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REVIEW

Esophageal lichen planus: Current knowledge, challenges and future perspectives

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Abstract

Lichen planus (LP) is a frequent, chronic inflammatory disease involving the skin, mucous membranes and/or skin appendages. Esophageal involvement in lichen planus (ELP) is a clinically important albeit underdiagnosed inflammatory condition. This narrative review aims to give an overview of the current knowledge on ELP, its prevalence, pathogenesis, clinical manifestation, diagnostic criteria, and therapeutic options in order to provide support in clinical management. Studies on ELP were collected using PubMed/Medline. Relevant clinical and therapeutical characteristics from published patient cohorts including our own cohort were extracted and summarized. ELP mainly affects middle-aged women. The principal symptom is dysphagia. However, asymptomatic cases despite progressed macroscopic esophageal lesions may occur. The pathogenesis is unknown, however an immune-mediated mechanism is probable. Endoscopically, ELP is characterized by mucosal denudation and tearing, trachealization, and hyperkeratosis. Scarring esophageal stenosis may occur in chronic courses. Histologic findings include mucosal detachment, T-lymphocytic infiltrations, epithelial apoptosis (Civatte bodies), dyskeratosis, and hyperkeratosis. Direct immuno-fluorescence shows fibrinogen deposits along the basement membrane

zone. To date, there is no established therapy. However, treatment with topical steroids induces symptomatic and histologic improvement in two thirds of ELP patients in general. More severe cases may require therapy with immunosuppressors. In symptomatic esophageal stenosis, endoscopic dilation may be necessary. ELP may be regarded as a precancerous condition as transition to squamous cell carcinoma has been documented in literature. ELP is an underdiagnosed yet clinically important differential diagnosis for patients with unclear dysphagia or esophagitis. Timely diagnosis and therapy might prevent potential sequelae such as esophageal stenosis or development of invasive squamous cell carcinoma. Further studies are needed to gain more knowledge about the pathogenesis and treatment options.

Key Words: Lichen planus; Esophagitis; T-lymphocytes; Budesonide; Dysphagia; Precancerosis

Core Tip: Lichen planus (LP) is a frequent, chronic inflammatory disease involving the skin, mucous membranes and/or skin appendages. Esophageal involvement in lichen planus (ELP) is an underdiagnosed inflammatory condition. ELP mainly affects middle-aged women. The principal symptom is dysphagia. Aymptomatic cases may occur. An immune-mediated pathogenesis is probable. Endoscopy shows mucosal denudation and tearing, trachealization, and hyperkeratosis. Scarring esophageal stenosis occurs. Histology includes mucosal detachment, T-lymphocytic infiltrations, epithelial apoptosis, dyskeratosis, and hyperkeratosis. Direct immuno-fluorescence shows fibrinogen deposits along the basement membrane zone. Treatment with topical steroids or immunosuppression may induce symptomatic and histologic improvement. ELP can be regarded as a precancerous condition.

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INTRODUCTION

Inflammatory esophageal diseases comprise a broad spectrum of differential diagnoses [1-3]out of which reflux esophagitis is the most frequent condition[4]. Infectious etiologies include Candida or viral esophagitis which are mainly linked to compromised immune function[5]. Esophageal disorders based on immunological background include Crohn's disease[6], Behçet's disease[7], graft-versus-host disease after allogeneic stem cell transplantation[8], and eosinophilic esophagitis (EoE)[9-12]. The spectrum of differential diagnoses ranges to less defined subtypes such as lymphocytic[13] or sloughing esophagitis [14]. These differential diagnoses as summed up in Table 1 encompass additional manifestation of autoimmune bullous diseases such as mucous membrane pemphigoid or pemphigus vulgaris[2,3,15] as well as lichen planus (LP). Esophageal lichen planus (ELP), a mucocutanous manifestation of LP, should be considered in patients with signs and symptoms corresponding to esophageal inflammation. Since many aspects of this disease are still poorly understood, ELP tends to be underreported and often misdiagnosed. However, in the last decade, gastroenterologists and researchers provided more emphasis to this condition. Likewise, proposals for macroscopic and histopathologic diagnostic criteria were made and data on therapy has been increasingly available[16-20].

This narrative review aims to summarize current knowledge on ELP in order to increase awareness about this clinically important esophageal inflammatory disease and make it more accessible in clinical practice.

MAIN BODY

LP

LP is a frequent mucocutaneous disease whose pathogenesis is only partly understood[21-24]. It affects 0.5%–2% of the general population and has female predominance (65%)[21,23,24]. Lesions of skin, oral, and genital mucosa are the most frequent manifestations, however involvement of nails, scalp, genitoanal mucosa, eyes, ears, urinary bladder, or nasal mucosa are also seen. Classic exanthematic,

Table 1 Inflammatory diseases of the esophagus

Chemical or physical damages
Reflux esophagitis
Chemical esophagitis (acids, leach)
Radiation induced esophagitis
Drug-induced esophagitis *e.g.* NSAID, bisphosphonates, tetracyclines, KCl, ferric sulfate, ascorbinic acid
Infectious esophagitis
Candida *spp.*
Viruses, *e.g.* Cytomegalovirus, Herpes simplex, HIV
Immune-mediated esophagitis
EoE
Crohn's disease
GVHD
Behçet's disease
Systemic sclerosis
Lymphocytic esophagitis
Lichen planus
Mucus membrane pemphigoid
Pemphigus
Congenital skin disease
Esophageal involvement in epidermolysis bullosa
Others
EIPD
Sloughing esophagitis

NSAIR: Non-steroidal anti-inflammatory drug; KCl: Kalium chloride; HIV: Human immunodeficiency virus; GVHD: Graft-versus-host disease; EIPD: Esophageal intramural pseudodiverticulosis; EoE: Eosinophilic esophagitis.

cutaneous LP manifests as flat, reddish, itching papules in the face, arms, wrists, with a tendency to develop postinflammatory hyperpigmentation. In two-thirds of patients, an oral manifestation is observed with reticular, erythematous, and erosive subtypes. Patients with oral LP complain of oral discomfort or pain, exhibit characteristic fine white buccal lines (Wickham striae) and often have visible ulcerations on gingiva and palate, tongue and/or labial mucosa. Genital LP may cause itching lesions on glans penis, prepuce or scrotum in men, and on vulva or vagina in women. Involvement of genital mucosa may show all stages of inflammation, starting with erythema, progressing to erosions, plaque formation, and scarring. LP pemphigoides is a rare, mostly IgG-mediated autoimmune variant of LP, exhibiting characteristics of bullous pemphigoid (reactivity against collagen XVII)[25]. As LP may involve multiple organ systems, this disease requires multidisciplinary approach involving dermatologists, dentists, gynaecologists, and gastroenterologists[26-29]. The European guidelines for therapy of LP have recently been published[30,31].

Pathogenesis

A T-cell mediated inflammatory reaction involving antigen-specific and antigen-unspecific mechanisms is regarded as the basic mechanism of pathogenesis[21,28,32]. A recent review about the immunogenetics of LP reported that multiple imbalances of cytokines or interleukins are involved[33]. In addition, genetic influences and MHC associations were found. Micro-RNAs might also be implicated in LP. Antigen-specific mechanisms include antigen presentation of an unknown trigger by basal keratinocytes, activation of CD4+ Th1-helper cells, cytokine production, and CD8-positive cytotoxic reaction against basal epidermal cells. On the other hand, antigen-unspecific mechanisms could involve upregulation of proinflammatory mediators such as interferon-γ, tumour necrosis factor-alpha, interleukins, and matrix metalloproteases, leading to T-cell infiltration in the epidermal cell layer.

The cytokine profile suggests a Th1/Th2-imbalance, whereas B-cells, plasma cells, or antibodies may play a minor role[33]. Similar to psoriasis or pemphigus[34-36], a disturbance in the IL17/IL23 axis was observed[37,38]. Bacterial or viral antigens may trigger LP. An association with chronic hepatitis C was described, however data remains controversial[39,40]. An association with IgG4-related disease is possible[41]. LP may be triggered by several drugs, *e.g.* NSAIDs, beta-blockers, ACE-inhibitors, and check-point inhibitors[42]. Amalgam or mercury are regarded as trigger for oral LP[43], while concomitant diabetes or smoking influence the clinical severity[44]. There are associations with systemic diseases and autoimmune disorders such as primary biliary cholangitis, autoimmune thyroiditis, myasthenia, alopecia areata, vitiligo, thymoma, and autoimmune polyendocrinopathy[28,45-47]. As in other immune-mediated diseases, psychological component may influence the disease progression[48-50].

ELP

Involvement of the esophagus in LP as another possible site of mucosal affection was first described in 1982[51,52], followed by case reports and small case series presenting this new type of esophageal inflammatory disease with lichenoid features[53-64]. ELP was regarded then as a rarity, likely because its clinical, endoscopic, and histologic features were not yet clearly understood. In recent years, interest about this "new" disease was growing and consequently, larger case series and studies[16-20,58,60,65-69],as well as two comprehensive reviews were published[70,71]. For this narrative review, studies were collected using PubMed/Medline and single case reports were excluded. Table 2 presents an overview of these studies and their key findings.

Epidemiology

The population-based prevalence of LP was estimated to reach an average of 1.3%[21,73]. Oral LP is considered the most predominant mucosal manifestation affecting two-thirds of patients with cutaneous LP[26-28]. A recent metaanalysis showed a varying global prevalence of oral LP (0.57% in Asia, 1.68% in Europe, and 1,39% in South America)[72,73]. Esophageal involvement was initially regarded as a rarity, however further studies showed an esophageal manifestation in up to 50% of patients presenting with cutaneous or oral LP[16,74]. Since the number of cases in these studies were limited and the patient groups non-randomized, the true prevalence of ELP might be overestimated. Surprisingly, ELP does not necessarily correlate with oral disease[20]. However, oral LP is found in most of the cases of severe ELP. Esophageal manifestation also correlates with the occurrence of other mucosal involvement such as genital LP. The median age at presentation is 60 years and 80% of patients are female[71,75]. Determining the true prevalence of ELP remains a challenge, as it would require endoscopic screening in a large group of patients with LP regardless of localization and symptoms. Focusing on patients with esophageal symptoms only, *e.g.* dysphagia, would underestimate the true prevalence of ELP. A previous study showed that more than 50% of patients with mild ELP did not report dysphagia[20]. Moreover, cases where the esophagus is the only affected site of LP could still be missed. Hence, the prevalence of ELP on a population-based level can only be roughly estimated thus far. Furthermore, assuming that about 10% of all LP patients would have an esophageal involvement, the prevalence could be as high as 0.1% in the general population, thus outnumbering the prevalence of eosinophilic esophagitis which has been reported to reach 0.04%–0.05% in Western countries[76].

Diagnostic features of ELP

Clinical symptoms: Dysphagia is the leading symptom found in 80%–100% of patients with ELP. Other symptoms include odynophagia, heart burn, regurgitation, weight loss, hoarseness, and chronic unproductive cough. In some studies, approximately 20% of patients with ELP did not manifest any esophageal symptoms[77]. Development of esophageal symptoms might be influenced by severity of disease. In a previously published study, 94% of patients with endoscopically severe ELP presented with dysphagia. However, only 44.4% of patients with mild ELP complained about dysphagia[20]. On the other hand, up to 6% of LP patients had symptoms of dysphagia without esophageal involvement. In clinical practice, ELP should be investigated in patients presenting with the above-mentioned symptoms, especially in patients with known LP. Moreover, ELP should be considered in all patients where other common causes of esophagitis (see Table 1) have been ruled out.

Diagnosis: Similar set of macroscopic and histologic features of ELP has been repeatedly described in literature (see Table 2). Alongside some findings which can be considered typical of ELP, some similarities with other esophageal disorders such as eosinophilic esophagitis, lymphocytic esophagitis, and sloughing esophagitis can be found[3,9-11,13,78-82], hence, making the diagnosis challenging. Based on published data and experience from our cohort of patients, a diagnostic score combining endoscopic and histopathologic findings, as well as direct immunofluorescence (DIF), and a severity grading (no ELP, mild ELP, and severe ELP) has been previously proposed by our group[20]. These criteria are not completely new, however existing criteria and our own findings were integrated into a comprehensive and reproducible scoring system. Examples for endoscopic, histopathologic, and DIF findings are shown in Figures 1-4.

Table 2 Studies on esophageal lichen planus (numbers in braces indicate number/percentage of patients from the cohort to which the criterion applies)

Ref.	Study design	Number of ELP cases	Further manifestation sites of LP	Macroscopic findings as described in the manuscript	Histologic findings as described in the manuscript	Signs and symptoms	Therapy
Keate *et al* [53], 2003	Case series	3 (all)	Cutaneous oral genital	Mucosal sloughing stenosis	Band-like infiltrate hyperkeratosis acanthosis	Dysphagia	Tacrolimus intralesional Pred. Response 3/3; Etretinate (no effect)
Donnellan *et al*[116], 2011	Case series	5 (all)	Oral (all), genital (2), cutaneous (1)	Ulcerations, strictures	Band-like lymphocytic infiltrate, civatte bodies	Dysphagia (all)	Dilation (4) Flut; Response 3/5
Franco *et al* [69], 2015	Case series	6 (83%)	Cutaneous and oral (4)	Ulcerations, strictures (5)	Band-like lymph infiltrate, civatte bodies, fibrinogen + in DIF	Dysphagia (all), food impaction (2)	Dilation (3) Flut/Pred/Triam. Response 5/5
Dickens *et al* [74], 1990	19 LP patients	5	Cutaneous (19), oral (4)	Papular lesions, mucosal detachment on biopsy, erosions	Submucosal lymphocytic infiltrate	Dysphagia (1)	
Harewood *et al*[65], 1999	Retrospective search in patient register	6 (100%)	Oral (5), genital (3), cutaneous (2), ELP as initial manifestation (5)	Proximal strictures (4)	Lymphocytic infiltration (4)	Dysphagia (6); odynophagia (2)	Dilation of strictures (6); Prednisone (40-60mg). Response 3/4
Quispel *et al* [16], 2009	24 LP patients	12	Oral and/or cutaneous (all)	Whitish papules (10), hyperemic lesions (3), mucosal detachment (2), submucosal plaques (3)	Lymphohistiocytic infiltrations para-/hyperkeratosis, hyperplasia, civatte bodies, glycogen akanthosis	Dysphagia (4), odynophagia (3), heart burn (3), regurgitation (2)	
Katzka *et al* [17], 2010	Retrospecitve review (10 years) of data base/ esophageal biopsies from patients with dysphagia	27 (92%)	Oral (19), genital (13), cutaneous (3), ELP as initial manifestation (13)	Strictures (18): Proximal (11), distal (3), both (4), mucosal detachment (11), erythema, plaques, whitish mucosa, superficial ulcerations, Koebner effect after dilat	Lichenoid lymphocytic infiltration, damage of ephithelial basal layer civatte bodies squamous cell carcinoma (1)	Dysphagia (27); odynophagia (2)	Dilation of strictures (17). Dilation + Fluticasone Response 10/11. No dilation plus intralesional corticosteroids (2) or swallowed Futicason/ Budesonide (2). Response 6/6
Fox *et al*[77], 2011	Review of published ELP cases until 2009 (including 4 own cases)	72 (87%)	Oral (89%), genital (42%), cutaneous (38%), scalp (7%); nails (3%), eyes (1%), ELP as initial manifestation (14)	Pseudomembranes, bleeding, fragility, inflammation; proximal (64%); distal (11%); Both (26%); Stenosis (47%)	Lichenoid lymphocytic infiltrates; dysplasia/squamous cell carcinoma (6%)	Dysphagia (81%); odynophagia (24%); weight loss (14%); heart burn (8%); regurgitation (3%); hoarseness (1%); asymptomatic (17%)	
Linton *et al* [66], 2013	Retrospective analysis of esophageal biopsies from 273 patients out of a large cohort	1 typical ELP; 6 possible ELP	No data	Inflammation (7); stricture (5); trachealization (4) mucosal fragility (1); ulcerations (3); nodules (3)	Lymphocytic infiltration (7); Civatte bodies (1); parakeratosis (6); mixed infiltration (6) elongation of lamina propria papillae (7) hyperplasia of basal cells (4); widened intercellular space (3); neutrophilic inflamm (1)	Dysphagia (7); odynophagia (4)	Dilation of stenosis (3). Topical Fluticasone (2). Response 2/2. Proton pump inhibitors (7). Sucralfate (2). 5-HT4-RA (1)
Podboy *et al* [19], 2017	Retrospective analysis of a cohort of ELP-patients	40 (80%)	Cutaneous (4), oral (19), genital (15), ELP as only; manifestation (13)	Strictures (29), ring formation (29), ulcerations (8), mucosal detachment (6), other mucosal, lesions (14), squameous cell carcinoma (2)	Common findings (> 5): Esophagitis (20), focal ulcerations (13), mucosal hyperplasia (10), intraepithelial lymphocytic infiltrate (13), eosinophilia < 5 (13) dyskeratosis (11). DIF positive: Lichenoid (2) equivocal (5) not evaluable because of mucosal detachment (13)	Dysphagia for solid food (32) even for fluids (8); odynophagia (6); reflux (1)	Topical corticosteroids: Budesonide in honey 2 x 3mg (32). Fluticasone spray 880 μg 2x/d (8). Response rate: Endoscopic (72,5%), clinical (62%)

Ravi *et al* [101], 2019	Retrospective analysis of ELP patients	132 (80%)		Clinical diagnosis (77)	"Specific histology" (55); Esophageal carcinoma (8)		Response to topical steroids 84/132 63.6%. Immunosuppressive; therapy necessary 38/132. Response: No data
Kern *et al* [18], 2016; Schauer *et al* [20], 2019	52 patients.with proven LP on other site (75%)	34mild (18); severe (16)	Oral 78-100% (*vs* 78% in non-ELP), genital 44-61% (*vs* 6% non-ELP). Cutaneous 25-44% (*vs* 28% non-ELP)	Mucosal detachment iatrogenic (12); spontaneous (16); hyperkeratosis (7); trachealization (10); stenosis/strictures (7)	Epithelial detachment, lymphocytic infiltration, Civatte bodies, dyskeratosis; DIF: Fibrinogen deposits (17); (85% in severe ELP)	Dysphagia. severe ELP: 15; mild ELP: 8	Topical corticosteroids (12). Budesonide gel 3x0.5mg. Fluticasone. Response 11/12. Stenosis: Topical corticosteroids dilation

LP: Lichen planus; ELP: Esophageal lichen planus;DIF: Direct immunofluorescence; Flut: Fluticasone; Bud: Budesonide; Pred: Prednisolone; Triam: Triamcinolone.

Macroscopy

The endoscopic hallmark in nearly all studies analysed (see Table 2) is denudation or sloughing of the esophageal mucosa. It may occur spontaneously or during the endoscopic procedure. Less specific indicators of ELP are "trachealization" (an endoscopic sign well known in EoE) and presence of a rough and whitish surface of the mucosa which is the macroscopic correlate of hyperkeratosis as seen in histology. Stenoses or strictures may occur as sequelae of chronic inflammation in ELP as in other chronic inflammatory esophageal disorders. Endoscopic images of mucosal alterations are shown in Figure 1. Endoscopic changes may be observed in all parts of the esophagus, but mainly in the middle third. As reflux esophagitis often occurs simultaneously, macroscopic and histologic alterations directly above the gastroesophageal junction may be ambiguous. Thus, biopsies should be taken at least 5 cm above the gastroesophageal junction. To evaluate microscopic changes in patients with known LP, we recommend to perform at least two biopsies (in the lower and upper third of the esophagus) regardless if the above-mentioned endoscopic signs are not present.

Histopathologic Features

Esophageal biopsies provide a reliable assessment of mucosal lesions characteristic of ELP (Figure 2). Band-like inflammatory infiltrates are observed at the interface between the squamous epithelium and the lamina propria corresponding to a lichenoid esophagitis pattern. The predominant cell type in the inflammatory infiltrate of ELP are CD3+ T cells which spill over into the adjacent epithelium involving the lower third or lower half of the epithelial thickness. CD4+ cells are the main T-cell subset reported in cutaneous LP while ELP also frequently harbors abundant intraepithelial CD8+ lymphocytes. Intraepithelial lymphocytosis is associated with scattered squamous cell apoptosis designated as Civatte bodies. The epithelium may become partially or completely detached from the tunica propria or show intraepithelial splitting reminiscent of sloughing esophagitis. However, superficial necrosis and neutrophilic aggregates seen in sloughing esophagitis are not a feature of ELP. The squamous epithelium may be hyperplastic and exhibit acanthosis similar to the saw-toothed rete ridges of cutaneous LP especially in long-standing esophageal involvement. In contrast to the normal esophageal epithelium, hypergranulosis is frequently observed in the superficial epithelium of ELP. Surface orthokeratosis, also termed esophageal epidermoid metaplasia (EEM), is the histologic correlate of the rough and whitish mucosal surface with leukoplakia (Figure 3). This lesion is referred to as uncomplicated EEM as long as epithelial maturation is preserved and dysplasia/intraepithelial neoplasia (IEN) is absent. Chronic

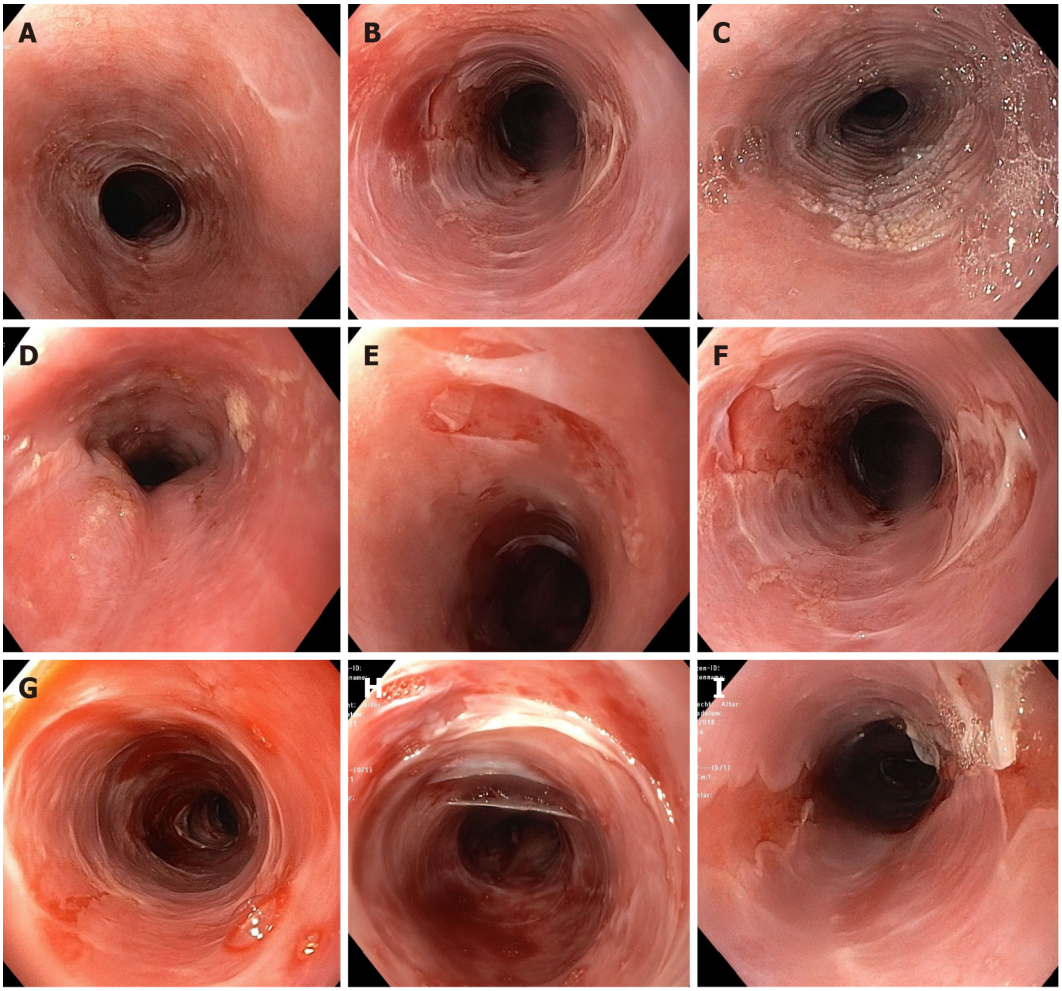

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Figure 1 Endoscopic findings in esophageal lichen planus. A: Trachealization; B: Trachealization and fragile mucosa; C: Hyperkeratosis; D: Hyperkeratosis and stenosis; E and F: Tearing and localized denudation of the mucosa; G-I: Tearing and spacious denudation of the mucosa. Endoscopic images were taken from our cohort of patients.

inflammation may lead to fibrosis and scarring of the tunica propria resulting in strictures and dysphagia.

DIF

In ELP, DIF often highlights fibrinogen deposits along the basal membrane as another important criterion (Figure 4). This is based on the data on oral LP, where linear fibrinogen deposition (or granular IgG and IgM deposits) in DIF could discriminate the diagnosis from other lichenoid lesions[83] and mucus membrane pemphigoid[15,27]. Therefore, positive results in DIF support the diagnosis of ELP yielded by conventional histopathology and, in turn, differentiate the findings from diseases like mucous membrane pemphigoid or pemphigus vulgaris in erosive stages.

Therapy

In contrast to cutaneous and oral LP[30,31], there are no generally accepted guidelines for therapy of ELP. Conventional management of cutaneous LP with retinoids does not seem to prevent the emergence of ELP, nor is it suitable for therapy of ELP[20,53,84,85]. However, a few case reports described successful therapy using alitretinoin[62] . Good therapeutic response was reported with topical corticosteroids such as fluticasone or budesonide leading to clinical and/or endoscopic response rate of 62% up to 74% in ELP[17-20]. The type of budesonide preparation might play an important role for its efficacy. Viscous syrups or gels offer better adherence to the esophageal mucosa than swallowed sprays, and led to good response rates[20]. However, for a comparison of response rates based on specific preparation, case numbers in literature are too limited (see Table 2). Orodispersible tablets designed for eosinophilic esophagitis might play an interesting role but have not yet been studied in ELP. Intralesional injection of triamcinolone has also been described in literature[53,69,86]. Systemic corticosteroids have been proposed to induce rapid response in severe cases[66]. However, they are not suitable for maintenance therapy and tapering may lead to reoccurrence of symptoms. Therefore, more severe cases not

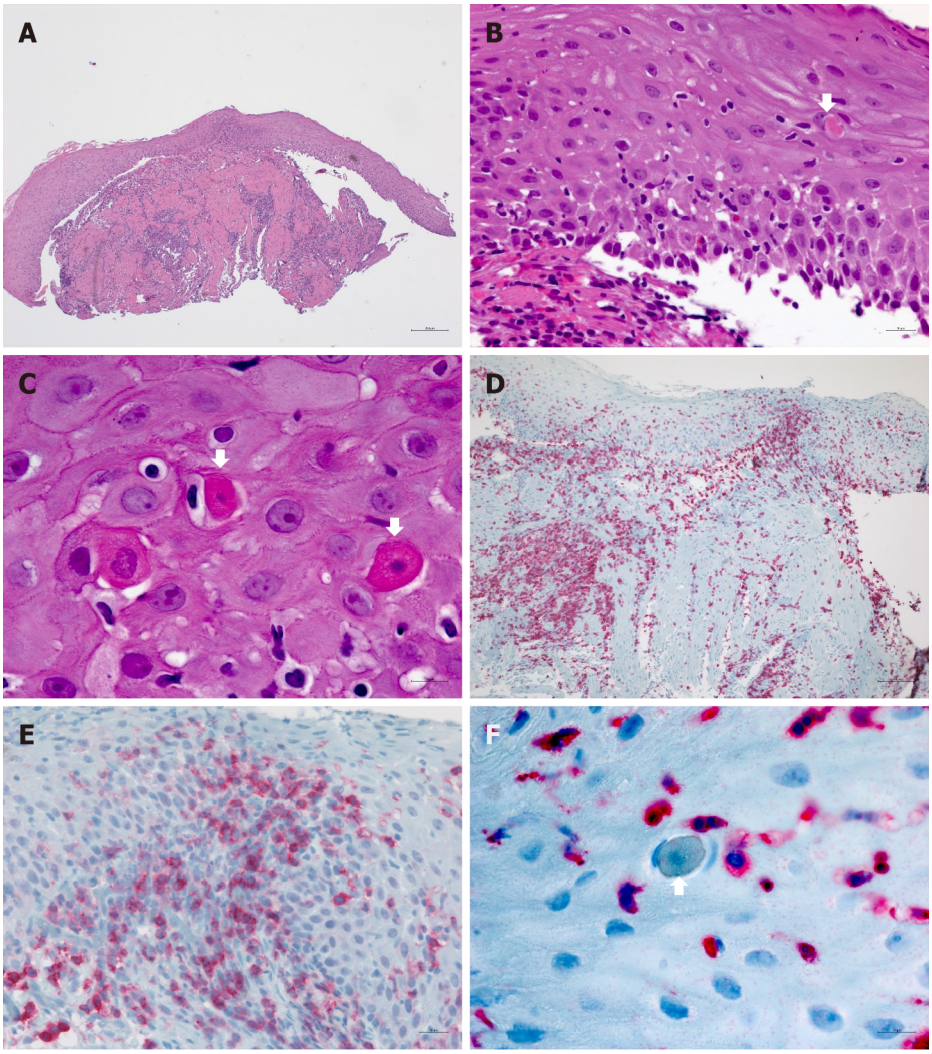

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Figure 2 Histologic findings in esophageal lichen planus. A and B: Lichenoid lymphocytic infiltrate of the lamina propria spilling over to the partially detached squamous epithelium; B and C: Intraepithelial lymphocytosis associated with apoptotic squamous cells (Civatte bodies, arrows); D: Dense CD3+ T-cell rich inflammation of the lamina propria involving 2/3 of surface epithelium and muscularis; E: Presence of a CD4+T-cell subset in the infiltrate; F: Civatte body rimmed by CD3+ T-cells.

responding to topical corticosteroids require therapy with systemic immunosuppressants. Different types of immunosupressors such as adalimumab, hydroxychloroquine, mycophenolate, azathioprin, cyclosporine, tacrolimus or rituximab have been used[24,53,54,63,67,68,87,88]. In one of our patients, cyclophosphamide was the only drug which effectively induced at least a partial remission. Refractory cases also exist[64].

Since ELP mainly occurs as part of a systemic or multilocular LP, treatment should always be initiated in a multidisciplinary approach involving at least gastroenterologists and dermatologists, especially when topical therapy is not effective and systemic immunosuppressive therapy is necessary.

Complications

Esophageal stenosis/Food impaction: As with other inflammatory esophageal diseases, inflammatory or scarring stenosis can be a sequela of chronic untreated or refractory course leading to typical complications such as dysphagia, odynophagia, food impaction, and weight loss[17]. Therefore, ELP should be considered as one of the potential causes of food impaction[89], together with achalasia or eosinophilic esophagitis, or of unexplained esophageal stenosis[90-92]. This applies, not only, but especially to patients with known LP on other site or to patients presenting with signs of undiagnosed mucocutaneous disease.

Treatment of esophageal stenosis

In symptomatic esophageal stenosis, endoscopic dilation may be necessary and has been successfully performed in multiple cases[17,93]. The possibility of considerable mucosal denudation, the main feature of florid ELP, prompted some authors to advice against endoscopic dilation in the past.

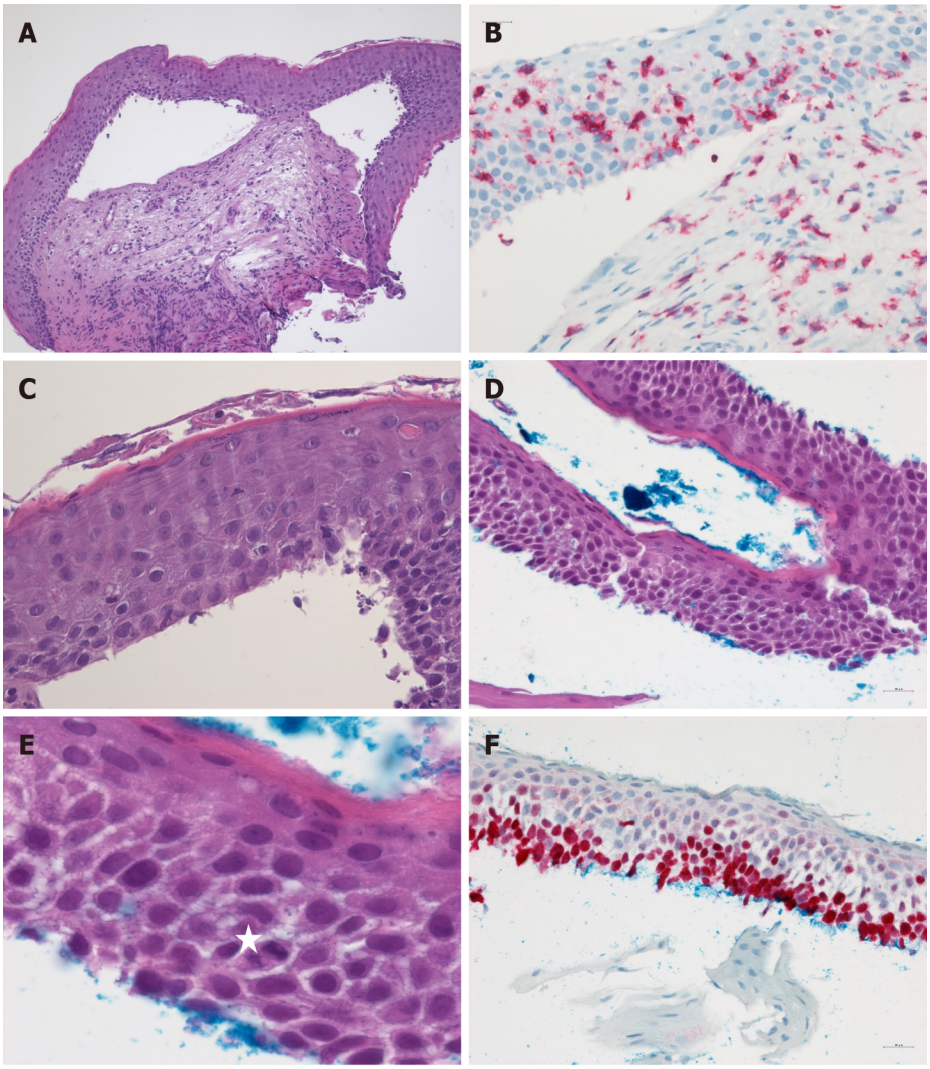

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Figure 3 Esophageal epidermoid metaplasia in esophageal lichen planus. A-C: Atrophic squamous epithelium showing extensive detachment from the lamina propria, subtle hyperkeratosis (A, C) and mild intraepithelial CD3+ T-lymphocytosis (B) associated with scattered Civatte bodies (C, arrow); D, and E: Low-grade squamous orthokeratotic dysplasia in detached epithelium of ELP. Presence of basal-type cells in the lower half of the flat epithelium, note presence of scattered mitosis (E, star); F: An increased Ki67+ proliferation index.

However, this can be overcome by simultaneously treating the underlying inflammation as recommended in other esophageal inflammatory conditions. Anti-inflammatory treatment can reduce mucosal fragility, making it more resistant to physical stress, consequently preventing the reoccurrence of stenosis and inducing remission. The need for endoscopic dilation has been reported to decrease under anti-inflammatory therapy[71] and in a few cases, budesonide alone led to relief of symptomatic stenosis [20]. However, vis-a-vis therapy of stenosis in Crohn's disease, this may only apply for inflammatory and not for scarring stenosis.

Precancerous lesions and esophageal squamous cell carcinoma

Several factors may limit the life expectancy of patients with LP[94,95]. Oral squamous cell carcinoma is one of them, as oral LP is widely regarded as a precancerous condition, even though the exact rate of malignant transformation is a matter of debate[55,96-99].

Accordingly, correlation between ELP and development of esophageal squamous cell carcinoma (ESCC) has been well documented. The number of case reports has been increasing in which esophageal inflammatory and hyperkeratotic lesions have progressed to squamous cell dysplasia/IEN and even to invasive ESCC. In some studies, development of ESCC has been reported in up to 4.5% of ELP patients [100,101].

ELP-associated esophageal precancerous squamous lesions are generally detected in areas of EEM [102-104]. In low-grade dysplasia, cytologic and structural epithelial abnormalities are confined to the lower half of the esophageal epithelium, while high-grade dysplasia involves more than half of the epithelial cell layers with lack of surface maturation. Therefore, endoscopically detected areas of EEM/leukoplakia should be systematically sampled for histologic evaluation since these constitute a

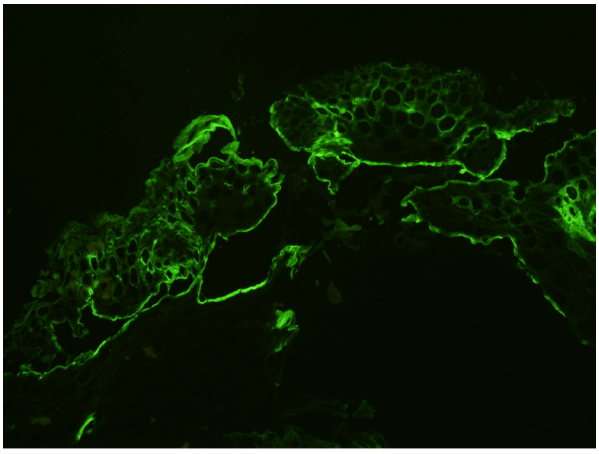

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Figure 4 Direct immunofluorescence. Fibrinogen deposits in the basal membrane as a characteristic feature of Lichen planus. Direct immunofluorescence image was taken from one of our patients.

hallmark of orthokeratotic dysplasia (Figure 3). It should be noted that invasive ESCC may be detected underneath or adjacent to EEM. Our experience showed uncomplicated hyperkeratosis/EEM in a considerable number of patients with severe ELP (37.5%), while predominantly low-grade orthokeratotic dysplasia was rare (6%) and the transition to an early invasive ESCC was diagnosed in only one patient[20]. Anti-inflammatory therapy did not lead to regression of hyperkeratotic areas in this cohort. New therapeutic strategies should aim to either slow down or arrest the development of EEM.

According to Singhi *et al*[103], mutation in TP53 correlates with occurrence of or progression to ESCC in ELP. *p53* overexpression in immunohistochemistry has been frequently observed in our cohort. Additional molecular analyses have yet to be performed to gain more knowledge on risk stratification. Future advances in identifying the molecular landscape which drives the development of precancerous lesions and overt invasive carcinoma may help establish prognostic biomarkers for early detection of ELP cases at high risk of progression to overt ESCC.

Translating this knowledge to clinical practice, we recommend regular endoscopic surveillance of ELP patients for development of dysplasia. Detection of suspicious areas may be assisted by chromoendoscopy. Patients with known hyperkeratotic regions or florid inflammation should be assessed more often. In cases of low grade dysplasia, we recommend further endoscopy every six months; in cases of transition to high grade dysplasia, endoscopic mucosal ablation should be performed similar to patients developing dysplasia in Barrett's esophagus. Furthermore, other known risk factors for development of ESCC such as nicotine or alcohol intake should be discouraged.

Proposal for management of ELP

Figure 5 presents a proposal for clinical management of ELP. We recommend esophago-gastro-duodenoscopy (EGD) in every patient with known LP (skin or mucosal manifestation) and with any associated esophageal symptoms as described above. Diagnosis can be established using the above-mentioned criteria (Table 3). We recommend to treat every newly diagnosed ELP initially with topical steroids and then to reevaluate therapeutic response after a certain time interval (*e.g.* three months). In our clinical experience, 0.5 mg budesonide in 5 mL viscous solution three time a day for the initial treatment period is used. Further therapy would depend on whether a clinical and/or histological remission has been established. Otherwise, systemic immunosuppressive therapy may be necessary as described above. At present, there is not enough data on recommended immunosuppressant. Every patient diagnosed with ELP with no known LP on other sites should also be assessed by a dermatologist.

To date, there is still no consensus on how to identify and treat asymptomatic ELP patients, specifically patients with asymptomatic hyperkeratosis, a potential precursor of ESCC. A wait-and-see strategy seems to be warranted[20,70]. However, in patients with EEM, we recommend EGD every six months to screen the emergence of dysplasia.

Future perspectives

Investigation of pathogenesis and search for targeted therapy: Current data on the pathogenesis of LP suggest an (auto)-immunological background with T-cells as key players. As in other diseases triggered by overactive immune system, environmental or lifestyle factors may play an important role, as well as psychological circumstances. Further investigation of mucosal lymphocyte populations in ELP might yield more insights on pathogenesis and establish new options for targeted therapies. Evaluation of environmental factors might lead to identification of triggers (*e.g.* dental fillings with gold or amalgam).

Table 3 Diagnostic criteria to establish diagnosis and assess disease severity (modified from Schauer *et al*[20])

Macroscopic-endoscopic criteria	
Specific signs	
D	Denudation/sloughing of the mucosa
D1	Iatrogenic denudation (caused by biopsies)
D2	Spontaneous localized denudation < 1 cm^2
D3	Spontaneous spacious denudation > 1 cm^2
Possible signs	
S	Stenosis/stricture
S1	Passable with standard endoscope
S2	Not passable with standard endoscope
H	Hyperkeratosis (whitish, rough mucosa)
T	Trachealization
N	None of the criteria fulfilled
Microscopic criteria- histopathology and direct immunofluorescence	
HP	Sloughing of the epithelia (subepithelial, intraepithelial)
	Lymphocytic infiltrate, mainly T-lymphocytes subepithelial, intraepithelial, junctional (region of the basal membrane)
	Intraepithelial apoptosis of keratinocytes (Civatte bodies)
	Dyskeratosis
HP0	Negative
HP1	Weakly positive
HP2	Positive
HP3	Strong positive
F	Fibrinogen deposition along the basal membrane
F0	No visible reaction
F1	Weak positive, discrete depositions visible
F2	Marked fibrinogen depositions along the basal membrane
Severity grading	
Severe ELP	≥ D2 and HP ≥ 1 and/or F ≥ 1
Mild ELP	D1 and HP ≥ 1 and/or F ≥ 1; S, H, T, N and HP ≥ 1 and F ≥ 1
No ELP	Criteria not fulfilled in a patient with LP on other localization

HP: Histopathology; F: Immunofluorescence; ELP: Esophageal lichen planus.

As no therapeutic option has been universally approved for ELP so far, there is a need for further investigation in larger cohort of patients. Although several studies had demonstrated beneficial effects of topical glucocorticoids, duration and maintenance of treatment still need to be defined. In terms of galenics, an orodispersible preparation of budesonide has recently been licensed for eosinophilic esophagitis[105-107] and should be evaluated in ELP.

New therapeutic approaches may be chosen vis-a-vis contemporary therapy of inflammatory bowel disease[108]. A favorable candidate could be ozanimod, an SP-1-modulator recently licensed for therapy of ulcerative colitis[109,110]. Available data suggest a disturbance in the IL12/23 cytokines and/or IL-17 axis in ELP quite similar to psoriasis[34-38], promising possible targeting of these regulatory factors[24]. A candidate influencing the interleukin 12 and 23 pathways would be tyrosine-kinase 2-inhibitor deucravacitinib[111] which has been already used in other diseases with an autoimmune background (*e.g.* Crohn's disease, ulcerative colitis) and localized or systemic lupus erythematosus[112-116]. In patients with precancerous lesions, new endoscopic mucosal resection techniques can prevent progression to invasive carcinoma.

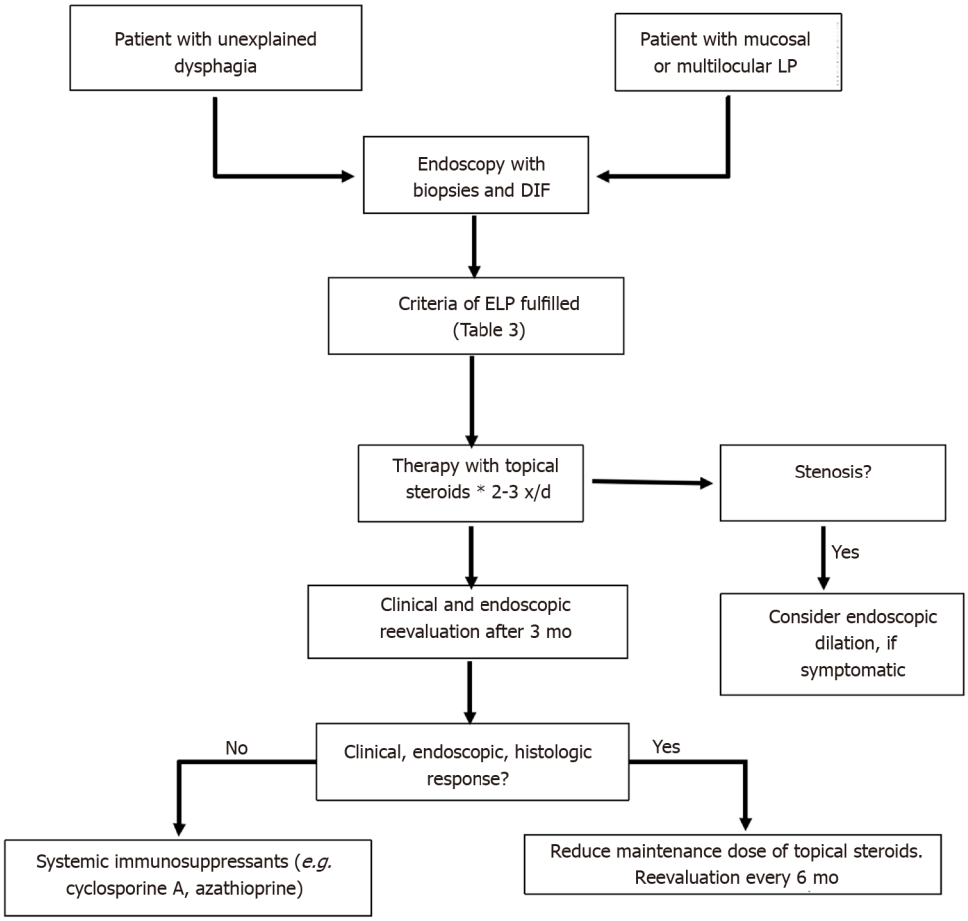

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Figure 5 Proposal for management of esophageal lichen planus. * As topical steroids (*e.g.* budesonide or fluticasone), swallowed spray, viscous solution, or orodispersable tablets might be adminstered. LP: Lichen planus; DIF: Direct immunofluorescence; ELP: Esophageal lichen planus.

CONCLUSION

ELP is an underdiagnosed yet clinically important inflammatory disease of the esophagus which should be considered in patients with unclear dysphagia or esophagitis, especially but not limited to those with history of mucocutaneous LP. Its diagnosis may be based on endoscopic features and typical findings in histopathology and immunofluorescence. Management and treatment of ELP patients is a multidisciplinary challenge. Further understanding of the pathogenesis and new options for targeted therapies need to be established.

FOOTNOTES

Author contributions: Decker A, and Kreisel W designed the manuscript; Schmitt-Graeff A performed the histological evaluation; Schauer F evaluated dermatological findings and performed direct immunofluorescence; All authors collected and interpreted data from patients of their own cohort and from literature; All authors contributed to writing the text. The final stylistic corrections were made by Lazaro A.

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REVIEW

Epidemiology of liver cirrhosis and associated complications: Current knowledge and future directions

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Abstract

Cirrhosis causes a heavy global burden. In this review, we summarized up-to-date epidemiological features of cirrhosis and its complications. Recent epidemiological studies reported an increase in the prevalence of cirrhosis in 2017 compared to in 1990 in both men and women, with 5.2 million cases of cirrhosis and chronic liver disease occurring in 2017. Cirrhosis caused 1.48 million deaths in 2019, an increase of 8.1% compared to 2017. Disability-adjusted life-years due to cirrhosis ranked 16th among all diseases and 7th in people aged 50-74 years in 2019. The global burden of hepatitis B virus and hepatitis C virus-associated cirrhosis is decreasing, while the burden of cirrhosis due to alcohol and non-alcoholic fatty liver disease (NAFLD) is increasing rapidly. We described the current epidemiology of the major complications of cirrhosis, including ascites, variceal bleeding, hepatic encephalopathy, renal disorders, and infections. We also summarized the epidemiology of hepatocellular carcinoma in patients with cirrhosis. In the future, NAFLD-related cirrhosis will likely become more common due to the prevalence of metabolic diseases such as obesity and diabetes, and the prevalence of alcohol-induced cirrhosis is increasing. This altered epidemiology should be clinically noted, and relevant interventions should be undertaken.

Key Words: Causes; Cirrhosis; Complications; Cost; Epidemiology; Burden; Feature

Core Tip: The global burden of liver cirrhosis continues to rise. In 2017, there were 520000 new cases of cirrhosis and chronic liver disease. In 2019, cirrhosis caused 1.48 million deaths, an increase of 8.1% compared to 2017, and its disability-adjusted life-years ranked 16th among all diseases. The global burden of cirrhosis due to hepatitis B virus and hepatitis C virus infection is decreasing, while the burden of cirrhosis due to alcohol and nonalcoholic fatty liver disease is increasing rapidly. We also outlined the recent epidemiology of the major complications and hepatocellular carcinoma in cirrhosis.

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INTRODUCTION

Cirrhosis is a consequence of chronic liver damage and inflammation, and it is characterized by diffuse hepatic fibrosis and normal liver structures being replaced by regenerative liver nodules[1,2]. As the end stage of chronic liver disease (CLD), it can be caused by a variety of conditions, such as alcohol consumption, nonalcoholic fatty liver disease (NAFLD), hepatitis viruses, and autoimmune diseases. The progressive course of cirrhosis can generally include asymptomatic stages, such as compensated cirrhosis, and decompensated stages, which are frequently associated with the development of a range of complications, such as ascites, gastro-esophageal variceal (GEV) bleeding, and hepatic encephalopathy (HE); furthermore, cirrhosis may advance to liver failure and lead to death[3]. These complications impose a heavy burden on global public health in terms of significant quality of life impairment and associated high mortality in patients[4].

Despite the global prevalence and disease burden of cirrhosis, there is less public awareness and concern regarding cirrhosis than for other common chronic diseases, such as congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease[5]. Currently, there remains an insufficient understanding of the clinical relevance of cirrhosis, which can therefore lead to unnecessary disease progression and outcomes[5]. In this review, we comprehensively overview and synthesize the recent epidemiological features of cirrhosis and its complications and discuss the changing trends in epidemiology. This could provide definite value for the clinical diagnosis and management of cirrhosis.

METHODS

The PubMed electronic database was manually searched to obtain relevant literature. The reference lists of the primary included literature were also searched to identify potentially eligible articles. Only articles published in English were included. There was no restriction regarding the publication year. The index terms included "cirrhosis", "ascites", "spontaneous bacterial peritonitis", "variceal bleeding", "hepatic encephalopathy", "acute kidney injury", "hepatorenal syndrome", "infection", "hepatocellular carcinoma", "epidemiology", "prevalence", "incidence", "mortality", "disease burden", "hospitalization", and "cost". A critical evaluation was carried out for all studies included in this paper.

CURRENT EPIDEMIOLOGY OF LIVER CIRRHOSIS

Prevalence

The most recent data available on the global prevalence of cirrhosis are from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017[6]. The GBD 2017 reported the burden of cirrhosis based on pooled epidemiological data from 195 countries and territories stratified by cause, age, and sex from 1990 to 2017. The results for prevalence are presented as numbers and age-standardized or age-specific rates per 100000 populations with 95% uncertainty intervals (UIs). In 2017, there were an estimated 112 (107-119) million cases of compensated cirrhosis and 10.6 (10.3-10.9) million cases of decompensated cirrhosis prevalent worldwide. This represented a huge increase compared to the prevalence figures for 1990, when 65.9 (63.4-68.7) million cases of compensated cirrhosis and 5.20 (5.08-5.32) million cases of decompensated cirrhosis were observed. The age-standardized prevalence of compensated cirrhosis increased from 1354.5 (1300.6-1411.7) per 100000 in 1990 to 1395.0 (1323.5-1470.5) in 2017, while decompensated cirrhosis increased from 110.6 (108.0-113.0) per 100000 in 1990 to 132.5 (128.6-136.2) in 2017. In 2017, 58.8% of compensated cirrhosis cases and 60.3% of decompensated cirrhosis cases were observed in males, suggesting that men suffer from cirrhosis at higher rates. In

males, the age-standardized prevalence of compensated cirrhosis increased by 2.9% from 1990 to 2017; the prevalence of decompensated cirrhosis increased by 21.1%. In females, these figures were 3.5% and 18.1%, respectively. Overall, the prevalence of liver cirrhosis increased by 74.53% from 1990 to 2017[7].

At the regional level, the GBD 2017 also provided relevant epidemiological characteristics[6]. In 2017, the high-income Asia-Pacific region had the highest age-standardized prevalence of both compensated [2455.0 (2344.9-2575.8) per 100000] and decompensated [267.4 (259.8-275.1) per 100000] cirrhosis. Most cases in this region were from Japan and were largely due to hepatitis C. In contrast, Australia reported the lowest age-standardized prevalence of both compensated and decompensated cirrhosis, with hepatitis C also being the main etiology. High-income regions in North America showed the lowest age-standardized prevalence of compensated cirrhosis (mainly caused by hepatitis C), while the lowest prevalence of decompensated cirrhosis was found in South Asia. At the country level, Moldova, Taiwan (Province of China), and Slovakia had the highest prevalence of compensated cirrhosis, while for decompensated cirrhosis, the Philippines had the lowest prevalence, and Slovakia had the highest.

Etiology-specific statistics on the prevalence of cirrhosis are also currently available. In a recent systematic review (retrieved until August 1, 2021) that included 520 studies from 86 countries or territories (reporting a total of 1376503 patients with cirrhosis), 42% of patients with cirrhosis worldwide had hepatitis B virus infection (HBV), and 21% had hepatitis C virus infection (HCV)[8]. The prevalence of HBV infection in cirrhosis was higher in Africa and Asia (8%-61%) than in Europe, the Americas, and Oceania (3%-14%). In contrast, the prevalence of HCV infection in cirrhosis was considerably heterogeneous by country and region (12%-83%). However, in general, the overall prevalence of HBV and HCV exceeded 50% in most parts of Asia and Africa. In China, 68% [95% confidence interval (CI) 60%-74%] of patients with cirrhosis had HBV infection, while only 7% (95%CI 5%-9%) reported HCV infection. In 2017, the age-standardized prevalence of HBV-related compensated cirrhosis did not change significantly compared to 1990, but the prevalence of decompensated cirrhosis increased from 30.9 (95%UI 29.3-32.2) to 36.6 (95%UI 34.7-38.4) per 100000 population[6]. The age-standardized prevalence of HCV-associated compensated cirrhosis increased to 341.1 (314.1-368.7), and the prevalence of decompensated cirrhosis increased to 32.5 (30.6-34.5) per 100000 population in 2017[6]. Regarding cirrhosis due to alcohol consumption, the highest prevalence was recorded in Europe (16%-78%), the Americas (17%-52%), and Oceania (15%-37%), while the lowest was reported in Asia (0%-41%)[8]. In 2017, the global age-standardized prevalence for alcohol-related compensated cirrhosis remained stable compared to 1990 (288.1 in 2017 compared to 290 per 100000 in 1990). However, the global prevalence of alcohol-related decompensated cirrhosis increased from 1990 (30 in 2017 compared to 25.3 per 100000 in 1990)[6]. Another important cause that should not be overlooked is NAFLD-related cirrhosis. According to the aggregate data of the GBD 2017, there were 9.42 million (8.57-10.34) cases of compensated cirrhosis and 917000 (850000-986000) cases of decompensated cirrhosis attributed to non-alcoholic steatohepatitis (NASH) in 2017, showing an impressive increase compared to 1990[6]. The age-standardized prevalence of NASH-related compensated cirrhosis was 115.5 (105.0-126.5) per 100000 in 2017, indicating a 33.2% increase compared to 1990; the prevalence of decompensated cirrhosis showed a 54.8% increase to 11.3 (10.4-12.1) per 100000. However, there is a lack of recent global or regional reported epidemiological data on other causes of cirrhosis, such as drugs, autoimmune liver disease, and metabolic disorders.

Additional profiles were also provided by some newer regional or organizational epidemiological studies (Table 1). A recent study from the United States reported summary statistics on the prevalence and disease burden of digestive diseases in a commercially insured adult population for the period 2016 to 2018. Of the total population, 7297435 (24%) individuals had a diagnosis of digestive disease, and the prevalence of nonalcoholic cirrhosis in the digestive disease population was 0.389% compared to 0.090% in the overall population[9]. Gu *et al*[10] evaluated all hospital admissions within the diagnosis-related group (diagnosis based on ICD-10-GM codes) in Germany from 2005 to 2018. A total of 248085936 admissions were recorded during this period, of which 2302171 admissions were diagnosed with cirrhosis, reflecting a prevalence of 0.94%[10]. A cross-sectional study conducted in Japan in 2020 randomly selected 6000 general citizens from 2 cities, and 488 individuals underwent fatty liver and advanced fibrosis screening. The prevalence of cirrhosis based on liver stiffness measurement (LSM) was 1%, with a markedly higher prevalence in men than in women (1.6% compared to 0.4%)[11]. Finally, a study using a commercial medical claims database yielded an adult prevalence of 0.21% for cirrhosis in 2018 (estimated at 536856 cases)[12].

In specific at-risk populations, there were significant increases in the prevalence of cirrhosis (Table 2). In a 2017-2018 cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES), which included 825 United States adults with type 2 diabetes who had reliable transient elastography results, the prevalence of cirrhosis was 7.7% (95%CI 4.8%-11.9%)[13]. Another study also analyzed NHANES data from 2017-2018 and found a 4.4% prevalence of suspected cirrhosis among patients with fatty liver disease[14]. A recent study utilizing NHANES data from 2001 to 2018 included 3115 HBsAg-negative/HBcAb-positive subjects in which the prevalence of cirrhosis/advanced liver fibrosis based on FIB-4 diagnosis was 3.76% (95%CI 2.80%-4.72%), notably higher than in the general US population[15]. A systematic review and meta-analysis summarized the prevalence of cirrhosis in HBV-infected populations in sub-Saharan Africa. A total of 17 studies were included, including 22 cohorts from 13 countries (13 with HBV infection alone and 9 with HIV/HBV coinfection).

Table 1 Recent local epidemiological data on liver cirrhosis in the general population

Ref.	Country	Study population	Study period	Diagnostic methods	Presented data
[9]	US	7297435 patients with a GI diagnosis in a commercial insurance database	2016-2018	ICD-10 code	Nonalcoholic cirrhosis prevalence: 0.389%; average inpatient cost: 43733 dollars; annualized total costs: 53214 dollars
[10]	Germany	All hospital admissions (248085936 patients)	2005-2018	ICD-10 code	Prevalence: 0.94%
[11]	Japan	488 randomly selected individuals underwent fatty liver and advanced fibrosis screening	From October to November 2020	Liver stiffness measurement	Prevalence: 1%
[12]	US	Adult patients in a commercial medical claims database	2018	ICD-9 or ICD-10 code	Prevalence: 0.21%
[28]	China	503993 participants prospectively included in China Kadoorie Biobank	2004-2008 (10 years of follow-up)	ICD-10 code	Incidence: 756.4 and 397.4 per 100000 among diabetic patients and nondiabetic patients, respectively
[30]	Korea	Adult patients in the HIRA-NPS database	2012-2016	ICD-9 code	Alcoholic cirrhosis incident cases: 7295 cases
[31]	Sweden	All patients at Halland Hospital	2011-2018	ICD-10 code and SNOMED code	Age-standardized incidence: 23.2 per 100000 person-years
[32]	Korea	Adult patients in the NHIS database	2011-2015	KCD-7 code	Primary biliary cirrhosis average annual cumulative incidence: 68.32 cases per 10000000
[33]	Canada	Adult patients in the ICES databases	1997-2016	ICD-10 code	Age-standardized incidence: 70.6 in 1997 and 89.6 per 100000 person-years in 2016
[34]	Canada	Children in the ICES databases	1997-2017	ICES-validated algorithm	Age- and sex-adjusted incidence: 2.7 in 1997 and 10.6 per 100000 person-years in 2017
[44]	US	NIS	2003-2017	ICD-10 code	Alcoholic cirrhosis deaths in women: 14330 cases
[45]	Mexico	National Institute of Statistics and Geography	2000-2017	ICD-10 code	Alcoholic cirrhosis mortality rate: From 20.55 to 10.62 per 100000
[54]	US	Adult patients in the NIS	2008-2014	ICD-9 code	Hospitalization costs: 7.37 billion dollars in 2014

US: United States; ICD: International classification of diseases; HIRA-NPS: Health insurance review and assessment-national patient samples; SNOMED: Systematized nomenclature of medicine; NHIS: National Health Insurance Service; KCD: Korean standard classification of diseases; ICES: Institute for clinical evaluative sciences; NIS: National inpatient sample.

The prevalence was 4.1% (95%CI 2.6%-6.4%) in primary care or the general population and significantly higher at 12.7% (95%CI 8.6%-18.3%) in referral or tertiary care settings, with no effect of HIV coinfection on cirrhosis[16]. In a recent Spanish population survey on the prevalence of NASH-related liver fibrosis, the prevalence of cirrhosis in the current biopsy-proven NASH cohort (a total of 501 patients from 2015-2020) was 0.70% (95%CI 0.10%-4.95%)[17]. A survey analyzing the Korea National Health and Nutrition Examination Survey (KNHANES) between 2015 and 2019 reported prevalence rates of cirrhosis in metabolically healthy obesity and metabolically unhealthy obesity populations of 0.5% and 0.4%, respectively[18]. In the TARGET-NASH study conducted from August 2016 to March 2019, researchers revealed that lean participants had a lower prevalence of cirrhosis (22.6% *vs* 40.2% of nonlean participants), with almost half of the lean subjects being Asian. Lean Asians were half as likely to develop NAFLD-related cirrhosis as nonlean individuals [odds ratio (OR) 0.47; 95%CI 0.29-0.77][19]. Furthermore, different diagnostic tools can have varied diagnostic accuracy and cost-effectiveness for cirrhosis. A cost-effectiveness study found high diagnostic accuracy and cost-effectiveness of fibrosis-4 (FIB-4), followed by either vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), or liver biopsy[20]. In terms of the combination of diagnostic tools, FIB-4 + VCTE was the least costly combination, whereas the incremental cost-effectiveness ratios (ICERs) for the combination of FIB-4 and MRE were lower than those for FIB-4 and liver biopsy[20]. The prevalence of cirrhosis in older patients with multiple comorbidities has recently been addressed. In a study that included a cohort of 6,193 elderly patients admitted to acute medical wards between 2010 and 2018, 315 patients (5%) were diagnosed with cirrhosis[21]. Finally, a pooled meta-analysis including 15 studies with a total of 320777 patients suggested that among those receiving dialysis, the prevalence of cirrhosis was 5% and associated with higher mortality, with further analysis showing that hepatitis B and C,

Table 2 Epidemiology of cirrhosis in specific at-risk populations

Ref.	Country	Study population	Study period	Diagnostic methods	Presented data
[13]	US	825 adults with type 2 diabetes who had reliable TE results from the NHANES	2017-2018	TE	Prevalence: 7.7%
[14]	US	Patients with NAFLD from the NHANES	2017-2018	TE	Prevalence: 4.4%
[15]	US	3115 HBsAg-negative/HBcAb-positive subjects from the NHANES	2001-2018	FIB-4	Cirrhosis/advanced liver fibrosis prevalence: 3.76%
[16]	13 countries in sub-Saharan Africa	HBV-infected population	2012-2019	TE, APRI and Fibrotest	Prevalence: 4.1% in primary care or the general population and 12.7% in referral or tertiary care settings
[17]	Spain	501 biopsy-proven NASH patients with paired TE data from tertiary centers	2015-2020	TE	Prevalence: 0.70%
[18]	Korea	27629 adults with MHO or MUHO from the KNHANES	2015-2019	Self-report survey or by an AST level ≥ 23.5 IU/L	Prevalence: 0.5% and 0.4% in MHO and MUHO, respectively
[19]	US	3386 patients with NAFLD in the TARGET-NASH study	2016-2019	Pragmatic case definitions	Prevalence: 22.6% in lean patients
[21]	Italy	6193 older subjects admitted to acute medical wards and included in the REPOSI registry	2010-2018	ICD-9 code	Prevalence: 5%
[22]	10 countries in the world	320777 dialysis patients	1980-2019	TE, histopathology, radiology, and ICD codes	Prevalence: 5%
[36]	NR	902 patients with a Fontan circulation	NR	NR	Cumulative incidence: 27.5%
[39]	Japan	1260 patients who underwent the Fontan procedure and survived to discharge from 9 institutions	From before 2011 to 2021 (median10.2 of years follow-up)	Biopsy or imaging or extrahepatic features	Cumulative incidence at 10, 20, and 30 years after the Fontan procedure: 0.9%, 11.6%, and 25.7%, respectively
[41]	Italy	All adults aged 30 years or older without cirrhosis in Rome	From 2001 follow up to 2015	A validated algorithm	Crude incidence rate: 67 per 100000 person-years

US: United States; TE: Transient elastography; NHANES: National Health and Nutrition Examination Survey; NAFLD: Nonalcoholic fatty liver disease; HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; FIB-4: Fibrosis-4; HBV: Hepatitis B virus; APRI: Aspartate transferase-to-platelet ratio index; NASH: Nonalcoholic steatohepatitis; MHO: Metabolically healthy obesity; MUHO: Metabolically unhealthy obesity; KNHANES: Korea National Health and Nutrition Examination Survey; AST: Aspartate transferase; IU/L: International unit per liter; REPOSI: Registro Politerapia Società Italiana di Medicina Interna; NR: Not recorded.

rather than diabetes, contributed to the increased risk of cirrhosis[22].

Incidence

The global number of incident cases of cirrhosis and CLD in 2017 was 5.2 million according to the GBD 2017, although the incidence was not available[23]. However, the latest global incidence of NASH-associated cirrhosis has been mentioned in recent publications using data from the GBD 2017[24,25]. In 2017, the global incidence of cirrhosis due to NASH was 367780 cases, an increase of approximately 105.56% compared to 1990 (178430 cases in 1990). The age-standardized incidence rate (ASR) was 4.81 (95%UI 4.38-5.28) per 100000 population in 2017 compared to 3.31 (95%UI 3.02-3.63) per 100000 population in 1990, with an estimated annual percentage change (EAPC) of 1.35% (95%CI 1.28-1.42%). Gender and regional differences in incidence were also observed. The incidence was higher in males than in females [5.54 (5.06-6.07) compared to 4.08 (3.69-4.49) per 100000 population], although the EAPC was higher in females. The middle-high sociodemographic index (SDI) region featured the highest incidence, while that of the low SDI was the lowest [6.14 (5.60-6.70) compared to 2.72 (2.43-3.05) per 100000 population]. A more pronounced increase in the ASR was recorded in Eastern Europe, Andean Latin America, and Central Asia, while the Asia Pacific region showed a decline. In terms of HBV and HCV-associated cirrhosis, the overall incidence has shown a relatively encouraging trend both in men and women. Veracruz *et al*[26] exploited GBD statistics from 2010-2019 to analyze the global incidence and mortality trends in HBV and HCV infection, cirrhosis, and hepatocellular carcinoma (HCC) over this period. The worldwide incidence of HBV-related cirrhosis decreased by 15% from 5.78 (95%CI 4.3-7.3) in 2010 to 4.91 (95%CI 3.5-6.5) in 2019 per 100000 individuals, with the greatest reduction occurring

in Eastern Europe at 36%. This trend may be related to widespread HBC vaccination[27]. However, the 2019 incidence of HCV-associated cirrhosis amounted to 6.7 (95%CI 5.0-8.6) per 100000 population, an increase of 5.6%, with the greatest increase of 27.8% in central sub-Saharan Africa and the greatest decrease of 13.5% in the high-income Asia-Pacific region.

The China Kadoorie Biobank prospectively included 512891 adults (210222 men and 302669 women) aged 30-79 years in 10 geographically disaggregated sites. During the 10-year follow-up period, 2082 cases of cirrhosis occurred in 503993 participants with an excluded history of CLD. The incidence of cirrhosis among diabetic patients was 756.4 per 100000 compared to 397.4 per 100000 among nondiabetic patients, and the Cox regression yielded a hazard ratio (HR) of 1.81 (95%CI 1.57-2.09) for cirrhosis among diabetic patients[28]. Another modeling study employed a multicohort state-transition (Markov) model to predict the epidemiological trends in alcohol-related liver disease in the US from 2019 to 2040[29]. In this model, researchers modeled prevalence and mortality trends of decompensated cirrhosis in three projection scenarios, including a status quo scenario (current trends continued), a moderate intervention scenario (high-risk alcohol intake receded to 2001 levels), and a strong intervention scenario (high-risk alcohol intake trends decreased by 3.5% per year). In the status quo scenario, the age-standardized incidence of alcohol consumption-related decompensated cirrhosis was projected to increase from 9.9 (95%CI 9.3-10.9) cases per 100000 person-years in 2019 to 17.5 (15.8-18.4) cases per 100000 person-years in 2040, which would be a 77% increase. In the moderate intervention scenario, the age-standardized incidence of alcohol drinking-related decompensated cirrhosis would be expected to increase by 69% to 16.7 (95%CI 14.2-16.4) cases per 100000 person-years in 2040. Conversely, the incidence of alcohol-related decompensated cirrhosis associated under the strong intervention scenario would decrease by 11% compared to 2019, which is encouraging. From 2019 to 2040, the cumulative incidence was projected to reach 1118200 cases (95%CI 1005400-1123500), 1067000 (943400-1084600) and 786400 cases (711200-819300) for the status quo, moderate and strong intervention scenarios, respectively, with the strong intervention scenario achieving a 30% reduction compared to the status quo scenario. In a large national cohort study conducted in Korea, the incidence of alcoholic cirrhosis showed an overall increase between 2012 and 2016, from 1463 cases in 2012 to 1530 cases in 2016[30]. A Swedish population-based cohort study including 310000 inhabitants analyzed epidemiological trends in the incidence, causes, and complications of cirrhosis in the last decade (2011-2018). The incidence of cirrhosis was assessed at 23.2 per 100000 person-years, with a higher rate of 30.5 in men and 16.4 in women[31]. Stratifying by age showed the highest incidence in the 60-69 age group, and alcohol was the leading cause of all cases (50.5%). In a study conducted in South Korea using the National Health Insurance Service database, trends in the incidence of rare diseases were explored for the period 2011-2015. The average annual cumulative incidence of primary biliary cirrhosis was 68.32 cases per 10000000 and was increasing at an annual trend of 6.32[32]. A retrospective study conducted in Ontario, Canada, used health data from the period 1997-2016 to determine the incidence of cirrhosis in young birth cohorts. During this period, 165979 cases of cirrhosis were diagnosed, with an increasing trend in age-standardized incidence from 70.6 in 1997 to 89.6 per 100000 person-years in 2016. The incidence was higher in the younger birth year cohort than in the middle-aged birth cohort and was more evident in women[33].

In pediatric populations, the incidence and current trends of cirrhosis have also been reported in the recent literature. A population-based study from Ontario, Canada, analyzed changes in the incidence of cirrhosis in children from 1997-2017[34]. Over the past two decades, 2966 new cases of cirrhosis were diagnosed in children (median age 9 years), and the age- and sex-adjusted incidence of cirrhosis increased significantly by nearly fourfold (from 2.7. in 1997 to 10.6 per 100000 person-years in 2017). Notably, the most marked increases were identified in infants < 1 year and adolescents > 11 years old. After the age-period-cohort study, the authors found that children born in 2010 had twice the risk of developing cirrhosis than those born in 2001. Dong *et al*[35] prospectively included 139 children with biopsy-proven cirrhosis (median age at initial diagnosis 2 years) from January 2010 to January 2020, 93 of whom had a definite cause. HBV infection was the most common cause (33.3%), followed by glycogen storage disease (17.2%) and Wilson disease (15.1%).

The incidence of cirrhosis has also been investigated in specific populations in recent studies. A recent meta-analysis pooled 14 studies including 902 patients with Fontan circulation and estimated the incidence of cirrhosis in this population[36]. Fontan circulation is characterized by an increase in central venous pressure, which in turn affects back-stream veins and can lead to congestive hepatopathy known as Fontan-related liver disease[37,38]. There were 241 patients with reported cirrhosis following a mean follow-up period of 17.9 ± 4.5 years, with a cumulative incidence of 27.5% (95%CI 16.9%-34.4%). Another updated study included 1250 patients (median age 3.6 years, 47.5% female) who underwent their first Fontan procedure, with cirrhosis diagnosed in 5.8% of patients over a median follow-up period of 10.2 years. The cumulative incidence of cirrhosis at 10, 20, and 30 years after Fontan surgery was 0.9%, 11.6%, and 25.7%, respectively[39]. The high incidence of cirrhosis in this population can be a substantial disease burden and therefore should be taken seriously. A nested case control study conducted in Taiwan found that the presence of diabetes and associated extrahepatic complications, such as hypertensive cardiovascular disease and chronic kidney disease, were associated with an increased incidence of treatment-naïve HCV-related cirrhosis[40], suggesting an important role for metabolic risk factors in the increased risk of developing cirrhosis. A nationwide cohort study including

approximately 1.2 million people aged 30 years or older in Rome analyzed the association between long-term exposure to air pollution and the incidence of cirrhosis, of which 10111 cases occurred during a 14-year follow-up period, yielding a crude incidence of 67 per 100000 person-years[41]. Long-term exposure to PM10, PM coarse, PM2.5, and NO2 was associated with the incidence of cirrhosis.

Mortality

The most recent GBD 2019 describing global mortality from cirrhosis is available. A recent systematic analysis of the GBD 2019 highlighted that the total number of deaths from cirrhosis worldwide was 1.43 million in 2019, an increase of 8.1% compared to the number of deaths in 2017 according to the GBD 2017 (1323000 cases)[42]. In a recent report, the GBD 2019 assessed the health progress of subnational regions in Ethiopia in 2019. In 2019, the all-cause age-standardized mortality rate was 993.52 (95%UI 914.97-1070.55), and for cirrhosis and other CLDs, it was 52.18 (95%UI 44.17-62.07) per 100000 population[43].

In 2017, 31.5% of cirrhosis deaths among men were caused by HBV, 25.5% by HCV, 27.3% by alcoholic liver disease (ALD), 7.7% by NASH, and 8.0% by other factors[6]. Among women, the proportion of deaths from cirrhosis due to HBV, HCV, ALD, NASH, and other causes was 24.0%, 26.7%, 20.6%, 11.3%, and 17.3%, respectively[6]. Deaths from hepatitis B-related cirrhosis were 321000 in 2019, representing 22% of all cirrhosis deaths. In 2017, the number of associated deaths was 384000 (29%), which indicated a 16.4% decrease in the mortality rate[42]. A previous study investigated trends in the incidence and mortality of acute infections, cirrhosis, and HCC by exploring the GBD for HBV and HCV from 2010-2019[26]. The 2019 global mortality rate for HBV-associated cirrhosis was 4.03 (95%CI 3.39-4.76) per 100000 population, showing a 23.2% reduction over this decade. The highest death rate for cirrhosis due to HBV infection was recorded in western sub-Saharan Africa at 16.49 (95%CI 12.69-21.35), while the lowest was seen in high-income North America at 0.35 (95%CI 0.29-0.42). The largest reduction in mortality compared to 2010 was in East Asia at 46.5%. The global mortality rate for HCV-related cirrhosis was 4.82 (95%CI 4.09-5.57) per 100000 in 2019, a 7.4% decrease compared to 2010. The highest mortality rate was 15.4 (95%CI 12.52-19.04) in Eastern sub-Saharan Africa, and the lowest was 1.79 (95%CI 1.41-2.25) per 100000 population in Western Europe. The greatest decrease of 23.9% was seen in the high-income Asia Pacific region, although several regions, such as the Caribbean and high-income North America, experienced an upward trend. In 2017, the global age-standardized mortality rate for ALD was 6.2 (5.7-6.9) and 2.1 (1.9-2.6) per 100000 for men and women, respectively[6]. The estimated number of deaths due to NASH cirrhosis worldwide in 2017 was 118,030, an increase of 90.7% compared to 1990, with an age-standardized death rate of 1.5 (1.3-1.6) per 100000 population, which was not significantly different compared to that of 1990[25].

The trend in the in-hospital burden of ALD among women was analyzed using data from the 2003 to 2017 National Inpatient Sample (NIS). In 2017, there were 14330 deaths from alcoholic cirrhosis (2.05% of all deaths), a relative decrease of 21.27% compared to 2003, although deaths from alcoholic hepatitis have increased rapidly[44]. Another study analyzed trends in mortality from alcohol-related cirrhosis in Mexico from 2000-2017 and found a decrease in mortality in all age groups, with the associated mortality rate falling from 20.55 to 10.62 per 100000 for all populations during this period[45]. However, there has been a rapid increase in alcohol consumption in the United States and other regions in recent years, and consequently, the mortality rate from ALD has shown a marked increase[46-49]. A study included underlying cause of death public-use data from January 1, 2017, to December 31, 2020, a dataset that contains death data for all United States citizens. Age-adjusted mortality from ALD increased from 13.1 (95%CI 12.9-13.3) to 16.9 (16.7-17.1) in men and 5.6 (5.4-5.7) to 7.7 (7.6-7.9) per 100000 in women[50].

Public health burden

In the latest analysis of the burden of 369 diseases and injuries in 204 countries and territories, the percentage of disability-adjusted life-years (DALYs) for cirrhosis and CLD at all ages in 2019 was 1.8 (95%UI 1.6-2.0), ranking 16th. The percentage increase in the number of DALYs compared to 1990 was 33.0 (22.4-48.2), while the age-standardized DALYs decreased by 26.8%[51]. In the age-stratified analysis, DALYs for cirrhosis in 2019 were ranked 12th at 2.8% of all diseases and injuries among individuals aged 25-49 years, 7th at 2.7% among individuals aged 50-74 years, and 19th at 1.1% among individuals aged 75 or older. Another recent study analyzed the impact of HBV and HCV infections on DALYs using data from the GBD 2010-2019. The 2019 DALYs for HBV cirrhosis decreased by 23% from 168.6 (95%CI 146.9-191.3) in 2010 to 129.8 (108.3-153.0), while the DALYs for HCV cirrhosis decreased by 8.2% to 146.2 (124.4-169.8) compared to that in 2010[52]. In 2019, HCV infection, alcohol, and HBV infection-related etiology were the most predominant sources of DALYs for cirrhosis, with prevalences of 26%, 24%, and 23%, respectively, and NAFLD contributed a relatively small proportion (8%) but showed a rapidly increasing trend[53]. In poorer countries, DALYs were higher, and cirrhosis due to HBV was the main source, whereas in wealthier countries, HCV and alcohol were the primary contributors. DALYs due to NAFLD cirrhosis are expected to become mainstream in the future in parallel with the epidemic of diabetes and obesity. Furthermore, the authors critically highlighted the current underestimation of the disease burden of cirrhosis (as compensated cirrhosis is currently considered no disability and decompensated cirrhosis only mild disability)[53].

The financial burden associated with hospitalized patients with cirrhosis was addressed in a recent study using data from the 2008-2014 NIS. Hospitalization costs for cirrhosis increased by 30.2% to $7.37 billion over the study period. Admissions for compensated and decompensated cirrhosis increased by 24% and 36%, respectively, while noncirrhotic populations dropped by 7.7%. The median length of stay (LOS) in the hospital was longer for cirrhosis than for other diseases. Implementing mechanical ventilation and complications associated with cirrhosis were the main drivers of the increased costs. More specifically, mechanical ventilation increased costs by 15%-152% in hospitalized patients with cirrhosis, and infection and nonhypertensive gastrointestinal bleeding led to increased costs in patients with compensated cirrhosis, while renal and infectious events were contributors to decompensated cirrhosis[54]. Jepsen *et al*[53] suggested that although the prevalence of cirrhosis was increasing, it would be simplistic to assume that costs for patients with cirrhosis were increasing, as the treatment currently provided for cirrhotic patients may be less or cheaper than before. However, the cost of NAFLD-related cirrhosis will likely continue to rise until an effective treatment becomes available[55].

EPIDEMIOLOGY OF MAJOR COMPLICATIONS

Ascites and ascites infection

Ascites is the most common complication in patients with cirrhosis and is defined as pathological fluid accumulation in the peritoneal cavity[56]. Ascites occurs only in the presence of portal hypertension, and approximately 75% of the occurrence of ascites is due to cirrhosis and portal hypertension[56,57]. The pathophysiological mechanisms may involve a complex interaction of the endogenous vasoactive system, portal hypertension, and renal dysfunction[58]. As a hallmark of decompensation, ascites has a prevalence of approximately 10% in patients with cirrhosis[58]. Approximately 60% of patients with compensated cirrhosis can develop this complication over a 10-year period, and it is associated with a high mortality rate of up to 50% within 3 years of onset[59,60]. A recent population-based study analyzed the epidemiology of ascites infection among patients with cirrhosis in Queensland, Australia, from 2008-2017. Of 103165 patients with cirrhosis, 16550 had ascites (16%)[61]. A further Korean study using a nationally representative database yielded a real-world burden of complications in patients with decompensated cirrhosis from 2016 to 2018, with ascites being the most common decompensated event (54.8%), followed by GEV bleeding, HE and hepatorenal syndrome (HRS)[62]. However, recent epidemiological information related to ascites in cirrhosis is relatively scarce.

Ascites infection is a frequent concurrent event in patients with cirrhosis and ascites, such as the prevalent spontaneous bacterial peritonitis (SBP) and, less commonly, fungal infections[63,64]. SBP is defined as spontaneous ascites infection in the absence of other causes of secondary peritoneal infection [65]. The diagnosis is based on the presence of > 250 polymorphonuclear cells/mm^3 in the ascites fluid as the high negative culture rate (up to 60% has been reported)[66,67]. Admissions for ascites infections increased by 76% in Queensland, Australia, from 2008 to 2017[61]. Another recent retrospective study included 1035 patients with cirrhosis from a single center in Israel between 1996 and 2020. A total of 173 (16.7%) of the patients developed SBP, and positive ascites fluid cultures were demonstrated in 47.4% of the SBP cases[68]. A recent meta-analysis including 99 studies comprising 5861142 patients with cirrhosis summarized the prevalence, resistance, and outcomes of SBP in cirrhosis worldwide[69]. The pooled global prevalence of SBP was 17.12% (95%CI 13.63%-21.30%), with Africa having the highest prevalence (68.20%) and North America having the lowest (10.81%). The prevalence of community-acquired SBP was 6.05% (95%CI 4.32%-8.40%) compared with 11.11% (95%CI 5.84%-20.11%) for health care-related SBP. The prevalence of antibiotic-resistant microorganisms in SBP was 11.77% (95%CI 7.63%-17.73%), with methicillin-resistant Staphylococcus aureus (6.23%), broad-spectrum β-lactamase-producing microorganisms (6.19%) and vancomycin-resistant enterococci (1.91%) being predominant. The incidence of SBP in outpatient paracentesis among patients with asymptomatic cirrhosis was estimated at 2% (95%CI 1%-3%) in a recent meta-analysis that included 16 studies with 1532 patients [70]. The global pooled mortality rate for SBP was 30.61% (23.30%-39.06%), with in-hospital, 30-d and 90-d mortality rates of 23.38%, 25.64% and 37.64%, respectively[69].

Variceal bleeding

Varices can be observed in up to two-thirds of patients with cirrhosis, while the annual incidence rate is 8%-10% and the rate of progression to large varices is 10%-12% annually[71]. Variceal bleeding is a common complication in cirrhosis associated with high mortality, with portal hypertension being the major driver. The common forms of variceal bleeding are esophageal and gastric variceal bleeding and, less commonly, rectal variceal bleeding. GEV bleeding can be present in 25%-35% of patients, which can develop in 40% of compensated cirrhosis patients and 85% of decompensated cirrhosis patients[72]. The six-week mortality rate for acute variceal bleeding ranges from 15% to 25%[73]. In a study that included 1902 children younger than 18 years who suffered esophageal variceal bleeding in 50 hospitals in the US from 2004-2019, the mortality rate for variceal bleeding was 7.3% (increasing to 8.8% after 6 wk) and 20.1% for any cause[74]. A retrospective study enrolled all patients in the NIS from 2016-2019 who were discharged with a diagnosis of esophageal variceal bleeding (166760 cases, of which 32.7% were

women), and found that males were associated with a higher mortality rate than females (9.91% compared to 8.31%, *P* value 0.008 after adjusting for confounders)[75]. However, there are relatively few relevant recent epidemiological reports.

HE

HE is a neuropsychiatric disorder in cirrhosis that is strongly associated with prognosis, and its clinical course can be divided into covert hepatic encephalopathy (CHE), which includes minimal hepatic encephalopathy (MHE) (cognitive deficits found on psychological tests) and Grade I HE, and overt hepatic encephalopathy (OHE), where clinically significant symptoms develop[76,77]. The median survival of patients with cirrhosis is significantly shorter at 0.95 years in those over 65 years after the diagnosis of HE was established[78].

The prevalence of CHE has been reported to be very high in patients with cirrhosis, but estimates vary considerably among studies depending on, for example, the diagnostic method and the severity of cirrhosis[79]. In a prospective multicenter study, the prevalence of MHE under the combined diagnostic criteria based on the critical flicker frequency (CFF) and Psychometric Hepatic Encephalopathy Score (PHES) was 18.2%, with 12.1% of patients having compensated cirrhosis and 22.5% of patients showing decompensated cirrhosis[80]. Another multicenter study validated the ability of the EncephalApp in diagnosing MHE. The prevalence of MHE was 51% for the norm-based EncephalApp, 37% for the PHES-based EncephalApp, and 54% for the inhibitory control test (ICT)-based EncephalApp[81]. In a recent study conducted in Turkey, the prevalence of MHE in compensated cirrhosis patients based on the PHES, CFF, and a combination of both was 29.8%, 27.4%, and 16.0%, respectively[82]. An attempt was made to examine the effect of single and combined diagnostic modalities in CHE. The prevalence of CHE varied among the different diagnostic sets, with rates of 18%, 25%, 29%, 35%, 37% and 54% for the PHES + ICT, ICT + Stroop EncephAlapp (StE), PHES + StE, ICT, PHES, and StE, respectively[83]. In addition, the underestimation of the burden of HE and other factors that may be regionally variable, such as smoking, diabetes, and alcohol intake, can impact the diagnosis of CHE[79], all contributing to the significant variability in the prevalence of CHE.

The incidence of OHE has also been described recently. A prospective study included 294 patients with Child A-B cirrhosis without previous HE from July 2016 to August 2018, with the incidence of OHE at one year being 14% in all patients, 10% in Child A patients, and increased to 25% in Child B patients[84]. A large population-based study included a randomized 20% of Medicare participants with cirrhosis and Part D prescription coverage from 2008-2014, with a total OHE incidence of 11.6 per 100 patient-years over a 5.25-year follow-up of 166,192 patients with cirrhosis (median age 65 years). Alcoholic cirrhosis and portal hypertension are key players in the development of OHE, and drug use, such as proton pump inhibitors (PPIs), benzodiazepines, gamma-aminobutyric acid and opioids, is also potentially relevant[85]. These findings indicate that other components may also be associated with the development of HE and influence the incidence. In fact, several factors, such as transjugular intrahepatic portosystemic shunts (TIPSs)[86], PPIs[87], albumin[88], sustained virological response (SVR) in HCV infection[89], and others, can contribute to the development of HE.

HE imposes a heavy burden on patients with cirrhosis, including increased hospitalization, costs, and readmissions, impairment of health-related quality of life (HRQOL), and decreased socioeconomic status[90]. During 2010-2014, data from the NIS show a 24.4% increase in the number of hospital admissions for HE and a 46.0% increase in the total cost of admissions (which reached $11.9 billion in the United States in 2014)[91]. HE-related 90-d readmissions comprised approximately 23.7% of patients with cirrhosis[92] and were significantly associated with readmission in patients with decompensated cirrhosis[93]. In a large multistate population-based study on the causes and rates of readmission in cirrhosis, HE was significantly correlated with both 30-d readmission and 90-d readmission, with adjusted ORs of 3.23 (95%CI 2.97-3.52) and 3.07 (2.86-3.30), respectively[94]. Moreover, HE is associated with an increased risk of falls and can cause serious outcomes leading to high comorbidity and mortality[95]. In socioeconomic terms, cognitive impairment due to HE has been shown to have a multilevel association with adverse outcomes of employment/income, driving ability, and HRQOL[79].

Acute kidney injury and HRS

Renal dysfunction is a common complication in patients with cirrhosis and ascites[96]. In 2015, the revised consensus of the International Club of Ascites defined acute kidney injury (AKI) in cirrhosis as an increase in serum creatinine (sCr) of 0.3 mg/dL in < 48 h or a 50% increase in sCr from baseline within the last 3 mo[97]. AKI comprises a variety of phenotypes, including functional AKI and structural AKI. Functional AKI includes volume-responsive prerenal azotemia (PRA) and HRS-AKI, while structural AKI presents with structural changes such as acute tubular necrosis (ATN). HRS-AKI (previously known as HRS-1) is defined as at least stage 2 or above AKI in patients with cirrhosis and ascites, while excluding other causes such as PRA and ATN[97]. HRS can thus be divided into HRS-AKI and HRS-non-AKI (previous HRS-2)[98].

In a prospective study of 405 patients with cirrhosis enrolled in 2016-2017, the prevalence of AKI was 19.3%, and survival was lower at 30 d and 90 d compared to that of non-AKI patients[99]. The prevalence of AKI ranges from 18.5% to 40.6% in some other regions[100-102]. A meta-analysis revealed that the prevalence of AKI in acute-on-chronic liver failure (ACLF) could be significantly increased to

41%[103]. The overall prevalence rates of PRA and ATN in patients with cirrhosis are 15%-45% and 15%-60%, respectively, which are higher than the 10-40% rate of HRS[104]. The prevalence of HRS in patients with decompensated cirrhosis was 3.6%, while the median LOS for HRS was 4 wk per year in a large representative Korean database from 2016-2018, significantly higher than that for patients with ascites (19 d) or GEV bleeding (13 d)[62]. A recent study that included patients with a primary diagnosis of HRS in the NIS from 2008-2018 found a notable increase in the number of HRS hospitalizations from 22864 in 2008 to 42985 in 2018; however, there was a decreasing trend in inpatient mortality (36.2% in 2008 to 25.7% in 2018)[105].

Infection

In addition to SBP, patients with cirrhosis are at substantially increased risk of developing infections, commonly urinary tract infections (UTIs), pneumonia, and soft tissue infections[106]. The most frequent types of infections in a study that included 877 hospitalized cirrhotic patients from 2011-2016 were UTI (33%), pneumonia (23%), SBP (14%), and bacteremia (11%)[107]. Using the Nationwide Readmissions Database from 2011-2014, the overall prevalence of infections was 29.2% in 1798830 admissions, including UTI (13.7%), pneumonia (8.9%), cellulitis (5.2%), *Clostridioides difficile* infection (CDI) (2.8%), and SBP (2.0%). Pneumonia, SBP, and CDI had notably higher mortality than cellulitis and UTI, and sepsis and organ failure were also more common. Pneumonia had the highest mortality in the multivariate regression analysis (OR 2.73, 95%CI 2.68-2.80) and caused multiple organ failure (OR 3.59, 95%CI 3.50-3.68)[108]. The prevalence of CDI in cirrhosis has shown an increasing trend at approximately 2.7% in 2014, while the mortality of CDI is on the decline, and in local hospitals, the incidence of CDI ranges from 4.9% to 18.8%[109]. In recent years, infections caused by multidrug-resistant organisms (MDRO) have posed a serious challenge in cirrhosis[110]. In a study conducted in Europe that prospectively included two series of cohorts of patients with decompensated cirrhosis in 2011 and 2017-2018, the prevalence of MDRO in culture-positive infections increased from 29.2% in 2011 to 38.0% in 2017-2018[111]. Another worldwide study enrolled 1302 patients with cirrhosis and infections at 46 centers (15 in Asia, 15 in Europe, 11 in South America, and 5 in North America) in 2015-2016 and found a 34% prevalence of MDROs with geographic variability (highest in Asia)[112].

EPIDEMIOLOGY OF HCC IN LIVER CIRRHOSIS

Primary liver cancer was the sixth most common and the third most deadly cancer in 2020, with HCC being the predominant phenotype[113]. According to the GBD 2019, the global age-standardized incidence rate, age-standardized mortality rate and age-standardized DALYs for liver cancer in 2019 were 6.51, 5.95, and 151.08 per 100000, respectively[114]. NASH is the fastest growing cause of liver cancer and is projected to continue to increase in the future[115]. In 2019, the most common contributing factor for liver cancer was hepatitis B (41%), followed by hepatitis C (28.5%), alcohol use (18.4%), NASH (6.8%) and other etiologies (5.3%)[115,116]. Cirrhosis is a precancerous lesion that predisposes patients to progressing to HCC. However, HCC can develop directly without the presence of cirrhosis in a proportion of individuals. In a large US multicenter study, 11.7% of 5,144 included HCC patients showed the absence of cirrhosis, with NAFLD (26.3%), HCV (12.1%) and HBV (10%) being the most common causes[117]. A recent meta-analysis concluded that 37% (95%CI 28%-46%) of patients with NAFLD-related HCC presented without cirrhosis[118]. The prevalence of NAFLD-related HCC was significantly higher in patients with cirrhosis than in those without (374.4/10000 *vs* 4.6/10000 persons)[119].

The epidemiology of HCC in patients with cirrhosis has recently been studied and is etiologically variable (Table 3). In a recent Swedish nationwide population-based cohort study, the incidence of HCC in the cirrhotic population was 23 per 1000 person-years (lowest in ALD at 15 per 1000 person-years and highest in viral hepatitis at 41 per 1000 person-years)[120]. The cumulative incidence of HCC in patients with cirrhosis at 5 and 10 years was 8.3% and 12.2%, respectively. At 10 years, the cumulative incidence was lowest in women with alcoholic cirrhosis (4.3%) and highest in men with viral hepatitis (26.6%)[120]. A study included two US prospective multiethnic contemporary cohorts of patients with cirrhosis, with a total enrolled population of 2733 patients with cirrhosis (19.0% had active HCV, 23.3% had cured HCV, 16.1% had ALD, and 30.1% had NAFLD). After 7,406 person-years of follow-up, the annual HCC incidence rate was 1.82%. The annual HCC incidence in patients with cured HCV, ALD and NAFLD was 1.71%, 1.32%, and 1.24%, respectively. The risk of developing HCC in patients with cured HCV cirrhosis was two-fold higher than that in patients with NAFLD (HR 2.04, 95%CI 1.24-3.35)[121]. Data on the mortality and public health burden of HCC in patients with cirrhosis are relatively scarce.

In a recent meta-analysis of patients with cured HCV, the incidence of HCC was 2.1 per 100 person-years and declined over time after the patients was cured[122]. A prospective study yielded a cumulative incidence of HCC of 7.4% at 5 years in patients with HBV cirrhosis receiving antiviral therapy[123], and partial virological response after two years of entecavir treatment was associated with an increased risk of HCC[124].

Table 3 Epidemiology of hepatocellular carcinoma in patients with cirrhosis

Ref.	Country	Study population	Study period	Study design	Epidemiology
[119]	US	392800 NAFLD patients from 26 major integrated US healthcare systems	2015-2020	Retrospective cohort study	Prevalence: 374.4/10000 persons
[120]	Sweden	15215 individuals with cirrhosis in the National Outpatient Register	2001-2016	Nationwide population-based cohort study	Incidence rate: 23 per 1000 person-years; cumulative incidence: 8.3% at 5 years and 12.2% (4.3% in women with alcoholic cirrhosis and 26.6% in men with viral hepatitis) at 10 years
[121]	US	2733 patients with cirrhosis in two contemporary prospective multiethnic cohorts	2016-2020 (with follow-up until June 30, 2021)	Prospective multiethnic cohort study	Annual incidence: 1.82% (1.71%, 1.32%, and 1.24% in cured HCV, ALD and NAFLD, respectively)
[122]	NA	29444 patients with HCV cure	NA	Meta-analysis	Incidence: 2.1 per 100 person-years
[123]	China	937 treatment-naïve adults with compensated HBV-induced cirrhosis	2012-2015 (with follow-up until June 30, 2019)	Prospective cohort study	Cumulative incidence: 7.4% at 5 years
[124]	Korea	359 patients with HBV-associated cirrhosis who were treated with ETV for at least 2 years	2007-2012 (median follow-up of 82 mo)	Retrospective cohort study	Cumulative incidence: 4.7%, 15.9%, 21.8% and 32.9% at 3, 5, 7 and 9 years, respectively
[125]	US	501 veterans with PBC and compensated cirrhosis	2008-2016 (with follow-up until December 31, 2019)	Retrospective cohort study	Incidence: 0.6 and 0.7 person-years in UDCA responders and UDCA partial responders, respectively
[126]	US	532 patients with PBC and compensated cirrhosis	2008-2016 (with follow-up until June 30, 2020)	Retrospective cohort study	Incidence: 0.9 and 0.3 person-years in males and females, respectively
[129]	NA	148333 patients with alcoholic cirrhosis	NA	Meta-analysis	Cumulative incidence: 1%, 2%, 3%, and 9% at 1, 3, 5, and 10 years, respectively
[131]	China	1095 patients with decompensated cirrhosis	2014-2019	Retrospective cohort study	Incidence: 3.92% in alcoholic cirrhosis
[132]	China	1515 patients with cirrhosis with alcoholism or/and HBV infection	2005-2020 (with follow-up until June 30, 2021)	Retrospective cohort study	Annual incidence: 3.5% (5.9%, 3.6%, and 2.9% in HBV plus alcoholism, HBV only and alcoholism only patients, respectively)

HCC: Hepatocellular carcinoma; US: United States; NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; ALD: Alcoholic liver disease; NA: Not available; HBV: Hepatitis B virus; ETV: Entecavir; PBC: Primary biliary cholangitis; UDCA: Ursodeoxycholic acid.

In a retrospective study that included 501 patients with primary biliary cholangitis and compensated cirrhosis, a total of 22 cases of HCC occurred during the study period (4.39%)[125], which is similar to the findings of another study (4.51%)[126]. In patients with primary sclerosing cholangitis and cirrhosis, the risk of HCC development is very low, although the risk of gallbladder cancer and cholangiocarcinoma is high[127].

The absolute risk of developing HCC in alcoholic cirrhosis seems to be lower than in viral hepatitis (annual incidence of approximately 2%-5%)[128]. A recent meta-analysis that included 18 studies outlined the incidence of HCC in alcoholic cirrhosis. After accounting for the competing risk of death without HCC, the cumulative incidence of HCC at 1, 3, 5, and 10 years was 1%, 2%, 3%, and 9%, respectively. The overall incidence of HCC in alcoholic cirrhosis was 8.29 (95%CI 4.77-14.39) per 1000 person-years[129]. However, the prognosis for HCC due to alcoholic cirrhosis appears to be worse[130]. Furthermore, alcohol consumption increases the incidence of HCC in HBV-related cirrhosis[131-133], while abstinence from alcohol significantly reduces the risk of developing HCC[133].

In a nationwide survey conducted in Japan, HCV-associated cirrhosis was the leading cause of HCC (60.3% of cases). The proportion of HCC from 2008 to 2016 due to hepatitis virus-related cirrhosis decreased, while HCC due to NASH and ALD-related cirrhosis increased from 1.5 to 7.2% and 8.5 to 18.6%, respectively[134].

The value of HCC surveillance in patients with cirrhosis remains to be addressed given the lack of sufficient randomized controlled trials to confirm the overall benefits and harms[135]. However, recent studies have provided robust evidence of the significance of HCC screening. A recent meta-analysis that included 59 cohort studies concluded that HCC surveillance was associated with improved early detection, curative treatment receipts and survival, although few studies weighed the benefits against the harms[136]. In another prospective cohort of patients with cirrhosis, HCC surveillance improved early detection, with physical damage observed in 8.8% of patients and mostly mild[137]. Furthermore, a survey performed in patients with cirrhosis found that patients were more concerned about early

HCC detection than about potential surveillance harm[138]. A survey conducted in the United States showed that gastroenterology and hepatology providers also prefer HCC surveillance when the risk of HCC is below the threshold recommended for surveillance by professional societies[139].

Ultrasound with or without alpha-fetoprotein (AFP) is recommended for HCC surveillance, and the addition of AFP to ultrasound significantly increases the sensitivity of early HCC detection[140]. Clinical HCC surveillance is still underused in patients with cirrhosis. A meta-analysis noted that only 24% of patients were screened, and this underutilization occurred particularly in patients with alcohol- or NASH-related cirrhosis and those not followed in subspecialty gastroenterology clinics[141]. In a United States nationwide cohort of patients with cirrhosis, only 8.78% of patients were under surveillance for HCC[142]. A retrospective multicenter cohort study found that the main reason for barriers to surveillance was lack of surveillance orders or nonadherence[143]. Another United States survey identified patient-reported barriers to surveillance as knowledge deficits about HCC surveillance, cost, difficulty scheduling and transportation[144]. Individualized predictive modeling for risk stratification in patients with cirrhosis can facilitate and improve the cost-effectiveness of surveillance[145,146].

FUTURE DIRECTIONS

In the early 2020s, the outbreak and subsequent epidemic of coronavirus disease 2019 (COVID-19) imposed heavy and multifaceted consequences globally[147]. The effect of COVID-19 on cirrhosis has also been extensively researched. COVID-19 infection is associated with significantly higher morbidity and mortality in patients with liver cirrhosis[148-151]. The COVID-19 epidemic may also have implications for the etiology of cirrhosis. The prevalence of COVID-19 promotes alcohol consumption and is associated with liver disease[152-155] and metabolic disorders[156]. Therefore, the newer epidemiology of cirrhosis may change due to the COVID-19 epidemic.

Alcohol consumption and NAFLD-induced liver disease are growing rapidly. A nationwide study in the United States showed that the charges of alcoholic cirrhosis exceeded the cost of other causes of cirrhosis combined[157]. NAFLD and ALD-related cirrhosis will account for almost all newly diagnosed cases in Canada by 2040[158]. Alcohol intake can influence cirrhosis of any etiology[133,159-161]. Therefore, effective measures to prevent and reduce the associated contributing factors will likely help mitigate the epidemic. One study found that alcohol control policies can have a significant and immediate effect on mortality from cirrhosis[162]. Alcohol abstinence reduced HCC due to alcoholic cirrhosis, although only in patients without previous decompensated disease[163]. NAFLD is emerging as another major epidemic due to the prevalence of metabolic disorders such as obesity and diabetes, and there is currently no effective treatment for NAFLD. Cirrhosis due to NAFLD is expected to be a major component in the future, representing a shift in the associated epidemiology. Therefore, utilization of available interventions such as weight loss and available medications to minimize the progression of NAFLD and the detection of early liver fibrosis using effective and accurate tools will be instrumental in mitigating the risk of cirrhosis.

CONCLUSION

The latest epidemiological data revealed the heavy burden of cirrhosis globally (Table 4). In 2017, the age-standardized global prevalence of compensated cirrhosis was 1395.0 per 100000, compared to 132.5 per 100000 for decompensated cirrhosis. In 2019, cirrhosis caused 1.48 million deaths worldwide, an increase of 8.1% compared to 2017. In 2019, liver cirrhosis ranked 16th among all diseases for DALYs. The burden of cirrhosis due to HBV and HCV is declining, while the burden of NAFLD and alcohol consumption is mounting. Furthermore, there is currently a changing epidemiology of the major complications of cirrhosis (Figure 1). The burden of HCC in patients with cirrhosis is etiologically variable, and HCC due to NASH and alcohol intake is increasing.

Table 4 Latest global epidemiological features of cirrhosis

Ref.	Epidemiological figures	Latest research	Type or etiology of cirrhosis	Reported data
Prevalence				
[6]	Age-standardized prevalence	GBD 2017	Cirrhosis	Compensated cirrhosis: 1395.0 (1323.5-1470.5); decompensated cirrhosis: 132.5 (128.6-136.2) per 100000
[6]	Age-standardized prevalence	GBD 2017	HBV-related cirrhosis	Compensated cirrhosis: 451.9 (420.0-485.9); decompensated cirrhosis: 36.6 (34.7-38.4)
[6]	Age-standardized prevalence	GBD 2017	HCV-related cirrhosis	Compensated cirrhosis: 341.1 (314.1-368.7); decompensated cirrhosis: 32.5 (30.6-34.5)
[6]	Age-standardized prevalence	GBD 2017	Alcohol-related cirrhosis	Compensated cirrhosis: 288.1 (267.5-311.3); decompensated cirrhosis: 30.0 (28.2-31.8)
[6]	Age-standardized prevalence	GBD 2017	NASH-related cirrhosis	Compensated cirrhosis: 115.5 (105.0-126.5); decompensated cirrhosis: 11.3 (10.4-12.1)
Incidence				
[24]	Age-standardized incidence	GBD 2017	NASH-related cirrhosis	4.81 (4.38-5.28)
[26]	Age-standardized incidence	GBD 2019	HBV-related cirrhosis	4.91 (3.50-6.50)
[26]	Age-standardized incidence	GBD 2019	HCV-related cirrhosis	6.7 (5.0-8.6)
Mortality				
[26]	Age-standardized Mortality	GBD 2019	HBV-related cirrhosis	4.03 (3.39-4.76)
[26]	Age-standardized Mortality	GBD 2019	HCV-related cirrhosis	4.82 (4.09-5.57)
[25]	Age-standardized mortality	GBD 2017	NASH-related cirrhosis	1.5 (1.3-1.6)
Public health burden				
[52]	DALYs	GBD 2019	HBV-related cirrhosis	129.8 (95%CI 108.3-153.0)
[52]	DALYs	GBD 2019	HCV-related cirrhosis	146.2 (124.4-169.8)

GBD: Global burden of diseases, injuries, and risk factors study; HBV: Hepatitis B virus; HCV: Hepatitis C virus; UI: Uncertainty interval; CI: Confidence interval; NASH: Nonalcoholic steatohepatitis; DALYs: Disability-adjusted life-years.

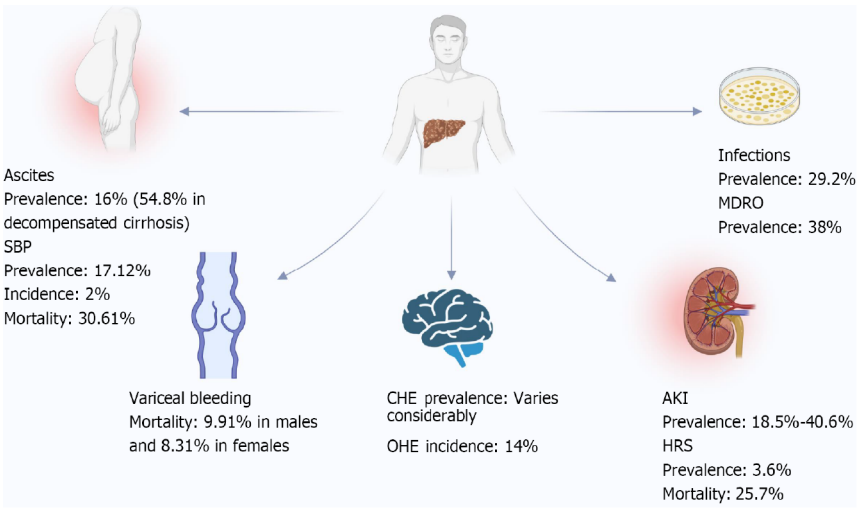

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Figure 1 The latest epidemiological data on the major complications of liver cirrhosis. The prevalence of covert hepatic encephalopathy depends on the means of diagnosis, the stage of cirrhosis, the underestimation of HE, and the presence of other factors affecting the prevalence. For the prevalence of infections, these data were obtained from the Nationwide Readmissions Database; therefore, the total population included readmissions. SBP: Spontaneous bacterial peritonitis; CHE: Covert hepatic encephalopathy; OHE: Overt hepatic encephalopathy; AKI: Acute kidney injury; HRS: Hepatorenal syndrome; MDRO: Multidrug-resistant organisms.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Enhanced segmentation of gastrointestinal polyps from capsule endoscopy images with artifacts using ensemble learning

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Abstract

BACKGROUND

Endoscopy artifacts are widespread in real capsule endoscopy (CE) images but not in high-quality standard datasets.

AIM

To improve the segmentation performance of polyps from CE images with artifacts based on ensemble learning.

METHODS

We collected 277 polyp images with CE artifacts from 5760 h of videos from 480 patients at Guangzhou First People's Hospital from January 2016 to December 2019. Two public high-quality standard external datasets were retrieved and used for the comparison experiments. For each dataset, we randomly segmented the data into training, validation, and testing sets for model training, selection, and testing. We compared the performance of the base models and the ensemble model in segmenting polyps from images with artifacts.

RESULTS

The performance of the semantic segmentation model was affected by artifacts in the sample images, which also affected the results of polyp detection by CE using a single model. The evaluation based on real datasets with artifacts and standard datasets showed that the ensemble model of all state-of-the-art models performed better than the best corresponding base learner on the real dataset with artifacts. Compared with the corresponding optimal base learners, the intersection over union (IoU) and dice of the ensemble learning model increased to different degrees, ranging from 0.08% to 7.01% and 0.61% to 4.93%, respectively. Moreover,

in the standard datasets without artifacts, most of the ensemble models were slightly better than the base learner, as demonstrated by the IoU and dice increases ranging from -0.28% to 1.20% and -0.61% to 0.76%, respectively.

CONCLUSION

Ensemble learning can improve the segmentation accuracy of polyps from CE images with artifacts. Our results demonstrated an improvement in the detection rate of polyps with interference from artifacts.

Key Words: Artifacts; Capsule endoscopy; Polyps; Ensemble learning; Segmentation; Robustness

Core Tip: Artificial intelligence has been widely used in capsule endoscopy to detect gastrointestinal polyps; however, it is often impaired by artifacts in clinical practice. At present, clear and high-quality images without artifacts are usually selected for research, which has not yet produced practical assistance regarding artifact interference. In this study, we demonstrated that ensemble learning can improve the segmentation performance of polyps under the interference of artifacts, which has a significant auxiliary role in the detection of polyps in clinical practice.

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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of death in the United States[1]. In China, an estimated 1101653 new cancer cases and 709529 cancer deaths from gastric cancer and CRC will occur in 2022, placing China first worldwide because of its large population[1]. Although other gastrointestinal lesions, such as erosions and ulcers, can also develop into cancers, most gastrointestinal cancers arise from precancerous polyps, which are the most common lesions found on endoscopy[2]. Therefore, early detection and removal of gastrointestinal polyps under endoscopy are critical for preventing gastrointestinal cancers[3-6]. Traditional gastroenteroscopy is widely used for the clinical assessment of gastrointestinal lesions. However, there are still some deficiencies, such as invasiveness and incomplete inspection of the site[7]. Additionally, some patients with small bowel diseases who have contraindications or are averse to undergoing gastroenteroscopy are more likely to use safer and non-invasive capsule endoscopy (CE) for visual examination of the digestive tract[8,9]. CE usually takes 8-12 h, which is not only time-consuming but also highly operator-dependent[10,11]. Otherwise, deep learning (DL) has greatly improved the sensitivity and specificity of CE for polyp detection while saving time[12]. Studies have indicated that for every 1% increase in the detection rate of colorectal adenoma, the risk of CRC can decrease by 3%[4]. However, inadequate intestinal cleansing can produce various artifacts, such as motion blur, specular reflections, bubbles, and debris (Figure 1), which can interfere with image reading, reduce the detection rate of polyps, cause patients to miss treatment, and increase the risk of tumor development[13,14]. In addition, high-quality and clear standard datasets that rarely appear in clinical practice are often used in these studies[15-17], and the intestinal lumen is often fully dilated in these images. This is significantly different from CE images with natural contraction of the intestinal lumen, which can present various artifacts (Figure 1). Therefore, these methods are often less effective in clinical practice. Hence, identifying gastrointestinal polyps and other lesions to the maximum extent when the gastrointestinal tract is insufficiently cleansed and dilated with interference factors, such as fecal residue, cloudy liquid, and bubbles in the lumen, is one of the biggest challenges in the application of artificial intelligence (AI) for CE in clinical practice and is of great concern to clinicians.

Currently, DL is a popular topic in the field of AI. It is based on the construction of computational models by simulating the neural network structure of the human brain[18]. Semantic segmentation is a part of DL algorithms that segments different objects according to each marked pixel in an image[19] (Figure 2). Some studies have proposed semantic segmentation models for medical images, such as SegNet[20], U-Net[21], Attention-UNet[22], Resnet-UNet[23], and HarDMSEG[24]. These studies have shown the significant superiority of various types of medical image semantic segmentation, as well as the feasibility of these models in tests with standard datasets. To improve the robustness of these

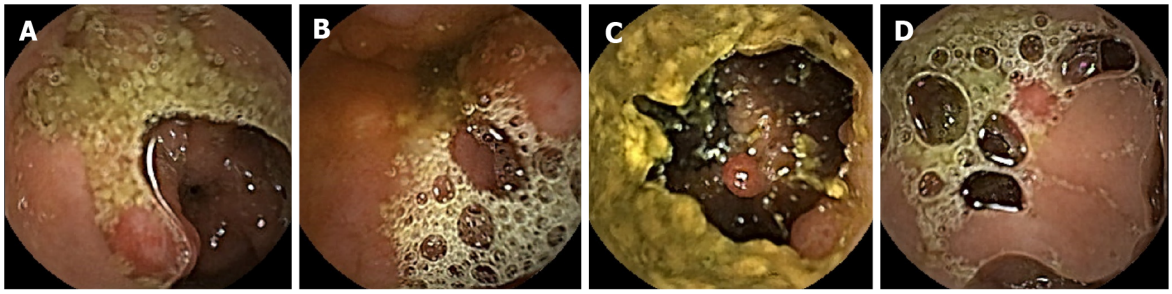

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Figure 1 Examples of artifact-infested endoscopy images used in our current study. A: Presence of cloudy liquid and specular reflections; B: Presence of bubbles and low contrast between lesion tissue and normal tissues; C: Presence of fecal residue; D: Presence of bubbles and specular reflections.

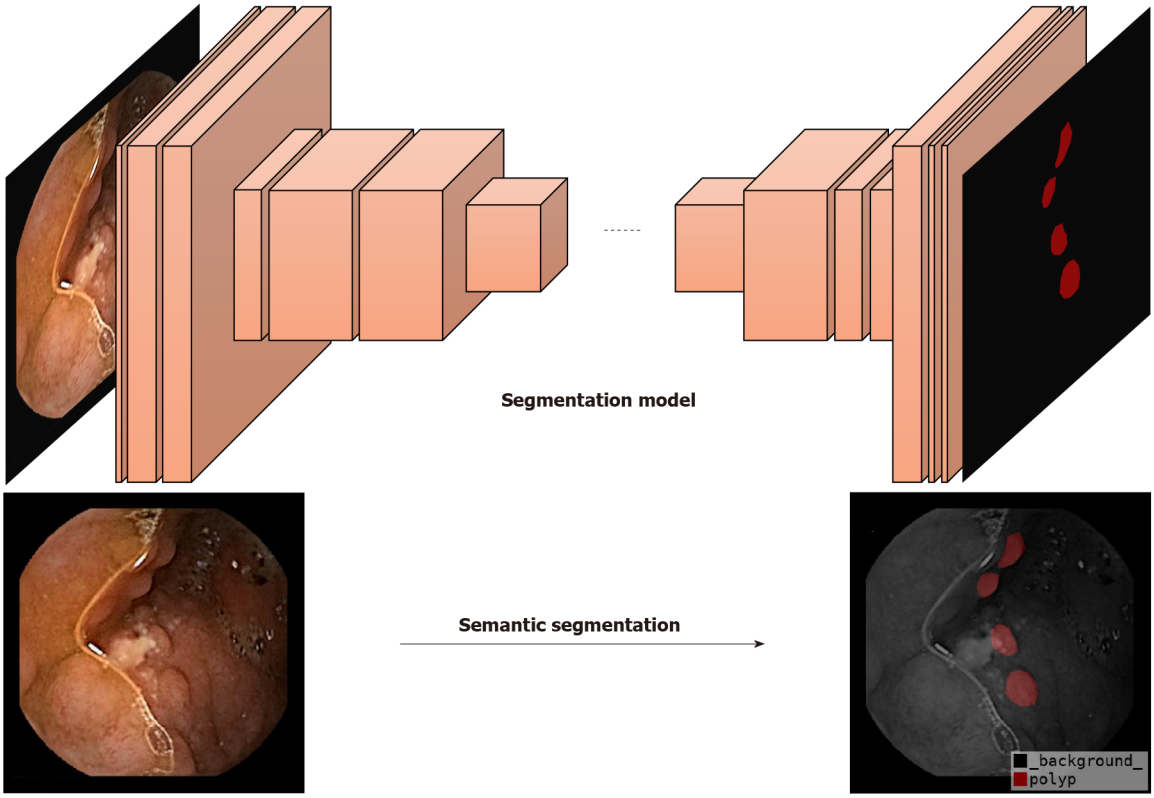

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Figure 2 Semantic segmentation problem in the field of computer vision.

models, researchers have begun to apply ensemble learning to medical image segmentation, not through a single model, but by combining several basic models to ensure the best prediction performance[25-27]. However, AI currently has limited ability to identify intestinal lesions with insufficient cleansing. For example, the detection rate of polyps in CE with a clean intestinal tract is significantly higher than that in CE with a dirty intestinal tract. In clinical practice, intestinal cleansing is not always performed well, and may not generate a clean image. Additionally, each patient has factors that can affect the identification by AI, such as insufficient intestinal distension, intestinal fecal residues, liquid residues, and air bubbles, resulting in the insufficient actual use of AI in clinical studies and low reliability.

In the present study, we combined semantic segmentation and ensemble learning methods for the first time to analyze CE images with artifacts. We then compared the performance of the ensemble and single models to further improve the detection rate of polyps. Our results demonstrate that ensemble learning can be used to reduce the influence of artifacts, which has a significant auxiliary role in the detection of polyps in clinical practice. To the best of our knowledge, this is the first study to propose the use of ensemble learning and semantic segmentation to reduce the negative impact of artifacts on model performance in clinical practice. Overall, our current findings have instructive significance for improving the analysis of medical images with artifacts in clinics.

MATERIALS AND METHODS

This retrospective study was approved by the Ethics Committee of Guangzhou First People's Hospital. All images were collected from videos of Ankon. This study has no conflicts of interest and did not receive any funding.

Data preparation

We collected 277 polyp CE images with artifacts selected from 5760 h of videos from 480 patients suffering from gastrointestinal disorders who received CE at Guangzhou First People's Hospital from January 2016 to December 2019. The selection criteria for the experimental images were as follows: (1) The lumen on the picture was in a natural contraction state; (2) Images of the digestive tract with polyps; and (3) Artifacts in the lumen, such as feces, motion blur, specular reflections, bubbles, and debris. The polyps in these experimental images were verified for authenticity by using a large number of clear videos and photos containing the polyps or double-balloon enteroscopy. Additionally, to ensure the accuracy and rigor of the data annotation, the image data were obtained by an experienced gastroenterologist who watched the video recordings, extracted the frames where the polyps were captured through ES Navi, and annotated the pixel points of the polyp lesions using Labelme. Next, the annotated polyp profiles were carefully reviewed by two other experienced gastroenterologists. The processing time for each patient's video was approximately 4-5 h. Before applying the dataset in the experiments, we cut off the black boxes of the images that typeset the patient's name and other information to obtain 512 × 512 images.

The other class of data comprehended publicly available high-quality datasets with images that rarely have artifacts and included the CVC_Colon[16] dataset (created by the Computer Vision Center and Computer Science Department, Universitat Autònoma de Barcelona) and the CVC_Clinic[17] dataset (captured by the Hospital Clinic, Barcelona, Spain and labeled by the Computer Vision Center, Barcelona, Spain). CVC_Colon provided 380 colonoscopy images containing polyps with a frame size of 500 × 574 pixels. Similarly, the CVC-Clinic contained 612 still images with a size of 288 × 384 from 29 different sequences. Both datasets are frequently used in gastrointestinal endoscopic computer-assisted polyp detection studies, and several representative studies have used these datasets in their experiments.

When using these datasets, we cropped or padded the edges of the images for two reasons. First, black edges or information, such as patient and time on the edges of the images, have no effect on the polyp region segmentation. Second and the main reason is that when we cross-sectionally compared various base learners in our experiments, the convolution and pooling designs of some of them were found to be more suitable for images whose length and width were both divisible by powers of two. Therefore, to minimize the changes in the hyperparameters of these base learners, we cropped or padded the input images to match the model hyperparameter design. Finally, the GZ_Capcam dataset contains 277 images of size 512 × 512, the CVC_Clinic contains 612 images of size 288 × 384, and the CVC_Colon dataset contains 380 images of size 512 × 576; all images are eight-bit three-channel color images[17]. All images used in this study contained at least one polyp class, including the standard datasets.

Snapshot ensemble method

In supervised learning problems, we always expect to obtain models that perform well and are stable in all aspects; however, owing to the presence of randomness, the trained models are not always ideal, and the models obtained always have prediction preferences. The main goal of ensemble learning is to combine weak models to build a more integrated and comprehensive model that integrates the strengths of weak models. The snapshot ensemble method is a type of ensemble learning for DL models and was used in the present study[28].

In the DL method, the model parameters are adjusted according to the gradient of the objective function, as shown in Formula 1:

$$\theta_t := \theta_{t-1} - \alpha \frac{\partial}{\partial \theta_{t-1}} J(\theta_{t-1})$$

The parameters of the model take a step in the direction of the gradient descent at each iteration, and the size of the step depends on both the size of the current gradient and the learning rate, as shown in Formula 1, where θ_t denotes the model parameters in time step t and α denotes the learning rate. Usually, to speed up convergence and prevent DL models from repeatedly jumping at different local optima during training, the learning rate decays as the number of iterations increases, eventually causing the model to fall into a certain local optimum and not jump out. The core idea of the snapshot ensemble method is to restart the learning rate when it decays to less than a certain threshold so that the model jumps out of the current local optimum and finds a new local optimum nearby and converges, and Formula 2 and Figure 3 show the specific changes in the learning rate:

$$\alpha(t) = \alpha_0 \gamma^{\left\lfloor \frac{mod(t-1,T)}{M} \right\rfloor}$$

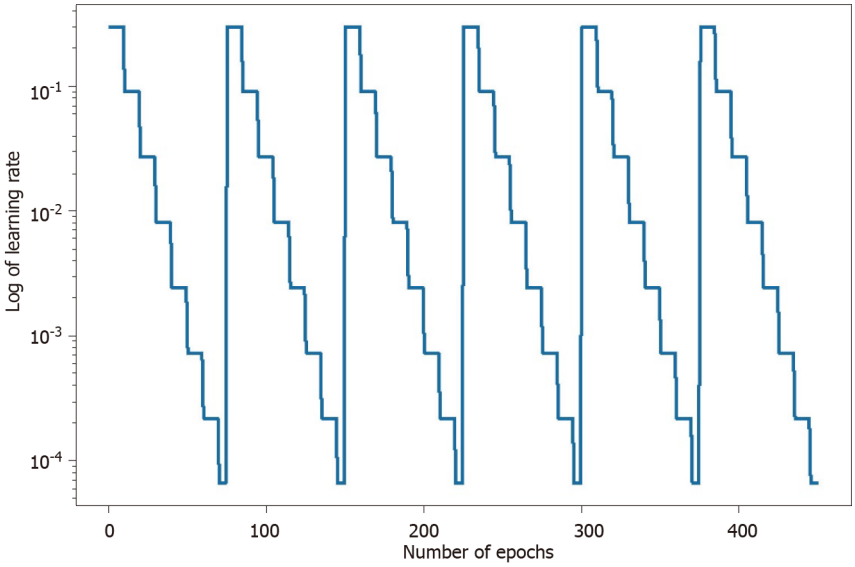

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Figure 3 Learning rate for each epoch in the snapshot ensemble learning, with γ and α_0 set for 0.3, M for 10, and T for 75.

Where α_0, γ, M, and T represent the initial learning rate, learning rate decay rate, number of epochs per learning rate decay, and number of epochs per learning rate restart cycle, respectively. In the snapshot ensemble method, the model that is at the local optimum before each restart learning rate is recorded as a weak model, and in the end, the prediction results of multiple weak models are integrated by ensemble voting. In the process of training, we set the number of learning rate restart cycles to 13, the learning rate decay rate to 0.3, and the number of epochs per learning rate decay to 10 and perform a total of 75 epochs in each cycle, *i.e.*, 0.3 for γ, 10 for M, and 75 for T in Formula 2. In other words, the learning rate is reduced to 0.3 of the previous value every 10 epochs of training and reverts to the initial learning rate setting of 0.3 after 75 epochs. The model parameters that perform best on the validation set are retained in these 75 epochs as the parameters of the weak model. The entire training process lasted for 13 cycles, that is, we ended up with 13 weak learners. In the integration phase of weak models, we selected three, five, and seven weak learners with the best performance on the validation set and obtained the prediction results of the ensemble model by vote ensemble. All computational processes, including data pre-processing, model training, validation, and testing, were performed through Python programming. We built the model using PyTorch, and all experiments were based on an NVIDIA Titan V GPU. Figure 4 shows the change in validation loss in the experiment with the UNet model on the CVC_Colon dataset. The light pink line indicates the epochs of the restart learning rate, and the red points indicate the epochs of preserving the weak models.

State-of-the-art segmentation models

To show that the ensemble classification is effective in improving the segmentation in comparison with the single model when dealing with medical images with artifacts, and to illustrate the generality of its enhancement effect, we used five existing state-of-the-art (SOTA) segmentation models as base learners; SegNet[20], which is proposed to solve the deep network model of image semantic segmentation for autonomous driving or intelligent robots, and is mainly based on full convolutional networks; U-Net [21], which performs well on neuron structure segmentation datasets with only a small number of annotations, and is a basic solution for medical image analysis of small datasets; Attention-UNet[22], which is an improved model based on U-Net, and achieves performance beyond that of the U-Net model for semantic segmentation of human organs on abdominal three-dimensional computed tomography scans; ResNet-UNet[23], which is also an improved version of U-Net, and gets outstanding performance on the public challenge of identifying pneumothorax diseases on chest X-rays; and HarDMSEG[24], which is an efficient image segmentation model, and achieves SOTA level in terms of both computational efficiency and analytical accuracy, in comparison experiments to illustrate that ensemble learning method improves their analysis capability in the face of images with artifacts.

Setup of comparison experiments

First, we randomly divided the experimental and public data into training (195 images), validation (41 images), and testing (41 images) sets. The model was trained using the training set, and the best model was selected for the final test on the validation set to ensure that the model did not overfit the final test data. Finally, we tested the model using the testing set. For each model and dataset pair, multiple cycles of the learning rate restart were performed during the training phase. The best-performing model,

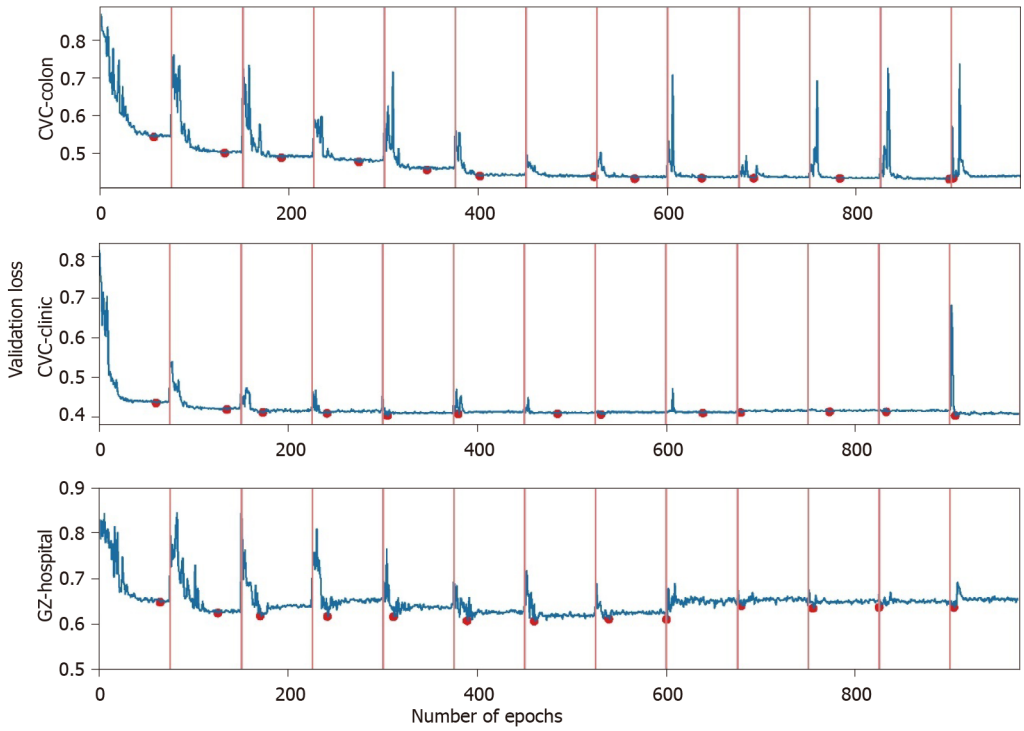

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Figure 4 Validation loss in training.

evaluated using the validation set data in each restart learning rate cycle, was retained as a weak model. Finally, every weak model and the strong model comprehending several of the best weak models were evaluated using the validation set and tested using the testing set. Figure 5 shows the overall experimental design.

Outcome measures

The intersection over union (IoU) and dice coefficients (Figure 6) are the most widely used metrics for semantic segmentation problems[29-31]. Both metrics measure the similarity between the sets of real and predicted regions. The calculation process is illustrated in Figure 6, where the area of intersection denotes the number of pixels in the intersection between the prediction area and ground truth, and the area of the union denotes that of the union. These two metrics were used to assess the performance of the segmentation models.

RESULTS

In summary, we performed two sets of comparison experiments using SOTA base models for the two types of datasets. In the first experiment, we compared the performance of the ensemble learning model with that of single models on a dataset with artifacts. In the second experiment, we compared the performance of the single models with that of the ensemble model on high-quality datasets without artifacts. Finally, we compared the differences between the improvements of the ensemble learning method for datasets with and without artifacts.

Comparison between the ensemble model and single models

First, we compared the performance of the ensemble learning model with that of single models on CE images for all the five aforementioned base learners. A total of 41 images from the test dataset of GZ_Capcam were used for the final test. These test images were used only in the final testing phase to avoid data leakage and the consequent erroneous evaluation of the models. To illustrate that the ensemble learning model improves the performance of the single model on the artifact-infected dataset, we replicated all base learners mentioned in the previous section to illustrate the robustness of the conclusions in this study.

For U-Net, three test samples in the GZ-Hospital dataset were selected to compare the performances of the single and ensemble models (Figure 7). We can see that the semantic segmentation model was affected by different noises, such as stains, blurs, and light-dark variations in the sample images, leading to results that were not always clear. However, the performance of the ensemble model often met or

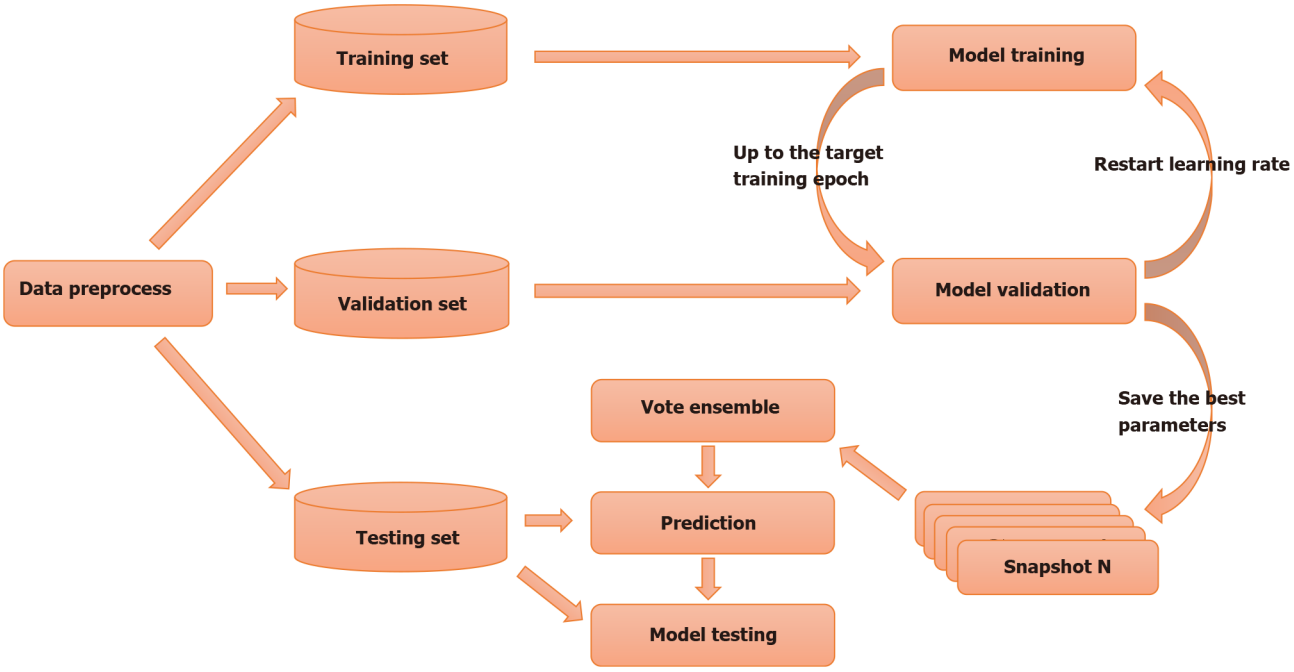

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Figure 5 Train-test workflow of the proposed method.

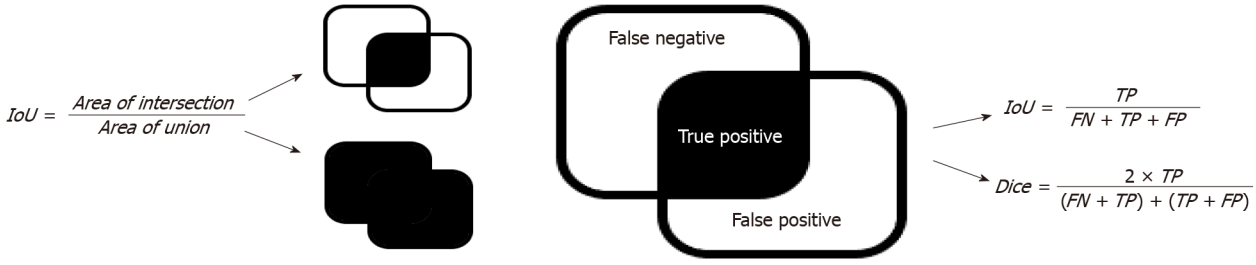

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Figure 6 Illustration of intersection over union and dice metrics. IoU: Intersection over union; FN: False negative; TP: True positive; FP: False positive.

exceeded the best results of a single model, indicating that a model constructed based on ensemble learning can effectively mitigate the effects of artifacts on the performance of the semantic segmentation model.

The results for the GZ_Capcam dataset are presented in Table 1, which includes images rich in artifacts. The IoU and dice metrics were calculated, as previously described. The performances of the single and ensemble models on the test set are presented in Supplementary Table 1. The results for all five basic learners on the CE dataset showed that the ensemble model outperformed the single models. Compared with single models, specifically, on the dataset with artifacts, the ensemble learning models with SegNet, U-Net, Attention-UNet, Resnet-UNet, and HarDMSEG as the base learners improved the detection by 0.08%, 7.01%, 3.88%, 5.13%, and 2.22%, respectively, using the IoU metric, and 1.71%, 4.93%, 1.40%, 2.86%, and 0.61%, respectively, using the dice metric. Overall, the ensemble model outperformed the single models. The performance of a truly single model, that is, a model obtained from a single training validation, was consistently worse than that of the ensemble model, as shown in the results for the weak models excluding the best one.

Comparisons using datasets without artifacts

Similarly, we checked the performance of the single and ensemble models using standard datasets (Figure 8, Tables 2 and 3). The performances of the single and ensemble models on the test set are presented in Supplementary Tables 2 and 3. By comparing the results presented in Figures 7 and 8, we found that the ensemble learning method can improve the robustness of the semantic segmentation model when the dataset is affected by artifacts.

Table 1 Comparison between the single and ensemble models on GZ_Capcam (artifact-affected) datasets

Model	SegNet		U-Net		Attention-UNet		ResNet-UNet		HarDMSEG	
Metric	IoU	Dice	IoU	Dice	IoU	Dice	IoU	Dice	IoU	Dice
Snap_max	0.341	0.454	0.379	0.507	0.361	0.502	0.414	0.522	0.538	0.649
Ens_max	0.341	0.462	0.406	0.532	0.375	0.509	0.435	0.537	0.550	0.653
Improve	0.000	0.008	0.027	0.025	0.014	0.007	0.021	0.015	0.012	0.004
Improve (%)	0.08	1.71	7.01	4.93	3.88	1.40	5.13	2.86	2.22	0.61

Snap_max and Ens_max denote the performance of the best performing single model and ensemble model, respectively, and the last two rows denote the improvement of the ensemble learning model compared to a single model. GZ_Capcam: The test set of experimental images from Guangzhou First People's Hospital. IoU: Intersection over union.

Table 2 Comparison between the single and ensemble models on CVC_Colon (clear) datasets

Model	SegNet		UNet		Attention-UNet		ResNet-UNet		HarDMSEG	
	IoU	Dice	IoU	Dice	IoU	Dice	IoU	Dice	IoU	Dice
Snap_max	0.700	0.780	0.713	0.788	0.754	0.830	0.747	0.819	0.840	0.901
Ens_max	0.702	0.779	0.711	0.783	0.752	0.829	0.750	0.816	0.840	0.901
Improve	0.002	-0.001	-0.002	-0.005	-0.002	-0.002	0.003	-0.002	0.000	0.000
Improve (%)	0.30	-0.08	-0.28	-0.61	-0.22	-0.22	0.42	-0.26	0.03	-0.01

Snap_max and Ens_max denote the performance of the best performing single model and ensemble model, respectively, and the last two rows denote the improvement of the ensemble learning model compared to a single model. IoU: Intersection over union.

Table 3 Comparison between the single and ensemble models on CVC_Clinic (clear) datasets

Model	SegNet		UNet		Attention-UNet		ResNet-UNet		HarDMSEG	
	IoU	Dice	IoU	Dice	IoU	Dice	IoU	Dice	IoU	Dice
Snap_max	0.814	0.890	0.816	0.884	0.836	0.900	0.823	0.884	0.845	0.893
Ens_max	0.815	0.890	0.826	0.891	0.838	0.898	0.824	0.884	0.844	0.892
Improve	0.001	0.001	0.010	0.007	0.002	-0.001	0.001	0.000	-0.001	-0.001
Improve (%)	0.13	0.07	1.20	0.76	0.23	-0.14	0.08	0.02	-0.08	-0.06

Snap_max and Ens_max denote the performance of the best performing single model and ensemble model, respectively, and the last two rows denote the improvement of the ensemble learning model compared to a single model. IoU: Intersection over union.

DISCUSSION

In the present study, we demonstrated that current computer-aided medical image analysis methods performed poorly in the presence of artifacts that were previously ignored. Nevertheless, almost every patient presents with insufficient intestinal cleansing. Thus, we used ensemble learning to improve the existing AI models and enhance their robustness in dealing with images with artifacts. Previous studies have extensively analyzed and concluded that integrated learning methods improve the robustness of medical image classification in a credible manner[32]. By improving the segmentation performance of the model, we can separate polyps more accurately from surrounding tissues, which can improve the detection probability of polyps and aid in monitoring the size of polyps in patients with unresectable polyps[33-36]. Semantic segmentation provides pixel-level classification and clearer polyp boundaries, which are also crucial in surgical procedures or radiofrequency ablation, and is expected to be used for real-time detection of polyp boundaries in surgical resection under gastroenteroscopy to assist polyp resection[33,36]. More in-depth studies have shown that the noise immunity of single models is weaker than that of integrated learning models[37], and clinical images, such as the CE images used in this study, are not always perfect in terms of image quality.

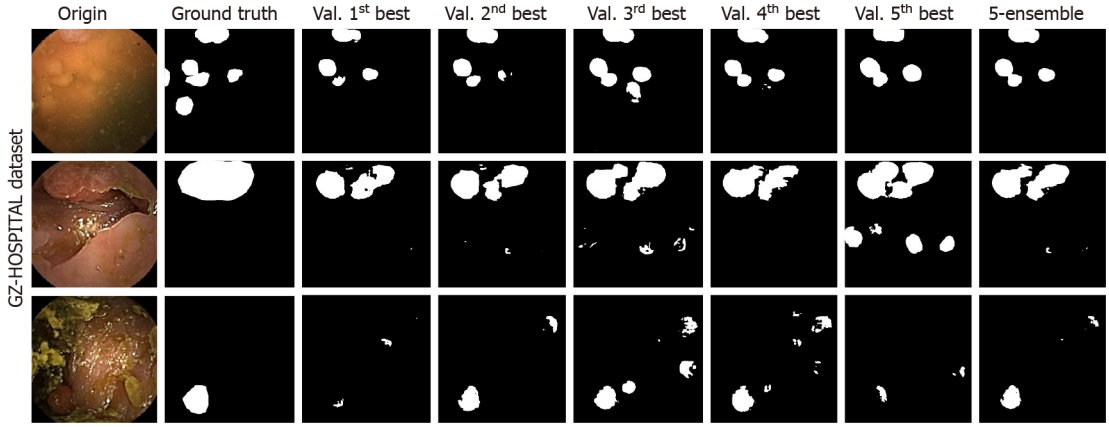

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Figure 7 Comparison between the ensemble and single models on artifact-affected images. Origin represents the images taken by the endoscope. Ground truth represents the anomalous locations marked by experts based on the original images. Val. 1st best to Val. 5th best represents the results of the five best-performing single models evaluated on the validation set. 5-ensemble represents the results of the ensemble model based on these single models.

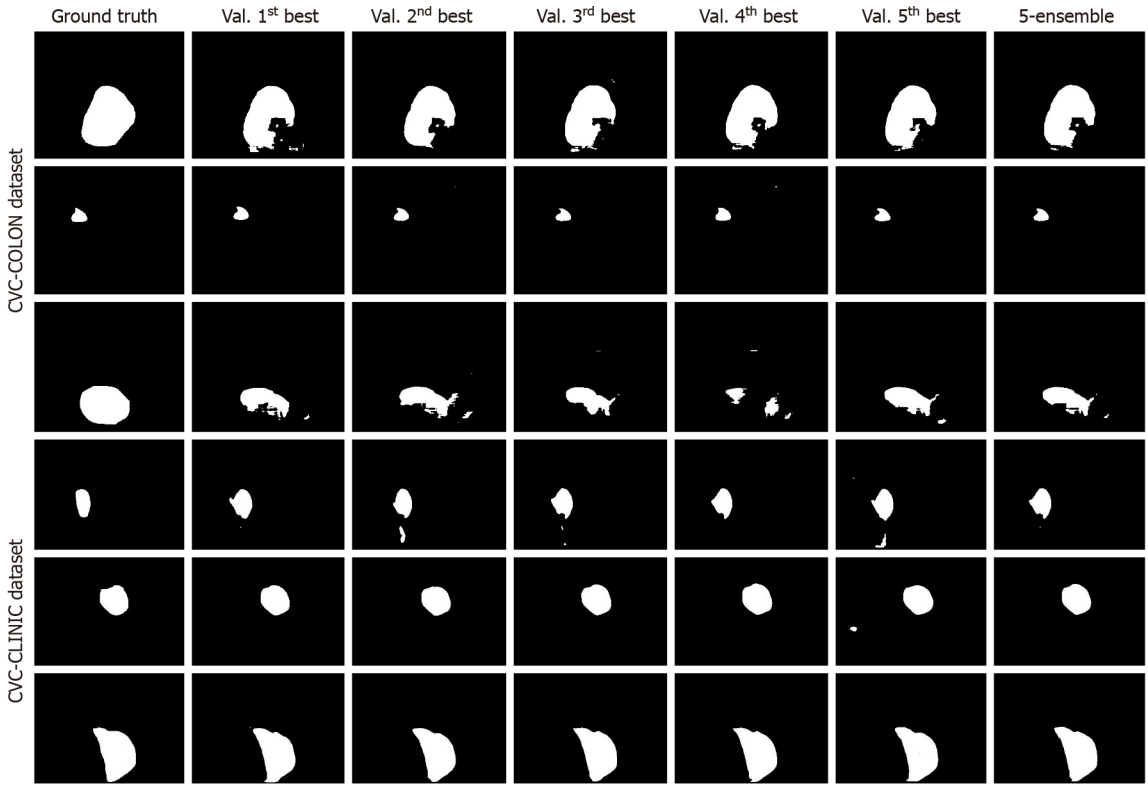

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Figure 8 Comparison between the ensemble and single models on standard (clear) images. Ground truth represents the anomalous locations marked by experts based on the original images. Val. 1st best to Val. 5th best represents the results of the five best-performing single models evaluated on the validation set. 5-ensemble represents the results of the ensemble model based on these single models.

We used CE image datasets as samples, mainly because CE is an increasingly widely used and safe form of endoscopy but also has many artifacts[15,38]. The ensemble learning approach was tested for 15 pairs, consisting of three datasets and five SOTA segmentation models. The results showed that for CE images with various artifacts, ensemble learning improved the analytical performance of AI models. Herein, we demonstrated that ensemble learning can reduce the influence of artifacts on the semantic segmentation of CE images, which might also apply to other medical images.

In general, artifacts are prevalent in medical images and seriously challenge the performance of existing computer-aided diagnosis (CAD) models; therefore, this study discusses the enhancement of ensemble learning methods for CAD models to analyze images with artifacts, mainly using CE images as an example in the experiments. In addition, our experiments did not involve the injection of a priori knowledge of gastroenterology; in other words, the use of the ensemble learning approach mentioned in

this paper does not imply any additional workload or workflow reordering. The only additional cost associated with the method is the computational resources. Additionally, from the perspective of DL, better model performance often relies on more model parameters and computational resources. Methods that already use DL models can easily apply ensemble learning methods to improve model performance without the need for additional workflow tuning. It is worth mentioning that, although the ensemble learning approach can improve the robustness of CAD image analysis models, misuse may lead to a less-than-expected improvement in the model's effectiveness, mainly because the essence of ensemble learning is to reduce model variance, and when the variance of a single model is already very low, the improvement brought by ensemble learning may be very limited.

From the experimental results, although the ensemble learning approach improves the performance of the segmentation model on the dataset with artifacts, there are still false-positive and false-negative cases. On the one hand, the main reason for false-negative cases was that the model confuses normal-color polyps with normal gastrointestinal folds or confuses abnormal-color polyps with artifacts, such as yellow bubbles. However, the main cause of false-positive cases was that some artifacts or normal folds had a high similarity with polyps in the image, which led the model to misidentify them as polyps. Overall, the main reason for segmentation errors is that the color and texture are highly confusing, and we will further attempt to improve the ability of the model to distinguish polyps, normal tissues, and artifacts in a subsequent study.

In clinical practice, video frames can be completely infested with artifacts, making the content of the image simply unrecognizable. Therefore, the appearance of these frames is inevitable in clinical practice. In the present study, we confirmed the authenticity of polyps in pictures with artifacts by using more images, videos, and other inspection methods. Thus, we solved the dilemma of applying AI to these medical images. However, our study has some limitations. For example, the images were insufficient and did not involve lesions other than polyps.

We believe that the direction of feature AI for CE imaging research lies in making existing computer models better serve clinical diagnosis in a practical sense rather than letting these methods stay in the laboratory. CE is commonly used to examine digestive diseases. In addition to polyps, many digestive diseases can be detected using CE. Thus, AI for CE imaging can be considered to enrich the diagnosis, localization, and grading of more forms of the disease, such as ulcers and erosions, to assist doctors in more refined disease research and diagnosis. In the future, we will validate the ensemble learning method in clinical practice to demonstrate that it can improve the detection rate of polyps in CE in the clinic and evaluate the potential of this method for other types of medical images or lesions[39].

CONCLUSION

Ensemble learning can improve the semantic segmentation performance of AI models on CE images with artifacts.

ARTICLE HIGHLIGHTS

Research background

Artificial intelligence (AI)-assisted capsule endoscopy (CE) can improve the detection rate of gastrointestinal polyps and reduce the incidence of gastrointestinal cancer.

Research motivation

Most previous studies ignored the serious impact of the existence of a large number of artifacts in the real world on the detection ability of existing AI models for polyps in CE images.

Research objectives

In this study, semantic segmentation and ensemble learning methods were combined to analyze polyp images of CE with artifacts, proving that ensemble learning methods can better solve the impact of artifacts in the real world.

Research methods

This study retrospectively analyzed CE images of patients at our research center from January 2016 to December 2019. Polyp images with artifacts were selected and randomly divided into a training set (195 images), a validation set (41 images), and a test set (41 images). Further validation was performed on two public datasets with good background quality.

Research results

Compared with the corresponding optimal base model, intersection over union and dice are improved

by 0.08%-7.01% and 0.61%-4.93%, respectively. For public datasets with good background quality, the segmentation performance of most ensemble learning models was better than that of a single model.

Research conclusions

The ensemble learning method can improve the performance of semantic segmentation of polyps in CE images with artifacts.

Research perspectives

We will validate other digestive tract lesions and other medical images and perform real-time detection during endoscopic and surgical procedures.

ACKNOWLEDGEMENTS

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FOOTNOTES

Author contributions: Zhou JX collected and compiled the data; Yang Z and Xi DH were responsible for coding the model; Zhou JX, Yang Z, and Li J drafted the manuscript; Dai SJ, Feng ZQ, and Wang H performed the capsule endoscopy examinations and reviewed the images; Xu W and Wang H contributed to the study design and manuscript writing.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Guangzhou First People's Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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ORIGINAL ARTICLE

Retrospective Study

Transjugular intrahepatic portosystemic shunt *vs* conservative treatment for recurrent ascites: A propensity score matched comparison

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Abstract

BACKGROUND

Transjugular intrahepatic portosystemic shunt (TIPS) placement is an effective intervention for recurrent tense ascites. Some studies show an increased risk of acute on chronic liver failure (ACLF) associated with TIPS placement. It is not clear whether ACLF in this context is a consequence of TIPS or of the pre-existing liver disease.

AIM

To better understand the risks of TIPS in this challenging setting and to compare them with those of conservative therapy.

METHODS

Two hundred and fourteen patients undergoing their first TIPS placement for recurrent tense ascites at our tertiary-care center between 2007 and 2017 were identified (TIPS group). Three hundred and ninety-eight patients of the same time interval with liver cirrhosis and recurrent tense ascites not undergoing TIPS placement (No TIPS group) were analyzed as a control group. TIPS indication, diagnosis of recurrent ascites, further diagnoses and clinical findings were obtained from a database search and patient records. The in-hospital mortality and ACLF incidence of both groups were compared using 1:1 propensity score

matching and multivariate logistic regressions.

RESULTS

After propensity score matching, the TIPS and No TIPS groups were comparable in terms of laboratory values and ACLF incidence at hospital admission. There was no detectable difference in mortality (TIPS: 11/214, No TIPS 13/214). During the hospital stay, ACLF occurred more frequently in the TIPS group than in the No TIPS group (TIPS: 70/214, No TIPS: 57/214, $P = 0.04$). This effect was confined to patients with severely impaired liver function at hospital admission as indicated by a significant interaction term of Child score and TIPS placement in multivariate logistic regression. The TIPS group had a lower ACLF incidence at Child scores < 8 points and a higher ACLF incidence at ≥ 11 points. No significant difference was found between groups in patients with Child scores of 8 to 10 points.

CONCLUSION

TIPS placement for recurrent tense ascites is associated with an increased rate of ACLF in patients with severely impaired liver function but does not result in higher in-hospital mortality.

Key Words: Liver cirrhosis; Ascites; Transjugular intrahepatic portosystemic shunt; Acute on chronic liver failure; Mortality; Propensity score

Core Tip: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective therapy for recurrent tense ascites, but there are concerns about further deterioration of liver function in patients with advanced cirrhosis. We retrospectively analyzed 214 patients receiving TIPS for ascites and compared their outcomes to matched conservatively treated patients. We found that TIPS can trigger acute on chronic liver failure (ACLF) in patients with severely impaired liver function. However, no increased mortality was found compared to conservatively treated patients. Despite an increased risk of ACLF, TIPS is a viable option for patients with ascites and hepatic impairment.

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INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is an effective therapy for complications of portal hypertension, such as ascites or esophageal variceal bleeding. Although TIPS placement is effective against ascites, early studies showed no survival benefit after TIPS placement compared to repeated paracentesis and albumin substitution[1-3]. More recent studies have shown more promising results, such as survival benefit[4-7], improved renal function[8,9] and better quality of life[10,11]. TIPS placement is therefore recommended as the treatment of choice[12,13].

Nevertheless, TIPS placement is an invasive procedure with considerable risks. In addition to hepatic encephalopathy and bleeding complications due to the placement procedure, sudden worsening of liver function is a serious complication. It has been observed after 5% to 10% of TIPS procedures and has a serious prognosis[14,15]. Such an acute deterioration of liver function accompanied by single- or multi-organ-failure is a common complication of advanced liver cirrhosis. This clinical syndrome has been described as acute on chronic liver failure (ACLF)[16]. Due to the risk of liver failure, TIPS placement for ascites is often limited to patients with good liver function and most randomized controlled trials have been conducted in patients with good liver function. It is still unclear how often ACLF occurs after TIPS placement and whether it is due to the TIPS procedure or rather to the severity of the underlying liver disease[17]. Recent recommendations argue against strict cut-off values for MELD, Child or other scoring systems. Instead, they recommend individual decision-making[18]. To better address the risk of ACLF in this challenging clinical situation the aim of this study was: (1) To determine whether ACLF occurs more often in patients with recurrent tense ascites treated with TIPS than in patients receiving conservative therapy; (2) to compare the outcome of ACLF associated with TIPS placement with the outcome of ACLF in patients receiving conservative therapy; and (3) to evaluate whether the risk of ACLF and death associated with TIPS placement increases disproportionately in patients with marginal

liver function.

MATERIALS AND METHODS

Selection of patients

A database was constructed containing ICD and OPS codes as well as laboratory values of all inpatients of the Division of Gastroenterology of the Rostock University Medical Center. Patients who were treated for liver cirrhosis between 2007 and 2017 were identified based on their discharge diagnosis using ICD10 codes K70.3, K70.4, K71.7, K74.6 and K76.6 (2197 cases of 1404 patients). Patients who received TIPS were identified using OPS codes 8-839*. Only cases of patients receiving their first TIPS for recurrent tense ascites were selected. Therefore there was only one case per patient in the TIPS group. Cases of patients who had liver cirrhosis and tense ascites requiring paracentesis, but did not undergo TIPS placement were selected for comparison (No TIPS group). If several cases were available for the same patient in the No TIPS group (*e.g.*, because of multiple hospital admissions), the latest case was selected. TIPS indication, diagnosis of recurrent tense ascites, further diagnoses and clinical findings were obtained from ICD codes and from patient files. Laboratory values were obtained from the data base. Cases with missing data on relevant clinical or laboratory findings were removed (43 cases). Cases with pre-existing renal insufficiency requiring dialysis (30 cases) or with malignant tumors (471 cases) were also excluded. Patient selection resulted in 398 patients in the No TIPS group and 214 patients in the TIPS group. After data collection was completed, all patient data were pseudonymized. Patient selection criteria and reasons for exclusion from data analysis are depicted in Figure 1. The study was approved by the local ethics committee of the Rostock University Medical Center (A2018-0127).

The MELD-score and ACLF grade as defined by Moreau *et al*[16] at hospital admission and the highest ACLF grade achieved during hospital stay were determined for each patient. Furthermore, the in-hospital mortality of both groups was determined. Multivariate logistic regressions revealed that bilirubin, creatinine, INR, CRP, sodium, white blood cell count, albumin and age were predictive either for survival or for group membership in TIPS *vs* No TIPS group or for both. Therefore these covariates were chosen for the propensity score matching procedure. The matching (1:1 greedy matching, nearest neighbor, without replacement) resulted in a matched sample of 428 patients (214 patients in the No TIPS and 214 in the TIPS group).

Statistical analysis

Statistical evaluation and matching were carried out using R (R version 3.6.3[19] and the R Package MatchIt, Version 4.1.0[20]). The distribution of most of the continuous data had significant positive skew, therefore non-parametric test methods were used. Continuous variables were compared using the Mann-Whitney *U* test and categorical variables using the chi-square or Fisher's exact test. Data on an ordinal scale (ACLF, hepatic encephalopathy) were treated as continuous. To account for the loss of statistical independence due to the matching procedure[21,22], comparisons between the matched groups were carried out using the Wilcoxon signed rank test or McNemar test. Additional multivariate logistic regressions were performed as sensitivity analysis and for further insights into effects of liver function, TIPS placement and their interaction on ACLF incidence and in-hospital mortality. The statistical methods of this study were reviewed by Henrik Rudolf from Rostock University Medical Center, Institute for Biostatistics and Informatics in Medicine and Ageing Research.

RESULTS

Patient characteristics and matching

Patient demographics and liver disease characteristics of the unmatched cohort are summarized in Table 1. Continuous values are given as median and range, categorical values as total number and percentage. Patients receiving TIPS had better liver function as assessed by MELD and Child score, bilirubin, INR, albumin and severity of hepatic encephalopathy. In addition, CRP, platelets and leukocytes differed significantly. Creatinine did not differ significantly. After propensity score matching all covariates were balanced in both groups (Table 2) and all variables used for matching did no longer predict group membership in the matched patients.

From 2007 to 2017, both covered and uncovered stents were used for TIPS at our institution. Uncovered stents were placed in 42% and covered stents in 58% of cases. Stents were mostly dilated to 7-8 mm. Smaller or larger diameters were rarely chosen (6mm in 2 patients, 9 or 10 mm in 15 patients). No effect of stent type or stent diameter on any of our endpoints was found in either univariate or multivariate analyses (data not shown).

Table 1 Baseline characteristics at hospital admission (all patients)

Characteristics	No TIPS	TIPS	*P* value
Patients	398	214	
Male	269 (68%)	153 (71%)	0.320
Age (yr)	59.5 (26.4-93.4)	59.1 (29.9-80.7)	0.190
Cause of cirrhosis			0.130
-Alcohol	305 (77%)	179 (84%)	
-Viral hepatitis	11 (3%)	4 (2%)	
-Other	82 (21%)	31 (14%)	
Child points (min-max)	10 (7-15)	9 (7-14)	< 0.001
Hepatic encephalopathy (West-Haven)			0.040
-None	276 (69%)	165 (77%)	
-Grade 1-2	73 (18%)	30 (14%)	
-Grade 3-4	49 (12%)	19 (9%)	
ACLF grade at hospital admission			0.020
-No ACLF	294 (74%)	173 (81%)	
-ACLF grade 1	64 (16%)	39 (18%)	
-ACLF grade 2	32 (8%)	1 (0.5%)	
-ACLF grade 3	8 (2%)	1 (0.5%)	
Laboratory findings			
-Meld	18 (7-40)	14 (7-40)	< 0.001
-Total bilirubin (μmol/L)	49.7 (5.9-668.0)	28.1 (6.1-688.5)	< 0.001
-Creatinine (μmol/L)	100.5 (23.1-781.0)	107.0 (42.3-783.5)	0.180
-INR	1.45 (0.92-9.2)	1.28 (0.97-2.5)	< 0.001
-Sodium (μmol/L)	134 (106-149)	133 (115-146)	0.760
-Albumin (g/L)	22.6 (7.9-48.7); NA: 55	26.1 (11.0-39.6); NA: 23	< 0.001
-CRP (mg/L)	25.6 (1.0-283.0)	18.0 (2.0-181.0)	< 0.001
-Hemoglobin (mmol/L)	6.8 (2.0-9.8)	6.7 (3.4-10.0)	0.310
-Platelets (Gpt/L)	134.5 (22.0-715.0)	153.5 (13.0-668.0)	0.002
-Leucocytes (Gpt/L)	8.76 (1.34-44.90)	7.34 (2.72-33.20)	< 0.001

Continuous variables are given as median and range, categorical variables as total number and percentage. Continuous variables were compared using the Mann-Whitney-*U*-test and categorical variables using the chi-square test. NA: Not available; ACLF: Acute on chronic liver failure; TIPS: Transjugular intrahepatic portosystemic shunt.

Incidence of ACLF and in-hospital mortality

Table 3 shows the incidence of ACLF as well as the in-hospital mortality of the matched patients. Patients receiving TIPS more often had ACLF of any grade (TIPS: 70/214 patients *vs* No TIPS 57/214 patients) and achieved higher ACLF grades ($P = 0.04$). An increase in ACLF grade (as compared to the ACLF grade at hospital admission) was more common in the TIPS group than in the No TIPS group (in 38/214 patients *vs* 23/214 patients). The hospital stay was longer in the TIPS group. The majority of patients in both groups had ACLF 1, which was due to renal failure. Organ systems affected in patients with ACLF > 1 were brain (hepatic encephalopathy grade 3-4) and/or liver function based on bilirubin in addition to renal failure. ACLF > 1 was mostly due to acute infections.

There was no difference in terms of in-hospital mortality. In the TIPS group 11 of 214 patients died, in the No TIPS group 13 of 214 patients died. The mortality increased with the ACLF grade in both groups. Multivariate logistic regressions were performed as a sensitivity analysis and confirmed that TIPS was a risk factor for ACLF but not for in-hospital mortality (Table 4). Mortality in any ACLF stratum except ACLF 2 was comparable in both groups. For patients with ACLF 2, we found a lower mortality in the

Table 2 Baseline characteristics at hospital admission (matched groups)

Characteristics	No TIPS	TIPS	*P* value
Patients	214	214	
Male	142 (66%)	153 (71%)	0.30
Age (yr)	59.4 (26.4-93.4)	59.1 (29.9-80.7)	0.14
Cause of cirrhosis			0.26
-Alcohol	163 (76%)	179 (84%)	
-Viral hepatitis	8 (4%)	4 (2%)	
-Other	43 (20%)	31 (14%)	
Child points (min-max)	9 (7-14)	9 (7-14)	0.76
Hepatic encephalopathy (west-haven)			0.65
-None	173 (81%)	165 (77%)	
-Grade 1-2	22 (10%)	30 (14%)	
-Grade 3-4	19 (9%)	19 (9%)	
ACLF grade at hospital admission			0.37
-No ACLF	176 (82%)	173 (81%)	
-AACLF 1	36 (17%)	39 (18%)	
-ACLF 2	2 (1%)	1 (0.5%)	
-ACLF 3	0 (0%)	1 (0.5%)	
Laboratory findings			
-Meld	14 (7-36)	14 (7-40)	0.97
-Total bilirubin (μmol/L)	29.7 (5.9-261.0)	28.1 (6.1-688.5)	0.10
-Creatinine (μmol/L)	90.9 (23.1-781.0)	107.0 (42.3-783.5)	0.08
-INR	1.32 (0.92-2.41)	1.28 (0.97-2.50)	0.28
-Sodium (mmol/L)	135 (106-144)	133 (115-146)	0.10
-Albumin (g/L)	24.3 (7.9-48.7); NA: 27	26.1 (11.0-39.6); NA: 23	0.61
-CRP (mg/L)	18.7 (1.0-283.0)	18.0 (2.0-181.0)	0.10
-Hemoglobin (mmol/L)	6.8 (2.1-9.8)	6.7 (3.4-10.0)	0.43
-Platelets (Gpt/L)	141.0 (23.0-715.0)	154.0 (13.0-668.0)	0.08
-Leucocytes (Gpt/L)	7.58 (1.34-44.90)	7.34 (2.72-33.20)	0.98

Continuous variables are given as median and range, categorical variables as total number and percentage. Continuous variables were compared using Wilcoxon signed-rank test and categorical variables using McNemar-Test. NA: Not available; ACLF: Acute on chronic liver failure; TIPS: Transjugular intrahepatic portosystemic shunt.

TIPS group compared to the No TIPS group (OR 0.09, 95%CI 0.01-0.87). The mortality of TIPS patients who increased in ACLF by 2 or 3 grades after TIPS placement was high (4/10 died). This also applies to the No TIPS group with an even higher mortality (4/5 patients with an increase of 2 or 3 ACLF grades compared to ACLF grade at hospital admission died).

Most patients in both groups (No TIPS 89%, TIPS 82%) without ACLF at admission did not develop any ACLF during hospital stay. Many patients who developed an ACLF grade 2 or 3 already had ACLF at hospital admission (5/10 patients in the No TIPS group and 11/20 patients in the TIPS group). Three patients in the TIPS group developed ACLF during the period between hospital admission and TIPS placement, *i.e.* before TIPS was implanted. Many of the pre-TIPS ACLFs resolved after TIPS placement. When comparing the highest ACLF grade before TIPS to the ACLF grade at hospital discharge (assuming ACLF 3 for patients who died), 32 patients (15%) improved their ACLF grade after TIPS placement while only 21 patients (10%) had a worse ACLF grade at discharge than at the time of TIPS placement.

Table 3 Changes of acute on chronic liver failure grade during hospital stay and in-hospital mortality (matched groups)

Event	No TIPS	TIPS	*P* value/OR (95%CI)
Hospital stay (d)	10 (1-78)	14 (3-64)	*P* < 0.001
Highest ACLF grade			*P* = 0.041
-No ACLF	157 (73%)	144 (67%)	
-ACLF 1	47 (22%)	50 (23%)	
-ACLF 2	8 (4%)	15 (7%)	
-ACLF 3	2 (1%)	5 (2%)	
-Any ACLF	57 (27%)	70 (33%)	
Mortality by ACLF			
-Over all	13/214 (6.1%)	11/214 (5.1%)	OR: 0.84 (0.33 -2.08)
-No ACLF	3/157 (1.9%)	0/144 (0%)	OR: 0 (0.00 -2.63)
-ACLF 1	3/47 (6.4%)	4/50 (8%)	OR: 1.27 (0.20 -9.18)
-ACLF 2	6/8 (75%)	3/15 (20%)	OR: 0.09 (0.01 -0.87)
-ACLF 3	1/2 (50%)	4/5 (80%)	OR: 3.16 (0.03 -389.17)
-Any ACLF	10/57 (17.5%)	11/70 (15.7%)	OR: 0.88 (0.31-2.52)
Increase in ACLF grade			*P* = 0.03
-No increase	191 (89.3%)	176 (82.2%)	
-1 grade	18 (8.4%)	28 (13.1%)	
-2 grades	4 (1.9%)	7 (3.3%)	
-3 grades	1 (0.5%)	3 (1.4%)	
Mortality by ACLF increase			
-No increase	5/191 (2.6%)	2/176 (1.1%)	OR: 0.43 (0.04-2.66)
-1 grade	4/18 (22.2%)	5/28 (17.9%)	OR: 0.77 (0.14-4.55)
-2 grades	3/4 (75.0%)	2/7 (20.0%)	OR: 0.16 (0.003-3.50)
-3 grades	1/1 (100%)	2/3 (66.7%)	OR: 0 (0.00-116.8)
-Any increase	8/23 (34.8%)	9/38 (23.7%)	OR: 0.58 (0.16-2.14)

OR: Odds ratio; ACLF: Acute on chronic liver failure; TIPS: Transjugular intrahepatic portosystemic shunt.

Estimated in-hospital mortality and risk of ACLF

Using multivariate logistic regression models based on the MELD or Child scores at admission, the probabilities of death in-hospital and of an increase in ACLF grade were estimated for the TIPS and the No TIPS group (Figure 2). The likelihood of death increases with the severity of the disease at admission; independent of whether this is assessed by MELD or by Child scores (Figure 2A and B). The regression curves for mortality are almost parallel, indicating that mortality depends only on liver function, but not on TIPS placement or an interaction between TIPS placement and the liver function. However, the regression curves for an increase in ACLF grade differ clearly between TIPS and No TIPS (Figure 2C and D). The probability of an ACLF in the TIPS group is lower than in the No TIPS group at low to moderate MELD-and Child-levels, but it is higher than in the No TIPS group at high MELD and Child scores. The intersection of the regression curves suggests an interaction between MELD/Child score and TIPS placement. In fact, the multivariate logistic regression shows a statistically significant interaction term for Child-score and TIPS (P = 0.03; Table 5). In our model the TIPS group has a lower ACLF incidence at Child scores lower than 8 points and a higher ACLF incidence at 11 points and higher. Between 8 and 11 points the standard errors of both groups overlap, indicating that there is no relevant difference between both groups. The same effect can be observed when using the MELD score instead of the Child score. However, the interaction is weaker and not statistically significant (P = 0.19).

Table 4 Sensitivity analysis: Multivariate regressions (main effects only)

Variable	Estimate	SE	*P* value	Estimate	SE	*P* value
	Complete model			Best model		
Mortality						
Intercept	3.63	3.27	0.268	4.39	3.22	0.173
Creatinine	1.59×10^{-3}	1.37×10^{-3}	0.246	1.99×10^{-3}	1.32×10^{-3}	0.132
Bilirubin	7.26×10^{-4}	1.10×10^{-3}	0.505	-	-	-
INR	3.49×10^{-1}	2.15×10^{-1}	0.104	3.47×10^{-1}	2.12×10^{-1}	0.101
CRP	3.27×10^{-3}	3.10×10^{-3}	0.292	-	-	-
Leucocytes	7.01×10^{-2}	2.64×10^{-2}	0.008	7.84×10^{-2}	2.53×10^{-2}	0.002
HE 1-2	-2.88×10^{-1}	4.28×10^{-1}	0.500	-2.67×10^{-1}	4.1×10^{-1}	0.523
HE 3-4	2.24	3.56×10^{-1}	< 0.001	2.26	3.50×10^{-1}	< 0.001
Albumin	-9.61×10^{-2}	2.76×10^{-2}	< 0.001	-1.02×10^{-1}	2.72×10^{-2}	< 0.001
Sodium	-6.21×10^{-2}	2.45×10^{-2}	0.011	-6.51×10^{-2}	2.45×10^{-2}	0.004
Age	1.22×10^{-4}	4.24×10^{-5}	0.004	1.16×10^{-4}	4.04×10^{-5}	0.004
TIPS	-7.29×10^{-1}	4.12×10^{-1}	0.077	-8.22×10^{-1}	4.01×10^{-1}	0.040
ACLF						
Intercept	-1.822	2.713	0.502	-2.70	8.51×10^{-1}	0.002
Creatinine	-1.06×10^{-3}	1.21×10^{-3}	0.384	-	-	-
Bilirubin	2.81×10^{-3}	9.50×10^{-4}	0.003	2.99×10^{-3}	8.69×10^{-4}	0.001
INR	2.16×10^{-1}	2.01×10^{-1}	0.281	-	-	-
CRP	5.21×10^{-3}	2.58×10^{-3}	0.043	4.67×10^{-3}	2.39×10^{-3}	0.050
Leucocytes	6.28×10^{-3}	2.43×10^{-2}	0.780	-	-	-
HE 1-2	1.22×10^{-1}	3.06×10^{-1}	0.690	1.47×10^{-1}	3.02×10^{-1}	0.627
HE 3-4	1.62	3.01×10^{-1}	< 0.001	1.63	2.94×10^{-1}	< 0.001
Albumin	-3.80×10^{-2}	2.00×10^{-2}	0.058	-3.98×10^{-2}	1.99×10^{-2}	0.046
Sodium	-1.03×10^{-2}	1.98×10^{-2}	0.603	-	-	-
Age	6.39×10^{-5}	3.11×10^{-5}	0.039	5.63×10^{-5}	2.96×10^{-5}	0.057
TIPS	5.17×10^{-1}	2.64×10^{-1}	0.050	4.39×10^{-1}	2.55×10^{-1}	0.085

Dependent variables were in-hospital mortality (upper panel) and any increase in acute on chronic liver failure grade (lower panel). The full models (left side) included all parameters used for propensity score matching as covariates. After stepwise backward elimination by Akaike information criterion, a model (best model, right side) was selected for each dependent variable. ACLF: Acute on chronic liver failure; TIPS: Transjugular intrahepatic portosystemic shunt.

DISCUSSION

Most of the randomized controlled trials (RCT) have been performed in patients with good liver function. This applies in particular to the RCTs that showed a survival benefit. In these studies the mean MELD was 9.6[6] to 12.1[7]). Therefore many patients with refractory ascites receive no TIPS due to impaired liver function. Others have considered MELD scores ≥ 18[13,23,24] to ≥ 24[25,26] and bilirubin levels ≥ 51.3 to ≥ 85.5 μmol/L[13,27] as contraindications for TIPS. Our TIPS patients had a comparatively poor liver function at hospital admission (MELD median 14, mean 15.2), allowing to describe mortality and morbidity in this high-risk group.

In our cohort of patients with significantly impaired liver function ACLF incidence and in-hospital mortality was within the range observed in other studies on ACLF[16,28,29]. The in-hospital mortality was neither positively nor negatively influenced by TIPS placement despite the comparatively poor liver function of our patients. In the matched cohorts ACLF occurred more frequently in the TIPS group than in conservatively treated patients. The results of the multivariate logistic regressions suggest that this effect depends on the extent of the pre-existing liver damage. In patients with good liver function

Table 5 Multivariate logistic regressions with interaction terms

Model	Dependent variable	Parameters	Estimate	SE	*z* value	*P* value
A		Intercept	-3.8600	0.4340	-8.887	$< 2 \times 10^{-16}$
	In-hospital	MELD-Score	0.0990	0.0180	5.628	1.82×10^{-8}
	Mortality (y/n)	TIPS	-1.3570	1.0590	-1.281	0.200
		MELD: TIPS	0.0330	0.0500	0.668	0.504
B		Intercept	-7.1320	0.9810	-7.271	3.56×10^{-13}
	In-hospital	Child (points)	0.4880	0.0840	5.814	6.09×10^{-9}
	Mortality (y/n)	TIPS	-1.6760	2.2350	-0.750	0.453
		Child: TIPS	0.0934	0.2020	0.463	0.643
C		Intercept	-3.1860	0.3610	-8.824	$< 2 \times 10^{-16}$
	Increase in	MELD	0.1020	0.0160	6.461	1.04×10^{-10}
	ACLF grade	TIPS	-0.7780	0.7120	-1.092	0.275
	(y/n)	MELD: TIPS	0.0480	0.0368	1.318	0.187
D		Intercept	-5.2640	0.7480	-7.040	1.93×10^{-12}
	Increase in	Child (points)	0.3880	0.0670	5.807	6.37×10^{-9}
	ACLF grade	TIPS	-3.1980	1.5300	-2.090	0.0366
	(y/n)	Child: TIPS	0.3190	0.1145	2.191	0.0285

For models C and D death was treated as an increase in acute on chronic liver failure. Models A and B show an effect of only the MELD/Child scores on mortality. Transjugular intrahepatic portosystemic shunt (TIPS) and the interaction of TIPS and MELD/Child scores (MELD: TIPS, Child: TIPS) have no significant influence on mortality (A and B). In model D a significant interaction term Child:TIPS exists. In model C the interaction term MELD: TIPS is not significant, indicating a weaker interaction than in model D. ACLF: Acute on chronic liver failure; TIPS: Transjugular intrahepatic portosystemic shunt.

(Child ≤ 8) an ACLF occurs less frequently in the TIPS group. However, at higher scores (Child ≥ 11), the probability of developing an ACLF is higher in the TIPS group than in the No TIPS group. This interaction blurs the effect of TIPS on ACLF incidence in univariate analyses.

Not all ACLFs in the TIPS group can be attributed to TIPS. The majority of the ACLFs occurred already before TIPS placement and many patients already had at least an ACLF grade 1 on hospital admission. ACLFs grade 1 were almost exclusively due to renal failure. This was to be expected in patients with recurrent tense ascites. Patients whose ACLF increased by 2 or 3 grades during hospital stay had a particularly poor outcome in both groups. A serious deterioration of liver function after TIPS placement is often attributed to TIPS placement. In our patients such events occurred in both groups when we considered the entire hospital stay (No TIPS group 5/214 patients, TIPS group 10/214 patients). Some of the ACLFs after TIPS placement are likely due to other causes than TIPS, such as bacterial infections or gastrointestinal bleeding. Such events precede most ACLFs and can occur with and without TIPS placement[29]. In line with that, TIPS was not a precipitant of ACLF in a recently published study on acute decompensation and ACLF[28]. Furthermore, the majority of pre-TIPS ACLFs resolved after TIPS placement, suggesting that TIPS is more capable to overcome an ACLF than causing it. We have studied patients with recurrent tense ascites. The most common cause of ACLF within this group was kidney failure. It is plausible that a TIPS can improve such an ACLF, *e.g.*, since dose of diuretics can be lowered or diuretics can be discontinued altogether.

We did not include an analysis of the effect of TIPS on ascites resolution since it typically takes up to several months after TIPS placement for the underlying circulatory, renal and neurohumoral dysfunction to normalize[27]. Therefore, the effect of TIPS placement on ascites cannot be reliably assessed during hospital stay.

When interpreting these results, the limitations of a retrospective analysis have to be considered. Since this is a retrospective study, many patients in the No TIPS group lack data on the further course after hospital discharge. For the selected endpoints (highest ACLF during inpatient stay, death during inpatient stay), complete data are available in both groups. Therefore, we had to limit the analysis to inpatient stay. In this study propensity score matching was used prior to comparing the TIPS and No TIPS group. However, even with propensity score matching, a similar distribution of unknown confounders cannot be guaranteed. We only evaluated the short-term outcome during hospital stay. It is well known that the positive impact of a TIPS only takes effect after a few weeks to months[23,27]. In fact, some studies have observed an increased mortality after TIPS placement during the first few weeks

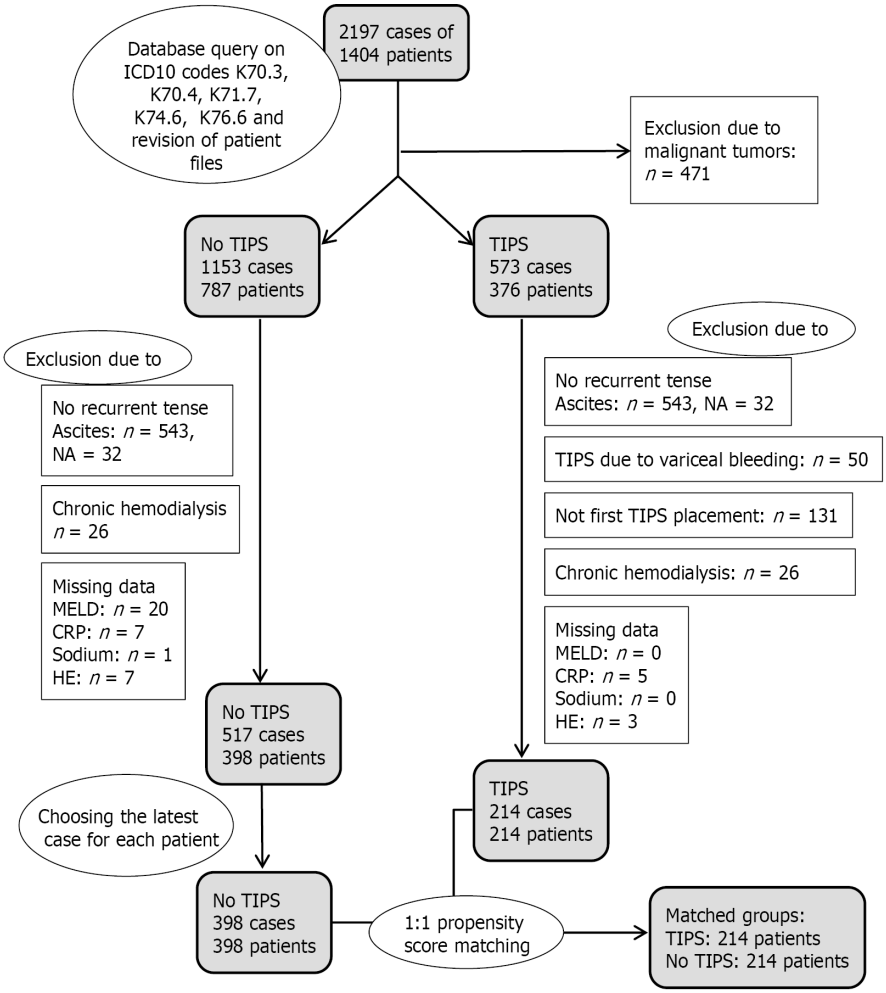

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Figure 1 Flow diagram showing the study population and reasons for exclusion from data analysis. HE: Hepatic encephalopathy; NA: Not available; TIPS: Transjugular intrahepatic portosystemic shunt.

[24,30]. Therefore, positive effects of TIPS on survival might be underestimated. On the other hand, our results were confirmed and extended by the multivariate logistic regressions (Table 5). The multivariate logistic regression also provided insight into the complex interactions between liver function and TIPS as seen in Figure 2.

Some ACLFs were already present on admission, some occurred before TIPS, and some ACLFs improved after TIPS. The fact that some patients already had ACLF prior to TIPS complicates the interpretation of the relationship between TIPS and ACLF. As in all retrospective studies, conclusions about the causal relationship between ACLF and TIPS are impossible. Furthermore, we cannot analyze systematically why TIPS was chosen in some patients and not in others. We can only compare the clinical outcome of both groups after very careful propensity score matching.

Our TIPS patients had a comparatively poor liver function, but a bilirubin of 85.5 μmol/L or a MELD of 24 points was rarely exceeded (approx. 8% and 6% of patients). In addition, in patients with very high MELD scores on hospital admission, TIPS placement was performed only after initial stabilization and after MELD had improved. Since the number of observations in our study is limited for this situation, a decision for TIPS placement should be made with caution in such patients. Nevertheless, as shown in Figure 2 and in accordance with other studies the mortality in the TIPS group is not higher than in the No TIPS group even at the highest MELD and Child scores[17,31-33].

Our data show an increased risk of ACLF in the TIPS group in patients with severely impaired liver function (Child ≥ 11 points), but not in patients with good or moderately impaired liver function. These findings may explain why TIPS is often considered a risky intervention with potentially unfavorable outcomes in patients with high MELD or Child scores. Nevertheless, we did not find such a negative effect of TIPS placement on in-hospital mortality in patients with high to very high MELD and Child scores. We found that many ACLFs in the TIPS group occurred before TIPS placement and often resolved after TIPS placement. Unlike several previous RCTs we did not find a positive effect of TIPS on mortality. Possible reasons are the comparatively short follow-up and the significantly worse liver function of our TIPS patients compared to the patients in the RCTs. In the presence of moderately to

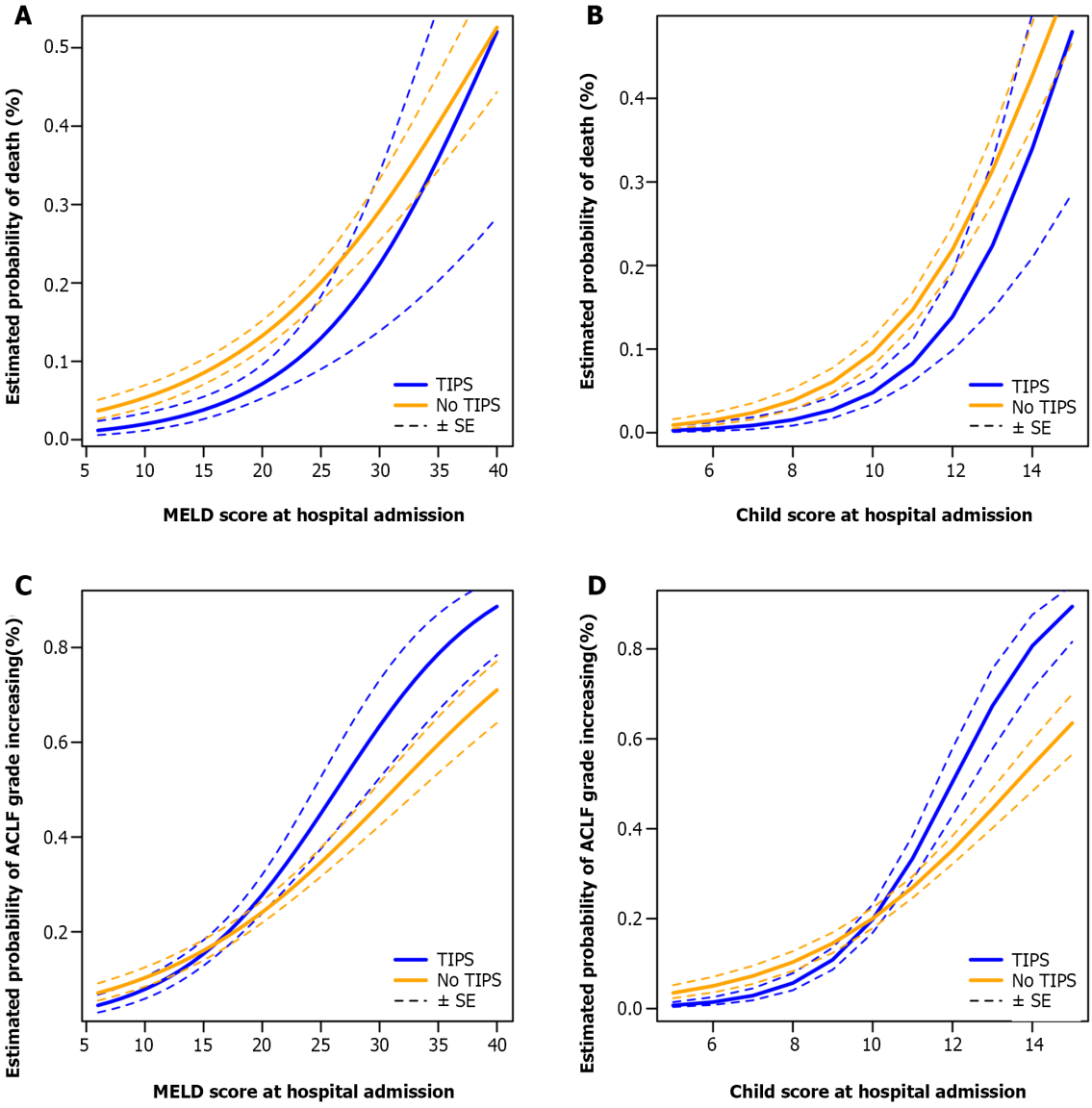

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Figure 2 Estimated in-hospital mortality and risk of acute on chronic liver failure depending on liver function. A and B: Estimated probability of dying in hospital depending on liver function at hospital admission; C and D: Estimated probability of acute on chronic liver failure (ACLF) occurring or existing ACLF worsening, depending on liver function at hospital admission. All probabilities were estimated using a multivariate logistic regression model based on the MELD and Child scores at hospital admission. TIPS: Transjugular intrahepatic portosystemic shunt.

severely impair liver function recurrent tense ascites may be a dominant symptom. TIPS is the most effective therapy for recurrent tense ascites. Therefore, we conclude that TIPS is a viable option not only for patients with good liver function but also for patients with high Child scores after carefully weighing the increased risk of ACLF against the expected benefits.

CONCLUSION

TIPS placement for recurrent tense ascites is associated with an increased incidence of ACLF. This effect occurs only in patients with severely impaired liver function (Child score ≥ 11) and does not lead to a higher in-hospital mortality compared with conservative treatment.

ARTICLE HIGHLIGHTS

Research background

Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for recurrent tense ascites.

Acute on chronic liver failure (ACLF) of various severities is a serious complication usually causally attributed to TIPS placement. But the potential of TIPS to improve ACLF grade 1 and 2, which is mostly related to acute kidney injury in these patients, may be underestimated.

Research motivation

TIPS placement for recurrent tense ascites may be beneficial even in patients with severely impaired liver and kidney function. But the exact medical limits need further clarification.

Research objectives

To retrospectively evaluate the in-hospital mortality of patients with recurrent tense ascites and reduced liver function-including severely reduced liver function-undergoing TIPS placement (TIPS group) and to compare these data to a carefully matched cohort with recurrent tense ascites receiving conservative treatment (No TIPS group). To better address the clinical scenario not only the time after TIPS placement but the entire hospital stays was analyzed.

Research methods

Two hundred and twenty-four patients undergoing TIPS placement for recurrent tense ascites were retrospectively compared to an equal number of propensity score matched, conservatively treated patients. Primary objectives were in-hospital mortality and the development or worsening or improvement of ACLF. Additional multivariate logistic regressions were performed as sensitivity analysis and for further insights into effects of liver function, TIPS placement and their interaction on ACLF incidence and in-hospital mortality.

Research results

TIPS placement did not result in an increased in-hospital mortality compared to the matched cohort. ACLF incidence in the TIPS group depended on liver function: At Child-Pugh-Scores < 8 TIPS reduced the risk of ALCF development, at scores of 8 to 10 ACLF risk did not differ between TIPS and No TIPS, and at scores ≥ 11 TIPS increased the risk of ALCF. Many preexisting ACLFs grade 1 resolved after TIPS placement. The relevant prognostic parameters for this need further elucidation. The data point to a biologic interaction of liver function and TIPS placement with regard to the development of ACLF, which needs further evaluation.

Research conclusions

In selected patients with severely impaired liver function TIPS placement does not result in an increased in-hospital mortality compared to conservatively treated patients. TIPS was associated with ALCF only in patients with severely impaired liver function (Child > 11 points).

Research perspectives

The medical limits of TIPS placement for recurrent tense ascites should be evaluated in prospective studies which need to address the indications, contraindications and the associated complex decision making.

FOOTNOTES

Author contributions: Philipp M, Blattmann T, Bienert J, Fischer K, and Hausberg L designed the research study and acquired the data; Philipp M and Lamprecht G analyzed the data and wrote the manuscript; Kröger JC, Heller T, and Weber MA performed transjugular intrahepatic portosystemic shunt placement and critically revised the manuscript; all authors have read and have approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Rostock University Medical Center (Approval No. A2018-0127).

Informed consent statement: The requirement for informed consent was waived by the Institutional Review Board considering the retrospective design of the study. Nevertheless, informed consent was obtained from all available patients.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: De-identified data and statistical code used in this study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Feasibility of same-day discharge following endoscopic submucosal dissection for esophageal or gastric early cancer

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Abstract

BACKGROUND

Endoscopic submucosal dissection (ESD) is an established technique for the treatment of early gastrointestinal neoplasia. Generally, multi-day (M-D) admission is required for patients undergoing ESD due to potential complications.

AIM

To evaluate the feasibility of a same-day (S-D) discharge strategy for ESD of the esophagus or stomach.

METHODS

The data of patients who underwent esophageal or gastric ESD were retrospectively collected from January 2018 to December 2021 at Peking University Cancer Hospital. The propensity score matching (PSM) method was applied to balance the unevenly distributed patient baseline characteristics between the S-D and M-D groups. Intraoperative and postoperative parameters were compared between the matched groups.

RESULTS

Among the 479 patients reviewed, 470 patients, including 91 in the S-D group and 379 in the M-D group, fulfilled the inclusion and exclusion criteria. Following

PSM, 78 patients in each group were paired using the 1:1 nearest available score match algorithm. No significant difference was found between groups with respect to intraoperative and postprocedural major adverse events (AEs). Tumor size, complete resection rate, and procedural duration were comparable between the groups. The S-D group demonstrated a significantly shorter length of hospital stay ($P < 0.001$) and lower overall medical expenses ($P < 0.001$) compared with the M-D group.

CONCLUSION

The S-D discharge strategy may be feasible and effective for esophagogastric ESD, and the procedural-related AEs can be managed successfully.

Key Words: Endoscopic submucosal dissection; Early esophageal cancer; Early gastric cancer; Same-day surgery; Adverse event

Core Tip: Generally, multi-day (M-D) admission is required for patients with early gastrointestinal neoplasia undergoing endoscopic submucosal dissection (ESD) due to potential complications. We evaluated the feasibility of a same-day (S-D) discharge strategy for ESD of the esophagus or stomach. No significant difference was found between the S-D and M-D groups with respect to intraoperative and postprocedural major adverse events. However, the S-D group demonstrated a significantly shorter length of hospital stay ($P < 0.001$) and lower overall medical expenses ($P < 0.001$) compared to the M-D group. The S-D discharge strategy may be feasible and effective for esophagogastric ESD.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) has been advocated as an effective treatment approach for early esophageal cancer and early gastric cancer[1-3]. ESD is safer, more cost-effective, has greater efficacy, and has a positive impact on health-related quality of life compared with surgery[4,5]. As ESD is associated with complications, including intraprocedural perforation rates between 2.2% and 4.5%[6-8] and postprocedural bleeding rates between 1% and 5.1%[6-9], a multi-day (M-D) hospital admission of 5 d to 7 d is generally required in daily practice[10]. Reducing the length of hospital stay can decrease medical expenses, and some studies have attempted to shorten the duration of postprocedural hospitalization after esophageal[11], gastric[12], and colorectal[13] ESD. However, data on the feasibility of same-day (S-D) discharge after esophagogastric ESD remain limited. Based on our previous studies with relatively low complications in ESD[14-16], our department has applied the S-D strategy to selected patients since 2020. In this study, we describe our preliminary experience with the S-D discharge strategy following ESD of the esophagus or stomach compared with conventional M-D hospital admission.

MATERIALS AND METHODS

Patients

We retrospectively reviewed clinical data from a prospectively maintained database of ESD for consecutive patients at Peking University Cancer Hospital between January 2018 and December 2021. The inclusion criteria were receipt of esophageal or gastric ESD and malignant final diagnosis. The exclusion criteria were receipt of laparoscopic endoscopic collaborative surgery, recurrent lesions, multiple lesions, or a history of esophagectomy or gastrectomy. The present study was approved by the Ethics Committee of Peking University Cancer Hospital (2022KT13) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients or their families.

Outcome measures

According to the length of hospitalization, patients were divided into S-D and M-D groups. Patients in the S-D group were admitted to the ambulatory care unit on the morning of the ESD procedure day, whereas patients in the M-D group were admitted to the hospital ward the day before ESD. After the ESD procedure, patients in the S-D group were discharged from the ambulatory care unit on the S-D, while the M-D group patients returned to the hospital ward for at least one night before discharge. Patients in the S-D group were informed that they might be transferred to a hospital ward for hospital stay after the procedure if there was an intraprocedural perforation, unsatisfactory postanesthesia recovery, or other serious unexpected adverse events (AEs). Concerning patients who received antithrombotic therapy, after consultation with a cardiologist, agents were discontinued 5-7 d before ESD and resumed on day 7 after the procedure.

The following demographic and clinical information were collected: Age, sex, American Society of Anesthesiologists (ASA) physical status classification, comorbidities, history of antithrombic agent use, duration of ESD procedure, length of hospital stay, cost of hospitalization, pathological evaluation of specimen, and AEs during or after the procedure.

In this study, the primary endpoint was the presence of ESD-related major AEs (MAEs) within 30 d of the procedure. MAEs included bleeding and perforation. Bleeding was defined as active or oozing bleeding of the ESD wound requiring hemostasis during scheduled second-look endoscopy (SSLE), with or without a decrease in hemoglobin level of ≥ 2 g/dL. Perforation was defined as a muscle layer defect, allowing the observation of mesenteric fat or intraabdominal space during the procedure or free air found on a radiograph in symptomatic patients after the ESD procedure. AEs were categorized as intraprocedural and postprocedural according to the time point in which they emerged.

The secondary endpoints were the rates of *en bloc* resection and complete resection, length of hospital stay, and medical expenses. The tumor location was divided into the esophagus, and the upper, middle, and lower stomach. The upper stomach consists of the cardia and upper part of the gastric body, the middle stomach consists of the angle and middle body, and the lower stomach consists of the pylorus, antrum, and lower body. The macroscopic classification was divided into elevated (0-I), flat (0-II), and depressed (0-III) types according to the Paris classification of superficial neoplastic lesions in the digestive tract[17]. *En bloc* resection was defined as resection of the lesion in a single piece, and complete resection was defined as resection of a tumor without histological evidence of tumor cell involvement on the lateral and vertical resection margins[18].

ESD procedures and postoperative management

All ESD patients in our department followed the M-D strategy before 2020. Patients with an estimated specimen size < 4 cm or who lived nearby were selected as S-D strategy candidates since 2020; they were assigned to the S-D or M-D group based on the anesthesiologist's recommendation and the patient's intention after full consultation. All ESD procedures were performed under general anesthesia with tracheal intubation and propofol administration. A single-channel upper gastrointestinal endoscope (GIF Q260J; Olympus Co., Tokyo, Japan) was used in all ESD procedures. A premixed sterilized solution of glycerol (10% glycerol and 5% fructose; Cisen Pharmaceutical, Co., Ltd., Shandong, China) with indigo carmine was injected into the submucosal layer. A single-use electrosurgical knife with water injection function (Micro-Tech Co., Nanjing, China) was used for lesion marking, incision, and dissection with an electrosurgical unit (VIO 200S; ERBE Elektromedizin GmbH, Tübingen, Germany). The ENDO CUT Q mode (parameter setting effect 3, cutting duration 2, and cutting interval 4) was applied for both mucosal incision and submucosal dissection. Hemostasis was achieved with the FORCED COAG E2 mode, and the power was set to 40 W in the esophagus and 50 W in the stomach. If perforation occurred during the procedure, suturing was performed using hemoclips (Micro-Tech Co.). All ESD wounds were sprayed with porcine fibrin sealant (5 mL kit; Guangzhou Bioseal Biotechnology Co., Ltd., Guangzhou, China) after the lesions were resected.

All ESD procedures were performed by the same endoscopist. For patients without intraprocedural perforation, nasogastric tube was not placed. For all patients, water drinking was initiated 2 h after anesthesia recovery. All patients also underwent an SSLE the next day to identify possible bleeding, even if they had been discharged on the same day of ESD. If no bleeding was discovered in the SSLE, oral enteral nutritional suspension was prescribed for 1 wk, followed by soft diet for 1 wk before the full diet resumption. For patients with intraprocedural perforation or postprocedural bleeding, the oral diet was postponed depending on recovery. For all patients, proton pump inhibitor therapy (standard dosing) was administered intravenously until the patient was discharged, followed by oral administration for 4 wk. Follow-up consisted of telephonic contact, and AEs reported after discharge were recorded by a physician associate.

Statistical analyses

To minimize the effect of selection bias, the propensity score matching (PSM) method was applied to balance the unevenly distributed patient baseline characteristics in this non-randomized trial. Individual propensity scores were generated through a logistic regression model that included the following covariates: Age, sex, ASA physical status, comorbidities, use of antithrombotic agent, tumor location,

macroscopic appearance, tumor differentiation, depth of invasion, and specimen size. Subsequently, patients in the S-D and M-D groups were paired using a 1:1 nearest available score match algorithm with a match tolerance of 0.02.

Further statistical analyses were conducted to compare the differences between the two groups based on the matched data. Quantitative data with normal distribution are presented as the means ± SD, and categorical data are presented as frequencies. Differences between groups were examined using the student's *t*-test, χ^2 test, or Fisher's exact test where appropriate. Logistic regression was used to identify the risk factors for AEs. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS statistical software (version 22.0; IBM Corp., Armonk, NY, United States).

RESULTS

Patient characteristics

A total of 479 patients who underwent 482 esophageal or gastric ESD procedures were reviewed retrospectively (Figure 1). Among these, 3 patients who underwent laparoscopic endoscopic collaborative surgery, 3 patients with multiple lesions, 2 patients with history of esophagectomy or gastrectomy, and 1 patient with a recurrent lesion were excluded. Therefore, 470 patients were enrolled in the study. The clinicopathological characteristics of the patients are presented in Table 1. Before PSM, there were 91 patients in the S-D group and 379 patients in the M-D group. There were significant differences in ASA score ($P = 0.039$), tumor differentiation ($P = 0.004$), depth of invasion ($P = 0.022$), and specimen size ($P < 0.001$) between the two groups. After PSM, there were 78 patients in each group, and all baseline parameters were balanced between the two groups.

Clinical outcomes of ESD

As shown in Table 2, after PSM, no significant difference was found between the groups across pathological parameters including tumor size, rate of free vertical margin, and complete resection. As shown in Table 3, the ESD procedural time was comparable between the two groups after PSM (60.5 ± 34.9 min in the S-D group *vs* 65.8 ± 43.0 min in the M-D group; $P = 0.397$). In addition, the duration of hospitalization was significantly shorter in the S-D group than in the M-D group (1 d *vs* 4.9 ± 2.5 d, respectively; $P < 0.001$). In this study, the total medical expense was determined by categorizing the costs of the procedure, medical devices, medication, diagnostic tests, and administration. The overall medical expenses and the subitem costs were lower in the S-D group.

Safety of the ESD procedure

Thirty-five MAEs occurred in 35 (7.4%) patients, including 14 intraprocedural perforations (1 in the esophagus), 18 cases of oozing bleeding (1 in the esophagus) without hemoglobin decreased, and 3 cases of active bleeding (all in the stomach) with hemoglobin decreased 2 g/dL to 2.5 g/dL during SSLE. All MAEs were managed endoscopically. There was no recurrent bleeding that occurred after SSLE, and no rehospitalization was needed within 7 d of discharge in either group. Both before and after PSM, no significant differences were found between the groups with respect to intraprocedural and postprocedural MAEs (Table 4). Factors associated with postprocedural bleeding and intraprocedural perforation were also investigated. Following multivariate analysis, lesions located in the middle and lower thirds of the stomach were significantly associated with postprocedural bleeding (odds ratio: 5.3, 95% confidence interval: 1.3-22.2; $P = 0.023$) (Table 5), whereas no risk factor was identified for intraoperative perforation.

DISCUSSION

In China, ESD has developed rapidly over the recent years due to the popularization of digestive endoscopic screening and the improved detection rate of early neoplastic lesions. Generally, an M-D admission is required for patients undergoing ESD because of the known potential complications[10]. Based on our previous experience, the risk of AEs is relatively low and generally can be managed conservatively or endoscopically in esophagogastric ESD, with reported intraprocedural perforation rates being between 1.9% and 2.6% and postprocedural bleeding rates between 1.4% and 8.7%[14-16]. Our department has performed the S-D discharge strategy since 2020, and this study demonstrates the feasibility and efficacy of S-D discharge procedures in selected esophagogastric ESD patients.

It was gratifying that we did not find any significant differences in the incidence of MAEs between the groups both before and after PSM in this study. Postprocedural bleeding is the most common complication in upper gastrointestinal ESD, with a reported incidence of 1% in the esophagus and 5.1% in the stomach[6-9]. Tumor in the lower third of stomach is an independent risk factor for post-ESD bleeding[19], and active antral peristalsis as well as bile reflux might lead to a higher incidence of post-ESD bleeding[8]. In our series, a slightly higher incidence of postprocedural bleeding (6.0%) was noted

Table 1 Comparison of clinicopathological features of the same-day discharge and multi-day discharge groups

Characteristics	Overall sample, *n* = 470		SMD value	*P* value	Matched sample, *n* = 156		SMD value	*P* value
	S-D, *n* = 91	M-D, *n* = 379			S-D, *n* = 78	M-D, *n* = 78		
Age in yr			-0.052	0.657			0.025	0.402
≤ 60	33 (36.3)	147 (38.8)			30 (38.5)	25 (32.1)		
> 60	58 (63.7)	232 (61.2)			48 (61.5)	53 (67.9)		
Sex			0.069	0.550			-0.057	1.000
Female	21 (23.1)	99 (26.1)			16 (20.5)	16 (20.5)		
Male	70 (76.9)	280 (73.9)			62 (79.5)	62 (79.5)		
ASA physical status			0.224	0.039			0.000	1.000
≤ 2	89 (97.8)	347 (91.6)			76 (97.4)	75 (96.2)		
≥ 2	2 (2.2)	32 (8.4)			2 (2.6)	3 (3.8)		
Comorbidities			-0.087	0.457			-0.050	0.423
No	45 (49.5)	171 (45.1)			37 (47.4)	42 (53.8)		
Yes	46 (50.5)	208 (54.9)			41 (52.6)	36 (46.2)		
Antithrombotic agents use			-0.164	0.141			-0.041	1.000
Yes	5 (5.5)	40 (10.6)			4 (5.1)	5 (6.4)		
No	86 (94.5)	339 (89.4)			74 (94.9)	73 (93.6)		
Location of lesion			-0.197	0.168			0.176	0.357
Esophagus	23 (25.3)	115 (30.3)			22 (28.2)	27 (34.6)		
Upper 1/3 of the stomach	18 (19.8)	97 (25.6)			14 (17.9)	20 (25.6)		
Middle 1/3 of the stomach	22 (24.2)	89 (23.5)			20 (25.6)	15 (19.2)		
Lower 1/3 of the stomach	28 (30.7)	78 (20.6)			22 (28.3)	16 (20.6)		
Macroscopic appearance, type			0.184	0.092			0.000	1.000
0-II	89 (97.8)	383 (93.1)			76 (97.4)	75 (96.2)		
0-I and 0-III	2 (2.2)	26 (6.9)			2 (2.6)	3 (3.8)		
Tumor differentiation			0.316	0.004			-0.064	0.442
Differentiated	85 (93.4)	307 (81.0)			73 (93.6)	76 (97.4)		
Undifferentiated	6 (6.6)	72 (19.0)			5 (6.4)	2 (2.6)		
Depth of invasion			0.258	0.022			0.030	1.000
Intramucosal	81 (89.0)	297 (78.4)			69 (88.5)	69 (88.5)		
Submucosal	10 (11.0)	82 (21.6)			9 (11.5)	9 (11.5)		
Specimen size in mm, mean ± SD	31.2 ± 12.3	43.9 ± 17.0	0.749	0.000	33.3 ± 11.9	33.6 ± 15.5	0.031	0.913

ASA: American Society of Anesthesiologists; M-D: Multi-day; S-D: Same-day; SD: Standard deviation; SMD: Standardized mean difference.

in the stomach, whereas mid- to lower location in the stomach was identified as the only risk factor for postprocedural bleeding, suggesting that we should not only pay attention to the lesions in the antrum but also those in the angle and gastric body to minimize the risk of postprocedural bleeding. In addition, male sex, antithrombotic drugs, tumor size > 20 mm, resected specimen size ≥ 40 mm, and flat/depressed lesion types are also risk factors for postprocedural bleeding[9,20], but none were identified in our study, possibly because we expanded the definition of postprocedural bleeding. We not only included patients with massive bleeding but also patients with active or oozing bleeding that necessitated hemostasis during SSLE without an overt hemoglobin decrease, which might maximize the safety of the S-D strategy in patients.

Although routine use of SSLE is not advocated as it does not reduce the risk of delayed bleeding[21,22], this technique has been carried out in many studies[23-25]. The purpose of SSLE in our study was to detect oozing and active bleeding and perform hemostasis. We did not perform prophylactic

Table 2 Pathological characteristics of the specimen in the same-day discharge and multi-day discharge groups

Characteristics	Matched sample, *n* = 156		*P* value
	S-D, *n* = 78	M-D, *n* = 78	
Tumor size in mm	17.8 ± 11.6	17.3 ± 10.4	0.778
En bloc resection	77 (98.7)	76 (94.7)	1.000
Free horizontal margin	78 (100.0)	77 (98.7)	1.000
Free vertical margin	76 (97.4)	76 (97.4)	1.000
Complete resection	75 (96.2)	73 (93.6)	0.719

Table 3 Comparison of procedural time, hospitalization, and cost in the same-day discharge and multi-day discharge groups

Characteristics	Matched sample, *n* = 156		*P* value
	S-D, *n* = 78	M-D, *n* = 78	
Procedure time in min	60.5 ± 34.9	65.8 ± 43.0	0.397
Hospitalization in d			
Total	1	4.6 ± 2.0	0.000
Postprocedural	0	3.0 ± 1.8	0.000
Medical expenses in CNY	25749.0 ± 4389.3	37000.8 ± 8510.7	0.000
Procedure: ESD, anesthesia, other procedures	3616.1 ± 942.8	6079.3 ± 1646.5	0.000
Medical devices	13112.0 ± 1884.5	17956.7 ± 4977.2	0.000
Medication	6390.7 ± 3866.4	7759.9 ± 2241.8	0.008
Diagnostic test: Endoscopy, laboratory, radiology, pathology	3625.5 ± 1133.9	4025.9 ± 1561.5	0.069
Administration: Hospitalization, nursing	260.0 ± 232.7	1178.9 ± 1506.7	0.000

CNY: Chinese Yuan; ESD: Endoscopic submucosal dissection.

Table 4 Major adverse events of same-day discharge and multi-day discharge groups

Characteristics	Overall sample, *n* = 470		*P* value	Matched sample, *n* = 156		*P* value
	S-D, *n* = 91	M-D, *n* = 379		S-D, *n* = 78	M-D, *n* = 78	
Total major adverse events	3 (3.3)	32 (8.4)	0.093	3 (3.8)	6 (7.7)	0.495
Intraprocedural perforation	0	14 (3.7)	0.083	0	3 (3.8)	0.245
Postprocedural bleeding during SSLE	3 (3.3)	18 (4.7)	0.778	3 (3.8)	3 (3.8)	1.000
Oozing bleeding	2 (2.2)	16 (4.2)	0.546	2 (2.6)	3 (3.8)	1.000
Active bleeding	1 (1.1)	2 (0.5)	0.476	1 (1.3)	0	1.000

M-D: Multi-day; S-D: Same-day; SSLE: Scheduled second-look endoscopy.

coagulation on nonbleeding visible vessels smaller than 0.3 mm in the post-ESD ulcer. Our previous study showed that a wound microvessel-protective hemostatic technique followed by porcine fibrin sealant can promote ESD-induced ulcer healing without increasing delayed bleeding events[15]. Prophylactic hemostasis-induced tissue damage or necrosis may lead to the exposure of arteries on the base of the ulcer, which in turn would contribute to delayed episodes of bleeding[21]. Although the inconvenience of SSLE might limit benefit of the S-D discharge strategy, it does provide help in the early detection of postprocedural bleeding, especially as a nasogastric tube is not routinely deployed in our department. Meanwhile, a fairly short distance to the hospital would allow for the patients to obtain timely treatments in the case of MAE development[11].

Table 5 Factors affecting endoscopic submucosal dissection procedure-related postprocedural bleeding, *n* = 470

Variable	Total, *n*	PB, *n* (%)	OR (95%CI)	*P* value
Male sex	350	17 (4.9)	3.0 (0.8-11.1)	0.105
Age ≤ 60 yr	180	10 (5.6)	1.5 (0.6-4.2)	0.392
ASA score ≤ 2	436	19 (4.4)	2.7 (0.2-38.3)	0.457
ATA usage	45	2 (4.4)	1.7 (0.2-12.7)	0.610
Multi-day discharge group	379	17 (4.5)	1.9 (0.5-7.4)	0.361
Non-flat appearance	28	2 (7.1)	1.4 (0.3-7.6)	0.710
Located in the lower 1/3 of the stomach	106	11 (10.4)	2.1 (0.7-6.2)	0.163
Located in the lower 2/3 of the stomach	211	17 (7.7)	5.3 (1.3-22.2)	0.023
Differentiated type	392	17 (4.3)	1.2 (0.3-5.2)	0.799
Submucosal invasion	92	4 (4.3)	1.3 (0.3-4.7)	0.723
Lesion ≥ 2 cm	236	11 (4.7)	1.2 (0.4-3.8)	0.818
Specimen ≥ 4 cm	234	10 (4.3)	1.1 (0.3-3.7)	0.879

ASA: American Society of Anesthesiologists; ATA: Antithrombotic agents; CI: Confidence interval; OR: Odds ratio; PB: Postprocedural bleeding.

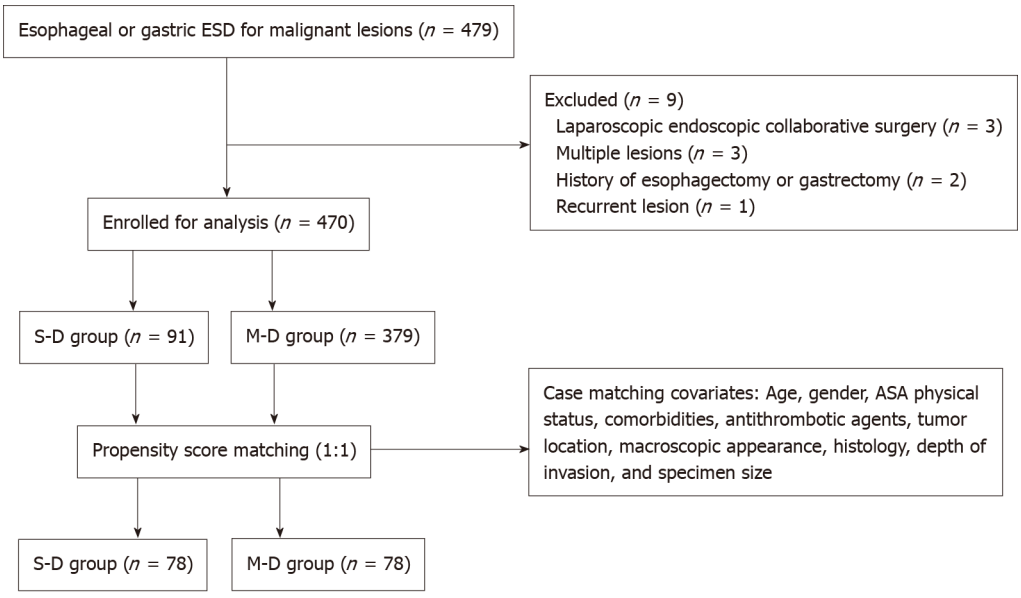

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Figure 1 Flow chart of patient enrollment for this study. A total of 479 patients received endoscopic submucosal dissection for the esophagus or stomach, and 470 cases met the inclusion and exclusion criteria. After propensity score matching, there were 78 patients in each group for further analysis. ESD: Endoscopic submucosal dissection; ASA: American Society of Anesthesiologists; M-D: Multi-day; S-D: Same-day.

As a relatively rare complication, intraprocedural perforation can be treated endoscopically in most cases, with a reported incidence of 2.2% in the esophagus and 4.5% in the stomach[6-8]. Larger tumor size (> 2 cm) and longer procedure time (> 2 h) are risk factors for perforation[26,27]. In this study, the rate of intraoperative perforation was 0.7% in the esophagus and 3.9% in the stomach. All perforations were sutured by hemoclips successfully, with no delayed perforation occurring. To avoid intraoperative perforation, it is important to obtain a good intraoperative field of view and to reliably discern the muscularis propria. The traction method is useful in many such cases[28], but we did not perform it routinely in our procedure. Greater experience and more delicate operation techniques might also reduce the risk of intraoperative perforation.

Achieving tumor-free margins is essential for the efficacy of ESD in early gastrointestinal malignancies. In this study, we obtained a similar complete resection rate of 96.2% and 93.6% in the S-D and M-D groups, respectively, which are comparable with previous studies[7,29,30]. Larger specimen sizes correlate with longer procedural duration[11], which is an independent risk factor for pulmonary

risk during anesthesia[31], and specimen size ≥ 4 cm is associated with delayed bleeding[20]. So when we started the S-D strategy in 2020, patients with estimated specimens smaller than 4 cm were selected as the S-D discharge candidates to minimize the associated risk above. Tumor differentiation should be noticed in specimen size estimation. In undifferentiated lesions, it is difficult to delineate the cancerous areas and easily obtain a positive lateral margin. Therefore, a further distance from the estimated border is usually needed to establish complete resection[32,33].

ASA physical status classification can reflect the severity of a patient's comorbidities, and those with an ASA score of 1 or 2 could be considered suitable for S-D discharge or outpatient ESD[11,34]. The results of the present study supported this data, as the proportion of patients with ASA score of 1 or 2 in the S-D group was more than that in the M-D group, but those patients experienced a similar profile of MAEs before and after PSM. Although the Charlson Comorbidity Index can provide a more detailed risk evaluation for patients with multiple comorbidities[35,36], the ASA score system is considered easier to apply in clinical settings.

ESD can greatly reduce the medical care costs associated with gastric cancer[37]. In Japan, ESD patients are usually admitted for 5-7 d, and in Europe for 2-4 d following ESD[10]. A reduction of hospitalization stay length or practice in an outpatient setting would minimize the medical expenses further[34]. A benchmark cost estimate for ESD treatment including 4 d of postoperative hospitalization in China is reportedly approximately 5400 United States Dollars[38], which is similar to our M-D group. Labor costs for doctors and nurses remain low in many East Asian countries, whereas medication and medical devices account for most of the total cost of ESD. A significant reduction in total cost could be established if ESD was performed with S-D discharge, as applied in our study. This is very important for Western countries, as their medical expenses increase with length of hospitalization. Using proper selection criteria, S-D discharge ESD could be a cost-effective strategy for esophagogastric early malignancies.

Our study had several limitations. First, all of the procedures were performed by a single skilled endoscopist with 14 years' experience in gastrointestinal ESD, and our experience reflected that of a high-volume center with a specialized endoscopist to perform ESD. Thus, our results might not be applicable to other centers. A further investigation involving more endoscopists, with varying degree of experience, from more centers, with diverse structure, is being designed and planned, and we hope to provide more conclusive findings in the future. Second, as a retrospective study, selection bias could not be ignored, although the PSM method was used to balance the characteristics of the patients in both groups. As an oncology-specific territory center, we lack specific experience in handling complex comorbidities. Most of the included patients had an ASA score of 1 or 2. Thus, we cannot generalize these results to patients with ASA scores of 3 or more. Third, we had implemented a S-D discharge policy for only 2 years. Due to a relatively small patient number, we were unable to identify a more detailed selection criterion other than an estimated specimen size of less than 4 cm for S-D discharge ESD to avoid potential complications during and after the procedure, and further investigation is needed.

CONCLUSION

In conclusion, this study, the first retrospective propensity score-matched study evaluating S-D discharge procedures for esophagogastric ESD in China, demonstrates that this strategy may be feasible and effective, and that the AEs related to ESD could be managed successfully. Additional prospective studies are warranted to establish more detailed standards to select patients for S-D discharge ESD.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) is an established technique for the treatment of early gastrointestinal neoplasia. Generally, a multi-day (M-D) admission is required for patients undergoing ESD due to potential complications. This retrospective study demonstrates that the same-day (S-D) discharge procedures for esophagogastric ESD may be feasible and effective.

Research motivation

ESD is safer, more cost-effective, has greater efficacy, and exhibits a positive impact on health-related quality of life in comparison with surgery. Reducing the length of hospital stay can decrease medical expenses, and some studies have attempted to shorten the duration of postprocedural hospitalization after esophageal, gastric, and colorectal ESD. However, data on the feasibility of S-D discharge after esophagogastric ESD remain limited.

Research objectives

In this study, we describe our preliminary experience with the S-D discharge strategy following ESD of the esophagus or stomach compared with conventional M-D hospital admission.

Research methods

To minimize the effect of selection bias, the propensity score matching method was applied to balance the unevenly distributed patient baseline characteristics in this non-randomized trial. Subsequently, patients in the S-D and M-D groups were paired using the 1:1 nearest available score match algorithm with a match tolerance of 0.02. Further statistical analyses were conducted to compare the differences between the two groups based on the matched data.

Research results

No significant difference was found between the groups with respect to intraoperative and postprocedural major adverse events (AEs). The tumor size, complete resection rate, and procedural duration were comparable between the groups. The S-D group demonstrated a significantly shorter length of hospital stay ($P < 0.001$) and lower overall medical expenses ($P < 0.001$) compared to the M-D group.

Research conclusions

This is the first retrospective study evaluating S-D discharge procedures for esophagogastric ESD in China. The result demonstrated the S-D discharge strategy may be feasible and effective for esophagogastric ESD, and the procedural-related AEs can be managed successfully.

Research perspectives

This first retrospective study evaluating S-D discharge procedures for esophagogastric ESD in China demonstrates that this strategy may be feasible and effective, and that the AEs related to ESD could be managed successfully. Additional prospective studies are warranted to establish more detailed standards to select patients for S-D discharge ESD.

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FOOTNOTES

Author contributions: Wang J and Li S contributed equally to this work; Wang J and Li S performed in analysis and interpretation of the data, and drafting of the manuscript; Wu Q and Chen K conceived of and designed the study; Yan Y, Yuan P, Li W, Cao C and Chen W helped to perform the analyses and critically revised the manuscript for important intellectual content; and all authors approved the final draft submitted.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic analysis of patients with combined hepatocellular-cholangiocarcinoma after radical resection: A retrospective multicenter cohort study

Ge Zhang, Bo-Wen Chen, Xiao-Bo Yang, Huai-Yuan Wang, Xu Yang, Fu-Cun Xie, Xiang-Qi Chen, Ling-Xiang Yu, Jie Shi, Yin-Ying Lu, Hai-Tao Zhao

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Abstract

BACKGROUND

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a form of rare primary liver cancer that combines intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma.

AIM

To investigate overall survival (OS) and recurrence-free survival (RFS) after radical resection in patients with cHCC-CCA, and the clinicopathological factors affecting prognosis in two center hospitals of China.

METHODS

We reviewed consecutive patients with cHCC-CCA who received radical rese-

ction between January 2005 and September 2021 at Peking Union Medical College and the 5th Medical Center of the PLA General Hospital retrospectively. Regular follow-up and clinicopathological characteristics were systematic collected for baseline and prognostic analysis.

RESULTS

Our study included 95 patients who received radical resection. The majority of these patients were male and 82.7% of these patients were infected with HBV. The mean tumor size was 4.5 cm, and approximately 40% of patients had more than one lesion. The median OS was 26.8 (95%CI: 18.5-43.0) mo, and the median RFS was 7.27 (95%CI: 5.83-10.3) mo. Independent predictors of OS were CA19-9 ≥ 37 U/mL (HR = 8.68, P = 0.002), Child-Pugh score > 5 (HR = 5.52, P = 0.027), tumor number > 1 (HR = 30.85, P = 0.002), tumor size and transarterial chemoembolization (TACE) after surgery (HR = 0.2, P = 0.005).

CONCLUSION

The overall postoperative survival of cHCC-CCA patients is poor, and most patients experience relapse within a short period of time after surgery. Preoperative tumor biomarker (CA19-9, alpha-fetoprotein) levels, tumor size, and Child-Pugh score can significantly affect OS. Adjuvant TACE after surgery prolongs RFS, suggesting that TACE is a possible option for postoperative adjuvant therapy in patients with cHCC-CCA.

Key Words: Combined hepatocellular-cholangiocarcinoma; Radical resection; Clinicopathological factor; Integrated nomogram; Multicenter cohort

Core Tip: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a relatively rare type of primary liver cancer. Hepatectomy combined with lymph node dissection is the only possible cure. In our study, we found that the prognosis for this group of patients is poor, with a 2-year survival rate of approximately 50% after radical resection. Preoperative CA19-9 Level, tumor number, tumor size and whether or not to receive tumor size and transarterial chemoembolization (TACE) after surgery were independent factors affecting overall survival. Therefore, we recommend that patients with cHCC-CCA actively receive adjuvant TACE therapy after surgery.

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INTRODUCTION

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a relatively rare primary liver cancer (PLC) and accounts for 0.4% to 14.2% of the incidence of PLC[1-4]. The definition of cHCC-CCA has been updated because of unclear understanding. In 2019, the WHO updated the cHCC-CCA classification[5], and in conventional histopathology of hematoxylin and eosin (H&E) staining, cHCC-CCA shows two different degrees of differentiation, hepatocellular and cholangiocarcinoma, within the same lesion. In contrast to the well-established management pathways for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), treatment remains a gray area for cHCC-CCA currently. The overall prognosis of patients with cHCC-CCA is worse than that of patients with HCC, and the prognosis is similar to that of patients with ICC. Vascular invasion actually seems to occur more frequently in cHCC-CCA than in HCC. In addition, lymph node metastases exhibit similar characteristics[6]. The treatment of cHCC-CCA has not been standardized in comparison to HCC and ICC, and a number of therapy strategies have been suggested. Radical tumor resection and lymph node dissection are the only curative options for patients with cHCC-CCA[7,8]. Nonetheless, the 5-year survival rate does not reach 30%, and the tumor recurrence rate is considerable (up to 80% after 5 years) in most studies[9-11].

In our research, we retrospectively analyzed cHCC-CCA patients who received surgical resection at two institutions to explore clinical case information for this rare tumor on prognosis, looking for factors affecting recurrence and long-term survival. All patients underwent rigorous organizational path-

ological confirmation to ensure cohort consistency.

MATERIALS AND METHODS

Patients

Among the patients who received hepatectomy for PLC in Peking Union Medical College Hospital and The 5th Medical Center of the PLA General Hospital from January 2005 to September 2021, 95 patients were pathologically diagnosed with cHCC-CCA based on the latest WHO criteria in 2019. Among these patients, 61 were treated in Peking Union Medical College Hospital, and 34 were treated in The 5th Medical Center of the PLA General Hospital. The inclusion criteria for these patients are described below: (1) Patients who received radical liver resection; (2) patients were pathologically diagnosed with cHCC-CCA; and (3) patients with complete clinical information and at least 2 follow-up visits after surgery. The exclusion criteria are described below: (1) Non-radical resection; (2) separated HCC and ICC; (3) incomplete clinical information, or irregular follow-up after surgery; and (4) history of other malignancies.

Based on regular medical records and telephone follow-up records, we determined how these patients were treated after surgery, whether they survived, and whether they experienced recurrence. Two patients had HCC and ICC at the same time, but the growth was dissociative, so they were excluded. Due to lost follow-up or too short follow-up time, another three patients were only used for baseline information statistics and not for prognosis analysis (Figure 1).

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (Reg. numbers JS-3390) and The 5th Medical Center of the PLA General Hospital (Reg. number KY-2022-4-23-1), and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki. All participants signed written informed consent.

Data collection

Through a search of the patients' medical records, we collected the following clinical information: Age, sex, background of liver disease, Eastern Cooperative Oncology Group (ECOG) score, gallstones, CA19-9 Level, alpha-fetoprotein (AFP) level, carcinoembryonic antigen (CEA) level, total bilirubin (TBil) level, direct bilirubin (DBil) level, albumin, ascites, and cirrhosis before surgery. The preserved liver functional was evaluated using the Child-Pugh (C-P) scoring system[12].

By reviewing the radiological reports, pathology reports and pathology sections of patients, we collected the following pathological information: tumor size, tumor number, macrovascular invasion (Macro VI), microvascular invasion (Micro VI), lymph node metastasis, distance to section, Ki-67, cytokeratin 7 (CK7), cytokeratin 19 (CK19), Hepatocyte paraffin 1 (HepPar-1), Glypican-3 (GPC-3), HCC differentiation, HCC percent, ICC differentiation, and ICC percent. HepPar-1 and GPC-3 were used as HCC markers, and CK7 and CK19 were used as biliary epithelial markers. Due to the absence of an optimal staging system for cHCC-CCA, we applied the American Joint Committee on Cancer (AJCC) staging manual (8th edition) to cHCC-CCA[13].

Overall survival (OS, defined as the time interval from the date of surgery to death or the last follow-up, depend on which came first) and recurrence-free survival (RFS, defined as the time interval from the date of surgery to recurrence, death, or the last follow-up, depend on which came first) were the primary measures for this study.

Statistical analysis

Normality tests for continuous variables were performed by the Shapiro-Wilk test[14]. Normal continuous variables were compared between patients in the two centers by analysis of variance. To compare nonnormal continuous variables, the Kruskal-Wallis test was utilized[15]. Categorical variable data were compared by Fisher's exact test[16]. Normal continuous variables were shown as the mean ± SD. Nonnormal continuous variables are shown as the median and IQR. Categorical variable data were displayed as numbers and percentages. The survival rate was determined using the Kaplan-Meier method. Univariate and multivariate analysis were performed using the log-rank test and Cox proportional hazards regression model, respectively. To identify independent prognostic factors, variables with P values < 0.15 in univariate analysis were incorporated into the Cox proportional hazards model. A P value with two tails < 0.05 was regarded as statistically significant. All analysis were performed using R 4.1.0.

RESULTS

Clinical characteristics of patients

In our research, we analyzed the preoperative clinical data of 98 (95 plus 3) patients (Table 1). Of the 98 patients, 86 (87.8%) were male. The mean age was 55.3 ± 10.4 years. The majority of patients had well-

Table 1 Demographic characteristics of patients with combined hepatocellular-cholangiocarcinoma before radical resection

	Overall	The 5th Medical Center of the PLA General Hospital	Peking Union Medical College Hospital	*P* value
Number	98	34	64	
Age, mean ± SD	55.3 (10.4)	53.5 (10.4)	56.3 (10.3)	0.219
Sex				
Male	86 (87.8)	32 (88.2)	56 (87.5)	1 (Fisher)
Female (%)	12 (12.2)	4 (11.8)	8 (12.5)	
ECOG (%)				0.009 (Fisher)
0	84 (85.7)	26 (76.5)	58 (90.6)	
1	11 (11.2)	8 (23.5)	3 (4.7)	
NA	3 (3.1)	0 (0)	3 (4.7)	
Child-Pugh class				0.435 (Fisher)
A	86 (87.8)	32 (94.1)	54 (84.4)	
B	6 (6.1)	1 (2.9)	5 (7.8)	
NA	6 (6.1)	1 (2.9)	5 (7.8)	
Liver disease (%)				0.823 (Fisher)
NA	4 (4.1)	1 (2.9)	3 (4.7)	
HBV	81 (82.7)	28 (82.4)	53 (82.8)	
HCV	4 (4.1)	2 (5.9)	2 (3.1)	
Fatty liver	2 (2.0)	0 (0.0)	2 (3.1)	
Alcohol	7 (7.1)	3 (8.8)	4 (6.2)	
Gallstones (%)	13 (13.3)	3 (8.8)	10 (15.6)	0.533 (Fisher)
CA19-9 (U/mL)	26.5 [13.1, 56.2]	29.7 [15.1, 46.5]	23.6 [12.4, 56.4]	0.775 (non-norm)
< 37	58 (59.2)	21 (61.8)	37 (57.8)	0.813 (Fisher)
≥ 37	31 (31.6)	11 (32.4)	20 (31.2)	
NA	9 (9.2)	2 (5.9)	7 (10.9)	
AFP (ng/mL)	44.1 [7.0, 338.4]	43.4 [5.8, 294.7]	44.1 [7.8, 724.3]	0.389 (non-norm)
< 200	61 (62.2)	24 (70.6)	37 (57.8)	0.122 (Fisher)
≥ 200	30 (30.6)	10 (29.4)	20 (31.2)	
NA	7 (7.1)	0 (0.0)	7 (10.9)	
CEA (ng/mL)	2.7 [1.6, 4.4]	2.5 [1.5, 3.5]	2.7 [1.7, 4.8]	0.173 (non-norm)
< 6	80 (81.6)	32 (94.1)	48 (75.0)	0.038 (Fisher)
≥ 6	9 (9.2)	0 (0.0)	9 (14.1)	
NA	9 (9.2)	2 (5.9)	7 (10.9)	
TBil (μmol/L)	12.6 [10.4, 16.4]	12.2 [10.4, 14.0]	12.9 [10.7, 17.8]	0.260 (non-norm)
DBil (μmol/L)	4.3 [3.8, 5.7]	4.2 [3.8, 5.0]	4.5 [3.8, 5.8]	0.334 (non-norm)
Albumin (g/L)	41.0 [39.0, 43.5]	40.0 [38.0, 42.0]	41.0 [39.0, 44.0]	0.055 (non-norm)
Ascites (%)				0.094 (Fisher)
No	75 (76.5)	30 (88.2)	45 (70.3)	
Yes	18 (18.4)	4 (11.8)	14 (21.9)	
NA	5 (5.1)	0 (0.0)	5 (7.8)	
Liver cirrhosis (%)	82 (83.7)	32 (94.1)	50 (78.1)	0.143 (Fisher)

ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: Alpha fetoprotein; CEA: Carcinoembryonic antigen; TBil: Total bilirubin; DBil: Direct bilirubin; NA: Not available.

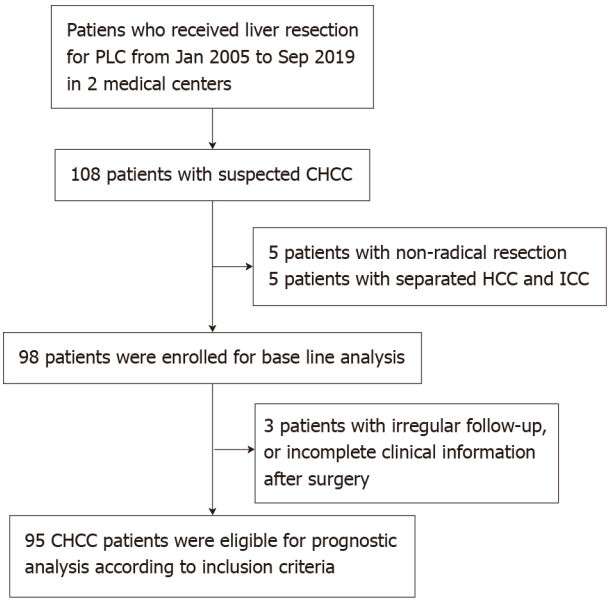

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Figure 1 Research framework of this study.

preserved liver function (Child-Pugh class A or B), the vast majority had an ECOG score of 0-1 (96.9%), and the majority had HBV infection (82.7%).

Most patients had well-preserved liver function (C-P class A or B), and most (96.9%) had an ECOG score of 0-1. HBV infection was present in 82.7% of the patients. Preoperative level of CA19-9 was higher than normal in 31 patients (31.6%) (≥ 37 U/mL), preoperative level of AFP was higher than normal in 51 patients (52.0%) (20 ng/mL, not listed), of which 30 patients (31.6%) had levels higher than 200 ng/mL, and preoperative CEA levels were higher than normal in 9 patients (9.2%) (≥ 6 ng/mL). Ascites and liver fibrosis were present in 18 patients (18.4%) and 82 patients (83.7%), respectively.

Pathological characteristics of patients

Table 2 demonstrated the pathological features of our two-center cohorts. In more than half (56.1%) of the patients, the number of lesions was more than one. The mean tumor size was 4.5 cm [range (2.9, 6.5)], and 62 patients (63.2%) had tumors smaller than 5 cm. Surgical margin did not exceed 1 cm in more than half (55.1%) of the cases. The proportions of macrovascular and microvascular invasion were 24.5% and 63.3%, respectively. Lymph node metastases were found in 12.2% of these patients. Using the AJCC staging system, we evaluated the TNM stage in 98 patients. 18 (18.3%) patients were stage I (17 IA, 1 IB), 59 (60.2%) patients were stage II, 19 (19.4%) patients were stage III (3 IIIA, 16 IIIB), and 2 patients could not be evaluated.

Survival and recurrence

Ninety-five patients with follow-up longer than 1 mo were used in survival and recurrence analysis. The median follow-up time was 34.2 mo (95%CI: 28.0-43.3), and the median OS was 26.8 mo (95%CI: 18.5-43.0) (Figure 2A). The estimated cumulative survival rates at 1, 2, 3, and 5 years were 73.9%, 51.7%, 38.2%, and 23.6%, respectively. The median RFS was 7.27 mo (95%CI: 5.83-10.3) (Figure 2B), and the estimated cumulative RFS rates at 6 mo, 1 year, and 2 years were 58.4%, 33.6%, and 30.4%, respectively. Most patients experienced relapse within 1 year after surgery. In addition, we further staged the patients using the AJCC Staging Manual (8th edition), and the results the results revealed a substantial difference in the median OS between stage I/II patients and stage III patients.

Prognostic factors of OS

Subgroup analysis showed that preoperative liver function grading (C-P score 5 *vs* > 5) remarkably affected prognosis, and patients with a preoperative C-P score of 5 had a significantly better survive than those with a preoperative C-P score greater than 5 (Figure 3A). The median OS was considerably lower for patients with baseline CA19-9 Levels over 37 U/mL than it was for those with levels below 37 U/mL (Figure 3B); however, subgrouping for AFP levels did not yield similar results (Supplemen-

Table 2 Clinicopathological characteristics of patients with combined hepatocellular cholangiocarcinoma

Item	Patients (*n* = 98)
Tumor number	
Solitary	55 (56.1)
Multiple	39 (39.8)
NA	4 (4.1)
Tumor size, median [IQR]	4.5 [2.9, 6.5]
≤ 3cm (%)	26 (26.5)
3-5 cm (%)	36 (36.7)
> 5 cm (%)	34 (34.7)
NA	2 (2.0)
Resection margin (%)	
≤ 1cm (%)	54 (55.1)
> 1cm (%)	21 (21.4)
NA	23 (23.5)
Macro VI (%)	24 (24.5)
Micro VI (%)	62 (63.3)
Lymph node metastasis (%)	12 (12.2)
TNM Stage (AJCC 8th) (%)	
I	18 (18.4)
II	59 (60.2)
III	19 (19.4)
NA	2 (2.0)
Ki-67 (%)	
≤ 50%	36 (55.4)
> 50%	29 (44.6)
CK7 (%)	
Negative	9 (11.1)
Weak positive	29 (35.8)
Strong Positive	43 (53.1)
CK19 (%)	
Negative	9 (10.8)
Weak positive	27 (32.5)
Strong Positive	47 (56.6)
HepPar-1 (%)	
Negative	29 (34.1)
Weak positive	23 (27.1)
Strong Positive	33 (38.8)
GPC-3 (%)	
Negative	16 (28.6)
Weak positive	13 (23.2)
Strong Positive	27 (48.2)
HCC differentiation (%)	

Poorly differentiated	19 (41.3)
Well or moderate differentiated	27 (58.7)
ICC differentiation (%)	
Poorly differentiated	30 (65.2)
Well or moderate differentiated	16 (34.8)
ICC percent (%)	
≤ 50%	11 (30.7)
> 50%	16 (59.3)

Macro VI: Macrovascular invasion; Micro VI: Microvascular invasion; AJCC: American Joint Committee on Cancer; CK7: Cytokeratin 7; CK19: Cytokeratin 19; HepPar-1: Hepatocyte paraffin 1; GPC-3: Glypican-3; HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma; NA: Not available.

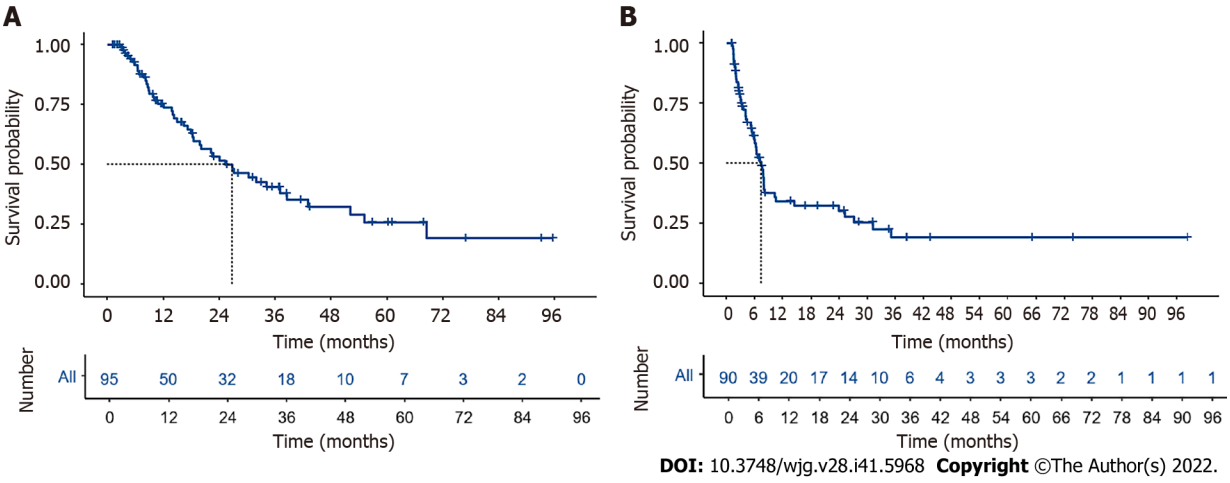

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Figure 2 Survival and recurrence in patients after radical resection. A and B: Overall survival (A) and recurrence-free survival (B) curves of patients with combined hepatocellular-cholangiocarcinoma from two medical centers.

tary Figure 1A). Additionally, when a lesion size of 5 cm was set as the threshold, subgroup analysis for pathological features revealed notably differences in OS between these two subgroups (Figure 3C). Further subgroup analysis among patients with a tumor size < 5 cm displayed that patient with a tumor size of less than 3 cm had a considerably better survive than those with a lesion size of between 3 cm and 5 cm (Figure 3D). The 3-year OS rates for these two subgroups were 67.1% and 30.9%, respectively. However, analysis for the number of lesions showed that patients with a single lesion did not show a significantly improved prognosis compared to patients with multiple lesions (Supplementary Figure 1B). Macrovascular invasion did not significantly affect prognosis (P = 0.07) (Supplementary Figure 1C), but showed a similar trend. The Micro VI grouping (with or without) did not demonstrate a meaningful predictive difference (Supplementary Figure 1D).

The results of univariate analysis indicated that the factors that prominently influenced OS were CA19-9 Level (≥ 37 U/mL *vs* < 37 U/mL), C-P score (> 5 *vs* 5), tumor size, and postoperative transarterial chemoembolization (TACE) intervention. The background of liver disease, macrovascular invasion, GPC-3 expression, and HCC differentiation showed similar effects (0.05 < P < 0.10). In contrast, age, gender, AFP level (≥ 200 ng/mL *vs* < 200 ng/mL), number of lesions, cut margins, and Micro VI were not associated with OS (Supplementary Figure 2). Further multivariate analysis revealed CA19-9 ≥ 37 U/mL (HR = 8.68, P = 0.002), C-P score > 5 (HR = 5.52, P = 0.027), tumor number > 1 (HR = 30.85, P = 0.002), tumor size, and postoperative TACE intervention (HR = 0.2, P = 0.005) as independent prognostic factors affecting OS (Figure 4A).

Prognostic factors of RFS

The similar subgroup analysis was carried out to further evaluate the variables impacting patient recurrence as patients with cHCC-CCA typically suffered recurrence within a short period of time. The results showed that patients with a preoperative C-P score of 5 had an actually longer RFS than patients with a C-P score greater than 5 (Supplementary Figure 3A). In addition, RFS was also significantly shorter in patients with multiple lesions (Supplementary Figure 3B), with patients with a tumor size ≤ 3 cm having a significantly longer RFS than those with tumors larger than 3 cm (Supplementary Figure 3).

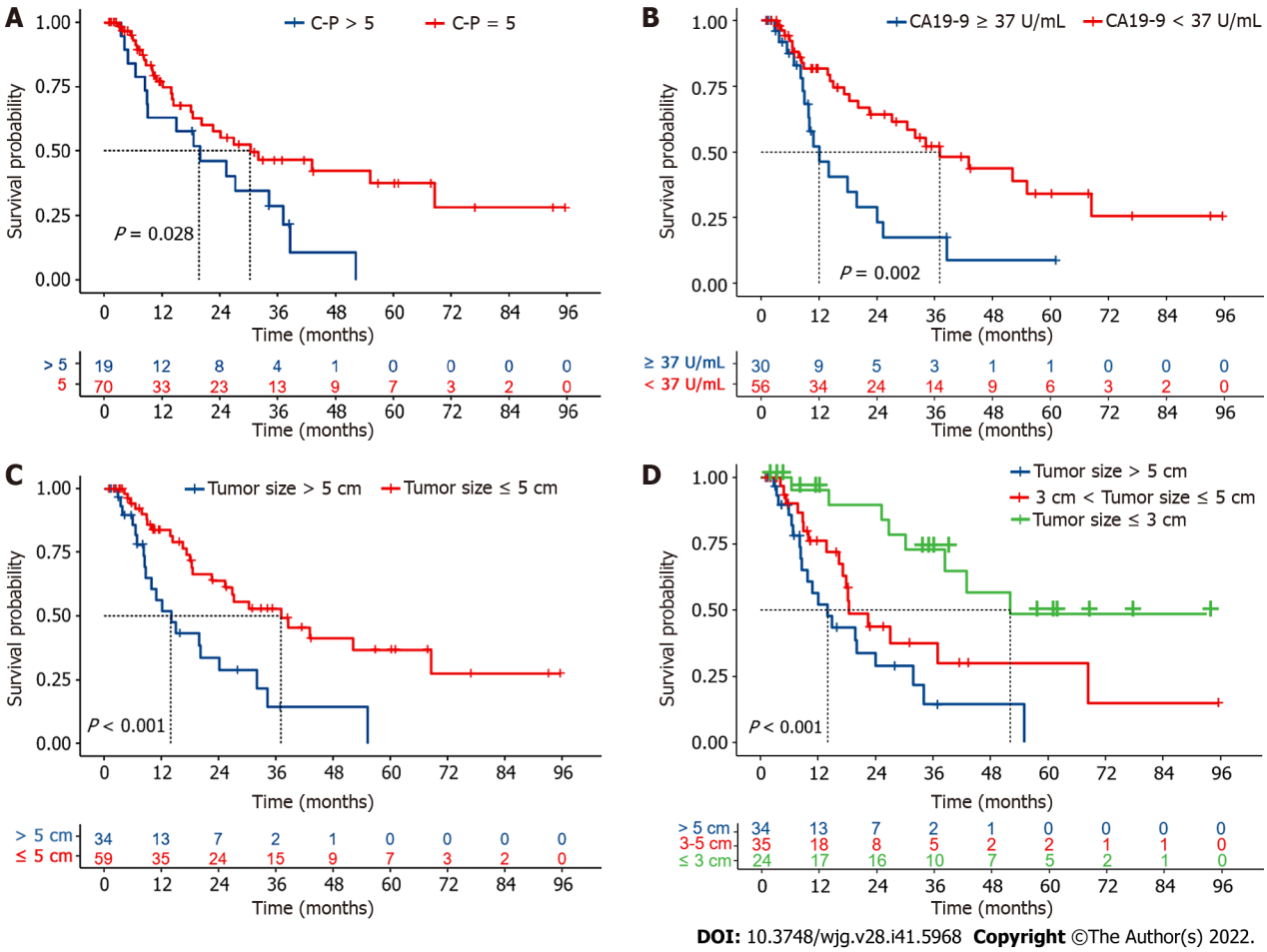

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Figure 3 Prognostic analysis between different subgroups. A-D: Overall survival between patients with different Child-Pugh (C-P) score (> 5 *vs* 5) (A), CA19-9 Level (≥ 37 U/mL *vs* < 37 U/mL) (B), tumor size (> 5 cm *vs* ≤ 5 cm) (C) and tumor size (≤ 3 cm *vs* 3-5 cm *vs* > 5 cm) (D).

The univariate analysis results were consistent with the subgroup analysis. Factors that significantly affected RFS were the C-P score, tumor number, tumor size and ICC differentiation ($P < 0.05$). In addition, postoperative TACE intervention was effective in prolonging patients' RFS (Supplementary Figure 4). Further multivariate analysis showed that the C-P score > 5 (HR = 3.57, $P = 0.001$), AFP ≥ 200 ng/mL (HR = 0.45, $P = 0.027$), tumor number (HR = 3.77, $P = 0.007$), tumor size, and TACE intervention before recurrence (HR = 0.51, $P = 0.032$) were independent prognostic factors affecting RFS. AFP ≥ 200 ng/mL and postoperative TACE treatment were protective factors for RFS (Figure 4B).

According to the results of the multivariate analysis, we constructed a nomogram which integrated the important factors for predicting OS and RFS in patients with cHCC-CCA. For predicting OS, Harrell's concordance index (C-index) was 0.767 (Figure 5A), and this value was 0.737 when predicting RFS (Figure 5B).

DISCUSSION

As a rare kind of PLC, the percentage of cHCC-CCA varies in different studies, with the vast majority of studies concluding that its incidence is less than 15%[3,17-19]. Previous definitions of cHCC-CCA have also been changing, from the Allen and Lisa class proposed in 1949[18]; to the Goodman type proposed in 1985[19], the 2010 WHO classification (4th edition) and the 2019 WHO classification (5th edition)[1]. Currently, the pathological definition of cHCC-CCA has been refined; however, its clinical features, treatment and prognosis are still controversial, with some studies suggesting that cHCC-CCA is more comparable to HCC, and some suggesting that it is analogous to ICC[20-22], and the latest AJCC Staging Manual also suggests applying the ICC staging system to cHCC-CCA[13].

The comparison of prognosis between cHCC-CCA, HCC, and ICC has long been contentious. In present research, the median OS of cHCC-CCA patients was 26.8 mo. In previous studies, most studies concluded that the long-term survival of cHCC-CCA was worse than HCC and better than ICC[23-25], and some researchers concluded that the prognosis of cHCC-CCA was comparable to ICC[26]. However, many recent studies using propensity score matching have found no significant differences

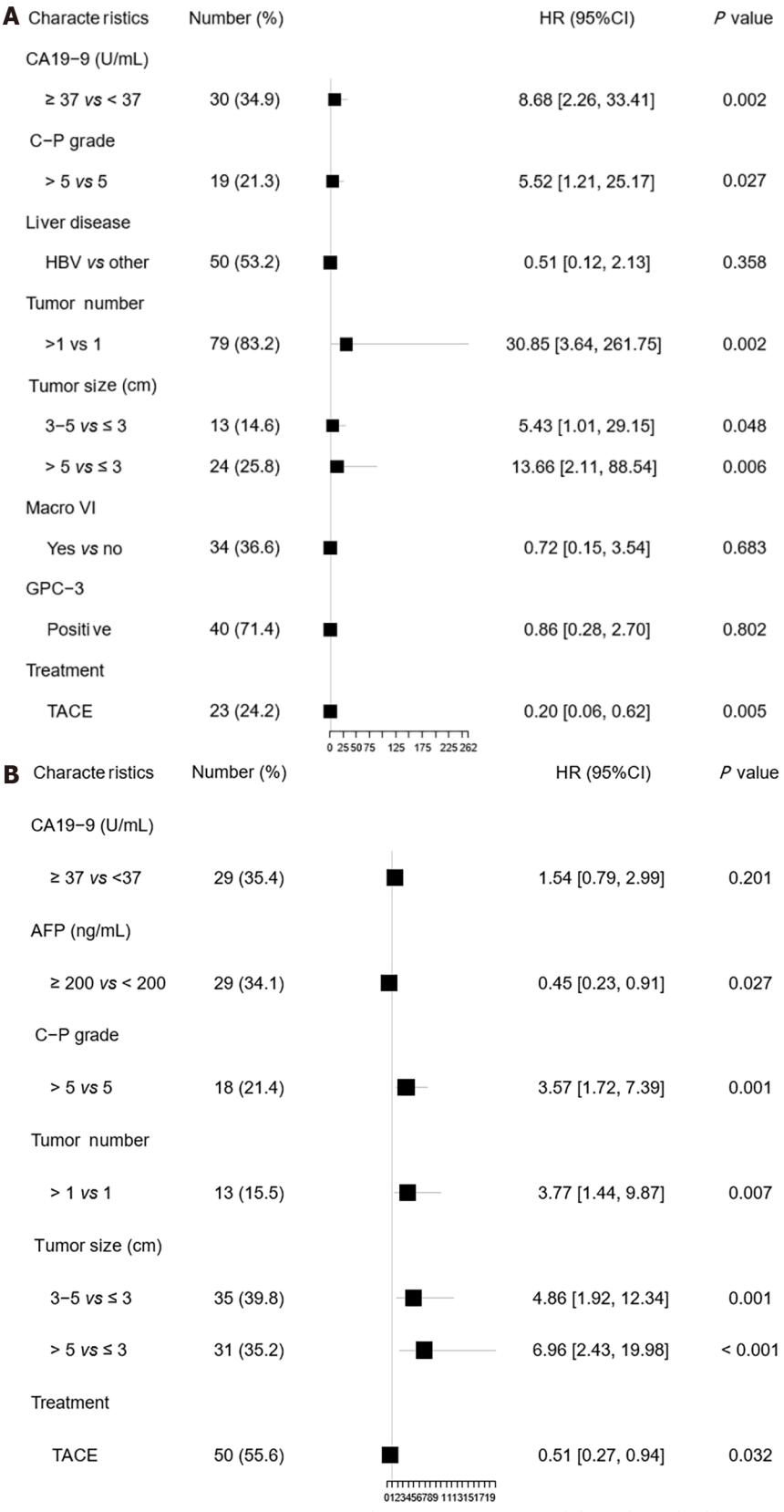

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Figure 4 Multivariate analysis of all patients on overall survival and recurrence-free survival. A: Overall survival; B: Recurrence-free survival. C-P: Child-Pugh; Micro VI: Microvascular invasion; GPC-3: Glypican-3; TACE: Transarterial chemoembolization.

between the prognosis of cHCC-CCA and HCC or ICC when appropriate matching conditions were used[25,27], suggesting that the poorer prognosis of cHCC-CCA may be related to the behavior of the tumor.

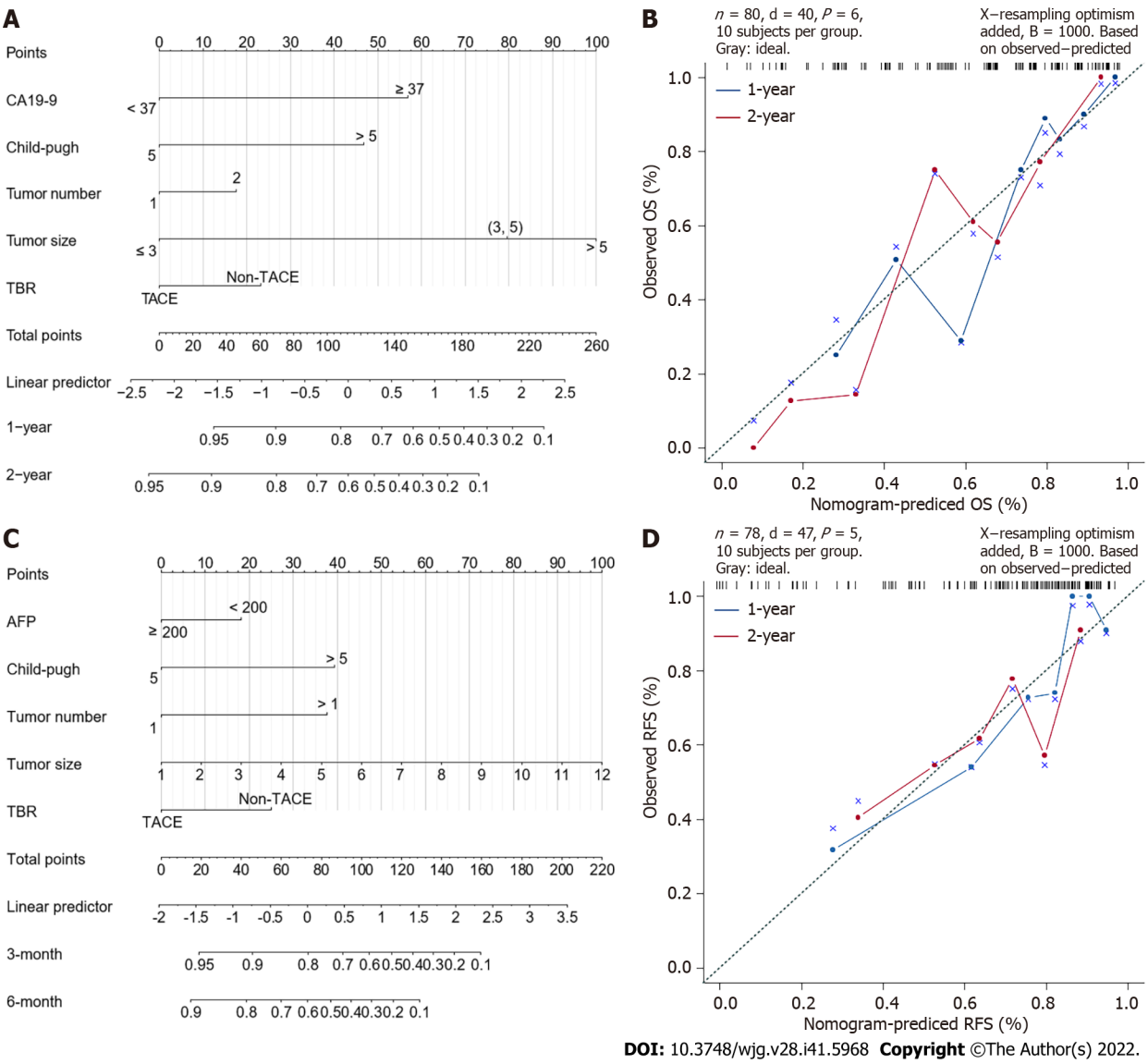

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Figure 5 Nomogram for overall survival and recurrence-free survival. A: Overall survival (OS) nomogram for patients with combined hepatocellular-cholangiocarcinoma (cHCC-CCA); B: Calibration curve of overall survival for 1- and 2-year OS; C: Recurrence-free survival (RFS) nomogram for patients with cHCC-CCA; D: Calibration curve of recurrence-free survival for 3-mo and 6-mo RFS. OS: Overall survival; RFS: Recurrence-free survival; TBR: Treatment before recurrence; AFP: Alpha-fetoprotein.

In terms of predictive factors of cHCC-CCA in our cohort, multivariate analysis showed that CA19-9 was an important factor influencing the survive after radical surgery, and patients with high CA19-9 had a significantly worse prognosis. This is consistent with previous studies[7,28], suggesting that the ICC component may be a key factor affecting the prognosis of cHCC-CCA. Notably, AFP ≥ 200 ng/mL was a protective factor for prognosis, although in another study, there was no significant correlation between AFP and prognosis[6]. Overall, few researches have stated the connection between AFP and cHCC-CCA prognosis, and more studies are needed to investigate it.

In addition to tumor biomarkers, tumor size was an important factor affecting prognosis in our study. The median OS for patients with tumors > 5 cm was only 14 mo, and the prognosis was significantly worse in this subgroup patients ($P < 0.001$). And this result is in line with the findings of several prior investigations[28-30]. Based on the latest AJCC Staging Manual, ICC staging system is also applicable to cHCC-CCA, and in this TNM staging system, 5 cm is also used as a basis for differentiating between stages IA and IB. However, considering that a variable proportion of cHCC-CCA also has an HCC component, a further stratified analysis was performed for these patients. This analysis showed that patients with tumors up to 3 cm in size had a significantly better prognosis than those with tumors 3-5 cm in size (median OS: 52.1 mo *vs* 18.5 mo, $P < 0.001$), whereas patients in the 3-5 cm subgroup did not have a significantly better prognosis than those in the > 5 cm subgroup (median OS: 18.5 mo *vs* 14.0 mo), a phenomenon that suggests the need for more precise differentiation of cHCC-CCA patients with a tumor size ≤ 5 cm. However, in a previously conducted study of small HCC[31], the three-year OS rate after surgical resection was 91.4%, and in another similar study enrolling small HCC patients (≤ 3 cm)

without vascular invasion, the 3-year survival rate after surgical resection was 96%[32]. In addition, in a recent retrospective study of ICC, the 5-year OS rate was 52.6% in 53 patients with small ICC (≤ 3 cm) [33]. In contrast, in another study, the 5-year OS rate was 40% in 44 patients with ICC, although the mean tumor size in that study was 5.5 cm[34]. These results imply that patients with cHCC-CCA have a considerably poorer prognosis than those with HCC of the same size, and their prognosis is even inferior to that of patients with ICC of the same size, suggesting that cHCC-CCA is a distinct entity of PLC that should be treated separately.

Due to the lack of accepted treatment protocols for cHCC-CCA, there are many discussions on postoperative adjuvant treatment choices for patients after resectable cHCC-CCA[22]. In our study, the univariate and multivariate results showed that postoperative TACE therapy significantly prolonged OS and RFS. TACE is a common adjuvant therapy after HCC, and previous studies have shown that TACE prolongs OS and RFS in HCC patients[35], which is based on the rationale of hindering the rich blood supply of HCC, thus promoting tumor necrosis[36]. TACE treatment has also been linked to improved survival in patients with cHCC-CCA following radical surgery, according to recent researches[24,25]. Studies including patients with unresectable cHCC-CCA have also shown that cHCC-CCA lesions with a rich blood supply have a higher response rate and better treatment outcomes for TACE[37]. These phenomena suggest that TACE might be an efficient postoperative adjuvant therapy modality for some patients with cHCC-CCA, and more studies are needed to further identify appropriate postoperative adjuvant treatment options.

Our study has some limitations. First, although our data were derived from multiple centers, selective bias in some of the data as a retrospective study and irregularities in postoperative follow-up are unavoidable. Second, our cohort was predominantly HBV-infected cHCC-CCA patients, and the applicability of these findings to non-HBV-infected cHCC-CCA patients remains to be further validated. Third, among patients with tumors ≤ 5 cm, our study found that the prognosis was significantly better for patients with tumors ≤ 3 cm, but further investigation with bigger samples is still required for this subgroup of patients. Fourth, there is still a large gap in postoperative adjuvant therapy for cHCC-CCA. In addition to TACE therapy, the role of targeted therapy and immunotherapy in preventing recurrence needs more research.

CONCLUSION

Herein, we discuss the clinical situation and prognostic features of resectable cHCC-CCA, using data from two centers. Overall, the prognosis of these patients is poor, with most patients recurring rapidly. TACE is an effective postoperative adjuvant therapy that may prolong RFS and improve patient prognosis.

ARTICLE HIGHLIGHTS

Research background

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a relatively rare type of primary liver cancer. For patients who undergo radical resection, despite being able to undergo surgery, the overall postoperative prognosis is poor and the factors affecting postoperative recurrence and survival are unknown.

Research motivation

The motivation for this study was the poor prognosis of patients with cHCC-CCA who underwent radical surgery. Factors affecting postoperative survival remain controversial. There is a lack of clear guidelines for the choice of postoperative adjuvant therapy.

Research objectives

To explore the factors affecting postoperative recurrence and survival in patients with cHCC-CCA who underwent radical resection, leading to better risk stratification of patients and to investigate the impact of postoperative adjuvant therapy on prognosis.

Research methods

This study is a multicenter retrospective study focusing on rare cancer types. Ninety-five patients who underwent radical resection and had surgical pathology confirmed cHCC-CCA were included. Clinical information was collected and follow-up was performed for these patients. The number of patients enrolled in this study was large and the follow-up was adequate.

Research results

For patients with cHCC-CCA undergoing radical resection, most patients recur within 1 year after surgery, with a median survival of approximately 2 years. The 5-year survival rate does not exceed 30%. In addition to the biological characteristics of the tumor, postoperative transarterial chemoembolization (TACE) can significantly affect the prognosis. This finding helps to assist physicians and patients in the selection of postoperative adjuvant therapy.

Research conclusions

Most patients with cHCC-CCA experience recurrence within a short period of time after surgery. Postoperative adjuvant TACE prolongs RFS and is a possible option for postoperative adjuvant therapy.

Research perspectives

The main direction of future research is to explore appropriate preoperative diagnostic methods as well as postoperative adjuvant treatment options.

FOOTNOTES

Author contributions: Zhao HT, Lu YY, and Shi J led the entire project, and all authors participated in the discussion and interpretation of the data and results; Zhang G, Chen BW, and Yang XB performed the data collection, main analysis, and wrote the original manuscript; Wang HY, Xie FC, and Yu LX were participated in data collection and generation of figures and tables; Yang X and Shi J were involved in pathology review.

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ORIGINAL ARTICLE

Retrospective Study

High incidence combination of multiple primary malignant tumors of the digestive system

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Abstract

BACKGROUND

Clinical reports of multiple primary malignant tumors (MPMTs) in the digestive system are increasing. In China, although the survival rate of patients with MPMTs is increasing, the quality of life is very low. Many patients have reached the advanced stage when the second primary tumor is found, resulting in no early intervention and treatment. This is due to the misunderstanding of MPMTs by clinicians, who treat such tumors as metastases. Therefore, before a patient has a second primary tumor, doctors should understand some common combinations of digestive system MPMTs to provide clinical guidance to the patient.

AIM

To explore the high incidence combination of digestive system MPMTs under heterochronism and synchronization.

METHODS

A total of 1902 patients with MPMTs at Peking Union Medical College Hospital were analyzed retrospectively. They were divided into metachronous MPMT and synchronous MPMT groups, and then the high incidence combinations of the first primary cancer and the second primary cancer in metachronous cancer and synchronous cancer were sorted. Sex and age differences between metachronous and synchronous tumors were tested by the chi square test and *t* test, respectively.

A P value < 0.05 was considered as statistically significant, and SPSS version 26.0 (SPSS Inc., Chicago, Illinois, United States) was used for statistical analysis.

RESULTS

Among the 1902 patients with MPMTs confirmed by pathology, 1811 (95.2%) cases were secondary primary cancers, 89 (4.7%) cases were tertiary primary cancers, and 2 (0.1%) cases were quaternary primary cancers. Most (88.2%) of the secondary primary cancers were identified as metachronous multiple primary cancers six months after diagnosis of the first primary cancer. The top ten most common MPMTs in the first primary cancer group ranged from high to low as follows: Breast cancer, thyroid cancer, nonuterine cancer, lung cancer, colon cancer, kidney cancer, uterine cancer, bladder cancer, rectal cancer, and gastric cancer. The highest incidence rate of the first primary cancer in male metachronous cancer was lung cancer (11.6%), the highest incidence rate of the second primary cancer was still lung cancer (24.9%), the highest incidence rate of the first primary cancer in female metachronous cancer was breast cancer (32.7%), and the highest incidence rate of the second primary cancer was lung cancer (20.8%). Among them, breast cancer, nonuterine cancer and uterine cancer were female-specific malignant tumor types, and thyroid cancer also accounted for 79.6% of female patients. The top five metachronous cancer combinations, independent of female-specific malignant tumor types and thyroid cancer, were colon cancer and lung cancer (26 cases), kidney cancer and lung cancer (25 cases), rectal cancer and lung cancer (20 cases), gastric cancer and lung cancer (17 cases), and bladder cancer and lung cancer (17 cases). The most common synchronous cancer combination was colon cancer and rectal cancer (15 cases).

CONCLUSION

Screening for lung cancer should be performed six months after the detection of colon cancer while rectal cancer screening should be performed within six months.

Key Words: Multiple primary malignant tumors; Colon cancer; Rectal cancer; Metachronous carcinoma; High incidence combinations; First primary carcinoma

Core Tip: This is a retrospective study to explore the high incidence combination of multiple primary malignant tumors (MPMTs). Among the 1902 patients with MPMTs confirmed by pathology, after excluding the effect of male-female specific malignancies, it was found that digestive system malignancies were very common as the first primary cancer. Therefore, the common combination of second primary cancers should be followed up at the limit of 6 mo after the detection of digestive system malignancies. Without excluding the influence of male-female specific malignancies, it was found that the combination of breast cancer and nonuterine cancer was the most common in metachronous multiple primary malignancies, and the combination of colon cancer and rectal cancer was the most common in synchronous multiple primary malignancies.

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INTRODUCTION

Multiple primary malignant tumors (MPMTs) are defined as the simultaneous or successive occurrence of two or more primary malignant tumors in the same individual, which can be derived from the same organ, paired organs, different parts of the same system or different organs of different systems[1]. The diagnostic criteria were as follows: (1) Each tumor must have definite malignant histopathological changes; (2) Each tumor must have an independent pathological type; and (3) The possibility of invasion and metastasis of the second cancer as the first primary cancer must be excluded. MPMTs were divided into metachronous cancer and synchronous cancer. Synchronous MPMTs are defined as the second primary cancer that occurs within 6 mo of the first primary cancer, and metachronous MPMTs are the opposite of synchronous cancer.

Table 1 Clinical characteristics of multiple primary cancers patients. Clinical characteristics of patients with metachronous and synchronous multiple primary cancers

Clinical variable	Metachronous multiple primary cancers (*n* = 1687, 88.2%)	Synchronous multiple primary cancers (*n* = 224, 11.8%)	Total (*n* = 1902)	*P* value
Sex				< 0.001[1]
Male	562 (33.5%)	119 (53.1%)	681 (35.8%)	
Female	1116 (66.5%)	105 (46.9%)	1221 (64.2%)	
Age				0.377[2]
Mean (SD)	60.5 (11.7)	59.8 (11.8)	60.5 (11.7)	
Rang	22.0-90.0	24.0-88.0	22.0-90.0	

[1]chi-squared test.
[2]*t*-test.

In recent years, as many as two to five primary cancers have been reported in a single case[2-5]. However, double primary MPMTs are more common[6,7]. This study investigated the combined association between second primary cancer and first primary cancer. With the development of cancer nanotechnology[8], cancer patients can be clearly diagnosed and properly treated, and the survival rate of cancer patients has been greatly improved[9-11]. Due to the long-term side effects of chemotherapy and/or radiotherapy[12,13], the improvement of diagnostic sensitivity and the continuous influence of genetic and behavioral risk factors, cancer patients have an increased risk of developing a second cancer due to the improvement of survival rate[14], which can threaten their health. Due to the complex pathogenesis of cancer and the influence of the tumor microenvironment[15], it is difficult to find a perfect anticancer therapy that can resist the growth of malignant tumors without increasing toxicity and causing adverse pharmacological interactions. Predicting the occurrence of the second cancer among cancer survivors is conducive to the diagnosis and treatment of cancer patients, and some MPMTs seem to have a correlation with one another, as they appear in specific combinations. Understanding common cancer combinations is of significance for the clinical diagnosis and treatment of cancer patients.

MATERIALS AND METHODS

A total of 1902 patients were diagnosed with MPMTs at Peking Union Medical College Hospital from January 1, 2000, to June 1, 2021. According to the 3rd Edition description and definition[16], the primary cancer site is divided into 23 main types of solid cancer. The types are breast cancer; thyroid cancer; nonuterine cancer; lung cancer; colon cancer; rectal cancer; renal cancer; uterine cancer; bladder cancer; gastric cancer; head and neck cancer; prostate cancer; renal pelvis and ureter; oesophageal cancer; liver cancer; skin cancer; pancreatic cancer; thymus cancer; non-prostate cancer; small intestine cancer; adrenal cortex; sarcoma; bone and chondroma. Male genital cancer is divided into prostate cancer and non-prostate cancer. Nonuterine cancer includes cervical, vaginal, ovarian and fallopian tube cancers. Sex and age differences between metachronous and synchronous tumors were tested by the chi square test and *t* test, respectively. A *P* value < 0.05 was considered as statistically significant, and SPSS version 26.0 (SPSS Inc., Chicago, Illinois, United States) was used for statistical analysis.

RESULTS

The top ten, first-diagnosed cancers of metachronous and synchronous multiple primary cancers. Among 1902 patients with multiple primary cancers, including 681 males and 1221 females (1:1.79), 1678 cases (88.2%) were metachronous multiple primary cancers, and 224 cases (11.8%) were simultaneous multiple primary cancers. The majority of patients with multiple primary cancers were women (64.2%). There was a significant difference in the distribution of metachronous and simultaneous cancers between gender groups ($^tP < 0.001$). The average age at diagnosis of the first metachronous and simultaneous cancers was 61 and 60 years, respectively (Table 1).

The first and second primary cancers in the top ten MPMTs

We found that the first primary cancer types of the top ten MPMTs were as follows (Figure 1A): Breast cancer (19.5%); thyroid cancer (15.7%); nonuterine cancer (8.9%); lung cancer (8.1%); colon cancer (6.7%);

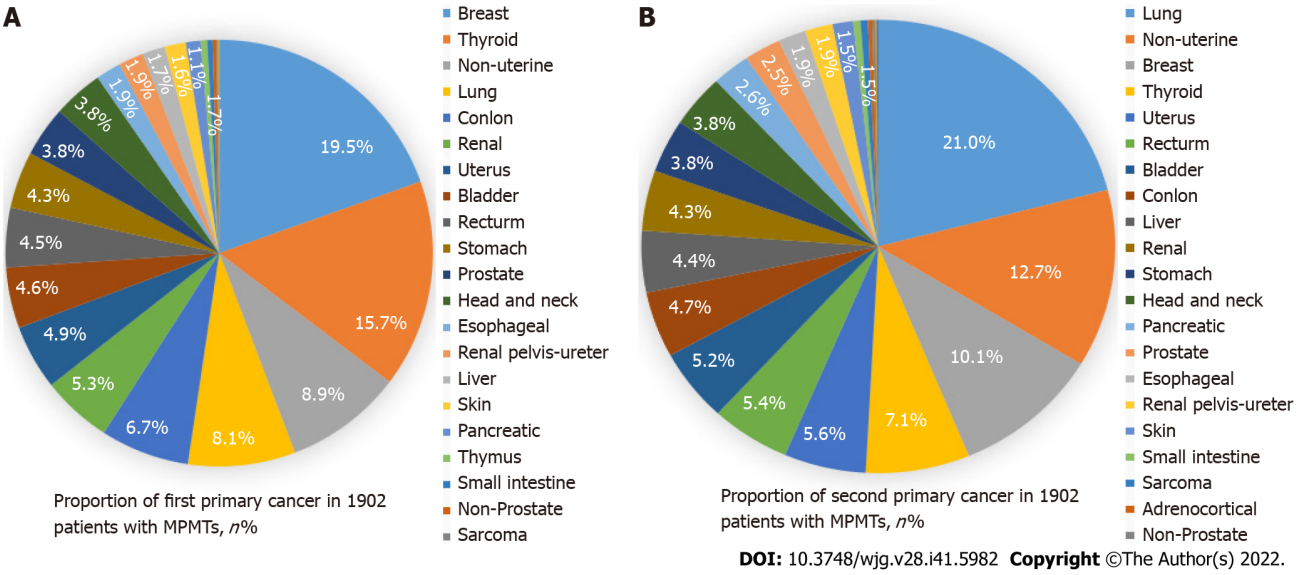

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Figure 1 Distribution of first and second primary cancers of multiple primary cancers. A: The first primary cancer; B: The second primary cancer.

renal cell carcinoma (5.3%); uterine cancer (4.9%); bladder cancer (4.6%); rectal cancer (4.5%); gastric cancer (4.3%). The second primary cancer types of the top ten MPMTs were as follows (Figure 1B): Lung cancer (21.0%); nonuterine cancer (12.7%); breast cancer (10.1%); thyroid cancer (7.1%); uterine cancer (5.6%); rectal cancer (5.4%); bladder cancer (5.2%); colon cancer (4.7%); liver cancer (4.4%); and renal cell carcinoma (4.3%).

The proportion of male to female first primary cancer and second primary cancer metachronous cases

The incidence rate of lung cancer in metachronous MPMTs as the first primary cancer (Figure 2A) was the highest in men (11.6%), and the second primary cancer in male metachronous MPMTs was still the highest in lung cancer incidence rate (Figure 2B) (24.9%). The incidence rate of breast cancer as the first primary cancer in metachronous MPMTs (Figure 2C) was the highest in women (32.7%), and the incidence rate of lung cancer (Figure 2D) was the highest (20.8%) in female metachronous MPMTs. It should also be noted that most second primary cancers occur more than 6 mo after the diagnosis of the first primary cancer.

The proportion of male and female cancers of the first primary cancer and the second primary cancer in synchronous cancer

Among synchronous cancers, the incidence rate of colon cancer (Figure 3A) was the highest among the first primary cancers in men (15.1%), the incidence rate of rectal cancer (Figure 3B) was the highest among the second primary cancers (21.0%), the incidence rate of nonuterine cancer (Figure 3C) was the highest among the first primary cancers in women (26.7%), and the incidence rate of nonuterine cancer (Figure 3D) was the highest among the second primary cancers (30.5%).

After excluding the influence of male-female specific malignant tumors, the proportion of male and female digestive system malignant tumors

After excluding male-female specific cancers, 749 patients (440 males and 309 females) were found to have metachronous cancers, of which 43.2% were digestive system malignancies in males and 44.7% were digestive system malignancies in females (Figure 4A). There were 143 patients (102 males and 41 females) with synchronous cancer. Among them, 49.9% of male and 34.0% of female digestive system malignancies were digestive system malignancies (Figure 4B).

The combination of the first primary cancer and the metachronous and synchronous second primary cancer in multiple primary cancers

The combination of the first primary cancer and the second primary cancer in the top ten metachronous multiple primary cancers was as follows (Figure 5A): Breast cancer and nonuterine cancer (105 cases); thyroid cancer and lung cancer (85 cases); breast cancer and lung cancer (79 cases); thyroid cancer and breast cancer (63 cases); breast cancer and thyroid cancer (52 cases); thyroid cancer and nonuterine cancer (41 cases); nonuterine cancer and breast cancer (34 cases); breast cancer and uterine cancer (34 cases); colon cancer and lung cancer (26 cases); and renal cancer and lung cancer (25 cases). Breast or

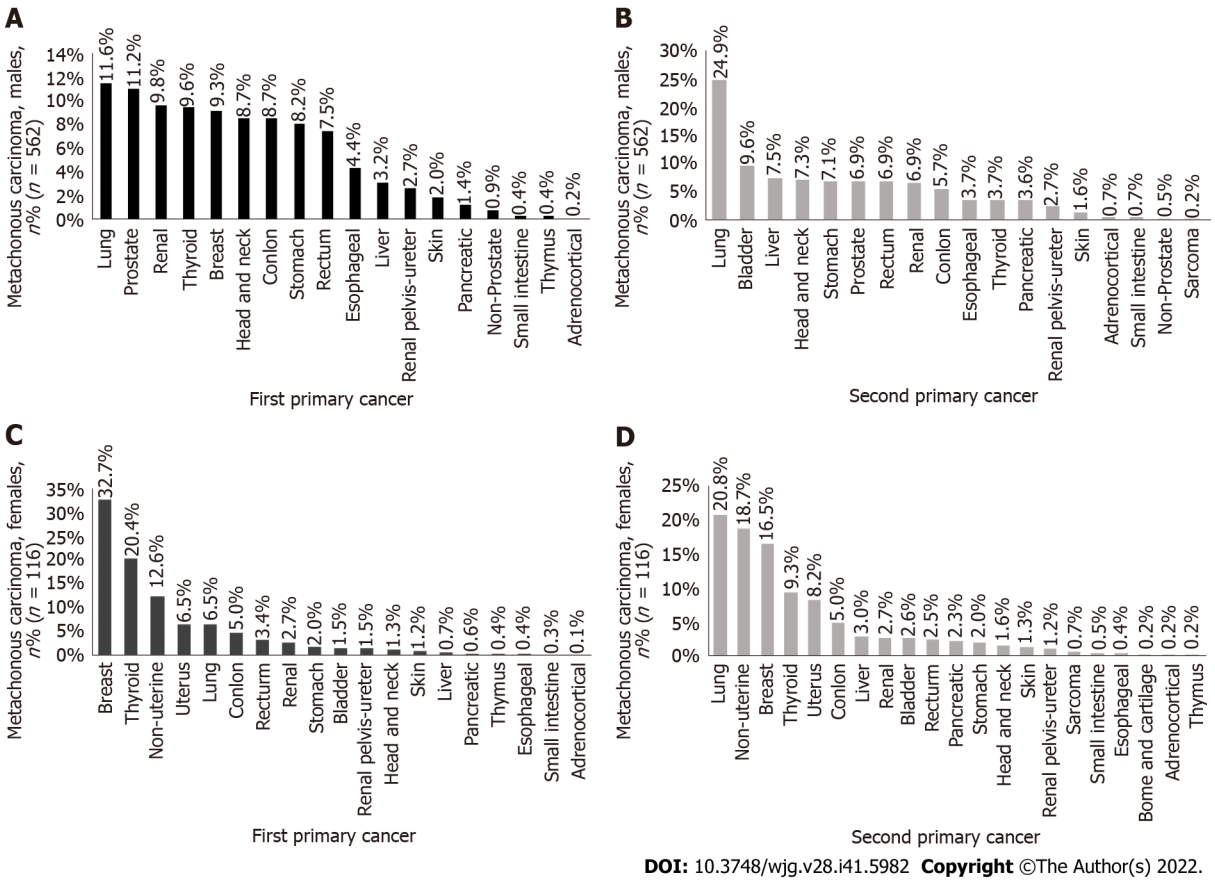

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Figure 2 The proportion of male to female first primary cancer and second primary cancer metachronous cases. A: The first primary cancer is distributed in men with metachronous cancer; B: The second primary cancer is distributed in men with metachronous cancer; C: The first primary cancer is distributed in women with metachronous cancer; D: The second primary cancer is distributed in women with metachronous cancer.

thyroid cancer may become the most prevalent second primary cancer among multiple primary cancers. The top five synchronous multiple primary cancers, the combination of the first primary cancer and the second primary cancer, were as follows (Figure 5B): Colon cancer and rectal cancer (15 cases); uterine cancer and nonuterine cancer (14 cases); nonuterine cancer and nonuterine cancer (13 cases); nonuterine cancer and uterine cancer (9 cases); and there were 8 cases of thyroid carcinoma.

Relationship between nonuterine cancer and nonuterine cancer in synchronous cancer

In the combination of nonuterine cancer and nonuterine cancer (Table 2), the results were as follows: Cervical cancer and ovarian cancer (5 cases); vaginal carcinoma and cervical carcinoma (3 cases); cervical vaginal cancer (2); fallopian tube carcinoma and cervical carcinoma (1 case); and ovarian cancer and cervical cancer (column 1). Nonuterine cancer and nonuterine cancer are not duplicates, as the term refers to any cancer occurring in the female reproductive system. Therefore, when a patient has one of the nonuterine cancers, doctors should check whether the other nonuterine organs have lesions at the time of diagnosis to avoid a missed diagnosis.

DISCUSSION

In our study, female-specific malignant tumors accounted for the vast majority. Therefore, to balance the influence caused by the excess of certain malignant tumors between male and female malignant tumors, we tried to distinguish the malignant tumors specific to male and female patients from the malignant tumors likely to affect both sexes for discussion and found that the combination of colon cancer and lung cancer (26 cases) was the most common in metachronous cancer, followed by renal and lung cancer (25 cases), rectal and lung cancer (20 cases), gastric and lung cancer (17 cases), and bladder and lung cancer (17 cases). The combination of colon cancer and rectal cancer (15 cases) was the most common in synchronous cancer. There is evidence that breast-cancer susceptibility gene 1 (BRCA1)/BRCA2 and MMR genes are indeed closely related to the occurrence of first and second colon cancer[17]. For the combination of colon cancer and rectal cancer, it is hoped that future genetic testing will be performed. Colon cancer is more likely to appear as the first primary cancer in the combination of synchronous

Table 2 Combination of non-uterine cancer and non-uterine cancer

	Cervix	Vagina	Ovary
Cervix	0	2	5
Vagina	3	0	0
Fallopian tube	1	0	1
Ovary	1	0	0

The row represents the first primary cancer and the column represents the second primary cancer.

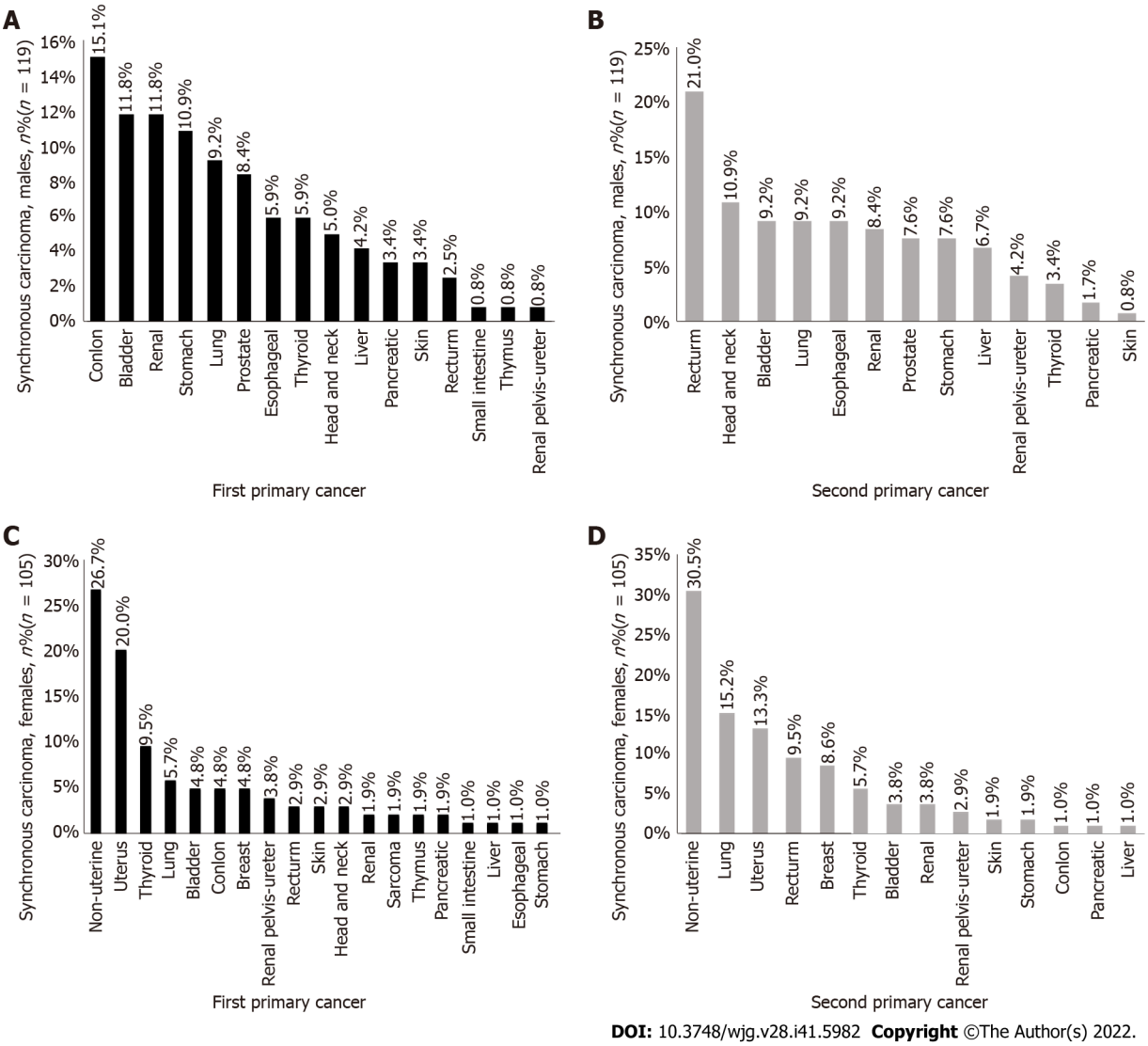

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Figure 3 The proportion of male and female cancers of the first primary cancer and the second primary cancer in synchronous cancer. A: The distribution of the first primary cancer in men with synchronous cancer; B: The second primary cancer in men with synchronous cancer; C: The distribution of the first primary cancer in women with metachronous cancer; D: The second primary cancer in women with metachronous cancer.

cancer and metachronous cancer. Since the majority of tumors occur in the digestive system, regular follow-up of the lungs should be performed 6 mo after the discovery of colon, rectal, or gastric cancer, and the rectum should be followed up and screened within 6 mo to prevent the occurrence of the second colorectal cancer[18-20].

We found that metachronous MPMTs are more common than synchronous MPMTs, which is consistent with a study conducted in Thailand last year[21]. However, Thailand has the highest incidence rate of liver cancer among metachronous cancer types, which is related to their eating habits. They like to eat sashimi, which leads to infection caused by parasitic liver flukes, resulting in a higher

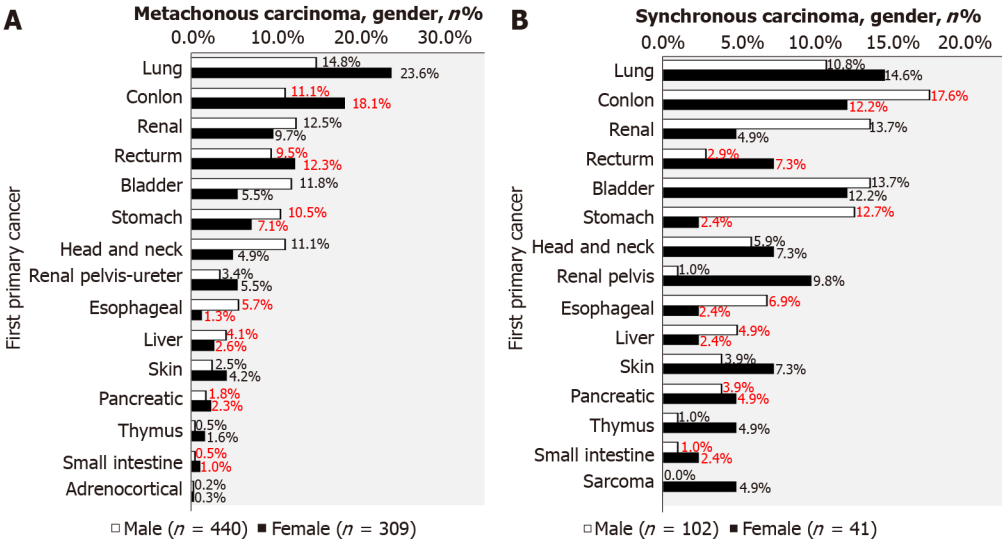

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Figure 4 After excluding the influence of male-female specific malignant tumors, the proportion of male and female digestive system malignant tumors. A: The proportion of male and female primary malignant tumors after excluding the influence of male-female specific cancers, the proportion of male and female primary tumors of metachronous cancer; B: The proportion of male and female primary malignant tumors of synchronous cancer. The red numbers represent the percentage of digestive tumors.

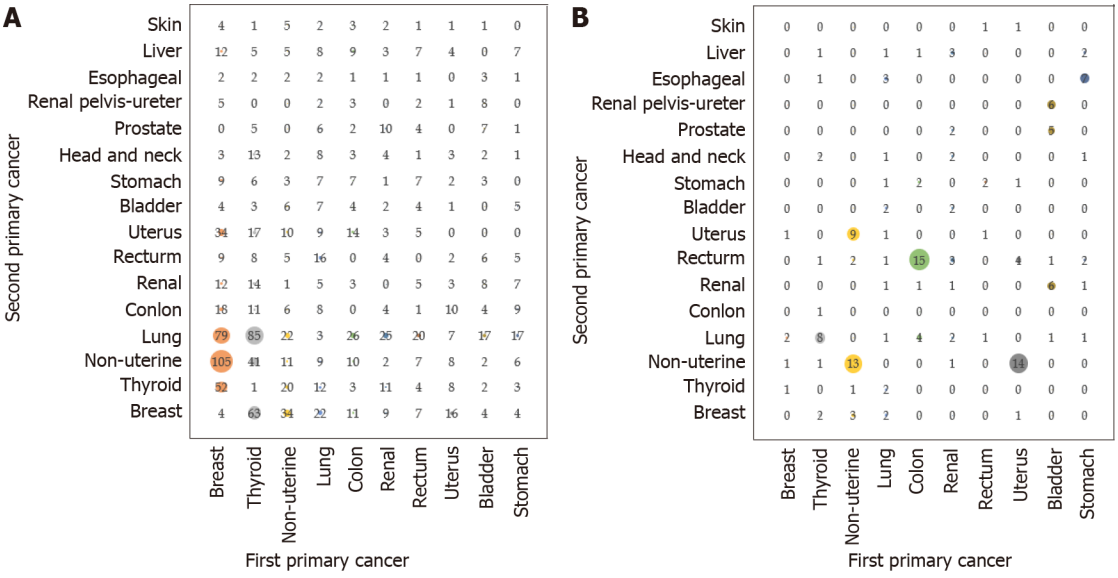

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Figure 5 The top ten combined cases of first primary cancer and subsequent second primary cancer of metachronous and simultaneous multiple primary cancer. A: The combination of first primary cancer and second primary cancer of metachronous cancer; B: The combination of first primary cancer and second primary cancer of synchronous cancer.

incidence of liver cancer than other cancer types[22]. On the other hand, we have less data on liver cancer because there are more cases of metastasis of other cancer species in the liver, so it was not included in the study. It is noteworthy that China has carried out systematic management of patients with hepatobiliary tumors in recent years, including clinical treatment and exploration methods (extended period), and proposed an ideal model (three-dimensional period) for future use[23]. Moreover, in recent years, China has made some progress in the treatment of hepatobiliary tumors, including the objective remission rate of lenvatinib and pembrolizumab in refractory biliary tract cancer reaching 25% and the disease control rate reaching 78.1%[24]. Stereotactic therapy is a feasible transformation therapy that can make patients with hepatocellular carcinoma with extrahepatic metastasis resectable[25]. In this new era for cancer treatment, targeted drugs, targeted immune checkpoint inhibitors or their combination bring new hope for the conversion of hepatocellular carcinoma to surgery and adjuvant therapy[26].

In this study, the number of single primary malignant tumors was not counted, so the incidence rate of MPMTs was not calculated, but this did not affect our study on the combination of the first primary cancer and the second primary cancer in MPMTs. Of all the statistics, we found that breast cancer is the most common primary cancer, which is also related to the high incidence of breast cancer in China[27]. The second most common primary malignant tumor is lung cancer, which has a high incidence in China [28]. Recent studies in the United States have shown that bladder cancer is the most common primary cancer, and lung cancer is the second most common primary cancer[29]. Compared with the first primary cancer, the cancer types in China and the United States are different. The reasons for this difference are as follows: (1) In China, there are more women than men with MPMTs, and the most common cancer among females is breast cancer. In contrast, in the United States, the incidence rate of bladder cancer is highest; (2) This difference is because the research subjects are different: We study Chinese people, mainly from some cities in northern China, while the main research subjects in Europe and America are Caucasian and Black people[29]; and (3) Different levels of development lead to different exposure factors, such as living habits, air pollution, occupational exposure, viruses, bacterial infection and other carcinogenic factors.

The incidence rate of breast cancer is the highest among the metachronous cancer types in China. Moreover, the male to female incidence rate of MPMTs is 1:1.79, which is different from the previously reported male to female incidence rate of cancer in China. The reason for this difference is that there are great differences in the natural ecological environment, lifestyle, and disease risk factors in the eastern, central and western regions of China, and there are regional differences in the incidence rate of malignant tumors between men and women[30]. This study is limited by the sample size, so it will have some impact on the study. It is worth noting that to facilitate the study, we regard each segment of the colon as a primary cancer because colon cancer seems to be segmented, but their pathogenesis is similar. Studies have shown that noncoding RNAs play a key role in the carcinogenesis and progression of the colon cancer[31].

In this study, for female patients, breast cancer and the second primary cancer nonuterine cancer had the most heterochronous combinations (105 cases). Gene analysis showed that the occurrence of breast cancer and ovarian cancer was related to the loss of BRCA1 or BRCA2 gene function leading to homologous recombination defects[32]. The common combinations of primary breast cancer and secondary breast cancer may be caused by chemotherapy and radiotherapy of primary tumors, genetic variation linking the two diseases, hormone signals from oestrogen, lifestyle and environmental factors [33], and the thyroid gland, whose cancer has a similar incidence pattern to breast cancer. The combination of the first or second primary cancer and thyroid cancer may be caused by thyroid hormone signals[33]. Therefore, when it is first discovered that a female patient has breast cancer, their vagina, cervix, fallopian tubes, ovaries and thyroid gland should be checked for lesions after 6 mo to achieve early detection and treatment[34-36]. Thyroid cancer was the second most common type of cancer in this study, and there were many combinations where the second primary cancer was lung cancer in metachronous MPMTs (85 cases). There is evidence that abnormalities in the oncogene rearrangement during transfection are the cause of lung cancer[37].

The metachronous combination of breast cancer and lung cancer (79 cases) should not be ignored. Lung cancer often appears in metachronous cancer in the form of a second primary cancer. There is evidence that the risk of primary lung cancer after treatment of breast cancer increases because smoking habits, age and the disease stage of breast cancer may affect the risk of secondary primary lung cancer in breast cancer patients[38]. Therefore, the regular follow-up of patients, including monitoring the lungs after 6 mo, should be carried out while breast cancer is treated. If lung cancer is found, it should be treated quickly, with both surgical treatment and adjuvant treatment[39,40].

We studied the high incidence combination of MPMTs, but there were some limitations. First, the population of this study is very limited. Most patients came from northern China, not all of China, and the basic data of the above foreign studies are from the Surveillance, Epidemiology and End Results program of the domestic population-based cancer registry or the data of many long-standing and highly reliable cancer centres on cancer diagnosis[41-42]. We recognize that this difference may also introduce bias to this study. Second, we have less synchronous cancer data, which is not enough to explain the strong association between synchronous cancer combinations. Third, we did not carry out genetic examination on patients, so the pathogenesis and aetiology of MPMTs were not discussed. Fourth, this study is a cross-sectional study involving 23 types of malignant tumors and describes the incidence of malignant tumors between men and women. It does not involve therapy, immune chemistry, next-generation sequencing, *etc.* Despite the limitations mentioned above, our results are informative. For patients treated with primary malignant tumors, attention should be given to the high incidence combination of the first and second primary cancers. In the absence of male-female specific cancer effects, attention should be given to the digestive system as a combination of primary malignancy and lung cancer. Without distinguishing between male-female specific malignancies, the possible metachronous cancer combination of breast cancer and nonuterine cancer and the synchronous cancer combination of colon cancer and rectal cancer should be given. After distinguishing synchronous cancer from metachronous cancer, the high incidence cancer combination should be followed up regularly for 6 mo. Through clinical experience and examination, some common cancers can be detected. If they can be removed surgically, they should be removed at the earliest stage possible. If the tumors cannot be

removed, they should also be treated with the best adjuvant treatment, such as radiotherapy and chemotherapy, targeted therapy, and endocrine therapy, among others, to achieve the maximum therapeutic benefits[43,44].

CONCLUSION

In conclusion, after excluding the effect of cancers specific to men and women, screening for lung cancer should be performed 6 mo after detection of colon cancer and for rectal cancer within 6 mo.

ARTICLE HIGHLIGHTS

Research background

Multiple primary malignant tumors (MPMTs) of the digestive system are common clinically, usually presenting as a metachronous combination of colon cancer and lung cancer and a synchronous combination of colon cancer and rectal cancer.

Research motivation

Understanding some common combinations of multiple primary malignancies can help in providing clinical guidance to patients.

Research objectives

This study aimed to classify MPMTs of the digestive system and explore the combination of high incidence with the second primary malignant tumors.

Research methods

This retrospective study analyzed patients diagnosed with multiple primary malignancies in our centre over a 20-year period, classified the tumors, and further explored the high incidence of digestive system malignancies in the combination of multiple primary malignancies.

Research results

The most common metachronous combination pairs of multiple primary malignancies of the digestive system were colon cancer and lung cancer (26 cases), and synchronous combination pairs were colon cancer and rectal cancer (15 cases).

Research conclusions

Through our retrospective study, we found that when patients were diagnosed with colon cancer, they should be screened separately for lung cancer and rectal cancer at the limit of 6 mo.

Research perspectives

To provide clinical guidance to patients based on the combination of common multiple primary malignancies.

FOOTNOTES

Author contributions: Yang XB, Zhang LH, Xue JN contributed equally to this work; Wang YC, Yang X, Liu D, Wang YY and Xun ZY performed the radiological diagnosis; Zhang LH, Xue JN performed pathological diagnosis; Yang XB, Zhang LH designed the research study; Xue JN, Zhang N, Li YR and Sun HS performed the primary literature and data extraction; Yang XB and Zhang LH analysed the data and wrote the manuscript; Zhao HT and Zhao LJ were responsible for revising the manuscript for important knowledge content and contributed equally to this work, and all authors read and approved the final version.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Peking Union Medical College (Approval No. K22C0171).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data. The ethical Committee of Peking Union Medical College Hospital agreed to waive the

informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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CASE REPORT

Collagenous gastritis in a young Chinese woman: A case report

Qing-Hua Zheng, Jie Hu, Xiao-Yuan Yi, Xu-Hua Xiao, Li-Na Zhou, Bin Li, Xiao-Tong Bo

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Abstract

BACKGROUND

Collagenous gastritis (CG) is a rare condition whose pathogenesis may be related to immune abnormalities. We report a case of CG from China.

CASE SUMMARY

A 24-year-old woman presented with recurrent abdominal distension and discomfort for 3 mo. Upper gastrointestinal endoscopy found diffuse nodular elevation-depression changes in the mucosa of the entire gastric corpus. Endoscopic ultrasound showed predominant involvement of the lamina propria and submucosa, and computed tomography imaging showed mild enhancement of the gastric wall. Pathological histology revealed that the thickness of the subepithelial collagen band was about 40 μm, and the Masson trichrome staining result was positive and the Congo red staining result was negative. This case is consistent with the child-adolescent type of CG.

CONCLUSION

Serum pepsinogen I, pepsinogen II, pepsinogen I/II ratio, and gastrin-17 may be potential non-invasive monitoring markers. Currently, treatments for CG vary, and the likely prognosis is unknown. Individual cases of gastric cancer in patients with CG have been reported.

Key Words: Endoscopy; Endoscopic ultrasound; Collagenous gastritis; Hematoxylin and eosin staining; Masson's trichrome staining; Case report

Core Tip: We report a case of collagenous gastritis. We introduce the clinical features, findings of esophagogastroduodenoscopy and endoscopic ultrasound, and response to treatment in this young female patient.

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INTRODUCTION

Collagenous gastritis (CG) is a rare condition characterized histopathologically by the deposition of collagenous bands under the mucosal epithelium and infiltration of inflammatory cells within the lamina propria of the mucosa. It is more prevalent in children and adolescents. The pathogenesis and clinical outcome remain unclear.

The first case of CG was reported in 1989 by Colletti and Trainer in the United States[1]. Since then, the literature on CG has predominantly included case reports. A search of PubMed using the keyword "collagenous gastritis" revealed < 100 reported cases. The first and second cases of CG in China were respectively reported in 2010[2] and 2018[3]. We now report the third Chinese case of CG diagnosed in 2020 at the Affiliated Hospital of Guilin Medical University.

CASE PRESENTATION

Chief complaints

A 24-year-old female patient presented to our outpatient service in June 2020 with the complaints of recurrent abdominal distension and discomfort for 3 mo.

History of present illness

The patient reported feeling epigastric distension after eating that could last anywhere from 30 min to 12 h, with no other significant discomfort.

Personal and family history

Following hospital admission, the patient denied a history of allergies, asthma, and pet exposure. Both her father and mother were living and healthy.

Physical examination

The physical examination on admission revealed stable vital signs, no yellow staining of the skin or sclera, and no enlargement of superficial lymph nodes. Cardiopulmonary and abdominal examinations showed no abnormalities.

Laboratory examinations

Laboratory tests revealed a normal blood count, liver function, and renal function and normal carcinoembryonic antigen, cancer antigen 125, cancer antigen 19-9, and alpha-fetoprotein values. Her liver fibrosis test was normal, and she had normal levels of immunoglobulins immunoglobulin (Ig) A, IgM, and IgG, as well as serum type III procollagen, type IV collagen, laminin, and hyaluronic acid. Her serum pepsinogen (PG) I value was 133.41 μm/L, her PG II value was elevated at 25.99 μm/L, her pepsinogen I/II ratio (PGR) value was reduced at 5.13, and her gastrin-17 value was 54.01 pmol/L. The ^{13}C urea breath test negative, the allergen assay was negative, and her extractable nuclear antigen antibodies were negative.

Imaging examinations

Eesophagogastroduodenoscopy (EGD) performed on June 28, 2020 revealed diffuse nodular elevation-depression changes in the mucosa of the entire gastric corpus (Figure 1A and B).

Nodular reddening-like changes were seen in the anterior wall of the gastric antrum (Figure 1C). Then, endoscopic ultrasound (EUS) completed in July 2020 suggested an intact 5-layer structure of the gastric corpus wall with hypoechoic changes in the mucosal layer (Figure 1D). Histopathology reported moderate chronic inflammation with erosion and mild activity (Figure 1E).

In May 10, 2021, EGD confirmed that no mass or ulcer could be found in the esophagus or duodenum. The mucosa of the angulus was smooth, while the mucosa of the gastric corpus and fundus appeared uneven, with elevation-depression changes (Figure 2A).

Magnifying endoscopy with blue laser imaging (ME-BLI) showed clear borders of the elevation, regular arrangement of the marginal crypt epithelium (MCE), and widening of the microvascular vessels. The MCE in the depression was indistinct, and the irregular microvascular pattern showed dendritic changes with a constant ductal diameter, and the microvessels here were thinner than those of

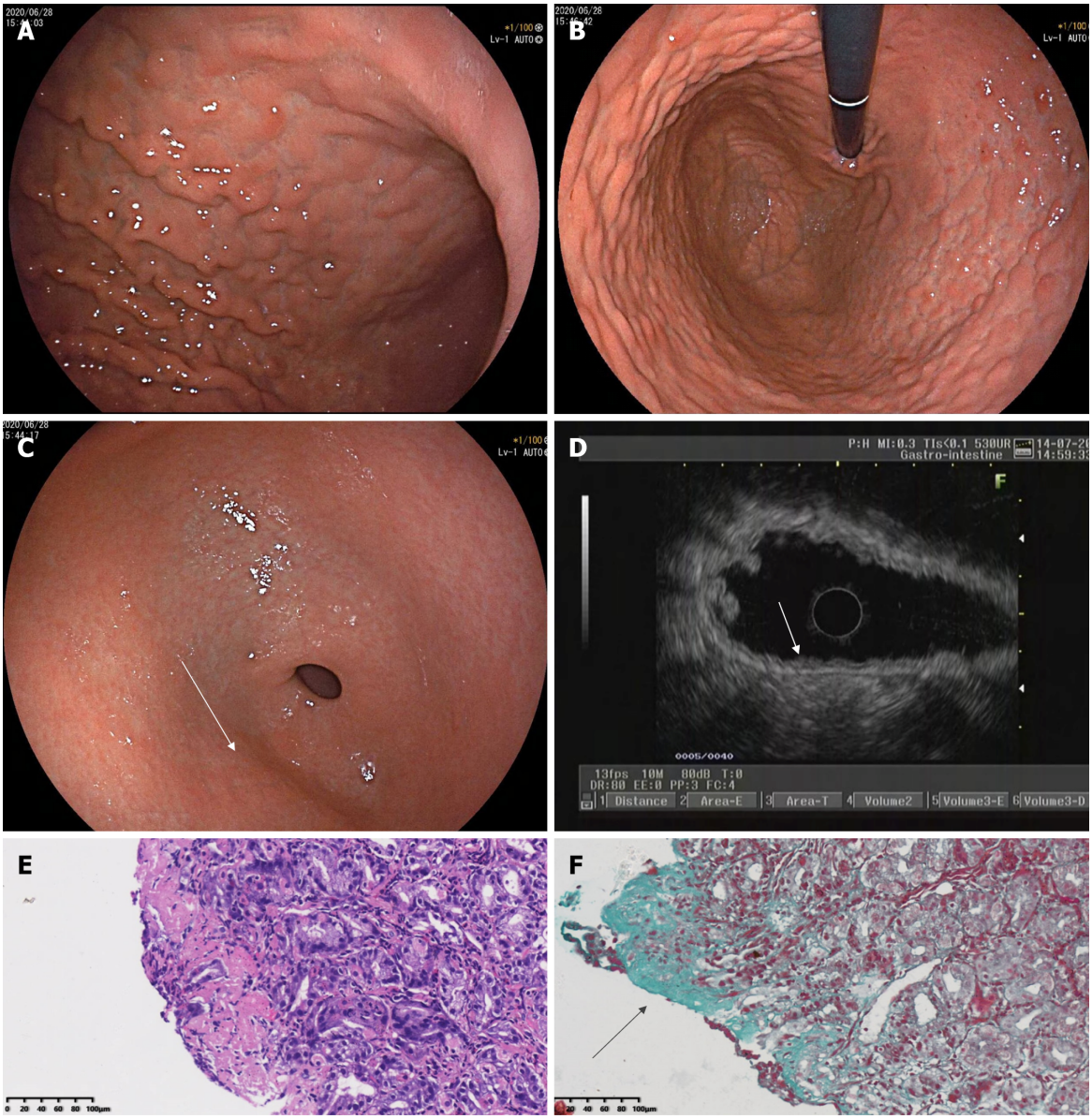

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Figure 1 Findings of white light endoscopy, endoscopic ultrasound, and histopathology in 2020. A: Esophagogastroduodenoscopy (EGD) in 2020 in a forward endoscopic view showed diffuse nodular elevation-depression changes in the mucosa of the entire gastric corpus; B: EGD in 2020 (in a retroflexed endoscopic view) showed diffuse nodular elevation-depression changes in the mucosa of the entire gastric corpus; C: EGD in 2020 showed nodular reddening-like changes in the anterior wall of the gastric antrum; D: Endoscopic ultrasound in 2020 showed an intact five-layer structure of the gastric corpus wall with hypoechoic changes in the mucosal layer, which is different from the echoes of normal mucosal layer; E: A biopsy of the gastric corpus in 2020 reported moderate chronic inflammation with erosion and mild activity; F: Masson staining of a gastric corpus specimen in 2020 showed collagen bands (blue areas).

the elevated area of the gastric antrum (Figure 2B). Nodular reddening-like changes were seen in the anterior wall of the gastric antrum (Figure 2C). The findings of ME-BLI were similar to those from the gastric corpus (Figure 2D). EUS showed that the mucosal layer of the gastric corpus was thickened, appearing slightly hypoechoic, with no thickening of its posterior submucosal layer (Figure 2E).

The normal structures of the mucosa, muscularis mucosa, and submucosa at the elevation of the gastric antrum had disappeared and were replaced by inhomogeneous hypoechoic changes, with the muscularis propria and serosa still intact (Figure 2F). Colonoscopy confirmed that the mucosa of the whole colon, rectum, and terminal ileum was smooth, and no mass or ulcer was visible. Computed tomography showed a relative thickening of the gastric wall in the gastric corpus and antrum, and mild enhancement was seen in the arterial phase (Figure 3A and B).

Histopathological findings of the gastric fundus, body, and antrum biopsies included moderate chronic inflammation with erosion, mild activity, a higher number of lymphocytes, a few neutrophils and eosinophils [20-30/high-powered field (HPF)] infiltrating the interstitium, multifocal lymphoid tissue hyperplasia, and negative Congo red staining (Figure 2G and H). Collagenous bands deposited under the mucosal epithelium (about 40 μm) were seen (Figure 2I and J). Angulus biopsy revealed moderate chronic inflammation with erosion and positive Masson's trichome staining. The bulbous,

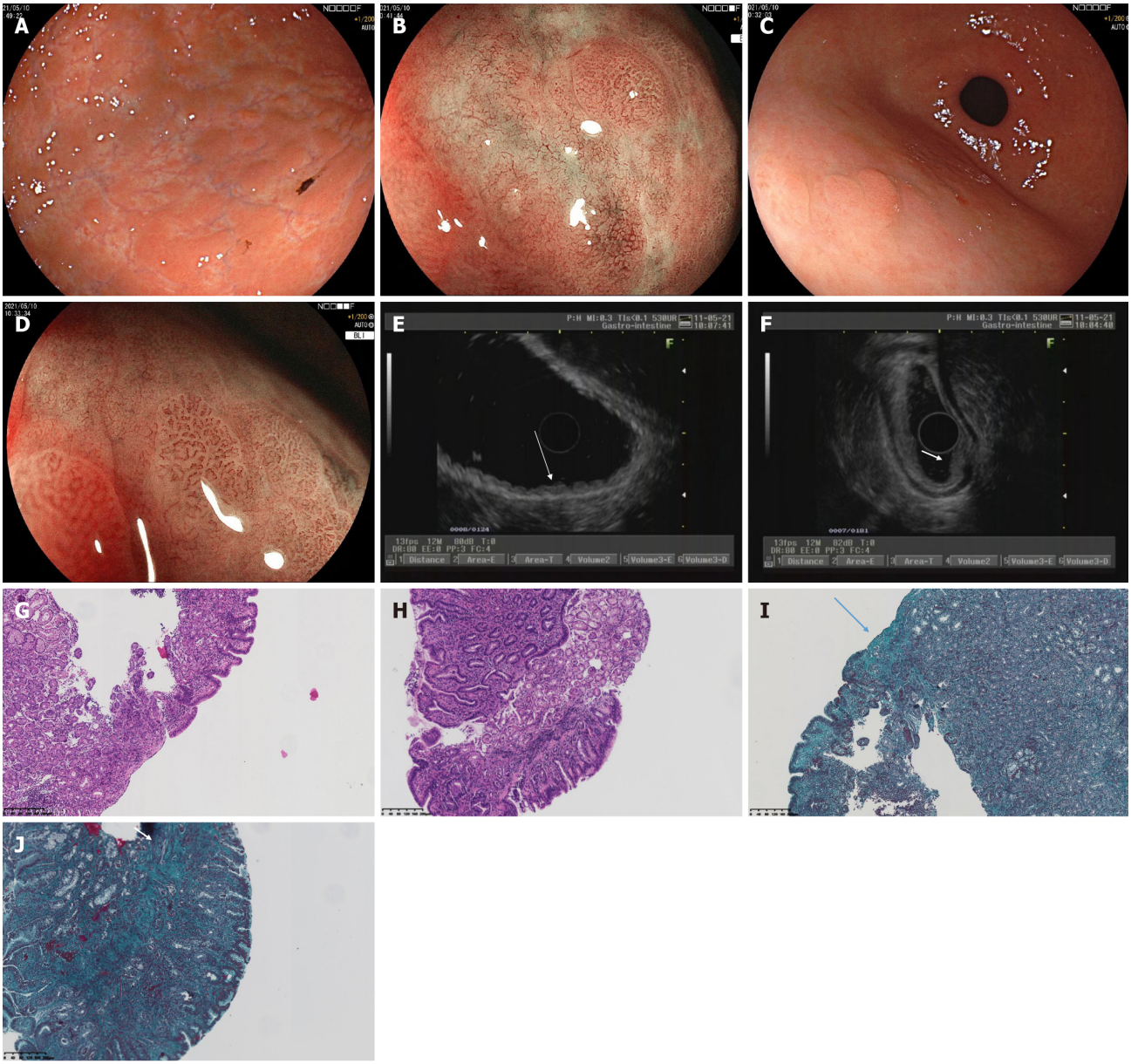

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Figure 2 Findings of white light endoscopy, magnifying endoscopy, endoscopic ultrasound, and histopathology in 2021. A: Esophagogastroduodenoscopy (EGD) in 2021 showed that the mucosa of the angulus was smooth, while the mucosa of the gastric corpus and fundus appeared uneven, with elevation-depression changes; B: Magnifying endoscopy with blue laser imaging (ME-BLI) in 2021 showed regular arrangement of the marginal crypt epithelium (MCE) and widened microvessels in the elevated area of the corpus, and dendritic irregular microvascular pattern and unremarkable MCE in the depressed area of the corpus; C: EGD in 2021 showed nodular reddening-like changes in the anterior wall of the gastric antrum, which is similar to those in 2020; D: ME-BLI in 2021 showed similar findings in the gastric antrum to those in the corpus; E: Endoscopic ultrasound (EUS) in 2021 showed that the mucosal layer of the gastric corpus was thickened, exhibiting slightly hypoechoic and wavy changes; F: EUS in 2021 showed that the normal five-layer structures in the gastric antrum were replaced by inhomogeneous hypoechoic changes; G: Histopathological findings of the gastric corpus in 2021 (corresponding to Figure 2A and B) included moderate chronic inflammation with erosion, mild activity, a higher number of lymphocytes, and a few neutrophils and eosinophils (20-30/high-powered fields); H: Histopathological findings of the gastric antrum in 2021 (corresponding to Figure 2C and D) showed moderate chronic inflammation with erosion and mild activity; I: Masson staining of a gastric corpus specimen obtained in 2021 (corresponding to Figure 2G). The arrow indicates the collagen band, which had a thickness of about 40 μm; J: Masson staining of a gastric antrum specimen obtained in 2021 (corresponding to Figure 2H). The arrow also indicates the collagen band.

terminal ileum, and ascending colon biopsies showed moderate mucosal chronic inflammation with erosion, mild activity, focal lymphocytosis, and positive Masson's trichome staining. The rectal biopsy showed moderate mucosal chronic inflammation with erosion and positive Masson's trichome staining. Furthermore, complementary Masson staining of the patient's gastric corpus biopsy specimen from June 28, 2020 revealed the presence of collagenous band deposited under the epithelium (approximately 40 μm) (Figure 1F).

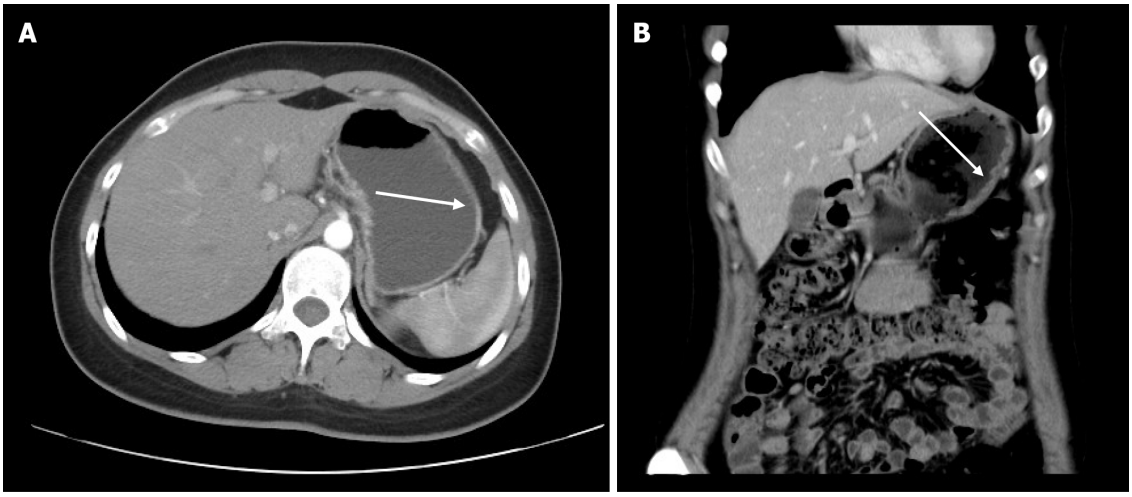

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Figure 3 Computed tomography findings in 2021. A: Computed tomography (CT) in 2021 showed a relative thickening of the gastric wall in the gastric corpus and antrum, and mild enhancement was seen in the arterial phase; B: Coronal CT in 2021 showed thickening of the gastric wall of the corpus, as indicated by the arrow.

FINAL DIAGNOSIS

The patient was diagnosed as having CG.

TREATMENT

Esomeprazole (20 mg every day, taken 30 min before breakfast) and mosapride (5 mg three times a day, *i.e.*, once before each of all 3 meals) were given orally for 2 wk, and the patient's abdominal distension was subsequently relieved. However, the patient continued to experience intermittent abdominal distension for > 6 mo thereafter, with episodes lasting for the same duration as before, while taking esomeprazole and mosapride irregularly. The patient was then hospitalized at the Affiliated Hospital of Guilin Medical University from May 9 to May 12, 2021.

Treatment with oral glucocorticoids was initiated for the patient in June 2021. Thirty milligrams daily of prednisone acetate was given for 2 wk, and then reduced by 5 mg every 2 wk thereafter and finally discontinued when the dose reached 5 mg daily and was maintained as such for 2 wk. During the 8 wk of treatment, the patient continued to present with intermittent abdominal distention, lasting 12 h in severe episodes, and she was given 5 mg of oral mosapride three times daily 30 min before meals. A re-examination showed that her PG I value was 105.21 μm/L, her PG II value was elevated to 24.3 μm/L, her PGR value was decreased to 4.33, and her gastrin-17 value was 46.99 pmol/L.

OUTCOME AND FOLLOW-UP

After treatment, the patient's abdominal distension was relieved for 2-3 d every week. Laboratory tests performed in October 2021 revealed that her PG I value was 118 μm/L, her PG II value was elevated to 33.74 μm/L, her PGR value was decreased to 3.5, and her gastrin-17 value was elevated to 39.69 pmol/L. As of November 2021, the patient was still undergoing follow-up (Table 1).

DISCUSSION

Pathology and pathogenesis

The pathology is characterized by a deposited collagen band with a thickness of > 10 μm under the epithelium, with an average thickness of 30 μm and a maximum thickness of up to 120 μm[4]. Inflammatory cell infiltration is seen in the lamina propria of the mucosa. Infiltrating inflammatory cells include lymphocytes, plasma cells, monocytes, and eosinophils. Collagenous gastritis can be classified as eosinophilic, lymphocytic, and atrophic according to the type of infiltrated cells. The main criteria for these types are as follows: Eosinophils in the lamina propria > 30/HPF (eosinophilic type); lymphocytes > 25/HPF (lymphocytic type); and a reduction in glands, a reduction in specialized cells such as parietal

Table 1 Timeline

Date	Description
June 2020	First visit, chief complaints: Recurrent abdominal distension and discomfort for 3 mo
June 2020	1st EGD + pathological histology
July 2020	1st EUS
July 2020	Esomeprazole and mosapride for 2 wk; abdominal distension subsequently relieved
Late 2020 to first half of 2021	Continued intermittent abdominal distension for > 6 mo
May 9 to May 12, 2021	Hospitalized; PG I, PG II, and PGR tested; 2nd EGD + pathological histology; ME-BLI; 2nd EUS
June 2021	Oral glucocorticoids for 8 wk and tapered; PG I, PG II, and PGR retested
October 2021	PG I, PG II, and PGR retested

EGD: Esophagogastroduodenoscopy; EUS: Endoscopic ultrasound; ME-BLI: Magnifying endoscopy with blue laser imaging; PGR: Pepsinogen I/II ratio.

cells and chief cells, pyloric gland metaplasia, and hyperplasia of smooth muscle in the lamina propria of the mucosa (atrophic type). The same case may contain just one or all of these types. Considering special staining in addition to Masson's trichome staining, tenascin positivity in immunohistochemistry may also be a characteristic indicator[5]. In addition to the stomach, the disease may include collagenous stomatitis and collagenous enteritis, depending on the site of onset, and these three locations are currently considered to be different sites of the same disease.

The pathogenesis of CG is unclear. Some pathological findings suggest an association with immune abnormalities. For example, signs of local immune activation were detected in some specimens, such as overexpression of human leucocyte antigen DR in epithelial cells, increased $CD3^+$ intradermal lymphocytes, and $CD25^+$ cells found in the lamina propria[6], as well as a large number of IgG4-positive plasma cells that failed to confirm an association with IgG4-related disease[5]. The histological changes in collagenous gastritis may be caused by a local immune response. In a few patient specimens, collagen bands can be isolated from type III and type IV collagen fibers. During the repair process, type III collagen is released by subepithelial fibroblasts[5]. Specimens were also found to be positive for tenascin, a marker suggestive of cell proliferation and migration[5]. Therefore, collagen synthesis in collagenous gastritis is a reparative response. In the pathogenesis of collagenous gastritis, an association with reduced serum IgA levels has also been reported[7].

Clinical features

Most of the CG studies reported so far are single case reports and retrospective analyses, lacking large sample data. Cases of CG have been documented mainly in Europe, the United States, and Japan. Women are more commonly afflicted than men, and the age of patients ranges from 7-85 years[8,9]. Clinical symptoms include abdominal pain, abdominal distension, diarrhea, nausea, vomiting, gastrointestinal bleeding, weight loss, anemia, fatigue, retrosternal pain, dyspepsia, perforation[10], dysphagia[11], and constipation.

Lagorce-Pages *et al*[4] classified CG into child-adolescent type and adult type. The child-adolescent type occurs mainly in early adolescence, where inflammation is usually limited to the stomach and anemia and abdominal pain are the main symptoms. The adult type often combines with collagenous enteritis, which is characterized by chronic watery diarrhea. CG and collagenous colitis exist on a clinical spectrum, with the difference being the site of involvement of the GI tract.

The typical endoscopic feature of collagen gastritis is the presence of mucosal nodules. These nodules vary in size and are often diffuse in the gastric corpus and antrum, with their size and number depending upon the severity of the inflammation. Endoscopic manifestations also include mucosal erythema, erosion, and exudation. The endoscopic presentation differs between pediatric and adult patients. Pediatric and adolescent patients usually present with gastric nodules, whereas adult patients often present with mucosal erythema, atrophy, and relatively uncommon nodules[9]. In image-enhanced endoscopy, glandular duct structures are seen on the surface of the nodules under magnifying narrow-band imaging, and microvascular thinning and tortuosity are seen in the structureless area[12,13].

Patients can also have other co-morbidities, including *Helicobacter pylori* infection[9], human immunodeficiency virus infection combined with gastric Kaposi's sarcoma[14], and Sjögren's syndrome [15].

Our case is a young female patient who presented with abdominal distension as the main manifestation, without obvious symptoms of anemia, abdominal pain, and diarrhea. Pathological findings supported the idea that the inflammation was limited to her stomach only, and colonoscopy and biopsy showed no intestinal involvement, consistent with the child-adolescent type. The

pathological histology of this case in our hospital showed the presence of a higher number of eosinophilic infiltrates in the lamina propria, consistent with the eosinophilic type. Endoscopy showed a depressed lesion surrounding the elevation of the gastric corpus and fundus greater curvature, with a structureless area in the depression under image-enhanced endoscopy and thinning microvessels, similar to the findings observed by Kawasaki *et al*[12] using magnifying narrow-band imaging in the gastric corpus.

EGD at both our hospital and Hangzhou No. 1 Hospital[3] showed redness on the elevation of the gastric antrum, and biopsy suggested a collagen deposition band of > 10 μm. A routine biopsy of the gastric angulus with a smooth surface mucosa failed to find a band of collagen deposition at our hospital, and it was hypothesized that the CG inflammation might be multifocal and discontinuously distributed. The EUS findings in this case are not exactly the same as those reported previously in China [3]. The similarity between these cases is that the lesion of the gastric antrum is a hypoechoic replacement of normal structures; however, the difference is that a rough and swollen mucosa with nodular elevation of the gastric corpus was seen under white-light in the case at Hangzhou First Hospital[3], which corresponds to thickening of the muscularis mucosa layer to the submucosal layer with an unclear boundary and low echoes, while, using EGD at our hospital, we found depressed lesions surrounding the elevated ones in the gastric corpus, which corresponds to the presence of five layers of the gastric wall with clear boundaries, as seen by EUS. The mucosal elevation under white-light endoscopy in the present case showed slightly hypoechoic thickening changes under EUS with no thickening of the posterior submucosa.

The white-light endoscopic findings in 2020 and 2021 were similar, both in the gastric corpus and in the antrum. In 2021, the white-light endoscopic findings were different in the gastric corpus and antrum, with elevation-depression changes in the gastric corpus and nodular reddening-like changes in the gastric antrum. EUS findings were also different in the gastric corpus and the gastric antrum. Only the mucosa was involved in the gastric corpus, while the mucosa, muscularis mucosa, and submucosa were all involved in the gastric antrum.

Considering the white-light endoscopic and EUS images, it was presumed that the development of CG inflammation might be progressively from the mucosal layer to the submucosal layer, and the progression of lesions in the gastric corpus and antrum might not parallel each other. The fact that the lesion is hypoechoic might be a EUS change of CG.

Management, follow-up, and prognosis

There are a number of treatments available for CG, some of which are merely symptomatic. H2 receptor antagonists or proton pump inhibitors, aluminum, iron supplementation in patients with anemia, a gluten-free diet in patients with celiac disease[16], glucocorticoids (prednisone[2,8,17], budesonide), other drugs including salicylic acid preparations such as mesalazine and salazosulfapyridine, and parenteral nutrition[9] have been used with varying degrees of efficacy according to different reports.

We gave our patient esomeprazole and mosapride successively, but she had no relief from her symptoms. Then, she was given prednisone acetate for 8 wk according to the treatment protocol for eosinophilic gastritis, and there was no significant relief of her abdominal distension.

The prognosis of CG at follow-up varies significantly, with some patients having reduced or even no collagen deposition and some experiencing recurrent symptoms[9]. The first reported CG case had unremarkable changes in collagen deposition during 12 years of follow-up[18] and showed mild dysplasia. One case of gastric adenocarcinoma positive for Epstein-Barr virus was confirmed after EGD follow-up 8 years after the diagnosis of collagenous gastritis in a patient with IgM reduction[19]. The duration of the follow-up interval and the endpoint are currently unclear.

At present, most facilities use EGD as a follow-up tool, but EUS can clearly identify all layers of the gastric wall, which helps to determine the depth of lesion involvement and is superior to EGD. The hypoechoic lesion may be an EUS change of CG. However, the availability of other non-invasive tests as tools of follow-up has not been clinically reported. The biochemical indices of PG I, PG II, PGR, and gastrin-17 in this patient in our hospital were consistent with atrophic gastritis, but the blood eosinophil and lymphocyte counts, IgA, type III procollagen, and collagen type IV findings were not abnormal. The patient continued to have episodes of abdominal distension after treatment with glucocorticoids, and the results of PG I, PG II, PGR, and gastrin-17 on several retests were abnormal, suggesting that the values obtained by this test may parallel the condition. PG I, PG II, PGR, and gastrin-17 may be used as biochemical indicators for disease treatment and follow-up. As of November 2021, the patient is still being followed up with.

CONCLUSION

In addition to histopathology, diffuse nodular elevation-depression under white-light endoscopy, hypoechoic changes in the lamina propria and submucosa under EUS, and tests of serum pepsinogen I, pepsinogen II, PGR, and gastrin-17 may be helpful in the diagnosis of CG. There is a lack of specific treatment for CG.

FOOTNOTES

Author contributions: Zheng QH performed the Eesophagogastroduodenoscopy and endoscopic ultrasound, made the clinical diagnosis and treatment plan, and wrote the manuscript; Hu J performed the histopathological diagnosis; Yi XY collected the clinical data and performed the follow-up; Xiao XH completed the magnifying endoscopy; Zhou LN helped the endoscopists with the endoscopic procedures as a nurse; Li B supervised the diagnosis and treatment of this patient; Bo XT wrote the English version of the paper; all authors have read and approved the final manuscript.

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