Complete closure of the defect after placement of one TTS clip.

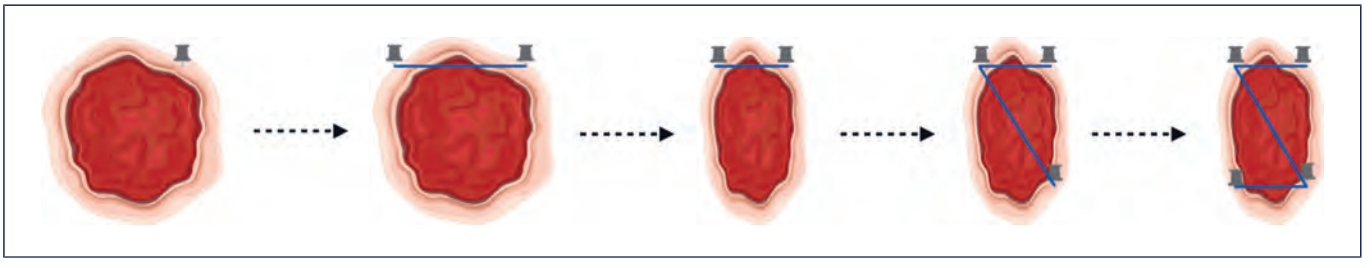

Fig. 3. X-Tack placement: the first tack should be placed distally to the margin, while the second tack should be placed vertically aligned (and not diagonally) with the first tack. The third tack should be applied diagonally to the second one, but also outside of the proximal edge of the lesion, while the fourth tack should be placed aligned and not diagonally to the third one (Z pattern).

(Fig. 1c). Based on our initial experience, we recommend that the closure sequence of gastric post-ESD defects in the antrum should be as detailed in Figure 3.

Although this device has demonstrated safety and effectiveness, allowing for earlier discharge of patients, the X-Tack appears to be best suited for addressing superficial rather than full-thickness defects. While successfully closed perforations or post-intervention defects revealed sustained long-term outcomes (7.2 ± 3.3 months), recent data showed that fistula closure was linked to lower success rates (57.1%) [8]. This is understandable, as the helical tacks are designed to achieve mucosal apposition by engaging the muscularis propria, which may limit their effectiveness due to the lack of full-thickness anchoring.

In conclusion, these cases underscore the ability of X-Tack to offer a practical solution for closing large mucosal defects after endoscopic resection. While demonstrating efficacy in managing sizable defects, further research is needed to comprehensively evaluate its performance in comparison with other emerging alternatives like clip-endoloop and zipline techniques, especially concerning the ability to handle full-thickness defects and ensure long-term outcomes.

Statement of Ethics

Ethical approval was not required for this study in accordance with the local/national guidelines. The patient provided written informed consent for publication of the case and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There were no sources of funding in relation to this work.

Author Contributions

João A. Cunha Neves and Jéssica Chaves participated in the endoscopic procedure and writing – original draft, review, and editing. All authors critically revised the manuscript. Mário Dinis-Ribeiro and Diogo Libânio approved the final version of the manuscript and agreed to be accountable for the accuracy of this work. João A. Cunha Neves is the article guarantor.

Data Availability Statement

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

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Hypertrichosis Lanuginosa Acquisita: When Hair Unravels the Unseen

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Keywords
Paraneoplastic syndrome · Hypertrichosis · Colorectal cancer

Hypertrichosis Lanuginosa Acquisita: quando o cabelo revela o desconhecido

Palavras Chave
Síndrome paraneoplásico · Hipertricose · Neoplasia colorretal

We present the case of a 78-year-old male with a history of atrial fibrillation, arterial hypertension, dyslipidemia, and past smoking habits. His medication included perindopril, simvastatin, edoxaban, and omeprazole. The patient presented with a 9-month history of abdominal pain, diarrhoea, anorexia, and a significant weight loss exceeding 20 kg.

He also reported the appearance of a painful, red, and fissured tongue, which made eating difficult (Fig. 1). Additionally, he experienced abnormal hair growth characterised by elongated, thin, and soft hair on his face, ears, back, and abdomen, as well as in his eyelashes (Fig. 1, 2).

Diagnostic work-up, including a computed tomography scan and colonoscopy, revealed a large neoplasm in the cecum/ileocecal valve region, extending into the terminal ileum and ascending colon (Fig. 3). Histological analysis confirmed adenocarcinoma, staged as a cT4aN2M0.

Given the suspicion of paraneoplastic hypertrichosis, a dermatological evaluation was conducted. This confirmed the presence of fine, non-pigmented, lanugo-type hair extensively distributed over the patient's skin, along with glossitis and eyelash trichomegaly. These findings were consistent with Hypertrichosis lanuginosa acquisita (HLA).

During the diagnostic work-up, the patient presented to the emergency department with signs of bowel obstruction and an urgent right hemicolectomy was performed. The surgical and post-surgical courses were uneventful, and the patient was started on chemotherapy. After this, he noted a slight improvement in hypertrichosis. Subsequent assessments revealed disease progression and the patient died 6 months after the diagnosis.

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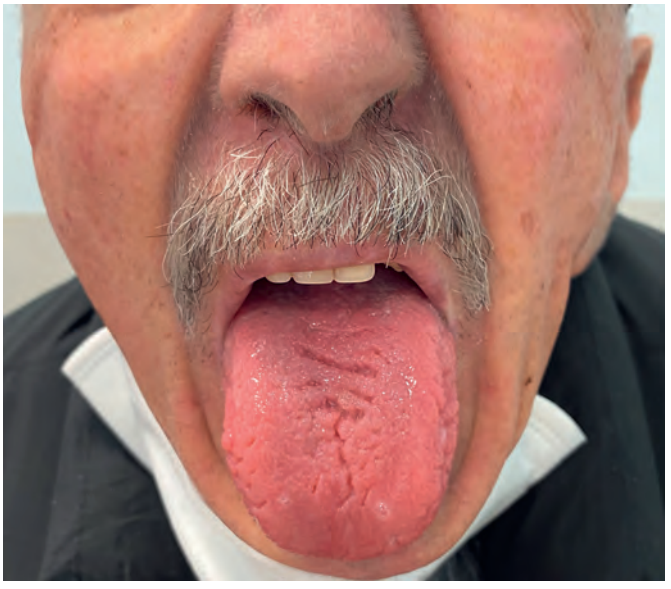

Fig. 1. Fissured tongue compatible with glossitis and elongated, soft, unpigmented hair around the nose.

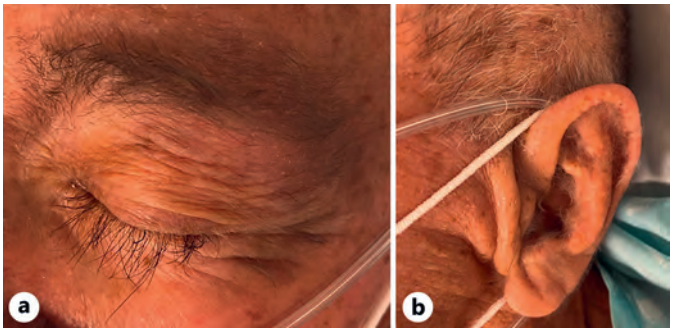

Fig. 2. Hypertrichosis lanuginosa acquisita presenting with trichomegaly of the eyelashes (**a**) and faint, unpigmented hair on the ear (**b**).

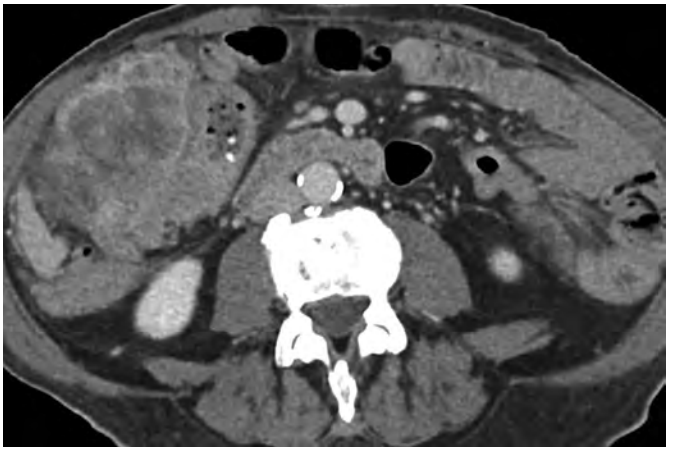

Fig. 3. Computed tomography (CT) showing neoplasia of the cecum/ileocecal valve region with transmural infiltration.

Discussion

Paraneoplastic HLA is a rare syndrome, with early case reports dating back to the late 19th century [1]. Despite its historical recognition, recent descriptions in the literature remain limited [2]. It affects more women than men but with a potential underreporting in men. The typical onset is between 40 and 70 years, often accompanied by glossitis, eyelash trichomegaly, and other paraneoplastic syndromes such as Acanthosis nigricans maligna. HLA needs to be differentiated from other causes of hypertrichosis, including endocrine or metabolic diseases (e.g., porphyria cutanea tarda and hyperthyroidism), and medication-related causes (e.g., cyclosporine, penicillamine, glucocorticoids, interferon, minoxidil, phenytoin, spironolactone, and cetuximab) [3].

In women, HLA is commonly associated with colorectal carcinoma, followed by lung and breast cancers. Conversely, in men, lung cancer predominates, followed by colorectal carcinoma. HLA may precede tumour diagnosis by approximately two and a half years. Still, its presence often indicates metastatic disease, associated with a poor prognosis, with a mean survival of less than 3 years. Successful tumour treatment can reverse abnormal hair growth [4].

The mechanism responsible for HLA is still unclear. Reports have linked anti-tumoural agents such as cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, to HLA. This underscores the potential involvement of epidermal growth factor signalling in HLA pathophysiology, given their role in both hair follicle development and numerous solid malignancies [5]. This case highlights the importance of considering malignancy in patients with unexplained excessive hair growth, particularly in men, and the poor prognosis associated with HLA.

Statement of Ethics

We obtained written informed consent from the participant's next of kin to publish the medical case details and any accompanying images. Ethical approval was waived according to local/institutional norms.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joana Revés and Catarina Gouveia contributed to the manuscript's design and wrote the manuscript. Catarina Bexiga and Alexandra Chaveiro provided significant revisions to the manuscript. All authors critically revised the manuscript and have approved the final version of the manuscript.

Data Availability Statement

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

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Hepatocellular Carcinoma with Vascular and Cardiac Involvement in a Young Patient with Non-Cirrhotic Hepatitis B: A Case Report

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Keywords
Hepatocellular carcinoma · Hepatitis B virus · Right atrial extension

Abstract
Introduction: Hepatocellular carcinoma (HCC) is a highly vascular malignancy with the potential for intravascular invasion. However, vascular extension into the cardiac chambers is extremely rare. ***Case Presentation:*** We present a 25-year-old male patient in whom the investigation of a cardiac murmur led to the discovery of an intracardiac mass that proved to be advanced-stage HCC with vascular invasion of the right heart. The patient had a previously unknown non-cirrhotic chronic hepatitis B virus (HBV) infection. Despite antiviral therapy and systemic treatment for HCC, he eventually died about 1 month later due to disease progression. ***Conclusion:*** This report highlights the importance of early HBV diagnosis and treatment for timely detection and management of HCC. Advanced-stage HCC, particularly with cardiac involvement, has an extremely poor prognosis.

Inês Botto and Juliana Serrazina shared first authorship.

Carcinoma hepatocelular com envolvimento vascular e cardíaco num jovem com hepatite B não cirrótica

Palavras Chave
Carcinoma hepatocelular · Vírus da hepatite B · Metastização auricular

Resumo
Introdução: O carcinoma hepatocelular é uma neoplasia com elevado risco de invasão vascular, porém, a invasão cardíaca está raramente descrita. ***Descrição do caso:*** Descreve-se um caso de um doente, do sexo masculino, de 25 anos, sem antecedentes de cirrose hepática, que se apresentou com queixas de cansaço, dispneia e perda ponderal. A investigação adicional mostrou um sopro cardíaco, resultante da invasão cardíaca direita por carcinoma hepatocelular e hepatite B crónica. Apesar da instituição da terapêutica dirigida ao carcinoma hepatocelular e terapêutica antiviral, verificou-se progressão da doença levando ao falecimento do doente um mês após o diagnóstico. ***Conclusão:*** Este caso destaca a importância do diagnóstico e tratamento precoces da hepatite B crónica, potenciando a deteção atempada do

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carcinoma hepatocelular. O carcinoma hepatocelular em estadio avançado, nomeadamente com invasão cardíaca, está associado a mau prognóstico.

Introduction

Hepatocellular carcinoma (HCC) is the sixth-most common cancer worldwide and accounts for 90% of all primary liver cancers [1]. Over 90% of HCC cases occur in the setting of chronic liver disease, with cirrhosis from several etiologies as the primary risk factor. Hepatitis B virus (HBV) infection is documented in approximately 50% of HCC cases [2]. HCC metastasis can occur in different locations, with the most affected sites being the lungs, lymph nodes, and bones. Despite being a highly vascular tumor with intravascular dissemination, cardiac involvement is a rare manifestation (1–4%) and is usually diagnosed in patients with known HCC during oncology follow-up or as an autopsy finding [3].

Case Report

A 25-year-old male patient from Guinea, in Portugal for 6 months, with no known medical history presented with a 2-week history of fatigue, exertional dyspnea, anorexia, and weight loss. He also mentioned abdominal pain for the last 4 days. The patient consumed 20 g of alcohol per week and had no history of drug consumption or tobacco smoking habits. He was employed as a construction worker and did not have any relevant travel history. Physical examination showed a systolic murmur in the tricuspid area, an enlarged liver and right upper quadrant pain, with no ascites or signs of chronic liver disease stigmata. The electrocardiogram revealed sinus tachycardia with a right bundle branch block and the chest radiograph showed an enlarged cardiac silhouette. An echocardiogram showed an intracardial mass in the right atrium (RA) (80 mm × 64 mm), obstructing the tricuspid valve and causing functional stenosis. His laboratory tests showed normocytic anemia (hemoglobin 11.6 g/dL [ref. 13–17.5]), slightly elevated liver enzymes (AST 91 U/L [ref. 0–34], ALT 68 U/L [ref. 10–49], GGT 68 U/L [ref. 0–60], ALP 393 U/L [ref. 35–105]), with normal bilirubin (1.12 mg/dL [ref. <1.2]), and elevated NT-proBNP (457 pg/mL [ref. <300]). He underwent a computed tomography scan of the thorax, abdomen, and pelvis, which revealed multiple coalescent lesions evolving mainly the left and caudate lobes, consistent with multicentric HCC (shown in Fig. 1). Additionally, macrovascular invasion was observed in the left portal vein, middle suprahepatic veins, and inferior vena cava, extending into the lumen of the right ventricle and atrium. The intracardiac component measured 9 × 7.5 × 6 mm (AP × T × L) (shown in Fig. 2). The computed tomography scan also identified bilateral pulmonary secondary lesions and signs of multiple segmental and sub-segmental bilateral pulmonary embolisms. Further investigation revealed an HBV infection (AgHbs positive, anti-Hbs negative, AgHbe positive, anti-Hbe negative) with a viral load of 1,160,000 IU/mL and an alpha-fetoprotein of 357,440 ng/mL (ref. <7). The patient was classified as Barcelona Clinic Liver Cancer (BCLC) Stage C due to the presence of extra-hepatic spread and portal invasion.

After being discussed at a multidisciplinary team meeting, the patient was initiated on a regimen of tenofovir (300 mg/day) and sorafenib (400 mg/day). A few days later, the patient developed gastrointestinal side effects and stopped therapy. Due to rapid clinical and liver function deterioration, a palliative option was considered, and he died 1 month after the diagnosis of disease progression.

Conclusion

It is estimated that 854,000 new cases of HCC are diagnosed per year, with a growing incidence worldwide, making HCC a major global health problem [1]. In approximately 50% of HCC cases worldwide there is a subjacent HBV infection [2]. Although cirrhosis is considered the primary risk factor for HCC, chronic hepatitis B has carcinogenic potential itself by several mutagenetic routes, and up to 30% of chronic hepatitis B-related HCCs arise in non-cirrhotic liver, mainly in Asian patients, and patients with a family history of HCC. Therefore, HCC surveillance is recommended in European guidelines not only in cirrhotic patients but also in hepatitis B carriers with risk factors (family history of HCC or Asian patients over 40 or 50 years old, in men and women, respectively) [1]. On the other hand, in 2019, the burden of HBV infection was significant globally, with an estimated all-age prevalence of chronic HBV infection at 4.1%, corresponding to approximately 316 million infected individuals [4]. Recent recommendations from the Centers for Disease Control and Prevention (CDC) suggest HBV screening at least once during a lifetime for adults aged ≥18 years [5].

The prevalence of metastatic disease in HCC has been reported to be 11.2–25.5%, with the lungs (55%), lymph nodes (41%) and bones (7%) being the most commonly affected sites [6]. HCC has a strong tendency for macrovascular invasion, with a high incidence of portal and hepatic vein thrombosis (35–44% and 2–12%, respectively) [7].

Direct tumor extension from the hepatic veins into the inferior vena cava and the RA is the primary mechanism of cardiac involvement in HCC, with a reported incidence of 1.4–4.9% [8]. Jun et al. [9] analyzed a cohort of 665 patients with HCC, 33 of which had RA invasion, and identified the following risk factors for its extension: invasion of the hepatic vein, simultaneous invasion of the portal vein and the inferior vena cava, the presence of

multinodular HCC and advanced disease stage (classified as modified TNM staging ≥ Iva). Tumor size and elevated alpha-fetoprotein levels are also associated with vascular invasion [10]. The clinical presentation of HCC with RA extension is primarily influenced by the size of the intracardiac component and can range from asymptomatic (39.5%) to bilateral lower limb edema (37.5%) and exertional dyspnea [11].

In this case, considering the presence of pulmonary metastasis and extensive liver involvement, systemic treatment emerged as the optimal option. However, due to the presence of pulmonary thromboembolism and the need for anticoagulation, as well as the presence of active hepatitis B infection, the utilization of bevacizumab-atezolizumab was precluded. Following the development of gastrointestinal intolerance to sorafenib, alternative therapies such as ramucirumab were considered. However, the deterioration in clinical functional status and liver function led to the progression to BCLC-D staging, preventing the initiation of a second-line systemic therapy. While aggressive approaches and multimodality have been reported in clinical cases, when HCC presents with cardiac involvement, it significantly restricts therapeutic options, and there is no consensus regarding the optimal treatment. In the absence of extrahepatic spread, transarterial chemoembolization (TACE) has been documented in earlier stages of HCC with atrial macrovascular invasion [12, 13]. Kolarich et al. [13] reported a retrospective series of 8 patients with macrovascular invasion treated with TACE, supplemented by lenvatinib in 4 cases, resulting in an 86 ± 19% reduction in intra-atrial tumor burden. Although surgery has shown good technical success, even in cases with extra-hepatic metastasis in patients with good hepatic reserve, with a 1-year survival of 29.2% in those undergoing non-curative surgery [14], the multicentric nature of the tumor burden precluded surgical intervention in our case. Wakayama et al. [14] described a retrospective cohort of 5 patients who underwent curative resection, all of whom experienced postoperative recurrence, with a median recurrence-free survival of 3.8 months. More recently, a case report detailed a HCC with RA involvement managed with multimodal therapy, incorporating systemic therapy followed by TACE and liver resection [15]. Despite the documentation of more aggressive and multimodality treatments in the literature, evidence regarding their efficacy and impact on survival remains sparse.

The prognosis for HCC with intra-cardiac involvement remains poor, with a median survival range of 1–4 months [15]. Cardiopulmonary complications include pulmonary embolism, heart failure, life-threatening arrhythmias, and systemic metastasis, with heart failure and sudden cardiac death being the primary causes of mortality, affecting up to 25% of patients [15].

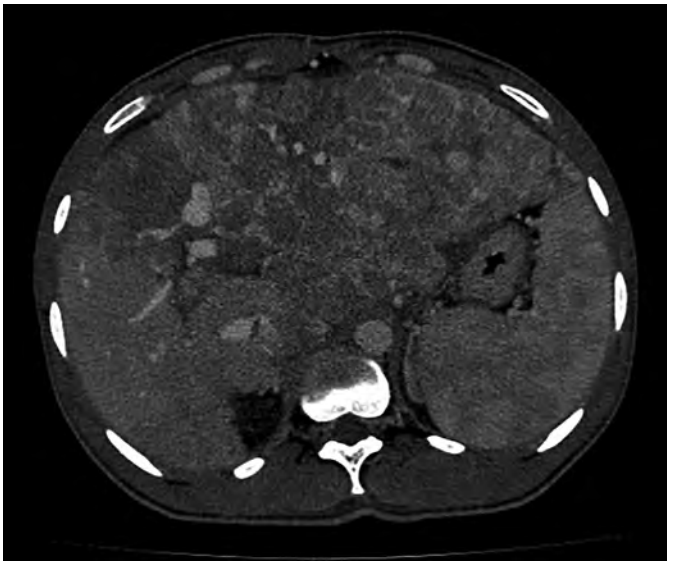

Fig. 1. CT scan of the abdomen. Heterogeneous hepatomegaly with multiple coalescent lesions involving most of the left and caudate lobes and also the right lobe, with arterial enhancement and washout, suggestive of multicentric HCC. CT, computed tomography.

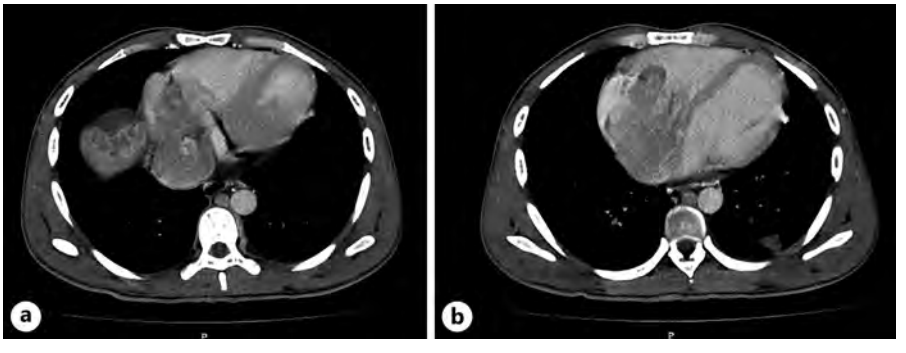

Fig. 2. CT scan of the thorax. **a** Macrovascular invasion of the left portal vein, middle suprahepatic veins, and inferior vena cava. **b** Tumoral extension into the lumen of the right ventricle and atrium, with an intracardiac component measuring 9 × 7.5 × 6 mm (AP × T × L). CT, computed tomography.

The severity and complexity of the case, combined with the patient's young age, make this an ethically challenging situation. The multidisciplinary interaction with oncology and palliative care was extremely important, not only for therapeutic decisions but also to ensure a dignified end of life.

This case report presents a rare case of HCC with extensive vascular and cardiac involvement in a young patient with previously unknown non-cirrhotic HBV infection. The presentation with mainly cardiac symptoms and the investigation of a cardiac mass that led to the diagnosis makes this case unusual and interesting. Furthermore, it highlights the importance of HBV screening and diagnosis since it may lead to timely detection of HCC – a crucial step in averting diagnosis at advanced stages.

We acknowledge the limitations of a case report approach such as the lack of ability to generalize or to infer a cause-effect association. Particularly in this rare presentation of HCC with cardiac involvement, further research is needed to determine the optimal approach to this complex situation.

Acknowledgment

The authors acknowledge the invaluable contributions and discussions with all members of the medical and nursing team involved in the care of this patient, particularly the multidisciplinary liver cancer team, whose invaluable contributions enhanced the management of this case.

Statement of Ethics

The authors have no conflicts of ethics. Ethical approval was not required for this study in accordance with local/national guidelines. A written informed consent was obtained from participants for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There were no funding sources relevant to this case report.

Author Contributions

Inês Botto and Juliana Serrazina (shared co-first authorship): drafting and preparation of the case report, literature research, and acquisition and interpretation of clinical data for the case report. Sofia Carvalhana, Carlos Freitas, Gonçalo Nogueira-Costa, and Helena Cortez Pinto: critically revising the case report and approving the final manuscript.

Data Availability Statement

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

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Aortoesophageal Fistula Mimicking Dieulafoy Disease: A Case Report

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Keywords
Esophageal fistula · Aortic diseases · Gastrointestinal bleeding · Computed tomography angiography · Aged 80 and over

Abstract
Introduction: Aortoesophageal fistula (AEF) is a rare and potentially fatal cause of upper gastrointestinal bleeding. The classic Chiari's triad of symptoms and typical endoscopic findings are not present in all patients, making diagnosis challenging. ***Case Presentation:*** An 86-year-old man was admitted to the emergency room for melena and hematemesis with hemodynamic instability. He had a previous hospitalization for cardioembolic stroke complicated by hematemesis of unknown etiology after initiation of anticoagulation (which was suspended), being discharged on aspirin. His medical history also included hypertension, diabetes, ischemic heart disease, and prostate cancer. On upper endoscopy, no lesions were found, despite the presence of a large non-mobilizable clot in the gastric fundus. He was admitted to the intensive care unit, and, on the next day, reassessment esophagogastroduodenoscopy was normal. On the eighth day of hospitalization, the patient presented with hemorrhagic shock due to new-onset hematemesis. Upper endoscopy revealed an esophageal 10-mm non-ulcerated mucosal depression with a visible vessel at 20 cm from the incisors, closed with 3 hemoclips. Thoracic CT angiography showed a brachiocephalic trunk aneurysm with aortoesophageal fistulization. He was deemed unsuitable for endovascular or surgical treatment. About 2 months later, the patient was admitted to the emergency room in cardiorespiratory arrest following an episode of hematemesis at home. ***Discussion:*** This report highlights the diagnostic and therapeutic complexity of AEF. Endoscopic treatment can be the main therapy in patients without indication for vascular intervention. The purpose was to palliate new bleeding episodes, maintaining a very poor prognosis.

Fístula Aortoesofágica que mimetiza Doença de Dieulafoy: Descrição de um caso

Palavras Chave
Fístula esofágica · Doenças da aorta · Hemorragia gastrointestinal · Angiografia por tomografia computadorizada · Idosos, 80 anos ou mais

Resumo
Introdução: A fístula aortoesofágica (FAE) é uma causa rara e potencialmente fatal de hemorragia digestiva alta. A tríade clássica de sintomas de *Chiari* e os achados

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endoscópicos típicos não estão presentes em todos os doentes, o que torna o diagnóstico desafiante. ***Apresentação do Caso:*** Um homem de 86 anos foi admitido na sala de emergência por melenas e hematemeses com instabilidade hemodinâmica. Apresentou internamento recente por AVC isquémico cardioembólico complicado por hematemeses de etiologia indeterminada após início de hipocoagulação (que foi suspensa), tendo alta sob aspirina. Acresciam os antecedentes de hipertensão, diabetes, cardiopatia isquémica e neoplasia prostática. Na endoscopia digestiva alta (EDA) não foram encontradas lesões, apesar de coágulo gigante não mobilizável no fundo gástrico. Foi internado em Unidade de Cuidados Intensivos, tendo repetido EDA no dia seguinte que foi normal. No oitavo dia de internamento, apresentou-se com choque hemorrágico devido a novo episódio de hematemeses. A EDA revelou, aos 20 cm, uma depressão da mucosa não ulcerada de 10 mm com vaso no leito, encerrada com 3 hemoclips. O AngioTC torácico mostrou aneurisma do tronco braquicefálico com fistulização aortoesofágica. O doente não era candidato a tratamento endovascular ou cirúrgico. Cerca de dois meses depois, o doente foi admitido na sala de emergência em paragem cardiorrespiratória após episódio de hematemeses no domicílio. ***Conclusão:*** Este caso destaca a complexidade diagnóstica e terapêutica da FAE. O tratamento endoscópico pode constituir a terapêutica principal nos doentes sem indicação para intervenção vascular. O objetivo é a paliação de novos episódios de hemorragia, mantendo-se o péssimo prognóstico.

Introduction

Aortoesophageal fistula (AEF) is a rare but catastrophic cause of upper gastrointestinal (GI) bleeding that occurs due to an abnormal communication between the aorta and the esophagus [1, 2]. The diagnosis should be suspected when upper GI bleeding occurs in the context of aortic disease, since the main etiology is secondary to aortic interventions, followed by native aortic aneurysm [2, 3]. Diagnosis is made based on clinical findings, upper endoscopy, and computed tomography angiography (CTA) [4–6]. The authors describe a rare case of an elderly patient who presented with intermittent bleeding and endoscopic findings suspicious of Dieulafoy disease, which were subsequently identified as an AEF.

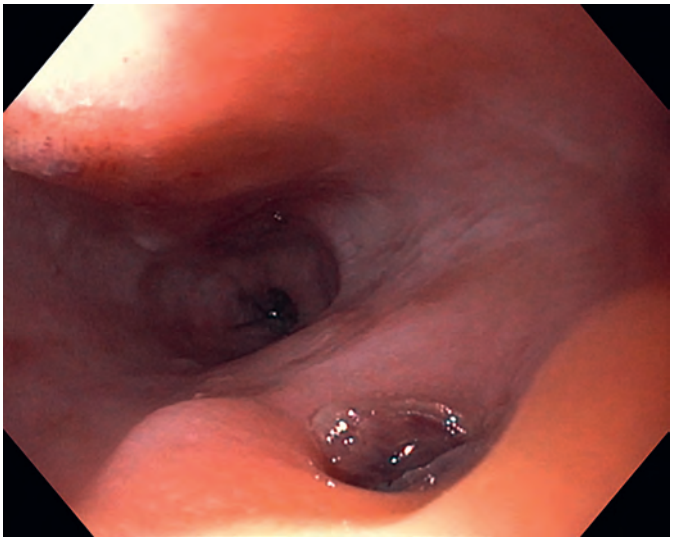

Fig. 1. Endoscopic image of AEF.

Case Report

An 86-year-old Caucasian male was admitted to the emergency department (ED) due to melena and hematemesis with hemodynamic instability. His medical history includes arterial hypertension, diabetes, ischemic heart disease, and prostate cancer under surveillance. The patient had a hospitalization 2 months prior for an ischemic cardioembolic stroke complicated by hematemesis of unknown etiology after initiation of anticoagulation, which prompted its cessation. He was discharged home on aspirin. After hospitalization, there were several visits to the ED due to melena, hematemesis, and symptoms related to anemia, requiring red blood cell transfusions and multiple upper endoscopies showing blood in the gastric lumen or no abnormal findings. Chronic medication also included bisoprolol, amlodipine, metformin, sitagliptin, esomeprazole, enzalutamide, and goserelin. He denied intake of alcohol or nonsteroidal anti-inflammatory drugs.

On admission, the patient was hypotensive, pale, and had cold extremities. His hemoglobin was measured at 6.1 g/dL; the remaining blood count was normal. There were no alterations in renal function, liver profile, and coagulation. He had hyperlactatemia (4.9 mmol/L) and troponin elevation (446 pg/mL) without chest pain or ischemic electrocardiographic changes. He received two units of packed red blood cells, fluid resuscitation, and intravenous esomeprazole, leading to hemodynamic stabilization in the ED. Upper endoscopy revealed a giant non-mobilizable clot in the gastric fundus, with no hemorrhagic lesions found throughout the exam. An abdominal CT angiogram showed no evidence of active GI bleeding. The patient was admitted to the intensive care unit, and next-day reassessment esophagogastroduodenoscopy (EGD) was normal. He remained clinically stable and without visible blood loss.

On the eighth day of hospitalization, the patient was readmitted to the intensive care unit in hemorrhagic shock due to new-onset hematemesis. He was intubated and treated with aggressive resuscitation and transfusion of red blood cells. EGD revealed an

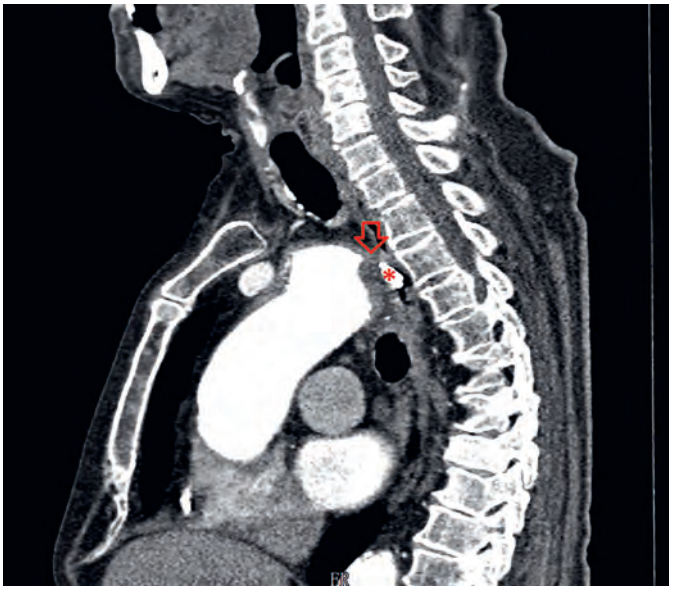

Fig. 2. Endoscopic clip (*) identifying the level of AEF (arrow) on CTA sagittal view.

esophageal 10-mm non-ulcerated mucosal depression with a visible vessel at 20 cm from the incisors (shown in Fig. 1), closed with 3 hemoclips. Thoracic CT angiography showed a brachiocephalic trunk aneurysm with aortoesophageal fistulization (shown in Fig. 2). The vascular surgery department at our hospital and the cardiothoracic surgery department at a tertiary center were consulted, but the patient was deemed unsuitable for endovascular or surgical treatment given the anatomical characteristics of the fistula and his general condition. He subsequently recovered and was able to be discharged home. About 2 months later, the patient was admitted to the emergency room in cardiorespiratory arrest following an episode of hematemesis at home.

Discussion

An AEF is an uncommon and potentially fatal cause of upper GI bleeding. As the name suggests, this condition arises from an abnormal communication between the aorta and esophagus, which allows high-pressure arterial blood to enter the esophagus [1, 2]. The middle portion of the esophagus is the most common site for aortoesophageal fistulization [3, 7]. This disease should be considered in patients who have a history of aortic intervention since most cases are secondary to vascular procedures. It can also originate from the native aorta, arising from thoracic aortic aneurysms, as in our patient, but also after ingestion of foreign bodies, or from tumor invasion [2, 3].

Although the first case of AEF was reported in 1818, the classic triad of symptoms was described by Chiari almost a hundred years later [8]. Patients may experience midthoracic pain, sentinel arterial hemorrhage, followed by a symptom-free interval, and finally a massive bleeding [7–9]. In a minority of cases, bleeding is intermittent, presumably due to the formation of a blood clot that temporarily seals the opening of the fistula [9, 10]. Our patient did not have known risk factors for the disease, such as previous aortic intervention, and presented with less typical symptoms, which may have contributed to a low index of clinical suspicion.

EGD plays an important role in the evaluation of upper GI bleeding; however, its sensitivity for AEF diagnosis is low. The diagnosis can easily go unnoticed in endoscopy if there is no active bleeding and because the typical endoscopic findings, such as submucosal tumor-like protrusion or pulsating arterial bleeding, are rarely found [3, 4, 10].

CTA is recommended as a first-line noninvasive examination in the suspicion of AEF and is diagnostic in most cases [4, 6]. In our case, the findings on EGD associated to intermittent bleeding raised the hypothesis of Dieulafoy lesion, which was not confirmed by CTA. In fact, the CTA was essential to establish the definitive diagnosis of AEF, as the clinical history and endoscopy findings were not suggestive. We emphasize the significance of performing a thoracoabdominal CTA when investigating the etiology of upper digestive bleeding. This is highlighted by the fact that the initial CTA was abdominal and unremarkable, while the subsequent thoracic CTA revealed the final diagnosis.

The management of AEF should involve a multidisciplinary approach and a therapeutic strategy individualized with consideration of both esophageal and aortic defects. A combination of surgery for the aorta (endovascular or open surgical repair) and esophagus (esophagectomy, esophageal stent, or repair) is usually adopted [2, 11]. In cases where correction of the aorta is not possible, as in our patient, the endoscopic treatment aims to palliate new episodes of bleeding, since the aortic defect and fistulous tract remain intact. The literature is scarce regarding the positioning of the different endoscopic interventions for palliation probably because cases of successful vascular treatment appear overwhelmingly more likely to be reported than cases of unfavorable clinical outcomes. Our therapeutic approach was chosen based on the location (20 cm of the incisors), the probable cause (Dieulafoy's lesion), as well as the difficult access and stabilization of the endoscope that precluded other therapeutic options. We considered that a subsequent change in the endoscopic therapeutic strategy could precipitate a new episode of bleeding, and none of the endoscopic options allows definitive treatment of AEF.

Perhaps there may be a role for combining other endoscopic techniques in cases similar to ours, with only an indication for endoscopic treatment, such as the injection of sclerosants or tissue adhesives, if the diagnosis of AEF is known from the beginning.

In conclusion, the case highlights the diagnostic and therapeutic complexity of AEF. A low threshold for performing a CTA is recommended, particularly when there are frequent symptoms of upper digestive bleeding and clear signs observed during endoscopy. Endoscopic treatment not only allows hemostasis in the episode of acute bleeding but also may become the main therapy of AEF in patients without indication for vascular intervention for palliation of new bleeding episodes.

Statement of Ethics

Ethical approval was not required for this study in accordance with national guidelines. Informed consent was obtained from the patient's relatives for the publication of the medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tatiana Pacheco: literature research, manuscript preparation, and drafting. Pedro Costa Moreira, Sara Monteiro, Joana Pinto, Luísa Barros, and Jorge Silva: critical revision of the manuscript. All authors have approved the final version of the manuscript.

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.

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Positive *Yersinia* Serology and Colonic Cobblestone Pattern: A Diversion or Main Culprit?

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Keywords
Yersinia enterocolitica · Colitis · Crohn's disease

Abstract
Yersinia enterocolitica infection, the third most prevalent gastrointestinal infection in Europe, poses a diagnostic challenge due to its resemblance to other common conditions such as acute appendicitis, Crohn's disease, and malignancy. We report the case of a 48-year-old female patient who sought medical attention for abdominal pain and diarrhoea. Her endoscopic examination revealed a cobblestone pattern affecting the entire colon, more pronounced in the right colon, but with normal mucosa in the terminal ileum. This unique presentation created a challenge in distinguishing Yersiniosis from Crohn's disease. This case report aimed to highlight this atypical endoscopic manifestation of *Y. enterocolitica* infection. We underline the subacute nature of the symptoms, which can last up to 4–6 weeks. This reinforces the importance of considering *Y. enterocolitica* infection as a diagnostic possibility, even when the endoscopic appearance closely resembles other chronic intestinal diseases.

Serologia *Yersinia* positiva e padrão do cólon em pedra de calçada: uma distração ou o principal culpado?

Palavras Chave
Yersinia enterocolitica · Colite · Doença de Crohn

Resumo
A infecção por *Yersinia enterocolitica*, a terceira infecção gastrointestinal mais prevalente na Europa, representa um desafio diagnóstico devido à sua semelhança com outras doenças, como a apendicite aguda, doença de Crohn e neoplasias. Apresentamos o caso de uma doente do sexo feminino, com 48 anos de idade, que recorreu ao serviço de urgência por dor abdominal e diarreia. A colonoscopia revelou um padrão em pedra de calçada envolvendo todo o cólon (sobretudo o cólon direito), mas com mucosa do íleon terminal normal. Esta forma de apresentação única com envolvimento isolado do cólon criou um desafio diagnóstico na distinção entre Yersiniose e doença de Crohn. Este caso tem como objetivo realçar uma manifestação endoscópica atípica da infecção por *Y. enterocolitica*. Para além disso, pretende destacar a natureza subaguda dos sintomas, que podem durar até 4 a 6 semanas. Assim, torna-se essencial

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considerar a infecção por *Y. enterocolitica* como uma possibilidade diagnóstica, mesmo quando a aparência endoscópica se assemelha a outras doenças intestinais crónicas.

Introduction

Yersinia enterocolitica (YE), an anaerobic gram-negative bacillus within the *Enterobacteriaceae* family, is a notable cause of food-borne gastroenteritis in Europe. It primarily affects the ileocaecal region, appendix, and mesenteric lymph nodes, leading to terminal ileitis, enteritis, mesenteric lymphadenitis, pseudo-appendicitis, and septicaemia. Transmission to humans commonly occurs through the faecal-oral route via contaminated water, food, soil, and animal sources, with rodents, domestic animals, and birds as significant reservoirs. Consumption of raw pork, contaminated water, or vegetables can trigger outbreaks of YE infection [1, 2].

The clinical spectrum of YE infection often resembles inflammatory bowel disease, acute appendicitis, and even neoplasia, particularly lymphoma, posing a diagnostic challenge [3–5]. Clinical, endoscopic, and histological features of YE infection can mimic those of Crohn's disease (CD). Furthermore, patients may present with extra-intestinal manifestations such as erythema nodosum and reactive arthritis, commonly observed in CD [6]. The endoscopic appearance of Yersiniosis usually includes aphthoid or irregular-shaped ulcers and thickened nodular mucosa in the terminal ileum and cecum, in contrast to the cobblestone pattern typically seen in CD [3]. Nevertheless, the endoscopic appearance is not always typical and the distinction between both diseases may sometimes be difficult. This clinical case describes a unique presentation of YE infection resembling an initial diagnosis of CD, with overlapping endoscopic features and isolated colonic involvement, a scenario, to our knowledge, not previously described.

Case Report

A 48-year-old female patient sought care at the Emergency Department with a 15-day history of non-bloody watery diarrhoea (7–8 bowel movements per day), including nocturnal episodes, accompanied by fever, lower abdominal pain, nausea, and vomiting. Denying any weight loss, she recalled consuming an undercooked pork steak at a restaurant before symptom onset, although none of her dining companions reported similar symptoms. A detailed timeline and clinical course of the disease are shown in Figure 1.

The patient had a significant medical history of a BRCA1 mutation with a previous diagnosis of localized breast cancer 9 years ago, for which she underwent bilateral mastectomy, radiotherapy, and hormone therapy. Subsequently, she underwent hysterectomy and bilateral oophorectomy. Additionally, she had a history of smoking and psoriasis vulgaris, with letrozole being her only medication over the past 4 years.

On examination at the Emergency Department, she was hemodynamically stable but exhibited tenderness in the right lower quadrant. Laboratory investigations revealed anaemia, elevated platelet count, and increased C-reactive protein (CRP) and procalcitonin (shown in Table 1). Given the significant right lower quadrant abdominal pain, a CT scan was performed, revealing thickening of the bowel wall in the ascending, transverse, and descending colon, with a slight thickening of the appendix, although without significant mesenteric fat hypertrophy (shown in Fig. 2). The surgical team assessed the patient and concluded that the presentation was atypical for appendicitis.

Due to the presence of diarrhoea, abdominal pain, and fever, a diagnosis of infectious colitis was considered. Stool samples were collected for bacterial, parasitological and *Clostridioides difficile* infection assessment. Also, testing for *Salmonella* and YE infection was performed, alongside faecal calprotectin measurement and blood cultures analysis. Empirical antibiotic therapy with ceftriaxone and metronidazole was initiated, leading to significant clinical improvement within 48 h, marked by decreased frequency of bowel movements, resolution of fever, and reduction in CRP levels. Subsequently, the patient was discharged and prescribed 1 week of oral antibiotic therapy.

Despite initial improvement, the patient's post-discharge assessment revealed the presence of severe fatigue and continuous diarrhoea with 2–3 bowel movements per day along with persistent microcytic anaemia, low iron stores, severe hypoalbuminemia (2.7 g/dL), and elevated faecal calprotectin (2,000 μg/g). Therefore, further investigation was deemed necessary. One month after the initial presentation, an endoscopic evaluation was conducted revealing normal mucosa in the terminal ileum but large, deep ulcerations in the ascending and transverse colon, with skip areas of normal mucosa resulting in a cobblestone-like appearance (shown in Fig. 3). The descending and sigmoid colon displayed smaller ulcers (less than 10 mm) with milder

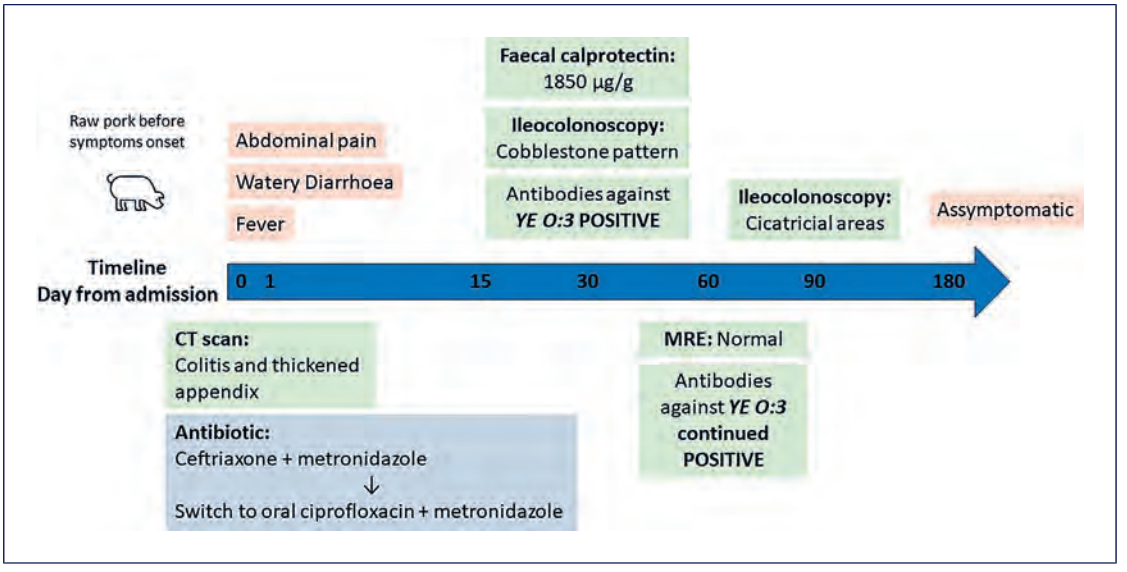

Fig. 1. Clinical course of *YE* infection and most relevant investigations.

Table 1. Laboratory evolution since admission until the last follow-up (6 months)

Laboratory tests	Admission	1 month	6 months
Haemoglobin, g/dL	9.8	10.7	13.5
Leukocytes	5.61 × 10^9/L	5.10 × 10^9/L	6.87 × 10^9/L
Platelets	465 × 10^9/L	532 × 10^9/L	316 × 10^9/L
CRP, mg/dL	45.27	1.68	0.19
Albumin, g/dL	2.7		
Faecal calprotectin, mg/g	2,000	1,850	48

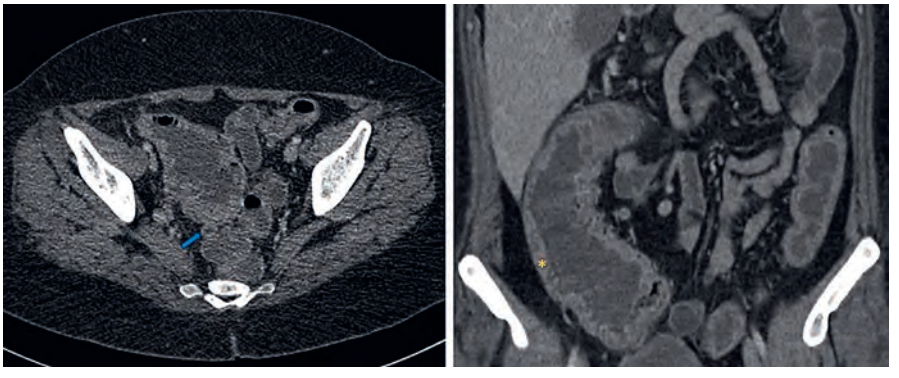

Fig. 2. CT scan at admission demonstrating a thickened appendix (left image, blue arrow) and a thickening of the bowel wall in the ascending colon (right image, yellow*).

inflammation compared to the right colon. Histopathological examination revealed nonspecific findings with an intact ileal mucosal architecture with slight lymphoplasmacytic infiltrate in the lamina propria and a colonic mucosa with normal caliciform cell population without architectural distortion, despite a moderate inflammatory infiltrate, but without epithelial lymphocytosis, basal membrane thickening, granulomas, or cryptitis.

Pending microbiological test results from the initial hospitalization were negative, including blood and stool

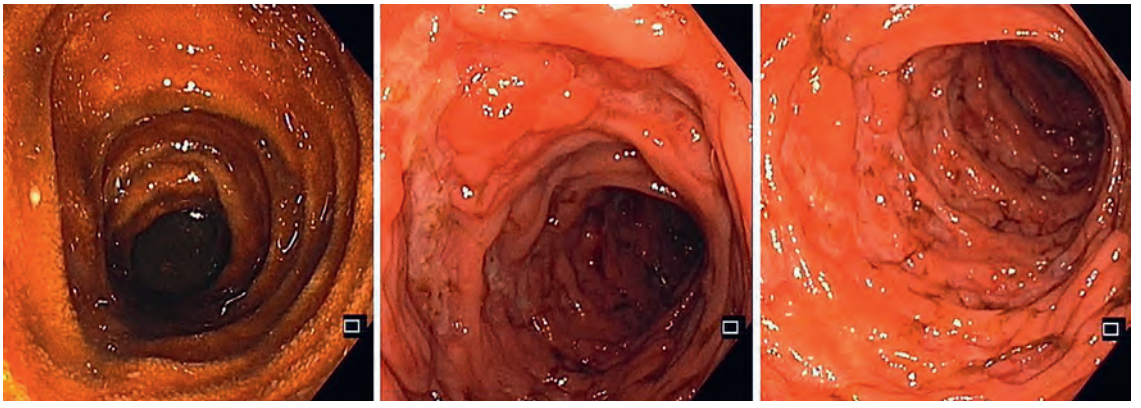

Fig. 3. Ileocolonoscopy 1 month after admission demonstrating a normal mucosa of the terminal ileum (left image) and a transverse and ascending colon with deep and large ulcers with cobblestone pattern (middle and right image).

cultures, Widal reaction for *Salmonella* infection, and *Clostridioides difficile* toxin. However, faecal calprotectin levels (1,850 μg/g) persisted elevated, while serological testing revealed positive antibodies against *YE* O:3.

Given the hypothesis of inaugural CD due to suggestive endoscopic findings, despite a positive *YE* serology, which could be a superimposed infection, a magnetic resonance enterography (MRE) was requested to assess small bowel involvement, which was only performed 2 months after the presentation. The MRE showed resolution of colonic bowel wall thickening, without complications such as stenosis or penetrating lesions.

The disparities observed among the endoscopic findings, histopathological results, and MRE evaluation did not permit a conclusive diagnosis. Consequently, a subsequent endoscopic re-assessment was conducted. This follow-up evaluation revealed substantial improvement, characterized by the absence of ulcerations and restoration of the typical vascular pattern of the colonic mucosa. Additionally, evidence of scar tissue from prior ulcerations was noted (shown in Fig. 4). Histopathology demonstrated preserved architecture, accompanied by oedema, vascular congestion, and mild inflammatory infiltrate yet no evidence of granulomas. Culture and polymerase chain reaction analyses yielded negative results for *Mycobacterium tuberculosis*. No stool or biopsy cultures were conducted to detect *YE* infection since the diagnostic yield was expected to be low at this time.

Following the second colonoscopy, the patient exhibited remarkable improvement without therapeutic interventions. At 6-month follow-up, she remained asymptomatic with normalized bowel movements, resolution of anaemia (Hb 13.5 g/dL), and decreased faecal calprotectin levels (48 μg/g) (shown in Table 1). Consequently, a probable diagnosis of *YE* infection was made based on the clinical presentation with spontaneous improvement and epidemiological association.

Differential Diagnosis

The acute/subacute presentation initially pointed towards an infectious aetiology for the colitis. However, the presence of additional factors such as anaemia, thrombocytosis, and consistently elevated CRP in a patient with an autoimmune background and smoking history raised suspicion of a chronic condition, such as CD. Furthermore, the initial endoscopic examination revealed a cobblestone appearance, which, though nonspecific, strongly suggested CD, particularly when compared to other differential diagnoses like tuberculosis or Behçet's disease [7].

Despite positive serology for *YE O:3*, the most reported strain in human Yersiniosis, the isolated colonic involvement was unusual, casting doubt on *YE* infection as the sole culprit. Nevertheless, upon retrospective analysis, considering the patient's presentation with pseudo-appendicitis and radiological evidence primarily affecting the right colon, a diagnosis of probable Yersiniosis gained support. While the terminal ileum is typically the primary site affected by *YE* infection, the involvement of other segments, including the colon, remains plausible.

Discussion

The 2021 epidemiological report from the European Centre for Disease Prevention and Control (ECDC) underscored Yersiniosis as the third most frequently

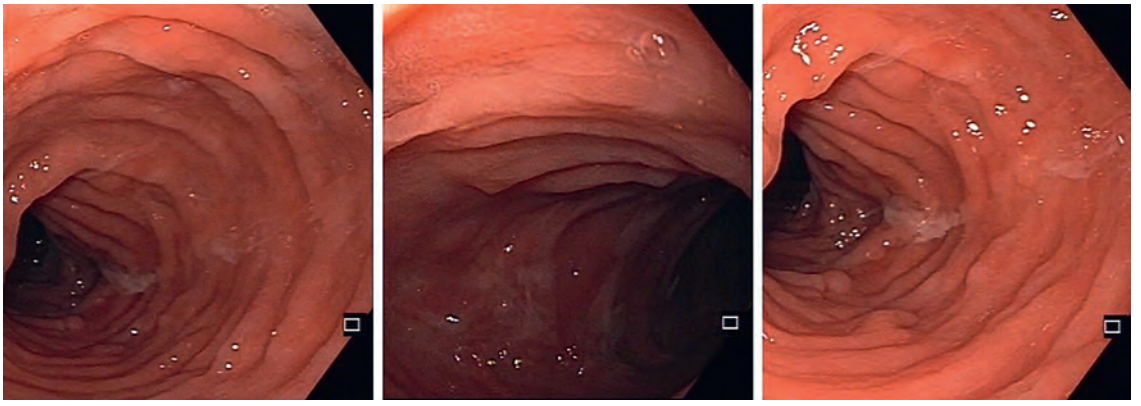

Fig. 4. Ileocolonoscopy 3 months following the initial admission demonstrating complete resolution of the endoscopic pattern with some cicatricial areas of previous deep ulcers (middle image).

reported gastrointestinal infection in the European Union/European Economic Area, after campylobacteriosis and salmonellosis. Notably, 2021 witnessed an 11.8% increase in notification rates compared to 2020 and the pre-pandemic years from 2017 to 2019. Germany, closely followed by France, reported the highest number of cases, in contrast to Portugal, where only 34 cases per 100,000 inhabitants were reported in 2021 [2]. *YE* O:3 strains are the most frequently encountered in Europe, primarily associated with pork products. Our patient's consumption of raw pork before symptom onset aligns with the typical incubation period of 4–10 days observed in Yersiniosis cases.

A previous review of endoscopic findings in *YE* infection highlighted a terminal ileum involvement, with no abnormalities in the left colon. Endoscopic findings typically featured round or oval elevations, and shallow and irregular ulcers scattered throughout an oedematous mucosa. However, this review had the limitation of including only 8 patients [8]. Despite this, a recent report showcased a cobblestone appearance resembling CD in a patient with sole terminal ileum involvement, contrasting with our case, which exhibited a similar endoscopic pattern but with exclusive colonic involvement, marking, to our knowledge, the first instance of this presentation in Yersiniosis [9]. However, the initial endoscopic assessment in our case was conducted approximately 6 weeks after the onset of the symptoms. Thus, the absence of ileal involvement at this evaluation does not exclude prior inflammation as the initial radiological findings indicated a thickening of the appendix and more pronounced radiological activity in the right colon. It is important to acknowledge the limitations in characterizing the endoscopic involvement of *YE* infection, as endoscopy is typically not warranted for Yersiniosis diagnosis and is reserved for cases with diagnostic uncertainty or need for biopsy specimen collection. Also, previous reviews have not established a clear correlation between endoscopic findings and infection duration. Nonetheless, earlier case reports based on imaging evaluations showed ulceration appearing 4–5 weeks after symptom onset and ileal perforation occurring 5 weeks afterwards [10, 11].

Similarly to previous reports, the endoscopic findings in our case, along with the subacute duration of the symptoms, raised suspicion of CD, supported by laboratory changes including anaemia, thrombocytosis, and hypoalbuminemia [9]. However, in patients presenting with subacute abdominal pain and evidence of enteritis or enterocolitis, it is crucial to consider other potential causes, such as drug-induced enterocolitis (especially with non-steroidal anti-inflammatory drugs or aspirin), intestinal tuberculosis, other infectious enterocolitis, collagen diseases, vascular lesions, and neoplasia like lymphoma. There is a high risk of clinical and histological mimicry between CD and *YE* infection as they have similar clinical manifestations, often affect the ileocaecal region, and can both present with granulomas on histopathological examination. However, *YE* infection may be distinguished histologically by central necrosis of the granulomas and a perigranulomatous lymphoid cuff [3].

According to the ECDC definition, our case report represents a probable diagnosis of Yersiniosis since it meets the clinical criteria including fever, diarrhoea, and abdominal pain, along with an epidemiological link of exposure to a common source of infection [12]. For a definite diagnosis of Yersiniosis, isolation of the organism in a clinical specimen is necessary, with prolonged low-temperature culture in a selective growth medium being

the most sensitive method [13]. Alternatively, virulence genes can be detected using molecular techniques, though these are not always readily available. The presence of positive serology is not part of the diagnostic criteria. Nevertheless, it might be used as a screening tool for the presence of the infection, although it requires further confirmation, most commonly through stool culture.

While an infectious aetiology was initially considered, *YE* was not immediately suspected. Only standard stool cultures were ordered, without a specific incubation growth medium for *YE*. Additionally, at the time of the endoscopic assessment, a chronic inflammatory condition was suspected due to the subacute course of the diarrhoea and suggestive laboratory features. This suspicion was further reinforced by endoscopic findings compatible with CD, leading to the omission of specific cold culture biopsies for *YE*. It is important to highlight that the microbiologist should be aware of the suspicion of Yersininosis so that specific molecular and cultural tests can be ordered, and, if necessary, performed in another institution as it would have been relevant in our case. Although some studies have suggested an association between *YE* infection and CD, further research has failed to find significant differences in *YE* infection rates between CD patients and controls. These discrepancies may result from variations in the diagnostic methods used to detect *YE* and from the different symptoms of *YE* infection, which can vary according to the virulence of the strains. Moreover, establishing an association between these two conditions does not necessarily mean a causal link.

While most cases of *YE* infection are self-limiting and do not require antibiotic treatment, in certain populations, such as the elderly, immunocompromised individuals, diabetics, iron overload, alcoholism, or chronic diseases, treatment should be considered. Aminoglycosides and fluoroquinolones are the most used antibiotics. Trimethoprim-sulfamethoxazole combination, tetracyclines, and third-generation cephalosporins are other options [1, 4]. In conclusion, it is imperative to consider infectious aetiologies, such as Yersiniosis, when evaluating patients with acute or subacute abdominal pain and diarrhoea, and this diagnostic suspicion should be promptly communicated to the microbiologist.

Statement of Ethics

We obtained written informed consent from the participant to publish the medical case details and any accompanying images. Ethical approval was waived according to local/institutional norms.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joana Revés, Catarina Frias-Gomes, and Lídia Roque Ramos contributed to the manuscript's design and wrote the manuscript. Luísa Glória provided significant revisions to the manuscript. All authors critically revised the manuscript and have approved the final version of the manuscript.

Data Availability Statement

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

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