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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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EDITORIAL

Intricacy of Crohn's disease: Incongruity between diagnostic modalities and histopathologic assessment

Hai-Ming Fang

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Abstract

Crohn's disease (CD) is a chronic and recurrent inflammatory condition. Histologic healing is associated with better outcomes in CD, while less is known regarding the assessment of histological condition. Recently, a study has examined the discordance between endoscopic and histopathologic assessment in ileal CD, revealing a poor correlation between endoscopic and histologic evaluations in assessing mucosal inflammation and disease activity. However, the involvement of CD can span the entire gastrointestinal tract, as well as numerous clinical manifestations and extraintestinal complications, and the patchy nature of transmural inflammation is a well-established characteristic of this disease. The diagnosis of CD relies on a comprehensive evaluation that includes clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations due to the incomplete understanding of its etiology and pathogenesis. Upon diagnosis, complimentary investigations should focus on markers of disease activity. Since transmural inflammation can only be assessed in resections, therefore, we primarily focused on the evaluation value of clinical aspects, histological scoring systems, particular *in vivo* imaging evaluation such as computed tomography enterography, magnetic resonance elastography, scintigraphy, sonographically measurement, endoscopic ultrasonography, and advanced endoscopic imaging techniques.

Key Words: Crohn's disease; Transmural inflammatory; Histopathological scoring system; Endoscopy; Cross-sectional imaging techniques

Core Tip: Histologic healing is associated with better outcomes in Crohn's disease, while less is known regarding the assessment of histological condition. This article evaluated value of clinical aspects, endoscopy, histological scoring systems, particular *in vivo* imaging evaluation in the assessment of Crohn's disease. A comprehensive evaluation encompassing clinical examinations, biochemical assessments, stool analyses, endoscopic examinations, cross-sectional imaging, and histological investigations is required for the diagnosis of this disease. Complete assessment involves laboratory abnormalities, including micronutrient deficiencies, cross sectional imaging to identify transmural disease extent, severity and complications, and a psychosocial assessment.

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INTRODUCTION

Crohn' disease (CD) is a chronic inflammatory condition that affects the gastrointestinal tract, most commonly the terminal ileum and proximal colon. The incidence of CD has rapidly increased in parallel with human civilization and population growth, with the highest incidence observed in Western regions[1]. The patchy nature of transmural inflammation is a well-known characteristic of CD. This chronic inflammation involves the entire intestinal wall, leading to recurrent intestinal damage and subsequent repair, characterized by a progressive and destructive nature, which can potentially result in irreversible structural bowel damage and disability[2]. Given the transmural characteristics of CD, fistulas, abscesses, and strictures frequently complicate the disease course. Extraintestinal manifestations, predominantly involving the joints, skin, and eyes, may be present in as many as 50% of patients[1].

Compared with endoscopic healing alone, transmural healing was found to be associated with superior outcomes in patients with CD, including reduced rates of hospital admission, therapy escalation, and surgery[3]. Thus, accurate assessment of inflammatory activity is a key element in the management of CD and therapeutic efficacy monitoring. Owing to the incomplete understanding of the etiology and pathogenesis of CD, a comprehensive evaluation encompassing clinical examinations, biochemical assessment, stool analyses, endoscopic examinations, cross-sectional imaging, and histological investigations is needed for the diagnosis of this disease. Upon diagnosis, complimentary investigations should focus on markers of disease activity.

In clinical practice, the diagnosis of CD is strongly indicated by the combination of clinical symptoms and endoscopic findings, while biopsy-based histopathology often lack supportive evidence for this diagnosis, which is commonly observed during the initial assessment of CD. Recently, Lee *et al*[4] examined the difference between endoscopic and histopathologic assessment of ileal CD. The protocolized biopsies were taken consecutively from the ulcer edge, 7 mm and 14 mm away from the ulcer edge, in patients with discrete ileal ulcers. These findings revealed the poor endoscopic-histologic correlation between mucosal inflammation and disease activity in patients with ileal CD. Thus, the method by which to incorporate histologic disease activity into the treatment paradigm remains unclear. Further research is needed to optimize biopsy protocols and histologic assessments for CD.

DIAGNOSTIC MODALITIES FOR CROHN'S DISEASE

Colonoscopy is commonly employed for the diagnosis of CD and evaluation of treatment efficacy. However, it only allows visualization of the terminal ileum rather than the entire small intestine. Additionally, it is unable to detect extraluminal complications and may fail to assess the complete extent of small intestinal disease. This incomplete examination could lead to an underestimation of disease activity. The advent of double-balloon enteroscopy marked a revolutionary breakthrough for deep enteroscopy. The diagnostic yield of balloon enteroscopy in suspected cases of CD has been reported to range from 44% to 100%. Motorized spiral enteroscopy and single-balloon enteroscopy demonstrate comparable technical success rates and diagnostic yields when evaluating the small bowel in suspected cases of CD. However, motorized spiral enteroscopy outperforms single-balloon enteroscopy in terms of achieving deeper small bowel evaluation with complete coverage and greater depth of insertion within a shorter timeframe[5]. The current situation, however, poses a challenge for accurate histopathological assessment and deep remission of CD when the disease is confined to the small intestine. When CD is confined to the small intestine, evaluating deep remission presents a significant challenge. A pilot study evaluated the effectiveness of endoscopic ultrasound (EUS) during double-balloon enteroscopy in distinguishing small bowel CD patients in endoscopic remission from those with active disease. Eighty-two patients (21 females and 61 males) were stratified into groups of endoscopic remission and endoscopic activity on the basis of the segmental simple endoscopic score for CD. The use of an ultrasonic catheter probe during EUS in double-balloon enteroscopy proves to be effective for assessing both mucosal and transmural healing in patients with small bowel CD. The active CD patients had significantly greater total wall thickness and submucosal thickness of the small intestine than the remission CD patients did. The cut-off values of 2.65 mm for total wall thickness and 0.95 mm for submucosal thickness can aid in the differentiation of active small-bowel CD from inactive disease (sensitivity of 91.5%,

specificity of 80.8% and sensitivity of 70.2%, specificity of 88.6%, respectively)[6]. Additionally, shear wave elastography is a widely utilized noninvasive ultrasonic technique for the quantitative assessment of tissue elasticity. The elasticity of various types of active perianal fistulas in CD patients was evaluated *via* EUS in conjunction with shear wave elastography, which revealed that the elastic modulus of the high-activity anal fistula group was significantly lower than that of the low-activity anal fistula group, providing a superior method for detecting and quantifying the activity of perianal fistulas, monitoring fibrosis in CD-related intestinal stenosis, and differentiating between inflammatory and fibrotic stenosis in CD patients[7].

Noninvasive evaluation and quantification of the relative degree of inflammation and/or fibrosis play crucial roles in the treatment of CD, enabling the selection of optimal treatments for individual patients and the assessment of treatment response. Cross-sectional imaging techniques, such as computed tomography enterography (CTE), magnetic resonance (MR) enterography, and bowel ultrasound, are used to assess small bowel CD and CD-related complications[8]. CTE, which involves thin section scanning with multiplanar reconstruction, has emerged as a valuable diagnostic modality for imaging the small bowel wall. The exceptional spatial resolution and multiplanar imaging capability of CTE can assist in delineating subtle changes in segmental mural hyperenhancement, wall thickening, and mural stratification; mesenteric findings such as an engorged vasa recta ("comb sign"); and increased attenuation in mesenteric fat, which is a potential radiologic marker of inflammation activity[8]. CTE can detect all lesions beyond the strictures as well as areas on the distal side of the strictures that cannot be passed with the enteroscope[9]. A combination of fecal calprotectin level measurement and CTE appears to be an effective approach for monitoring disease activity in patients with small intestinal CD, including those with strictures that are not accessible *via* conventional endoscopy[10].

As a noninvasive imaging modality, MR enterography (MRE) has played an increasing important role in the assessment of CD in clinical practice. According to the MRE diagnostic results, the arterial phase predominantly presented high signal intensity, and the venous phase mainly presented low signal intensity or isointensity. MRE presented an accuracy of 93.75%, sensitivity of 97.37%, and specificity of 80.00% in diagnosing CD[9]. The MR index of activity (MaRIA) is used to evaluate four parameters: Wall thickness, relative contrast enhancement, edema, and ulcers. The simplified MaRIA employs dichotomized scoring for the parameters (wall thickness > 3 mm, presence of edema, fat stranding, and ulceration). For the evaluation of luminal disease activity in CD, the evaluated MRE indices showed moderate-to-large responsiveness, and simplified MaRIA may be preferable because of its responsiveness and nonreliance on gadolinium administration[11]. Bowel ultrasonography serves as a noninvasive diagnostic tool for assessing bowel activity in CD patients in terms of complications and postoperative recurrence and monitoring the response to medical therapy, which is particularly valuable for monitoring the improvement or resolution of bowel activity induced by biological therapies in CD patients[12]. It reliably identifies postoperative recurrence and complications and provides a means to monitor disease progression[13]. Some studies have revealed that oral 67 Ga scintigraphy has similar accuracy and agreement to colonoscopy in the identification of inflammatory activity in patients with CD. This new approach may be useful and less invasive for long-term follow-up[14]. Positron emission tomography combined with MRE constitutes an outstanding noninvasive diagnostic modality. Both MR parameters and positron emission tomography findings provide high accuracy in detecting inflamed segments[15].

Cross-sectional imaging has emerged as a suitable and efficient diagnostic modality for patients with CD. However, to date, there is no consensus guidance on reporting the findings of cross-sectional imaging. A recent study evaluated the diagnostic accuracy of disease location and activity in various cross-sectional imaging modalities, including B-mode intestinal ultrasound, CTE and MRE, for CD[16]. These findings indicate that MRE is more sensitive for detecting small bowel CD, whereas B-mode intestinal ultrasound is more effective for identifying terminal ileal CD. Additionally, the international bowel ultrasound segmental activity score has potential for accurately defining CD activity[16]. The European Crohn's and Colitis Organization and the European Society of Gastroenterology and Abdominal Radiology have delineated various core elements required for reporting the findings of cross-sectional imaging for inflammatory bowel disease (IBD). These recommendations would facilitate comparisons across various reports and enhance communication among the diverse specialties involved in IBD management[17].

A systematic review was recently conducted, encompassing a total of 29 original histopathological scoring systems for the assessment of inflammation and/or fibrosis in patients with CD[18]. The methodological quality and operating properties of these scoring systems (validity, reliability, responsiveness and feasibility) were thoroughly evaluated, aiming to identify the most reliable and accurate scores applicable for clinical research and clinical practice settings[18]. They suggested that the most reproduced transmural histopathological scores were the scores for inflammation only (namely, its AIS component)[18] and for both inflammation and fibrosis[19,20] because of their ease of application in clinical studies. The high methodological quality of the studies (75%, 80%, and 77.5%, respectively) and adequate operating properties (validity, reliability, and responsiveness)[18]. However, assessments utilizing existing histological disease severity scoring systems for CD depend on highly trained experts and necessitate considerable time and effort. This approach has notable limitations, including the variability inherent in human evaluations and the intrinsic constraints of these scoring systems, such as limited dynamic range and inadequate sensitivity to clinically significant therapeutic effects. Artificial intelligence and machine learning technologies are capable of effectively addressing these limitations, and the applications in gastroenterology are expanding rapidly. Deep learning models based on the Global Histologic Disease Activity Score are effective at distinguishing the presence and absence of microscopic CD disease activity[21]. Fecal calprotectin has emerged as a well-validated, noninvasive biomarker that enables the assessment of gut inflammation. Fecal calprotectin levels are significantly correlated with clinical or endoscopic disease activity in patients with CD. Elucidating the regulatory mechanisms and biological functions of calprotectin in the gastrointestinal tract may pave the way for innovative diagnostic approaches and therapeutic strategies for IBDs[22].

Most existing histopathological scoring systems for CD were developed as a part of cross-clinical-endoscopic-imaging-pathological correlation studies. However, there is no universally accepted transmural histological grading system for CD that can be considered the best choice for assessing the severity of intestinal fibrosis or inflammation. The comprehensive evaluation of each measurement instrument is essential in clinical practice, encompassing a meticulous examination of the included items and domains, assessment forms, and operational properties of the scoring system. The coexistence of varying degrees of inflammation and fibrosis within the same lesion poses challenges in their differentiation, particularly in terms of fibrosis detection. The most prominent histological change in Crohn's fibrostenosing bowel strictures is characterized by smooth muscle hyperplasia/hypertrophy, whereas fibrosis is less significant. The "inflammation-smooth muscle hyperplasia axis" may be the most important factor in the pathogenesis of CD[23].

CONCLUSION

Given the limited understanding of the etiology and pathogenesis of CD, a comprehensive evaluation encompassing clinical examinations, biochemical assessments, stool analyses, endoscopic examinations, cross-sectional imaging, and histological investigations is required for the diagnosis of this disease. Complete assessment involves laboratory abnormalities, including micronutrient deficiencies, cross sectional imaging to identify transmural disease extent, severity and complications, and a psychosocial assessment.

FOOTNOTES

Author contributions: Fang HM conceived and designed the study, initially drafted and critically revised the manuscript for important intellectual content, and ultimately approved it.

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REVIEW

Advancements in the diagnosis of biliopancreatic diseases: A comparative review and study on future insights

Eyad Gadour, Bogdan Miutescu, Zeinab Hassan, Emad S Aljahdli, Khurram Raees

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Abstract

Owing to the complex and often asymptomatic presentations, the diagnosis of biliopancreatic diseases, including pancreatic and biliary malignancies, remains challenging. Recent technological advancements have remarkably improved the diagnostic accuracy and patient outcomes in these diseases. This review explores key advancements in diagnostic modalities, including biomarkers, imaging techniques, and artificial intelligence (AI)-based technologies. Biomarkers, such as cancer antigen 19-9, *KRAS* mutations, and inflammatory markers, provide crucial insights into disease progression and treatment responses. Advanced imaging modalities include enhanced computed tomography (CT), positron emission tomography-CT, magnetic resonance cholangiopancreatography, and endoscopic ultrasound. AI integration in imaging and pathology has enhanced diagnostic

precision through deep learning algorithms that analyze medical images, automate routine diagnostic tasks, and provide predictive analytics for personalized treatment strategies. The applications of these technologies are diverse, ranging from early cancer detection to therapeutic guidance and real-time imaging. Biomarker-based liquid biopsies and AI-assisted imaging tools are essential for non-invasive diagnostics and individualized patient management. Furthermore, AI-driven models are transforming disease stratification, thus enhancing risk assessment and decision-making. Future studies should explore standardizing biomarker validation, improving AI-driven diagnostics, and expanding the accessibility of advanced imaging technologies in resource-limited settings. The continued development of non-invasive diagnostic techniques and precision medicine approaches is crucial for optimizing the detection and management of biliopancreatic diseases. Collaborative efforts between clinicians, researchers, and industry stakeholders will be pivotal in applying these advancements in clinical practice.

Key Words: Biliopancreatic diseases; Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography; Magnetic resonance cholangiopancreatography; Peroral cholangiopancreatoscopy; Diagnostic advancements; Biomarkers in biliopancreatic diseases; Artificial intelligence in gastroenterology

Core Tip: Recent advancements in the diagnosis of biliopancreatic disease have significantly transformed clinical practice. Enhanced imaging techniques such as endoscopic ultrasound and computed tomography can provide detailed anatomical insights for accurate diagnosis. Additionally, the integration of biomarkers and artificial intelligence technologies can improve early disease detection and diagnostic precision. These innovations facilitate targeted treatment strategies tailored to individual patient needs, ultimately enhancing patient outcomes and quality of life. As the field continues to evolve, ongoing research and collaboration among healthcare professionals will be essential to further refine the diagnostic tools and approaches for biliopancreatic diseases.

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INTRODUCTION

Biliopancreatic diseases include a wide array of disorders of the bile ducts, gall bladder, and pancreas and are considered to be some of the primary antagonists in gastrointestinal pathology. Gastroenterological studies and analyses performed over the years have identified and described biliopancreatic diseases such as gallstones, cholecystitis, pancreatitis, and biliopancreatic malignancies[1]. According to Villari *et al*[1], elderly patients, particularly those aged > 70 years, have significantly elevated susceptibility to acute biliopancreatic diseases. Gallstones, inflammatory diseases of the biliary tree, and biliary malignancies are associated with the highest comorbidity and mortality rates in this cohort. Furthermore, results from a recent analysis by the Spanish Society of Pathology and the Spanish Society of Medical Oncology showed that patients diagnosed with biliopancreatic malignancies have a significantly poor prognosis[2]. However, diagnosing these diseases is a complex undertaking mainly attributed to their often subtle and nonspecific clinical presentations, which complicate the timely and accurate diagnosis of these diseases[3].

Within the past few decades, there has been remarkable advancement in diagnostic modalities for biliopancreatic diseases, with the enhancement of conventional imaging techniques such as ultrasonography and computed tomography (CT) into more advanced and intricate modalities such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS)[3]. These inventions have evolved the resolution and sensitivity landscape and offered an invaluable tool in the earlier and more precise detection of pathological changes in the biliary tree and pancreas[4-6].

Concurrently, significant strides made in the molecular diagnostic field for identifying substantial biomarkers, including genetic, epigenetic, and protein markers, have remarkably revolutionized and enhanced the specificity and sensitivity of diagnostic protocols[7]. These biomarkers provide significant insights into the underlying pathophysiology of biliopancreatic diseases and have significant potential for guiding personalized therapeutic strategies[7]. Endoscopic techniques have evolved considerably in recent years. For example, endoscopic retrograde cholangiopancreatography (ERCP) is complemented by less invasive procedures such as EUS-guided fine-needle aspiration (EUS-FNA). These advancements have led to accurate diagnosis and have been important in offering therapeutic interventions, thereby reducing the need for invasive surgical procedures[8].

The 21st century has been mainly characterized by significant technological innovations, which have had tremendous strides in the medical diagnostic field. In particular, artificial intelligence (AI) and machine learning (ML) technologies have emerged as transformative tools in the diagnostic landscape[9-11]. These technologies can enhance image analysis,

predict disease progression, and personalize patient management[12]. AI-driven algorithms assist clinicians in interpreting complex imaging studies and integrating diverse diagnostic data, leading to more informed decision-making [13].

Despite these advancements, challenges remain in the early detection and differentiation of biliopancreatic diseases, particularly in distinguishing benign from malignant conditions. Notably, global disparities in the accessibility of diagnostic technology substantially impact the diagnosis and management of biliopancreatic disease. Saeed and Masters [14] describe these disparities as "the digital divide," which is largely associated with poor health outcomes despite medical technological improvements. Given the severity of hepatocellular diseases and their poor prognoses, the need for highly specialized and complex diagnostic interventions, such as magnetic resonance imaging (MRI), CT, and molecular diagnostics, is highlighted[15]. Khaing *et al*[16] noted that access to advanced diagnostic tools is heavily skewed toward high-income countries (HICs), whereas low- and middle-income countries (LMICs) often experience severe shortages.

In HICs, advanced diagnostic tools routinely identify biliopancreatic diseases during the early disease stages-when treatment is most effective. For instance, EUS and MRCP are standard methods of evaluating biliary and pancreatic structures that enable the precise diagnosis and staging of cancers. Furthermore, biomarker tests, such as cancer antigen (CA) 19-9 for pancreatic cancer, complement imaging assessments by providing molecular insights guiding personalized treatment strategies. In contrast, LMICs often lack access to these technologies because of economic constraints, inadequate healthcare infrastructure, and shortages of trained specialists. Consequently, healthcare providers in these regions frequently rely on less accurate methods, such as basic abdominal ultrasound, which can overlook early symptoms of the disease. This diagnostic gap leads to delayed diagnosis, with several patients only obtaining a diagnosis at advanced stages, when treatment options are limited and prognoses are poor.

The consequences of such disparities are severe. Biliopancreatic diseases, particularly pancreatic cancer, are associated with high mortality rates worldwide; however, the burden is disproportionately borne by LMICs. Late-stage diagnoses in LMICs contribute to poor survival outcomes and place a remarkable economic strain on fragile healthcare systems. Moreover, the lack of advanced diagnostic technologies exacerbates health inequities, considering patients in LMICs are often cannot afford basic diagnostic services, let alone specialized tests. This leads to delayed care, increased morbidity, and high healthcare costs, which further widens the gap between HICs and LMICs.

Although efforts to address these disparities are underway, systemic and other challenges remain, such as funding shortages, political instability, and inequitable resource distribution across the globe. Thus, continuous research and innovation are required to refine the existing diagnostic tools and develop novel approaches to improve patient outcomes [3]. Therefore, this review aims to provide a comprehensive overview of recent advancements in the diagnosis of biliopancreatic diseases. By examining the latest developments in imaging techniques, molecular diagnostics, endoscopic procedures, and AI applications, we seek to highlight the progress and identify areas for future research and clinical practice improvements.

Our review included all available data in the Cochrane Library, Web of Science, PubMed, and Google Scholar databases until June 2024.

ADVANCEMENTS IN IMAGING MODALITIES FOR THE DIAGNOSIS OF BILIOPANCREATIC DISEASES

Imaging as a diagnostic modality in biliopancreatic diseases

As conventional radiographs can only detect a small proportion of biliopancreatic anomalies, imaging as a diagnostic modality for biliopancreatic diseases has significantly evolved over the years, with optical choledochoscopy being the earliest imaging modality reported in 1941[17]. Since the development of the optical choledochoscope, there has been significant progress in visualizing biliopancreatic anatomical structures over the 20th and 21st centuries, thereby significantly enhancing the ability of modern imaging modalities to detect, characterize, and monitor biliopancreatic diseases.

US and EUS

According to Novitch *et al*[18], the use of diagnostic ultrasonography dates back to the 1940s, based on the work of Dr. Tussik in 1942[19]. Thereafter, this technique has been widely adopted in the medical field because of its extensive availability and training by more clinicians[18]. Moreover, diagnostic ultrasonography has become an invaluable addition to the medical landscape because of its lack of ionizing radiation, which allows repetitive use, its non-invasive nature unlike other surgical alternatives, and its smooth learning curve by facilitating real-time, high-quality image resolution that allows real-time anatomical and functional learning opportunities[18].

The mechanisms underlying diagnostic ultrasonography are based on the transmission of extremely high-frequency sound waves produced by a transducer, which are then reflected to the transducer. These waves are reflected by different acoustic properties, through which images can be generated. Thus, EUS refers to the application of ultrasonographic images to diagnose and treat pathologies by a trained endoscopist during endoscopic examination[20]. After the development of medical diagnostic ultrasonography in 1940, the works of DiMagno and DiMagno[21] in the 1978s have provided key pioneering insights into endoscopic ultrasonography. DiMagno and DiMagno[21] was part of a team sponsored by the Development of Ultrasonic Endoscopic Probes for Cancer Diagnosis from 1978 to 1981, during which the first endoscopic probe was tested on an animal subject, a dog. Based on these investigations, DiMagno and DiMagno [21] hypothesized that EUS can visualize the gastrointestinal lumen while simultaneously providing high-resolution scans of adjacent anatomical structures. DiMagno and DiMagno[21] and the Mayo group, which comprised six co-investigators in 1979, were responsible for the first EUS test conducted on human subjects.

The initial EUS probe designed by DiMagno and DiMagno[21] comprised a 13-mm diameter American cystoscope, an fx-5 side-viewing endoscope paired with an 80-mm rigid tip comprised 10 megahertz, 64-element real-time image array (with a 30-frame capacity), and a 3 × 4 US probe[18]. Moreover, the design comprises a flag handle for tip maneuvering, which has now been rendered obsolete.

Since the 1980s, EUS technology has undergone significant advancements primarily based on its popularity in diagnostic imaging, which has introduced two types of echoendoscopes (linear echoendoscope and radial EUS)[22]. Radial EUS, which provides a 360º plane perpendicular to the field of view to the scope, first produces an image similar to a CT scan image[20]. The linear EUS model provides oblique images parallel to the scope, thereby facilitating therapeutic intervention using the endoscope, as shown in Figure 1.

In particular, EUS-FNA is advantageous for the diagnosis of pancreaticobiliary diseases because it can perform biopsies on extraluminal targets. This feature makes it invaluable to access and sample lesions located outside the gastrointestinal tract. These lesions include those in the pancreas, bile ducts, and surrounding lymph nodes, which are often difficult to reach using other modalities. The precision of EUS-FNA, facilitated by real-time imaging with a linear array endoscope, allows targeted tissue acquisition from deep-seated or small lesions, without the need for invasive surgery. This capability is important for diagnosing malignancies, cystic lesions, and lymphadenopathy in the pancreaticobiliary region, particularly in cases in which traditional endoscopic or imaging techniques may fall short. The ability of EUS-FNA to bypass anatomical barriers and accurately sample tissue contributes to the earlier diagnosis and more effective management of pancreaticobiliary diseases.

EUS can facilitate examination of the gallbladder in the stomach and duodenum. In particular, linear EUS can assess the gallbladder from four locations: the fundus, antrum, bulb, and descending duodenum, as depicted in Figure 2.

Transabdominal ultrasonography is non-invasive, can facilitate real-time imaging, and has a low overall cost. Therefore, it is the first-line and most commonly applied imaging modality for diagnostic workups in patients with biliopancreatic diseases[23]. However, pancreatic EUS is quite challenging to perform owing to the retroperitoneal location, overlying structures, and small size of the pancreas[23]. Advancements in the field in terms of radiologist training and the introduction of high-resolution scanners have remarkably improved imaging quality with the use of modern EUS to examine the whole pancreas, except in cases where patients present with impassable duodenal stenosis or nonamendable postsurgical anatomies[24].

Challenges and limitations associated with EUS

EUS is a valuable diagnostic tool that combines endoscopy and ultrasonography to produce detailed images of the gastrointestinal tract and the surrounding organs. However, their use is associated with several challenges and limitations. One significant challenge is the dependence on operator expertise[25-27]. Inexperienced practitioners may struggle with the complexity of the procedure leading to suboptimal results. Thus, the efficacy of EUS is highly reliant on the skill and experience of the operator[26]. In addition, the considerable learning curve can affect the widespread adoption and availability of EUS.

Moreover, interpreting EUS images can be subjective and vary between operators, potentially leading to inconsistent diagnostic outcomes and misdiagnosis. Therefore, extensive training is required to accurately interpret images, particularly when distinguishing benign from malignant lesions. Furthermore, although EUS is less invasive than other surgical procedures, it is associated with some risks. Complications, such as bleeding, infection, and perforation, are rare. However, they can also occur and require prompt management[28]. Patients may also experience discomfort or adverse reactions to sedatives used during the procedure. EUS-FNA has additional risks, including puncture site infection and bleeding, and is associated with a low risk of tumor cells spreading along the needle tract[29]. In addition, anatomical constraints and patient variability can affect EUS feasibility and efficacy. Specific anatomical locations may be difficult to access, thereby limiting the ability to evaluate and sample the lesions in these areas. Moreover, variations in patient anatomy, such as the presence of scar tissue, and previous surgical history can further complicate the procedure[29,30]. Despite these challenges, EUS remains an essential tool in the diagnostic arsenal, and addressing these limitations requires ongoing advancements in technology, training, and patient selection.

Summary of the current clinical trials on the use of EUS in biliopancreatic disease diagnosis are available in (Supplementary Table 1).

ERCP

ERCP is an imaging technique that combines endoscopy and fluoroscopy for the diagnosis and treatment of biliary and pancreatic ductal systems[31]. This imaging modality was introduced in the 1960s and has become valuable in gastroenterology with improvements in scope design and imaging quality. ERCP allows the visualization and injection of high-contrast medium into the pancreatic and biliary ducts, which allows a more straightforward interpretation of radiographic images and has been primarily used to diagnose and treat biliopancreatic diseases, including gallstones, inflammatory strictures, leaks, and malignancies[31].

Based on the study by Meseeha and Attia[31], the mechanisms behind ERCP involve the use of endoscopic papillotomy, sphincter of Oddi manometry, endoscopic papillary balloon dilation, tissue sampling, stone removal, placement of biliary and pancreatic stents, cholangiopancreatoscopy, and/or biliary and pancreatic drainage. The same study also presented a detailed procedure for the effective use of ERCP. Despite advancements associated with ERCP, several complications have been reported, reaching as high as 6.8% in all cases[31]. These complications are often associated with blood transfusion (> 4 units) and hospitalization for > 10 days[31].

The significant complications associated with ERCP include post-ERCP pancreatitis (mild to moderate severity), gastrointestinal bleeding, and duodenal and biliary perforations, ranked in order of frequency, with post-ERCP pancreatitis having the highest susceptibility to ERCP-related mortality[31-33]. Some rare or less frequent complications

Figure 1 Curved linear array.

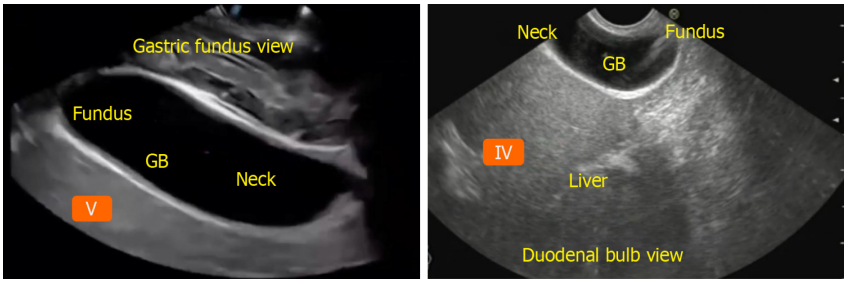

Figure 2 Curved linear array endoscopic utrasound technique in the gallbladder from the stomach and duodenal bulb[148]. Citation: Okasha HH, Gadour E, Atalla H, AbdEl-Hameed OA, Ezzat R, Alzamzamy AE, Ghoneem E, Matar RA, Hassan Z, Miutescu B, Qawasmi A, Pawlak KM, Elmeligui A. Practical approach to linear endoscopic ultrasound examination of the gallbladder. *World J Radiol* 2024; 16: 184-195. Copyright ©The Author(s) 2024. Published by Baishideng Publishing Group Inc.

associated with ERCP include cardiovascular events, pneumothorax, and hepatic hematoma.

FURTHER ADVANCEMENTS IN THE IMAGING DIAGNOSTICS OF PANCREATOBILIARY DISEASES

Peroral cholangiopancreatoscopy

Peroral cholangiopancreatoscopy (POC) is an advanced endoscopic technique that has transformed the diagnosis and treatment of biliary and pancreatic disorders[32]. This procedure combines the principles of endoscopy and fluoroscopy to visualize and manage bile and pancreatic ducts. Therefore, it has diagnostic and therapeutic capabilities[32]. POC can be performed using two primary technologies: An ultraslim endoscope and disposable POC, such as the SpyGlass system (Boston Scientific, United States). The ultraslim endoscope is directly inserted into the bile or pancreatic ducts after preliminary endoscopic papillotomy, thereby facilitating high-resolution imaging and providing therapeutic intervention capabilities *via* its working channel[32]. The Spy Glass system, which is inserted through the instrumental channel of a duodenoscope, also requires preliminary papillotomy and offers real-time, high-definition imaging that can perform targeted biopsies and other procedures[33]. Both technologies have similar advantages. For example, they can perform direct visualization and access the ductal system. However, they are technically demanding and carry risks such as bleeding and pancreatitis, which are associated with papillotomy. These methods were selected based on the clinical situation, patient anatomy, and available expertise and equipment. Despite this innovation, POC has several challenges and limitations that must be considered in clinical practice.

One of the primary advantages of POC is its ability to provide real-time visualization of the bile and pancreatic ducts, thereby enabling accurate diagnosis and intervention, which is particularly beneficial in identifying and treating conditions such as bile duct stones, strictures, and tumors[33]. The procedure involves insertion of an endoscope *via* the mouth and into the duodenum, followed by placement of a catheter in the bile or pancreatic duct. A contrast dye was injected and radiographic imaging was used to visualize the ducts[34]. This technique allows for detailed mapping of ductal anatomy, thereby facilitating the removal of stones, placement of stents, and dilation of strictures[34].

Nonetheless, POC faces certain drawbacks. One major hurdle is the intricate nature of this process. The success of POC is significantly based on the operator's skill and experience, with a steep learning curve that can affect the procedural success rate[32]. Inexperienced operators may encounter difficulties in navigating the endoscope and catheter, potentially leading to incomplete examinations or complications. In addition, the procedure requires high dexterity and familiarity with the equipment, which further underscores the need for specialized training and experience[32].

The risk of complications is another challenge associated with POC[33]. Although the procedure is generally safe, it is associated with a risk of adverse events, such as pancreatitis, bleeding, infection, and perforation. The incidence of postprocedural pancreatitis is particularly concerning, occurring in a small but significant number of cases[35]. This risk requires careful patient selection and prophylactic measures to prevent potential complications. Patients with a history of pancreatitis, complicated anatomy, or previous abdominal surgeries were at a higher risk. This may require additional precautions or alternative diagnostic approaches[36]. Moreover, technological limitations can affect the efficacy of POC. Imaging quality and procedure success are significantly dependent on the technological capabilities of the endoscopic equipment used[32]. Variations in the resolution of imaging systems and the performance of fluoroscopic units can affect the clarity of images, potentially compromising diagnostic accuracy. Moreover, the high cost of advanced endoscopic and imaging equipment can limit the availability of POC in some healthcare settings, particularly in resource-constrained environment[36].

Furthermore, although POC is a powerful diagnostic tool, its therapeutic role is limited by anatomical and physiological challenges. The accessibility of certain ductal segments can be challenging, particularly in patients with complex anatomy or those who have undergone previous surgeries that have altered the ductal system[37]. In addition, the procedure may be less effective in patients with extensive ductal strictures or severe inflammation who are at a higher risk of complications and have a lower likelihood of successful intervention[38]. This limitation often requires adjunctive procedures or alternative imaging modalities for a comprehensive diagnosis and treatment plan. Despite these challenges, POC continues to evolve, with technological advancements and techniques enhancing its capabilities. Table 1 presents a comparative review of the POC, ERCP, and EUS.

Balloon enteroscopy

Since its clinical introduction in 2003, balloon enteroscopy or balloon-assisted enteroscopy has become an essential technique for managing patients with surgically altered anatomy, such as those with a Roux-en-Y loop or an incomplete colon, owing to incomplete conventional colonoscopy[39,40]. Traditional endoscopy often has limitations in these cases owing to the length and complexity of the altered intestinal tract, which makes it difficult to reach the bile ducts or pancreatic ducts. Balloon enteroscopy, including single- and double-balloon enteroscopy, addresses this challenge by using balloons to anchor the enteroscope and allowing it to advance through complex anatomy[41]. This method is effective for diagnostic and therapeutic interventions such as stone removal, placement, and biopsy. Balloon enteroscopy complements small-bowel imaging modalities such as capsule endoscopy, abdominal ultrasonography, MRI, and CT scan [42]. The ability to navigate through an altered anatomy with balloon enteroscopy has significantly expanded the reach and utility of endoscopic procedures in patients with complex surgical histories, thereby improving the diagnostic capabilities and treatment outcomes[43,44].

Balloon enteroscopy is an effective tool for deep small-bowel exploration and intervention. However, this procedure has several limitations and challenges. The procedure is technically demanding and requires specialized training, as the insertion and manipulation of the endoscope *via* the small intestine can be complex, particularly in patients with an altered anatomy or adhesions[45]. It is also time-consuming and often requires prolonged procedures to reach deeper bowel sections. Patient discomfort and the need for sedation or anesthesia can be significant in addition to procedural risks. In addition, balloon enteroscopy may result in complications such as bowel perforation, bleeding, or pancreatitis, particularly during therapeutic interventions[46]. Despite these limitations, its diagnostic yield and therapeutic potential for small-bowel disease make it a valuable endoscopic procedure.

Optical biopsy and enhanced imaging techniques

Advancements in endoscopic techniques have significantly improved the diagnosis and management of pancreaticobiliary diseases, which facilitates more precise and real-time tissue evaluation. Enhanced imaging technologies, such as laser confocal endomicroscopy, can promote *in vivo* microscopic imaging of cellular architecture and vascular patterns during the procedure, thereby aiding in the early detection of malignancies and other pathologies[47-49]. Narrow band imaging enhances the visualization of mucosal and vascular structures, thereby improving the identification of neoplastic changes, particularly in the bile and pancreatic ducts[50-52]. Other digital enhancement technologies, such as flexible spectral imaging color enhancement and I-scan, further improve contrast and clarity, thereby allowing for better detection of subtle lesions[53].

High magnification techniques, such as ZOOM endoscopy[54-58] and autofluorescence imaging[59-62], which highlight abnormal tissue fluorescence, also improve the diagnostic accuracy. Optical coherence tomography provides cross-sectional imaging to assess deeper tissue layers. Meanwhile, endocytoscopy obtains ultra-high magnification images for real-time cellular analysis[59,60].

ADVANCEMENTS IN COMPUTER TOMOGRAPHY SCAN FOR THE DIAGNOSIS OF BILIOPANCREATIC DISEASES

CT technology has significantly advanced and revolutionized medical diagnostic imaging. Dual-energy CT (DECT), which utilizes two energy levels to acquire images and offers enhanced tissue characterization and improved contrast resolution, is a notable innovation[61-63]. DECT technology has been valuable in detecting kidney stones, gout, and vascular abnormalities, and in differentiating various tissue types[64]. Similarly, Spectral CT simultaneously captures images at multiple energy levels, thereby providing detailed tissue composition information[65]. This innovation has

Table 1 Comparative overview of proral colangioscopy, endoscopic retrograde colangiopancreatography, and edoscopic utrasound

Aspect	Endoscopic utrasound	Endoscopic retrograde cholangiopancreatography	Peroral colangioscopy
Technique involved	Combines endoscopy and ultrasonography	Combines endoscopy and fluoroscopy; use of contrast dye and radiography	Insertion of an endoscope *via* the mouth using advanced imaging
Purpose	Primarily diagnostic	Diagnostic and therapeutic	Detailed diagnostic imaging and therapeutic interventions
Procedure	Use of an endoscope with an ultrasound probe for internal imaging	Injection of contrast dye into the ducts, with radiographic images taken with real-time guidance	High-resolution visualization of the bile and pancreatic ducts
Imaging quality	High-resolution ultrasound imaging	Real-time fluoroscopic guidance	High-resolution; detailed visualization
Technology	Ultrasound-guided fine-needle aspiration biopsy	Fluoroscopy for real-time imaging	Often incorporates digital and high-resolution imaging systems
Primary clinical uses	Pancreatic cancer detection and staging	Diagnosing and treating bile duct obstructions	High-resolution imaging of the bile and pancreatic ducts
	Chronic pancreatitis and biliary disease evaluation	Gallstone removal, stent placement, and stricture dilation	Identifying small lesions and ductal changes
	Evaluation and sampling of submucosal lesions	Stricture and tumor management	Stone removal, stent placement, and dilation of strictures
Advantages	Minimally invasive with high-resolution imaging	Combined diagnostic and therapeutic capabilities	Enhanced imaging quality
	Guided biopsies, including extraluminal targets	Immediate symptom relief and treatment	Reduced radiation exposure
	Ability to reach and biopsy beyond the GI tract	Proven efficacy with a high success rate	Improved diagnostic accuracy *via* digital innovations
Risks and limitations	Procedure-related risks (*e.g.*, bleeding, infection, and perforation)	Higher rates of complications (*e.g.*, pancreatitis, infection, and bleeding)	Technically demanding; requiring specialized training
	Complementary to ERCP in therapeutic procedures	Radiation exposure from fluoroscopy	Operator dependency affecting outcomes
	Technically demanding	Technological limitations based on the equipment	Anatomical challenges in accessing the ducts
Patient selection	Excellent for staging, lesion assessment, and biopsies	Ideal for immediate therapeutic intervention during diagnosis	Useful for detailed diagnostic evaluations
	Complementary to ERCP in addressing limitations	Suitable for several biliary and pancreatic conditions	Challenges with a complex anatomy
Therapeutic role	Complementary to ERCP in therapeutic procedures	Notable therapeutic capabilities (stone removal, stenting)	Stone removal, stent placement, and dilation
Biopsy capability	Combines endoscopy with ultrasonography	Can collect small tissue samples (biopsies)	Can be performed under direct visualization
Invasiveness	Primarily diagnostic	More invasive with a higher risk of complications	Less invasive than surgery
Imaging *vs* therapeutics	Endoscope with an ultrasound probe for internal imaging	Balanced diagnostic and therapeutic functions	Useful for high-resolution imaging of small lesions and ducts
Complications	High-resolution ultrasound imaging	Higher risk of pancreatitis, infection, and perforation	Risk of infection, bleeding, and perforation

ERCP: Endoscopic retrograde cholangiopancreatography.

improved lesion detection and differentiation and reduced artifacts from metal implants, enhancing diagnostic accuracy in complex cases[66].

The development of iterative reconstruction techniques is another significant advancement[67-71]. These advanced algorithms iteratively refine the image reconstruction process, reduce noise, and improve overall image quality. This has significantly reduced the radiation dose without compromising the image quality, which is particularly beneficial in pediatric imaging and follow-up scans[72-74]. In addition, integrating AI and ML algorithms further enhanced CT scan imaging. These technologies allow automated lesion detection, improved image quality, reduced scan times, and enhanced diagnostic accuracy *via* AI-assisted interpretation.

The development of AI has revolutionized several medical fields and its impact on imaging modalities for biliopancreatic diseases is particularly significant. Biliopancreatic diseases encompass various conditions affecting the biliary system, pancreas, and the surrounding structures. These conditions are often complex and require precise diagnostic tools to improve the patient outcomes. Owing to its ability to analyze large datasets and recognize patterns, AI has significantly enhanced the diagnostic accuracy, efficiency, and predictive capabilities of imaging techniques in this domain.

ADVANCEMENTS IN MRCP

MRCP is a non-invasive imaging technique used to visualize the biliary and pancreatic ducts[70]. Unlike traditional cholangiography, MRCP employs MRI to produce detailed images without contrast injection into the ducts. MRCP is particularly valuable in diagnosing conditions such as bile duct stones, strictures, tumors, and congenital abnormalities [71]. Furthermore, it is used to evaluate the pancreatic duct in conditions such as chronic pancreatitis or pancreatic tumors. The technique works by identifying the difference in fluid content between the bile and pancreatic ducts and surrounding tissues, thereby making these ducts appear bright on MRI images and the surrounding tissues remain darker.

One of the main advantages of MRCP is its non-invasive nature, which prevents the risks associated with invasive procedures such as ERCP. Moreover, it is free of ionizing radiation. Thus, it is safer for patients who require repeated imaging or pregnant women. MRCP provides high-resolution images that can help in the detailed assessment of the ductal anatomy and pathology, and it can be used in conjunction with other imaging modalities to enhance diagnostic accuracy. However, MRCP has certain limitations. It may not detect extremely small stones or early-stage tumors, and the image quality can be affected by patient movement or the presence of metallic implants, which can cause artifacts. Despite these limitations, MRCP is still a highly useful tool for non-invasive evaluation of the biliary and pancreatic ductal systems, thereby providing essential information for the diagnosis and management of various conditions.

High-resolution MRCP represents a significant advancement in imaging technology as it provides more detailed and precise images of the biliary and pancreatic ducts. This technique utilizes high magnetic field strengths, typically 3T MRI machines, along with advanced imaging protocols to achieve a greater spatial resolution[71]. High-resolution MRCP enables the visualization of finer details within the ductal system, which allows for the detection of small stones, subtle strictures, early-stage tumors, and other minute abnormalities that may be missed by standard MRCP. This level of detail is particularly valuable in preoperative planning and in evaluating complex cases in which precise anatomical information is crucial[72].

Functional MRCP is an emerging technique that combines traditional MRCP with dynamic imaging sequences to assess the physiological function of biliary and pancreatic ducts[73]. Unlike standard MRCP, which provides static images, functional MRCP captures the movement of bile and pancreatic fluids over time, thereby offering insight into the functional status of these ducts[74,75]. This technique is particularly useful for diagnosing functional disorders such as biliary dyskinesia and sphincter of Oddi dysfunction, where the flow of bile or pancreatic juice is abnormal. Secretin-enhanced MRCP is a common approach in functional MRCP, where the administration of secretin (a hormone that stimulates pancreatic secretion) increases the volume of pancreatic fluid, distends the ducts, and allows for dynamic assessment of their function[76]. Functional MRCP can provide valuable information about ductal motility and fluid dynamics, which are essential for diagnosing conditions that are not associated with structural abnormalities[77,78].

Diffusion-weighted imaging (DWI) is an advanced MRI technique that measures the diffusion of water molecules within the tissues. When used in combination with MRCP, DWI offers additional diagnostic information by evaluating the cellular environment and microstructure of the bile ducts, pancreatic ducts, and surrounding tissues[79]. DWI is particularly useful in distinguishing benign from malignant lesions, as malignant tissues typically exhibit restricted diffusion owing to their higher cellularity and altered tissue architecture[80,81]. This ability of DWI-MRCP to assess tissues at the molecular level makes it a valuable tool for non-invasive characterization of biliary and pancreatic strictures, masses, and other abnormalities. Moreover, DWI can help detect early-stage tumors and assess the extent of disease spread, thereby potentially reducing the need for invasive diagnostic procedures, such as biopsies[82].

AI IN ULTRASOUND IMAGING AND EUS

Integrating AI into ultrasound imaging has significantly improved the detection and characterization of biliopancreatic diseases[83]. AI algorithms can analyze ultrasound images to identify subtle changes that indicate early-stage disease. For example, AI-powered software can differentiate benign from malignant lesions in the pancreas by analyzing texture patterns and echogenicity that are not easily discernible to the human eye. Thus, it enhances the accuracy of ultrasonography in diagnosing pancreatic cancer and potentially leading to earlier detection and improved survival rates[84-86]. In addition, AI can assist in real-time image acquisition, guiding the operator to obtain optimal images, and reducing operator variability[86].

The diagnostic capabilities of AI integration into EUS have been enhanced by assisting in interpreting EUS images by automatically identifying and characterizing lesions[87]. For example, AI algorithms can differentiate benign from malignant pancreatic lesions with high accuracy, thereby improving endoscopists' diagnostic confidence[84]. In addition, AI can guide FNA and FNB tissue acquisition procedures, optimize the sampling of lesions, and increase diagnostic yield [88]. Moreover, AI can be used to develop predictive models based on the EUS findings. By analyzing large datasets of

EUS images and associated clinical outcomes, AI can identify the patterns and predictors of disease progression, which helps in risk stratification and individualized treatment planning.

AI in CT scan and MRI

CT is a cornerstone in the imaging of biliopancreatic diseases owing to its high spatial resolution and ability to provide detailed cross-sectional images. AI applications in CT scans have focused on automating image analysis and improving the diagnostic accuracy. Deep learning algorithms can be trained to recognize and precisely segment pancreatic tumors, cysts, and other abnormalities[89]. Furthermore, these algorithms can analyze vascular involvement in pancreatic tumors, which is crucial for surgical planning. Moreover, AI can help detect incidental findings such as small pancreatic cysts and gallstones, which might be overlooked during routine scans[90,91]. AI-enhanced CT imaging also reduces radiation exposure. By optimizing image acquisition protocols and enhancing image reconstruction, AI can maintain high image quality while lowering the radiation dose, thereby decreasing patient risk[91]. MRI provides excellent soft tissue contrast, thereby making it a valuable tool for evaluating biliopancreatic diseases. AI applications in MRI have focused on improving image acquisition, enhancing image quality, and automating image interpretation[91]. AI algorithms can enhance MRI images by reducing noise and artifacts, thereby making the images more precise and accurate. This is particularly important for detecting small lesions or subtle changes in the biliary and pancreatic ducts. In addition, AI can accelerate MRI acquisition times, making the procedure more comfortable for patients and increasing the throughput in clinical settings. Furthermore, AI plays an important role in the interpretation of MRI findings. For example, ML models can analyze MRI sequences to identify and classify pancreatic cysts based on imaging characteristics. This aids in differentiating benign cysts from those with malignant potential, guiding clinical management, and reducing unnecessary interventions. Several clinical trials at various stages have emphasized the role and application of AI in imaging and diagnostic modalities. Tables 2 and 3[92-114] present a summaries of clinical trials and their statuses and stages, as well as the AI modalities used in the diagnosis of biliopancreatic diseases. The current clinical trials on the application of AI in the imaging of biliopancreatic disease are provided in (Supplementary Table 2).

USE OF BIOMARKERS IN THE DIAGNOSIS OF BILIOPANCREATIC DISEASES

CA 19-9 is among the most widely used biomarkers for pancreatic diseases, particularly pancreatic adenocarcinoma[115]. High CA 19-9 levels indicate pancreatic cancer. However, this marker has no specificity, as it can also be elevated in other conditions such as cholangiocarcinoma, pancreatitis, and benign biliary obstructions. Carcinoembryonic antigen, another marker often used in combination with CA 19-9, can also be elevated in pancreatic cancer. However, it is primarily used for colorectal cancer treatment[116,117]. For acute pancreatitis, high amylase and lipase levels are key indicators, with lipase being more specific and remaining elevated for a longer duration than amylase. In addition to these more commonly used markers, hormones such as insulin, C-peptide, and glucagon are valuable in diagnosing pancreatic neuroendocrine tumors, which can cause conditions such as hypoglycemia and hyperglycemia, attributed to excessive hormone secretion. The potential role of emerging biomarkers, such as microRNAs (miRNAs), in pancreatic cancer diagnosis is also being evaluated. Specific miRNAs, such as miR-21, miR-155, and miR-196a, are promising because of their stability in the blood and their involvement in cancer pathogenesis[118,119]. Furthermore, the detection of *KRAS* mutations, particularly *via* circulating tumor DNA (ctDNA), is becoming increasingly important for understanding the genetic profile of pancreatic tumors and facilitating their diagnosis and monitoring[120].

CA 19-9 is also a commonly used biomarker for biliary diseases, particularly cholangiocarcinoma. Nevertheless, its diagnostic utility is limited by its elevation in benign conditions such as cholangitis and biliary obstruction[121]. Alpha-fetoprotein is primarily used in hepatocellular carcinoma. However, it can also be elevated in combined hepatocellular cholangiocarcinoma and gallbladder carcinoma[122,123]. High bilirubin levels often indicate bile duct obstruction, which can occur in conditions such as gallstones, cholangitis, and bile duct tumors. Enzymes such as alkaline phosphatase and gamma-glutamyl transferase are useful for the diagnosis of biliary obstruction and cholestatic liver diseases, including primary biliary cholangitis and primary sclerosing cholangitis.

Other markers such as IgG4 are associated with autoimmune pancreatitis and IgG4-related sclerosing cholangitis, which are conditions that can mimic malignancy but respond well to steroid therapy[124,125]. In addition, mucin proteins, such as MUC1 and MUC5AC, are associated with biliary tract cancers, including cholangiocarcinoma and gallbladder cancer. High MUC1 and MUC5AC levels indicate the presence of malignancy. Fibroblast growth factor 19 is an emerging biomarker, and its role in cholangiocarcinoma is being evaluated, considering its involvement in bile acid metabolism and potential link to tumor growth[126]. These biomarkers play an important role in the early detection, diagnosis, and management of biliopancreatic diseases, thereby providing essential insights into their presence and progression.

Research on miRNAs has also progressed significantly, with specific miRNA profiles being identified as potential markers for the early detection and prognosis of pancreatic cancer and other biliary diseases. The stability of miRNAs in the blood and their role in gene regulation make them promising non-invasive biomarkers. Another notable advancement is the study of glycan structures, such as those found in MUC1 and MUC5AC, which are overexpressed in biliary and pancreatic cancers[127,128]. These glycan alterations can be detected in serum or tissue samples, and their potential for early detection and use as indicators of prognosis is being explored[129].

Exosomal biomarkers have emerged as a promising area of research. In pancreatic cancer, specific exosomal markers, such as glypican-1 and certain miRNAs, can distinguish patients with cancer from those with benign conditions or healthy controls, thereby offering a novel avenue for early detection and treatment response monitoring[130-132].

Table 2 Summary of artificial intelligence-based prediction models for computed tomography scan in clinical studies

Clinical data availability	AI agorithm	Equipment	Reference sandard	Outcome masured	AUC	Ref.
With clinical data	Boruta, gradient-boosting classifier	Siemens, GE	Surgical resection	Residual ALN metastasis	0.866	
	Lasso regression	Philips	Surgical resection	SLN metastasis	0.95	[93,94]
	CNN-fast and CNN	GE, Philips	Surgical resection	SLN metastasis	0.817	
Without or insufficient clinical data	DCNNs	18FDG-PET/CT (Philips, GE)	Surgical resection	ALN metastasis	0.868	
	DA-VGG19	GE, Philips	Surgical resection	ALN metastasis	0.9694	
	DT, RF, NB, SVM, ANN	Philips	Surgical resection	ALN metastasis	0.86	
	XGBoost	18FDG-PET/CT (GE)	Surgical resection	ALN metastasis	0.89	

AI: Artificial intelligence; ALN: Axillary lymph node; ANN: Artificial neural network; AUC: Area under the curve CT: Computed tomography; DA: Deformable attention; DCNNs: Deep convolutional neural networks; DT: Decision tree; RF: Random forest; NB: Naïve Bayes; SVM: Support vector machine; 18FDG-PET: Fluorodeoxyglucose positron emission tomography.

Table 3 AI-Assisted based prediction models for magnetic resonance imaging models

Clinical data availability	AI algorithm	Equipment	Reference standard	Outcome measured	AUC	Ref.
With clinical data	SVM	1.5 T GE	Surgical resection	ALN metastasis	0.87	
	SVM	3.0 T GE	Surgical resection	ALN metastasis	0.810	
	RF	N/A	Surgical resection	ALN metastasis	0.91	
Without or with insufficient clinical data	LDA, RF, NB, KNN, SVM	3.0 T Siemens	FNA or surgical resection	ALN metastasis	0.82	
	SVM, KNN, and LDA	3.0 T Siemens	FNA or surgical resection	ALN metastasis	0.8615	
	LDA	1.5 T Aurora	Surgical resection	ALN metastasis	0.812	
	SVM, XGBoost	3.0 T GE	Surgical resection	ALN metastasis	0.83	
	SVM	1.5 T Philips	Surgical resection	SLN metastasis	0.852	
	CNN	1.5 T GE	18FDG-PET	ALN metastasis	0.91	
	RF	1.5 T Philips	Surgical resection	SLN metastasis	0.868	
	Lasso regression	1.5 T Siemens	Surgical resection	ALN metastatic burden	0.81	

AI: Artificial intelligence; ALN: Axillary lymph node; ANN: Artificial neural network; AUC: Area under the curve; CNN: Convolutional neural network; DA: Deformable attention; DCNNs: Deep convolutional neural networks; DT: Decision tree; FNA: Fine-needle aspiration; KNN: k-nearest neighbors; LDA: Linear discriminant analysis; NB: Naïve Bayes; RF: Random forest; SLN: Sentinel lymph node; SVM: Support vector machine; 18FDG-PET: Fluorodeoxyglucose positron emission tomography.

Advancements in proteomic and metabolomic technologies have enabled the identification of novel proteins and metabolic biomarkers associated with biliopancreatic diseases. These approaches can identify complex biomarker patterns that may be correlated with disease presence, stage, and response to treatment, thereby offering a more individualized approach for diagnosis and management.

The integration of digital polymerase chain reaction and next-generation sequencing technologies into biomarker research has also improved the detection sensitivity of low-abundance biomarkers, such as ctDNA and miRNAs. These technologies allow the quantification of minute genetic changes, thereby enabling the detection of early-stage cancers and minimal residual disease after treatment. In addition, there have been advancements in the detection of autoantibodies against tumor-associated antigens, which can be early markers of pancreatic cancer and can facilitate earlier diagnosis before the disease becomes clinically apparent.

Genetic and epigenetic biomarkers have also undergone significant advancements, particularly in the understanding of epigenetic changes, such as DNA methylation and histone modification, in pancreatic and biliary cancers. These biomarkers can predict disease susceptibility, prognosis, and response to therapy, thereby offering valuable insights into

individualized treatment strategies. With the increased use of immunotherapy in cancer treatment, research on biomarkers that can predict the response to immunotherapy, such as PD-L1 expression and tumor mutational burden, is ongoing, with the goal of identifying patients who could benefit from immune checkpoint inhibitors[133,134]. These advancements in biliopancreatic disease biomarkers are improving the precision of diagnosis, promoting earlier detection, and offering new avenues for personalized treatment approaches, ultimately improving patient outcomes and providing more targeted therapeutic options.

Challenges in biomarker research include the standardization and validation of biomarkers. Large-scale prospective studies should be performed to validate the clinical utility of biomarkers and establish standardized protocols for their use in clinical practice[135-138]. Despite these challenges, the diagnosis and treatment of biliopancreatic diseases can potentially be transformed by advancements in biomarkers. Biomarkers can improve patient outcomes and quality of life by improving early detection, risk assessment, and treatment monitoring (Supplementary Table 3). The stratification of clinical trials assessing various key biomarkers in the diagnosis of biliopancreatic diseases are provided in Table 4.

ADVANCEMENTS IN THE USE OF AI IN THE DIAGNOSIS OF BILIOPANCREATIC DISEASES

AI involves the use of complex computer algorithms to analyze and manipulate vast amounts of data to examine patterns and make predictions[12,87]. Advancements in the use of AI in diagnosing biliopancreatic diseases have significant potential for enhancing diagnostic accuracy, efficiency, and personalized patient care. AI technologies, particularly ML algorithms, have been integrated into various aspects of medical imaging, pathology, and data analysis to improve the detection, characterization, and monitoring of biliopancreatic diseases[12].

Imaging is a key area in which AI has had substantial impact. AI algorithms can analyze complex imaging data with high precision using modalities such as CT, MRI, and EUS. These algorithms can detect subtle abnormalities that may be missed by the human eye, thereby improving the early detection rates. For example, AI-powered tools can automatically identify pancreatic lesions and classify them based on their malignant potential, which is important for early intervention and better patient outcomes.

In addition to enhancing image interpretation, AI has improved the efficiency of imaging workflows with AI algorithms used to automate routine tasks such as organ segmentation and quantification, which reduces the workload for radiologists and allows them to focus on more complex cases[139]. This accelerates the diagnostic process and ensures measurement consistency and accuracy. AI has also been used to analyze pathological data. For example, ML models can examine histopathological slides to identify malignant cells, differentiate various tumors, and predict disease progression [140]. These models can learn from vast datasets, which can continuously improve their accuracy and provide valuable insights into the pathological characteristics of biliopancreatic diseases[140].

Moreover, AI-driven liquid biopsy analysis is promising for non-invasive detection of biliopancreatic cancers. AI algorithms can detect genetic mutations and molecular alterations associated with cancer by analyzing ctDNA, RNA, and other biomarkers in blood samples. This approach offers a less invasive alternative to traditional biopsy, thereby enabling earlier diagnosis and real-time monitoring of disease progression. The predictive analytics capabilities of AI represent another area of advancement. AI can predict disease outcomes and treatment responses by analyzing large datasets that include the demographic characteristics of patients, medical history, imaging findings, and genetic information. This allows for more personalized treatment plans based on the specific needs of each patient, ultimately improving clinical outcomes.

Despite these advancements, the widespread adoption of AI for the diagnosis of biliopancreatic diseases still faces several challenges. Therefore, it is important to ensure the robustness and generalizability of AI models across diverse patient populations[141]. In addition, integrating AI tools into clinical workflows requires collaboration between technologists, clinicians, and regulatory bodies to address issues related to data privacy, ethical considerations, and clinical validation[142,143].

RECOMMENDATIONS

Further research must be performed to identify novel biomarkers and imaging techniques that require collaborative effort among researchers, clinicians, and industry partners. Standardized protocols for biomarker testing and imaging interpretation should be established to ensure consistency and reliability, with large-scale prospective studies validating the clinical utility of these advancements[144,145]. To improve the diagnostic accuracy and implement personalized treatment strategies, healthcare institutions should integrate biomarkers and advanced imaging modalities into their diagnostic algorithms for biliopancreatic diseases.

The need for optimal and efficient competency among healthcare professionals is essential. Therefore, healthcare professionals should undergo regular education and training regarding the latest advancements in biomarkers and imaging modalities to ensure their optimal utilization in clinical practice. A patient-centric approach should be adopted when selecting diagnostic modalities and treatment strategies, considering individual patient characteristics and preferences[146-148]. Integrating AI algorithms into biomarker analysis and imaging interpretation can enhance diagnostic accuracy and efficiency, which requires investment in AI technologies.

A multidisciplinary approach involving radiologists, gastroenterologists, surgeons, oncologists, and pathologists is essential for optimal management of biliopancreatic diseases. Collaboration among these professionals can improve the diagnostic and treatment outcomes. Cost-efficacy analyses should be conducted to evaluate the economic impact of

Table 4 Summary of key biomarkers and their diagnostic performance

Biomarker	Primary use	Sensitivity	Specificity	Detection method	Clinical applications	Limitations
CA 19-9	Pancreatic cancer	80%-90%	70%-80%	Enzyme-linked immunosorbent assay (ELISA)	Used in monitoring disease progression and treatment response	Elevated in benign conditions; lacks specificity
KRAS mutations	Pancreatic cancer	High	High	Polymerase chain reaction (PCR); next-generation sequencing (NGS)	Identifies high-risk patients, guides targeted therapies	Limited sensitivity in early-stage cancer
Amylase/lipase	Acute pancreatitis	> 90%	70%-80%	Serum biochemical assays	First-line test for diagnosing acute pancreatitis	Cannot distinguish between acute and chronic cases
Alpha-fetoprotein	Hepatocellular and biliary carcinoma	60%-70%	80%-90%	ELISA, chemiluminescent immunoassay	Used in screening for hepatocellular carcinoma	Limited specificity in biliary malignancies
MicroRNAs (miR-21, miR-196a)	Early detection of pancreatic cancer	85%	90%	Reverse transcription PCR (RT-PCR); RNA sequencing	Potentially noninvasive biomarker for early detection	Requires further validation and standardization

CA 19-9: Cancer antigen 19-9.

integrating biomarkers and imaging modalities into clinical practice, thereby helping healthcare institutions to allocate resources efficiently. By implementing these recommendations, healthcare institutions can enhance the diagnosis and management of biliopancreatic disease, leading to better patient outcomes and quality of life.

CONCLUSION

Advancements in biomarkers, imaging modalities, and other diagnostic technologies have collectively revolutionized the diagnosis and management of biliopancreatic diseases. Biomarkers, such as CA 19-9, *KRAS* mutations, and inflammatory markers, offer valuable insights into disease progression and treatment response. Imaging modalities such as CT, MRI, EUS, and ERCP can provide detailed anatomical and functional information, thereby helping in the early detection and accurate staging of biliopancreatic diseases. Other advancements, including genetic testing, liquid biopsies, and AI, can further enhance the diagnostic accuracy and personalized treatment strategies.

Despite these promising developments, the implementation of AI technologies across different healthcare settings faces substantial challenges. High technological costs and the need for specialized infrastructure limit widespread adoption, particularly in resource-limited regions. Furthermore, the effectiveness of AI models is contingent on high-quality data, requiring the implementation of robust data governance policies for security and privacy. Addressing these hindrances needs investment in training programs to equip healthcare professionals with the required skills to effectively utilize AI-enhanced diagnostics.

Another critical issue is the standardization of biomarkers. Although biomarkers, such as CA 19-9 and *KRAS* mutations, have diagnostic utility, variability in laboratory methodologies and interpretation criteria hampers their widespread clinical application. Standardized protocols and validation frameworks are essential for enhancing reliability and comparability across different institutions. Furthermore, regulatory bodies must establish guidelines to ensure the clinical integration of AI-assisted biomarker analysis while maintaining transparency and accountability in AI-driven decision-making.

Future efforts should entail developing cost-effective AI solutions tailored to diverse healthcare settings, implementing standardized biomarker validation protocols, and fostering interdisciplinary collaboration to optimize the clinical utility of these technologies. By addressing these challenges, AI- and biomarker-based diagnostics can achieve their full potential in improving patient outcomes and advancing pancreaticobiliary disease management.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopists and endoscopic assistants' qualifications, but not their biopsy rates, improve gastric precancerous lesions detection rate

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Abstract

BACKGROUND

Detecting gastric precancerous lesions (GPLs) is critical for the early diagnosis and treatment of gastric cancer. Endoscopy combined with tissue examination is an important method for detecting GPLs. However, negative biopsy results often increase patients' risks, economic burdens, and lead to additional healthcare costs. Improving the detection rate of GPLs and reducing the rate of negative biopsies is currently a key focus in endoscopic quality control.

AIM

To explore the relationships between the endoscopist biopsy rate (EBR), qualifications of endoscopists and endoscopic assistants, and detection rate of GPLs.

METHODS

EBR, endoscopists, and endoscopic assistants were divided into four groups: Low, moderate, high, and very high levels. Multivariable logistic regression analysis was used to analyze the relationships between EBR and the qualifications of

endoscopists with respect to the detection rate of positive lesions. Pearson and Spearman correlation analyses were used to evaluate the correlation between EBR, endoscopist or endoscopic assistant qualifications, and the detection rate of positive lesions.

RESULTS

Compared with those in the low EBR group, the odds ratio (OR) values for detecting positive lesions in the moderate, high, and very high EBR groups were 1.12 [95% confidence interval (CI): 1.06-1.19, $P < 0.001$], 1.22 (95%CI: 1.14-1.31, $P < 0.001$), and 1.38 (95%CI: 1.29-1.47, $P < 0.001$), respectively. EBR was positively correlated with the detection rate of gastric precancerous conditions (atrophic gastritis/intestinal metaplasia) ($\rho = 0.465$, $P = 0.004$). In contrast, the qualifications of the endoscopists were positively correlated with GPLs detection ($\rho = 0.448$, $P = 0.005$). Compared to endoscopists with low qualification levels, those with moderate, high, and very high qualification levels endoscopists demonstrated increased detection rates of GPLs by 13% (OR = 1.13, 95%CI: 0.98-1.31), 20% (OR = 1.20, 95%CI: 1.03-1.39), and 32% (OR = 1.32, 95%CI: 1.15-1.52), respectively. Further analysis revealed that the qualifications of endoscopists were positively correlated with the detection rates of GPLs in the cardia ($\rho = 0.350$, $P = 0.034$), angularis ($\rho = 0.396$, $P = 0.015$) and gastric body ($\rho = 0.453$, $P = 0.005$) but not in the antrum ($\rho = 0.292$, $P = 0.079$). Moreover, the experience of endoscopic assistants was positively correlated with the detection rate of precancerous lesions by endoscopists with low or moderate qualifications ($\rho = 0.427$, $P = 0.015$).

CONCLUSION

Endoscopists and endoscopic assistants with high/very high qualifications, but not EBR, can improve the detection rate of GPLs. These results provide reliable evidence for the development of gastroscopic quality control indicators.

Key Words: Endoscopist biopsy rate; Endoscopist qualifications; Gastric precancerous conditions; Gastric precancerous lesions; Gastric cancer

Core Tip: This study demonstrates that endoscopists and endoscopic assistants with high qualifications, rather than the endoscopist biopsy rate, significantly improve the detection of gastric precancerous lesions (GPLs). Qualified endoscopists showed higher GPLs detection rates, particularly in the gastric cardia, angularis, and body regions. This suggests that a high endoscopist biopsy rate alone is not sufficient for detecting GPLs. Instead, greater emphasis should be placed on improving the qualifications of endoscopists and appropriate collaboration between endoscopists and assistants to perform accurate biopsies. These findings provide valuable insights for developing gastroscopic quality control standards.

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INTRODUCTION

Gastric cancer (GC) remains a critical global public health challenge. Despite advancements in therapeutic strategies, the 5-year relative survival rate for GC remains suboptimal at 36%[1]. Current therapeutic paradigms integrate multimodal strategies, however, challenges including tumor heterogeneity and therapeutic resistance necessitate biomarker-driven precision strategies to achieve clinically meaningful improvements in survival[2]. In China, GC remains a common malignant tumor, with incidence and mortality rates ranking at the forefront among malignant tumors[3], imposing significant economic pressure on the health care system. The development of intestinal-type GC typically follows the Correa cascade model, from normal gastric mucosa to nonatrophic gastritis (NAG), atrophic gastritis (AG), intestinal metaplasia (IM), gastric dysplasia/intraepithelial neoplasia (Dys/IN), and ultimately, GC[4]. Gastric precancerous conditions (GPCs) include AG and IM[5], whereas gastric precancerous lesions (GPLs) include Dys/IN, which play crucial roles in malignant transformation of the gastric mucosa[6]. Therefore, the early identification of GPCs and GPLs is essential for improving patients' quality of life and enhancing treatment outcomes.

By regularly undergoing gastroscopy screening, Japan and South Korea have successfully increased the diagnosis and treatment rates of GC and GPLs, improved patient prognosis, and effectively lowered the incidence and mortality of GC [7,8]. Gastroscopy combined with biopsy is the main method for detecting and monitoring GC and precancerous lesions. However, there is significant heterogeneity among different examiners, and the diagnosis rate often depends on the examiner[9]. A meta-analysis revealed a misdiagnosis rate of 9.4% for GC[10], highlighting the necessity to improve the quality of gastroscopy examinations and implement strict biopsy strategies in clinical practice.

The complex mucosal background of the stomach makes the diagnosis of GPLs and early GC (EGC) challenging[9]. The sensitivity of white light endoscopy in diagnosing GPLs is only 51%-74%[11,12]. Although new endoscopic technologies such as chromoendoscopy, narrow-band imaging, and magnifying endoscopy have shown certain advantages in identifying precancerous lesions in the stomach, advanced imaging techniques often require a certain level of expertise [13], and the diagnostic rate is limited by the endoscopist's experience. Unnecessary biopsies not only cause trauma to patients but also increase the workload of pathologists. Therefore, the ability of endoscopists to identify lesions and obtain accurate samples is crucial[14-17], though there is currently limited research regarding the relationships between different endoscopist biopsy rates (EBRs) and the qualifications of endoscopists and lesion detection.

In China, endoscopic assistants are essential collaborators during gastroscopy examinations. Endoscopic assistants are required not only to master fundamental theoretical knowledge and technical skills, but also to demonstrate proficiency in operating endoscopic instruments and critical thinking capabilities, enabling them to deliver holistic care and comprehensive emergency nursing interventions[18]. Globally, endoscopic assistants play a pivotal role in gastrointestinal endoscopic examinations. The adaptability and operational autonomy of endoscopic assistants significantly contribute to optimizing healthcare resource utilization efficiency. Their performance has been shown to achieve patient satisfaction levels comparable to those of physicians[19]. However, there is very little research on the correlation between the qualifications of endoscopy assistants and the positive lesion detection rate of endoscopists.

This study analyzed 5 years of gastroscopy data from our center to explore the relationships between EBR, endoscopist qualifications, and positive lesion detection rate. We further analyzed the relationship between endoscopic assistants with different qualifications and the positive lesion detection rate. These findings provide reliable clinical evidence for improving the positive rate of gastroscopic biopsies and the development of endoscopic quality control indicators.

MATERIALS AND METHODS

Ethics

This study was reviewed and approved by the Ethics Committee of Wuxi People's Hospital of Nanjing Medical University on July 17, 2023 (No. KY23001) and was conducted in strict accordance with the ethical principles of the Helsinki Declaration. This study has been registered in the Chinese Clinical Trial Registry with the registration number ChiCTR2400082985.

Inclusion criteria

This single-center retrospective cohort study included all patients who underwent gastroscopic and histopathological examinations of the cardia and stomach at Wuxi People's Hospital from January 2018 to April 2023. All the endoscopists involved in the study received specialized training in upper gastrointestinal endoscopy prior to performing gastroscopy and were capable of independently conducting gastroscopic examinations and making diagnoses. All the endoscopic assistants involved in the study received specialized training in nursing care for upper gastrointestinal endoscopy prior to assisting in gastroscopic procedures and were capable of independently assisting endoscopists in completing gastroscopic examinations. Both Olympus CV290 gastroscope machines and Olympus GIF-HQ290 gastroscopes were used in this study.

Exclusion criteria

The exclusion criteria for this study were as follows: (1) Age younger than 18 years; (2) Incomplete gastroscopy examination data; (3) Esophageal or duodenal biopsy; (4) Endoscopic treatment such as endoscopic submucosal dissection, endoscopic mucosal resection, or surgical operation; and (5) Endoscopic ultrasonography examination.

Patient information

The research data were obtained from the endoscopic workstation of our unit and included the following.

General information: Patient identification number, hospital registration number, sex, and age.

Gastroscopy information: Examination date, findings, diagnosis, endoscopist, and endoscopic assistant.

Pathological information: Pathological examination number, name of requesting endoscopist, name of pathological reviewing endoscopist, site and quantity of specimens submitted, gross findings of submitted specimens, microscopic findings of submitted specimens, and pathological diagnosis.

Pathological diagnosis, disease definition and grouping

All gastric biopsy pathologies were reviewed by two senior pathologists. In the case of a disagreement regarding the diagnosis, a third, more senior pathologist made the final diagnosis. Diagnoses were defined as follows.

NAG: An inflammatory reaction of the surface layer of the gastric mucosa, without accompanying mucosal atrophy or other epithelial lesions, that endoscopically manifests as redness or edema of the gastric mucosa[20].

AG: A disease characterized by a gradual reduction in and atrophy of the intrinsic glands of the gastric mucosa. Endoscopically, the gastric mucosa appears with a red and white alternating color, with white predominance. The gastric mucosa becomes thinner, with some mucosal blood vessels exposed, and the folds may become flat or disappear,

accompanied by mucosal granules or nodular manifestations[21].

IM: Pathological changes in which the gastric mucosal epithelial cells are replaced by intestinal-type epithelial cells[22] are classified as late changes in AG, "light blue crests" can be observed *via* high-definition staining and magnifying endoscopy[23], and metaplastic atrophy confirmed by pathology is a reliable indicator for diagnosing gastric mucosal atrophy[5].

Dys/IN: A key stage before the occurrence of GC, Dys/IN is characterized by cells of varying sizes and shapes, enlarged cell nuclei, increased nuclear-cytoplasmic ratio, and coarse chromatin. Endoscopically, it may present as densely packed glands, increasingly distorted structures, irregular microvascular patterns, and "acanthosis nigricans appearance"[5,24]. Dys includes low-grade Dys, moderate-grade Dys, and high-grade Dys. IN includes low-grade IN and high-grade IN.

GC: Malignant tumor originating from the epithelium of the gastric mucosa. The main pathological type is adenocarcinoma, where cancer cells can form gland-like structures of varying sizes, irregular shapes, and arrangements with varying degrees of nuclear atypia. It includes EGC limited to the mucosal layer and submucosal layer, as well as advanced GC that extends beyond the submucosal layer. Histologically, it can be classified into tubular adenocarcinoma, mucinous adenocarcinoma, poorly cohesive carcinoma, and other rare types[25].

Other tumors: Epithelial tumors and nonepithelial tumors. Epithelial tumors include lymphomas, and nonepithelial tumors include neuroendocrine tumors, stromal tumors, and smooth muscle tumors.

Research parameters and definitions

Total number of endoscopist examinations: The total number of gastroscopies completed by endoscopists from 2006 (endoscopy workstation data traceable to 2006) to April 2023.

Qualifications evaluation and grouping: Endoscopists are required to meet certain procedural thresholds to achieve specific objective skill criteria in order to obtain the qualification for independent endoscopic procedures[26-28]. The technical skills and experience of endoscopists often require extensive hands-on practice[28]. Previous studies have also used the number of endoscopic procedures performed to assess the qualifications of endoscopists[29-32]. For example, in Yuan *et al*'s study, performing over 7000 endoscopic procedures was considered high experience, while performing over 1000 procedures was considered low experience[29]. Januszewicz *et al*[33] reported using quartiles to grade the biopsy rates of endoscopists. Therefore, in this study, the number of procedures by endoscopists/assistants was chosen as the standard for assessing the qualifications of endoscopists/assistants, and the quartile method was used to categorize qualifications into four levels: Low-, moderate-, high-, and very high.

EBR: The proportion of gastroscopies in which endoscopists perform biopsies during gastroscopy.

EBR grouping: Endoscopists are divided into low-, moderate-, high-, and very high-EBR groups on the basis of the quartile distribution of the endoscopists' EBR values[33].

Positive lesions: Pathological diagnoses include AG, IM, Dys/IN, GC, and other tumor lesions.

Positive detection rate/positive biopsy rate: The proportion of patients with positive lesions among those who underwent biopsy to the total number of patients who were biopsied.

The negative biopsy rate: The number of cases in which pathological diagnosis did not detect AG/IM, Dys/IN, GC, or other tumors as a proportion of the total number of biopsy cases[33].

Detection rate of lesions in different areas: During gastroscopy, when biopsies are taken in different areas, such as the cardia, gastric fundus, gastric body, gastric angle, gastric antrum, and pylorus, the number of positive lesions detected is the proportion of the total number of biopsies in that area.

Statistical analysis

Baseline data are described using medians, interquartile ranges, and contingency tables in this study. The distributions of various pathological diagnoses and biopsy sites are depicted using percentage pie charts. The distribution of pathological diagnoses for each biopsy site is described using percentage stacked bar charts. The Shapiro-Wilk test was used for normality testing, followed by the Pearson correlation coefficient and Spearman correlation coefficient to measure the relationships between EBR, qualifications, and the detection rates of various lesions and negative biopsy rates. A multivariate logistic regression model was used to assess the association between the EBR group and GPCs and GPLs, adjusting for patient gender and age at diagnosis. The model included these variables as covariates to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), reflecting the independent relationship between the EBR group and the outcomes, while controlling for potential confounding effects of gender and age. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 27.0 software.

RESULTS

Research process diagram

This study included a total of 200910 patients who underwent gastroscopy at our center from January 2018 to April 2023. Among them, 903 patients (0.45%) were younger than 18 years old; 5485 patients (2.73%) had incomplete gastroscopy data; 23561 patients (11.73%) underwent endoscopic submucosal dissection, endoscopic mucosal resection, or surgical treatment; 4750 patients (2.36%) underwent endoscopic ultrasonography; and 2279 patients (1.13%) underwent biopsy histopathology of the esophagus and duodenum. Therefore, total of 36981 patients (18.41%) were excluded, and 169417 patients were included in the final analysis. Biopsy specimen from 45805 patients underwent histopathological examination. The study flowchart is shown in Figure 1.

Baseline data, biopsy pathological diagnosis, and distribution of lesion sites

The median (quartile) age of the patients was 55 (46, 64) years, with an age range of 18-95 years. The proportion of males was greater than that of females (males = 53.39%, females = 46.61%), and the largest population undergoing gastroscopy was the 50-69 years age group. There were 1696 male (3.7%) and 886 (1.93%) female patients with GPLs, and the number of male patients with GPLs was 1.9 times greater than the number of female patients. A total of 872 male (1.9%) and 386 female (0.84%) patients had GC, and the number of male patients with GC was 2.26 times greater than the number of female patients (Table 1). A total of 53584 biopsies were performed (Table 2), including 2135 in the Cardia (3.98%), 1730 in the gastric fundus (3.23%), 13599 in the gastric body (25.38%), 8583 in the gastric angle (16.02%), 27201 in the gastric antrum (50.76%), and 336 in the pylorus (0.63%). The highest number of biopsies was performed in the gastric antrum (Figure 2A). Pathology revealed that NAG accounted for 28607 cases (62.45%), AG accounted for 13274 cases (28.92%), GPLs accounted for 2582 cases (5.64%), GC accounted for 1258 cases (2.93%), and other tumor lesions accounted for 84 cases (0.18%) (Figure 2B). The detection rates of GC at each site were as follows: Cardia, 6.79%; pylorus, 3.57%; gastric angle, 3.39%; gastric body, 3.33%; gastric antrum, 1.57%; and gastric fundus, 1.16%, with the highest incidence in the cardia and the lowest incidence in the gastric fundus. The detection rates of GPLs at each site were as follows: Gastric angle, 9.04%; cardia, 6.28%; gastric antrum, 5.41%; pylorus, 4.17%; gastric body, 2.37%; and gastric fundus, 0.75%, with the highest incidence in the gastric angle and the lowest incidence in the gastric fundus. The detection rates of AG at each site were as follows: Gastric angle, 48.56%; pylorus, 31.25%; gastric antrum, 30.47%; cardia, 24.96%; gastric body, 13.63%; and gastric fundus, 1.73%, with the highest incidence in the gastric angle and the lowest incidence in the gastric fundus (Figure 2C).

Correlation between EBR and the detection rate of positive lesions

The total number of examinations performed by 37 endoscopists ranged from 1466 to 132205, with a median of 17985 examinations. According to the quartiles of the total number of examinations, the endoscopists were divided into groups as follows: Low-level experience group (1466-7379 examinations, 10 endoscopists), moderate-level experience group (7380-17985 examinations, 9 endoscopists), high-level experience group (17986-25385 examinations, 9 endoscopists), and very high-level experience group (25386-132205 examinations, 9 endoscopists). The negative biopsy rate of each endoscopist ranged from 40.50%-72.41%, with a median negative biopsy rate of 63.09%. The EBR values of the 37 endoscopists ranged from 13.94%-40.17%, with a median EBR value of 25.98%. According to the quartiles of EBR values, the endoscopists were grouped as follows: Low-EBR group (13.94%-23.44%, 10 endoscopists), moderate-EBR group (23.45%-25.98%, 9 endoscopists), high-EBR group (25.99%-31.39%, 9 endoscopists), and very high-EBR group (31.40%-40.17%, 9 endoscopists). Compared with those in the low-EBR group, the OR values for detecting positive lesions in the moderate-, high-, and very high-EBR groups were 1.12 (95%CI: 1.06-1.19, $P < 0.001$), 1.22 (95%CI: 1.14-1.31, $P < 0.001$), and 1.38 (95%CI: 1.29-1.47, $P < 0.001$), respectively, indicating that as the EBR increased, the detection rate of positive lesions also increased. Compared with those in the low-EBR group, the OR values for detecting GPCs in the moderate-, high-, and very high-EBR groups were 1.16 (95%CI: 1.09-1.24, $P < 0.001$), 1.28 (95%CI: 1.19-1.38, $P < 0.001$), and 1.48 (95%CI: 1.38-1.58, $P < 0.001$), respectively, indicating that as the EBR increased, the detection rate of GPCs also increased. In contrast, the OR values for detecting GPLs in the moderate-, high-, and very high-EBR groups were 0.98 (95%CI: 0.87-1.11, $P = 0.79$), 1.11 (95%CI: 0.96-1.27, $P = 0.159$), and 1.10 (95%CI: 0.97-1.25, $P = 0.138$), respectively, indicating no significant difference in the detection rate of GPLs as the EBR increased. The OR values for negative biopsies in the moderate-, high-, and very high-EBR groups were 0.89 (95%CI: 0.84-0.95, $P < 0.001$), 0.82 (95%CI: 0.76-0.88, $P < 0.001$), and 0.73 (95%CI: 0.68-0.77, $P < 0.001$), respectively, indicating that as the EBR increased, the negative biopsy rate decreased (Table 3).

We further analyzed the correlation between EBR and endoscopist qualifications. There was no statistically significant correlation between EBR and endoscopist qualifications ($\rho = 0.044$, $P = 0.796$), indicating that the EBR was similar among endoscopists with different qualifications (Figure 3A). Moreover, the EBR value was positively correlated with the GPC detection rate ($\rho = 0.465$, $P = 0.004$), though the correlation with the GPL detection rate was not statistically significant ($\rho = 0.141$, $P = 0.406$). In contrast, the EBR value was negatively correlated with the GC detection rate ($r = -0.728$, $P < 0.001$) and negative biopsy rate ($\rho = -0.389$, $P = 0.017$) (Figure 3B).

Correlation between endoscopist qualifications and the detection rate of positive lesions

According to the multivariable logistic regression analysis data, compared with those in the low-seniority endoscopist group, the OR values for detecting GPCs in the moderate-, high-, and very high-seniority endoscopist groups were 0.92 (95%CI: 0.84-1.00, $P = 0.059$), 1.03 (95%CI: 0.94-1.12, $P = 0.57$), and 0.98 (95%CI: 0.91-1.07, $P = 0.663$), respectively, indicating no significant difference in the detection rate of GPCs among endoscopists with different seniority levels. In

Table 1 Baseline data and proportions of pathological diagnoses by biopsy site, *n* (%)

	Gastroscopes	NAG, %	AG/IM, %	GPLs, %	GC, %	Other tumors, %
Total	45805 (100)	62.45	28.98	5.64	2.75	0.18
Age groups (median age, 55 years; range: 18-95 years)						
18-49 years	15005 (32.76)	25.13	6.38	0.94	0.28	0.03
50-69 years	25037 (54.66)	31.69	18.02	3.53	1.32	0.10
≥ 70 years	5763 (12.58)	5.64	4.58	1.17	1.15	0.05
Sex						
Male	24455 (53.39)	31.56	16.16	3.70	1.90	0.06
Female	21350 (46.61)	30.89	12.82	1.93	0.84	0.12

NAG: Nonatrophic gastritis; AG/IM: Atrophic gastritis/intestinal metaplasia; GPLs: Gastric precancerous lesions; GC: Gastric cancer.

Table 2 Distribution of diseases in different regions of the stomach, *n* (%)

	Total	NAG, %	AG/IM, %	GPLs, %	GC, %	Other tumors, %
Total	53584 (100)	64.22	27.94	5.09	2.71	0.17
Cardia	2135 (3.98)	2.47	0.99	0.25	0.27	0.00
Gastric body	13599 (25.38)	20.36	3.46	0.60	0.96	0.10
Antrum	27201 (50.76)	31.71	15.47	2.75	0.84	0.04
Angularis	8583 (16.02)	6.23	7.78	1.45	0.57	0.02
Fundus	1730 (3.23)	3.09	0.06	0.02	0.05	0.01
Pylorus	336 (0.63)	0.38	0.20	0.03	0.02	0.00

NAG: Nonatrophic gastritis; AG/IM: Atrophic gastritis/intestinal metaplasia; GPLs: Gastric precancerous lesions; GC: Gastric cancer.

contrast, the OR values for detecting GPLs in the moderate-, high-, and very high-seniority groups were 1.13 (95%CI: 0.98-1.31, P = 0.03), 1.20 (95%CI: 1.03-1.39, P = 0.003), and 1.32 (95%CI: 1.15-1.52, P < 0.001), respectively. The OR values for negative biopsies in the moderate-, high-, and very high-seniority groups were 1.04 (95%CI: 0.95-1.13, P = 0.387), 0.92 (95%CI: 0.85-1.00, P = 0.059), and 0.93 (95%CI: 0.86-1.00, P = 0.054), respectively (Table 4). Compared with low qualification level endoscopists, those with moderate, high, and very high qualification levels increased detection rates of precancerous lesions by 13% (OR = 1.13, 95%CI: 0.98-1.31), 20% (OR = 1.20, 95%CI: 1.03-1.39), and 32% (OR = 1.32, 95%CI: 1.15-1.52), respectively.

Correlation analysis revealed that the qualifications of endoscopists were positively correlated with the detection rate of GPLs (ρ = 0.448, P = 0.005), with no statistically significant correlation with the detection rate of GPCs (ρ = 0.288, P = 0.084) or GCs (ρ = -0.064, P = 0.709) or with the negative biopsy rate (ρ = -0.293, P = 0.079) (Figure 4A). The data above indicate that the greater the degree of seniority of the endoscopist, the higher the detection rate of GPLs.

We further analyzed the relationship between the qualifications of endoscopists and the detection rates of GPLs in different areas of the stomach. The results showed that the qualifications of endoscopists were positively correlated with the detection rates of GPLs in the cardia (ρ = 0.350, P = 0.034), angularis (ρ = 0.396, P = 0.015), and gastric body (ρ = 0.453, P = 0.005). However, no statistically significant correlation was found between the qualifications of endoscopists and the detection rates of GPLs in the antrum (ρ = 0.292, P = 0.079) (Figure 4B). Due to the very low biopsy rates in the fundus and pylorus, which were 3.23% and 0.63%, respectively, and the even fewer cases of GPLs positivity, no further correlation analysis was conducted for these sites in this study. These data indicate that the endoscopists qualifications were particularly correlated with the detection rates of GPLs in the cardia, angularis and gastric body.

Relationship between endoscopic assistant qualifications and gastroscopic detection by endoscopists with low- and moderate-level qualifications

An additional 752 cases lacking endoscopic assistant data were excluded from this analysis. A total of 45381 examinations were assisted by 32 endoscopic assistants (ranging from 445 to 45381 per assistant), with a median examination volume of 12264.5 examinations. The correlation analysis revealed that in gastroscopic examinations conducted by endoscopic assistants with different levels of qualification, the qualifications of endoscopic assistants were closely related to the detection rates of low- and moderate-quality endoscopists for GPLs (ρ = 0.427, P = 0.015). However, there was no statist-

Table 3 Relationship between endoscopist biopsy rate and positive/negative lesion detection, *n* (%)

Endoscopist	EBR	Gastroscopes	GPCs	GPLs	Negative biopsies	EBR group	OR for GPCs, 95%CI	OR for GPLs, 95%CI	OR for negative biopsies, 95%CI
1	13.94%	1466	19 (21.84)	0 (0)	63 (72.41)	Low EBR (13.94%-23.44%)	1.00, -	1.00, -	1.00, -
2	17.06%	1668	29 (23.58)	3 (2.44)	86 (69.92)				
3	18.95%	108865	527 (29.28)	136 (7.56)	1052 (58.44)				
4	21.23%	5268	118 (25.93)	22 (4.84)	303 (66.59)				
5	21.53%	32126	347 (24.47)	52 (3.67)	968 (68.27)				
6	21.96%	19484	238 (24.64)	52 (5.38)	645 (66.77)				
7	22.15%	16212	280 (23.08)	66 (5.44)	820 (67.6)				
8	22.30%	7349	139 (25.23)	37 (6.72)	357 (64.79)				
9	23.16%	35092	277 (21.9)	64 (5.06)	883 (69.8)				
10	23.44%	39896	487 (28.15)	113 (6.53)	1083 (62.6)				
11	23.48%	10006	267 (30.34)	37 (4.2)	551 (62.61)	Moderate EBR (23.45%-25.98%)	1.16, 1.09-1.24	0.95, 0.86-1.05	0.89, 0.84-0.94
12	23.67%	6820	189 (28.29)	31 (4.64)	429 (64.22)				
13	23.68%	16172	311 (23.52)	46 (3.48)	924 (69.89)				
14	23.72%	3992	103 (29.26)	15 (4.26)	222 (63.07)				
15	24.18%	18608	350 (29.79)	52 (4.43)	737 (62.72)				
16	24.42%	27558	415 (27.36)	103 (6.79)	957 (63.09)				
17	24.80%	9816	279 (31.89)	51 (5.83)	518 (59.2)				
18	24.96%	132205	1638 (27.42)	358 (5.99)	3717 (62.23)				
19	25.98%	27800	423 (29.27)	131 (9.07)	846 (58.55)				
20	26.35%	4666	171 (36.85)	24 (5.17)	255 (54.96)	High EBR (25.99%-31.39%)	1.28, 1.19-1.38	0.94, 0.84-1.05	0.82, 0.76-0.88
21	27.49%	5890	185 (29.55)	21 (3.35)	398 (63.58)				
22	28.15%	22349	409 (30.16)	61 (4.5)	855 (63.05)				
23	28.37%	17985	383 (27.81)	71 (5.16)	887 (64.42)				
24	28.90%	12956	412 (27.93)	86 (5.83)	947 (64.2)				
25	29.65%	18638	426 (30.45)	82 (5.86)	864 (61.76)				
26	30.16%	18413	292 (26.67)	50 (4.57)	732 (66.85)				

27	31.08%	19148	397 (33.5)	64 (5.4)	698 (58.9)				
28	31.39%	25385	379 (29.61)	57 (4.45)	829 (64.77)				
29	32.55%	18142	421 (43.49)	126 (13.02)	392 (40.5)	Very high EBR (31.40%-40.17%)	1.48, 1.38-1.58	0.9, 0.81-1	0.73, 0.68-0.77
30	32.58%	26041	460 (31.68)	65 (4.48)	888 (61.16)				
31	32.69%	7379	244 (28.91)	50 (5.92)	519 (61.49)				
32	33.09%	12300	418 (31.19)	74 (5.52)	812 (60.6)				
33	33.29%	35746	748 (36.65)	129 (6.32)	1121 (54.92)				
34	33.83%	8756	410 (33.61)	71 (5.82)	718 (58.85)				
35	34.89%	23507	488 (29.24)	81 (4.85)	1055 (63.21)				
36	35.98%	1642	72 (24.83)	5 (1.72)	207 (71.38)				
37	40.17%	12100	523 (27.32)	96 (5.02)	1269 (66.3)				

EBR: Endoscopist biopsy rate; GPCs: Gastric precancerous conditions; GPLs: Gastric precancerous lesions; OR: Odds ratio; CI: Confidence interval.

ically significant correlation with the negative biopsy rate of endoscopists (ρ = -0.306, P = 0.088), the detection rate of GPCs (ρ = 0.148, P = 0.419), or the detection rate of GC (ρ = 0.047, P = 0.799) (Figure 4C). In contrast, there was no correlation with the detection rate of GPCs (ρ = 0.187, P = 0.305), GPLs (ρ = 0.254, P = 0.161), GC (ρ = -0.169, P = 0.356), or the negative biopsy rate (ρ = 0.034, P = 0.855) of highly/very highly qualified endoscopists (data not shown). These findings indicate that high/very high-quality endoscopic assistants may increase the detection rate of GPLs by low- and moderate-quality endoscopists.

DISCUSSION

GPCs and GPLs are independent risk factors for GC, providing a potential pathological basis for GC[34]. A follow-up study in South Korea in 2017 involving 3714 patients diagnosed with AG for up to 6.9 years revealed that the incidence of GC progression in patients with mild, moderate, and severe AG was 1.6%, 5.2%, and 12.0%, respectively, with the presence of IM further increasing the risk of GC[35]. A meta-analysis in 2018 also revealed a greater risk of GC development in patients with IM[35]. The risks of progression to GC in patients with confirmed low-grade IN and high-grade IN are 2.8%-11.5% and 10%-68.8%, respectively[36-40]. Therefore, early identification and intervention of GPCs and GPLs are highly clinically important. Patients with GPCs and GPLs often lack specific symptoms, and gastroscopy combined with pathological biopsy is the gold standard for diagnosis. However, the correlation between histological changes and endoscopic findings in the diagnosis and monitoring of GPCs and GPLs is often poor, with the sensitivity of white light endoscopy in diagnosing AG being only 42%[41] and even lower at 24% for IM[42] and 51%-74% for GPLs[11, 12]. In addition, there is a certain degree of pathological improvement between the pathology results of endoscopic biopsy and those of endoscopic resection of GPLs[14-17]. Unnecessary biopsies not only increase patient trauma[43] and economic burden but also add to the workload of pathologists. Systematic training can significantly improve the ability of endoscopists to diagnose and grade lesions[44]. As endoscopists use discretion and subjectivity to decide whether and where to biopsy, their ability to identify lesions and accurately sample them is crucial for the accurate detection of lesions [14-17,45]. Therefore, understanding the relationships between the EBR and the experience of endoscopists; between EBR and the experience of endoscopists and the detection rate of positive lesions, and the role of endoscopist assistants in the detection rate of positive lesions by endoscopists is highly valuable for guiding rational biopsies and improving strategies for increasing the detection rate of positive lesions during gastroscopy.

This study revealed that AG accounted for the highest proportion (28.92%) of histopathological diagnoses. A cross-sectional survey in 2014 revealed that the pathological detection rate of AG was 25.8%[41], whereas a retrospective analysis in 2016 reported that the detection rate of CAG in patients over 35 years of age who underwent gastroscopy was 22.4%[46]. The detection rate of AG in this study was slightly higher than that in previous studies, which may be related to the increasing incidence of chronic gastritis in our country[46,47]. In addition, AG is more common in elderly individuals in different regions of the world, and its prevalence gradually increases with age[41]. In this study, the prevalence of AG in patients aged 18-49, 50-69, and ≥ 70 years was 19.47%, 32.98%, and 36.39%, respectively, showing a

Table 4 Relationship between endoscopists qualifications and positive/negative lesion detection, *n* (%)

Endoscopist	EBR	Gastroscopes	GPCs	GPLs	Negative biopsies	Qualification group	OR for GPCs, 95%CI	OR for GPLs, 95%CI	OR for negative biopsies, 95%CI
1	13.94%	1466	19 (21.84)	0 (0)	63 (72.41)	Low qualification (1466-7379)	1.00, -	1.00, -	1.00, -
36	35.98%	1642	72 (24.83)	5 (1.72)	207 (71.38)				
2	17.06%	1668	29 (23.58)	3 (2.44)	86 (69.92)				
14	23.72%	3992	103 (29.26)	15 (4.26)	222 (63.07)				
20	26.35%	4666	171 (36.85)	24 (5.17)	255 (54.96)				
4	21.23%	5268	118 (25.93)	22 (4.84)	303 (66.59)				
21	27.49%	5890	185 (29.55)	21 (3.35)	398 (63.58)				
12	23.67%	6820	189 (28.29)	31 (4.64)	429 (64.22)				
8	22.30%	7349	139 (25.23)	37 (6.72)	357 (64.79)				
31	32.69%	7379	244 (28.91)	50 (5.92)	519 (61.49)				
34	33.83%	8756	410 (33.61)	71 (5.82)	718 (58.85)	Moderate qualification (7380-17985)	0.92, 0.84-1	1.13, 0.98-1.31	1.04, 0.95-1.13
17	24.80%	9816	279 (31.89)	51 (5.83)	518 (59.2)				
11	23.48%	10006	267 (30.34)	37 (4.2)	551 (62.61)				
37	40.17%	12100	523 (27.32)	96 (5.02)	1269 (66.3)				
32	33.09%	12300	418 (31.19)	74 (5.52)	812 (60.6)				
24	28.90%	12956	412 (27.93)	86 (5.83)	947 (64.2)				
13	23.68%	16172	311 (23.52)	46 (3.48)	924 (69.89)				
7	22.15%	16212	280 (23.08)	66 (5.44)	820 (67.6)				
23	28.37%	17985	383 (27.81)	71 (5.16)	887 (64.42)				
29	32.55%	18142	421 (43.49)	126 (13.02)	392 (40.5)	High qualification (17986-25385)	1.03, 0.94-1.12	1.20, 1.03-1.39	0.92, 0.85-1.00
26	30.16%	18413	292 (26.67)	50 (4.57)	732 (66.85)				
15	24.18%	18608	350 (29.79)	52 (4.43)	737 (62.72)				
25	29.65%	18638	426 (30.45)	82 (5.86)	864 (61.76)				
27	31.08%	19148	397 (33.5)	64 (5.4)	698 (58.9)				
6	21.96%	19484	238 (24.64)	52 (5.38)	645 (66.77)				
22	28.15%	22349	409 (30.16)	61 (4.5)	855 (63.05)				

35	34.89%	23507	488 (29.24)	81 (4.85)	1055 (63.21)				
28	31.39%	25385	379 (29.61)	57 (4.45)	829 (64.77)				
30	32.58%	26041	460 (31.68)	65 (4.48)	888 (61.16)	Very high qualification (25386-132205)	0.98, 0.91-1.07	1.32, 1.15-1.52	0.93, 0.86-1.00
16	24.42%	27558	415 (27.36)	103 (6.79)	957 (63.09)				
19	25.98%	27800	423 (29.27)	131 (9.07)	846 (58.55)				
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3	18.95%	108865	527 (29.28)	136 (7.56)	1052 (58.44)				
18	24.96%	132205	1638 (27.42)	358 (5.99)	3717 (62.23)				

EBR: Endoscopist biopsy rate; GPCs: Gastric precancerous conditions; GPLs: Gastric precancerous lesions; OR: Odds ratio; CI: Confidence interval.

clear trend of increasing with age. The detection rate of GC was 2.26 times greater and that of GPLs was 1.9 times greater in males than in females. These findings are consistent with the results of several previous studies that revealed that the incidence of GC in males is 2-2.7 times greater than that in females[41,48,49].

Lesions associated with gastric mucosal atrophy are often located in the gastric antrum or corpus[5], with the corpus and antrum being common sites for GC. A consensus[5,47,50] on the biopsy strategy for gastric mucosal lesions recommends biopsies at the antrum, corpus, and angle of the stomach to ensure a comprehensive evaluation of the gastric mucosa. In the present study, most of the biopsies were obtained from the gastric antrum (50.76%), corpus (25.38%), and angle (16.02%), accounting for 92.16% of all biopsy sites. In terms of the detection rate of GC at different biopsy sites, the corpus (453 biopsies, 0.85%) and antrum (426 biopsies, 0.80%) had the highest rates; in terms of the detection rate of GPLs, the angle (1472 biopsies, 2.75%) had the highest rate; and in terms of the detection rate of GC, the cardia region had the highest rate (6.79%). Despite recommended biopsy strategies, the selection of biopsy sites in clinical practice may be influenced by several factors, including the experience of the endoscopist and the visual assessment of lesions. Therefore, there are significant differences in biopsy site proportions, emphasizing the importance of standardizing biopsy strategies to ensure that all patients are treated using a standardized diagnostic process. A study of patients with GC who were treated within 25 years revealed that the cardia was the second most common site for GC after the antrum, with an increasing trend in the incidence of cardia cancer[51]. This study also revealed that, compared with other gastric regions, the cardia had the highest detection rate of GC. Therefore, even though the cardia is not a primary biopsy site recommended by consensus, it should be emphasized in observation and biopsy during gastroscopy procedures.

Upper gastrointestinal endoscopy, the earliest digestive endoscopy technique that is used clinically, plays an essential role in tumor screening and GPL follow-up. This approach is highly important for ensuring the quality control of upper gastrointestinal endoscopy. In recent years, quality control indicators for upper gastrointestinal endoscopy examinations have received widespread attention. However, unlike colonoscopy, which has multiple established quality control indicators, high-quality validation of quality control indicators for upper gastrointestinal endoscopy remains lacking. EBR, as an important indicator in the quality assessment system for upper gastrointestinal endoscopy, has been the subject of several studies examining its relationship with the detection rates of GC and precancerous lesions. A multicenter study found that EBR is closely related to the detection rates of CAG, IM, and Dys, and it can reduce the rate of missed diagnoses[33]. Another study also demonstrated a close correlation between EBR and the detection rate of GC [52]. Furthermore, the expertise of endoscopists serves as another pivotal factor in ensuring the quality of upper gastrointestinal endoscopic examinations. Experienced endoscopists are capable of executing essential procedural steps during gastroscopy, including comprehensive mucosal visualization, precise lesion identification, and appropriate biopsy sampling. Such proficiency enables them to conduct higher-quality examinations, thereby effectively minimizing the occurrence of missed lesions[53-55]. In this study, the overall EBR at our center was 26.68%, with significant differences between the EBR achieved by different endoscopists, ranging from 13.94%-40.17%. A retrospective study conducted in Japan in 1998 reported an average gastric EBR of 55%[56]; a study conducted in South Korea in 2017 reported that the EBR among endoscopists ranged from 6.9%-27.8%[52]; and a multicenter study conducted in Poland in 2019 reported significant differences in EBR among different endoscopists in two high-volume outpatient centers (22.4%-65.8%)[33]. A

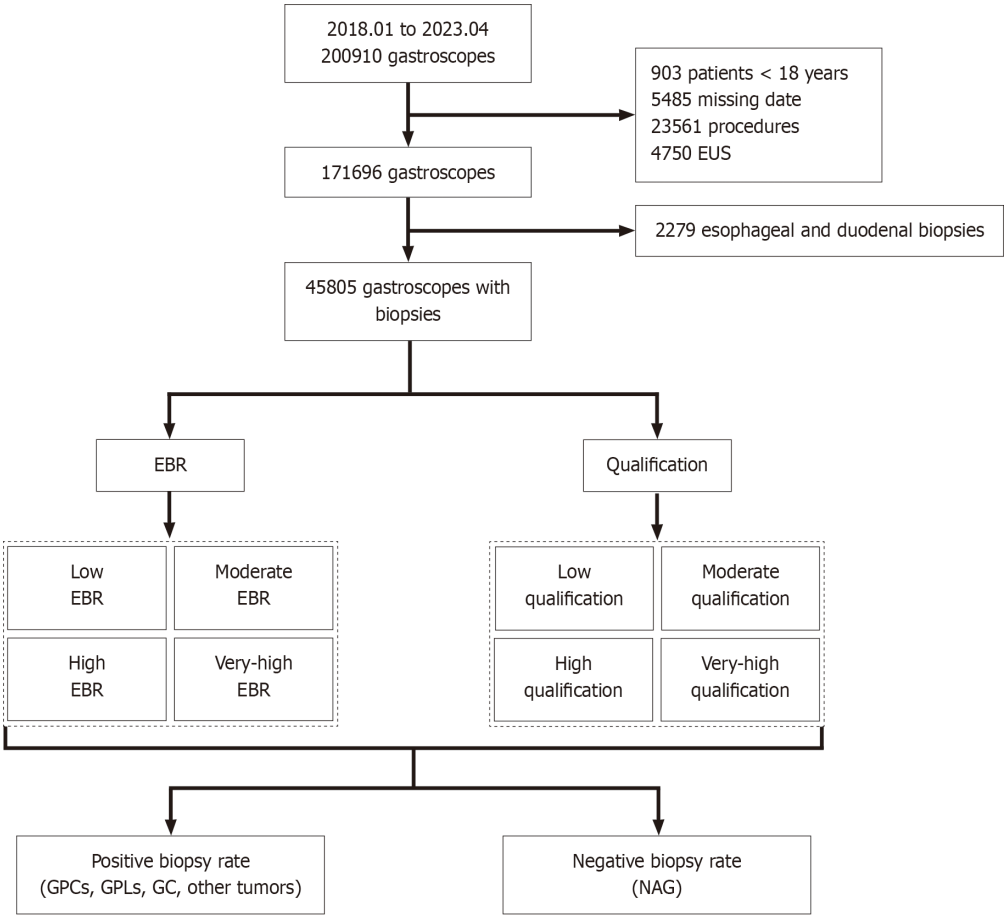

Figure 1 Study population flowchart. A total of 200910 patients underwent gastroscopy at our center from January 2018 to April 2023 Among them, 903 patients were younger than 18 years old; 5485 patients had incomplete gastroscopy data; 23561 patients underwent endoscopic submucosal dissection, endoscopic mucosal resection, or surgical treatment; 4750 patients underwent endoscopic ultrasonography; and 2279 patients underwent biopsy histopathology of the esophagus and duodenum. Exclusion criteria and reasons: (1) This study focuses on adult patients, so individuals under 18 years old were excluded; (2) To ensure the completeness and reliability of the data for analysis, patients with incomplete gastroscopy examination data were excluded; (3) This study only focuses on gastric biopsy-related issues, so esophageal or duodenal biopsies were excluded; (4) Gastroscopic treatments such as endoscopic submucosal dissection, endoscopic mucosal resection, or gastric surgery were excluded, as these procedures may alter the normal anatomical structure of the stomach and affect the data analysis; and (5) Endoscopic ultrasonography was excluded to avoid introducing additional variables that could interfere with the study's findings. A total of 36981 patients were excluded, and 169417 patients were included in the analysis. The biopsy specimen of 45805 patients underwent histopathological examination. EUS: Endoscopic ultrasonography; EBR: Endoscopist biopsy rate; GPCs: Gastric precancerous conditions; GPLs: Gastric precancerous lesions; GC: Gastric cancer; NAG: Nonatrophic gastritis.

study evaluating the quality of upper gastrointestinal endoscopy nationwide in Italy in 2023 reported that only 32.7% of included patients did not undergo biopsy, and 50.5% of patients had adequate biopsy sampling (at least two biopsy samples from both the gastric antrum and corpus)[57]. Therefore, there are certain differences in the EBR among endoscopists in different countries, which may be related to the incidence of diseases, endoscopists' understanding of diseases, and differences in gastroscopy techniques. In reports from Japan, Poland, and Italy, patients are mostly referred to or evaluated by general practitioners for upper gastrointestinal symptoms, unlike the asymptomatic screening population in South Korea; therefore, the EBR may be greater. The study population in our cohort mainly consisted of patients in outpatient/inpatient settings who required evaluation of upper gastrointestinal symptoms with a subset of the population undergoing asymptomatic screening; therefore, the overall EBR includes the EBR for asymptomatic screening and the EBR for the evaluation of upper gastrointestinal symptoms. Gastroscopy, an examination that is dependent on the operator's ability, results in significant differences in examination quality among different operators. Only endoscopists who have undergone proper training and possess relevant capabilities can independently perform upper gastrointestinal endoscopy[58,59].

A previous study reported a significant correlation between EBR and the tumor detection rate (R^2 = 0.76; P = 0.0015)[52]. A multicenter study in 2019 revealed the importance of EBR for diagnosing GPCs and GPLs, especially with a significant correlation with the total detection rates of AG, IM, and GPLs (ρ = 0.83, P < 0.001), and that endoscopists with a higher EBR have a lower risk of missing cancer during gastroscopy[33]. This study revealed a positive correlation between EBR and the detection rate of positive lesions. Further analysis revealed that EBR was positively correlated with only the detection rate of GPCs, whereas the correlation with the detection rate of GPLs was not statistically significant. This may be related to the higher prevalence of GPCs in our study population. However, biopsies are more important for detecting and diagnosing GPLs and GC. Therefore, clinicians should not only emphasize EBR but also focus on the

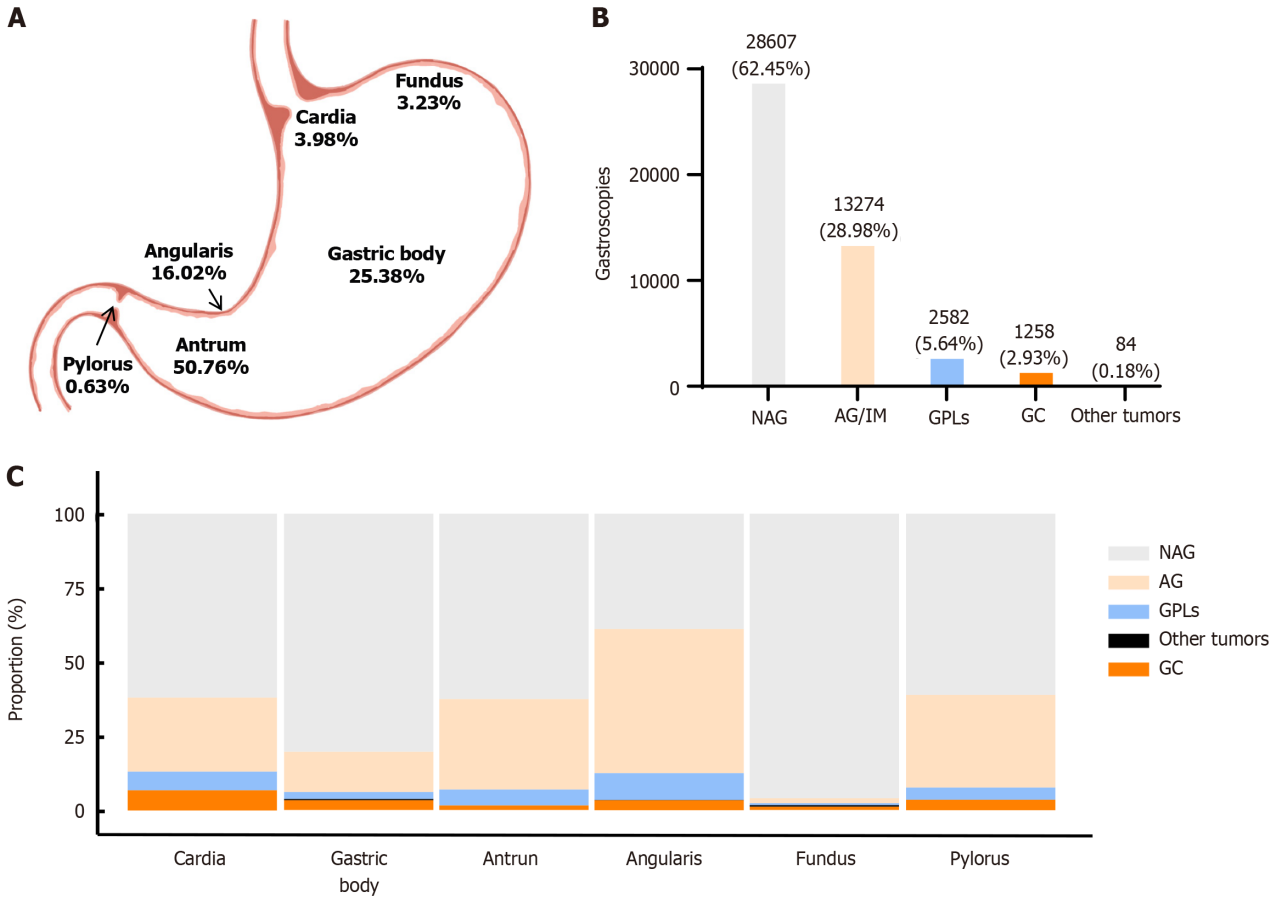

Figure 2 Proportion of biopsies from different sites and distribution of gastric diseases. A: The proportions of biopsies from different sites are shown; B: The proportions of different diseases are shown. The horizontal axis represents different diseases, and the vertical axis represents different proportions (%); C: The proportions of different diseases in different regions of the stomach are shown. The horizontal axis represents different regions of the stomach, and the vertical axis represents different proportions (%). NAG: Nonatrophic gastritis; AG/IM: Atrophic gastritis/intestinal metaplasia; GPLs: Gastric precancerous lesions; GC: Gastric cancer.

experience of the endoscopist for identifying high-risk lesions and optimizing EBR to perform rational biopsies that improve the detection rate of GPLs and GC. We also observed a negative correlation between EBR and the rate of negative biopsies, indicating that an increase in EBR may reduce the rate of negative biopsies and the risk of missed diagnoses. These results indicate that EBR is a parameter worthy of attention in gastroscopy and that clinicians should not emphasize only EBR. However, further research is needed to determine the optimal EBR practice standards to improve the detection rate of GPLs and GC.

The qualifications of endoscopists are often evaluated on the basis of whether they have reached specific standards in terms of the number of upper gastrointestinal endoscopies or various surgical procedures performed. In addition, key performance indicators, such as the adenoma detection rate in colonoscopy and the selective duct cannulation rate in endoscopic retrograde cholangiopancreatography, are also important supplementary measures of evaluation. These assessment methods have been widely recognized and applied both domestically and internationally[58]. The present study also adopted this method and used the total number of examinations completed by endoscopists as the basis for assessing endoscopist qualifications. In this study, there were differences in the qualifications of gastroscopy endoscopists, and further analysis revealed that there was a positive correlation between the qualifications of gastroscopy endoscopists and the detection rate of GPLs. Therefore, the importance of gastroscopy endoscopists' qualifications is evident. When performing gastroscopy, the endoscopist must possess a high level of professional skill to evaluate lesions comprehensively and perform accurate biopsies. This requires endoscopists to enhance their practice and accumulate rich diagnostic experience to address complex gastric mucosal backgrounds.

In this study, we also studied the relationship between the endoscopists' qualifications and the detection rates of GPLs in different anatomical areas of the stomach. It was found that the detection rates of GPLs in the cardia, angularis, and gastric body, but not the antrum were positively correlated with the qualifications of endoscopists. Considering that the antrum is relatively easy to observe during gastroscopy and is one of the biopsy sites recommended by several consensus [5,47,50], the likelihood of detecting diseases in this area is relatively higher. Endoscopists with different levels of experience are able to identify suspicious lesions in the antrum and perform biopsies or routine screening biopsies. Compared to the antrum, the cardia is located at the junction of the esophagus and the stomach, a position that is relatively deep and has a complex angle. The upper part of the stomach, especially the anterior and posterior walls of the cardia, may be obscured by structures of the esophagus and other areas of the stomach, making it difficult to accurately

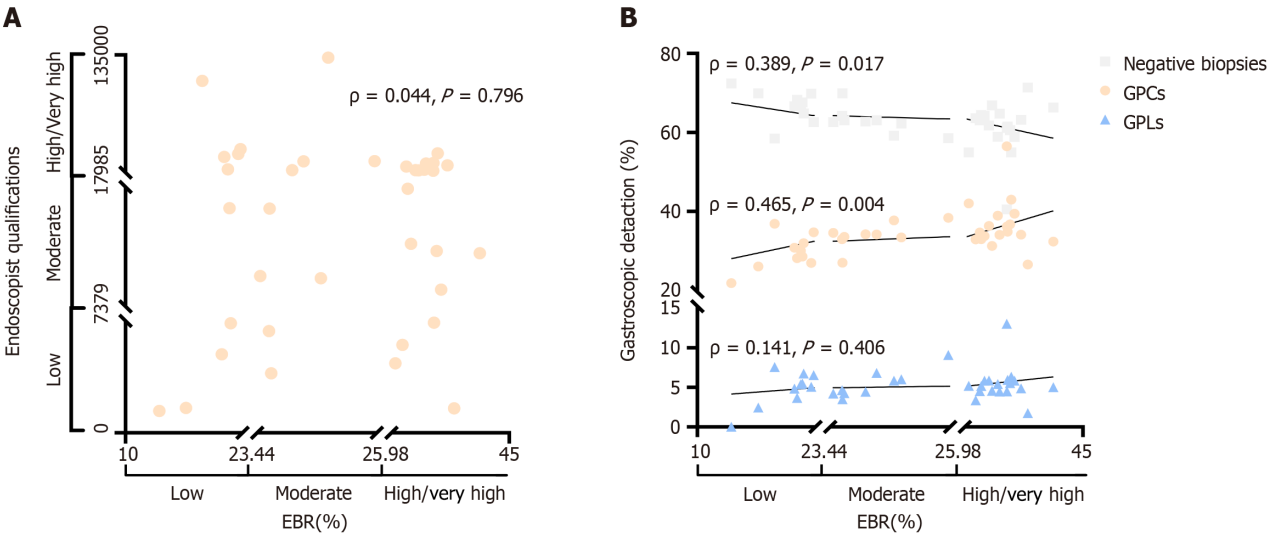

Figure 3 Relationships between endoscopist biopsy rate, endoscopist qualifications and endoscopic detection. A: The relationship between endoscopist biopsy rate (EBR) and endoscopist qualifications is shown. The horizontal axis represents different groups of EBR (low, moderate, high/very high), and the vertical axis represents different groups of endoscopist qualifications (low, moderate, high/very high); B: The relationship between EBR and the positive detection rate is shown. The horizontal axis represents different EBR groups (low, moderate, high/very high), and the vertical axis represents endoscopic detection rates for different diseases (%). *ρ*: Spearman's correlation coefficient. $P < 0.05$ indicates statistical significance. EBR: Endoscopist biopsy rate; GPCs: Gastric precancerous conditions; GPLs: Gastric precancerous lesions.

locate and observe during endoscopic procedures[60]. In addition, observation of the cardia is also influenced by factors such as the filling status of the stomach, the physiological function of the cardia area, and patient discomfort[61,62]. Therefore, when performing biopsies for GPLs in these areas, there is a greater reliance on the endoscopist's recognition of the lesions and their ability to accurately sample. These findings still require validation through more cases or multicenter data.

Studies have shown that there are no significant differences in clinical outcomes, examination costs, or complications between endoscopic assistants who have received systematic training and doctors performing endoscopy[63]. This finding highlights the importance of endoscopic assistants in gastroscopic examinations. As essential assistants in endoscopic examinations, the appropriate combination of endoscopic assistants with different qualifications and endoscopists may have a positive impact on the smooth progress of examinations and the detection rate of lesions. This study revealed that the ability of endoscopic assistants was positively correlated with the detection rate of GPLs by low- and mid-level endoscopists, indicating that the use of highly qualified endoscopic assistants can increase the detection rate of GPLs by endoscopists with low- and mid-level experience. This finding highlights the importance of the professional competence and experience of endoscopic assistants in improving the quality of diagnosis and treatment in medical teams. Highly qualified endoscopic assistants typically accumulate clinical knowledge and skills over time, enabling them to more effectively assist endoscopists with low- and mid-level experience when performing precise endoscopic operations to increase the detection rate of lesions.

This study revealed that the detection rate of EBR was negatively correlated with that of GC. The analysis revealed that advanced GC typically presents as obvious masses or ulcers, making it easier to identify and diagnose than GPLs and EGC. A higher EBR may indicate increased detection of NAG, GA or IM, which leads to a reduced relative detection rate of GC. With accumulated experience, endoscopists have gained more accurate lesion recognition skills, suggesting that endoscopists may reduce unnecessary biopsies by more accurately identifying easily recognizable lesions, leading to a decrease in the demand for EBR in these lesions while maintaining the detection rate. Therefore, as the identification of advanced GC is relatively intuitive, endoscopists may not need to rely on a higher EBR to improve the detection rate. A previous study revealed that after systematic training, endoscopists can significantly improve the detection rate of GC [64]. The endoscopists at this center had performed endoscopy for at least 1 year prior to the start of the study, with a median number of 7379 gastroscopies per endoscopist. These data indicate that the endoscopists included in this study received adequate training and may have sufficient recognition skills for advanced GC, resulting in no significant difference in the detection rates of GC among endoscopists with different qualifications.

In summary, gastric endoscopy, it is important to perform biopsies after improving the understanding of GPLs and GC rather than solely emphasizing EBR. Endoscopists with higher qualifications are more likely to identify GPLs; therefore, it is crucial to enhance the training and practical training of endoscopists in clinical practice. Furthermore, to improve the quality of gastroscopy examinations, medical institutions should also focus on the professional development and continuing education of endoscopic assistants to increase their professional skills and work efficiency. It is also important to consider the rational allocation of endoscopic assistants with different qualifications in endoscopy work to maximize the effectiveness of gastroscopy examinations and provide every patient with high-quality care and examination services.

This study has several limitations. First, as a single-center retrospective study, our findings may be limited by the specific medical environment and patient characteristics. Additionally, as our data do not include biopsy information from the esophagus or duodenum, our conclusions can only reflect the observations of patients who underwent gastric

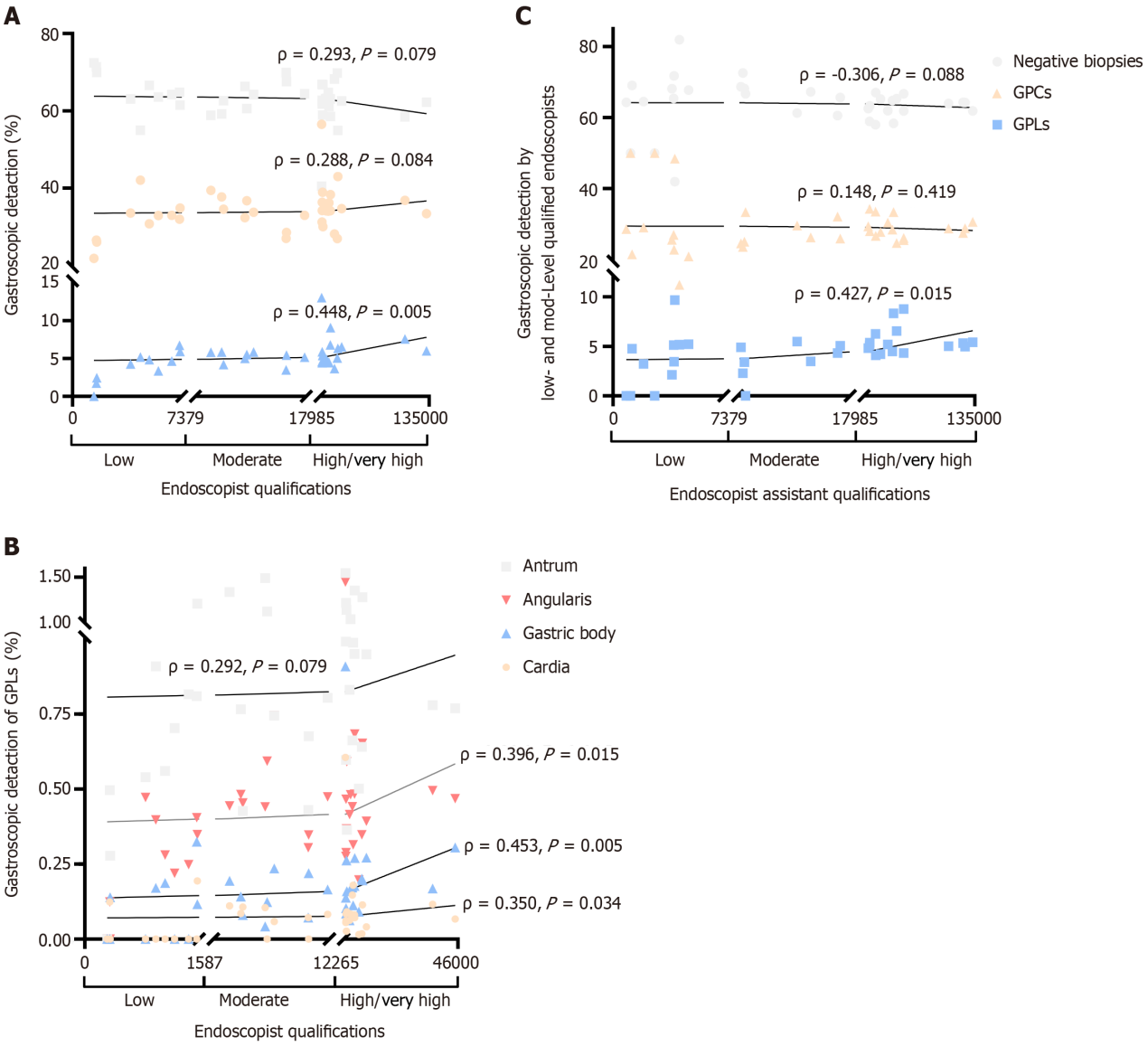

Figure 4 Relationships between endoscopists' and endoscopic assistants' qualifications and endoscopic detection. A: The relationship between endoscopist qualifications and endoscopic detection is shown. The horizontal axis represents different qualifications of the endoscopist (low, moderate, high/very high), and the vertical axis represents endoscopic detection rate of different diseases; B: The relationship between the endoscopists' qualifications and the detection rates of gastric precancerous lesions in different anatomical areas of the stomach is shown. The horizontal axis represents different qualifications of the endoscopist (low, moderate, high/very high), and the vertical axis represents gastroscopic detection rate of gastric precancerous lesions; C: The relationship between endoscopic assistant qualifications and endoscopic detection is shown. The horizontal axis represents different qualifications of the endoscopist (low, moderate, high/very high), and the vertical axis represents gastroscopic detection by low- and moderate-level qualified endoscopists. *ρ*: Spearman's correlation coefficient. $P < 0.05$ indicates statistical significance. GPCs: Gastric precancerous conditions; GPLs: Gastric precancerous lesions.

biopsies at our center during the study period and may not represent the actual situation of upper gastrointestinal endoscopy in the entire region. In terms of endoscopy usage, differences in the endoscopic techniques used by different endoscopists (such as narrow band imaging or magnifying endoscopy) may indirectly affect the endoscopists' careful observation of the mucosa and decisions regarding biopsies. We found it difficult to fully consider the impact of this variable in our study. *Helicobacter pylori* (*H. pylori*) infection is closely associated with the occurrence of GC and can affect the metastasis of GC cells and the clinical prognosis of patients[65]. After *H. pylori* infection, the gastric mucosa typically exhibits characteristics such as thick mucus attachment, diffuse or punctate redness, mucosal swelling, and enlarged folds with a serpentine appearance[66]. After *H. pylori* eradication, the gastric mucosa may display a gastritis-like appearance [67]. These endoscopic features can influence the endoscopist's ability to recognize and assess EGC. Therefore, *H. pylori* infection should also be considered a factor affecting endoscopic quality control and should be included in related studies. As this study is retrospective, the data on *H. pylori* infection were incomplete, and therefore this factor was not included in the data analysis. Future prospective studies could be designed for more in-depth research on this topic. In addition to the EBR and endoscopist qualifications, the duration of endoscopic procedures has also been identified as a crucial quality metric for esophagogastroduodenoscopy[68]. However, our research data lack records of examination time, which may reflect the thoroughness of endoscopists in mucosal examination, thus affecting the detection of lesions and the selection of biopsies. Therefore, we could not evaluate the potential impact of examination time on the biopsy rate

or lesion detection rate. Our study population included patients with upper gastrointestinal symptoms and asymptomatic screening populations. This diversity makes it difficult for us to determine whether endoscopists are adopting targeted biopsies or multipoint random biopsies when performing biopsies, therefore, we could assess the impact of different biopsy strategies on outcomes. Finally, similar to studies on other endoscopic quality control indicators, endoscopists may manipulate the results by adjusting the number of biopsies or modifying gastric endoscopy reports, and the potential bias caused by this behavior[33,69] is beyond our control. Subsequent studies should focus on improving the quality of endoscopic workstation data and adopting prospective designs while recruiting researchers from multiple centers to increase the representativeness and generalizability of the study so that our findings can be extended to a wider range of regions and patient populations. Patient-derived xenograft (PDX) models have been widely used, and some studies have utilized PDX models to investigate the effects of different formulations of anesthetic drugs on breast cancer metastasis[70]. In future research, we can use PDX animal models to validate our findings. In addition, the number of patients with missed diagnoses of GC in our study cohort was small; therefore, we did not include relevant analyses in this study, though we will conduct further research in future studies. Additionally, due to the low number of patients with GC, we did not further investigate missed diagnoses. Furthermore, the proportion of other tumors was also very low; therefore, we did not conduct any related further analysis.

CONCLUSION

In summary, this study revealed that the detection rate of GPLs is positively correlated with endoscopist qualifications. The detection rate of GPLs by endoscopists with low to moderate qualifications is lower, but the cooperation of highly-qualified endoscopic assistants can improve the detection rate. Future research should focus on establishing and validating quality control standards for upper gastrointestinal endoscopy. In addition, exploring optimal EBR practices for different patient populations with varying GC risk factors to ensure the specificity and efficiency of biopsies and further increase the detection rates of GPLs and EGCs.

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FOOTNOTES

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ORIGINAL ARTICLE

Randomized Clinical Trial

Prospective randomized study comparing Franseen 22-gauge *vs* standard 22-gauge needle for endoscopic ultrasound guided sampling of pancreatic solid lesions

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Abstract

BACKGROUND

This is a randomized study to compare the diagnostic accuracy of endoscopic ultrasound (EUS)-guided sampling of pancreatic solid lesions obtained with the 22-gauge Franseen (EUS-fine needle biopsy) *vs* the 22-gauge standard needle (EUS-fine needle aspiration) without rapid onsite evaluation (ROSE), since, in most endoscopy units around the world ROSE is not routinely available.

AIM

To investigate the accuracy of EUS-guided sampling of pancreatic solid lesions obtained between two different needles without ROSE.

METHODS

Patients with a solid pancreatic were included. Patients were biopsied in a randomized order. The primary endpoint was the diagnostic sensitivity for pancreatic malignancy (PM). Secondary outcomes were adequacy of the sample, the mean tissue area, the mean tumor area, and the adverse event rate.

RESULTS

The final diagnosis was pancreatic adenocarcinoma in 38 (76%), neuroendocrine tumor in 4 (8%), chronic pancreatitis in 3 (6%) patients. The sensitivity for PM with Franseen needle was 0.91 [95% confidence interval (CI): 0.80-0.98], *vs* 0.8 (95%CI: 0.67-0.91) (P = 0.025) with standard needle. The specificity for PM did not differentiate. The accuracy of the standard needle for PM was 0.80 (95%CI: 0.66-

0.90), and the Franseen group was 0.90 (95%CI: 0.78-0.97) (P = 0.074). The technical success rates for the standard and Franseen needle groups were 94% (95%CI: 0.83-0.99) and 100% (95%CI: 0.92-1.00), respectively. The mean total tissue area in mm² (SD) was greater in the Franseen group, 2.07 (0.22) *vs* 1.16 (0.17) (P < 0.01). The mean tumor area in mm² (SD) was not different in Franseen group *vs* standard group, 0.42 (0.09) *vs* 0.47 (0.09) (P = 0.80). There were no adverse events.

CONCLUSION

The sensitivity for PM and mean total tissue area, was greater in the as compared with standard needle. The mean tumor area did not differ between the groups.

Key Words: Franseen needle; Standard needle; Endoscopic ultrasound; Pancreatic solid lesions; Rapid onsite evaluation

Core Tip: The main of the study was based in assess the sensitivity of endoscopic ultrasound needles for diagnosing pancreatic malignancy. We found that the diagnostic sensitivity for pancreatic malignancy as well as the mean total tissue area collected was greater with the Franseen needle group compared with the standard needle group. Taking into account, the procedure was done in the absence of an onsite site pathologist for evaluation of the sample collected, bringing important contribution to institutions that do not have pathologist in the examination room.

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INTRODUCTION

Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) was initially introduced in the early 1990s and was quickly recognized as the most efficient technique for sampling pancreatic lesions[1].

The use of 22-gauge and 25-gauge needles for solid pancreatic lesions has a sensitivity ranging from 64% to 95%, a specificity ranging from 75% to 100%, and a diagnostic accuracy ranging from 78% to 95%[2,3].

Several strategies have been used to enhance the diagnostic yield of EUS-FNA, such as larger gauge needles[4], rapid onsite evaluation (ROSE)[5], implementation of suction[6], slow withdrawal of the stylet[7], wet suction[8], macroscopic onsite assessment of the material (MOSE)[9], and even the detection of *KRAS* mutation in the aspirate[10].

The ROSE involves the immediate analysis of the material by the cytopathologist or a cyto technician to guarantee the quality of the aspirated material and even perform a preliminary diagnosis. There is evidence that evaluation at the puncture site by the pathologist increases the diagnostic yield[11], particularly in difficult cases such as lymphoma and association of malignancy with chronic pancreatitis. In a study with 230 patients, the investigators concluded that, in the absence of ROSE, the probability of inconclusive results increased by more than twice (P = 0.03) and by 3 times the number of inappropriate samples for evaluation in block (P < 0.001)[12]. However, availability, logistics, and costs are relevant limitations for the implementation of ROSE in EUS-FNA routine.

Recently, the Franseen needle was designed to obtain samples that allow histological rather than cytological analysis. The puncture performed with these needles has been called endoscopic ultrasound-guided fine needle biopsy (EUS-FNB). The Franseen needle features a crown tip, with three symmetrical surfaces that exhibit three cutting edges. This geometry contributes to a long insertion length and crown tip area that aids better tissue acquisition.

In a pilot study with 30 patients, in which EUS-FNB samples were obtained from pancreatic lesions or other solid masses using Franseen needles, adequate samples with diagnostic capacity were confirmed onsite by the pathologist in 96% of patients, with histological diagnoses by cell block in 96.6% of patients[13]. It is possible that the triple cutting edge could provide more tissue volume than the standard 22-gauge needle.

Some randomized clinical trials (RCT) studies have compared 22-gauge FNB and standard needles for solid pancreatic lesions[14-18]. In the majority of them, ROSE was available.

The objective of this study was to compare the diagnostic accuracy of Franseen 22-gauge needle *vs* standard 22-gauge needle for EUS-guided sampling of pancreatic solid lesions without ROSE. In most endoscopy units around the world ROSE is not routinely available.

MATERIALS AND METHODS

This was a randomized study conducted at the Instituto do Cancer do Estado de Sao Paulo between December 2019 and January 2023 (registration number at clinicaltrials.gov: NCT04877340). The study protocol was approved by the institutional review board (No. 26962419.3.0000.0065).

Patients with suspected solid pancreatic lesions larger than 15 mm, identified by tomography or magnetic resonance imaging, referred for EUS-guided sampling were eligible for inclusion. Patients willing to participate provided a written informed consent. Patients were submitted to a minimum of two passes with the standard needle and two passes with the Franseen needle. The order of the use of the needles was randomized using permutation blocks.

A function was created with MS Excel, with randomization between blocks of 6, 8, and 10, generating a sequential list of 50 numbers, between 1 and 2 (each number representing a needle type). Randomization process used sealed and sequentially numbered envelopes. Patients were excluded if they had cystic lesions or abnormal coagulation parameters (international normalized ratio > 1.5, platelet count < 50000 cells/mm^3).

The primary endpoint was the diagnostic accuracy for the pancreatic malignancy (PM) (pancreatic adenocarcinoma, neuroendocrine tumor, metastatic lesion). Secondary endpoints were adequacy of the sample (technical success rate), the mean tissue area, the mean tumor area, and the adverse event rate.

Pancreatitis (defined as abdominal pain associated with a 3× elevation of serum amylase or lipase), and bleeding (defined as haematemesis or melaena requiring blood transfusion or endoscopic or radiological intervention), occurring within the first 7 days after the endoscopic procedure were considered as adverse events. In the period of 7 days after the procedure, the patients were contacted by phone call in order to evaluate any related adverse event.

Technique

The procedures were performed using a linear echoendoscope (UCT180; Olympus America Corp, Centre Valley, Pa), in propofol-sedated patients, positioned in left lateral decubitus.

The pancreatic mass was firstly punctured with a needle determined by randomization, followed by the other needle in the sequence. Four endoscopists, all with more than 1500 echoendoscopy exams, and fellows under their supervision performed the procedures.

With the first randomized needle, we performed two passes-the first with a slow pull and the second with a 20cc syringe aspiration. Each pass had at least 20 back-and-forth movements. Then, we performed two more passes with the second needle, also using the slow pull and 20cc syringe aspiration sequence. This means that a minimum of four needle passes were performed in all patients. Additional punctures, with both needles, were performed at the discretion of the operator if he or she judged that the material was insufficient. This evaluation was not considered MOSE because we did not evaluate the specimen under a magnifying lens.

Part of the specimen from each pass was smeared onto three slides, and the remaining material was immersed in a formaldehyde solution for cell block analysis.

Cell block preparation, histologic assessement, scanning and measures

Specimens were collected for cell block in a methanol-based preservative solution which was subsequently centrifuged, decanted, and combined to form a tissue clot. After forming a tissue clot, specimens were fixed in formalin, embedded in paraffin, sectioned, and stained using haematoxylin and eosin for histological interpretation. The block was scanned and Panoramic Viewer 1.15.3 (3DHISTECH) was used to photograph the block cuts, always with a measurement reference ruler.

The areas in the photo fields were measured using ImageJ 1.53k (National Institutes of Health, United States; public domain), always calibrating the scale immediately after each photo, and then measuring the non-tumor areas (fibrosis, non-neoplastic pancreas, non-neoplastic intestinal wall tissue, or any other non-neoplastic pathway tissue) and tumor areas. Areas of necrosis, haemorrhage and mucus were not considered as tissue.

Definitions

Possible histological findings were classified as positive for malignancy, suspicious for malignancy, negative for malignancy, and insufficient material for analysis.

Diagnosis accuracy was defined as a correct diagnosis provided by the needle specimen. The definitive diagnosis of malignancy was based on surgical or clinical assessment (*e.g.* histology of a surgically resected specimen, or histology of a biopsy of a distant metastasis associated with a clinical course compatible with malignant disease). The definitive diagnosis of benign disease was based on benign histology findings associated with a clinical course compatible with benign disease. The minimum follow-up duration was established as 6 months.

Technical success rate was defined as the presence of samples adequate for cytology or histology. When neither the smears nor the cell-blocks samples allowed a diagnosis, this situation was considered as insufficient material for analysis, and a technical failure.

In the presence of malignancy in the tissue sample, the proportion of the positive area for malignancy was calculated and divided by the total area of the sample. This calculation was performed for specimens obtained from both needles.

Diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value for malignancy were calculated for both needles. Truly positive cases for malignancy were considered based on the association of imaging findings, clinical evolution and histology (see above). True negative cases for malignancy were considered when the association of histology findings, imaging and clinical evolution were inconsistent with malignancy after a minimum follow up of 6 months.

All the specimens were analysed by a senior pathologist who was masked to the type of needle that was used.

Sample size calculation and statistical analysis

In our center, the historical diagnostic accuracy for EUS-FNA for solid pancreatic masses using standard 22-gauge needles prior to this study was 75% (unpublished data). This is a superiority trial, where we hypothesised an increase in diagnostic yield of 25% with the use of the Franseen needle compared to standard needles (75%-95%). Adopting a statistical power of 80% and a *P* alpha level of 5%, 98 patients should be included. Considering that both needles will be used in all patients, 49 patients would be sufficient. Adopting a loss rate of 10%, we estimated the inclusion of 54 patients. Continuous variables were described as means and SD or medians and interquartile range. The analysis was carried out in two stages. The first stage consisted of calculating descriptive statistics of the variables of interest. The second step, in calculating the comparisons of prediction metrics. The prediction metrics evaluated were sensitivity, specificity, positive value prediction and negative value prediction. For to carry out these comparisons, the McNemar tests were used, for sensitivity and specificity, and the Moskowitz and Pepe test, for prediction of positive value and prediction of negative value. All of these analyzes were performed with the DTComPair package of the R language.

RESULTS

From December 2019 and January 2023, we screened and included 50 consecutive patients with solid pancreatic lesions referred to EUS-guided sampling. There was no screen failures.

Patient demographics and tumor characteristics

The mean age of the study cohort was 64 years (range 36-88 years), and 24 patients (48%) were male. The mean size of the pancreatic mass was 3.47 cm (range 1.7 cm-7.0 cm). Most lesions were located in the pancreatic head (62%) or uncinate process (12%). Vascular invasion was observed in 64% of patients (Table 1). The pathological analysis diagnosis was pancreatic adenocarcinoma in 74%, neuroendocrine tumor in 8 % and chronic pancreatitis in 6% (Table 2).

Final diagnoses were based on histological examination. No additional passes were necessary. In one case, the diagnosis was established by immunohistochemistry (as a B-cell lymphoma). The sensitivity for a final diagnosis of PM was significantly greater in the Franseen group 0.91 [95% confidence interval (CI): 0.80-0.98] *vs* standard group 0.81 (95%CI: 0.67-0.91) ($P = 0.025$). The specificity was 0.67 (95%CI: 0.09-0.99) for PM in the standard and 0.67 (95%CI: 0.09-0.99) for the Franseen needle groups, without difference between the groups. The accuracy of the standard needle for PM was 0.80 (95%CI: 0.66-0.90). In the Franseen needle group, accuracy for PM was 0.90 (95%CI: 0.78-0.97) ($P = 0.074$). The positive predictive value for the standard group for PM was 0.97 (95%CI: 0.87-1.00) and for the Franseen group, 0.98 (95%CI: 0.88-1.00), ($P = 0.36$). The negative predictive value for PM in the standard needle group was 0.18 (95%CI: 0.02-0.52), compared to 0.33 (95%CI: 0.04-0.78) in the Franseen needle group, with $P = 0.028$ (Tables 3, 4 and 5). Although this study only enrolled patients with solid lesions, one patient was diagnosed with an intraductal papillary mucinous neoplasm. This patient had a solid tumor on both computed tomography scan and EUS imaging.

The technical success rates for standard and Franseen needle groups were 94% (95%CI: 0.83-0.99) and 100% (95%CI: 0.92-1.00), respectively.

Histology assessment

The mean total tissue area mm^2 (± SD) was significantly higher for the Franseen than for the standard needle group, 2.07 ± 0.22 *vs* 1.16 ± 0.17 ($P < 001$). The mean total tumor area, mm^2 (± SD) did not differ between the Franseen, and in the standard needle groups 0.42 ± 0.09 *vs* 0.47 ± 0.09, $P = 0.8$ (Table 6). In Figure 1, there are examples of pathology images from samples obtained with the standard and Franseen needles, respectively.

Adverse events

In this study, we observed mild abdominal pain in only 5 patients, that resolved with simple analgesia and did not required hospitalization, three in the FNA and two in the FNB group. There were no cases of pancreatitis or bleeding related to the procedure.

DISCUSSION

We conducted a randomized study to compare the diagnostic accuracy of EUS-guided sampling of pancreatic solid lesions obtained with the 22-gauge Franseen *vs* the 22-gauge standard needle with no ROSE. The justification of the study design relies on the fact that ROSE is not routinely available in many centers in our country and around the world.

Our findings suggest a better diagnostic performance with the Franseen needle translated in a better sensitivity and negative predictive value for the diagnosis of PM. In fact, with the Franseen needle it was possible to correctly diagnose pancreatic adenocarcinoma in four misdiagnosed patients (inconclusive diagnosis in three and chronic pancreatitis in one patient) with the standard needle. The technical success rates for the standard and Franseen needle groups were 94% (95%CI: 0.83-0.99) and 100% (95%CI: 0.92-1.00) respectively, which reflects the greater amount of tissue samples obtained by the Franseen needle (mean total tissue area in mm^2, standard *vs* Franseen needles, 1.16 *vs* 2.07, $P = 0.001$). Recently, Kovacevic *et al*[19] also used a Franseen needle (TopGain; Medi-Globe GmbH, Grassau, Germany), as in our study, and

Table 1 Patient details and pancreatic mass characteristics (*n* = 50)

Characteristics	*n* (%)
mean age	64.1
Range	(36-88)
Gender	
Female	26
Male	24
Mean pancreatic mass size (cm)	
Mean	3.47
Range	1.7-7.0
Pancreatic mass location	
Head	31 (62)
Uncinate	6 (12)
Neck	6 (12)
Body	5 (10)
Tail	2 (4)
Vascular invasion	32 (64)
Venous vascular invasion	
Portal vein	16 (51.6)
Superior mesenteric vein	19 (61.3)
Splenic vein	13 (41.9)

Table 2 Pathological analysis diagnosis

Definitive diagnosis (*n* = 50)	Standard needle (*n* = 50)		Franseen needle (*n* = 50)	
Adenocarcinoma/pancreatic cancer (*n* = 38)	*n* = 31		*n* = 35	
	Benign lesion	Chronic pancreatitis (*n* = 3)	Benign lesion	Chronic pancreatitis (*n* = 2)
		Mucinous neoplasia (*n* = 1)		Mucinous neoplasia (*n* = 1)
	Inconclusive (*n* = 3)		Inconclusive (*n* = 0)	
Neuroendocrine tumor	*n* = 4		*n* = 4	
Metastasis	*n* = 2		*n* = 2	
Lymphoma	Chromic pancreatitis (*n* = 1); Lymphoma (*n* = 0)		Chronic pancreatitis (*n* = 1); Lymphoma (*n* = 0)	
Plasmocitoma	*n* = 1		*n* = 1	
Solid pseudopapillary tumor	*n* = 1		*n* = 1	
Chronic pancreatitis	*n* = 3		*n* = 3	

found a larger area of tissue with the FNB *vs* the FNA needle (2.74 mm^2 *vs* 0.44 mm^2, $P < 0.001$).

Facciorusso *et al*[20], in a network meta-analysis, observed no significant difference in diagnostic accuracy between EUS-guided tissue acquisition for sampling pancreatic masses using different needle models. However, this systematic review was based mainly on studies that used first-generation reverse-bevel FNB needles because only a limited number of RCTs that tested newer end-cutting FNB needles were available at that time.

We found five RCTs comparing FNA *vs* FNB needles. Their results are summarized in Table 7.

In a more recent network meta-analysis of different FNB needles, Gkolfakis *et al*[21] found that Franseen and fork-tip needles, particularly those of 22-gauge size, showed the highest performance for tissue acquisition. One observation was that the availability of ROSE had a great impact on the comparative efficacy of different techniques for tissue sampling of pancreas.

Table 3 Performance of standard needle for the diagnosis of pancreatic malignancy

Diagnostic method	Disease		
	Pancreatic malignancy[1] (*n* = 47)	Chronic pancreatis (*n* = 3)	Total
Positive for malignancy	38	1	39
Negative for malignancy	9	2	11
Total	47	3	50
95%CI			
Sensitivity		0.81 (0.67-0.91)	
Specificity		0.67 (0.09-0.99)	
PPV		0.97 (0.87-1.00)	
NPV		0.18 (0.02-0.52)	
Accuracy		0.80 (0.66-0.90)	

[1]Pancreatic malignancy included adenocarcinoma, neuroendocrine tumor, distant metastasis, lymphoma, plasmocitoma, solid pseudopapillary tumor.
CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

Table 4 Performance of Franseen needle for the diagnosis of pancreatic malignancy

Diagnostic method	Disease		
	Pancreatic malignancy[1] (*n* = 47)	Chronic pancreatis (*n* = 3)	Total
Positive for malignancy	43	1	44
Negative for malignancy	4	2	6
Total	47	3	50
95%CI			
Sensitivity		0.91 (0.83-0.98)	
Specificity		0.67 (0.09-0.98)	
PPV		0.98 (0.88-1.00)	
NPV		0.33 (0.04-0.78)	
Accuracy		0.90 (0.78-0.97)	

[1]Pancreatic malignancy included adenocarcinoma, neuroendocrine tumor, metastasis, lymphoma, plasmocitoma, Frantz tumor.
CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

Table 5 Comparison of the diagnostic performance of standard (fine needle aspiration) and Franseen (fine needle biopsy) needles

Metrics	FNA	FNB	Statistical difference	*P* value[1]
Sensitivity	0.809	0.915	5.000	0.025
Specificity	0.667	0.667	-	-
PPV	0.974	0.977	0.913	0.361
NPV	0.182	0.333	2.202	0.028
Accuracy	0.800	0.900	3.200	0.074

[1]McNemar (for sensitivity and specificity comparisons), Moskowitz and Pepe (for positive predictive value and negative predictive value comparisons) tests.
FNA: Fine needle aspiration; FNB: Fine needle biopsy; PPV: Positive predictive value; NPV: Negative predictive value.

Table 6 Comparison of procured histologic tissue areas (in mm²) between standard needle versus Franseen needle

	Standard needle	Franseen needle	*P* value
Mean total tissue area, mm^2 (SD)	1.16 (0.17)	2.07 (0.22)	0.001
Median	0.45	1.09	
75% IQR	1.53	2.89	
Range	0-9.76	0-9.22	
Mean total tumor area, mm^2 (SD)	0.42 (0.09)	0.47 (0.09)	0.8
Median	0.05	0.05	
75% IQR	0.51	0.50	
Range	0-7.03	0-4.88	

IQR: Interquartile range

Table 7 Randomized clinical trials comparing fine needle aspiration *vs* fine needle biopsy needles for endoscopic ultrasound-guided sampling of solid pancreatic tumors

Ref.	FNA (*n*)	FNB (*n*)	ROSE	Randomization	Technique of sampling	Sensitivity for malignancy (95%CI)-FNA	Sensitivity for malignancy (95%CI)-FNB	*P* value	Accuracy malignancy (95%CI)-FNA	Accuracy malignancy (95%CI)-FNB	*P* value
Bang *et al* [14]	22-gauge (28)	Reverse bevel (28)	Yes	Sequence of the needle	Capillarity and dry suction				100	83.3	0.26
Bang *et al* [15]	22-gauge (46)	Franseen 22-gauge (46)	Yes	Sequence of the needle					82.6	97.8	0.03
Noh *et al*[16]	22-gauge (30)	Reverse bevel 22-gauge (30)	Yes	Sequence of the needle	Dry suction				95	93.3	0.564
Vanbiervliet *et al*[17]	22-gauge (39)	Reverse bevel 22-gauge (41)	Yes	First needle FNA	Dry suction				92.5	90	0.68
Mavrogenis *et al*[18]	22-gauge (19)	Reverse bevel 25-gauge (19)	No	Sequence of the needle	Capillarity and dry suction	89.5 (66.82-98.39)	89.5 (66.82-98.39)		84.8 (67.3-94.2)	84.8 (67.3-94.2)	
Kovacevic *et al*[19]	22-gauge (33)	22-gauge (31)	No	Sequence of the needle	Capillarity	65.5%	89.7%	> 0.5	69.7 (51.3-84.4)	90.3 (74.2-98%)	
Our study	22-gauge (50)	Franseen 22-gauge (50)	No	Sequence of the needle	Capillarity and dry suction	0.83 (0.69-0.92)	0.91 (0.80-0.98)		0.84 (0.71-0.93)	0.92 (0.81-0.98)	

CI: Confidence interval; FNA: Fine needle aspiration; FNB: Fine needle biopsy; ROSE: Rapid onsite evaluation.

In a retrospective study, Wong *et al*[22] found that the diagnostic yield of solid pancreatic mass was higher with FNB using the Franseen needle than in FNA using the conventional FNA needle in a center where ROSE was unavailable[22]. Therefore, it seems that a main advantage of EUS-FNB needles, particularly with newer end-cutting needles, is to obviate the use of ROSE by performing the EUS-FNB sampling without an on-site pathologist[16]. Our findings are in line with this concept.

In times of personalised medicine, molecular profiling of pancreatic cancer and application of next-generation sequencing may provide an opportunity to advance the development of targeted therapies. Asokkumar *et al*[23] demonstrated that the Franseen EUS-FNB device can obtain better nucleic acid yield than EUS-FNA, with quality and quantity sufficient for downstream genomics applications. Therefore, the FNB can become a convenient and safe method

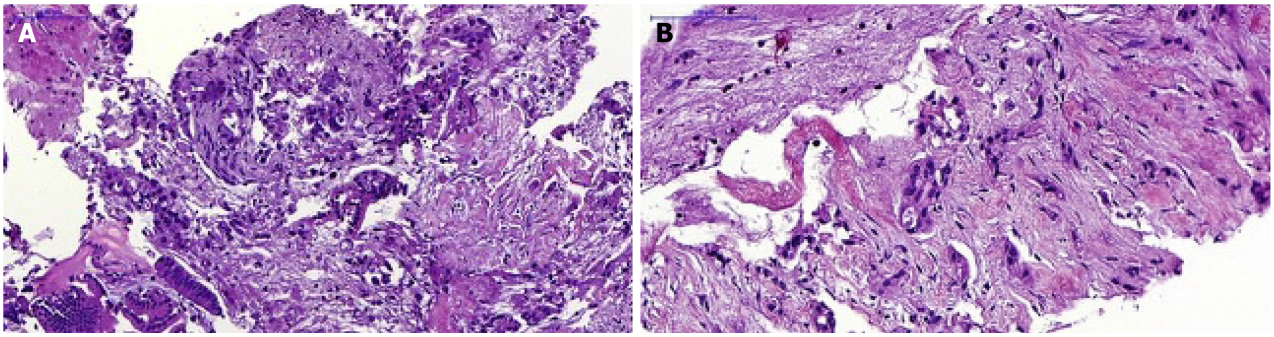

Figure 1 Pathology images from samples obtained of pancreatic adenocarcinoma. Both specimens showing desmoplastic fibrosis and malignant ductal epithelium in cell block. A: Standard needle (100×); B: Franseen needle (100×).

for obtaining tumor material for precision genomics. This could have implications for the outcome of pancreatic cancer treatment in the near future.

There are a few limitations of this study. First, we included only pancreatic masses, and therefore the performance of the Franseen and standard needles for evaluating other solid mass lesions could not be evaluated. A second limitation was the small number of patients. Maybe we could have detected a greater diagnostic accuracy in the Franseen needle group with a larger number of patients. Third, we did not compare the performance of the strategies of sampling, *i.e.*, stylet retraction *vs* suction. This comparison was not among the study aims, and the sample size was not gauged for it. Finally, the pathologist was masked to the type of needle. However, the pathologist evaluated all the processed slides and cell blocks of a specific patient at once. It is possible that the results of the interpretation of the specimen obtained with one needle model influenced the interpretation of the specimen obtained with the other needle.

CONCLUSION

In conclusion, for the EUS-guided tissue sampling of solid pancreatic lesions, the Franseen needle obtained a greater tissue area compared to the standard needle. The diagnostic sensitivity and negative predictive value of the Franseen needle was greater for the diagnosis of any PM.

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FOOTNOTES

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CASE REPORT

Clinical, endoscopic and histopathological observation of a rare case of esophageal submucosal gland duct adenoma: A case report

Ting Lu, Jun-Xing Liu, Yin Xia, Yan Zhao

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Abstract

BACKGROUND

Esophageal submucosal gland duct adenoma (ESGDA) is very rare, and easily diagnosed as adenocarcinoma.

CASE SUMMARY

A 70-year-old man presented with abdominal discomfort and intermittent dull pain during swallowing for 10 days. Digestive endoscopy revealed a polypoid bulge at the esophago-gastric junction, which was resected by endoscopic submucosal dissection (ESD). Routine pathological examination showed intestinal metaplasia of the glandular epithelium on the mucosal surface, with serous tumor-like complex glands in the submucosa which showing significant hyperplasia. This initially diagnosis was early gastric adenocarcinoma. However, we still observed a few points that did not meet the criteria for cancer such as lack of malignant features. Following multidisciplinary discussion and consultation with the experienced specialist pathologists, we finally diagnosed the lesion as a rare ESGDA by further immunohistochemistry. The follow-up examination results for the patient were satisfactory, with no evidence of tumor recurrence. And we summarize the ESGDAs reported in the literature, aiming to enhance understanding of this tumor type.

CONCLUSION

ESGDA is a benign tumor that can be cured by ESD. Accurate diagnosis can prevent unnecessary extensive therapeutic interventions.

Key Words: Esophagus; Submucosal gland; Duct; Adenoma; Case report

Core Tip: We present an exceedingly rare case of esophageal submucosal gland duct adenoma and conduct a comprehensive literature review to elucidate the origin, pathogenesis, clinical features, endoscopic and pathological characteristics, as well as potential genetic alterations of this tumor, thereby enhancing our understanding and preventing misdiagnosis.

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INTRODUCTION

It is well known that the submucosal glands of the normal esophagus are composed of lobules and extrolobular ducts. Each submucosal glandular lobule comprises multiple acini and intralobular ducts that converge to form an external lobule duct, which opens into the esophageal cavity. The submucosal glands and ducts are distinctive features of the esophagus and absent in the stomach. The acinus can be mucinous or mucous and serous mixed parotid acinus, which produce mucin and bicarbonate to neutralize gastric acid and growth factors, which are secreted through the extrolobular ducts to the surface of the esophageal mucosa to protect the esophagus[1]. They differ from the gastric cardia-type mucinous glands that are distributed in the lamina propria at the upper and lower end of the esophagus. Intralobular and extralobular ducts have no mucous cells[2]. Esophageal submucosal gland duct adenoma (ESGDA), a benign tumor originating from the esophageal submucosal gland, is extremely rare. Due to the lack of knowledge of clinical pathologists, it is easy to be diagnosed as adenocarcinoma. We encountered an extremely rare case that was initially misdiagnosed as early stage gastric adenocarcinoma by our pathologists. After following multidisciplinary discussion, carefully the available literature reviews, and consultations with the experienced specialist pathologists, we finally diagnosed the condition as ESGDA. Here we report this ESGDA and review the literature with the intent to enhance the understanding of this lesion.

CASE PRESENTATION

Chief complaints

A 70-year-old patient presented to our hospital with a 10-day history of upper abdominal discomfort and intermittent dull pain during swallowing. He reported no significant changes in mental status, appetite, or sleep patterns, no food reflux or acid reflux, no nausea, vomiting, abdominal distension, palpitations, chest tightness, chills fever or weight loss.

History of present illness

The patient underwent upper gastrointestinal endoscopy at our hospital. Conventional endoscopy revealed a hemispherical bulge which had superficial erosion of the surface mucosa and a soft touch within the dentate line of the esophago-gastric junction (Figure 1A). Ultrasound endoscopy indicated that the bulge was located in the submucosal layer, with clear boundaries and smooth edges. It exhibited an anechoic mass and had relatively normal blood flow signals (Figure 1B). Magnifying narrow-band imaging endoscopy revealed the mass had a borderless mucosal surface with a mucosal microstructure and regular microvessels (Figure 1C).

History of past illness

The patient has a 20-year history of hypertension and diabetes. He takes oral Amlodipine daily and receives insulin injections subcutaneously with good control of blood sugar levels. His highest recorded blood pressure was 170/100 mmHg. He underwent a 'left inguinal hernia repair' three years ago. No history of other diseases and no food or drug allergies.

Personal and family history

The patient denied any family history of hereditary diseases or tumors.

Physical examination

The dimension of the resected tissue measured 3.5 cm × 2.6 cm × 0.2 cm, with a hemispherical polypoid mass measuring 0.7 cm protruding from the mucosal surface (Figure 1D). It was vertically sectioned into strips of tissue, each 2 mm width.

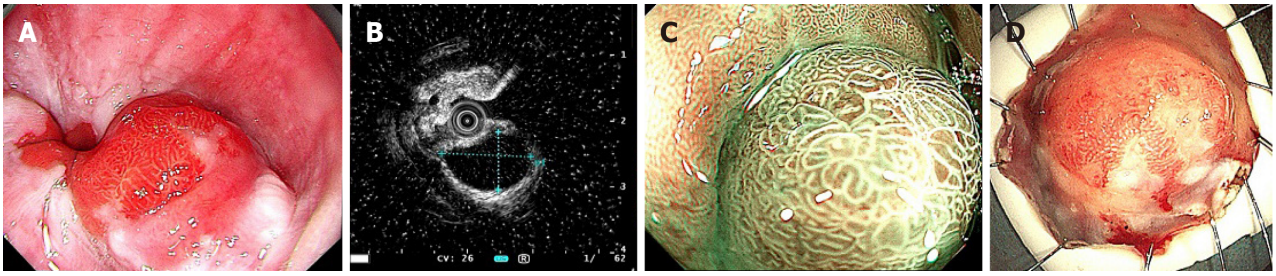

Figure 1 Endoscopic images of esophageal submucosal gland duct adenoma. A: The hemispherical polyp was located at the gastro-esophageal junction with superficial erosion of the surface mucosa; B: Ultrasound endoscopy showed an anechoic lesion located in the submucosa with a clear and smooth boundary; C: Magnifying narrow-band imaging endoscopy revealed a mass with borderless mucosal surface along with a slightly irregular microstructure, twisted and thickened glands, but regular microvessels; D: Gross observation showed a hemispherical bulge on the surface of the specimen removed by endoscopic submucosal dissection, and the surface mucosa was smooth.

Based on the incision profile, the mass was situated beneath the mucous membrane, which appeared largely normal on its surface. The mass exhibited a grayish-white coloration, had a medium consistency, and was distinctly demarcated from adjacent tissue.

Laboratory examinations

Histologic studies: All tissue strips were cut into slices by the conventional methods, and stained with H&E. The lesion was 0.5 cm × 0.5 cm in size and was located on the submucosal layer without any envelope wrapping (Figure 2A). It was composed of several ducts or cysts with papillary and tubular structures; moreover, lymphocyte clusters were observed in its interstitia along with germinal centers (Figure 2B and C). Furthermore, these ducts or cysts had an inner luminal duct cell layer and an outer myoepithelial cell layer. Both these layers had oncocytic differentiation with granular and eosinophilic cytoplasms. The luminal cells had micropapillary and microglandular hyperplasia in the glandular cavity. There were few nuclear atypicals, lack of mitotic figures, necrosis and mucin production (Figure 2D).

Immunohistochemical studies: Immunohistochemical assay was carried out in strict accordance with the kit instructions. We used EDTA heat antigen repairing methods, with a DAB chromogen. Antibodies used in the immunohistochemistry included: CK7 (OV-TL 12/30; Dako), CK20 (KS20.8; Dako), P63(4A4; Dako), CDX2 (EPR2764Y, Dako), MUC1 (MRQ; Dako), MUC2 (Ccp58; Dako), MUC6 (MRQ-20; Dako), MUC5AC(45M1; Dako), MDM2 (SPM14; Dako) , P53 (BP-53-12; Dako), and Ki-67 (Mib1; Dako).

The luminal duct cells were positive for CK7 (Figure 2E), whereas the myoepithelial cells were positive for P63 (Figure 2F). Both the two-layer cells were negative for CK20, CDX2, MUC1, MUC2, MUC6, and MUC5AC (Figure 2G), and there was no evidence of *P53* mutation and *MDM2* gene expansion. In fact, Ki-67 showed almost no expression of ductal epithelial cells and expressed in only a few myoepithelial cells (< 5%; Figure 2H).

The patient learned that the tumor was considered benign and successfully removed, he declined our suggestion to conduct relevant gene sequencing for further analysis of the tumor.

MULTIDISCIPLINARY EXPERT CONSULTATION

After the initial multidisciplinary team discussion, we performed an endoscopic submucosal dissection (ESD) for the patient's tumor. Following a preliminary pathological examination of the postoperative specimen, we reconvened a multidisciplinary expert consultation which included specialists from both within and outside our institution for the diagnosis of this patient.

FINAL DIAGNOSIS

After a thorough review of pertinent literature, we arrived at a finally diagnosis of ESGDA.

TREATMENT

Following a multidisciplinary discussion and the formulation of a comprehensive treatment plan, we proceeded with ESD on the patient. Tumor was successfully resected *en bloc* from the submucosa with an estimated blood loss of approximately 10 mL. After the surgery, the patient was placed on fasting status for the first day and received intravenous fluid resuscitation. From the second day, the patient was transitioned to a liquid or semi-liquid diet. Throughout the postoperative period, the patient remained asymptomatic and was subsequently discharged on the fifth postoperative day.

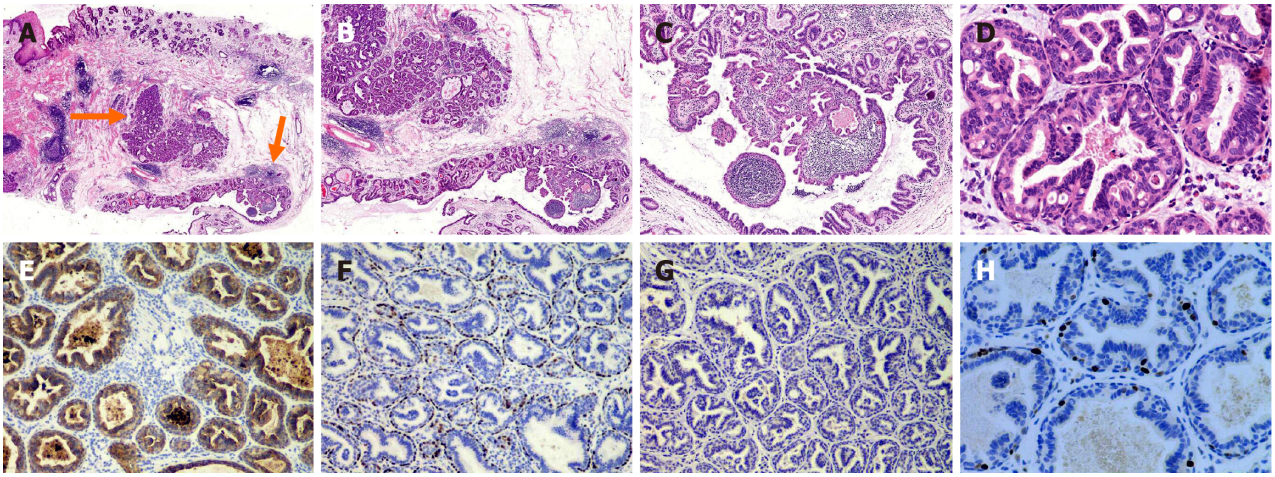

Figure 2 Pathological images of esophageal submucosal gland duct adenoma. A: The orange arrow denoted the submucosal lesion within the esophagus (original magnification × 40); B and C: The lesion was composed of ducts or cysts containing papillary and tubular structures with lymphocytic infiltrates in the interstitial (B: Original magnification × 100, C: Original magnification × 200); D: Tumor cells were composed of moderate bilayer epithelium with no mitotic figures (original magnification × 400); E: CK7 was positive in inner cells and negative in outer cells (original magnification × 200); F: P63 was negative in inner cells and positive in outer cells (original magnification × 200); G: All cells were negative for MUC5AC (original magnification × 200); H: Ki-67 showed only expression in a few myoepithelial cells(original magnification × 400).

OUTCOME AND FOLLOW-UP

Endoscopic examinations were conducted at 3 months and 1 year post-operation, all of which revealed complete healing of the scar in the surgical area. The patient had no discomfort. Subsequently he underwent biennial endoscopic examinations, and no evidence of tumor recurrence was observed over a period of 69 months.

DISCUSSION

Rare adenomas of the esophagus have been reported since the middle of the last century. Unfortunately, these reports lacked detailed histological descriptions and photomicrographs[3,4]. ESGDA was first comprehensively introduced by Takubo *et al*[5] in 1993 and identified as esophageal submucosal tumor. The rarity of this neoplasm has resulted in terminological ambiguity, with various designations including esophageal pleomorphic adenoma, serous cystadenoma, and sialadenoma papilliferum[6,7]. In 1995, Rouse *et al*[8] formally designated it as ESGDA and posited that it may originate from the ductal components of the submucosal glands. We reviewed the existing literature and found 23 cases in which ESGDA was adequately described in case reports. The clinical characteristics of these cases are summarized in Table 1[5-18].

The average of the 23 patients with ESGDA was 66 years (range: 45-81 years), exhibiting a male predominance (male:female = 15:8). Among them, 2 cases of ESGDA were incidentally discovered due to the presence of esophageal squamous cell carcinoma alongside gastric adenocarcinoma[5,12]; the remaining cases primarily presented with initial symptoms of abdominal discomfort, dysphagia, belching, vomiting, loss of appetite, wasting, acid reflux and abdominal pain, which occasionally posed challenges to their condition and complicated the diagnosis of gastroesophageal reflux disease. During digestive endoscopy, these lesions manifested as small hemispherical or dome-shaped submucosal protrusions. All patients had single ESGDA, which ranged in diameter from 0.3 to 3.5 cm, with an average of 1.0 cm. They were removed by ESD or endoscopic mucosal resection. All ESGDAs exhibited well-defined bondaries but lacked an envelope. Histologically, they were characterized by multiple cystic dilatations of glandular ducts, which contained two layers of epithelial cells exhibiting proliferation and papillary folds. The cytoplasm of the inner luminal ductal epithelial cells was granular and eosinophilic, featuring round to oval nuclei with minimal nuclear atypia. The outer basal cells were spindle with distinct or weak eosinophilic cytoplasms. All the tumors showed a low mitotic activity without necrosis. Diffuse or focal lymphocytic infiltration in the interstitium was commonly observed. In immunohistochemical analysis, both layers expressed epithelial markers like pan cytokeratin and epithelial membrane antigen. The inner ductal epithelial cells demonstrated low molecular weight cytokeratins such as CK7 and CK18, while the outer layer expressed basal cell markers including CK5/6, P63, S-100 among others. Markers such as CK20, CDX2, MUC1, MUC2, MUC5AC, MUC6 and P53 were all negative. The proliferations index of Ki-67 was very low (1%-5%). Few reports on the molecular genetic changes of ESGDA, only Hua *et al*[18] conducted genomic analysis on 7 cases of ESGDA, and found 5 of them exhibited a *BRAF V600E* mutation (71.4%). There were no recurrences of ESGDA, and the prognosis was highly favorable.

The glands of the esophagus are categorized into esophageal cardiac glands and submucosal glands, which are distributed in different levels. The esophageal cardiac gland is situated within the mucosal lamina propria and exhibits structural similarities to gastric glands. It comprises MUC6-positive glandular ducts, with a rare presence of parietal cells and chief cells. The epithelium of the glandular pit shows positive expression for MUC5AC, while MUC2 positivity may

Table 1 Clinicopathological characteristics of the present case of esophageal submucosal gland duct adenoma and the 23 cases in prior literature

Ref.	Age (years)/gender	Symptoms	Location	Gross morphology/size (cm)	Histological morphology	Dysplasia	Necrosis/mitotic figures	Ki-67 index	Follow-up
Tsutsumi *et al*[6], 1990	77/male	Nausea	M	Globoid polyp/1.0	Multiple mycrocysts and papillary proliferation with two layers of cells	Mild and moderate	None/some	NM	Well over 2 years
Takubo *et al*[5], 1993	58/male	Abdominal discomfort	M	Dome-like polyp/0.8	Papillary and tubular structures with two layers of cells	None	None/none	NM	Well over 6 months
Rouse *et al* [8], 1995	81/male	Dysphagia	GEJ	Pedunculated polyp/1.5	Tubules and cystic lumens filled with papillae by two layer of cells	None	None/rare	NM	Well over 12 months
Su *et al*[7], 1998	70/male	Abdominal fullness	L	Broad-based polypoid/1.0	Papillary glandulars with two layers of cells	Benign	None/none	NM	Well over 12 months
Agawa *et al* [9], 2003	71/male	NM	L	Sessile polypoid tumor/1.5	Dilated gland ducts containing papillary and tubular components with two layers of cells	Benign	None/ none	NM	Well over 12 months
Hayashi [10] 2004	60/female	Abdominal discomfort	M	Dome-like protruding lesion/1.1	Cysts, papillary and tubular proliferation with two layers of cells	Minimal	None/none	NM	Well over 11 years
Chinen *et al* [11], 2004	67/female	None	L	Polypoid lesion/0.6	Multiple cysts, tubules and papillae with two layers of cells	Mild	None /rare	NM	Well over 6 months
Harada *et al*[12], 2007	75/male	NM	L	Well demarcated without a capsule/0.3	Papillary and cystic structures with two layers of cells	Minimum	None/rare	1%-2%	NM
Nie *et al* [13], 2016	74/male	Retrosternal discomfort	L	Dome-like polypoid tumor/0.5	Multiple glandular cysts and papillary folds with two layers of cells,	Minimum	None/none	1%	Well over 4.5 years
	54/female	Abdominal discomfort and heartburn	L	Hemispherical protruding lesion/0.3	Multiple glandular cysts and papillary folds with two layers of cells,	Minimum	None/none	1%	Well over 4 years
	45/male	NM	L	Hemispherical protruding lesion/0.4	Multiple glandular cysts and papillary folds with two layers of cells,	Minimum	None/none	1%	Well
Shibata *et al*[14], 2017	66/female	None	L	Slightly protruding tumor/0.5	Dilated ducts and papillary proliferations with two layers of cells	Slight	None/none	2%	NM
Genere *et al* [15], 2019	78/female	Dysphagia	U	Submucosal mass with well-defined borders/2.0	Multiple lobulated cystic proliferations of two layers of cells	Mild	None/rare	NM	Well
Yamamoto *et al*[16], 2020	73/female	None	L	Subepithelial tumor with a central depression/0.8	Tubular and cystic pattern with two-cells	None	None/none	NM	Well

					layers				
Chen *et al* [17], 2023	58/male	Gastro-esophageal reflux symptoms	L	Hard mass with well-defined hetero-geneous/3.5	Cystic pattern with two layers of cells	Benign	None/rare	NM	Well over 12 months
Hua *et al* [18], 2025	65/male	None	U	SMT/0.5	Glandular ducts, cysts and papillae, with two-cells layers	Bland	None/none	< 1%	Well over 68 months
	75/male	Loss of appetite	U	SMT/1.5					Well over 46 months
	65/male	Belching, acid reflex	M	SMT/1.5					Well over 36 months
	55/female	Discomfort during swallow	L	SMT/0.5					Well over 25 months
	51/female	Acid reflux, vomiting	L	SMT/0.8					Well over 24 months
	73/male	Abdominal pain	L	SMT/0.3					Well over 50 months
	63/male	None	GEJ	SMT/2.0					Well over 37 months
Our case	70/male	Abdominal discomfort	GEJ	Hemispherical bulge/0.5	Tubular, cysts and papillary structures with two layers of cells	Few	None/none	< 5%	Well over 69 months

M: Middle esophagus; GEJ: Gastroesophageal junction; L: Lower esophagus, U: Upper esophagus; SMT: Submucosal tumor, NM: Not mentioned.

occur in cases of intestinal metaplasia. Esophageal submucosal glands reside in the submucosa and function as exocrine glands, considered an extension of the small salivary glands of the oropharynx. These glands are dispersed throughout the esophagus along its longitudinal axis but exhibit greater concentration at the junction between the lower esophagus and cardiac, where significant alterations in physical and chemical properties occur. Submucosal gland acinar secretions are collected *via* ducts that transport them to the esophageal lumen; initially covered by a single cuboidal epithelium, these ducts subsequently transition into a double-layered epithelium before traversing through various layers including the muscularis mucosa, lamina propria mucosa, and the epithelium of the esophagus[17,19].

The occurrence location of ESGDA mirrors that of esophageal submucosal glands. It resided within the submucosa where normal submucosal gland tissues frequently surrounded it. Occasionally observed transitional relationships between both structures suggested an intuitive possibility that ESGDA might originate from these submucosal glands, which was further corroborated by immunohistochemical findings. The immunophenotypic characteristics of the inner ductal epithelial cells of ESGDA were closely align with that of the normal esophageal submucosal duct epithelium. Tumor cells expressed MUC5B, CK7, CK5/6, and CK19 while showing no expression for CK20, CDX2, Villin, MUC5AC, MUC6, MUC2 or GCDFP15. All these indicated a lack of differentiation phenotype characteristic typical to digestive tract-type glandular epithelia or submucosal mucous acinoid epithelia. It is worth mentioning that Harada *et al*[12] found through immunohistochemistry of MUC5B and electron microscopy that a few ductal epithelial cells in ESGDA displayed limited mucus secretion localized to their subapical regions, implying that tumor cells may have the ability of terminal duct (intercalated duct) differentiation. And They effectively delineated microvilli on both the basement membrane and the apical surface of the luminal duct cells with Alcian blue (PH 2.5) and periodic acid-Schiff (AB-PAS) staining, corroborating the findings from MUC5B immunostaining. The basal layer cells of ESGDA expressed P40, P63, SMA, Calponin, and S-100 protein, suggesting characteristics of myoepithelial differentiation.

Current research indicates that gastroesophageal reflux not only serves as the primary etiological factor in the development of Barrett's esophagus (BE) but is also intricately linked to the progression of ESGDA[12]. Other environmental factors include long-term smoking, drinking, overheated diet and other irritants. These factors induced injury to the esophageal mucosa and promotes inflammatory cell infiltration within both the mucosal and submucosal layers. This results in a dual impact: On one hand, inflammatory cells impair myoepithelial contractile function; on the other hand, inflammatory exudates or epithelial debris obstruct the ducts of submucosal glands. The cumulative effects of these detrimental factors hinder proper secretion discharge from esophageal submucosal glands, leading to noticeable expansion or contraction of acini when these symptoms persist. Prolonged exposure to secretions and inflammatory cells stimulates precursor cells with multidirectional differentiation potential to proliferate, resulting in multilayered epithelium (some studies suggest this may represent a precursory lesion for BE) and papillary formations, which contribute

to the distinctive histological characteristics observed in ESGDA[19]. Concurrently, cyst formation within submucosal glands is regarded as a precursor for ESGDA due to their overlapping clinicopathological features and ongoing interrelationship[12,13]. No family history of ESGDA has been found in the literature. Whether genetic susceptibility and other factors may also affect the occurrence of ESGDA remains to be further studied.

Adenomas of the esophagus are infrequent and typically associated with intestinal metaplasia, specifically BE, which is a consequence of GERD. These lesions are characterized by raised polypoid mucosal formations composed of intestinal or gastric glandular epithelium exhibiting varying degrees of dysplasia. They may be not represent true adenomas in nature but precursor lesions for BE-related adenocarcinoma[20]. ESGDA discussed in this paper is a true primary submucosal adenoma which is extremely rare and located in the submucosal layer, originating from the submucosal gland duct cells. Its immunophenotypic profile indicates a closer association with tumors of salivary adenoid origin.

In terms of molecular genetics, only Hua *et al*[18] found *BRAF V600E* mutations in five of the seven ESGDAs. Given that the *BRAF V600E* mutation has been previously confirmed in sialadenoma papilliferum, this finding provides additional evidence that ESGDA is an esophageal counterpart of minor salivary gland tumors. The *BRAF V600E* mutation may promote cell proliferation by activating the MAPK signaling pathway, and its role in ESGDA and whether it may lead to malignant transformation require further investigation.

The pathological diagnostic criteria supporting the diagnosis of ESGDA include: (1) Multiple glands or cysts arranged in a lobular configuration and covered by two layers of cells, the inner luminal epithelial cells and the outer basal or myoepithelial cells; (2) The existence of multilayered epithelium and papillary structures within the glands or cysts, without necrosis and significant cytologic atypia, and nuclear mitotic figures are infrequent; (3) Lymphocytic infiltration accompanied by acinar atrophy or disappearance; and (4) Luminal lining cells exhibiting positivity for MUC5B and various cytokeratins (such as CK5/6, CK7, CK18, CK19), whereas outer cell markers P40, P63, S-100, Calponin and SMA show positive expression alongside a low Ki-67 proliferation index. AB-PAS staining reveals microvilli on the apical surface adjacent to the basement membrane along with tubular epithelial cell[21].

The most important aspect of the diagnosis was identifying the adenocarcinoma, which was always invasive, had an obvious structure and cytological atypia, and was accompanied by multiple mitotic figures and abnormal mitotic figures. The presence of ESGDA bilayer epithelium, lack of cytologic atypia, and lack of mitoses were key criteria for the identification. Similarly, another rare tumor, known as oxyntic gland polyp/adenoma or adenocarcinoma of fundic gland (chief cell-predominant type), was identified[22]. It was mainly composed of proliferation of the chief cells and oxyntic cells along with low-grade cytology and a similar low Ki-67 index as that observed for ESGDA. This tumor showed low-grade malignancy with rare occurrences of lymphatic and venous invasion[23,24].

ESGDA can be cured by ESD regardless of whether it occurs at upper or lower esophagus, and whether it is 0.3 cm or 3.5 cm in size. No recurrence or malignant transformation cases have been found in the literature. We think the incomplete resection may be the root cause of recurrence. And if the tumor has sufficient growth time in a suitable environment, the possibility of malignant transformation cannot be ruled out. Especially if the tumor suddenly increased in size in a short period of time, the possibility of malignant transformation should be vigilantly considered. When the pathological morphology shows highly anaplastic tumor cells, accompanied by significantly active pathological mitotic figures and necrosis, even invasive growth, it suggests tumor malignant transformation. We believe that long-term regular follow-up of this tumor is very necessary. As with other gastrointestinal tumors, we recommend endoscopic examination every one or two years when the patient has no digestive discomfort symptoms, and at any time once there are gastrointestinal discomforts.

CONCLUSION

To summarize, ESGDA is a benign neoplasm that can be completely resected by ESD. It occurs predominantly in the lower third of the esophagus and is more common in elderly male patients. Symptoms include abdominal discomfort or difficulty swallowing, although it may occasionally be asymptomatic. They are small hemispherical or dome-shaped polypoid submucosal polypoid lesions that can be resected endoscopically, but it is still uncertain whether they can progress from adenoma to adenocarcinoma. Extensive ductal metaplasia, hyperplasia and/or retention cyst formation are considered to be the basis or precursors of ESGDA. The histological, immunohistochemical and molecular evidence of ESGDA support that it is a esophageal counterpart of minor salivary gland tumors.

FOOTNOTES

Author contributions: Lu T and Liu JX contribute equally to this study as co-first authors; Lu T carried out experiments; Liu JX searched the literature and drafted manuscript; Xia Y aided in specimens collection; Zhao Y designed experiment methods, analyzed results, and revised manuscript; all authors had access and approved the last version of the manuscript.

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LETTER TO THE EDITOR

Endoscopic intervention in hematologic malignancy patients with severe thrombocytopenia: Methodological concerns, clinical implications, and future research directions

Arunkumar Krishnan

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Abstract

Gastrointestinal bleeding (GIB) presents a significant challenge for patients with hematologic malignancies, especially those with severe thrombocytopenia. Although endoscopic intervention is frequently used in managing GIB, its safety and effectiveness in this high-risk group remain unclear. A recent study by Alhumayyd *et al* provided insight into this issue. However, it has notable limitations, including its retrospective nature, small sample size, and failure to adjust for important confounding factors such as disease severity, hemodynamic status, and platelet function. The study's findings indicated that urgent endoscopy may help decrease the incidence of recurrent bleeding; however, it did not show a clear benefit in terms of mortality. Future research ought to prioritize prospective, multicenter studies that employ standardized protocols and incorporate risk stratification models to better understand the impact of endoscopic treatment for GIB in these patients. Additionally, integrating platelet function assays could improve clinical decision-making. Addressing these research gaps is essential for improving patient outcomes and developing effective guidelines for managing GIB in individuals with thrombocytopenia.

Key Words: Gastrointestinal bleeding; Thrombocytopenia; Hematologic malignancies; Endoscopic intervention; Clinical outcomes; Hemostatic management

Core Tip: Endoscopic intervention for gastrointestinal bleeding in patients with severe thrombocytopenia is debated due to the lack of standardized platelet thresholds and procedural risks. A recent study by Alhumayyd *et al* highlighted these challenges but was limited by small sample sizes, retrospective design, and inadequate adjustment for confounders. Key factors like hemodynamic stability, hematologic malignancy severity, and platelet function assessments were insufficiently addressed. Variations in endoscopic timing and hemostasis techniques further complicate results. Prospective, multicenter studies incorporating platelet function assays and standardized protocols are essential to improve gastrointestinal bleeding management in thrombocytopenic patients.

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TO THE EDITOR

Patients with hematologic malignancies often present with complex hematological challenges, including anemia and thrombocytopenia, which significantly increase the risk of bleeding during endoscopic interventions. Gastrointestinal bleeding (GIB) is a significant cause of morbidity and mortality in patients with hematologic malignancies, particularly those with severe thrombocytopenia[1]. Thrombocytopenia, commonly worsened by the underlying malignancy or the effects of cytotoxic therapies, significantly increases the risk of spontaneous and severe bleeding[2]. Endoscopy is critical in managing GIB; however, its use in patients with thrombocytopenia remains controversial[3]. This is mainly due to the increased risk of procedural complications and the absence of established guidelines regarding optimal platelet count thresholds for safe endoscopic interventions. The decision to proceed with endoscopy in these patients must carefully consider the platelet count, coagulation status, and overall hemodynamic stability.

Despite the high prevalence of GIB in this population, there is a paucity of robust data on the safety and efficacy of endoscopic interventions in severely thrombocytopenic patients. Current practices are predominantly guided by expert opinions, with a commonly suggested platelet threshold of greater than 50×10^9/L for considering endoscopic intervention[4]. However, this guideline is not universally applicable as a threshold for endoscopic procedures, particularly in patients with underlying platelet dysfunction or those receiving anticoagulant or antiplatelet therapies. Therefore, a comprehensive assessment of hematological parameters, including platelet function assays, is essential to minimize procedural risks and optimize outcomes. In addition, the clinical implications of endoscopy for these high-risk patients, particularly concerning mortality rates, recurrent bleeding, and the need for blood transfusions, remain poorly understood.

The recent study by Alhumayyd *et al*[5] attempts to address this knowledge gap by examining the outcomes of endoscopic intervention compared to conservative management in patients with hematologic malignancies and severe thrombocytopenia (platelet count $\leq 50 \times 10^9$/L). While the study findings provide valuable insights, it is important to consider some study limitations. Additionally, we would like to propose recommendations for future research to improve understanding and patient care.

METHODOLOGICAL CONSTRAINTS

When evaluating the results of a single-center study, it is important to recognize its inherent limitations. The retrospective design and focus on a single center restrict the ability to generalize the findings to a broader population[6]. Retrospective studies often face challenges such as selection bias, and the dependence on electronic health records can result in incomplete or inconsistent data collection. Furthermore, a single-center approach may not adequately represent the diversity of clinical practices and patient demographics in various healthcare settings. As a result, such studies' conclusions may not apply to broader populations or different clinical scenarios. It is recommended that studies utilize a prospective, multicenter design to improve the external validity of future research. Such studies would improve the external validity of findings and provide more robust evidence to guide clinical practice. Additionally, implementing standardized data collection protocols will help reduce bias and ensure a thorough and accurate data capture.

The study involved 76 patients, constituting a relatively small sample size, especially when conducting subgroup analyses. This modest sample size may have limited the statistical power required to identify significant differences in key outcomes such as mortality rates, transfusion requirements, and instances of recurrent bleeding. Therefore, larger studies with sufficient power are essential to validate the findings and investigate potential differences among subgroups [7]. Additionally, power calculations should be performed in advance to determine the required sample size for detecting clinically meaningful differences and to improve the statistical robustness of the results[8].

Endoscopic procedures can be classified into three categories based on the potential risk of hemorrhagic complications: Low, moderate, and high risk. Low-risk procedures, such as diagnostic endoscopy, can generally be performed safely in patients with thrombocytopenia, as they pose a minimal risk of significant bleeding. In contrast, high-risk procedures such as therapeutic interventions involving tissue resection or hemostatic measures necessitate carefully evaluating the

patient's platelet count and function. Platelet transfusions are frequently employed to reduce the risk of bleeding in these higher-risk scenarios; however, the optimal timing and dosage for these transfusions are still not well-defined. Future research is needed to investigate the efficacy of prophylactic platelet transfusions in various procedural settings and the advantages of newer hemostatic agents that could help decrease the dependency on transfusions.

When assessing preprocedural prophylaxis in patients with thrombocytopenia, a nuanced approach is important, as relying solely on platelet count may not adequately reflect the bleeding risk. Guidelines have proposed a platelet count threshold of ≥ 50000/μL for endoscopic procedures[5]; however, recent recommendations indicate that many procedures can be conducted safely, even at lower platelet counts[5]. Current evidence highlights that specific interventions may be feasible with diminished platelet counts, provided other hemostatic factors, such as platelet function and coagulation status, are meticulously evaluated. This approach necessitates thoroughly considering the patient's overall clinical condition, including the severity of thrombocytopenia, the potential for platelet dysfunction, and the specific endoscopic procedure being performed. The absence of standardized protocols for preprocedural prophylaxis is a significant challenge, emphasizing the importance of individualized risk assessments and collaborative decision-making among healthcare professionals.

To improve patient safety, platelet function assessments, primarily through techniques like thromboelastography, offer a more thorough evaluation of hemostatic competence in individuals with hematologic malignancies. These patients often show alterations in platelet functionality due to either the disease itself or the effects of cytotoxic treatments, which are not accurately captured by platelet count alone. Thromboelastography provides real-time information about platelet performance and clot stability, which is crucial in making informed decisions regarding the timing and safety of endoscopic interventions. Moreover, it is vital to consider how hematological malignancies affect other facets of hemostasis, including coagulation and fibrinolysis, as these factors can further modify the bleeding risk and procedure outcomes. Future research should focus on establishing evidence-based thresholds encompassing these variables, potentially integrating platelet function assessments and additional hemostatic parameters to improve decision-making processes.

UNADDRESSED CONFOUNDERS

The study has certain limitations that may impact the interpretation of its outcomes. Notably, it did not account for various potential confounders that could affect results, including the severity of the underlying hematologic malignancy, concomitant comorbidities, hemodynamic stability, and the use of anticoagulant or antiplatelet medications[9]. Although the study stratified patients by platelet count, it overlooked the assessment of platelet function, an essential factor in determining bleeding risk. Furthermore, the role of platelet transfusions in determining procedure outcomes was not adequately explored. Additionally, the classification of endoscopy as "urgent" (within 24 hours) *vs* "non-urgent" (beyond 24 hours) did not take into account the timing of the initial bleeding onset or the clinical severity of the situation[10]. The decision-making process for endoscopic procedures appeared to be influenced more by physician preference than established criteria, introducing the potential for bias in treatment allocation. Lastly, variations in clinical decision-making were not considered, including the thresholds for transfusion and stabilization efforts prior to endoscopy, which could influence patient outcomes[11]. Future research should prioritize using multivariable regression analyses or propensity score-matching to adjust for potential confounders that may impact study outcomes. To draw more accurate conclusions, it is essential to explicitly evaluate the effects of platelet transfusions and other hemostatic interventions.

Additionally, integrating thromboelastography or platelet function assays could enhance patient stratification, allowing for more tailored treatment approaches. In addition, these methods would offer a more comprehensive assessment of hemostatic competence, enabling better risk stratification and tailored treatment approaches. Future studies should incorporate these tools to provide more accurate insights into the safety and efficacy of endoscopic interventions in thrombocytopenic patients. On the other hand, validated scoring systems, such as the Rockall or Glasgow-Blatchford scores, would improve risk stratification in clinical settings[12]. Furthermore, developing standardized protocols for determining the necessity of endoscopic interventions is crucial for minimizing subjective biases. Lastly, future analyses should include a comprehensive assessment of pre-endoscopic interventions to ensure a thorough evaluation of patient outcomes.

CHALLENGES IN DATA INTERPRETATION: ADDRESSING BIAS AND STATISTICAL LIMITATIONS

This study's statistical analysis was restricted to descriptive statistics and univariate comparisons. Since multivariate analysis was not performed, this limitation hinders the evaluation of the independent effect of endoscopy on patient outcomes. Additionally, the research did not investigate potential interactions between critical variables, including the timing of endoscopy and platelet counts. The study did not address several potential sources of bias, such as selection bias, information bias, and confounding by indication. For instance, patients experiencing more severe bleeding or hemodynamic instability may have been more likely to receive endoscopy, which could have influenced the study's findings.

Furthermore, the authors did not consider the risk of type II error, particularly given the small sample size[13]. Advanced statistical techniques, such as multivariate regression or propensity score matching, would improve the analysis[14]. These methods could help control for confounding variables and better assess the independent impact of endoscopy[14]. Including interaction terms could further clarify potential effect modifiers. Lastly, sensitivity analyses

would be required to evaluate the robustness of the findings, considering these potential biases. It is important for the study to explicitly acknowledge its limitations concerning bias and the possibility of type II error. Additionally, the small sample size increases the risk of type II error, highlighting the need for larger, adequately powered studies to validate these findings.

The study indicated that while there was no significant mortality benefit associated with endoscopy, the lack of statistical significance does not necessarily mean that the findings lack clinical importance. It suggests that urgent endoscopy may help reduce the rate of recurrent bleeding within 30 days; however, this observation does not account for differences in bleeding severity or the types of interventions used. Larger studies using rigorous statistical methodologies are important to verify these findings. Future research should also focus on distinguishing between various sources of bleeding and different treatment options to provide more precise insights into these findings.

CHALLENGES IN ENDOSCOPIC TIMING AND STANDARDIZATION: IMPLICATIONS FOR RECURRENT BLEEDING

The authors examined the effects of urgent endoscopy performed within 24 hours on patients experiencing bleeding. The findings indicated that such timely interventions were associated with a lower rate of recurrent bleeding; however, the timing of endoscopy did not significantly influence mortality or other clinical outcomes. Notably, the study did not investigate how clinical factors, including the severity of bleeding or patients' hemodynamic stability, might affect the timing of endoscopy. Additionally, the study lacked detailed information regarding the standardization of endoscopic interventions, particularly in using various hemostatic techniques, such as thermal coagulation and mechanical clipping [15,16]. The variability in these interventions may have impacted the study's outcomes.

Future research should investigate the relationship between endoscopy timing and clinical outcomes to improve understanding. Assessing how factors like hemodynamic stability and bleeding severity influence the necessity for urgent endoscopy is important. Furthermore, standardization of endoscopic techniques and comprehensive documentation of the methods employed will be essential to evaluate the effects of different hemostatic approaches on patient outcomes [17].

KEY INSIGHTS AND THEIR ROLE IN CLINICAL MANAGEMENT

The discussion highlighted a notable lack of evidence supporting the benefit of endoscopy in reducing mortality rates. However, it did not thoroughly examine the potential factors that could explain this finding. For instance, the study did not consider whether the underlying hematologic malignancy or the severity of thrombocytopenia might have influenced the outcomes apart from the effects of endoscopic intervention. Furthermore, the role of platelet function assays, such as thromboelastography, in informing endoscopic decision-making is not addressed. An in-depth analysis of the mechanisms contributing to the observed outcomes would provide a more comprehensive understanding. Future research should explore the role of platelet function assays in evaluating the safety and effectiveness of endoscopic procedures for patients with thrombocytopenia.

FUTURE DIRECTIONS

Future research initiatives should prioritize conducting prospective, multicenter studies to validate the current study's findings. These investigations ought to involve larger and more diverse patient populations to improve the generalizability of the results and increase statistical power. Additionally, the potential of platelet function assays, such as thromboelastography, in influencing endoscopic decision-making warrants further exploration. These assays may offer a more precise evaluation of hemostatic function and assist in identifying patients who are suitable candidates for endoscopic procedures. Moreover, studies implementing standardized protocols for endoscopic interventions, including adopting specific hemostatic techniques, are needed. Establishing such protocols will help determine the most effective and safe methods for managing GIB in patients with thrombocytopenia.

Furthermore, it is essential to investigate the role of platelet transfusions in improving outcomes for thrombocytopenic patients undergoing endoscopic procedures[18]. Research should focus on evaluating the optimal timing and dosage of platelet transfusions to reduce the risk of bleeding. Long-term outcome studies should also be conducted to assess quality of life, recurrent bleeding, and mortality rates in patients with hematologic malignancies experiencing GIB. Understanding these outcomes will provide a more comprehensive view of the effects of endoscopic interventions in this population. Finally, developing risk stratification models is vital for identifying patients most likely to benefit from endoscopic interventions. Such models could integrate clinical, laboratory, and endoscopic findings to report decision-making processes effectively.

Future research should focus on several critical questions to enhance our understanding of endoscopic procedures for patients with low platelet counts. First, it is essential to determine the optimal platelet transfusion thresholds tailored to various endoscopic procedures, distinguishing between diagnostic and therapeutic interventions. Second, the effectiveness of newer hemostatic agents, including fibrin sealants and hemostatic powders, in minimizing bleeding risks for thrombocytopenic patients warrants investigation. Lastly, there is a need to explore how platelet function assays, such as

thromboelastography, can be effectively incorporated into clinical decision-making processes to enhance procedural safety. Addressing these issues will lead to a deeper comprehension of the risks and benefits associated with endoscopic procedures in this vulnerable patient population.

CONCLUSION

The study by Alhumayyd *et al*[5] offered valuable insights into using endoscopy to manage GIB in patients with hematologic malignancies and severe thrombocytopenia. However, the study's design, sample size, statistical analysis, and failure to account for certain confounding factors present notable limitations. Further research is necessary to understand better how to manage GIB in this high-risk population. Future studies should be prospective and multicenter, utilizing standardized protocols and advanced statistical techniques to provide more comprehensive findings.

FOOTNOTES

Author contributions: Krishnan A contributed to the concept of the study, drafted the manuscript, performed the review and editing, and critically revised and finalized the manuscript for important intellectual content.

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LETTER TO THE EDITOR

Assessing endoscopic remission in small bowel Crohn's disease: Are markers enough?

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Abstract

Mucosal healing in Crohn's disease (CD) has been established as a crucial target of treatment, leading to long term remission and decrease in complication rates. Endoscopy still serves as the gold standard for assessment, particularly in the small bowel where balloon or capsule enteroscopy is frequently needed. However, these modalities are often unavailable, expensive, and invasive, posing risks to patients. Consequently, the identification of accessible and reliable biomarkers, especially in small intestinal CD, remains a challenge. The study by Ohno *et al*, published in this issue, further illuminates this field. It confirms the potential role of fecal biomarker leucine-rich α2 glycoprotein (LRG) and validates findings from previous smaller trials. Comparing to other markers LRG showed a much higher predictive value for mucosal healing of the small bowel, making it a useful option for small intestinal CD follow up. In this editorial, we explore the optimal marker of inflammation or mucosal healing in CD, particularly in the small bowel. We provide an overview of available conventional biomarkers and introduce several novel biomarkers, including an update on emerging technologies and innovations.

Key Words: Biomarker; C-reactive protein; Crohn's disease; Diagnosis; Fecal calprotectin; Inflammatory bowel disease; Leucine-rich α2 glycoprotein

Core Tip: Small bowel Crohn's disease can be challenging to monitor during treatment. Balloon endoscopy is an invasive procedure, and capsule enteroscopy is costly. The identification of the optimal biomarker remains an ongoing research area. Leucine-rich α2 glycoprotein presents a promising solution, which is discussed in the trial conducted by Ohno *et al*.

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INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory condition that primarily affects the digestive tract. The underlying pathogenesis remains largely undefined, despite numerous theories proposed over the years. Recent data indicates a continuous and steady rise in CD cases, with a prevalence approaching 1%[1]. CD can potentially impact the entire gastrointestinal tract, causing transmural inflammation of the bowel wall[2]. The primary objective of therapeutic interventions is to induce and maintain remission, while simultaneously preventing long-term complications such as hospitalizations and surgery. Ultimately, the goal is to enhance the overall quality of life. Significant efforts have been invested over the past decade in identifying appropriate and relevant therapeutic targets[3]. The Treat-To-Target approach has gained widespread acceptance and has successfully defined specific therapeutic endpoints within a predetermined time frame[4,5]. Among these targets, mucosal healing (MH) appears to be of paramount importance. Data suggests that mucosal normalization leads to long-term clinical remission and a reduction in intestinal resection rates[6,7].

Nonetheless, the complexity of this issue is further compounded by the absence of a universally accepted definition of MH. Only recently has there been a proposal to include histologic healing in the definition[8]. In a recent trial, Sands *et al* [9] conducted a systematic review of 5530 patients diagnosed with CD, confirming that MH offered patients long-term clinical remission and a reduction in surgery and hospitalization rates. Traditionally, MH has been assessed through ileocolonoscopy, enteroscopy, or small bowel capsule endoscopy[5]. However, these procedures are expensive, invasive, and not readily accessible. Thus, a simpler, cost-effective, and more accessible MH marker is needed.

Biomarkers for CD

The National Institute of Health defines biomarkers as "a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" [10]. Ideally, biomarkers should possess simplicity, accessibility, non-invasiveness, cost-effectiveness, sensitivity, and specificity to the relevant disease[11]. All biomarkers have advantages and limitations; therefore, a concise summary of the available molecules and those potentially useful in the near future is provided below (Table 1).

Conventional biomarkers

C-reactive protein: Discovered in the 1930s, C-reactive protein (CRP) is an acute phase reactant produced in the liver by interleukin (IL)-6 and secreted during inflammation[12,13]. Widely available in most medical centers, CRP results can be obtained rapidly. While CRP levels increase with inflammation, they also correlate with various other disorders, including infections, autoimmune diseases, and cardiovascular conditions. The accuracy of disease monitoring and MH varies, with stronger correlations observed in CD rather than ulcerative colitis (UC)[14]. Sensitivity of up to 79.5% has been reported[15], although a recent study suggests that this value is primarily applicable to ileocolonic and colonic disease, with significantly lower sensitivity in isolated small bowel CD[16]. Hence, based on the available data, CRP does not appear to be a reliable marker for CD of the small intestine.

Erythrocyte sedimentation rate: Erythrocyte sedimentation rate is a well-established and one of the oldest diagnostic markers, dating back to the 1820s. It has been utilized since then to identify subacute and chronic inflammation[17]. However, its slow regulation in the body and lack of specificity (as it increases during pregnancy, anemia, and various other conditions) render it unsuitable for monitoring CD progression[18].

Fecal calprotectin: Calcium-binding protein, discovered in the 1980s and released by intestinal epithelial cells during inflammation[19,20], is a highly stable molecule. Its secretion in the gut makes it a valuable tool for measuring intestinal inflammation rather than systemic inflammation. Fecal calprotectin (FCP) has been shown to correlate well with gut inflammation, particularly in the colon, with low levels observed during endoscopic and histologic remission[21,22]. Compared to CRP, FCP has demonstrated superior diagnostic accuracy in inflammatory bowel disease (IBD), leading to its increased use in monitoring treatment responses[23]. The International Organization for the Study of IBD recommends an FCP level below 150 micg/g as a reasonable indicator of MH[5]. However, this threshold remains controversial, and no consensus has been reached. A recent systematic review demonstrated the sensitivity and specificity of FCP for endoscopic remission to be 89.7% and 93.3%, respectively, when using a strict cutoff level of 58 micg/g[24]. Another extensive review involving over 1000 patients further confirmed the positive correlation between histologic remission and FCP levels, although the authors emphasized the need for further clarification regarding the optimal cutoff level[25].

Table 1 Biomarkers and their attributes in inflammatory bowel disease

	Marker	Advantages	Limitations
Conventional markers	CRP	Readily available. Cheap. Sensitive for inflammation	Not disease specific. More sensitive for CD than UC. Lower sensitivity for small bowel disease
	ESR	Readily available. Cheap. Sensitive for inflammation	Not disease specific. Elevated in non-inflammatory conditions. More relevant for subacute than acute
	FCP	Readily available. Cheap Sensitive for gut inflammation. Can be used to monitor treatment response	Not specific for IBD. Influenced by external factors (exercise…). Lower sensitivity for small bowel disease
	FIT	Readily available. Cheap. Fair sensitivity for gut inflammation	Low specificity for IBD. Low accuracy for small bowel disease
	LRG	Independent of IL-6. More sensitive for intestinal inflammation than CRP. Acceptable correlation with small bowel disease	Not very cheap. Limited availability
Novel markers	OM	Correlates with inflammation. Can be useful in IBD	Not readily available yet. Not studied for small bowel disease
	FM	Correlates with inflammation. Can be useful in IBD	Not readily available yet. More useful in UC than CD. Not studied for small bowel disease
	F mRNA	Correlates with inflammation. Can be useful in IBD	Expensive. Not tested for small bowel disease
	BAF	Can be useful in IBD. Available data in both UC and CD. Potential role in treatment	Expensive. Not tested for small bowel disease. Not specific to IBD

CRP: C-Reactive protein; ESR: Erythrocyte sedimentation rate; FCP: Fecal calprotectin; FIT: Fecal immunohistochemical test; LRG: Leucine-rich α2 glycoprotein; OM: Oncosttatin M; FM: Fecal myeloperoxidase; Fm RNA: Fecal microRNA; BAF: B-cell activating factor; IBD: Inflammatory bowel disease: UC: Ulcerative colitis; CD: Crohn's disease; IL-6: Interleukin 6.

Conversely, studies have suggested that the accuracy of FCP in predicting MH may be higher for UC compared to CD [24], and even lower for isolated small bowel disease[26]. Furthermore, FCP levels exhibit inter-individual variability, prompting experts to suggest that multiple samples may be necessary on different days[27]. Additionally, dietary factors and exercise can influence FCP levels[28]. So despite its common use and advantages FCP remains far from optimal for use in CD.

Fecal immunohistochemical test: The fecal immunohistochemical test (FIT), commonly employed in primary care as a screening tool for colorectal cancer, detects hemoglobin in the stool[29]. Notably, its additional capability to discern inflammation suggests its potential use as a marker for IBD[30,31]. FIT demonstrated a high sensitivity for diagnosing MH in CD (0.96), although this sensitivity decreased to 0.4 in CD confined to the small bowel[32]. An intriguing hypothesis proposed combining FIT with FCP, which is favored due to its cost-effectiveness. While this combination yielded a robust predictive score for MH, it exhibited a significantly higher predictive value for UC compared to CD[33]. However, it is important to acknowledge the limitations of this approach, including low specificity and questionable accuracy for the small bowel[34].

Leucine rich α2 glycoprotein: A protein that has garnered significant attention and momentum in recent years is leucine-rich α2 glycoprotein (LRG). Secreted by hepatocytes, macrophages, and neutrophils in response to elevated cytokines, LRG has been shown to be elevated in various inflammatory conditions, including primary biliary cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, and IBD during clinical or endoscopic flare-ups[35-38]. Unlike CRP, LRG is not solely dependent on IL-6, suggesting a stronger correlation with intestinal inflammation[39]. Numerous published studies have demonstrated the role of LRG in IBD, with encouraging and positive outcomes[38].

Despite initial conflicting results, more recent studies have confirmed the utility of LRG in CD. One study from Japan validated the predictive ability of LRG for MH with a cut-off value of 16 micg/mL, achieving near-perfect accuracy when the value is below 13 micg/mL[40]. While FCP is an acceptable marker of inflammation in CD, its utility is limited in the small bowel, as previously discussed. This appears not to be the case for LRG, as evidenced by a well-designed trial conducted by Saiki *et al*[41]. In this trial, a small number of CD patients with isolated small bowel disease were identified through gastroscopy, colonoscopy, and capsule enteroscopy. The study found a strong correlation between LRG levels and the extent of mucosal damage in the small intestine. Moreover, the patient population had mild to moderate disease, suggesting that LRG can be utilized in the absence of severe disease.

The current study, published in this issue by Ohno *et al*[42], further reinforces the significance of this marker. Although it employs a retrospective design, the authors include a substantially larger sample size compared to previously published trials. This study reiterates the utility of LRG, particularly in small bowel CD, where other markers demonstrate limitations. Furthermore, it confirms the cut-off level, which appears to be within the range of 12-13 micg/mL (consistent with previous data). While well-designed randomized controlled trials are still necessary, the available data suggest a strong correlation between LRG levels and MH in the small bowel, suggesting it might currently be the most

acceptable marker for this patient population.

Novel biomarkers

Oncostatin M: The cytokine family encompasses oncostatin M (OSM), which regulates a diverse range of factors, including IL-6[43]. Elevated OSM levels have been observed in patients with IBD and may correlate with the severity of the disease and the level of inflammation[44]. OSM can be detected in fecal samples and has been demonstrated to be useful in conjunction with FCP[45]. However, to date, there has been no verification of a correlation between OSM levels and isolated small bowel CD.

Fecal myeloperoxidase: Similar to FCP, this fecal neutrophil marker plays a significant role in defending against bacteria while also promoting inflammation[46]. Previous small-scale studies have suggested a role in IBD, particularly in UC[47,48]. A larger study that included both UC and CD patients demonstrated a correlation between disease severity and the marker's performance, comparable to that of FCP[49]. However, the study did not stratify patients based on disease location.

Fecal micoRNAs: Small, non-coding RNAs are present in extracellular fluids and are believed to contribute to inflammation in IBD. Studies have demonstrated their elevated level in the stool of patients with active inflammation[50,51]. Ongoing research suggests a correlation between the level of these RNAs and disease activity in CD patients[52].

B-cell activating factor: A cytokine belonging to the tumor necrosis factor family, B-cell activating factor (BAFF), plays a role in the development of immune cells[53]. Several autoimmune diseases, such as rheumatoid arthritis and Sjogren's syndrome, are associated with elevated BAFF levels[54]. BAFF has been demonstrated to correlate with inflammation in IBD patients, including both UC and CD, with high expression in the intestinal mucosa[55,56]. It is present in feces, serum, and colonic tissues[57]. Furthermore, studies have shown a correlation between BAFF levels and disease activity [55]. Fu *et al*[58] conducted a noteworthy trial in which BAFF was compared to FCP and fecal occult blood test for the prediction of IBD from irritable bowel syndrome (IBS). The results demonstrated that BAFF (levels ≥ 227.3 pg/mL) exhibited superior accuracy in distinguishing IBD from IBS, as well as a higher correlation with the endoscopic inflammatory score in both UC and CD patients. More recent publications have also suggested the potential therapeutic role of BAFF blockade in the management of IBD[59,60]. It appears that this marker will play a significant role in the future diagnosis and potentially treatment of CD patients, although data for small bowel disease remains pending.

Future trends

New markers need proper validation through both large scale pre-clinical and clinical trials to establish and confirm their usefulness. In addition to these novel molecules being studied, newer methods of measuring older markers are currently being developed. For instance, one advancement includes a rapid point-of-care (POC) test for FCP that replaces the time-consuming ELISA technique. A study has demonstrated the rapidity and reasonable agreement of this test with the conventional test[61]. Another novel approach involves a smartphone application that can scan stool and calculate FCP concentration, enabling results for patients at the comfort of their own home[62]. An additional innovation includes a sensor bracelet that can measure CRP and IL-1β levels through sweat gland secretions and provide continuous monitoring throughout the day[63]. Furthermore, there is growing interest in urinary markers as a method for measuring inflammation in IBD, which may provide patients with a more convenient option compared to stool tests, which can often be cumbersome[64].

Artificial intelligence (AI) and machine learning (ML) are revolutionizing various fields, including healthcare. The utilization of AI in the diagnosis and management of IBD has demonstrated remarkable diversity and efficacy[65]. Novel AI-powered programs possess the capability to analyze a comprehensive range of variables, including biomarkers, symptoms, radiologic, and endoscopic images, with the aim of predicting flare-ups and subsequently generating precise, personalized treatment plans tailored to individual patients[66]. One notable example is the application of support vector machines (SVM), an AI model capable of predicting the disease course and response to therapy by analyzing a multitude of subjective and objective variables. Consequently, personalized medical protocols are generated[67]. Several ML models have been developed, but the SVM model appears to be particularly impressive, exhibiting notable performance in predicting inflammation scores among patients with CD, with sensitivity of 0.95, specificity of 0.92, and accuracy of 0.93[68]. As with any innovation or technological advancement, including the development of new devices, it is imperative to acknowledge the potential limitations, particularly ethical and patient privacy concerns. Consequently, it is crucial to draft appropriate legislation and enforce rigorous validation studies to ensure the safety and efficacy of these technologies.

CONCLUSION

The treatment of CD has undergone significant advancements over the past decade, resulting in improved outcomes and increased rates of remission with reduced disease-related morbidity. However, follow-up of patients with small bowel CD remains challenging for physicians. The available modalities are invasive and costly, and the current biomarkers are not yet optimal. LRG offers a novel potential, sensitive, and specific option for this subtype of patient population. The study by Ohno *et al*[42] confirms previous encouraging results and defines the suspected cut-off level in a retrospective trial with a relatively large patient cohort. Nevertheless, prospective randomized trials are still necessary to validate this marker and incorporate it into our diagnostic arsenal. With the advent of AI and deep learning models, the progression of methods for diagnosing and managing IBD patients will be highly exciting to observe in the coming years.

FOOTNOTES

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LETTER TO THE EDITOR

Leucine-rich alpha-2 glycoprotein for detecting small bowel lesions in Crohn's disease: A critical review and the path forward

Arunkumar Krishnan

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Abstract

The study by Ohno *et al* provides valuable insights into the role of leucine-rich alpha-2-glycoprotein (LRG) as a potential biomarker for identifying small bowel lesions in Crohn's disease (CD). However, several methodological challenges hinder its immediate use in clinical practice. Notably, the current research was retrospective, lacks comparative studies with fecal calprotectin, and did not provide long-term predictive data. Further prospective studies are needed to improve the applicability of LRG. Moreover, integrating LRG with additional biomarkers and employing artificial intelligence techniques may improve its effectiveness in disease monitoring. Future research should address interobserver variability, assess LRG's cost-effectiveness, and standardize endoscopic healing definitions to ensure broader applicability. Advancing these areas is vital for establishing LRG's role in precision medicine strategies for the management of CD.

Key Words: Crohn's disease; Leucine-rich alpha-2 glycoprotein; Biomarkers; Small bowel lesions; Inflammatory bowel disease; Disease monitoring; Precision medicine

Core Tip: A recent study by Ohno *et al* indicated that leucine-rich alpha-2 glycoprotein (LRG) has potential as a biomarker for identifying small bowel lesions in Crohn's disease. However, several methodological challenges are required to be addressed. The retrospective nature, the lack of direct comparisons with fecal calprotectin, and the absence of long-term data highlight the need for further validation. Moreover, there is potential for improving the utility of LRG by integrating it with other biomarkers and artificial intelligence to improve its effectiveness in disease monitoring. Future research should address interobserver variability, assess the cost-effectiveness, and standardize definitions for endoscopic healing.

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TO THE EDITOR

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can cause transmural inflammation throughout any part of the gastrointestinal tract[1]. One of the key treatment objectives is achieving endoscopic healing (EH), which is linked to improved long-term outcomes, such as decreased hospitalization rates, fewer surgeries, and improved quality of life for patients[2]. However, accurately assessing EH, particularly in the small intestine, presents challenges due to the limitations of existing biomarkers like C-reactive protein (CRP) and fecal calprotectin (FC)[3]. Recently, leucine-rich alpha-2 glycoprotein (LRG), a 50-kilodalton protein produced in response to inflammatory conditions, has garnered attention as a potential biomarker for monitoring disease activity in CD[4]. Emerging research indicates a strong correlation between LRG levels and endoscopic and clinical activity in CD, particularly concerning small bowel lesions[1, 4]. However, its effectiveness in predicting EH compared to CRP has not been thoroughly investigated.

LRG shows promise for application in several clinical contexts, particularly in the early detection and monitoring of small bowel lesions associated with CD. It can complement endoscopic evaluations, offering a more comprehensive assessment of disease activity[2]. For patients with suspected CD who have inconclusive imaging or endoscopic results, LRG levels can serve as an additional diagnostic tool, aiding in the direction of further investigations. Furthermore, LRG has the potential to be incorporated into routine follow-up protocols to monitor treatment responses and predict the likelihood of disease relapse. By delivering real-time insights into disease activity, LRG can assist clinicians in tailoring treatment strategies to meet the specific needs of individual patients, thereby enhancing overall patient outcomes.

In observance of this, we read with great interest the manuscript by Ohno *et al*[5] entitled "Leucine-rich alpha-2 glycoprotein as a superior biomarker to CRP for detecting small bowel lesions in Crohn's disease". The study studies an important clinical question regarding the utility of LRG as a biomarker for detecting small bowel lesions in CD, particularly in comparison to the widely used CRP. The study presented important preliminary data suggesting that LRG may be more effective than CRP in identifying small bowel lesions in CD. These findings show a basis for future research and emphasize the necessity for additional validation of LRG as a biomarker.

While the study provides valuable insights into the potential superiority of LRG over CRP in assessing EH in CD, several methodological, statistical, and interpretative limitations warrant discussion that need to be addressed to understand the clinical applicability of LRG in practice. By addressing the methodological and analytical limitations pointed out in this critique, subsequent studies can enhance the work of Ohno *et al*[5] and work towards establishing LRG as a dependable tool for managing CD.

Methodological limitations

The study was retrospective in nature, which could introduce the risk of selection bias. Despite the analysis of consecutive patients, the established exclusion criteria, including active perianal disease and varying disease conditions or treatments, may have resulted in the omission of patients with more severe or complex disease phenotypes. This limitation could affect the generalizability of the findings to the broader CD population, particularly those with comorbidities or more aggressive forms of the disease. We recommend that the authors consider adopting a prospective study design with clearly defined inclusion and exclusion criteria, thereby minimizing selection bias to improve upon this. Additionally, it would be beneficial to include a more diverse patient population, particularly those with perianal disease or other comorbidities, to enhance the external validity of the findings.

The current exclusion criteria did not consider systemic inflammatory conditions that could elevate LRG levels. Furthermore, this study only included one patient using steroids, restricting the ability to generalize the results to those on corticosteroids or other immunosuppressants. Future studies should consider stratifying patients based on their disease-modifying therapies and any coexisting inflammatory conditions to help mitigate this source of bias.

Another point of consideration is the median period of 18 days between LRG measurement and BAE, with a range extending up to 60 days. This delay may introduce variability in the correlation between LRG levels and endoscopic findings, as disease activity can fluctuate over time. Although the authors assert that this timeframe is similar to prior studies, it still represents a potential confounding factor. Future studies should minimize the interval between biomarker measurements and endoscopic evaluations to reflect disease activity during assessment better and increase accuracy. This study primarily concentrated on the ileum and colon, offering a limited assessment of the jejunum due to the retrograde approach of BAE. Considering that CD can affect any area of the gastrointestinal tract, excluding the jejunum could lead to an underestimation of the true extent of small bowel involvement and the efficacy of LRG as a biomarker[6]. Future research should utilize antegrade BAE or alternative imaging techniques, such as capsule endoscopy, to comprehensively evaluate the entire small bowel, including the jejunum[7].

Analytical concerns

The study's sample size of 133 participants was relatively small for conducting subgroup analyses, which may increase the risk of type. It is recommended that a power analysis be conducted and the sample size II errors be increased to ensure that future studies yield statistically meaningful comparisons.

Spearman's rank correlation coefficient was employed to evaluate the relationship between LRG and endoscopic activity, which is suitable for non-parametric data[8,9]. However, the analysis did not account for potential confounding factors such as medication usage (*e.g.*, biologics, immunomodulators) or disease behavior (*e.g.*, stricturing *vs* penetrating disease). These variables may affect LRG levels and endoscopic results, potentially introducing bias into the findings. Future research should utilize multivariate regression analysis to adjust for these confounding variables, mainly focusing on medication use and disease phenotype to more accurately determine the independent predictive value of LRG.

The receiver operating characteristic analysis indicated that LRG exhibited a higher area under the curve than CRP for predicting EH in the ileum. However, the study did not investigate the possible added value of combining LRG with other biomarkers, such as FC, which has been previously shown to correlate with small bowel disease activity. Moreover, the LRG cutoff value of 12.4 μg/mL was derived from a single cohort, raising questions about its generalizability to other populations. Exploring the combined use of LRG and FC or other biomarkers is important to enhance EH's prediction accuracy. Furthermore, external validation of the LRG cutoff value in independent cohorts is crucial to confirm its clinical utility[10].

While patients were categorized based on EH, the study did not fully account for disease severity at baseline, treatment history, or previous surgical interventions. These factors could significantly influence biomarker levels. Future research should integrate disease severity scoring and perform stratified analyses based on prior treatments to enhance the interpretation of results. Lastly, the study did not include FC, a well-established biomarker for CD. Without comparing LRG to FC, the clinical significance of LRG as a superior biomarker remains uncertain. Future studies should aim to compare LRG with FC and other emerging biomarkers to establish its relative efficacy.

Bias and result interpretation

The study involved three expert endoscopists who conducted the procedures; however, it is important to note that interobserver variability was not evaluated. This lack of assessment introduces a degree of subjectivity in the endoscopic evaluations, which may have influenced the findings[11]. Future research should employ standardized scoring methods and interobserver agreement analyses to reduce potential bias.

Additionally, the study presents cross-sectional data, which limits the ability to determine whether LRG levels can predict long-term clinical outcomes or treatment responses. Longitudinal studies are needed to understand better LRG's role in predicting disease progression and treatment efficacy[12]. The patient population under study demonstrated significant heterogeneity concerning disease behavior, medication usage, and prior intestinal resections. For instance, the use of biologics differed notably between the EH group, with 83.6% receiving treatment, and the ileal group, at just 42.6%. This variability could potentially confound results, as biologics are known to affect both biomarker levels and EH. Future studies should stratify patients according to disease behavior and medication use to evaluate LRG's performance in more homogeneous subgroups.

The definition of EH as the absence of ulcerative lesions (mSES-CD < 3 points) is used in this study. However, it is worth noting that definitions of EH can differ across studies, with some employing stricter criteria (*e.g.*, mSES-CD = 0). This variability in the definition may impact both the interpretation of the results and the generalizability of the findings. Standardizing definitions of EH, as suggested by international consensus guidelines, could facilitate comparison across different studies. Moreover, the study did not control for disease severity, duration, or previous surgical interventions, which can affect biomarker levels[13]. Variations in treatment regimens among different patient subgroups may also influence the results. Therefore, it is recommended that future studies include stratified analyses based on disease duration, phenotype, and treatment history.

Furthermore, the analysis relied on a single measurement of LRG and CRP, which might not adequately reflect the dynamic nature of disease activity in CD. Although three experts carried out the endoscopic scoring, the lack of reported interobserver variability raises concerns about potential measurement bias[14]. Future research should incorporate repeated biomarker measurements to account for fluctuations in disease activity and ensure that interobserver agreement for endoscopic scoring is reported to confirm the findings' reliability.

Finally, the study did not address the possibility of publication bias, especially given its positive findings on LRG's superiority over CRP. Negative or inconclusive results from similar studies may remain unpublished, potentially leading to an overestimation of LRG's effect size. Therefore, further analysis should be conducted to comprehensively assess the overall evidence for LRG as a biomarker in CD, including consideration of unpublished data to provide a more objective perspective on its clinical utility.

Future directions

Future studies need to be conducted across multiple centers, employing a prospective design that includes larger and more diverse patient populations to overcome the limitations identified in the current research. Such an approach would significantly improve the generalizability of the findings, enabling researchers to perform subgroup analyses that consider various factors, including disease phenotype, types of medication used, and other pertinent characteristics that could influence outcomes.

Moreover, future investigations should focus on integrating LRG with additional biomarkers such as FC and advanced imaging techniques like magnetic resonance enterography[15]. This multifaceted methodology could lead to a more holistic understanding of disease activity in CD, facilitating improved diagnostic precision and management strategies.

Longitudinal studies are also crucial to thoroughly assess LRG's potential as a biomarker for monitoring the progression of CD and evaluating the response to various treatment regimens over an extended period. Gaining insights from such studies would enhance our understanding of LRG's role within the treat-to-target strategy, ultimately improving patient therapeutic outcomes.

Additionally, the application of artificial intelligence (AI) holds promise for gastroenterology[16]. By utilizing AI-driven pattern recognition algorithms, researchers can refine predictive models for assessing disease activity, allowing for more accurate forecasts of disease course and better-informed clinical decisions[17,18]. Establish consistent definitions of EH to enhance the ability to compare results across different studies and streamline clinical decision-making processes. It is important to use an advanced statistical methodology, including sophisticated machine learning algorithms, to delve into extensive datasets and uncover innovative combinations of biomarkers that could significantly elevate the efficacy of disease monitoring[19].

Similarly, the cost-effectiveness of LRG, in contrast to traditional biomarkers, should be assessed to assess its viability for integration into routine clinical practice. Evaluating the cost-effectiveness of LRG as a biomarker for managing CD is another crucial area for further investigation for its potential implementation in clinical settings. Although LRG demonstrates promise in identifying small bowel lesions, it is important to assess its economic viability compared to established biomarkers like CRP and FC. This includes considering the costs associated with LRG testing, such as laboratory processing and necessary equipment, its diagnostic accuracy, and its potential to lower long-term healthcare expenses through enhanced disease monitoring and improved treatment outcomes. Future research should consider incorporating cost-benefit analyses to determine if LRG presents a cost-effective or complementary alternative to current biomarkers. Furthermore, it would be beneficial to examine how integrating LRG with other diagnostic modalities, including imaging techniques, may influence overall healthcare costs. Finally, explore the promise of LRG in steering personalized treatment approaches for CD, aligning with a treat-to-target strategy aimed at maximizing patient outcomes and ensuring tailored interventions.

CONCLUSION

The present study offered encouraging insights into the potential of LRG as a biomarker for detecting small bowel lesions in CD; it is essential to recognize several methodological and interpretative challenges that need to be addressed. Tackling these limitations and adopting the recommendations outlined previously can pave the way for future research to elucidate the true significance of LRG in CD management, ultimately enhancing patient care and outcomes. Furthermore, integrating cutting-edge AI-driven analytics and comprehensive multimodal biomarker evaluations is crucial for solidifying LRG's pivotal role in the intricate landscape of managing CD.

FOOTNOTES

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