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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

Computed tomography for the prediction of oesophageal variceal bleeding: A surrogate or complementary to the gold standard?

Yasser Fouad, Mohamed Alboraie

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Abstract

In this editorial we comment on the in-press article in the *World Journal of Gastrointestinal endoscopy* about the role of computed tomography (CT) for the prediction of esophageal variceal bleeding. The mortality and morbidity are much increased in patients with chronic liver diseases when complicated with variceal bleeding. Predicting the patient at a risk of bleeding is extremely important and receives a great deal of attention, paving the way for primary prophylaxis either using medical treatment including carvedilol or propranolol, or endoscopic band ligation. Endoscopic examination and the hepatic venous pressure gradient are the gold standards in the diagnosis and prediction of variceal bleeding. Several non-invasive laboratory and radiological examinations are used for the prediction of variceal bleeding. The contrast-enhanced multislice CT is a widely used non-invasive, radiological examination that has many advantages. In this editorial we briefly comment on the current research regarding the use of CT as a non-invasive tool in predicting the variceal bleeding.

Key Words: Computed tomography; Esophageal varices; Bleeding; Non-invasive predictor; Endoscopy

Core Tip: Predicting the patient at a risk of variceal bleeding is extremely important and receives a great deal of attention, paving the way for primary prophylaxis either using medical treatment including carvedilol or propranolol, or endoscopic band ligation. Endoscopic examination and the hepatic venous pressure gradient are the gold standards in the diagnosis and prediction of variceal bleeding. The computed tomography (CT) is a widely used non-invasive, radiological examination that can be used as a predictor of variceal bleeding and has many advantages. Conflicting results have been shown regarding the effectiveness of CT in predicting variceal bleeding and more studies are needed.

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INTRODUCTION

A well-known complication of chronic liver disease, with a high mortality rate, is bleeding esophageal varices. Mortality and morbidity rates are significantly increased in patients with chronic liver disease when complicated with variceal bleeding[1,2]. For logical reasons, many researchers have been keen to study the use of non-invasive techniques in the field of liver diseases. Patient comfort, avoiding high costs, and saving time were the main factors that stimulated research in this aspect. Predicting a patient's risk of bleeding is extremely important and receives a great deal of attention, as it paves the way for primary prophylaxis with either medical therapy including carvedilol or propranolol, or endoscopic band ligation[3,4].

Predictors of variceal bleeding

Although esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis, management, and prognosis of bleeding esophageal varices, it is invasive, costly, and sometimes lacks inter-observer agreement regarding the size of the varices compared to computed tomography (CT) in some previous studies[5].

Another gold standard is the hepatic venous pressure gradient (HVPG). Although the HVPG can predict the occurrence of variceal bleeding and assess the response to medical treatment, it is an invasive and expensive procedure, requires high expertise and is not widely available in clinical practice[3,6,7].

Several non-invasive laboratory and radiological examinations are used for the prediction of variceal bleeding. A recent systemic review highlighted the predictive factors of variceal bleeding. These factors included Child-Pugh score, ultrasound parameters, ascites, specific endoscopic findings, Fibrosis Index, portal vein diameter, CT scan findings, presence and size of collaterals, platelet counts, Von Willebrand Factor, coagulation parameters, and the use of β-blocking agents. Although this systemic review identified multiple potential predictive factors for esophageal variceal bleeding, several limitations and biases could influence the conclusions with further validations needed[8].

The role of ultrasound in the prediction of variceal bleeding was studied. The relation between left gastric vein diameter and variceal bleeding revealed significant results. Moreover, a comprehensive Model for End-Stage Liver Disease-Ultrasound Doppler index emerged as another predictive factor with better performance as a predictor of varices and its complications[9,10].

Assessment of liver and splenic stiffness in patients with chronic liver diseases has been shown in a few studies. High splenic and liver stiffness predicted esophageal variceal bleeding[11-13].

The role of CT in prediction of variceal bleeding

In a recent meta-analysis, CT imaging, as a non-invasive method, was superior to liver stiffness measures (LSM) and magnetic resonance imaging for predicting esophageal varices and variceal bleeding in patients with cirrhosis[14].

CT is a widely used non-invasive, contrast-enhanced multislice radiological examination. It is a well-tolerated, cost-effective procedure, requiring no sedation with the advantage of simultaneous detection of hepatic benign and malignant lesions. The three-dimensional post-processing of imaging data allows precise examination of the portal vein and its branches with subsequent guidance of decision-making and surgical or radiological interventions using transjugular intrahepatic portosystemic shunt. The CT can differentiate between peri esophageal and submucosal gastroesophageal varices in a matter closely related to the endoscopic examination results. The CT contrast can be seen in the portal vein and parallel vascular pathways and may reach the esophagus in patients with active variceal bleeding[14,15].

The CT findings in cirrhotic patients with esophageal varices include the presence and size of various collaterals (including paraesophageal and paraesophageal draining collaterals, coronary and short gastric veins). These findings are accurate predictors of either oesophageal varices or recurrence of oesophageal variceal bleeding[16]. Furthermore, in patients with uncontrolled variceal bleeding, intraluminal protrusion of gastric varices, gastric varix size, and larger spleen and liver volumes, were predictive of refractory variceal bleeding and portal venous intervention[17].

Investigators included CT in a nomogram for better prediction of the risk of variceal bleeding. A nomogram including CT, hemoglobin, platelet count, albumin to globulin ratio, fasting blood glucose, and serum chloride, has been found to be significantly associated with the risk of variceal bleeding[18].

Recently, a machine learning model based on contrast-enhanced CT was developed to predict the risk of complications or death in patients with acute variceal bleeding. The Liver-Spleen model based on contrast-enhanced CT was effective in predicting the prognosis of patients with variceal bleeding with a positive impact on decision-making and personalized therapy in the clinical settings[19].

In the current issue of *World Journal of Gastrointestinal Endoscopy*, Martino *et al*[20] in their systemic review explored the role of CT in the prediction of oesophageal variceal bleeding. They included 9 articles in their analysis. The studies were geographically covering most parts of the world and significant findings were recorded. Conflicting results are shown with some recommendations from the authors. The most important recommendation is the need for large multicentre prospective studies[20].

Although a lot of research studies highlighted the importance of CT in the prediction of esophageal variceal bleeding, there are no guidelines or societal recommendations regarding the use of CT in cirrhotic patients to predict variceal bleeding risk. Recently, the Chinese Societies of Gastroenterology endorsed a recommendation for the use of LSM combined with platelet count and multislice contrast-enhanced CT as non-invasive examinations for the diagnosis of portal hypertension in cirrhosis[21].

CONCLUSION

We believe that CT, when used in combination with other tools, can help predict patients at very high risk, but currently it cannot replace EGD or HPVG in predicting the risk of variceal bleeding. We may recommend reminding clinicians and radiologists to invest in the regular use of CT scan in monitoring patients with liver disease to highlight indicators of portal hypertension and risk of variceal bleeding (*e.g.* coronary veins and short gastric veins). Routine screening of these indicators will be crucial for better follow-up of liver patients and help in making decisions for endoscopic or medical prophylaxis. Further research integrating CT with other non-invasive measures and artificial intelligence will have tremendous value in clinical applications and personalized medicine.

FOOTNOTES

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EDITORIAL

Precision in detecting colon lesions: A key to effective screening policy but will it improve overall outcomes?

Luis Ramon Rabago, Maria Delgado Galan

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Abstract

Colonoscopy is the gold standard for the screening and diagnosis of colorectal cancer, resulting in a decrease in the incidence and mortality of colon cancer. However, it has a 21% rate of missed polyps. Several strategies have been devised to increase polyp detection rates and improve their characterization and delimitation. These include chromoendoscopy (CE), the use of other devices such as Endo cuffs, and major advances in endoscopic equipment [high definition, magnification, narrow band imaging, i-scan, flexible spectral imaging color enhancement, texture and color enhancement imaging (TXI), *etc.*]. In the retrospective study by Hiramatsu *et al*, they compared white-light imaging with CE, TXI, and CE + TXI to determine which of these strategies allows for better definition and delimitation of polyps. They concluded that employing CE associated with TXI stands out as the most effective method to utilize. It remains to be demonstrated whether these results are extrapolatable to other types of virtual CE. Additionally, further investigation is needed in order to ascertain whether this strategy could lead to a reduction in the recurrence of excised lesions and potentially lower the occurrence of interval cancer.

Key Words: Colonoscopy screening; Interval colorectal cancer; Post colonoscopy colorectal cancer; chromoendoscopy; Virtual chromoendoscopy; high-definition white-light endoscopy; Texture and color enhancement imaging; Indigo carmine; Adenoma; Sessile serrated lesion

Core Tip: The endoscope's texture and color enhancement imaging mode, combined with chromoendoscopy, has demonstrated improvements in the characterization of mucosal colonic lesions, providing better visualization of their borders and lesion surfaces. However, its real impact on lesion recurrence and rates of interval cancers is yet to be proven through more prospective studies.

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INTRODUCTION

Colorectal cancer (CRC), as the authors point out, is the third most prevalent cancer in men and women, representing 10% of global cancer cases. The risk of cancer increases with age, and it is most frequently diagnosed after the age of 50[1].

The colonoscopy study is the most widely accepted method for screening and diagnosing CRC, and is considered the gold standard in the field[2]. It allows for the diagnosis and resection of many preneoplastic lesions, directly contributing to the decrease in the incidence and mortality of this disease[3]. However, the efficacy of colonoscopy is closely related to its ability to detect these preneoplastic lesions[4,5].

Colonoscopy studies showed a rate of undetected polyps of approximately 22%-26% of adenomas smaller than 5 mm, and 13% of adenomas about 5-10 mm[6]. Additionally, there is some evidence suggesting that colonoscopy is more effective in preventing left-sided CRC compared to right-sided CRC[3,7]. This discrepancy is likely associated with challenges such as inadequate cleansing of the right colon and the frequent presence of pale mucosal lesions with a flat morphology in this region.

ENHANCING THE DETECTION OF COLONIC LESIONS: METHODS AND STRATEGIES

In the interest of improving the detectability of colonic lesions, scientific societies have developed various guidelines for clinical practices, aiming to recommend the most effective methods to achieve appropriate colon cleansing[4,8].

At the same time, they have advocated for the utilization of colonoscopy with the assistance of chromoendoscopy (CE); initially defined as a method of staining tissues using pigments and colorants[9].

These substances are applied to the mucosa using an endoscopic catheter[10] to characterize and enhance the visualization of preneoplastic lesions. The ultimate objective is to facilitate their complete excision, thereby enhancing the overall efficiency of colonoscopy[11,12].

The types of colorants can be classified based on their interaction with the colonic mucosa[10,12]. (1) Reaction colorants: Examples include Congo red stain. This colorant reacts with components of the mucosa, thereby inducing characteristic color changes; (2) Absorption colorants: Examples are methylene blue, gentian violet, or acetic acid. These colorants are absorbed by the cells into the cytoplasm or nucleus, triggering changes in coloration[13]; and (3) Contrast colorants: Indigo carmine is an example. This colorant accumulates on the mucosal surface, aiding in delineating the mucosa itself and providing visual contrast[10,12].

The application of colorants can be selective, focusing on specific lesions once they have been detected with white-light imaging (WLI). Alternatively, it can be unselective, involving the spraying of larger areas of the mucosa to improve the detectability of lesions. Nevertheless, pan-CE of the colon has not shown a significant increase in the detection rate of polyps when compared to standard colonoscopy. Nevertheless, its use is not recommended as a conventional screening method[14], but it proves highly valuable in the surveillance colonoscopy of inflammatory bowel[15]. Furthermore, this complex procedure increases the duration of the exploration and costs.

The primary advantages of employing colorants reside in the simplicity of the technique and its relatively low cost, as it does not require specific or sophisticated devices. This approach enables the differentiation between neoplastic and nonneoplastic lesions, characterizes their boundaries, and examines their surface, thereby predicting the risk of deep invasion of the mucosa[16].

Essentially, this technique enhances resection procedures, mitigates the risk of interval CRC, and assists in selecting the most appropriate treatment approach. Consequently, it reduces the likelihood of unnecessary and potentially risky resections, ultimately leading to a decrease in undesirable adverse events[10,17].

Even though CE significantly increases the positive and negative predictive values in the characterization of colonic lesions, it is still inaccurate when it comes to predicting histology. As a result, CE is not considered a substitute for histologic biopsy, especially in lesions without an apparent risk of malignization.

It is worth noting that most CE studies have been conducted by expert endoscopists with considerable experience in CE. The significance of expertise becomes evident when considering the limited utility of CE in the hands of endoscopists lacking extensive experience in this technique, highlighting the importance of skill in achieving accurate results[18].

CLINICAL IMPLICATIONS OF SCREENING COLONOSCOPIES USING CONTRAST-ENHANCED IMAGING AND ADVANCED ENDOSCOPIC EQUIPMENT

In the past 15 years, there have been substantial advancements in endoscopic equipment, markedly improving the visualization of the colonic mucosa and enhancing the detection of mucosal lesions. Modern colonoscopes now boast high-definition capabilities with resolutions surpassing a million pixels. However, despite these technological enhancements, the utilization of high-tech colonoscopes has only yielded a modest 3.5% improvement in the rate of adenoma detection compared to conventional endoscopes[19].

Various devices have been developed to adhere to the endoscope, aiming to increase the rate of colonic lesion detection. In 2018, Williet *et al*[20] published the results of a meta-analysis involving the Endo Cuff, encompassing over 12 trials and more than 8000 patients. The study demonstrated a higher rate of adenoma detection, particularly proving relevant for endoscopists with a moderate adenoma detection rate[20,21].

Various companies have developed diverse endoscopic tools to better characterize lesions and establish a strong correlation with endoscopic histology, enabling more informed decisions and maximizing the benefits of CE.

The magnification capability enables image enlargement of up to 150 times, facilitating the analysis of characteristics of colonic polyps[22] such as those obtained using the Kudo pattern. This analysis aids in distinguishing neoplastic from non-neoplastic lesions by examining the type of crypts and mucosal surface[23].

A meta-analysis comprising over 20 studies and involving a total of 5111 colorectal lesions[24], revealed a sensitivity of 89% and a specificity of 85.7% when using magnification to differentiate between neoplastic and non-neoplastic lesions. Additionally, the Kudo's classification demonstrates good concordance in both inter and intraobserver agreement for histologic prediction among expert endoscopists[25].

Virtual CE is an innovative endoscopic imaging technology that captures a more detailed image of the mucosa surface and vessels[26]. This enhancement is achieved through the use of a short-wavelength narrow-band red/green/blue filter, that selects specific wavelengths of light (415- and 540-nm short- and medium-wavelength filters), such as narrow band imaging[27] , or by employing different postprocessing systems for WLI like flexible spectral imaging color enhancement (FICE) or i-scan[23,26].

Utilizing NBI, a new international classification of colorectal lesions, known as NBI international colorectal endoscopic (NICE), has been developed. This classification relies on the assessment of color, vascularization, and the pattern of the mucosal surface of the lesions[28,29].

One of the most significant advantages of this classification is its versatility, as it can be applied both with and without magnification. It boasts a diagnostic accuracy of 89%, with an impressive sensitivity of 98%. Moreover, it demonstrates a negative predictive value of 95%, making it particularly useful for effectively ruling out adenomas in small polyps[27].

Additionally, a recently introduced Japanese classification system using NBI is known as the Japanese NBI Expert Team (JNET)[28]. This classification further refines the NICE classification by subdividing it into 4 types. Within this system, NICE 2 lesions are further categorized into 2A for low-grade adenomas and 2B for high-grade adenomas, necessitating the use of magnification. Unlike NICE, the JNET classification requires the use of magnification, consequently limiting its broader applicability[22]. Another drawback is its inapplicability to serrated polyps, mirroring the limitations observed in the NICE classification.

The workgroup serrated polyps and polyposis classification combines the findings of the NICE classification with four other characteristic features commonly associated with serrated polyps. The presence of two or more of these features is adequate for diagnosing a serrated sessile lesion[30].

Several studies have also compared high-definition colonoscopy with NBI colonoscopy, revealing no discernible differences in the rate of polyps and adenomas detection. However, the NBI classification has proven to be significant in the characterization and classification of polyps. It excels in differentiating between adenomatous and hyperplastic polyps, particularly when in the hands of expert endoscopists[26,28].

Similarly, additional studies have found comparable effectiveness between colonoscopy using I-scan mode and FICE mode[26]. While both techniques demonstrate efficacy in detecting non-neoplastic lesions, there are no significant differences observed when compared to high-definition WLI regarding the rate of adenoma detection.

Studies comparing NBI with i-scan and NBI with FICE have not revealed any significant differences in the characterization of mucosal lesions or in the detection of polyps[28].

Blue laser imaging (BLI) produces an image by combining two sources of laser light with different wavelengths. It utilizes a laser of 450 nm with fluorescence light equivalent to xenon light, and another laser of 410 nm within the blue light spectrum. The simultaneous use of both lasers enhances the information about the mucosal surface and vascular pattern[31]. This system offers four modes that can be selected on the endoscope, each with a distinct contrast, making it more suitable for the exploration of specific characteristics of the lesion.

Very recently, a new system called TXI (Texture and color enhancement imaging) has been developed to improve endoscopic visualization. It enhanced three aspects of white light—texture, brightness, and color—allowing for better definition of subtle changes in the explored tissues[32].

In the recent issue of the *World Journal of Gastrointestinal Endoscopy*, the study by Hiramatsu *et al*[33] aims to explore the variances in detectability of the borders and surface characteristics of polypoid lesions seen during a screening colonoscopy, employing various endoscopic modes including WLI, CE, TXI, and TXI + CE. This retrospective study, conducted by a board-certified fellow/trainer, is characterized by its simplicity, intelligence, and effective execution. The recorded images were subsequently assessed retrospectively by a team of senior endoscopists using a straightforward scoring system. The outcome of the author's study demonstrates that the combination of TXI and CE is the most effective method for characterizing the features of polypoid lesions, surpassing WLI and even CE alone.

DISCUSSION

For many years, it has been widely established that initially, CE[10,15,17] or, to a lesser extent, virtual CE with NBI, BLI, or I-Scan, were promising methods for enhancing the detectability of colonic lesions[23,26,27]. However, the use of CE from the outset of the exploration resulted in increased time consumption and added expenses.

Undoubtedly, the skills of the endoscopist, the use of efficient colon cleansing techniques for a clear colon, and the duration of the procedure - especially during scope withdrawal[34] - greatly impact the detection of different lesions, particularly serrated ones in the cecum or ascending colon. These factors also reduce the likelihood of interval CRC[35].

While there is a well-established understanding that detecting a higher number of polyps during procedures correlates with a reduced rate of interval cancers[4,5], it's important to recognize that this correlation may be influenced by the ability to accurately identify and delineate challenging lesions, like sessile serrated adenomas (SSAs). The author's study is not designed to investigate this topic directly, but rather to analyze various methodologies to enhance the visualization of surface characteristics and polypoid lesion borders.

It is crucial to acknowledge that, based on our current knowledge, there is no definitive evidence establishing a direct correlation between the number of polyps detected during a screening procedure and an immediate increase in the detection of colon cancer in the same session, nor a decrease in morbidity within the studied cohort. However, it is recognized that a relationship exists between missed lesions or incomplete resected lesions and interval colon cancer[35], and it's conceivable that the number of missed lesions might be higher in procedures with a low rate of adenomas detected.

The complexity involved in surface identification and border delineation, especially for SSAs, highlights the need for the implementation of advanced screening techniques and a comprehensive approach. This is crucial to reduce the likelihood of missing these lesions or conducting incomplete resections during colonoscopy procedures[36].

It is essential to address certain limitations identified in the study. One significant drawback pertains to the subjective nature of the scoring system employed. The scale, ranging from 1 (not detectable without repeated careful observation) to 4 (easily detectable), may introduce a notable level of subjectivity. This subjectivity should be considered when evaluating the robustness of the study results.

An additional important consideration, and an ongoing limitation for future research, is whether these findings can be replicated using other imaging technologies, such as NBI, BLI, or i-scan in conjunction with CE. Demonstrating consistency across various modalities would enhance the generalizability and robustness of the results.

Additionally, an unexplored aspect of this research is whether the enhanced detectability of lesion borders contributes to achieving R0 resection and subsequently decreases the recurrence rate of the lesion.

Presently, our understanding suggests that for many polyps, particularly those exceeding 2 cm in size, the risk of interval colon cancer appears to be more closely associated with the type of resection—specifically, endoscopic submucosal dissection and *en bloc* resection—compared to piecemeal endoscopic mucosal resection[37].

This emphasizes the importance of achieving an R0 resection to minimize local recurrence. Moreover, the timing of the first surveillance, typically recommended between 3 to 6 months post-resection, is crucial for effective monitoring and early detection of any recurrence.

CONCLUSION

We need to emphasize certain evident facts derived from this study. For instance, the combined use of TXI and CE proves to be most effective, surpassing the individual efficacy of both WLI and CE. Additionally, smaller lesions could also be more effectively detected, and the surface pattern and borders of the lesions could be better characterized and analyzed.

Reducing the rate of incomplete resection holds the potential to decrease the percentage of interval cancer. However, from my perspective, it is challenging to believe that these improvements will lead to a further decrease in morbidity and mortality rates related to colon cancer. This skepticism stems from the fact that these patients are already involved in a follow-up surveillance program, which is truly the primary factor responsible for saving lives.

In any case, considering the author's findings, the next step should be to investigate and confirm whether implementing this methodology results in a significant decrease in polyp recurrence.

In conclusion, the authors' proposed method of TXI plus CE is recommended for incorporation into our current screening colonoscopy methodology.

The improved characterization of polypoid lesions and enhanced visualization of their borders will significantly contribute to enhancing the overall quality of the procedure. This suggests a crucial follow-up study to assess the real-world impact of implementing the methodology described in the research. Confirming a substantial reduction in polyp recurrence rates would validate the practical efficacy of the proposed methodology and further establish its relevance in clinical settings. This has the potential to reduce the rate of interval colon cancer, emphasizing the importance of adopting advanced techniques to improve outcomes in colorectal screening. However, the impact on decreasing the burden of colon cancer remains to be substantiated.

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EDITORIAL

Future directions of noninvasive prediction of esophageal variceal bleeding: No worry about the present computed tomography inefficiency

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Abstract

In this editorial, we comment on the minireview by Martino A, published in the recent issue of *World Journal of Gastrointestinal Endoscopy* 2023; 15 (12): 681-689. We focused mainly on the possibility of replacing the hepatic venous pressure gradient (HVPG) and endoscopy with noninvasive methods for predicting esophageal variceal bleeding. The risk factors for bleeding were the size of the varices, the red sign and the Child-Pugh score. The intrinsic core factor that drove these changes was the HVPG. Therefore, the present studies investigating noninvasive methods, including computed tomography, magnetic resonance imaging, elastography, and laboratory tests, are working on correlating imaging or serum marker data with intravenous pressure and clinical outcomes, such as bleeding. A single parameter is usually not enough to construct an efficient model. Therefore, multiple factors were used in most of the studies to construct predictive models. Encouraging results have been obtained, in which bleeding prediction was partly reached. However, these methods are not satisfactory enough to replace invasive methods, due to the many drawbacks of different studies. There is still plenty of room for future improvement. Prediction of the precise timing of bleeding using various models, and extracting the texture of variceal walls using high-definition imaging modalities to predict the red sign are interesting directions to lay investment on.

Key Words: Esophageal variceal bleeding; Prediction; noninvasive; Computed tomography; Hepatic venous pressure gradient; Endoscopy

Core Tip: Current imaging techniques, especially computed tomography, are helpful for describing some of the characteristics that may explain the severity of portal hypertension. However, studies on radiomics have not achieved good results in accurately predicting variceal bleeding. In future studies, more delicate features of the images (especially the texture of variceal walls) could be focused on to reveal subtle signs of correlation.

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INTRODUCTION

Esophageal variceal bleeding (EVB) is one of the deadliest complications of portal hypertension[1,2], and is usually secondary to portal hypertension-triggering diseases, one of which is liver cirrhosis. Therefore, accurately recognizing and grading the severity of esophageal varices (EVs) is critical for prognostic prediction and the selection of prophylactic treatment. Generally, the scopes of dealing with EVs include: (1) Identifying the existence of EVs; (2) correctly grading the severity of EVs; (3) accurately predicting the bleeding risk within a certain period of time; and (4) administering prophylactic treatment. In this editorial, the main topic that we focus on is the former three scopes. Endoscopic examination usually provides direct visualization of EVs, which is the gold standard, while computed tomography (CT) or magnetic resonance imaging (MRI) and corresponding angiography provide indirect evidence. Although the severity of EVs can be evaluated by signs of enlargement and tortuosity of the varices, the hepatic venous pressure gradient (HVPG) defines the true essence of varices, namely, increased venous pressure. When the HVPG surpasses 10 mmHg, clinically significant portal hypertension (CSPH) occurs[3]. In regard to bleeding risk, both invasive and noninvasive techniques have been proposed in recent decades.

While the HVPG is able to provide the exact number of intravenous pressure, it is invasive, costly, and requires special facilities and expertise. Several investigations have been performed in recent decades to identify noninvasive predictive modalities. Encouraging results have been obtained across the globe, although these results are not satisfactory enough to replace HVPG and endoscopy. In the following paragraphs, we provide a mini discussion on invasive and noninvasive modalities and shed some light on future directions.

MODALITIES FOR EVALUATING EVB RISK

Currently, high-risk EVs are defined as medium-to-large EVs with red signs and late-stage liver disease[4,5]. Bleeding relies mostly on the intravariceal pressure and wall tension[6]. The HVPG and endoscopy constitute the backbone for pressure evaluation. Endoscopic characteristics, such as the size of the varices and the presence of the red sign, may help predict the chance of bleeding[7]. However, these signs occur in only approximately 30% of bleeding varices[8]. There is a debate over the predictive value of the HVPG for bleeding because bleeding and nonbleeding varices may have similar high pressures[9]. Additionally, large varices may not indicate proportionally high pressures. Since the indications of the Gold standards (HVPG and endoscopy) are not absolute, why do we not find some less invasive evaluation tools? Over the years, efforts to investigate noninvasive alternatives for HVPG evaluation have been made.

Radiological examinations, the most commonly applied techniques in clinical settings (*i.e.*, CT, MRI, and endoscopic ultrasound), have been investigated for their ability to stratify EVs and determine the risk of EVB. These modalities are good at describing the shape and distribution of vasculatures and organs beyond the esophageal wall. T1 MR liver image and splenic artery velocity correlated well with the HVPG (r = 0.90)[10]. As Martino *et al*[11] illustrated in the review we are now commenting upon, CT can be used to evaluate the size of entire varices, while endoscopy can be used to reveal only the portions protruding into the lumen. CT can also reveal other branches of the portal venous system and collateral veins. However, the evidence showing correlation between CT radiomics features and the HVPG or EVB risk is not solid.

Ultrasound elastography [*i.e.*, transient elastography, two dimensional elastography (2D-SWE)[12]] and magnetic resonance elastography[13] are reliable methods for liver stiffness measurement (LSM). LSM has a fair ability to distinguish CSPH (AUC = 0.90) and is correlated with the HVPG (coefficient = 0.783), although it cannot be used to estimate the exact HVPG[14]. However, the predictive value of LSM for the size of varices is relatively low.

Moreover, laboratory test results are also candidates for prediction. A decade ago, researchers tried to exploit metabolic data to predict HVPG and found that the homeostasis model assessment index was associated with high risk of EVB[15]. Ibrahim *et al*[16] reported that the serum vWF antigen level and vWF antigen/platelet ratio (VITRO) could help stratify the risk of bleeding, with AUCs of 0.982 and 0.843, respectively, although this study had a small sample size. Kothari *et al*[17] argued that the platelet count-to-spleen diameter ratio and FIB-4 index might be useful for predicting EVB, with AUCs of 0.78 and 0.74, respectively.

Since a single parameter, either radiological or laboratory, is insufficient to predict EVB, combinations of different modalities were studied. Liang *et al*[18] proposed a statistical model named SSL-RS, which consists of the spleen diameter, splenic vein diameter, and lymphocyte ratio, to predict the red sign. The authors showed that the sensitivity

and specificity could be greater than 70%. Another team tried to manipulate an ANN model, which included both demographic and laboratory parameters, to estimate the 1-year EVB risk[19]. The model was able to perform the prediction with an AUC of 0.959. Recently, two other models were proposed. A nomogram combining several laboratory markers with computed tomography portal vein diameter had an AUC of 0.893[20], while another model combining radiomics, CT and clinical features reached a predictive AUC of 0.89[21]. The better performance of the combination of parameters reveals at least one fact, which is, that EVB is a consequence of multiple factors.

CAN NONINVASIVE MODALITIES REPLACE HVPG AND ENDOSCOPY?

As mentioned above, endoscopic manifestations and the Child-Pugh score are risk factors indicative of possible EVB. Although the HVPG is the core factor that determines EVB risk, it is already reflected in these two indicators. An increased HVPG is a consequence of increased liver stiffness and disease progression. The stages of disease can be described using symptoms, physical signs, laboratory tests and radiography. The size of EVs can be determined by CT or MRI, although the sensitivity of identifying varices is limited. Therefore, the remaining question concerns the pressure and tension of the varices. The ultimate goal of describing different factors using multiple modalities, *e.g.* demographics, radiomics, and laboratory test results, is to reach as closely as possible to the real HVPG. Therefore, replacement is possible. CT or MRI has partly replaced endoscopy for assessing the size of varices. However, the efficacy of the present models is not enough to have a stable and reliable correlation with the HVPG, and the present radiological techniques cannot describe the delicate superficial characteristics. However, we do not need to worry too much, plenty of improvement will occur.

FUTURE DIRECTIONS FOR IMPROVING NONINVASIVE PREDICTIVE MODALITIES

Much has been done to improve the predictive ability of noninvasive modalities. Accurate measurement and stratification are helpful for precision medicine[22]. The goal must be to represent features equivalent to the HVPG and endoscopy using noninvasive methods. There are many directions to be taken in future researches.

One interesting question is how precise could one modality be in predicting when EVB may occur, instead of just determining the bleeding risk. The present risk stratification system could only identify the chances of EVB within one year for the population. This may be helpful for clinical decisions with regard to administering prophylactic treatments. However, for individuals, this approach is insufficient. Patients would like to know precisely when (although not possible scientifically) and under what conditions may they experience the first EVB. Instead of the already known risk factors discussed above, are medication, food intake, sports and other activities candidate factors that may ultimately determine the final bleeding event? Future models may take these factors into consideration.

Another question, from the perspective of endoscopy, is how to detect the red sign noninvasively. Put differently, how can the precise characteristics of the variceal walls be better delineated using high-definition imaging? One of the foci may be on superficial varices protruding into the esophageal lumen, which are responsible for bleeding. Researchers may also study the radiological features of variceal surfaces, *e.g.* the change in the variceal wall thickness and variceal wall textures, which may indicate points of weakness. In addition, the distribution pattern and 3D structural shapes of varices may also be taken into consideration. However, these methods may require imaging techniques with higher resolution. Deep learning is a promising method for integrating all these data, and might bring us some surprise one day.

Of course, appropriate study design may provide better and convincing evidence. It will be better should the study be well designed in a cohort way, with a statistically significant sample size to provide a more conclusive result.

CONCLUSION

The present imaging techniques (including CT) can provide a primary prediction for EVB. However, these methods are far from useful in actual clinical application. Future studies are needed to explore features that are equivalent to the real HVPG and endoscopic presentations. Combinations of different modalities to accomplish this goal are still encouraged.

FOOTNOTES

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EDITORIAL

Anal pruritus: Don't look away

Andreia Albuquerque

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Abstract

Anal pruritus is a common anorectal symptom that can significantly impair a patient's quality of life, including their mental health. It can be one of the most difficult proctological conditions to treat. Patients often delay seeking medical attention, since it is an embarrassing but non-life-threatening situation. Pruritus ani can be associated with idiopathic and secondary causes, such as anorectal diseases, cancer (anal or colorectal), dermatological and sexually transmitted diseases, fungal infections and systemic diseases. If patients are referred for a colonoscopy, this can sometimes provide the first opportunity to evaluate the perianal area. Classifications of anal pruritus are based on the abnormalities of the perianal skin, one of the most commonly used being the Washington classification. A proper digital anorectal examination is important, as well as an anoscopy to help to exclude anorectal diseases or suspicious masses. Endoscopists should be aware of the common etiologies, and classification of the perianal area abnormalities should be provided in the colonoscopy report. Information on treatment possibilities and follow-up can also be provided. The treatment normally consists of a triple approach: proper hygiene, elimination of irritants, and skin care and protection. Several topical therapies have been described as possible treatments, including steroids, capsaicin, tacrolimus and methylene blue intradermal injections.

Key Words: Anal pruritus; Colonoscopy; Washington classification; Hemorrhoids; Fissure; Cancer

Core Tip: Anal pruritus is a common anorectal symptom that can significantly impair a patient's quality of life. Endoscopists should be aware of the possible etiologies, including anorectal diseases and anal or colorectal cancer. Classifications of anal pruritus are based on the abnormalities of the perianal skin. It is important to carry out a proper digital anorectal examination and an anoscopy in these patients.

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INTRODUCTION

Anal pruritus is a common anorectal condition, and it is estimated that it affects between 1% to 5% of the population at some point in their lives[1]. It is an embarrassing condition, which can impair a patient's quality of life[2,3]. Anal pruritus can also have a negative effect on a patient's mental health[4].

Idiopathic pruritus is generally considered to be associated with fecal contamination of the skin, which initiates a vicious cycle of itching and scratching[3,5]. This results in skin maceration and a decrease in thickness of the fatty skin layer with hypertrophy and lichenification[3,5]. There are also several secondary causes that might be associated with anal pruritus[6]. Benign and malignant anorectal conditions such as hemorrhoids, fissures, fistulas, rectal prolapse, condylomas, Crohn's disease, squamous cell carcinoma, colorectal cancer, Paget's disease and melanoma are all possible secondary causes[6,7]. Hemorrhoids and anal fissures are the most common anorectal diseases associated with pruritus [8]. Dermatological and sexually transmitted diseases, fungal infections and systemic diseases such as diabetes mellitus, lymphoma, renal failure, hyperthyroidism disorders or iron deficiency anemia can also be associated[6,7].

A prospective two-year study, including 109 patients with anal pruritus as the only presenting complaint[8], showed that 35% of the patients had an abnormal proctosigmoidoscopy or colonoscopy. In total, 11% of patients had rectal cancer, while 5% had anal cancer and 2% had colon cancer. The duration of the pruritic symptoms and an age greater than 50 years were risk factors for a diagnosis of a neoplasm[8].

Patients with anal pruritis may be referred for a colonoscopy for several reasons, some unrelated to this condition, or to exclude a possible secondary cause. Endoscopists should start by conducting a proper examination of the perianal area, looking for erythema, fissures, ulceration or lichenified skin. The Washington classification is based on the appearance of the perianal area and can be provided in the examination report: stage 0 is normal skin; stage 1 is erythematous and inflamed skin (Figure 1); stage 2 is lichenified skin (Figure 2); and stage 3 is lichenified, coarse skin often with ulcerations (Figure 3)[9]. Endoscopists should also look for other conditions that might be associated, such as hemorrhoids or fissures. A proper anorectal digital examination should then be performed, with a search for suspicious masses. If possible, this should be followed by an anoscopy[7]. This detailed examination of the perianal area, combined with digital anorectal examination and an anoscopy, will allow a correct evaluation and classification of the situation, and should exclude anorectal diseases that might be associated with anal pruritis. It should be carried out before colonoscopy.

Treatment normally consists of a triple approach: Proper hygiene, elimination of irritants, and skin care and protection [6]. The area should be always clean and dry, avoiding overwiping, soaps, lotions and wet wipes that cause irritation[6]. Some foods and drinks should be avoided, such as coffee, tea, beer, chocolate, citrus fruits, cola, dairy products, and spicy foods (Figure 4A and B)[6].

A randomized control trial of 1% hydrocortisone ointment or placebo for 2 wk followed by the opposite treatment for a further 2-wk period, with a washout period of 2 wk between treatments, showed that treatment with 1% hydrocortisone ointment resulted in a 68% reduction in a visual analogue score compared with placebo[10]. Long-term topical steroids should be avoided as they cause skin atrophy and rebound symptoms after withdrawal[3,5].

A randomized control trial compared topical capsaicin 0.006% and placebo for idiopathic intractable pruritus ani for four weeks 3 times a day and showed that 31 of the 44 patients improved with capsaicin[11]. There were 4 patients who dropped out of capsaicin treatment because of side effects, three patients due to perianal burning and one due to urticaria. This substance seems to act by reducing the synthesis, storage, transport, and release of substance P, a neuropeptide that is a mediator of itching[11].

A recent meta-analysis and systematic review has evaluated the efficacy and safety of methylene blue injection for intractable idiopathic pruritus ani and included 7 studies with 225 patients[12]. This seemed to be a relatively efficacious therapy, but higher quality studies are necessary, including randomized control trials. Methylene blue destroys the intra-dermal nerve endings[13]. Skin necrosis was reported as a possible complication when large volumes were injected[13]. Temporary staining of the skin, perianal area numbness and transient fecal incontinence can occur as side effects[12].

A randomized, double-blind, placebo-controlled clinical trial, including 21 patients with intractable idiopathic pruritus ani treated with tacrolimus 0.1% ointment, showed a significant positive effect of tacrolimus in reducing pruritus intensity and frequency, with symptom reduction in 68% of the patients 2 wk after treatment[14].

A case report has also described a case of a man with long-term anogenital pruritus that was refractory to multiple therapies and that responded to dupilumab, an interleukin-4 receptor alpha blocker[15].

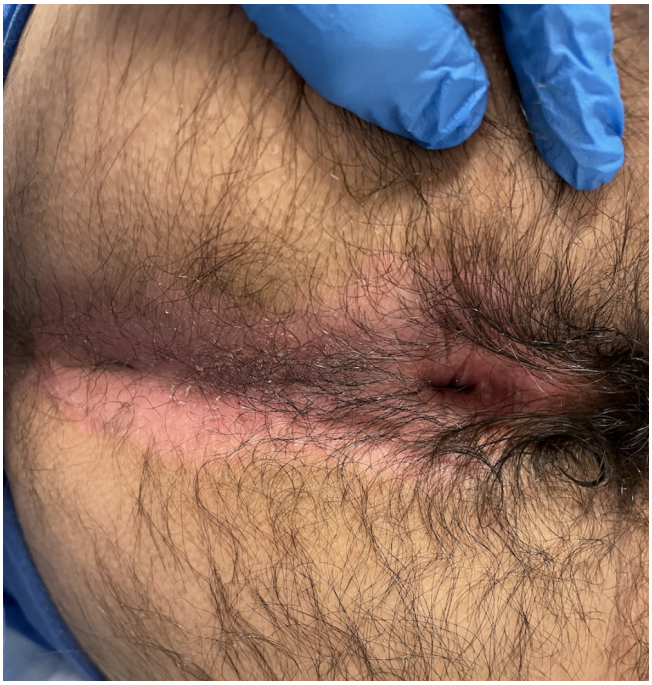

Figure 1 Erythema in the perianal area (stage 1 Washington classification).

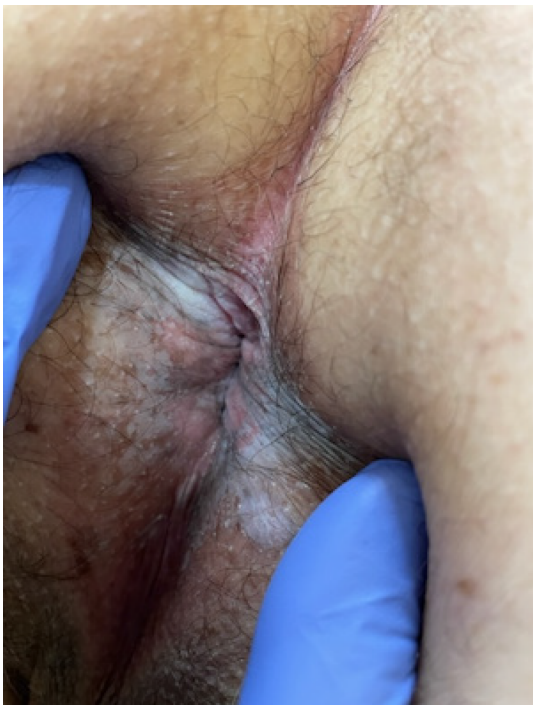

Figure 2 Lichenified skin (stage 2 Washington classification).

CONCLUSION

Anal pruritus is a common anorectal condition that can either be idiopathic or have secondary etiologies, including anorectal diseases or even malignancies. It is important to conduct a detailed examination of the perianal area, a proper digital anorectal examination and an anoscopy. For treatment it is important to promote correct hygiene, the elimination of irritants and skin care. Several topical therapies have been described, including steroids, capsaicin, tacrolimus and methylene blue intradermal injections.

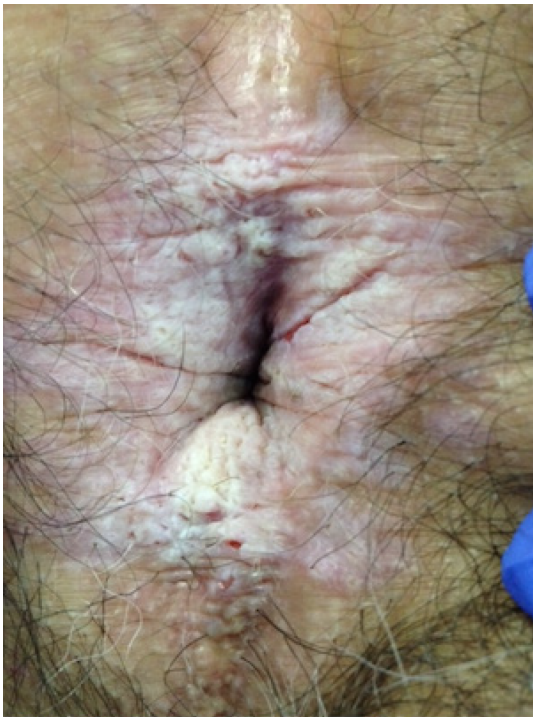

Figure 3 Severe lichenified skin with ulcerations (stage 3 Washington classification).

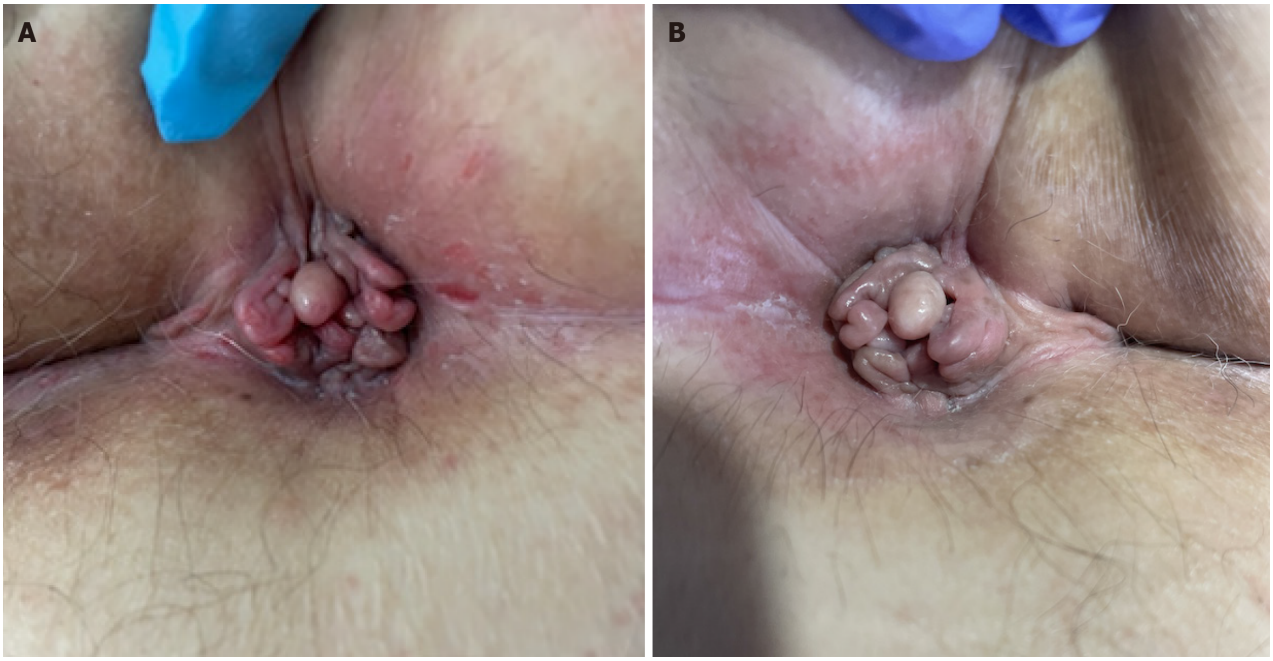

Figure 4 Initial evaluation and follow-up after treatment. A: In a woman with anal pruritus, observation revealed skin tags and lichenified skin with small ulcerations of the perianal area; B: One month after treatment (proper hygiene, elimination of irritants and topical capsaicin 0.006%) anal pruritus resolved with improvement of the perianal area.

FOOTNOTES

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MINIREVIEWS

Methods to increase the diagnostic efficiency of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesions: An updated review

Xin Yang, Zi-Ming Liu, Xue Zhou, Fan Yang, Wen-Zhuang Ma, Xin-Zhu Sun, Si-Yu Sun, Nan Ge

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Abstract

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a means to procure adequate specimens for histological and cytologic analysis. The ideal EUS-FNA should be safe, accurate, and have a high sample adequacy rate and low adverse events rate. In recent years, many guidelines and trials on EUS-FNA have been published. The purpose of this article is to provide an update on the influence of some of the main factors on the diagnostic efficiency of EUS-FNA as well as a rare but serious complication known as needle tract seeding.

Key Words: Endoscopic ultrasound; EUS-FNA; Pancreatic cancer; Diagnostic efficiency

Core Tip: This review evaluates the influencing factors and limitations of endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic lesions. The information presented here highlights multiple factors and the latest results, such as mass size, rapid on-site evaluation, and needle tract seeding for improving diagnostic efficiency. Therefore, this review may be highly beneficial for clinicians focusing on the management of endoscopic ultrasound-guided fine-needle aspiration.

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INTRODUCTION

Pancreatic cancer is one of the worst solid pancreatic lesions. The incidence of pancreatic cancer is increasing year by year [1], and the 5-year survival rate is no more than 10%[2]. Due to the low early diagnostic rate, approximately 80% of patients are diagnosed when pancreatic cancer has reached an unresectable stage[3]. Therefore, a reliable and widely applicable early assessment of pancreatic cancer is extremely important for personalized therapies[4]. Decades after endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was designed in the early 1990s by Vilmann *et al*[5], it is considered a recommended method when the diagnosis is unclear in patients with suspected pancreatic cancer following the computed tomography scan pancreatic protocol[6-8]. According to the latest research, genetic testing technology such as whole-exome sequencing and nuclear DNA content assessment can also be used with EUS-FNA[9]. In recent years, many guidelines and trials on EUS-FNA have been published[10,11]. In the past few years, endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) has become a useful tool. The newer fine-needle biopsy (FNB) needles are equally effective in pancreatic lesions and non-pancreatic lesions, such as subepithelial lesions and abdominal lymph node lesions, which can improve the sample adequacy rate and diagnostic accuracy[12,13]. However, the evidence relating to this is limited and further multiple large sample studies and randomized clinical trials are warranted to improve the diagnostic efficiency of EUS-FNA[14].

MASS SIZE

With the development of pancreatic cancer diagnosis technology, early detection of small solid pancreatic lesions is increasingly common. In the past, it was believed that there was no relationship between lesion size and EUS-FNA diagnostic yield[15,16]. However, previous related research was conducted with rapid on-site evaluation (ROSE), in which the procedure was repeated until the representative cells were confirmed from the target lesion. Nevertheless, according to a retrospective cohort study by Crinò *et al*[17], the adequacy, accuracy, and sensitivity of EUS-FNA for solid pancreatic lesions without ROSE are related to the size of the mass. This finding indicates that endoscopists need to be more cautious when diagnosing small solid pancreatic lesions without ROSE, especially in patients with lesions less than 20 mm[6].

NEEDLE SIZE

According to the latest guidelines in United Kingdom, Japan, and China, there is still uncertainty regarding the optimal needle size for EUS-FNA in solid pancreatic lesions supported by high-level evidence. Generally, in terms of needle choice, a 19-gauge needle is used for interventional surgery. A 22-gauge needle is usually used for histologic evaluation, while a 25-gauge needle has been widely used in cytologic assessment with ROSE[18,19].

In recent years, due to their manageability and safety, 22-gauge and 25-gauge needles have gained increasing popularity in clinical trials[20]. According to a meta-analysis which included 7 trials with 689 patients and 732 lesions from 2007 to 2014, there was no significant difference between a 22-gauge needle and a 25-gauge needle on cytologic evaluation in terms of diagnostic sensitivity, specificity, sample adequacy, and adverse events[21]. In addition, a retrospective study of 153 patients with pancreatic ductal adenocarcinoma showed that both 22-gauge and 25-gauge needles both provided equal adequate specimens for immunohistochemical analysis[22].

With regard to the 19-gauge needle, it has advantages over the 22-gauge and 25-gauge needle in terms of the size and quality of tissue samples obtained without ROSE[23]. However, as a result of its stiffness and difficulty in use, the 19-gauge needle often fails when performed *via* the transduodenal approach in a bent position, essentially in pancreatic head or uncinate process tumors[23]. To overcome this problem, a flexible 19-gauge needle with a nitinol shaft (19 G Flex) was introduced. However, according to a randomized study by Laquière *et al*[24], the 19 G Flex needle was inferior to a standard 22-gauge needle in diagnosing pancreatic head cancer and was still difficult to use in the transduodenal approach. Intermediate size needles (20-G or 21-G) are on the way[25,26].

SUCTION, SLOW-PULL OR NON-SUCTION

Suction is commonly used to obtain adequate samples, but it may damage cellular structures and contaminate the sample with blood, clouding cytologic interpretation[27]. Compared with dry suction, wet suction has better sample adequacy and higher diagnostic accuracy without increasing blood contamination[28,29]. In addition, slow-pull and non-suction sampling are techniques that procure samples of good quality with only slight blood contamination[30-32]. According to a prospective randomized trial by Cheng *et al*[30] and a multicenter randomized trial by Saxena *et al*[32], both suction and slow-pull sampling need 2 passes on average and show equivalent sensitivity, specificity, and accuracy. The combination of these two techniques shows better sampling results than each alone. This study also concluded, in contrast to the study by Mohammad Alizadeh *et al*[33], that suction did not increase blood contamination of the sample compared with slow-pull sampling in solid pancreatic lesions.

WITH OR WITHOUT STYLET

The use of a stylet during EUS-FNA prolongs the procedure time with an increased risk of unintentional needle stick injury due to repeat passes during reinsertion of the stylet[34]. However, a longer operation time does not mean better diagnostic efficiency. As indicated by prospective studies and meta-analyses, the use of a stylet during EUS-FNA confers no significant difference in terms of technical success, the mean number of needle passes, needle malfunction, complications, adequate sample rate, cellularity, contamination rate, bloodiness, cytological diagnostic accuracy, and histological diagnostic accuracy[35-38].

RAPID ON-SITE EVALUATION

In the past, it was believed that ROSE could help the diagnostic accuracy of pancreatic EUS-FNA and reduce the number of needle passes and inadequate samples[39]. However, recent comprehensive data on the impact of ROSE have been conflicting. In a multicenter randomized controlled trial and a meta-analysis, no statistical difference was demonstrated in diagnostic accuracy, adequacy rate, procedure time, and the average number of needle passes between EUS-FNA with and without ROSE[40,41]. However, a study that considered pancreatic, submucosal upper gastrointestinal tract and adjacent lesions indicated that ROSE does improve the adequacy rate and diagnostic accuracy of EUS-FNA, especially in solid pancreatic lesions[42]. The variety of conclusions among different studies may be related to other factors such as the difficulty in implementing blind methods, additional passes when malignant cells are not detected, and the experience of endoscopists and cytopathologists[43]. Therefore, ROSE alone may not be the predominant factor. It could be considered an essential part of the learning period and in hospitals where the diagnostic accuracy rate is lower than 90%[44].

CONTRAST-ENHANCED HARMONIC ENDOSCOPIC ULTRASOUND AND ELASTOGRAPHY

Contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) and elastography have been widely used to assist in the diagnosis of pancreatic indeterminate lesions[45]. It can correctly distinguish false negative diagnoses of EUS-FNA, thus improving the diagnostic rate of pancreatic diseases and EUS-FNA[46,47]. CEH-EUS-guided fine-needle aspiration (CEH-EUS-FNA) avoids fibrosis, necrotic areas, and blood vessels in pancreatic lesions, and can locate the sampling site more accurately[48]. Compared with the standard EUS-FNA, it can reduce the number of punctures when obtaining equivalent sufficient samples, thus reducing the incidence of adverse events related to EUS-FNA, such as bleeding, perforation, infection, and pancreatitis *etc*[46,49]. Elastography strain imaging is accessible through EUS, wherein it gauges tissue distortion by the application of a predetermined pressure. The combined utilization of CEH-EUS or elastography appears to enhance the diagnostic capability of EUS[50]. However, a meta-analysis suggested that more studies are needed to assess the combined utilization[51].

NEEDLE TRACT SEEDING

Apart from common complications such as pancreatitis and bleeding, a rare but serious complication has also received increasing attention since 2003. Cancer recurrence due to needle tract seeding after EUS-FNA was first reported by Hirooka *et al*[52] in a patient with a pancreatic tumor. Since then, relevant studies have been published continuously, discussing the impact of tumor cell seeding *via* the needle tract on short-term prognosis[53]. According to several retrospective studies, although pre-operative EUS-FNA has not been proved to be associated with overall survival or an increased rate of gastric and peritoneal cancer recurrence, its potential long-term prognosis is still non-negligible[54-57]. Furthermore, this phenomenon is unique to tumors in the pancreatic body and tail, considering that the needle tract is not included in the surgical resection of these tumors[58-65]. Therefore, if possible, more attention to the imaging findings of the needle tract in the postoperative follow-up is necessary or including the needle tract during the surgical resection may improve long-term prognosis[66]. In addition, appropriate risk information on needle tract seeding before EUS-FNA is necessary[65].

EUS-FNB AND MACROSCOPIC ON-SITE EVALUATION

EUS-FNB has become the first choice when multiple immunohistochemical staining is required to assist in the diagnosis of diseases such as autoimmune pancreatitis and pancreatic metastasis[67]. At present, relevant studies have mainly focused on the research and development of puncture needles of different types and shapes. The most common ProCore® biopsy needle improves the adequacy of tissue specimens, and the Acquire® biopsy needle improves the quality of the tissue specimen due to its tip stability and more controllable puncture site[19,67]. However, a study demonstrated that the 22G Acquire® needle achieved better accuracy than the 20G needle due to more pancreatic mass tissue for histologic assay[68].

A trial by Yousri *et al*[69] reported that both FNA and FNB are safe and effective for accurately diagnosing pancreatic and non-pancreatic abnormalities. In comparison to tissue examination alone, FNB demonstrates higher sensitivity and diagnostic accuracy when diagnosing pancreatic lesions. Additionally, FNB can provide a higher quality histological specimen with reduced contamination due to blood. A randomized controlled trial suggested that EUS-FNB without ROSE showed great diagnostic accuracy in solid pancreatic lesions, and ROSE might not be recommended when new FNB needles are used[70]. Although newer FNB needles have the advantage of being self-assisting in diagnosing diseases, standard FNA needles are still very competitive as their high flexibility allows them to puncture difficult target sites and allow for ROSE[25]. A meta-analysis found evidence to suggest that EUS-FNB with ROSE was not significantly better than EUS-FNB with newer end-cutting needles. However, there may still be a potential role for ROSE when reverse bevel needles are utilized[71]. However, ROSE necessitates the presence and expertise of a pathologist, incurs supplementary expenses, and is not accessible in many medical centers. The macroscopic on-site evaluation (MOSE) by an endoscopist was introduced as an alternative to ROSE, and two studies found that MOSE is a complementary technology that reduces the number of needles necessary for sample acquisition and improves diagnostic accuracy in some clinical conditions[71,72] (Table 1).

DISCUSSION

EUS-FNA plays a pivotal role in the diagnosis and evaluation of solid pancreatic lesions. Although there are still no globally accepted guidelines for the application of EUS-FNA in solid pancreatic lesions, relevant and clinically meaningful studies on techniques are increasing. The ideal EUS-FNA is safe, accurate, and has a high sample adequacy rate and low adverse events rate. Studies are even exploring its use in cancer diagnosis beyond the digestive system[73-75].

Needle size for EUS-FNA has always been a popular research topic. According to a network meta-analysis involving 27 randomized controlled trials and 2711 patients, there was no significant difference in diagnostic accuracy and sample adequacy among 19-gauge, 22-gauge, and 25-gauge needles[76]. This means that endoscopists can choose the needle size based solely on the purpose of the operation, for instance, interventional surgery, histological evaluation, and cytologic assessment. It is also important to note that although the 19-gauge needle has advantages in terms of the quantity and quality of tissue samples obtained without ROSE, it does not perform well *via* the transduodenal approach in a bent position[23]. Modification of a 19-gauge needle, such as material and shape, to make it flexible and easier to use seems warranted.

Inconsistent findings in studies of ROSE may be due to the difficulty of performing the blind method, additional punctures when no malignant cells are detected, and the difference in the experience of endoscopists and cytopathologists[43]. This prevents ROSE itself from being considered as a major factor affecting the diagnostic accuracy of EUS-FNA, at least without sufficient evidence. However, it is almost certain that ROSE plays a role in the effect of mass size on the accuracy of EUS-FNA. Thus, in hospitals without ROSE, endoscopists should be more cautious in patients with small solid pancreatic lesions[17].

According to a prospective randomized trial by Cheng *et al*[30], there was no statistically significant difference between slow-pull and suction EUS-FNA techniques in terms of safety, accuracy, and blood contamination. Several slow-pull and suction techniques, for instance, wet suction, have also been modified to enhance tissue acquisition or reduce tissue damage[77]. However, sufficient evidence to prove that one technique is superior to another is still required.

As mentioned above, it would be reasonable not to use a stylet during the EUS-FNA process, which may make the operation easier, reduce labor intensity, take less time and be more cost-effective without affecting the quality of the results.

In recent years, although the incidence of needle tract seeding is low, due to its serious consequences, this complication has received more and more attention from endoscopists. This may also be precisely because of its low incidence that the results of its impact on overall survival rate were not obtained in relevant previous studies and meta-analyses[54-57]. In order to fully clarify the clinical characteristics of EUS-FNA posterior needle tract seeding, further prospective studies are warranted. However, in current clinical practice, it is still recommended that attention is paid to needle tract seeding and appropriate risk information is necessary.

Organoids offer a comprehensive depiction of the intricate diversity inherent in tumors, covering their genetic constitution, transcriptional landscape, metabolic dynamics, cytological intricacies, and histological characteristics. Organoids serve as a synthesized representation of multiple tumoral features *in vivo*, thereby serving as a pivotal conduit between fundamental tumor research and clinical applications, such as drug screening[78]. With the exploration and development of new technologies, tissues obtained by EUS can also be used for organoid culture[79].

Tumor organoids are mainly cultured from surgically resected samples, the inherent difficulty in obtaining viable specimens from advanced-stage tumors, such as pancreatic cancer, poses a significant impediment to this approach. In contrast, EUS-FNA is a versatile methodology, applicable across all disease stages, encompassing preoperative, perioperative, post-therapeutic, and recurrent phases. This methodological flexibility means that EUS-FNA is unconstrained by disease staging, thereby facilitating the establishment of a dynamic organoid that faithfully mirrors the temporal progression of the disease[80]. In contrast to traditional methods, these specimens after ROSE can be used immediately in the laboratory to generate organoid cultures, and samples can be taken as the disease progresses, not just after the lesion requires surgical excision.

Table 1 Characteristics of the study

Ref.	Number of patients	Study design	Result (Diagnosis accuracy)
Karsenti *et al*[68]	60	Randomized controlled trial	87% with 22G needle and 67% with 20G needle for FNB, $P = 0.02$
Yousri *et al*[69]	100	Prospective study	98% with FNA and 90% with FNB only depending on tissue
Crinò *et al*[70]	800	Randomized controlled non-inferiority trial	96.4% with ROSE and 97.4% without ROSE, $P = 0.396$
Facciorusso *et al* [71]	2147	Meta-analysis	FNB with ROSE group better than the FNB only group (OR = 2.49, 1.08-5.73; $P = 0.03$)

FNA: Fine-needle aspiration; ROSE: Rapid on-site evaluation; FNB: Fine-needle biopsy.

CONCLUSION

In conclusion, short-term outcomes of the factors introduced above are necessary for the improvement of EUS-FNA. Multiple large sample studies and prospective randomized trials are still warranted to discuss cytopathologic support, modification of techniques, materials, and long-term consequences.

FOOTNOTES

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Human-artificial intelligence interaction in gastrointestinal endoscopy

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Abstract

The number and variety of applications of artificial intelligence (AI) in gastrointestinal (GI) endoscopy is growing rapidly. New technologies based on machine learning (ML) and convolutional neural networks (CNNs) are at various stages of development and deployment to assist patients and endoscopists in preparing for endoscopic procedures, in detection, diagnosis and classification of pathology during endoscopy and in confirmation of key performance indicators. Platforms based on ML and CNNs require regulatory approval as medical devices. Interactions between humans and the technologies we use are complex and are influenced by design, behavioural and psychological elements. Due to the substantial differences between AI and prior technologies, important differences may be expected in how we interact with advice from AI technologies. Human–AI interaction (HAII) may be optimised by developing AI algorithms to minimise false positives and designing platform interfaces to maximise usability. Human factors influencing HAII may include automation bias, alarm fatigue, algorithm aversion, learning effect and deskilling. Each of these areas merits further study in the specific setting of AI applications in GI endoscopy and professional societies should engage to ensure that sufficient emphasis is placed on human-centred design in development of new AI technologies.

Key Words: Artificial intelligence; Machine learning; Human factors; Computer-aided detection; Colonoscopy; Adenoma detection rate

Core Tip: As an endoscopist you should familiarise yourself with the capabilities, strengths and weaknesses of any artificial intelligence (AI) technology you intend to use. It is important to be cognisant of the human factors and psychological biases that influence how you as an individual user treat advice from AI platforms. Those using AI technologies in healthcare should be involved in the development of those technologies and should advocate for a human-centred approach to their design and implementation.

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INTRODUCTION

Artificial intelligence (AI) encompasses a wide variety of applications for sophisticated computer algorithms that use large volumes of data to perform tasks traditionally thought to require human intelligence[1]. There is a growing list of current and proposed applications for AI in medicine, including direct patient interaction with AI chatbots to answer patient queries, analysis of a large amount of disparate data to predict disease diagnosis and course, and interpretation of images from radiological investigations[2-4]. In gastroenterology, potential clinical applications span from use of domain-specific large-language models (LLMs) in the triage of specialist referrals to prediction of early-stage pancreatic cancer before it becomes overtly visible on imaging[5,6].

Following the development of convolutional neural networks (CNNs) for computer-aided detection and diagnosis of pathology in the fields of radiology and dermatology, gastrointestinal (GI) endoscopy became an area of early research into applications of CNNs in medicine[7-10]. Among the most promising initial applications of AI in GI endoscopy were computer-aided detection (CADe) and computer-aided diagnosis (CADx) of premalignant polyps during colonoscopy using machine learning (ML) systems[11,12]. These applications were prioritised in an effort to improve adenoma detection rate (ADR) and to differentiate premalignant polyps from those without malignant potential, with the attendant possibility of reducing incidence of colorectal cancer (CRC) and reducing costs and complications associated with unnecessary polypectomy[13,14]. Additional applications have developed rapidly to include detection and diagnosis of other pathology in upper and lower GI endoscopy, capsule endoscopy and biliary endoscopy. There has also been initial exploratory use of LLMs to aid decision-making on management of early CRCs and patient-facing applications to determine adequacy of bowel preparation prior to colonoscopy[15-19].

While initial results on colorectal polyp CADe showed impressive improvements in key metrics of colonoscopy quality [20], some subsequent real-world studies showed more modest effects or even no effect, and noted an increased rate of unnecessary resection of non-neoplastic polyps[21-23]. It is possible that factors involved in real-world human-AI interaction (HAII) are a driver of such differences between experimental and real-world results[24].

More than most other advances in medical science, successful implementation of AI platforms will depend not solely on the technical success and technical efficacy of the platform, but equally on the ability of the technology to interact with its human operators[25]. There was early adoption of CADe technology in the field of breast radiology, based on experimental evidence of benefit[26]. Analysis of real-world data from those systems later showed that early iterations contributed to greater resource utilisation due to false positives and increased additional radiological investigations[27]. It is an important lesson for application of AI in GI endoscopy, that effectiveness of AI platforms and their impact on patient outcomes can only be properly assessed in real-world settings. Despite the high speed of progress in development and roll-out of new applications for AI in GI endoscopy, the real-world effects of AI on clinician decision-making remain underexplored[28]. Multiple factors can affect HAII at each phase of the development and deployment of an AI platform (Figure 1). Areas of interest in the interaction between humans and AI in GI endoscopy, which will be explored in this review, include: (1) Human design choices in creation of AI platforms and their user interfaces; (2) Regulatory processes and interventions for new AI platforms; (3) Human factors influencing user interaction with AI platforms; and (4) Clinician and patient attitudes toward individual platforms and AI broadly.

FROM HUMAN–COMPUTER INTERACTION TO HUMAN–AI INTERACTION

Growth in use of information and computer technologies in the 1980s led to recognition of the importance of studying the relationship between humans and these new technologies[29]. The field of human–computer interaction (HCI) sought to investigate social and psychological aspects of interactions that would influence the acceptability and utility of these new technologies[30]. Humans interacted with early computers by inputting code *via* keyboard, but as humans' methods of interacting with technology have become more sophisticated, the influences on and impact of HCI have also become more complex[31]. Ease of use is recognised as an important driver of uptake of new technological products or platforms [32].

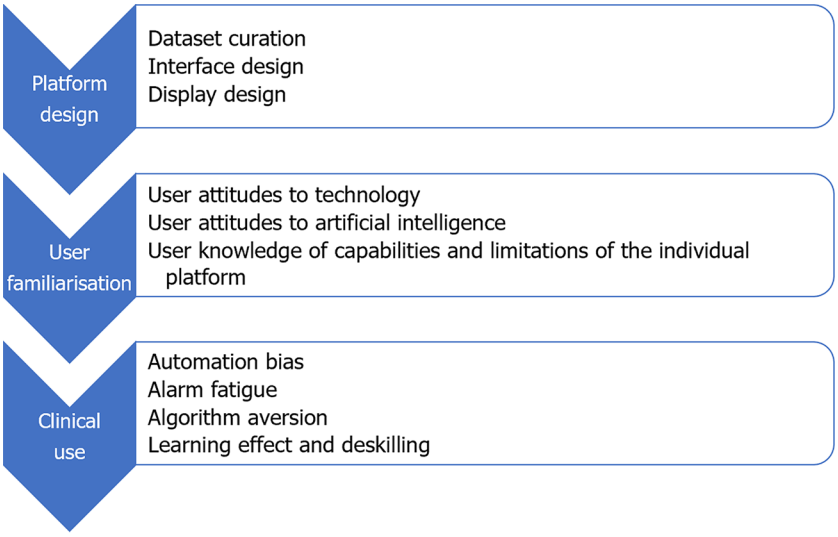

Figure 1 Major factors affecting human–artificial intelligence interaction in gastrointestinal endoscopy by phase of platform development and deployment.

Psychological aspects of HCI were extensively explored in the pre-AI era. The 'computers are social actors' (CASA) theory held that, because psychological mechanisms evolve over centuries rather than decades, the human brain reflexively treats any entity with human-like abilities as human[29,33]. Recent work has queried the durability of the CASA effect, and suggested that the human brain's treatment of interactive technology as human may relate more to a technology's relative novelty than to its existence[34]. Whether human operators innately regard new technologies as tools or as other humans has significant ramifications for how the presence of AI may affect human performance.

A key question with regard to technological development in any sector is that of function allocation *i.e.* deciding which roles should be performed by the human and which by the technology. AI has led to a rapidly burgeoning cadre of tasks that can be performed by technology, with an ever-diminishing number of tasks the sole preserve of humans[29]. Since the conception of AI, there has been disagreement between researchers on what the aim of AI should be; to replace human labour or to augment human performance. The prevailing view on this has changed from one position to the other frequently in the intervening period[35]. At the current juncture, it appears that the decision will be made by the speed at which the technology can be developed, rather than by specific ethical considerations. A contrast between HCI and HAII is seen in the view by the former that computers and new technologies should be assistive, whereas the latter field recognises that AI has the possibility to replace human efforts entirely in some instances, so-called agential AI[36].

ALGORITHM DESIGN AND INTERFACE DESIGN

CADe and CADx platforms based on CNNs are created by training the programme on large volumes of data *e.g.* images and videos with a defined diagnosis, allowing the programme to learn patterns in the images that are suggestive of the presence of pathology or of the specific diagnosis of interest[37]. Design of CADe and CADx systems requires the selection, curation and annotation of a large number of images of relevant pathology, to use as 'ground truth' for training and testing of the algorithm, while design of LLMs require large volumes of text data. Selection and curation of such image or text data represents the first point of contact between humans and the AI platform. There are several ways in which human decisions on training and design can influence the long-term operation of the AI platform. The functioning of the AI platform after its creation and the mechanism by which it arrives at its decisions are both opaque, with the processes being described as a 'black box'[38]. The possibility of building biases into the platform's functioning makes selection of the best possible training database imperative, as unintended consequences of biased training data have been shown in other applications to have negative consequences on health outcomes for patients from minority groups[39].

Difficulties can arise due to a number of problems with the training dataset, giving rise to different types of selection bias. When a CADe algorithm is trained using images from prior colonoscopies, those images are typically compressed and altered in the process of saving them to a database. The compression may introduce artefact and alter the value of the image for the CNN's learning. It may also cause changes to the image that are imperceptible to the human but integrated into the algorithm's processing. Choosing images that are too idealised may lead the algorithm to be poor at detecting pathology that deviates from archetypal descriptions[40]. There is also concern that if a CNN is trained on data that comes from homogenous Western populations in the most developed countries, this may weaken the algorithm's ability to give appropriate advice in racially diverse groups[41]. An unbalanced dataset with too many instances of pathology and not enough images without pathology may skew the algorithm causing decreased specificity. The larger the number of images used to train the algorithm, the better the system can be expected to perform[42]. When the algorithm encounters, in real-world use, images outside what it encountered in the training set, it is more likely to flag those images as pathology[40]. A novel methodology to train a CADe algorithm that involves training the platform by teaching it to

read images in a similar fashion to an expert clinician, has recently been described[43].

Design of the user interface is an important factor in optimising CADe/CADx performance. Design features that minimise additional cognitive burden and make alarms and advice coherent can result in synergistic effects. Conversely, poorly-designed platforms may increase the risk of automation bias, discussed later[44]. The effect of presenting, alongside a CADx bounding box, additional data regarding the algorithm's confidence in the given diagnosis, may alter the endoscopist's trust in the AI advice and influence their likelihood to endorse the same diagnosis[45,46].

REGULATION, SUPERVISION AND ACCOUNTABILITY

Precise definitions and classifications for medical device software and AI systems differ between jurisdictions but in general AI or ML-based tools or algorithms when used for diagnostic or therapeutic purposes, including applications for GI endoscopy, will meet the definition of a medical device and should be appropriately developed and evaluated before they are approved for clinical use in accordance with the relevant regional regulation[47]. Similarly, clinical research including pilot studies to generate the clinical data required to validate and appraise novel and uncertified AI tools in endoscopy should be performed in accordance with applicable regulatory and ethical requirements.

To facilitate new and potentially beneficial advancements while protecting patients, regulation and scrutiny should be proportionate to the risk of the software and it is recognised that regulation of AI systems as medical devices is challenging and this is not unique to GI applications[48]. The intended use of the AI and not simply the technology is a critical determinant of risk so for example CADx for malignancy diagnosis would generally fall into a higher risk category and require sufficient evidence and evaluation to support its use. Other important principles influencing risk evaluation include transparency, explainability, interpretability and control of bias. In CADe in GI endoscopy this includes the ability of the clinician user to detect erroneous output information compared to so called 'Blackbox' algorithm-based interpretations. While many AI and ML applications have been approved, some experts have questioned the ability of currently emerging LLM products to meet these principles and GI clinicians must consider the evidence base and reliability of such devices for clinical practice use[49]. Outside of basic regulation and licensing, clinicians and health systems trialling or implementing AI in GI endoscopy practice have a responsibility to ensure the applications (whether diagnostic or therapeutic) have a sufficient evidence base and the clinical data supporting algorithms for example is reliable and representative for the intended use patient population.

HUMAN FACTORS INFLUENCING USER INTERACTION WITH AI

Analysis of the interaction between humans and AI platforms in GI endoscopy can be informed by a human factors approach, examining how human work interacts with work systems[50]. Human factors theories help to study and optimise components of work systems to allow human workers to get the most from the system[25]. Human factors research also recognises that there are several cognitive biases that can affect human interaction with AI[51]. Some of the cognitive biases that are most relevant to applications of AI in GI endoscopy are discussed below.

Automation bias

Automation bias refers to the human propensity to disengage cognitively from tasks that are assigned for execution or support by an external technology, usually resulting in decreased situational awareness[52]. The potential for negative outcomes due to automation bias has been explored through a human factors paradigm in healthcare and other settings requiring high levels of accuracy[50,52]. In the example of AI in GI endoscopy, automation bias may manifest as an over-reliance on a CADe or CADx platform to rapidly detect and diagnose all pathology encountered during the endoscopic procedure[46]. The use of automated decision support systems that are presumed to be highly accurate can lead to an over-reliance on the part of users, which may manifest as bias or as complacency.

Automation complacency may manifest with the endoscopist paying less attention to the presence of on-screen pathology during endoscopy, due to an assumption that the software will detect any pathology that appears[53]. This reduced vigilance, whereby the user becomes dependent on the software to shoulder the detection burden, can result in reduced human detection of pathology[54,55]. Second, the user can become progressively more confident in the AI platform's performance, to the point where they over-rely on its advice against their own correct judgement[56,57]. Studies of mammography and histology showed concerning over-reliance of clinicians on incorrect AI advice labelling cancers as benign[57]. The complexity of verifying that the AI platform is performing appropriately impacts on the degree of automation bias that arises in a given task[44]. In endoscopy, the ease of that verification task may vary depending on the endoscopist's experience, where the complexity of verification is higher for non-expert endoscopists than for experts.

It is important that users of AI platforms are educated on the limitations of the individual platform. The latency of the system *i.e.* the time difference between pathology appearing on-screen and recognition of the pathology by the computer system is typically as short as 0.2 s in the current generation of CADe platforms[37]. The cumulative time taken for the platform to identify the pathology, activate the alarm and for the user to register the alarm may be significantly longer, however.

A related cognitive bias is anchoring bias, which posits that when presented with external advice, humans tend to adjust insufficiently from that advice toward their own opinion, in reaching their decision[58]. It has been suggested that this insufficient adjustment is due to a trade-off between the accuracy required in the decision and the time required to

fully consider the difference between the external advice and one's own opinion[59]. Taking longer to consider a decision may be an effective mitigation against anchoring bias[51]. In real-time CADe-assisted endoscopy, however, the rapidity of decisions is an important factor in the efficiency of the procedure.

In CADx applications, the effect of AI may be synergistic for both expert and non-expert endoscopists[46]. A study that reached this conclusion advised endoscopists to treat advice from CADx as that from a colleague, weighing it against how accurate it usually is compared to the endoscopist. A simple adjustment to reduce automation bias may involve decreasing the prominence of alarms on screen[60]. More comprehensive strategies to mitigate automation bias could aim to decrease cognitive load on the endoscopist, instigate thorough training on use of the specific AI platform, address explainability and transparency of decision making and design adaptive user interfaces[44,52,61].

False positives and alarm fatigue

False positives are of significant interest in CADe, as they may negatively affect the efficiency and economy of endoscopic procedures[62]. A false positive may prolong the procedure as the endoscopist reviews the highlighted area[63]. It may also add to the cost of the procedure by increasing use of implements *e.g.* forceps/snares and raising the number of normal tissue samples submitted for processing and pathologic analysis[64]. In colonoscopy, a CADe false positive may be caused by a normal colonic fold, other normal anatomy *(e.g.* the ileocaecal valve), a non-polypoid abnormality *e.g.* a diverticulum, or luminal contents[63]. In commercially-available CADe systems, false positives in colonoscopy may occur in a ratio to true positives as high as 25:1[63].

The incidence of false positives during colonoscopy has been reported to range from 0.071 to 27 alarms per colonoscopy, depending heavily on the definition used[11]. Whereas some studies defined a false positive as any activation of a bounding box, others defined it as an activation that resulted in resection of normal tissue. Most studies examined the incidence of false positives only during withdrawal, as the CADe system was typically only active during withdrawal. In real world practice, however, the CADe platform is often active during both insertion and withdrawal, likely leading to more false positives than in the reported experimental studies. False positive alarms may be categorised according to the amount of time the endoscopist spends examining the area involved in the false positive alarm: mild (< 1 s), moderate (1-3 s) or severe (> 3 s)[63]. While most false positives in the published studies did not result in additional examination time, the endoscopists involved in those studies were experts, so may have been more easily able to dismiss false alarms than non-expert endoscopists.

Alarm fatigue is a well-described phenomenon whereby the repetitive activation of visual or audio alarms causes diminished, delayed or absent response in the user over time[65]. Alarms have the potential to add to cognitive burden on the endoscopist, increasing fatigue and negatively impacting performance[66]. While the amount of time taken to examine the site of each false alarm is low in published studies, the effect of repeated activations (at a rate of 2.4 +/- 1.2 false positive alarms per minute of withdrawal time) on endoscopist fatigue and possibly on algorithm aversion remains to be elucidated[63].

The frequency of alarms may be addressed by altering the confidence level of the CADe *i.e.* decreasing the sensitivity of the platform, though this would need to be balanced against the resulting risks of decreased sensitivity. AI may also provide part of the solution for this problem, through development of CADe platforms with better accuracy and through filtering technology that uses generative learning to suppress false positives in real-world use[67]. Another approach may be to increase the latency of output, so that activations of the bounding box of less than one second duration, which are almost always spurious, are suppressed and do not trigger an alarm. Alarm fatigue may also be reduced by minimising the alarm stimulus *e.g.* visual alarm without audio alarm, or altering the prominence or display of the bounding box.

Algorithm aversion

The 'CASA' phenomenon, discussed earlier, was a cornerstone of early HCI research. More recent research has shown that the way humans interact with technology is more nuanced than simply treating a new technology as they would another human. There are multiple influences on how humans interact with technology and how they use or discard advice given by technology, though the interaction of these factors is poorly understood[68,69].

Several studies have shown that a human user is likely to judge an AI algorithm more harshly for a mistake in advice than they would judge another human. This results in the user being substantially more likely to disregard the algorithm's future advice, a phenomenon known as algorithm aversion[70]. In contrast to automation bias, algorithm aversion suggests that once a human user notices the imperfect nature of the algorithm advising them, their adherence to the algorithm's future suggestions decreases, causing under-reliance on the AI system[71]. More recent work suggests that there are many factors affecting whether a user develops algorithm aversion, and durability of the phenomenon; these may include the individual endoscopist's expertise, attitudes to AI and expectations of the system. Experts may be more likely to reduce their adherence to AI advice after a false alarm than non-experts, even when later advice is correct [72,73].

In the CADe setting, where the platform alerts for many more false positives than true positives, the impact of algorithm aversion may be important. A systematic review of the factors influencing algorithm aversion identified incorrect expectations of the algorithm, control of decision making and external incentives as significant contributors[55]. With respect to AI in GI endoscopy, these factors may provide a framework for research on the human and AI platform variables that affect the propensity of a user to develop algorithm aversion.

Learning effect and deskilling

The effect of CADe and CADx platforms on an endoscopist's learning and on their development of skills essential to performance of endoscopy is uncertain. Several studies have shown that CADe may improve a trainee's ADR to close to that of an expert, providing additional safety and reducing the adenoma miss rate[74]. It is not clear, however, whether

this improved performance produces a persistent learning effect or whether it may bring about dependence of trainees on the CADe platform. There is some evidence that the ability of such platforms to draw a trainee endoscopist's eye to a polyp and to give advice on the likely histologic type of the polyp may improve the trainee's recognition and diagnosis of such lesions[46].

Evidence from non-endoscopic applications of AI show that the potential for non-expert clinicians and female clinicians to over-estimate the reliability of an AI platform raises concerns for poor training outcomes and for inequitable distribution of performance benefits[68]. Interestingly, providing an explanation for its decision does not appear to improve the application of AI for training. In explainable AI platforms that showed the user how it had arrived at its advice, trainees were more likely to accept the advice, even when it was incorrect, than if no explanation was given, the so-called 'white box paradox'[75].

Visual gaze pattern (VGP) is an important metric in vigilance tasks including detection of pathology during endoscopy, with substantial differences between VGPs of experts and those of non-experts[66,76-78]. Analysis of the VGP of endoscopists with high ADRs showed a positive correlation with VGPs that tracked the periphery of the bowel wall and the periphery of the screen in a 'bottom U' configuration during colonoscopy[76,79]. The repeated attraction of the endoscopist's attention to a bounding box on screen may serve to embed alterations in the endoscopist's VGP, which have been posited to have a negative effect on an endoscopist's attainment of expertise in polyp detection in colonoscopy [80]. In the eye-tracking experiment, endoscopists' gaze patterns focused more on the centre of the screen when using CADe, reducing their likelihood of detecting pathology peripherally.

CLINICIAN AND PATIENT ATTITUDES TO AI

The quality of HAII depends to a significant degree on the attitudes of users and patients toward the technology. Levels of trust in technology generally, and in AI technologies specifically, are heterogenous across groups of clinicians and groups of patients[81]. They depend on many factors including personal, professional, organisational and broader cultural considerations[82]. Research and speculation on the role of AI platforms have occupied increasing amounts of space in the endoscopy literature. The promise of AI in revolutionising patient care and administrative burden have been much-vaunted in academic literature and in popular media, leading to high levels of awareness of AI among the general population, but low levels of knowledge on specific applications[83].

Knowledge of AI is seen to correlate with a positive perception of the benefits of AI, and perhaps an underestimation of its risks[84]. Surveys of the attitudes of gastroenterologists and other endoscopists in the United States and the United Kingdom show a high degree of optimism on the potential role of AI to improve quality of care for patients[85]. They also support development of guidelines for use of AI devices[86] and endorse concerns that CADe technology will create operator dependence on the technology[87].

Patient attitudes toward AI algorithms making decisions or offering advice appear more cautious[88]. When used as a tool by their clinician, patients perceive benefit in AI in specific settings including cancer diagnosis and treatment planning[89]. Patient attitudes to use of AI in GI endoscopy require further research.

CONCLUSION

In many of its current applications, AI marks a fundamental transition from technology as a tool to technology as a team member. Research is required to define what skills clinicians will need to optimally leverage AI technologies and to apply AI advice with adequate discrimination. It will then be necessary to decide how best to teach these skills from undergraduate to expert endoscopist level.

While there are regulatory pathways for appropriate trialling and development of AI software applications, guidance for clinical evidence requirements is lacking for medical AI software in general and not limited to software devices in GI endoscopy. Frameworks for design and reporting of trials involving AI are therefore to be welcomed[90]. Uniform definitions of variables (*e.g.* false positive) are needed for research and reporting of real-world performance of AI platforms. Several professional societies have published opinions on priority areas for future research on AI in GI endoscopy[91,92]. These opinions place a notable emphasis on technical outcomes, rather than on outcomes related to human interaction or patient-centred endpoints. It can be expected that priorities will need to be updated and redefined by professional societies frequently, as new technologies emerge. The medical community and professional societies should lead the way in defining the research agendas for AI platforms including the clinical evidence base required for their validation, adoption into clinical practice and continuous appraisal, while ensuring that patient priorities, human factors and real-world evidence are prioritised[93].

Priorities for research on HAII in GI endoscopy should include factors predicting individual clinician variations in utility of AI and the effect of AI use on trainees' development of core competencies for endoscopy[94]. A HAII focus in platform development may give rise to AI that learns how best to interact with each clinician based on their performance and use style, and adapts accordingly. Complementarity may be enhanced by prioritising study of human interaction with novel AI platforms that can perform tasks at which human clinicians are poor *e.g.* measurement of polyps or other pathology, measurement/estimation of the percentage of the stomach/colon visualised during a colonoscopy[95].

HAII will be a key determinant of the success or failure of individual applications of AI. It is therefore essential to optimise interface elements, as clinician frustration with poorly-designed platforms now may have a negative impact on later engagement and uptake[96]. The rapid development and implementation of AI platforms in GI endoscopy and

elsewhere in medicine has been performed while studying mainly technical outcomes in idealised settings. This trend of adopting a technology-first approach expects clinicians and patients to adapt to the AI platforms, and risks taking insufficient account of human preferences and cognitive biases[50]. Reorienting the focus toward development of human-centred AI and incorporating the study of human interaction at each stage of a new platform's development, while aligning to appropriate regulation and governance, may allow creation of AI that is more user-friendly, more effective, safer and better value[90].

FOOTNOTES

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Tumor size discrepancy between endoscopic and pathological evaluations in colorectal endoscopic submucosal dissection

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Abstract

BACKGROUND

Tumor size impacts the technical difficulty and histological curability of colorectal endoscopic submucosal dissection (ESD); however, the preoperative evaluation of tumor size is often different from histological assessment. Analyzing influential factors on failure to obtain an accurate tumor size evaluation could help prepare optimal conditions for safer and more reliable ESD.

AIM

To investigate the tumor size discrepancy between endoscopic and pathological evaluations and the influencing factors.

METHODS

This was a retrospective study conducted at a single institution. A total of 377 lesions removed by colorectal ESD at our hospital between April 2018 and March 2022 were collected. We first assessed the difference in size with an absolute percentage of the scaling discrepancy. Subsequently, we compared the clinicopathological characteristics of the correct scaling group (> -33% and < 33%) with that of

the incorrect scaling group (< -33% or > 33%), which was further subdivided into the underscaling group (-33% or less of the discrepancy) and overscaling group (33% or more of the discrepancy), respectively. As secondary outcome measures, parameters on size estimation were compared between the underscaling and correct scaling groups, as well as between the overscaling and correct scaling groups. Finally, multivariate analysis was performed in terms of the following relevant parameters on size estimation: Pathological size, location, and possible influential factors ($P < 0.1$) in the univariate analysis.

RESULTS

The mean of absolute percentage in the scaling discordance was 21%, and 91 lesions were considered to be incorrectly estimated in size. The incorrect scaling was significantly remarkable in larger lesions (40 mm *vs* 28 mm; $P < 0.001$) and less experience ($P < 0.001$), and these two factors were influential on the underscaling (75 lesions; $P < 0.001$). Conversely, compared with the correct scaling group, 16 lesions in the overscaling group were significantly small (20 mm *vs* 28 mm; $P < 0.001$), and the small lesion size was influential on the overscaling ($P = 0.002$).

CONCLUSION

Lesions indicated for colorectal ESD tended to be underestimated in large tumors, but overestimated in small ones. This discrepancy appears worth understanding for optimal procedural preparation.

Key Words: Endoscopic submucosal dissection; Colorectal tumor; Tumor size; Size estimation; Size discrepancy

Core Tip: Tumor size impacts the technical difficulty and histological curability of colorectal endoscopic submucosal dissection (ESD). However, the preoperative evaluation of tumor size is often different from histological assessment. We retrospectively investigated the colorectal tumor size discrepancy between endoscopic and pathological evaluations and influential factors on the discordance. Conclusively, the data demonstrated that the accuracy in the size estimation of candidates for colorectal ESD was influenced by the tumor size and much experience. These lesions tended to be underestimated in large tumors, but overestimated in small ones. This discrepancy appears worth understanding for optimal procedural preparation.

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INTRODUCTION

Colorectal cancer is one of the most common malignancies and relevant disease worldwide[1]. The early detection and treatment of this disease are significant to prolong life expectancy; therefore, aggressive removal of colorectal polyps including precancerous lesions is recommended using colonoscopy[2,3].

Small colorectal polyps can be easily removed by polypectomy or endoscopic mucosal resection (EMR), whereas large lesions require technically challenging techniques including endoscopic submucosal dissection (ESD). Due to anatomical characteristics, including a thin intestinal wall and the presence of folds and bends, colorectal ESD is technically more difficult than upper gastrointestinal tract ESD. Intraoperative perforation, which is one of the major adverse events in colorectal ESD, is reported to be 1.3%-18.0%[4-7]. Influential factors on the perforation in colorectal ESD include tumor diameter, fibrosis, and flexure[5]. Moreover, it is reported that a larger tumor[6,7], less experience of endoscopists[6], and paradoxical movement[7] are independent factors contributing to the difficulty of colorectal ESD. Particularly, a strong correlation is observed between tumor diameter and treatment duration[8].

Accordingly, an accurate understanding of tumor characteristics including tumor size, is significant for a safe and time-saving procedure. However, the preoperative estimation of the tumor diameter is often different from the postoperative histological size, and when a novice endoscopist is to treat an unexpectedly large lesion, unfavorable events can occur with a long procedural time.

There have been several studies on the discrepancy in the tumor diameter of colorectal neoplasia[9-12]. However, these studies are mainly on small polyps, wherein tumors of approximately 10 mm are believed to be often overestimated[9,10]. Conversely, pieces of evidence remain lacking on large tumors[12], particularly tumors that can be candidates for resection by ESD.

In this study, to investigate the accuracy of the preoperative endoscopic evaluation of tumor size, we retrospectively assessed the discrepancy between pre- and postoperatively evaluated tumor diameters of lesions that are indicated for colorectal ESD. Subsequently, influential factors on failure for an accurate tumor size evaluation were investigated.

MATERIALS AND METHODS

Study design

This was a retrospective study conducted at a single institution. In accordance with the Declaration of Helsinki, we obtained approval from the institutional review board of our hospital before study initiation. Consent from each patient was obtained as an opt-out; therefore, written consent was waived.

Data collection and ESD procedure

Of the 395 lesions removed by colorectal ESD performed between April 2018 and March 2022, 6 lesions with insufficient description of data on preoperative and/or pathological tumor diameter and 12 lesions with incomplete resection were excluded. Finally, we collected 377 lesions in this study (Figure 1).

ESD indication criteria were based on the Japanese Colorectal ESD/EMR guidelines[4]. We mainly used the PCF-290ZI endoscope (Olympus Co., Ltd., Tokyo, Japan) with a transparent straight hood (D-201-12704; Olympus) under carbon dioxide insufflation. A 0.4% sodium hyaluronate solution (Ksmart; Olympus) diluted five times with normal saline, which included a small amount of indigo carmine, was used for submucosal injection. A mucosal incision was made around the tumor, and submucosal dissection for *en bloc* removal was performed using the DualKnife (KD-655Q; Olympus). A high-frequency generator (VIO 3; Erbe Elektromedizin GmbH, Tübingen, Germany) was used during ESD. ST-hood (DH-29CR; Fujifilm Co., Ltd., Tokyo, Japan), hemostatic forceps (FD-411QR; Olympus), or other endoscopic devices were used according to the situation. The transanally retrieved specimen was promptly spread, pinned on a sponge board, and immersed into 10% neutral buffered formalin for fixation for histological evaluation by pathologists.

Pre- and postoperative size assessment

For the preoperative tumor size evaluation, we referred to endoscopic reports, which were documented in preoperative colonoscopy before ESD. The tumor size, which was described as the largest diameter, was obtained from the endoscopic report at our institution when we performed the preoperative check or at other clinics where the tumor was indicated and introduced to us when ESD was directly booked without preoperative colonoscopy at our institution.

Postoperative size evaluation was performed using the largest diameter on the pathological report. In detail, board-certificated pathologists evaluated the specimen, which was sliced at 2-3-mm intervals. Based on the final pathological diagnosis, the pathologists in charge demarcated the neoplastic area on the specimen photo that was taken before slicing, and the maximal diameter of the tumor was described in a pathological report.

Outcome measures

As a primary outcome measure, the scaling discrepancy, which indicated an absolute percentage of the size discordance (a preoperatively estimated endoscopic diameter minus a postoperatively measured histological diameter) in a postoperatively measured diameter, was evaluated (Figure 2). Subsequently, lesions were divided into the following two groups according to the degree of discrepancy: The correct scaling group (> -33% and < 33% of the discordance) and the incorrect scaling group (≤ -33% or ≥ 33% of the discordance). Lesion-related parameters including pathological size, location, morphology, histology, localization, and degree of circumference were used to investigate influential factors on the discrepancy. Furthermore, endoscopist-related parameters included the experience of endoscopists who performed preoperative colonoscopy and the hospital type where the preoperative colonoscopy was performed. The multivariate analysis was followed by univariate analyses, which focused on the tumor size, location, and other parameters that seemed to be influential by showing that the P value was < 0.1 in the preceding univariate analysis.

As secondary outcome measures, the abovementioned parameters were compared between the underscaling (-33% or less of the discrepancy) and correct scaling groups as well as between the overscaling (33% or more of the discrepancy) and correct scaling groups, respectively. Subsequently, multivariate analysis was performed in terms of the following relevant parameters on size estimation: Pathological size, location, and possible influential factors (P < 0.1) in the univariate analysis. When the size, a continuous parameter, was indicated as the influential factor, we drew a receiver operating characteristic (ROC) curve to investigate an optimal cut-off value of the size to differentiate the under/overscaling group from the correct scaling group.

Tumor locations were grouped into the colon and rectum. Morphology was divided into the following two macroscopic groups according to the Paris classification: The protruded type, which is 0-I with protruded features; and the flat type, which is 0-II with flat features. Histology was grouped into adenoma and adenocarcinoma. Regarding the localization, we focused on whether the lesion is over the haustra because it may hamper an entire lesion in a single visual field. Regarding the degree of circumference, lesions were divided into two groups by setting one-third as the cut-off value. The experience of endoscopists was classified on the basis of the years of experience in endoscopy and the number of ESD performed; those with 5 years or more of endoscopic experience and at least 100 cases of ESD were defined as experienced, and those who did not meet these criteria were defined as less-experienced. As all doctors at the clinics were general physicians and their experience in ESD is unknown, they were defined as less-experienced in this study. Regarding the hospital type, we set two groups, a referral hospital (our institution) and clinics, according to where the preoperative colonoscopy was performed just before ESD.

Statistical analysis

Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Continuous variables were tested for normality and analyzed using the Mann-Whitney U test between the two groups and using the Kruskal-Wallis H test among the three groups. To adjust for potential confounders, we used multivariate logistic regression. The Pearson

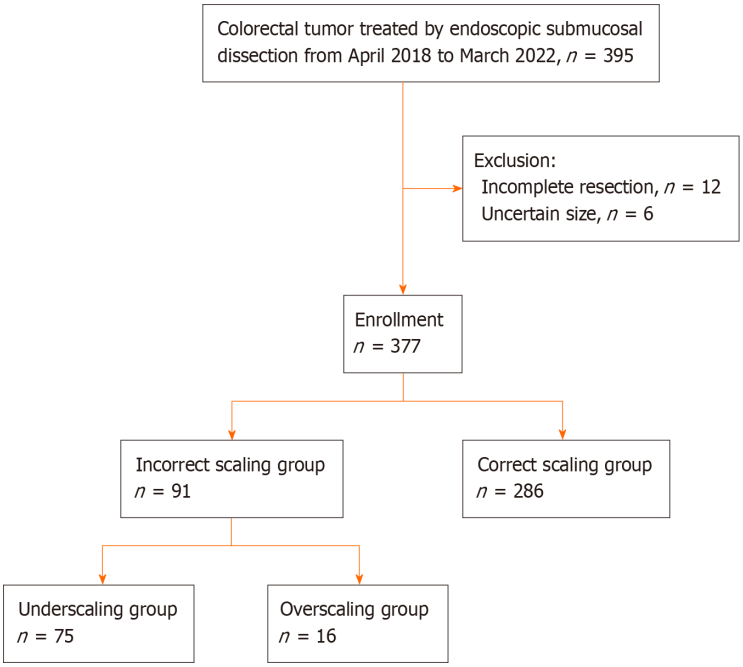

Figure 1 Flowchart of lesion enrollment in this study. Of the 395 colorectal lesions removed by endoscopic submucosal dissection, 377 were enrolled in this study. A total of 286 lesions obtained correct size evaluation. Most of the incorrect scaling lesions were underscaled (75 of 91 lesions).

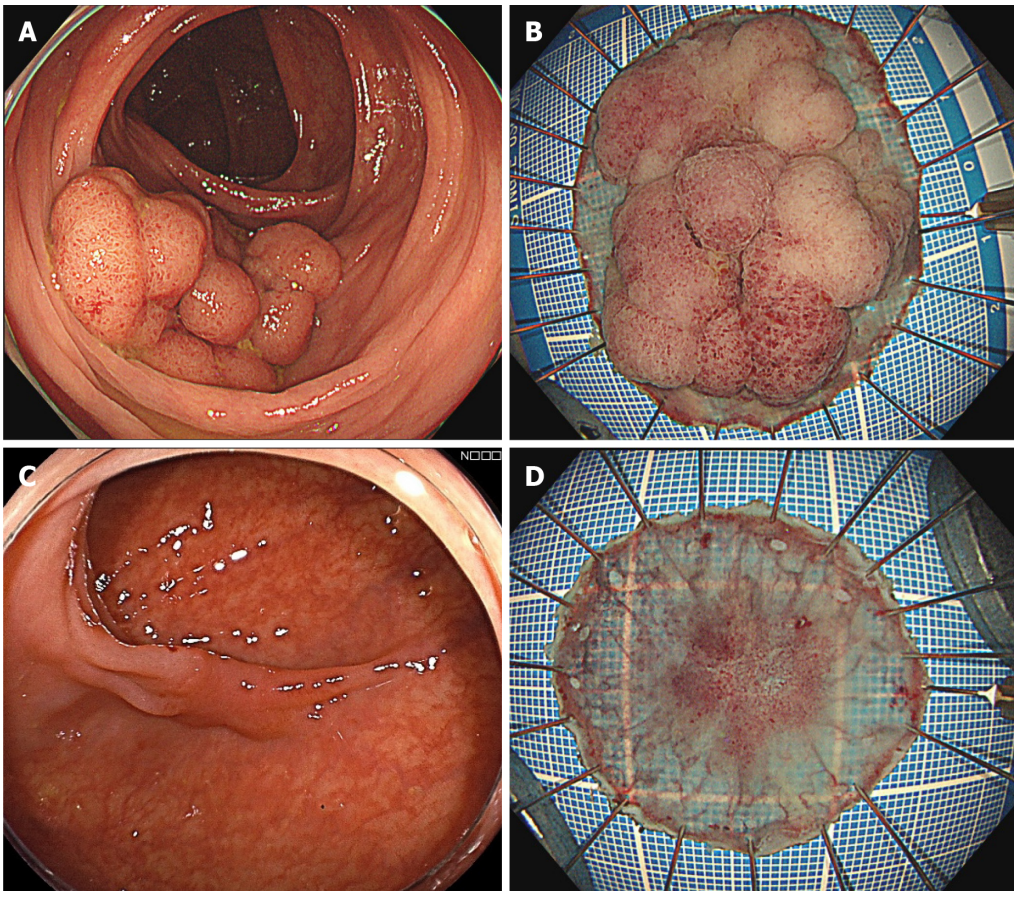

Figure 2 Representative cases of incorrect scaling. A: Underscaling case. The tumor size was evaluated as 30 mm; B: Pathology revealing the maximal diameter as 49 mm, wherein the size discrepancy was -39%; C: Overscaling case. The cancerous lesion was evaluated as 20 mm; D: The pathological size was 15 mm, resulting in a size discrepancy of 33%.

product-moment correlation coefficient was used for regression analysis. The cut-off value was evaluated in the point with the highest Youden's index. All statistical analyses were performed using Statistical Package for the Social Sciences (version 27, IBM, Armonk, NY, United States), and $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics and size discrepancy

The mean age of patients was 70 years, and 61% of them were males. Approximately one-fifth of cases were located on the rectum. The number of experienced endoscopists in preoperative diagnosis was almost similar to that of less-experienced endoscopists. The mean size of preoperatively estimated and postoperatively measured tumors was 26.0 mm ± 10.5 mm and 31.0 mm ± 15.2 mm, respectively, and the mean of absolute percentage in the scaling discordance between pre- and postoperative evaluations was 21.0% ± 15.4% (Table 1). The distribution of lesions regarding the discordance is shown in Figure 3.

Influential factors on the incorrect scaling

Regarding the scaling discrepancy, the numbers of lesions in the incorrect and correct scaling groups were 91 and 286, respectively (Figure 1). As shown in Table 2, large lesions, the involvement of the haustra, over one-third of the lumen, and the assessment by less-experienced are significantly common in the incorrect scaling group. Multivariate analysis demonstrated that larger tumor size and less experience were significantly influential on the incorrect scaling of the size assessment (Table 3).

Influential factors on under/overscaling

The incorrect scaling group (91 lesions) was further divided into the under- and overscaling groups, with 75 and 16 lesions, respectively (Figure 1). As shown in Table 4, the influential factors on underscaling include tumor size, the involvement of the haustra, and over one-third of the lumen. Multivariate analysis showed that larger size and less experience significantly affected the underestimation of the scaling in lesion size (Table 5). The ROC curve indicated that the optimal cut-off value was 29.5 mm in 0.779 of the maximal area under the curve (AUC), with sensitivity and specificity of 80.0% and 69.9%, respectively.

Regarding overscaling, tumor size was the sole influential factor. However, lesions in the overscaling group were smaller than those in the correct scaling group, which was the opposite result in the analysis on underscaling (Table 6). Multivariate analysis showed that smaller size was significantly influential on overscaling (Table 7). In the ROC curve, the optimal cut-off value was 18.5 mm when the maximal AUC was 0.768, with sensitivity and specificity of 88.5% and 56.2%, respectively.

DISCUSSION

The present study showed that the tumor size was approximately ± 20% of the scaling discrepancy before colorectal ESD. One-fourth of those lesions were incorrectly evaluated in size, mainly toward the underestimation; this tendency was likely observed in large tumors > 3 cm and less-experienced endoscopists. By contrast, the overestimation, although occurred less frequently, tended to be made in smaller lesions < 2 cm. Overall, in the preoperative colonoscopy before ESD, lesions at both extremities in size were likely to be adjusted to the moderate diameter.

In this study, the mean pathological diameter of colorectal lesions that were removed by ESD was 31 mm, whereas the mean preoperative endoscopic evaluation diameter was 26 mm, indicating that the lesion size was almost correctly estimated before the procedure. The mean scaling discrepancy (± 21%) appeared to be an acceptable discordance. However, considering that the correct scaling was defined as from -33% to 33% of discrepancies, one-fourth (91/377) of lesions were incorrectly evaluated preoperatively. Multivariate analysis suggested that large lesions and less experience were independent influential factors on incorrect scaling. Regarding large lesions, the reason for the incorrect scaling may be attributed to the structure of the lens mounted on an endoscope. An endoscopic lens is designed as a fish-eye, which can visualize a wider field than reality. Therefore, a large objective tends to appear smaller. On the other hand, less ESD experience may contribute to incorrect size evaluation of large lesions due to less experience both in visualizing the actual specimen pinned following ESD and reviewing pathological results. In clinical practice, endoscopists can adjust the preoperative endoscopic size to the actual pathological size by repeatedly reviewing pathological diagnoses of endoscopically removed polyps. However, lesions that are candidates for ESD are not frequently encountered compared with small polyps. Therefore, endoscopists with less ESD experience should have less opportunity of providing feedback on the pathological diagnosis of ESD to further endoscopic evaluation.

In the incorrect scaling, underestimation mainly occurred in 82% of lesions (75/91). The comparison between the underscaling and correct scaling groups showed similar results to that between the incorrect and correct scaling groups. This suggests that the abovementioned speculations are considered appropriate. Particularly, lesions > 3 cm in actual size are inclined to be underscaled, as indicated in the ROC curve analysis. In contrast, 18% of the incorrect scaling was misdiagnosed as overestimation. Interestingly, the overestimation was also influenced by lesion size; however, small lesions tend to appear larger, which is the opposite phenomenon of underestimation. This reason may not be because of endoscopic visualization but the indication criteria of colorectal ESD. Considering the medical insurance from the

Table 1 Background characteristics and size assessment, *n* (%)

Item	Value
Background characteristics	*n* = 377
Lesion-related factors	
Age in yr, mean	70
Sex	
Male	231 (61)
Female	146 (39)
Location	
Colon	298 (79)
Rectum	79 (21)
Morphology	
Protruded	84 (22)
Flat	293 (78)
Histology	
Adenoma	84 (22)
Adenocarcinoma	293 (78)
Localization	
Over the haustra	212 (56)
On a flat lumen	165 (44)
Degree of circumference	
≥ 1/3	40 (11)
< 1/3	337 (89)
Endoscopist-related factors	
Experience	
Experienced	186 (50)
Less-experienced	191 (50)
Hospital type	
Referral hospital	351 (93)
Clinics	26 (7)
Size assessment	
Endoscopic size in mm, mean ± SD	26.0 ± 10.5
Histological size in mm, mean ± SD	31.0 ± 15.2
Absolute percentage of the size discordance, mean ± SD	21.0 ± 15.4

Japanese government, the indication criteria of colorectal ESD for cancers are lesions ≥ 2 or ≥ 1 cm with possible severe submucosal fibrosis. In this condition, when endoscopists detect a small tumor that should be removed in an *en bloc* fashion but consider it difficult by snaring, they may be psychologically inclined to diagnose it as larger than the actual size to meet the ESD criteria. The small number of lesions in the overscaling group may be due to the nature of the lesions included in this study. Previous studies have indicated that small polyps are likely to be overestimated[9,10]. In this study, the lesions were relatively large because this study included lesions removed by ESD. Therefore, we consider that the lesions in this study were less likely to be overscaled.

If we are aware that the larger the lesion appears, the much larger it may be, we can prepare an optimal condition for safe and reliable ESD as per operator's discretion, including an endoscopic room for a long procedure time and the degree of sedation needed. Moreover, appropriate informed consent can be provided to patients and families. This tendency will be more distinct when the preoperative colonoscopy is performed by an endoscopist with less experience. Conversely, when an ESD candidate is small, it may be smaller than it appears, thereby making it suitable for removal *via* snaring resection, wherein unnecessary ESD can be avoided; however, sufficient technical skills for *en bloc* EMR are

Table 2 Univariate analysis of influential factors on incorrect scaling, *n* (%)

Item	Incorrect scaling group	Correct scaling group	*P* value
	n = 91	*n* = 286	
Lesion-related factors			
Pathological size in mm, mean	40	28	< 0.001
Location			0.750
Colon	73 (80)	225 (79)	
Rectum	18 (20)	61 (21)	
Morphology			0.210
Protruded	16 (18)	68 (24)	
Flat	75 (82)	218 (76)	
Histology			0.830
Adenoma	21 (23)	63 (22)	
Adenocarcinoma	70 (77)	223 (78)	
Localization			0.001
Over the haustra	65 (71)	147 (51)	
On a flat lumen	26 (29)	139 (49)	
Degree of circumference			< 0.001
≥ 1/3	21 (23)	19 (7)	
< 1/3	70 (77)	267 (93)	
Endoscopist-related factors			
Experience			0.050
Experienced	37 (41)	150 (52)	
Less-experienced	54 (59)	136 (48)	
Hospital type			0.900
Referral hospital	85 (93)	266 (93)	
Clinics	6 (7)	20 (7)	

required.

This study had several limitations. First, it was a retrospective single-center study. Second, several endoscopists and pathologists were involved in the pre- and postoperative diagnoses, respectively. Third, since the shape of tumors was flexibly changed under intraluminal conditions, some lesion characteristics regarding the haustra or the degree of circumference could not be completely objective. Fourth, the threshold of discrepancies (33%) was subjectively determined in this study because referable previous papers were lacking. Lastly, the tumor size was slightly shortened following fixation with formalin; however, this change should be negligible[13].

CONCLUSION

The present study demonstrated that the accuracy in preoperative size estimation of large colorectal tumors that could be indicated for ESD was influenced by the tumor size and much experience. These lesions tended to be underestimated in large tumors, whereas overestimated in small ones, suggesting that endoscopists, particularly less-experienced in ESD, were inclined to change the lesions to a "moderate" size. The understanding of this discrepancy may be helpful for preoperative informed consent for patients and the decision-making of operative conditions.

Table 3 Multivariate analysis of influential factors on incorrect scaling

Factor	Odds ratio	95%CI	*P* value
Pathological size	1.05	1.030-1.080	< 0.001
Location			
Rectum	1.00		
Colon	1.20	0.612-2.360	0.590
Localization			
Over the haustra	1.00		
On a flat lumen	1.56	0.877-2.750	0.130
Degree of circumference			
< 1/3	1.00		
≥ 1/3	1.09	0.414-2.870	0.860
Experience			
Less-experienced	1.00		
Experienced	0.44	0.259-0.760	0.003

95%CI: 95% confidence interval.

Table 4 Univariate analysis of influential factors on underscaling, *n* (%)

Item	Underscaling group	Correct scaling group	*P* value
	n = 75	*n* = 286	
Lesion-related factors			
Pathological size in mm, mean	44	28	< 0.001
Location			0.800
Colon	58 (77)	225 (79)	
Rectum	17 (23)	61 (21)	
Morphology			0.150
Protruded	12 (16)	68 (24)	
Flat	63 (84)	218 (76)	
Histology			0.400
Adenoma	20 (27)	63 (22)	
Adenocarcinoma	55 (73)	223 (78)	
Localization			0.001
Over the haustra	54 (72)	147 (51)	
On a flat lumen	21 (28)	139 (49)	
Degree of circumference			< 0.001
≥ 1/3	20 (27)	19 (7)	
< 1/3	55 (73)	267 (93)	
Endoscopist-related factor			
Experience			0.056
Experienced	30 (40)	150 (52)	
Less-experienced	45 (60)	136 (48)	

Hospital type			0.760
Referral hospital	69 (92)	266 (93)	
Clinics	6 (7)	20 (7)	

Table 5 Multivariate analysis of influential factors on underscaling

Factor	Odds ratio	95%CI	*P* value
Pathological size	1.08	1.05-1.11	< 0.001
Location			
Rectum	1.00		
Colon	1.07	0.510-2.250	0.840
Localization			
On a flat lumen	1.00		
Over the haustra	1.36	0.705-2.600	0.340
Degree of circumference			
< 1/3	1.00		
≥ 1/3	0.65	0.227-1.890	0.290
Experience			
Less-experienced	1.00		
Experienced	0.36	0.192-0.666	0.001

95%CI: 95% confidence interval.

Table 6 Univariate analysis of influential factors on overscaling, *n* (%)

Factor	Overscaling group	Correct scaling group	*P* value
	n = 16	*n* = 286	
Lesion-related factors			
Pathological size in mm, mean	20	28	< 0.001
Location			0.210
Colon	15 (94)	225 (79)	
Rectum	1 (6)	61 (21)	
Morphology			1.000
Protruded	4 (25)	68 (24)	
Flat	12 (75)	218 (76)	
Histology			0.210
Adenoma	1 (6)	63 (22)	
Adenocarcinoma	15 (94)	223 (78)	
Localization			0.180
Over the haustra	11 (69)	147 (51)	
On a flat lumen	5 (31)	139 (49)	
Degree of circumference			1.000
≥ 1/3	1 (6)	19 (7)	
< 1/3	15 (94)	267 (93)	

Endoscopist-related factor			
Experience			0.500
Experienced	7 (44)	150 (52)	
Less-experienced	9 (56)	136 (48)	
Hospital type			0.610
Referral hospital	16 (100)	266 (93)	
Clinics	0 (0)	20 (7)	

Table 7 Multivariate analysis of influential factors on overscaling

Factor	Odds ratio	95%CI	*P* value
Pathological size	0.86	0.779-0.945	0.002
Location			
Rectum	1.00		
Colon	3.67	0.464-29.000	0.220

95%CI: 95% confidence interval.

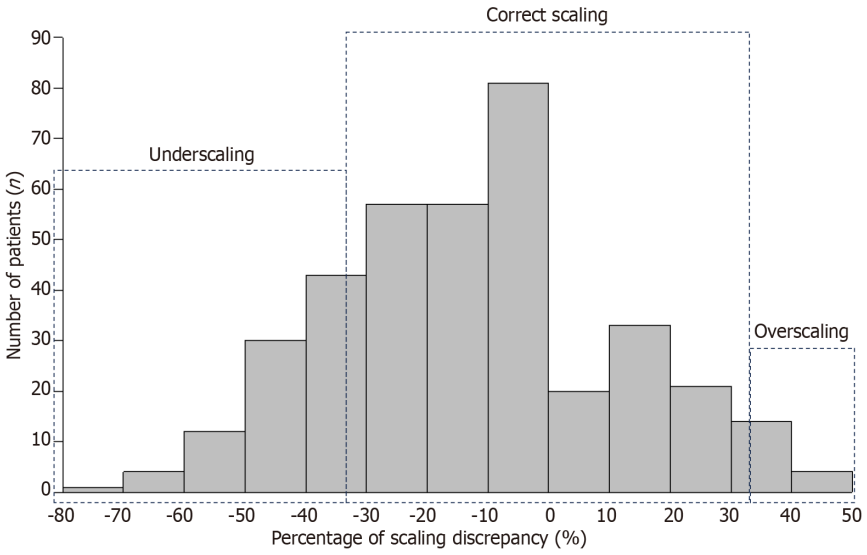

Figure 3 Lesion distribution in terms of size discrepancy. Incorrect scaling was made in 24%, which were mostly underscaled.

ARTICLE HIGHLIGHTS

Research background

Pathological assessment of tumor size often differs from preoperative evaluation, which could render treatment difficult. This study retrospectively investigated size discrepancies between endoscopic and pathological assessment and factors influencing this discordance.

Research motivation

The preoperative estimation of the tumor size is often different from the postoperative histological size, and when a novice endoscopist is to treat an unexpectedly large lesion, unfavorable events can occur with a long procedural time. Accordingly, an accurate understanding of tumor characteristics including tumor size, is significant for a safe and time-saving procedure.

Research objectives

To analyze the discrepancy between tumor size in endoscopic and pathological assessment and the factors influencing this discrepancy will enable a more accurate prediction of tumor size in the preoperative phase.

Research methods

We included 377 lesions removed with colorectal endoscopic submucosal dissection (ESD) at our hospital between April 2018 and March 2022. We classified three groups to analyze the discrepancy by size variation: Overestimation, underestimation, and the correct diagnosis groups. We compared clinicopathological characteristics among these groups.

Research results

We showed that the larger the lesion, the more likely it is to be underestimated. This preoperative underestimation was contrary to previous reports for small polyps. The larger the lesion, the longer the ESD treatment time needed because ESD treatment time is influenced by lesion size. The present study results revealed that larger lesions should be assumed to require longer-than-predicted treatment time.

Research conclusions

Recognizing that the larger the lesion appears, the more likely it is to be a larger lesion, optimal conditions for safe and reliable ESD can be prepared according to the operator's judgment, including an operation room for longer procedure times and the degree of sedation required.

Research perspectives

To investigate how tumor size discrepancies between endoscopic and pathological assessment affect ESD outcomes.

FOOTNOTES

Author contributions: Onda T collected the research study data, analyzed the data, and wrote the manuscript; Goto O conceived the study and design and interpreted the data; Otsuka T and Hayasaka Y performed the statistical analyses; Nakagome S, Habu T, Ishikawa Y, Kirita K, Koizumi, E, Noda H, Higuchi K, Omori J, and Akimoto N critically revised the manuscript for important intellectual content; Iwakiri K provided research supervision.

Institutional review board statement: The study was reviewed and approved by the Nippon Medical School, Graduate School of Medicine Institutional Review Board (Approval No. 30-02-1077).

Informed consent statement: Informed consent was obtained by opting out, not in writing, as this is a retrospective analysis.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Retrospective Study

Impact of frailty on endoscopic retrograde cholangiopancreatography outcomes in nonagenarians: A United States national experience

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Abstract

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential therapeutic tool for biliary and pancreatic diseases. Frail and elderly patients, especially those aged ≥ 90 years are generally considered a higher-risk population for ERCP-related complications.

AIM

To investigate outcomes of ERCP in the Non-agenarian population (≥ 90 years) concerning Frailty.

METHODS

This is a cohort study using the 2018-2020 National Readmission Database. Patients aged ≥ 90 were identified who underwent ERCP, using the international classification of diseases-10 code with clinical modification. Johns Hopkins's adjusted clinical groups frailty indicator was used to classify patients as frail and non-frail. The primary outcome was mortality, and the secondary outcomes were morbidity and the 30 d readmission rate related to ERCP. We used univariate and multivariate regression models for analysis.

RESULTS

A total of 9448 patients were admitted for any indications of ERCP. Frail and non-frail patients were 3445 (36.46%) and 6003 (63.53%) respectively. Indications for ERCP were Choledocholithiasis (74.84%), Biliary pancreatitis (9.19%), Pancreatico-biliary cancer (7.6%), Biliary stricture (4.84%), and Cholangitis (1.51%). Mortality rates were higher in frail group [adjusted odds ratio (aOR) = 1.68, P = 0.02]. The Intra-procedural complications were insignificant between the two groups which included bleeding (aOR = 0.72, P = 0.67), accidental punctures/lacerations (aOR = 0.77, P = 0.5), and mechanical ventilation rates (aOR = 1.19, P = 0.6). Post-ERCP complication rate was similar for bleeding (aOR = 0.72, P = 0.41) and post-ERCP pancreatitis (aOR = 1.4, P = 0.44). Frail patients had a longer length of stay (6.7 d *vs* 5.5 d) and higher mean total charges of hospitalization ($78807 *vs* $71392) compared to controls (P < 0.001). The 30 d all-cause readmission rates between frail and non-frail patients were similar (P = 0.96).

CONCLUSION

There was a significantly higher mortality risk and healthcare burden amongst nonagenarian frail patients undergoing ERCP compared to non-frail. Larger studies are warranted to investigate and mitigate modifiable risk factors.

Key Words: Endoscopic retrograde cholangiopancreatography; Nonagenarians; Frailty; Mortality; Healthcare burden

Core Tip: In this comprehensive national study, frail nonagenarians undergoing endoscopic retrograde cholangiopancreatography (ERCP) faced heightened mortality, prolonged hospital stays, and increased healthcare costs compared to non-frail counterparts. Surprisingly, intra-procedural and post-procedural complications showed no significant difference between the frail and non-frail groups, including bleeding and accidental punctures. Notably, post-ERCP pancreatitis rates were also comparable. Despite similar 30 d readmission rates, frailty emerged as an independent predictor of post-ERCP mortality in nonagenarians. With limited guidelines for such advanced procedures in this population, careful consideration of benefits *vs* risks is crucial, urging a personalized approach for those with approved indications for ERCP.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is indeed a high-risk endoscopic procedure to assess and treat conditions involving the pancreaticobiliary ductal system. ERCP was initially developed in the late 1960s as a diagnostic

procedure. Over time, it has evolved from being primarily a diagnostic tool to a therapeutic procedure, enabling the treatment of various conditions like choledocholithiasis, acute cholangitis, bile duct strictures, *etc.*[1,2]. Both ERCP and procedures associated with therapeutic ERCP have the potential for complications, such as bleeding, pancreatitis, duodenum and pancreaticobiliary perforations, and cardiopulmonary distress[3,4]. Mortality rates up to 6%-7% related to ERCP procedures have also been documented[5-7].

While age has traditionally been employed as a predictor of clinical outcomes in ERCP, it alone proves insufficient for a comprehensive assessment of risk-benefit trade-offs. A more holistic approach is essential to gauge physiological resilience and functional capacity, which are crucial in determining overall risk. Several studies have employed the use of Johns Hopkins's Adjusted Clinical Groups (ACG) frailty indicator to overcome this[8-10]. Frailty encompasses a physiological decline in function, manifesting as an inability to adapt and respond to stressors[11]. It should be perceived as a vulnerability stemming from a combination of internal physiological factors and external stressors.

Several studies have shown adverse surgical outcomes in frail patients including Orthopedic, Urological, and Otolaryngological procedures[10,12-14]. However, the data on ERCP, especially in the nonagenarian population, is scarce. Therefore, we aimed to investigate the impact of frailty on ERCP-related hospitalization in this high-risk population.

MATERIALS AND METHODS

Data sources

Data was extracted from the National Readmission Database (NRD) from 2018 to 2020. The NRD is part of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality. The NRD contains data from approximately 18 million discharges each year across 28 geographically dispersed states. This data set accounts for 60% of the total United States resident population, 59% of all United States hospitalizations, and includes all tax-payer data[15]. The present study was deemed exempt by the institutional review board because the database contained de-identified data sets with prior ethical committee approval. The NRD is publicly available and can be procured from the Healthcare Cost and Utilization Project website[15].

Patient selection

We identified 9448 patients who underwent elective or emergent ERCP, aged ≥ 90 years, using previously validated *International Classification of Diseases, Tenth Revision, and Clinical Modification* (*ICD-10-CM*) codes[16]. These patients were stratified into two cohorts based on Johns Hopkins' ACG frailty indicator. These codes and strategies were validated and used in the previous studies[17]. Patients were excluded if they were aged < 90 years and were admitted in December.

Baseline variables

We used the variables provided in the NRD by the Healthcare Cost and Utilization Project to identify patients' baseline characteristics, including age, sex, primary expected payer, median household income category by patient zip code, and hospital information such as bed size, teaching status, and location. We used *ICD-10-CM* codes given by the Elixhauser comorbidity index calculator provided by the Healthcare Cost and Utilization Project to report hypertension, diabetes, hyperlipidemia, peripheral vascular disease, chronic heart failure, chronic pulmonary disease, anemia, obesity, smoking, and coagulopathy (Supplementary Table 1). Frailty was defined using Johns Hopkins's ACG frailty indicator, which is based on a binary classification system, considering numerous clinical conditions as defined in Supplementary Table 1. Patients were classed as either frail or non-frail.

Data analysis

Statistical analyses were conducted using Stata, version 17.0 BE (StataCorp, College Station, TX, United States). The NRD is based on a complex sampling design that includes stratification, clustering, and weighting. Stata has a set of commands specifically designed to analyze the data while taking into consideration its complex design and produce nationally representative unbiased results, variance estimates, and *P*-values. A weighting of patient-level observations was implemented to obtain estimates for the entire population who underwent ERCP in the United States.

The Wilcoxon rank sum test was used for comparing continuous variables and χ^2 tests for categorical variables. A multivariate regression analysis was used to calculate odds of all-cause 30 d readmission, inpatient mortality, length of stay, and total hospital charge (THC) after appropriately adjusting for age, gender, Elixhauser index, type of insurance, mean household income, and hospital characteristics, which included size, teaching status, and location.

The THC from 2018 through 2020 was adjusted for inflation in the healthcare sector using the Consumer Price Index inflation calculator maintained by the United States Bureau of Labor Statistics.

Multivariate regression models were used to adjust for confounders and were built using the following method: Univariate regression analyses on possible confounding factors were used to calculate the unadjusted odds ratio. Those with *P*-value ≤ 0.2 were chosen as potential confounding factors, along with clinical judgment. Indications for ERCP, which could also potentially be a part of Elixhauser's co-morbidity score were not included in the final analysis to prevent co-linearity. Potential confounding factors were then added to the final multivariate regression model. Missing values were not imputed. Two-sided *P*-values < 0.05 were taken to indicate statistical significance. We adhered to all methodological standards[18].

Outcome measures

The primary outcome was in-hospital mortality following ERCP. Secondary outcomes were divided into in-hospital morbidity and 30 d readmission rates. In-hospital morbidity outcomes were Intra-procedural and post-procedural complications rates. Intra-procedural complications included bleeding, accidental punctures/lacerations of the biliary or gastrointestinal (GI) tract, and the need for mechanical ventilation. Post-procedural complications included bleeding (and post-ERCP pancreatitis. We described the *ICD-10-CM* coding of each outcome in Supplementary Table 1.

Unmeasured bias analysis and sensitivity analysis

To evaluate the robustness of our findings, we conducted a falsification endpoint and E-value analysis to determine the validity of the study[19]. The E-value identifies the minimum strength of association that unmeasured confounders may need to have with both treatment and outcome, conditional on measured covariates, to fully explain the observed association. This estimates what the relative risk may have to be for any unmeasured confounder to overcome the observed association of study intervention with study outcomes.

RESULTS

Comparative analysis of hospitalization characteristics between frail and non-frail patients

Amongst patients aged 90 years or above, a total of 9448 underwent ERCP from 2018-2020 in the United States, excluding December (Figure 1). Of them, 3445 (36.46%) were frail while 6003 (63.53%) were non-frail. Females constituted 2305 (66.92%) and 3853 (64.19%) of Frail and the Non-frail population respectively. From a co-morbidity perspective, the number of patients progressively increased with the increasing score of the Elixhauser co-morbidity index. 81.29% of Frail patients had an Elixhauser score of 3 while in the non-frail group, it was 72.57% ($P < 0.001$). Frail patients had a higher proportion of Skilled nursing facility discharges (37.5%) while non-frail patients had a higher proportion of Routine/home discharges (49.18%) ($P < 0.001$). Frail patients had higher rates of sphincterotomies compared to non-frail patients (7.76% *vs* 5.62%; $P = 0.002$).

Comparative analysis of morbidity during index hospitalization

The intraprocedural complications including bleeding [0.11% *vs* 0.15%; adjusted odds ratio (aOR): 0.72] and accidental puncture/laceration of the biliary or GI tract (0.54% *vs* 0.65%; aOR: 0.77) between the frail and non-frail patients were insignificant ($P > 0.05$). Post-procedural complications including bleeding (0.49% *vs* 0.67%; aOR: 0.72) and post-ERCP pancreatitis (0.58% *vs* 0.4%; aOR: 1.4) were also insignificant between the two groups ($P = 0.4$).

Indication of index hospitalization, mortality predictors, and healthcare utilization

Indications for ERCP included choledocholithiasis (74.84%), biliary pancreatitis (9.19%), pancreaticobiliary cancer (7.6%), biliary stricture (4.84%), idiopathic pancreatitis (1.89%), cholangitis (1.51%), abnormal liver function tests (0.08%), and pancreatic pseudocyst (0.02%) shown in Figure 2. The mortality rate in frail patients was 2.03% *vs* 1.13% (aOR = 1.68%; $P = 0.02$) in non-frail patients. Female sex (aOR: 0.5, $P = 0.02$), stent placement (aOR: 9.8, $P = 0.006$), intraprocedural puncture/laceration of the biliary or GI tract (aOR: 11.3, $P = 0.004$) and post ERCP pancreatitis (aOR: 18.3, $P < 0.001$) were found to be an independent risk factor for mortality in the frail nonagenarian population (Figure 3). Frail patients also had a higher mean length of hospital stay (6.7 d *vs* 5.5 d; $P < 0.001$) and mean total hospital charges ($80490 *vs* $72878; $P < 0.001$) compared to non-frail patients.

Readmission rates and causes

The 30 d all-cause readmission rates between frail and non-frail patients were similar. (8.84% *vs* 8.57%, aOR: 0.99; $P = 0.96$). The most common causes of readmission included sepsis (44.8%), aspiration pneumonitis (13.03%), hypertensive heart disease with heart failure (19.7%), urinary tract infection (12.87%) and choledocholithiasis (12.29%).

DISCUSSION

To the best of our knowledge, this is the inaugural investigation employing the validated John Hopkins ACG frailty indicator to analyze clinical outcomes among nonagenarian patients who have undergone ERCP in the United States. In this study encompassing a national cross-section, we have noted several significant findings. First and foremost, frailty has exhibited an association with increased mortality rates following ERCP within this specific population, regardless of whether the admission was elective or emergent. Secondly, frailty has also shown a correlation with extended hospitalization durations and higher total hospital costs. Thirdly, the morbidity linked to the procedure and the readmission rates within 30 d did not exhibit substantial variations between frail and non-frail individuals.

Our study found that frail nonagenarian patients had a higher mortality risk compared to non-frail patients undergoing ERCP (aOR: 1.68, $P = 0.02$). Frailty has been identified as an independent risk factor of mortality across various surgical specialties[20]. Acosta *et al*[21] found a similar association between frailty and mortality in patients undergoing esophagogastroduodenoscopy for GI bleeding[21]. Traditionally, older age and/or multiple co-morbidities have been misunderstood as frailty. However, Frailty should be seen as a susceptibility to various internal physiological

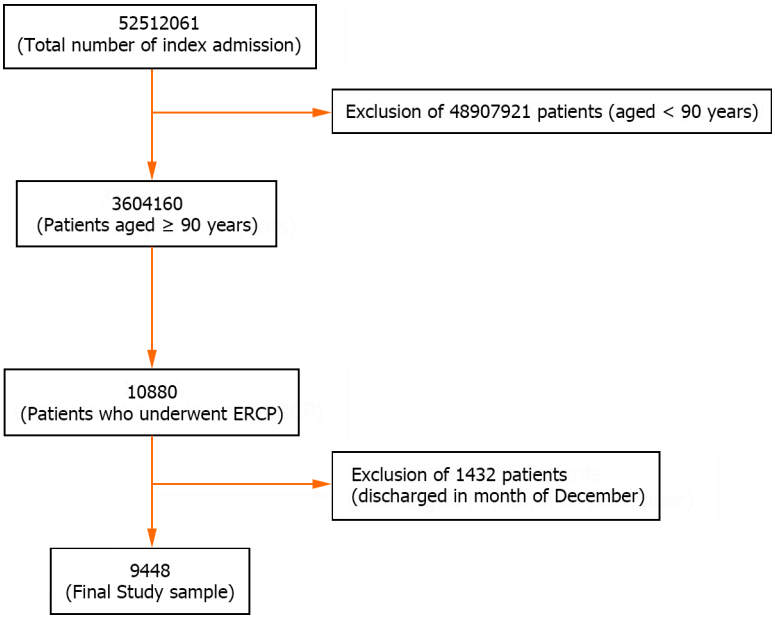

Figure 1 Patient selection flowchart. ERCP: Endoscopic retrograde cholangiopancreatography.

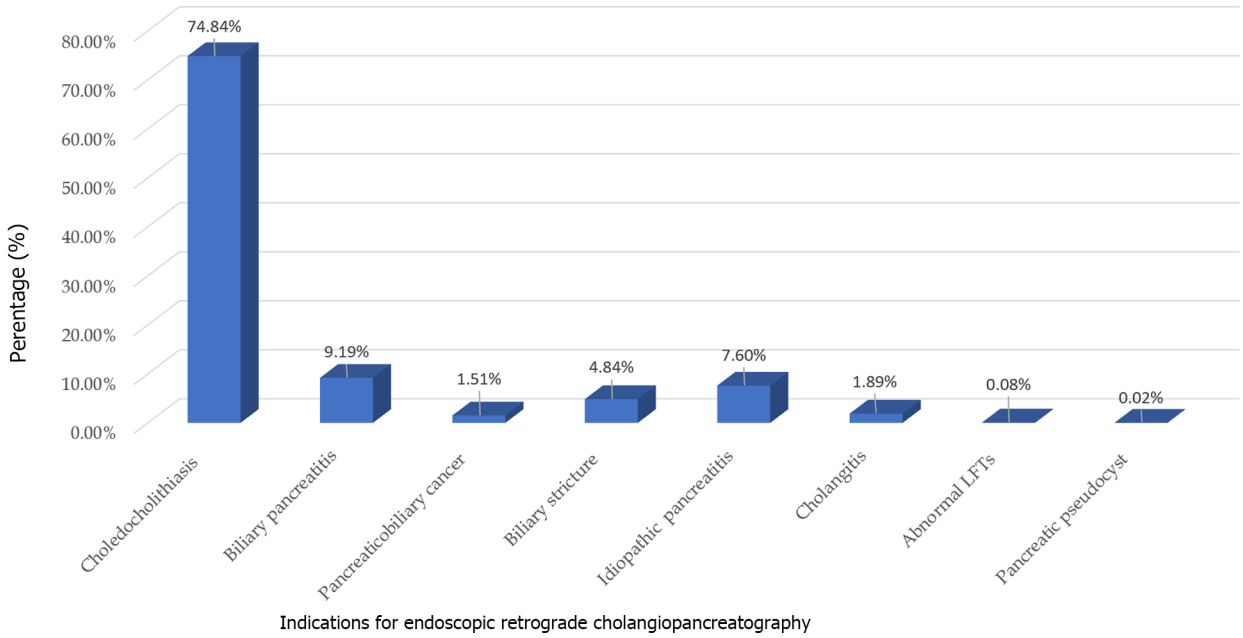

Figure 2 Indications for endoscopic retrograde cholangiopancreatography. LFTs: Liver function test.

elements and external pressures. This phenomenon can manifest at different paces in various individuals, transcending age and impacting younger patients who have chronic illnesses or cognitive impairments[22]. Frail individuals tend to exhibit alterations in glucose metabolism, disruptions in the autonomic nervous system, modifications in the renin-angiotensin system and mitochondrial function, as well as irregularities in stress response systems[17]. These factors collectively contribute to unfavorable outcomes in these patients post-ERCP, as shown in our study. As for other predictors, female sex (aOR: 0.5, $P = 0.02$), stent placement (aOR: 9.8, $P = 0.006$), intraprocedural puncture/laceration of the biliary or GI tract (aOR: 11.3, $P = 0.004$) and Post ERCP pancreatitis (aOR: 18.3, $P < 0.001$) were found to be an independent risk factor for mortality in the frail nonagenarian population. Co-morbidities as defined by the Elixhauser co-morbidity index were significant in univariate analysis but lost their significance in the multivariate model to contribute towards mortality post-ERCP. This further re-reinforces the clinical significance of frailty in measuring outcomes.

We analyzed that the intra-procedural and post-procedural complication rates were insignificant between frail and non-frail patients, regardless of frailty and emergency of the procedure. Several studies have investigated whether elderly patients are at a higher risk for post-ERCP complications compared to their younger counterparts[23-26]. Sobani *et al*[27] showed that emergency ERCP and Charlson Comorbidity Index (CCI) ≥ 2 are associated with an increased adverse event

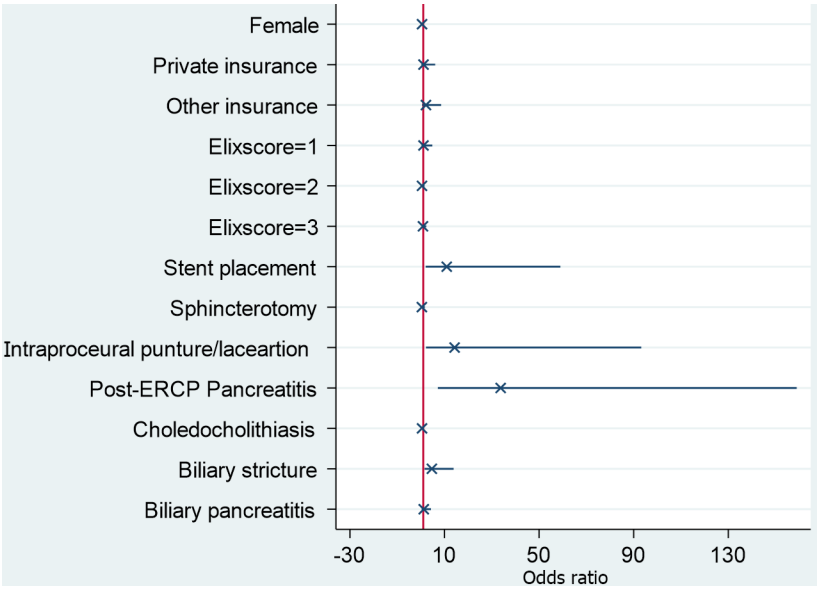

Figure 3 Predictors of mortality in frail nonagenarians undergoing endoscopic retrograde cholangiopancreatography. ERCP: Endoscopic retrograde cholangiopancreatography.

rate in elderly patients[27]. Tabak *et al*[28] in their prospective study of 614 patients found that patients with a CCI ≥ 2 and difficult cannulation are associated with an increased overall adverse events rate, while age ≥ 80 years is not[28]. Takahashi *et al*[29] in their study found that age is a risk factor for increased rate of complications following ERCP[29]. There are several limitations in these studies including smaller sample size, overreliance on age and co-morbidities, and exclusion of the concept of frailty from the study.

In our study, frail patients exhibited a prolonged length of hospital stays compared to their non-frail counterparts (6.7 d *vs* 5.5 d; $P < 0.001$). Additionally, the mean total hospital cost for frail individuals was significantly higher, reaching $80490 compared to $72878 for non-frail individuals ($P < 0.001$). The observed numbers underscore the clinical significance of frailty, as they contribute to a notable increase in both healthcare costs and burden. Previous studies done by McDermott *et al*[30] and Khandelwal *et al*[31] have shown a similar association between frailty and increased mean length of hospital stay[30,31]. As previously discussed, altered physiological responses to stressors increase recovery time. The economic and healthcare implications of frailty emphasize the need for targeted interventions and strategies to address and mitigate the impact of frailty on both patient outcomes and healthcare resources.

The comparison of 30 d readmission rates between frail and non-frail patients yielded non-statistically significant results ($P = 0.96$). This discovery holds particular significance when it comes to the risk stratification of patients who might otherwise be overlooked or denied ERCP. While our study stands as the pioneering effort to employ frailty as a risk stratification tool for ERCP in the nonagenarian population, prior investigations have adopted a more limited approach by stratifying patients based on age. We consider this approach to be outdated for comprehending physiological reserve and capacity. Relatively older studies have demonstrated that increasing age among ERCP patients was not correlated with 30 d readmissions[32]. As our study was specifically tailored to assess in-patient cases, it remains uncertain how frailty might impact ERCP patients in the outpatient setting, which has been associated with a marginally higher readmission rate[33]. Additionally, the study is limited by only capturing patients with frailty who underwent ERCP. For patients deemed poor procedural candidates secondary to frailty, ERCP would not have occurred. This likely reflects an underestimation of the impact frailty has on ERCP outcomes.

Our study exhibits several strengths and, at the same time, some limitations. One notable strength is our utilization of a study population derived from the NRD, one of the largest and most ethnically diverse inpatient databases in the United States. Consequently, the findings from our study can be extrapolated to encompass all index hospitalizations and readmissions across the nation. Moreover, our study is among the few that scrutinize clinical outcomes of ERCP in frail nonagenarians at a national level, thereby providing a comprehensive perspective on the United States healthcare landscape. However, we must acknowledge the limitations associated with our study. Admissions were identified based solely on the primary diagnosis, aligning with the best practice methodologies outlined by the Healthcare Cost and Utilization Project. This established protocol ensures the accurate identification of cases requiring ERCP. However, it is important to note that there is a probability for patients to go undetected if their admission was a result of the disease, but the primary diagnosis did not reflect this.

Nonetheless, despite these limitations, we believe that the substantial sample size and our comprehensive analytical approach significantly contribute to a more profound understanding of the clinical outcomes of ERCP in the fragile nonagenarian population in the United States.

CONCLUSION

Identifying factors affecting inpatient mortality following ERCP is paramount as it furnishes therapeutic endoscopists with practical, real-world insights into individuals at an elevated risk of such outcomes. This information is instrumental in devising strategies that effectively reduce the mortality rates and the healthcare burden associated with these procedures. Furthermore, it is important to employ the concept of Frailty in daily clinical practice to help make better decisions in routine patient care.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) stands as a vital therapeutic instrument in the management of biliary and pancreatic disorders. Individuals classified as frail and elderly, particularly those aged ≥ 90 years, are commonly perceived as a high-risk demographic concerning complications associated with ERCP.

Research motivation

There is a paucity of literature and data in terms of large-scale multicenter retrospective studies that have investigated an association between Frailty and ERCP outcomes in the nonagenarian population.

Research objectives

To determine the association between Frailty and ERCP outcomes in the nonagenarian population. Outcomes included mortality, intra and post-procedural complication rates, length of hospital stay, healthcare cost, and 30 d readmission rates.

Research methods

The 2018-2020 national readmission database was queried for patients aged ≥ 90 who underwent ERCP, using the international classification of diseases-10 code with clinical modification. Johns Hopkins's adjusted clinical groups frailty indicator was used to classify patients as frail and non-frail. The primary outcome was mortality, and the secondary outcomes were morbidity and the 30 d readmission rate related to ERCP. We used univariate and multivariate regression models for analysis.

Research results

The population size included 9448 patients who were admitted for any indications of ERCP. Frail and non-frail patients were 3445 (36.46%) and 6003 (63.53%) respectively. Frail patients had higher mortality rates compared to non-frail individuals [adjusted odds ratio (aOR) = 1.68, P = 0.02]. There was no significant difference in intraprocedural complication rates, which included bleeding (aOR = 0.72, P = 0.67), accidental punctures/lacerations (aOR = 0.77, P = 0.5), and mechanical ventilation rates (aOR = 1.19, P = 0.6), between the two groups. Post-ERCP complication rate was similar for bleeding (aOR = 0.72, P = 0.41) and post-ERCP pancreatitis (aOR = 1.4, P = 0.44). Frail patients had a longer length of stay (6.7 d *vs* 5.5 d) and higher mean total charges of hospitalization ($78807 *vs* $71392) compared to controls (P < 0.001). The 30 d all-cause readmission rates between frail and non-frail patients were similar (aOR: 0.99; P = 0.96).

Research conclusions

Frailty is associated with higher mortality post-ERCP in the nonagenarian population. Frailty is also associated with higher in-hospital length of stay and hospital costs.

Research perspectives

There is a need for further prospective studies and randomized clinical trials to evaluate the impact of frailty in the nonagenarian population undergoing ERCP.

FOOTNOTES

Co-first authors: Sanket Dhirubhai Basida and Dushyant Singh Dahiya.

Author contributions: Basida SD, Dahiya DS, and Yousaf MN contributed to conception and design; Basida SD, Ali H, Ahluwalia D, Shah MP, and Singh S contributed to administrative support; Basida SD, Basida B, Shah YR, Pinnam BSM, Ahluwalia D, Shah MP, Ali H, Gangwani MK, Chandan S, and Dahiya DS contributed to provision, collection, and assembly of data; Basida SD, Yousaf MN, Dahiya DS, Ali H, Gangwani MK, Chandan S, Basida B, Shah YR, Pinnam BSM, Singh S, Sharma NR, and Thakkar S contributed to the review of the literature and drafting the manuscript; Basida SD, Yousaf MN, Dahiya DS, Chandan S, Sharma NR, and Thakkar S contributed to revision of key components of the manuscript and final approval of manuscript; Basida SD, Yousaf MN, Dahiya DS, Basida B, Pinnam BSM, Gangwani MK, Ali H, Singh S, Shah YR, Ahluwalia D, Shah MP, Chandan S, Sharma NR and Thakkar S are accountable for all aspects of the work.

Institutional review board statement: This study, utilizing the National (or Nationwide) Readmission Database (NRD), is exempt from full Institutional Review Board (IRB) review as it involves secondary analysis of de-identified data collected for administrative purposes. The exemption is granted by federal regulations governing research involving publicly available data and poses minimal risk to subjects, maintaining their anonymity. No identifiable information was used, ensuring strict confidentiality. This exemption aligns with ethical standards and guidelines.

Informed consent statement: This letter is to confirm that our study did not require informed consent as it did not contain de-identified.

Conflict-of-interest statement: The authors have no financial relationships or conflicts of interest to disclose.

Data sharing statement: Not available.

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P-Editor: Cai YX

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ORIGINAL ARTICLE

Observational Study

Could near focus endoscopy, narrow-band imaging, and acetic acid improve the visualization of microscopic features of stomach mucosa?

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Abstract

BACKGROUND

Conventional magnifying endoscopy with narrow-band imaging (NBI) observation of the gastric body mucosa shows dominant patterns in relation to the regular arrangement of collecting venules, subepithelial capillary network, and gastric pits.

AIM

To evaluate the effectiveness of a new one-dual (near) focus, NBI mode in the assessment of the microscopic features of gastric body mucosa compared to conventional magnification.

METHODS

During 2021 and 2022, 68 patients underwent proximal gastrointestinal endoscopy using magnification endoscopic modalities subsequently applying acetic acid (AA). The GIF-190HQ series NBI system with dual focus capability was used for the investigation of gastric mucosa. At the time of the endoscopy, the gastric body mucosa of all enrolled patients was photographed using the white light endoscopy (WLE), near focus (NF), NF-NBI, AA-NF, and AA-NF-NBI modes.

RESULTS

The WLE, NF and NF-NBI endoscopic modes for all patients (204 images) were classified in the same order into three groups. Two images from each patient for the AA-NF and AA-NF-NBI endoscopic modes were classified in the same order. According to all three observers who completed the work independently, NF magnification was significantly superior to WLE ($P < 0.01$), and the NF-NBI mode was significantly superior to NF magnification ($P < 0.01$). After applying AA, the three observers confirmed that AA-NF-NBI was significantly superior to AA-NF ($P < 0.01$). Interobserver kappa values for WLE were 0.609, 0.704, and 0.598, respectively and were 0.600, 0.721, and 0.637, respectively, for NF magnification. For the NF-NBI mode, the values were 0.378, 0.471, and 0.553, respectively. For AA-NF, they were 0.453, 0.603, and 0.480, respectively, and for AA-NF-NBI, they were 0.643, 0.506, and 0.354, respectively.

CONCLUSION

When investigating gastric mucosa in microscopic detail, NF-NBI was the most powerful endoscopic mode for assessing regular arrangement of collecting venules, subepithelial capillary network, and gastric pits among the five endoscopic modalities investigated in this study. AA-NF-NBI was the most powerful endoscopic mode for analyzing crypt opening and intervening part.

Key Words: Gastric mucosa; Endoscopic microanatomy; Magnifying endoscopy; Near focus; Narrow-band imaging; Acetic acid

Core Tip: Narrow-band imaging has enabled the analysis of gastrointestinal mucosa in microscopic detail. However, this technique gives a dark image and makes it impossible to identify the color and structural microanatomy changes of the stomach mucosa, and it is necessary to combine it with the mechanical addition on the top of the scope (conventional magnification). These additions improve the visualization of the gastric mucosa but significantly complicate the procedure. We presented a new endoscopic mode called "near focus" that achieves the same or better visualization and does not require any additional accessories.

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INTRODUCTION

Currently, endoscopic platforms offer high-resolution images, image-enhanced endoscopy (IEE) techniques, and magnification, allowing for the inspection of gastric mucosa at a more detailed level. Endoscopic microscopic features (microanatomy) of the gastric body mucosa are classified into the microvascular architecture, such as the regular arrangement of collecting venules (RAC) and the regular honeycomb subepithelial capillary network (SECN). The microsurface structure is characterized by regular round gastric pits (GP), regular oval crypt opening (CO), and the intervening part (IP), which constitutes the space between the crypts. In gastric-related diseases such as *Helicobacter pylori* (*H. pylori*) infection, intestinal metaplasia, and gastric atrophy, the microanatomy has been structurally changed to an absence of venules, irregularity of capillary network, and enlarging pits and crypts[1-6].

In previous reports, white light endoscopy (WLE) has failed to assess endoscopic microanatomy. The need and wish to improve the differentiation of normal, inflammatory, and malignant lesions by gastrointestinal endoscopy has fueled research to accelerate the development of novel types of video endoscopy systems, based on new optical technologies. Electronic chromoendoscopy *via* narrow-band imaging (NBI) (the most useful tool in the many clinical trials) has

highlighted the vascular patterns of gastric mucosa[1,3,6-8]. Three studies focused on acetic acid (AA), which enhances and determines the pathology of gastric lesions[9-11].

There has been a need for increased magnification to assess the endoscopic microscopic features in more detail. Conventional magnifying endoscopy (ME) with NBI observation of the normal gastric mucosa has been described previously; studies reported dominant patterns with RAC, SECN, and GP[2-4,6,7]. Recent, optical innovation relating to the dual focus function allows the endoscopist to select between a normal mode and a near focus (NF) mode. The NF mode is optimized for near-field observation with 45-fold magnification. Studies have reported that NF-NBI successfully replaced ME-NBI in the detection of pathological lesions in the esophagus and pharynx as well as the identification of celiac disease[12-15]. Recent studies reported the ability of the NF-NBI mode for the detection of early gastric cancer lesions[16,17]. Two recently published studies considered NF endoscopy in the evaluation of gastric atrophy, intestinal metaplasia, and *H. pylori* infection[18,19].

Conventional ME uses a soft rubber at the top of the scope due to the demanding manipulation in the remaining stomach can be replaced with the simple, more pragmatic, and novel endoscopic way of magnification. Therefore, in this study, we evaluated the possibility of a new one-dual (near) focus, NBI mode in the assessment of RAC, SECN, GP, and CO in the gastric body for the visualization of microscopic features of the mucosa.

The first aim of this study was to determine the clinical (endoscopic) usefulness of the NF-NBI mode in the observation of gastric microvascular architecture and microsurface structure. Secondly, by applying 1.5% AA, we compared the power of visualization of the AA-NF and AA-NF-NBI mode when assessing microsurface patterns containing CO and IP.

MATERIALS AND METHODS

Patients

Between September 2021 and May 2022, 68 patients underwent proximal gastrointestinal endoscopy using conventional WLE, NF magnification, and NF-NBI with the subsequent application of AA. The patients consisted of 30 males and 38 females with a mean age of 38.5 years (range: 25-65 years).

The study excluded patients who were *H. pylori* positive (either one serology or rapid urease test), those who had received anticoagulant therapy or drugs for chronic metabolic diseases (diabetes mellitus, hypothyroidism) and systemic inflammation disease as well as nonsteroidal anti-inflammatory drugs and anxiolytics, and patients with chronic decompensated liver and kidney diseases. The study was approved by the ethical committee of the Blue Medical Group, and signed, well-informed consent was obtained from all participants.

Endoscopic modalities

The endoscopic video information system, EVIS EXERA III CLV-190, was used with an Olympus high-resolution endoscope, GIF-190HQ series NBI system, with dual focus capability for the investigation of the gastric mucosa. This scope allows switching between two focus settings: "normal mode" and "near focus mode". The "normal mode" or WLE suits normal observation at 5-100 mm and a 170° field of view, while the NF magnification of up to × 70 allows close observation of the finest mucosal surfaces at 2-6 mm. When switching to the NF mode at the simple touch of a button, the field of view will remain almost the same (160°).

NBI is based on the principle that depth of light penetration into tissues is directly proportional to the wavelength, which implies that the shorter the wavelength, the more superficial the penetration. The NBI resembles chromoendoscopy without dye, focusing on the capillaries.

AA *via* magnification enables vivid observation of the CO of the glandular epithelium, which has a deep brown appearance. The IP has a whitish appearance because of reversible alterations in the molecular structure of the cellular proteins that are induced by AA and lasts from several seconds to several minutes.

Endoscopic procedure

Two hours before the procedure all patients took 80 mg of simethicone with a small amount of water to remove gastric mucus. The procedure was performed under intravenous application of propofol. An experienced gastroenterologist (Kurtcehajic A) performed all the procedures. The whole esophagus, stomach, and duodenum were examined to exclude obvious lesions with conventional WLE, followed by the manufacturer incorporated NF-NBI mode in the scope, by applying 3 mL of AA *via* a single catheter. The focus area was the anterior wall or greater curvature of the upper gastric body. Biopsies were taken from the antrum and corpus mucosa, and rapid urease test was performed to evaluate *H. pylori* infection.

Endoscopic patterns and scoring

At the time of the endoscopy, the gastric body mucosa of all enrolled patients was photographed using the WLE, NF, NF-NBI, AA-NF, and AA-NF-NBI modes. Regarding the WLE, NF and NF-NBI endoscopic modalities, the regular/clear appearance of each mucosa microscopic feature, RAC, SECN, GP, and CO scored 1 point. The unclear appearance of each scored a half point, and the absence of each scored 0.

In relation to the WLE mode, the WLE-1a and WLE-2a patterns clearly show the RAC and score 1 point. WLE-2a presents a faded appearance of the RAC. The WLE-b pattern shows the RAC less clearly and scores a half point. The WLE-c pattern does not show the RAC and scores 0 (Figure 1).

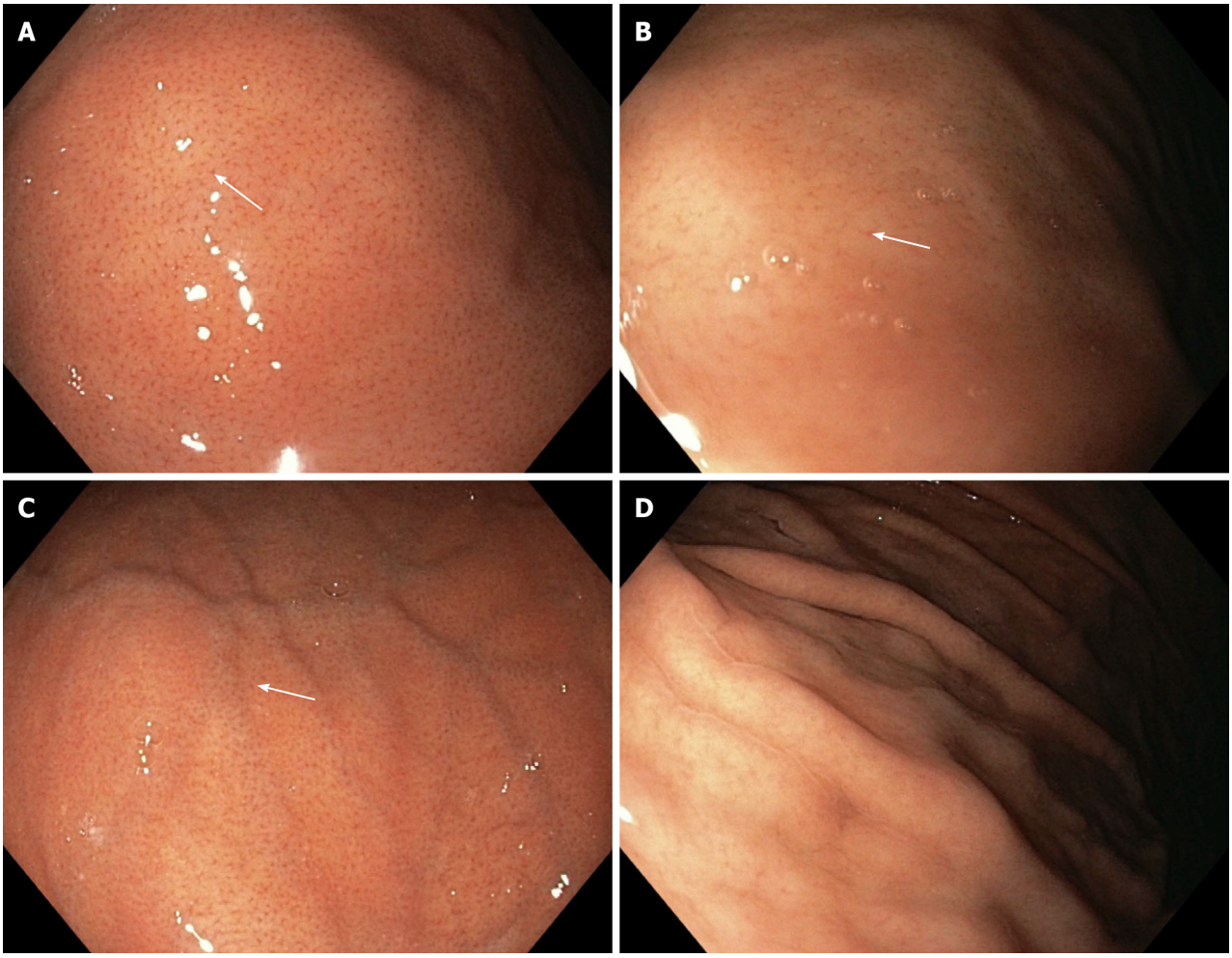

Figure 1 White light endoscopy from the point of view of the first observer. A and B: White light endoscopy (WLE)-1a pattern and WLE-2a pattern shows a clear appearance of the regular arrangement of collecting venules (RAC) (white arrow); C: WLE-b pattern shows a less clear appearance of the RAC (white arrow); D: WLE-c pattern shows the absence of the RAC.

With reference to the NF magnification, the NF-a pattern clearly shows the RAC, SECN, and GP and scores 3 points. The NF-b pattern shows the RAC less clearly but clearly shows the SECN and GP and scores 2.5 points. The NF-c pattern does not show the RAC but clearly shows the SECN and GP and scores 2 points (Figure 2).

Regarding the NF-NBI endoscopic visualization, the NF-NBI-1a and NF-NBI-2a patterns clearly show the RAC, SECN, GP, and CO and score 4 points. The 2a pattern has less distribution of the RAC and a slightly enlarged GP and CO than the 1a pattern. The NF-NBI-b pattern does not show the RAC, clearly shows the SECN and GP, and shows the CO less clearly and scores 2.5 points (Figure 3).

According to the scoring rules, one pattern could score the most points (4) (clear presence of all microscopic features) or the least number of points (0) (absence of all microscopic features). After enhancing the area of observation with AA, a pattern was suddenly visible on the AA-NF and AA-NF-NBI containing CO and IP. On the AA-NF mode, the pattern shows small, brown, oval CO and light white IP. On the AA-NF-NBI mode, the pattern shows small, black, oval CO and dense white IP (Figure 4). The strong contrast between the CO regarding the shape/size and the IP on these two patterns within the same patient is graded as 1 point, medium contrast is graded as 0.5 points, and low contrast is graded as 0 points. Endoscopic patterns were observed and scored by three independent endoscopists.

Statistical analysis

The differences between the scoring of each endoscopic modality for all observers were compared using the Wilcoxon Matched Pairs Test. *P* values < 0.05 were considered significant. The interobserver diagnostic agreement was analyzed with a kappa value. In theory, perfect disagreement has a kappa value of -1, and perfect agreement has a kappa value of +1. A value of 0 means an agreement by chance alone. As per the Landis and Koch scale, kappa values were graded as follows: 0.01-0.20 slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; and 0.81-1.00 almost perfect. Cohen's suggested interpretation may be too lenient for health-related studies because it implies that a score as low as 0.41 might be acceptable[9,14,20]. Data were analyzed using SPSS 23 (IBM, United States).

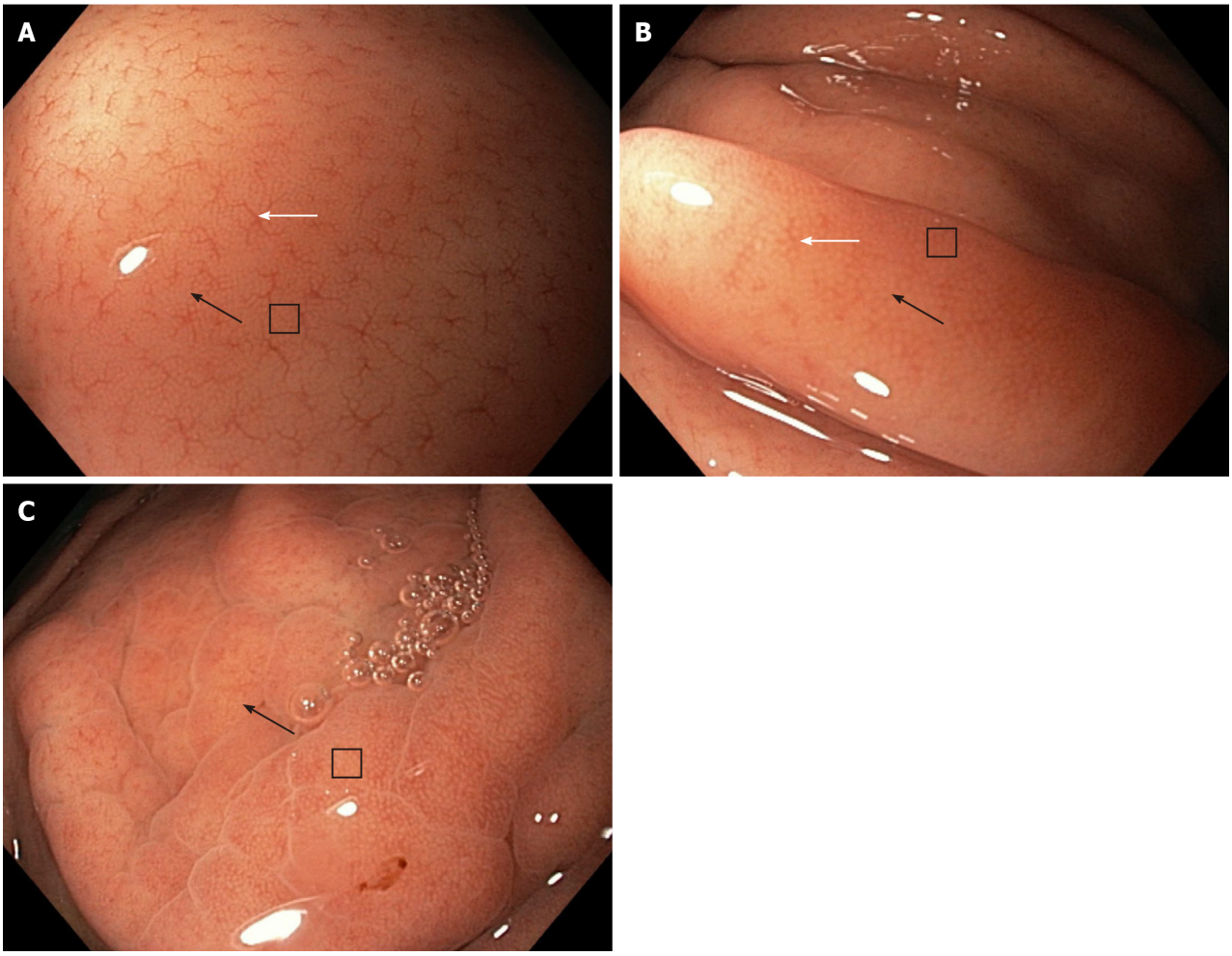

Figure 2 Near focus mode from the point of view of the first observer. A: Near focus (NF)-a pattern shows a clear appearance of the regular arrangement of collecting venules (white arrow), subepithelial capillary network (SECN) (black arrow), and gastric pits (GP) (square); B: NF-b pattern shows a less clear appearance of the regular arrangement of collecting venules (white arrow) and a clear appearance of the SECN (black arrow) and GP (square); C: NF-c pattern shows a clear appearance of the SECN (black arrow) and GP (square).

RESULTS

After meeting the criteria of long-term epigastric discomfort and non-specific abdominal pain, the study initially included 74 patients. During the endoscopy, 4 patients (three male, one female) did not undergo NF magnification due to 1 patient having benign stenosis of the distal esophagus, 1 patient having cancer of the cardia, and 2 patients having pyloric stenosis. Two patients (one male, one female) were excluded due to severe bile reflux.

Finally, 68 patients underwent proximal gastrointestinal endoscopy using the WLE, NF and NF-NBI modes to analyze the microscopic features of the gastric body mucosa. The images from all patients (204 images in total) were classified in the same order into three groups in relation to the above endoscopic modality by endoscopist AK. They were observed separately and scored by two experienced endoscopists, JF (observer I) and PJ (observer II), and one inexperienced endoscopist, OZ (observer III).

Moreover, after applying AA in the area of observation, the CO and IP were suddenly visible. Regarding the AA-NF and AA-NF-NBI endoscopic modes, 136 images (2 images per patient) were classified in the same order. The contrast between the CO and IP in the same patient was observed and graded separately by the three observers. All observers had previously passed a live course regarding NF magnification and NBI chromoendoscopy mode with AA enhancing. The course was based on the 12 endoscopic patterns that would form part of this study. Each pattern presented with ten images.

The frequency and scoring for the WLE, NF, and NF-NBI endoscopic modalities from the point of view of all three observers are shown in Table 1. According to the experienced observers (observer I and observer II), NF magnification was significantly superior to WLE ($P < 0.01$), and the NF-NBI mode was significantly superior to NF magnification ($P < 0.01$). Regarding the third inexperienced observer, NF magnification was significantly superior to WLE ($P < 0.01$), and the NF-NBI mode was significantly superior to the NF magnification ($P < 0.01$).

The frequency and scoring for the AA-NF and AA-NF-NBI endoscopic modalities from the point of view of all three observers are shown in Table 2. According to the experienced observers (observer I and observer II), AA-NF-NBI was significantly superior to AA-NF ($P < 0.01$). For the third inexperienced observer, AA-NF-NBI was significantly superior to

Table 1 Frequency and scoring of the endoscopic patterns in white light endoscopy, near focus, and narrow-band imaging modes

Observer I			Observer II			Observer III		
WLE	NF	NF-NBI	WLE	NF	NF-NBI	WLE	NF	NF-NBI
1a (44 × 1)	a (55 × 3)	1a (53 × 4)	1a (47 × 1)	a (58 × 3)	1a (60 × 4)	1a (51 × 1)	a (56 × 3)	1a (51 × 4)
2a (2 × 1)	b (9 × 2.5)	2a (12 × 4)	2a (4 × 1)	b (7 × 2.5)	2a (6 × 4)	2a (0 × 1)	b (7 × 2.5)	2a (12 × 4)
b (9 × 0.5)	c (4 × 2)	b (3 × 2.5)	b (7 × 0.5)	c (3 × 2)	b (2 × 2.5)	b (2 × 0.5)	c (5 × 2)	b (5 × 2.5)
c (13 × 0)			c (10 × 0)			c (15 × 0)		
50.5	195.5	267.5	54.5	197.5	269.0	52.0	195.5	264.5

NBI: Narrow-band imaging; NF: Near focus; WLE: White light endoscopy.

Table 2 Frequency and scoring of the endoscopic patterns with acetic acid, near focus and acetic acid, near focus, and narrow-band imaging modes

Observer I		Observer II		Observer III	
AA-NF	AA-NF-NBI	AA-NF	AA-NF-NBI	AA-NF	AA-NF-NBI
58 × 0.5	63 × 1	62 × 0.5	64 × 1	55 × 0.5	62 × 1
3 × 1		2 × 1		7 × 1	
7 × 0	5 × 0.5	4 × 0	4 × 0.5	6 × 0	6 × 0.5
32.0	65.5	33.0	66.0	34.5	65.0

AA: Acetic acid; NBI: Narrow-band imaging; NF: Near focus.

AA-NF ($P < 0.01$).

The interobserver diagnostic agreement for all five endoscopic modalities was analyzed with a kappa value. Interobserver kappa values for WLE were 0.609 for observer I and observer II, 0.704 for observer I and observer III, and 0.598 for observer II and observer III. Interobserver kappa values for NF magnification were 0.600 for observer I and observer II, 0.721 for observer I and observer III, and 0.637 for observer II and observer III. Interobserver kappa values for the NF-NBI mode were 0.378 for observer I and observer II, 0.471 for observer I and observer III, and 0.553 for observer II and observer III. Interobserver kappa values for AA-NF were 0.453 for observer I and observer II, 0.603 for observer I and observer III, and 0.480 for observer II and observer III. Interobserver kappa values for AA-NF-NBI were 0.643 for observer I and observer II, 0.506 for observer I and observer III, and 0.354 for observer II and observer III.

DISCUSSION

According to the results of our research into the investigation of gastric mucosa at a detailed microscopic level, NF-NBI was the most powerful endoscopic mode for evaluating the RAC, SECN, and GP, and AA-NF-NBI was the most powerful endoscopic mode for analyzing the CO and IP. There have been many advances in endoscopic imaging technologies. Standard definition endoscopy produces image signals with a resolution of 100000-400000 pixels. High-resolution or high-definition endoscopy produces image signals with a resolution of up to 1000000 pixels, which has the same effect as visualizing a surface at a 30-35-fold magnification. A novel IEE technique is electronic chromoendoscopy, which includes NBI, i-Scan, and flexible spectral imaging color enhancement. Over the last 15 years, NBI has been used most in clinical practice. However, it is too dark to identify the color and structural mucosal changes in organs with a large lumen, such as the stomach. Therefore, these should be combined with ME[1,6,8,14].

Over the last two decades, conventional ME was carried out with a soft rubber. Before the procedure, soft black rubber was attached at the top of the scope. In this way, the area of interest was magnified, However, the view for normal observation was reduced. Magnification with soft rubber requires skill and special training. For this reason, ME is not frequently used in Western countries[1-4,6].

Several studies using high-definition endoscopy, IEE, conventional magnifying, and histopathology have confirmed the normal appearance of gastric body mucosa with the RAC, SECN, and GP[1-3,6-8,21-25]. In our study, we successfully replaced conventional ME with the dual focus (NF magnification). Regarding our results, all three observers noted independently that the NF magnification showed a higher power of visualization than WLE ($P < 0.01$). NF magnification from the point of view of all three observers assessed the microscopic features of the gastric body mucosa, such as the RAC at 94%, 95%, and 92%, respectively, and the SECN and GP at 100%, in the same way as it was reported in studies

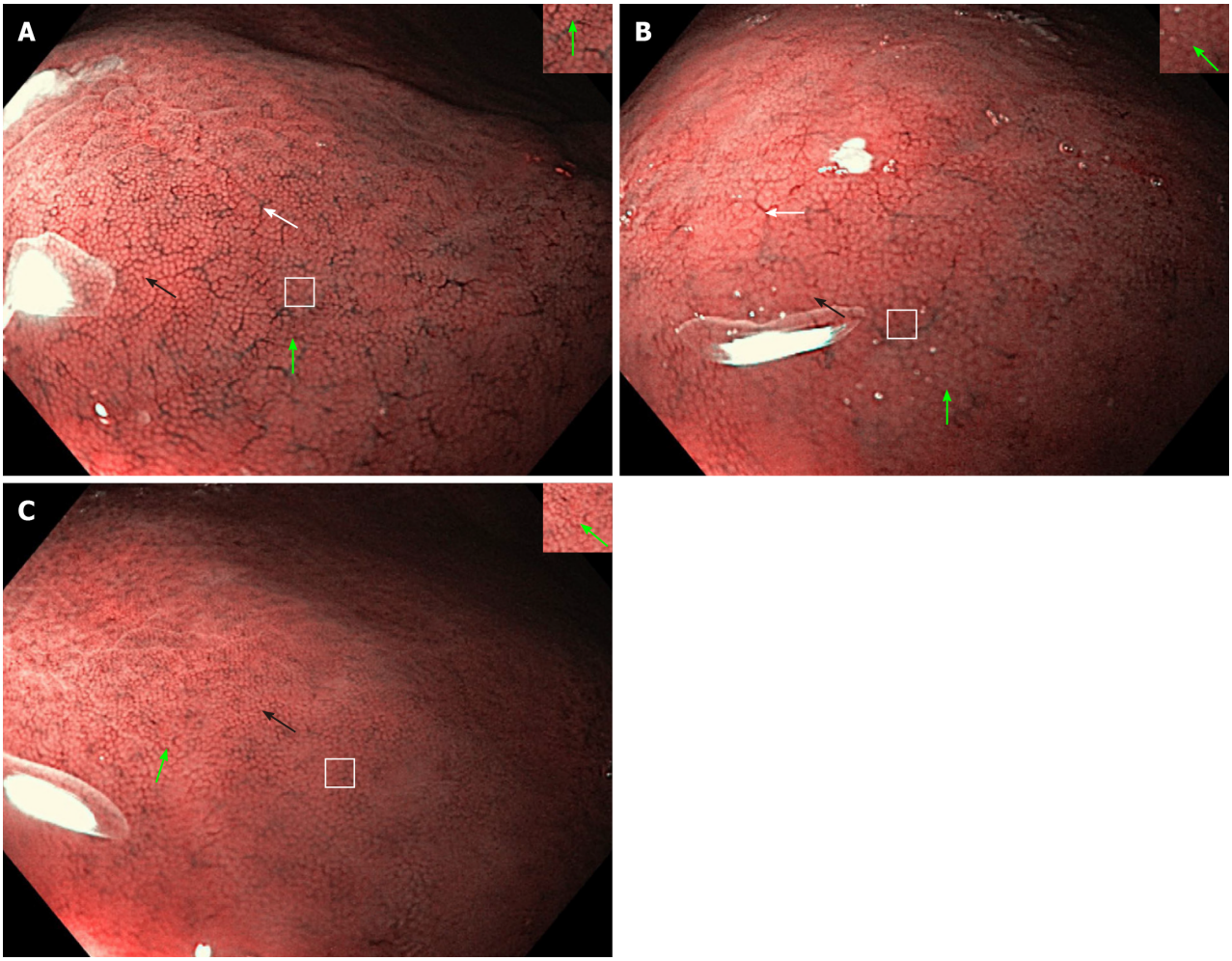

Figure 3 Near focus, narrow-band imaging mode from the point of view of the first observer. A and B: Near focus (NF)-narrow-band imaging (NBI)-1a pattern and NF-NBI-2a pattern show a clear appearance of the regular arrangement of collecting venules (white arrow), subepithelial capillary network (black arrow), gastric pits (square), and crypt opening (green arrow, right upper corner); C: NF-NBI-b pattern shows a clear appearance of the subepithelial capillary network (black arrow) and gastric pits (square). A less clear appearance of the crypt opening (green arrow, right upper corner) is observed.

powered by conventional ME[4,22,23]. The diagnostic interobserver agreement for the NF magnification showed a "substantial" level.

A retrospective study from the United Kingdom demonstrated that NF magnification improved the diagnostic yield of upper gastrointestinal mucosal lesions. However, its usefulness for gastric lesions is questionable[15]. In our study, all three observers noted independently that the NF with the NBI showed significantly more power of visualization than the NF magnification ($P < 0.01$). In the NF-NBI mode, from the point of view all three observers, SECN, GP, and CO were clearly seen at levels of 95.5%, 97% and 92.6%, respectively. The diagnostic interobserver agreement in relation to the NF-NBI mode from the perspective of the experienced observers (one side) and the third inexperienced observer was at the "moderate" level. The diagnostic interobserver agreement among the experienced observers was at the "fair" level. The clinical explanation could be that NF-NBI "1a" and "1b" patterns were scored the same and that the differences were qualitative (distribution of the RAC, size of GP and CO).

In the progression of gastric-related diseases, microscopic features of the stomach mucosa such as venules, capillary network, and the shape and size of gastric fossa and recess have been structurally changed. For the first time, two studies used the NF-NBI mode in the stomach for the evaluation of a tumor lesion and its margin[16,17]. The role of the NF-NBI mode has been assessed recently for atrophic gastritis, according to the Kimura-Takemoto classification and intestinal metaplasia (tubular/granular GP pattern of the corpus)[18]. This study considered the shape of the GP without analyzing the RAC, SECN, and CO. In the absence of the previously verified gastric NF-NBI magnification pattern, it could not be an appropriate definition of the pathology pattern.

In a recently published study by Fiuza *et al*[19], NF magnification was evaluated for the assessment of the mucosal surface pattern in *H. pylori*-related gastritis. This study used the NF mode without NBI chromoendoscopy and was unable to consider the appearance of the CO.

Conventional ME requires more time, skill, and special endoscopic training. The mechanical addition on the top of the scope (rubber) and the view of visualization becomes less. On the other hand, NF magnification may be easily manipulated, there is no need for the mechanical attachment, the view of visualization remains normal, and as observed in our study NF magnification with NBI chromoendoscopy showed the presence of CO.

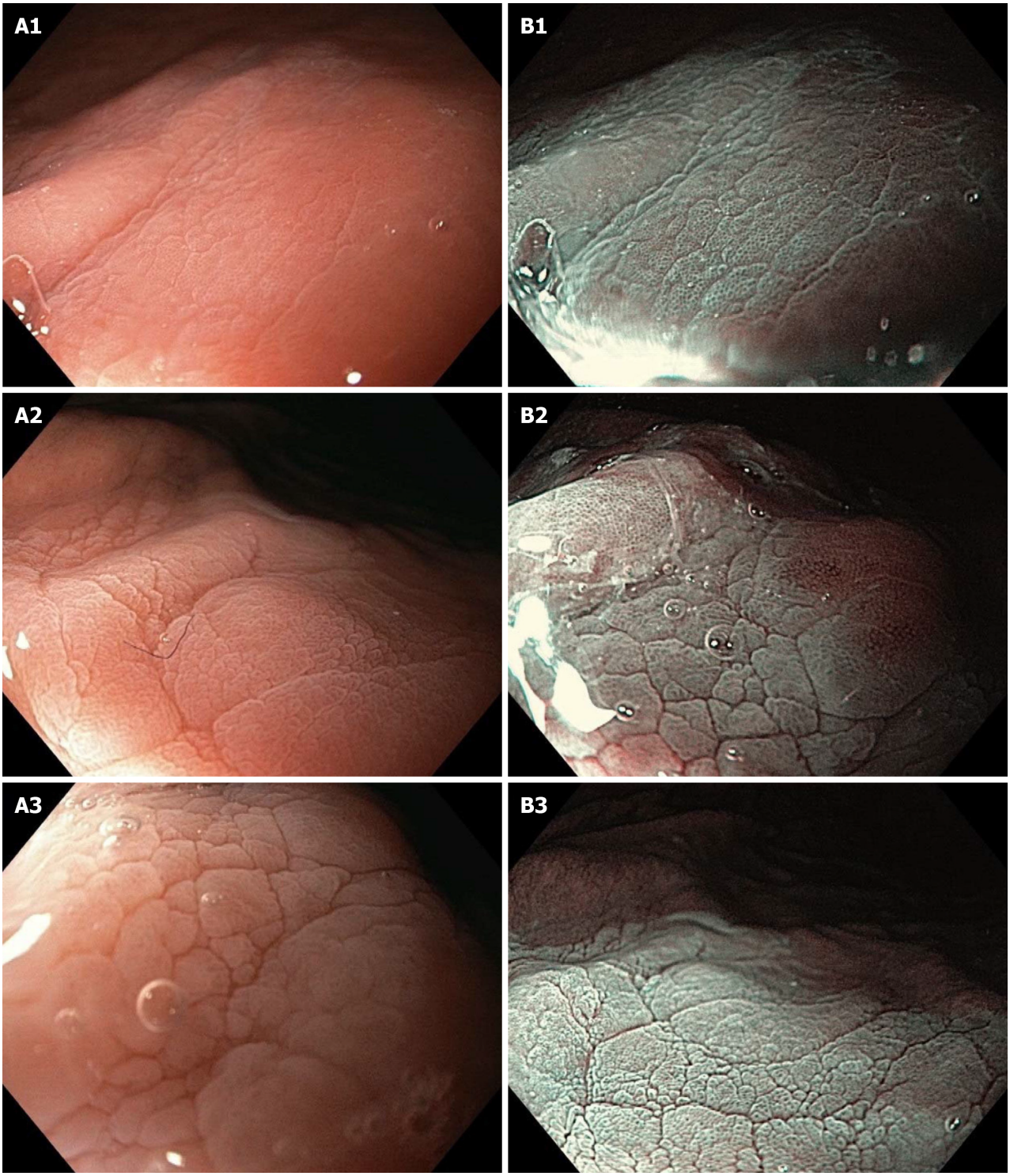

Figure 4 Acetic acid, near focus and acetic acid-near focus, narrow-band imaging mode from the point of view of the first observer. A and B: A1 image [acetic acid (AA)-near focus (NF) pattern] was scored at 0.5; B1 image [AA-NF-narrow-band imaging (NBI) pattern] was scored at 1; A2 image (AA-NF pattern) was scored at 1; B2 image (AA-NF-NBI pattern) was scored at 1; A3 (AA-NF pattern) was scored at 0; B3 image (AA-NF-NBI pattern) was scored at 0.5.

The current era of NF magnification endoscopic technology may be contrasted with the research of Cho *et al*[25] who recently used conventional ME for the evaluation of *H. pylori*-associated gastritis. The forthcoming studies *via* NF-NBI endoscopy aim to evaluate the presence/absence of RAC, the regularity/irregularity of SECN, and the shape and size of the GP and CO in relation to the *H. pylori* infection, intestinal metaplasia, and atrophic gastritis, *etc.*

In the previous studies, the focus on the CO was less. A study by Kawamura *et al*[26] evaluated the role of conventional ME (without NBI) by analyzing the CO as part of *H. pylori*-related gastritis. The whiteness of the CO was classified as the "white-edged dark spot" type, the "white" type, and the "dense white pit" type. Regarding our results, the NF-NBI mode assessed the presence of the CO as a black point, but to visualize the CO in more detail, enhancement was carried out using AA. By applying AA in the area of observation, we highlighted a unique pattern containing regular round brown CO and whiteish IP in the normal gastric body mucosa. In the AA-NF-NBI mode, the CO suddenly became black,

creating a clear contrast between the CO and IP.

Our results, independently noted by all three observers, showed that AA-NF-NBI was superior to AA-NF. Our results clearly indicate the superiority of the AA-NF-NBI mode in terms of analyzing the shape and size of the CO and IP. The diagnostic interobserver agreement for the AA-NF-NBI mode among the experienced observers was at a "substantial" level. The diagnostic interobserver agreement between the experienced observers (one side) and the third inexperienced observer was at the "moderate" level and "fair" level, respectively. An explanation for this could be that there was no question about the existence of the contrast and that the discrepancy related to the grade of the contrast between the CO and IP.

One limitation of this study (as well as other studies related to this issue) was the relatively small number of patients included. Additional research (preferably randomized trials or prospective collaborative studies) is required to improve the endoscopic investigation of gastric mucosa at a detailed microscopic level and to create the conditions for a better diagnosis and treatment of these diseases.

CONCLUSION

NF-NBI was the most effective endoscopic mode for evaluating RAC, SECN, and GP. AA-NF-NBI was the most effective endoscopic mode for analyzing CO and IP. It provides a higher resolution for evaluating the relationship between the progress of gastric diseases and the existence of gastric venules, the regularity/irregularity of capillary network, and the shape and size of GP and recesses.

ARTICLE HIGHLIGHTS

Research background

Narrow-band imaging (NBI) is too dark to identify the color and structural microanatomy of stomach mucosa due to large lumen. Therefore, these should be combined with magnification.

Research motivation

Conventional magnification endoscopy using a soft rubber at the top of the scope, which requires demanding manipulation, could be replaced with a simple, more pragmatic, and novel endoscopic magnification technique.

Research objectives

We evaluated the possibility of a near focus (NF) magnification, NBI mode with acetic acid (AA), in the assessment of venules, capillary network, pits, and crypts in the gastric body mucosa.

Research methods

The endoscopic video information system, EVIS EXERA III CLV-190, was used with an Olympus high-resolution endoscope, GIF-190HQ series NBI system, with dual focus capability for the investigation of the gastric mucosa. At the time of the endoscopy, the gastric body mucosa of all enrolled patients was photographed using the white light endoscopy (WLE), NF, NF-NBI, AA-NF, and AA-NF-NBI modes.

Research results

From 68 patients, 204 images were classified in the same order into three groups (WLE, NF, and NF-NBI). They were observed separately and scored by two experienced endoscopists and one inexperienced endoscopist. According to all three observers independently, NF magnification was significantly superior to WLE ($P < 0.01$), and the NF-NBI mode was significantly superior to NF magnification ($P < 0.01$). Interobserver kappa values for WLE were 0.609, 0.704, and 0.598, respectively, and in the case of NF magnification, they were 0.600, 0.721, and 0.637, respectively. For the NF-NBI mode, the values were 0.378, 0.471, and 0.553, respectively. AA-NF-NBI was significantly superior to AA-NF ($P < 0.01$) by all three observers independently. Interobserver kappa values for the AA-NF were 0.453, 0.603, and 0.480, respectively, and for AA-NF-NBI, they were 0.643, 0.506, and 0.354, respectively.

Research conclusions

Among the five endoscopic modalities investigated in this study, NF-NBI was the most powerful endoscopic mode for assessing venules, capillary network, and gastric pits. AA-NF-NBI was the most powerful endoscopic mode for analyzing crypts and space between crypts.

Research perspectives

The forthcoming studies of NF-NBI and AA-NF-NBI endoscopic modalities aim to evaluate the presence/absence of venules, the regularity/irregularity of capillary network, and the shape and size of the gastric pits and crypts in relation to *Helicobacter pylori* infection, intestinal metaplasia, and atrophic gastritis, *etc.*

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FOOTNOTES

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ORIGINAL ARTICLE

Prospective Study

Using a novel hemostatic peptide solution to prevent bleeding after endoscopic submucosal dissection of a gastric tumor

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Abstract

BACKGROUND

Endoscopic mucosal dissection has become the standard treatment for early gastric cancer. However, post-endoscopic submucosal dissection (ESD) ulcer occurs in 4.4% of patients. This study hypothesized whether applying PuraStat, a novel hemostatic peptide solution, prevents post-ESD bleeding.

AIM

To investigate the preventive potential of PuraStat, a hemostatic formulation, against bleeding in post-ESD gastric ulcers.

METHODS

Between May 2022 and March 2023, 101 patients (Group P) underwent ESD for gastric diseases at our hospital and received PuraStat (2 mL) for post-ESD ulcers. We retrospectively compared this group with a control group (Group C) comprising 297 patients who underwent ESD for gastric diseases at our hospital between April 2017 and March 2021. *P* values < 0.05 on two-sided tests indicated significance.

RESULTS

Post-ESD bleeding occurred in 6 (5.9%) (95%CI: 2.8–12.4) and 20 (6.7%) (95%CI: 4.4–10.2) patients in Groups P and C, respectively, with no significant between-group difference. The relative risk was 1.01 (95%CI: 0.95–1.07). The lesser curvature or anterior wall was the bleeding site in all 6 patients who experienced postoperative bleeding in Group P. In multivariate analysis, the odds ratios for resection diameter ≥ 50 mm and oral anticoagulant use were 6.63 (95%CI: 2.52–14.47; *P* = 0.0001) and 4.04 (1.26–0.69; *P* = 0.0164), respectively. The adjusted odds ratio of post-ESD bleeding and PuraStat was 1.28 (95%CI: 0.28–2.15).

CONCLUSION

PuraStat application is not associated with post-ESD bleeding. However, the study suggests that gravitational forces may affect the effectiveness of applied PuraStat.

Key Words: Endoscopic submucosal dissection; PuraStat; Bleeding; Gastric cancer; hemostatic forceps; Proton pump inhibitor; hemostatic peptide solution

Core Tip: In this investigation, we assessed the potential of PuraStat®, a hemostatic formulation, to prevent bleeding in post-endoscopic submucosal dissection (ESD) gastric ulcers. Application of PuraStat (2 mL) to the post-ESD ulcer in 101 patients who underwent ESD for gastric diseases at our hospital did not exhibit an association with post-ESD bleeding. However, our observations suggest that gravitational forces may affect the efficacy of applied PuraStat. Therefore, we aim to develop strategies to mitigate the risk of PuraStat flowing away from the targeted area of interest in further investigations.

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INTRODUCTION

Endoscopic mucosal dissection (ESD) has become the standard treatment for early gastric cancer. However, bleeding from the post-ESD ulcer occurs in 4.4% of patients[1]. To prevent this complication, recommended measures include coagulating blood from the remaining vessels on the ulcer surface using hemostatic forceps or a similar device and admin-istering proton pump inhibitors[2]. However, it is essential to note that excessive vascular coagulation increases the risk of delayed perforation, necessitating caution. With the aging population, the number of patients taking oral antithrombotic drugs will likely increase, leading to more cases of larger post-ESD ulcers due to the expansion of ESD-adapted lesions. As a result, controlling post-ESD bleeding poses a considerable challenge.

PuraStat (3D-Matrix Europe Ltd., France) is a novel hemostatic peptide solution designed to reduce the need for cauterization using hemostatic forceps in managing exudative bleeding during gastrointestinal endoscopy. The material comprises peptide molecules comprising three amino acids (arginine, alanine, and aspartic acid) that rapidly form fibers and transform into peptide hydrogels on contact with body fluids such as blood. By covering the bleeding point with this hemostat, the collapsed parenchymatous organ and superficial portions of the blood vessels are physically occluded, and blood coagulation occurs to stop bleeding.

We aim to investigate whether applying PuraStat to post-ESD gastric ulcers can prevent post-ESD bleeding.

MATERIALS AND METHODS

Patients and methods

From May 2022 to March 2023, 101 patients (Group P) who underwent ESD for gastric diseases at our hospital received PuraStat 3 mL formulation. PuraStat (1 mL) was used to stop bleeding during ESD, and after ESD, bleeding from the remaining blood vessels in the post-ESD ulcer was stopped by initiating coagulation using hemostatic forceps. Subsequently, the remaining 2 mL of PuraStat was applied to the post-ESD ulcer (Figure 1). Two experienced endoscopists (over 300 ESD cases) applied the medication to the post-ESD ulcers. Each patient received a proton pump inhibitor (PPI) for 8 wk starting from the day of the ESD. An endoscopic examination was performed on the day following the ESD day to address any potential bleeding. Hemostatic treatment with argon plasma coagulation or clips was performed in cases where bleeding was identified.

A control group (Group C) com-prising 297 patients who underwent ESD for gastric diseases at our hospital from April 2017 to March 2021 was retrospectively compared with group P.

Consultations with physicians were conducted to consider the discontinuation of antithrombotic medications. In cases where discontinuation was not feasible, ESD was performed while maintaining the continuation of aspirin. Antiplatelet medications eligible for resumption were restarted 2 d after the ESD procedure. Warfarin use was not discontinued during ESD. In the case of direct-acting oral anticoagulants, they were not administered on the day of ESD but resumed on the following day.

This study was approved by the Showa University Institutional Review Board (2023-052-A) and complied with the 1989 revised version of the Declaration of Helsinki.

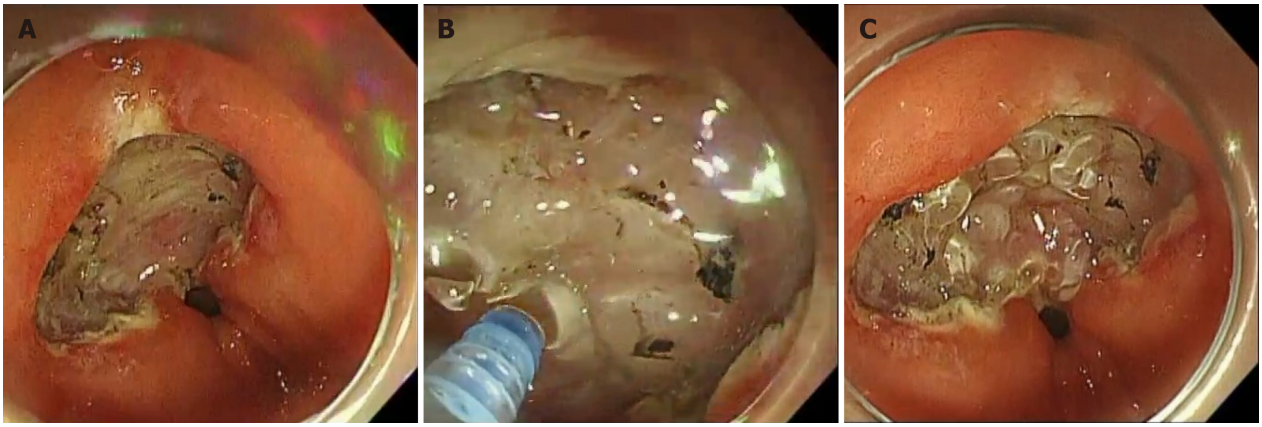

Figure 1 Applying PuraStat to post-endoscopic submucosal dissection gastric ulcers. A: Post-endoscopic submucosal dissection gastric ulcer; B: Applying PuraStat with a special catheter; C: Ulcer after application.

Outcome parameters

Post-ESD bleeding was the primary study endpoint of the study. In contrast, the secondary endpoints included the duration from ESD to the onset of post-ESD bleeding and adverse events associated with PuraStat administration. Post-ESD bleeding was defined as bleeding from a post-ESD ulcer that required emergency endoscopic hemostasis or a ≥ 2 g/dL reduction in hemoglobin at week 8 after ESD.

Statistical analyses

The primary endpoint, post-ESD bleeding, was analyzed using the χ^2 test. Mann–Whitney *U*-test was employed for the duration from ESD to the onset of post-ESD bleeding. Logistic regression analysis was performed for multivariate analysis. *P* values < 0.05 on two-sided tests were considered statistically significant. JMP Pro 16 (SAS Institute Inc., North Carolina, United States) for Windows was used for the statistical analyses.

RESULTS

Patients' background characteristics in Groups P and C were comparable (Table 1). ESD lesions were comparable between the groups. Notably, non-experts conducted 71 (70.3%) and 143 (48.1%) of the ESD procedures in Groups P and C, respectively, with a higher proportion in Group P (*P* = 0.0001). The median resection times for Groups P and C were 64 (10–320) and 68 (7–445) min, respectively, exhibiting comparability. However, lesions with resection diameters ≥ 50 mm were lower in Group P *vs* C [3 (3.0%) *vs* 32 (10.8%); *P* = 0.0167]. The *en bloc* and the complete *en bloc* resection rates for Groups P and C were comparable (Table 2).

Post-ESD bleeding occurred in 6 (5.9%) (95%CI: 2.8–12.4) and 20 (6.7%) (95%CI: 4.4–10.2) patients in Groups P and C, respectively, with no significant between group difference (*P* = 0.7804) (Table 2). The relative risk as 1.01 (95%CI: 0.95–1.07). No adverse events were observed with PuraStat application. In addition, the median number of days between when ESD was performed and when post-ESD bleeding started was 2 (1–12) and 7.5 (1–14) days in Groups P and C, respectively, with no significant difference between the groups (Figure 2). Other complications were not significantly different between the groups (Table 2).

Multivariate analysis was performed for the factors associated with postoperative bleeding due to PuraStat application, with ESD practitioner, resection diameter ≥ 50 mm, oral antiplatelet drugs, and oral anticoagulant drugs as explanatory variables. The odds ratio for resection diameter ≥ 50 mm and oral anticoagulant use were 6.63 (95%CI: 2.52–14.47; *P* = 0.0001) and 4.04 (1.26–0.69; *P* = 0.0164), respectively. Adjusted OR of post-ESD bleeding and PuraStat was 1.28 (95%CI: 0.28–2.15; *P* = 0.6363) (Table 3).

DISCUSSION

PuraStat is an absorbable local hemostatic agent for reducing the requirement of cauterization using hemostatic forceps to stop exudative bleeding in gastrointestinal endoscopic treatment. PuraStat is highly useful for combating intraoperative bleeding. When the peptide molecules in the hemostatic material contact body fluids, such as blood, they rapidly form fibers and become peptide hydrogels, covering bleeding points and physically occluding collapsed parenchymatous organs and superficial blood vessels, enabling blood coagulation.

Several randomized controlled trials have compared vascular coagulation procedures during ESD. In one randomized controlled trial, the PuraStat group exhibited a significantly shorter duration of coagulation treatment device usage than the control group (49.3% *vs* 99.6%, *P* < 0.001)[3]. In another trial[4], the mean number of coagulation procedures using a hemostat was significantly lower in the PuraStat group than in the control group (1.0 ± 1.4 *vs* 4.9 ± 5.2, *P* < 0.001), proving

Table 1 Clinical characteristics of the patients, *n* (%)

	Group P	*n* = 101	Group C	*n* = 297	
Age, median (range)	75	(48–93)	75	(40–90)	0.8831
Sex					
Male	72	(71.3)	219	(73.7)	0.3676
Female	29	(28.7)	78	(26.3)	
Diabetes mellitus	17	(16.8)	41	(13.8)	0.7054
Chronic kidney disease on dialysis	3	(3.0)	4	(1.4)	0.9287
Liver cirrhosis	7	(6.9)	9	(3.0)	0.7777
Anti-platelet agents	14	(13.9)	65	(21.9)	0.1485
Continuation	3	(3.0)	18	(6.1)	
Discontinuation	11	(10.9)	47	(15.8)	
Duration of re-starting, median (range)					
Anticoagulants	10	(9.9)	28	(9.5)	0.9355
Continuation	3	(3.0)	6	(2.0)	
Discontinuation	7	(6.9)	22	(7.5)	
Helicobacter pylori infection status					
Not infected	2	(2.0)	15	(5.1)	0.1524
Persistent infection	27	(26.7)	92	(31.0)	
After eradIcation	72	(71.3)	189	(63.6)	
Unknown	0	(0.0)	1	(0.3)	

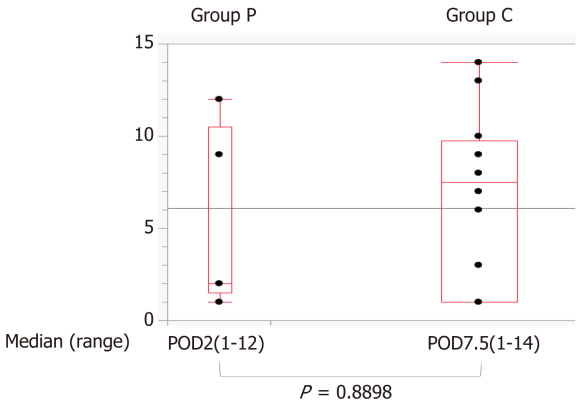

Figure 2 Date of post-endoscopic submucosal dissection bleeding.

the efficacy of PuraStat in managing intraoperative bleeding.

PuraStat is expected to accelerate the healing of post-ESD ulcers and reduce the post-ESD bleeding rate[5,6]. Additionally, PuraStat has been confirmed to prevent post-ESD bleeding in the United States and Europe. However, only one report[6] of its usefulness in preventing post-ESD bleeding and its impact on post-ESD bleeding rate exists. PuraStat was applied to 65 Lesions in the esophagus (*n* = 8), stomach (*n* = 22), duodenum (*n* = 10), ampulla of Vater (*n* = 3), colon (*n* = 7), and rectum (*n* = 15). Therefore, our study aimed to investigate the effect of applying PuraStat to post-ESD gastric ulcers, assessing its potential in preventing exudative bleeding following ESD.

PuraStat was administered to post-ESD gastric ulcers immediately after ESD in 101 patients who underwent ESD for gastric disease at our hospital from May 2022 to March 2023. However, the postoperative bleeding rate was not reduced with PuraStat use compared with previous ESD cases in our hospital. Significantly, PuraStat application was not associated with post-ESD bleeding.

An essential observation was that PuraStat did not demonstrate a sustained effect. Therefore, we suspect it had a minimal hemostatic impact on postoperative bleeding over time. We expected reduced postoperative bleeding within the first few days after ESD; however, no significant difference was observed in the occurrence of postoperative bleeding

Table 2 Characteristics of the lesions and treatment outcomes, *n* (%)

	Group P	*n* = 101	Group C	*n* = 297	
Location 1					
U	11	(10.9)	43	(14.5)	0.2573
M	54	(53.5)	129	(43.4)	
L	36	(35.6)	125	(42.1)	
Location 2					
L	57	(56.4)	136	(45.8)	0.1295
G	11	(10.9)	41	(13.8)	
A	16	(15.8)	52	(17.5)	
P	17	(16.8)	68	(22.9)	
Endoscopists					
Expert	30	(29.7)	154	(51.9)	0.0001
Non-expert	71	(70.3)	143	(49.4)	
Resection time (min), median (range)	64	(10–320)	68	(7–445)	0.0991
Resection size (mm), median (range)	30	(14–60)	33	(5–80)	0.0106
En bloc resection	100	(99.0)	295	(99.3)	0.7506
R0 resection	95	(94.1)	274	(92.3)	0.2267
Post-ESD bleeding	6	(5.9)	20	(6.7)	0.7804
Intraoperative perforation	0	(0.0)	3	(1.0)	0.3106
Delayed perforation	0	(0.0)	0	(0.0)	-
Aspiration pneumonia	6	(5.9)	7	(2.4)	0.0801

ESD: Endoscopic submucosal dissection.

Table 3 Factors involved in post-operative bleeding

	Univariable OR	95%CI	*P* value	Multivariable OR	95%CI	*P* value
Pura Stat® application	0.87	0.34–2.24	0.7806	1.28	0.28–2.15	0.6363
Endoscopists: Expert	1.18	0.53–2.60	0.6904	1.14	0.36–2.12	0.7654
Resection size ≥ 50 mm	7.05	2.86–17.34	< 0.0001	6.63	2.52–17.47	0.0001
Anti-platelet agents	1.88	0.79–4.51	0.1545	2.07	0.83–5.16	0.1185
Anticoagulants	4.04	1.58–10.36	0.0036	3.49	1.26–9.69	0.0164

between the PuraStat and non-PuraStat groups. This suggests that PuraStat's hemostatic effect might be minimal and not enduring, warranting further investigation into its efficacy and potential limitations in post-ESD bleeding.

The bleeding site for all 6 patients who experienced postoperative bleeding in the PuraStat group was consistently identified as the lesser curvature or anterior wall (Table 4). Comparatively, in previous cases at our hospital, post-ESD bleeding originated from the lesser curvature in 35.0%, anterior abdominal wall in 15.0%, greater curvature in 20.0%, and posterior abdominal wall in 30.0% of cases. This discrepancy suggests that gravitational forces may affect the efficacy of applied PuraStat. Specifically, PuraStat appeared less effective for lesions on the anterior wall and lesser curvature than lesions on the greater curvature and posterior wall. Adjusting the patient's position during application could potentially enhance PuraStat's effectiveness by preventing the hemostatic material from flowing away from the targeted area.

The limitations of this study include its single-center basis and retrospective design. Therefore, conducting large-scale, multicenter prospective studies on this subject is highly desirable to provide more comprehensive and generalizable insights.

Table 4 Location of post-operative bleeding lesions, *n* (%)

	Group P	Group C	*P* value
L	5 (83.3)	7 (35.0)	0.735
A	1 (16.7)	3 (15.0)	1
G	0 (0.0)	4 (20.0)	0.566
P	0 (0.0)	6 (30.0)	0.342

CONCLUSION

Our findings indicate that PuraStat application is not associated with post-ESD bleeding. However, we infer that gravitational forces may affect the effectiveness of applied PuraStat. As a result, we aim to explore and develop strategies to prevent PuraStat from flowing away from the target area of interest in further investigation. Addressing this aspect may contribute to optimizing the hemostatic efficacy of PuraStat in the context of post-ESD procedures.

ARTICLE HIGHLIGHTS

Research background

Endoscopic mucosal dissection (ESD) has become the standard of care for early gastric cancer, but bleeding from ulcers after ESD occurs in 4.4% of patients. We aim to minimize post-ESD bleeding to the greatest extent possible. PuraStat (3D-Matrix Europe Ltd., France) is a novel hemostatic peptide solution aiming to reduce the need for cautery with hemostatic forceps in treating exudative bleeding during gastrointestinal endoscopy. We hypothesized that applying PuraStat to gastric ulcers after ESD could prevent post-ESD bleeding.

Research motivation

Reducing post-ESD bleeding is a crucial goal. If PuraStat can be applied to post-ESD gastric ulcers to prevent post-ESD bleeding, it may have broader applications in gastrointestinal bleeding.

Research objectives

The purpose of this study is to determine whether the application of PuraStat to gastric ulcers after ESD can prevent post-ESD bleeding.

Research methods

From May 2022 to March 2023, 101 patients (Group P) who underwent ESD for gastric diseases at our hospital received PuraStat (2 mL) applied to their post-ESD ulcer. We retrospectively compared this group with a control group (Group C) com-prising 297 patients who underwent ESD for gastric diseases at our hospital between April 2017 and March 2021. Post-ESD bleeding was the primary endpoint, while the secondary endpoints included the number of days from ESD to post-ESD bleeding and adverse events associated with PuraStat administration.

Research results

Post-ESD bleeding occurred in 6 (5.9%) (95%CI: 2.8–12.4) and 20 (6.7%) (95%CI: 4.4–10.2) patients in Groups P and C, respectively, with no significant between-group difference. The relative risk was 1.01 (95%CI: 0.95–1.07). Therefore, PuraStat application was not associated with post-ESD bleeding. The lesser curvature or anterior wall was the bleeding site in all 5 patients who experienced postoperative bleeding in the PuraStat group. This suggests that gravitational forces may affect the efficacy of applied PuraStat. Specifically, PuraStat seemed less effective for lesions on the anterior wall and lesser curvature than those on the greater curvature and posterior wall. Adjusting the patient's position during its application could potentially enhance PuraStat's effectiveness by preventing the hemostatic material from flowing away from the targeted area.

Research conclusions

PuraStat application is not associated with post-ESD bleeding.

Research perspectives

We infer that gravitational forces may affect the efficacy of applied PuraStat. Hence, we aim to explore and develop strategies to prevent PuraStat from flowing away from the targeted areas of interest in further investigation.

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LETTER TO THE EDITOR

Computed tomography for prediction of esophageal variceal bleeding

Mohammed Elhendawy, Ferial Elkalla

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Abstract

This letter to the editor relates to the study entitled "The role of computed tomography for the prediction of esophageal variceal bleeding: Current status and future perspectives". Esophageal variceal bleeding (EVB) is one of the most common and severe complications related to portal hypertension (PH). Despite marked advances in its management during the last three decades, EVB is still associated with significant morbidity and mortality. The risk of first EVB is related to the severity of both PH and liver disease, and to the size and endoscopic appearance of esophageal varices. Indeed, hepatic venous pressure gradient (HVPG) and esophagogastroduodenoscopy (EGD) are currently recognized as the "gold standard" and the diagnostic reference standard for the prediction of EVB, respectively. However, HVPG is an invasive, expensive, and technically complex procedure, not widely available in clinical practice, whereas EGD is mainly limited by its invasive nature. In this scenario, computed tomography (CT) has been recently proposed as a promising modality for the non-invasive prediction of EVB. While CT serves solely as a diagnostic tool and cannot replace EGD or HVPG for delivering therapeutic and physiological information, it has the potential to enhance the prediction of EVB more effectively when combined with liver disease scores, HVPG, and EGD. However, to date, evidence concerning the role of CT in this setting is still lacking, therefore we aim to summarize and discuss the current evidence concerning the role of CT in predicting the risk of EVB.

Key Words: Esophageal variceal bleeding; Variceal upper gastrointestinal bleeding; Portal hypertension; Computed tomography; Computed tomography angiography

Core Tip: Esophagogastroduodenoscopy is presently regarded as the established diagnostic standard for anticipating esophageal variceal bleeding (EVB) in individuals with cirrhosis. Computed tomography (CT) has recently surfaced as a potential non-invasive method for predicting EVB. However, comprehensive evidence on the role and efficacy of CT in this context is currently insufficient. Consequently, the study seeks to assess the existing evidence concerning the use of CT in predicting EVB.

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TO THE EDITOR

We have perused with interest the review conducted by Martino *et al*[1], entitled "The role of computed tomography for the prediction of esophageal variceal bleeding: Current status and future perspectives ". This review study highlights the potential use of computed tomography (CT) as a hopeful technique for the non-invasive anticipation of esophageal variceal bleeding (EVB).

Bleeding from esophageal varices (EV) is a potentially life-threatening complication associated with clinically significant portal hypertension (PH), representing a noteworthy economic and health concern[2]. Hence, it is crucial to conduct upper endoscopy screening for esophagogastric varices in patients exhibiting clinically significant PH [hepatic venous pressure gradient (HVPG) higher than 10 mmHg] and liver stiffness exceeding 25 kPa. Patients with varices at high-risk of bleeding should undergo primary prophylaxis through nonselective beta-blocker medication or variceal band ligation. For those experiencing variceal bleeding, an upper endoscopy should be conducted within 12 h following resuscitation and hemodynamic stabilization. If the patients' condition is unstable, endoscopy should be performed at the earliest opportunity[3].

PH is a significant complication of liver cirrhosis, leading to EV. Even in the presence of clinical and/or imaging indicators of PH, the definitive diagnostic method for EV remains esophagogastroduodenoscopy (EGD), considered the gold standard. EGD serves the primary purpose of diagnosing and risk-stratifying varices by evaluating their size and identifying high-risk stigmata, whereas the HVPG is employed to assess the severity of PH[2].

Due to endoscopy being regarded as an invasive method for evaluating varices, as well as the accompanying patient discomfort and high cost, other alternative tests have been evaluated over time[4,5].

The Baveno VII guidelines do not advise upper endoscopy as a screening method for EV in patients with liver stiffness below 20 kPa, platelet counts exceeding 150 × 10^9/L and spleen stiffness measurement ≤ 40 kPa[6].

Due to the ineffectiveness of the non-invasive Baveno VII criteria in screening for varices in patients with porto-sinusoidal vascular disorders, it is necessary to perform endoscopy for diagnosis. The endoscopic screening frequency should adhere to the guidelines established for liver cirrhosis[6].

We would like to draw attention to several aspects concerning this study

The authors analyzed a number of retrospective studies and single center studies incorporating small numbers of patients, which could influence the completeness and precision of the findings. The studies analyzed were not uniform regarding the manner of research, comparison factors, grading classifications of the varices, and Child scores posing a potential bias of the study cohort that could affect the validity of the review.

Secondly, this review did not include studies that focused solely on assessing the presence of EV or those comparing CT findings with the endoscopic grading of EV.

The percentage of patients with decompensated cirrhosis remains uncertain in the studies under review. As non-invasive measures are predominantly employed for patients with compensated cirrhosis, clarification on this aspect is needed.

The primary cause of liver cirrhosis in this review is predominantly attributed to alcohol, with no comparison to other etiologies such as viral hepatitis. This limitation has the potential to limit the generalizability of the review findings to various populations and settings. Additionally, the possible effect of antiviral treatment on cirrhosis and varices has been not studied.

CT is a diagnostic modality that can detect maximal EV diameter, paraumbilical and coronary vein diameters, and ascitic fluid presence. However, it is incapable of detecting variceal risk signs.

There exists a time gap between the occurrence of bleeding and the execution of CT scans. During this interval, patients may experience improvement, leading to the potential for CT results to be misleading.

Another constraint in the study involves incorporating patients who are receiving pharmacological prophylaxis for EVB either primary or secondary with no mention of comparison or statistics in correlation with the bleeding varices, even though it is well established that these drugs alter the hemodynamics and therefore would affect the CT findings.

There are no data about correlation between other shunts, and the size and risky signs of bleeding varices as these shunts may decrease intravariceal pressure.

Moreover, none of the included studies compare CT-measured liver volume and liver function in correlation with variceal bleeding.

Furthermore, the bleeding and non-bleeding groups in the reviewed studies significantly differ regarding model for end-stage liver disease score and Child-Pugh class, both of which may affect liver function, coagulation profile of the patient, pathogenesis of varices formation and bleeding liability. All these strong limitation factors have not been studied.

CT may prove valuable in identifying patients at an elevated risk of variceal bleeding, but should not be intended to replace endoscopy.

We concur with the authors' viewpoint, emphasizing the importance of investigating the role of CT in predicting EVB. This entails measuring various EV indicators and collateral veins. We advocate for large-scale, multicenter prospective controlled trials integrating liver disease scores and simultaneous performance of endoscopy and/or HVPG conducted concurrently without significant delays and with adequate follow-up. Furthermore, the results ought to be categorized according to liver disease scores, endoscopic scores, and the etiology of cirrhosis. This comprehensive approach is essential for generating high-quality evidence to validate and advance our understanding.

Utilizing CT findings of portal-systemic collaterals can help identify their impact on PH and their association with variceal bleeding. This is particularly relevant because these collaterals are influenced by the etiology of cirrhosis and exhibit variability among patients. They can manifest either as single entities or a combination of multiple collaterals, each having distinct effects on PH and its association with variceal bleeding.

To bolster the credibility of the study's conclusion, we suggest conducting a larger-scale investigation, among patients with diverse etiologies and various forms of cirrhosis. Such a study would contribute to enhancing the applicability and practicality of clinical practice, providing a more precise assessment of patients' conditions.

CT can be used as a screening strategy together with other noninvasive methods, to alleviate the burden on endoscopy units and optimize the utilization of healthcare resources, all the while minimizing the potential risks and discomfort for patients. Finally, we recognize and appreciate the efforts and contributions of the authors and recommend further prospective validation.

FOOTNOTES

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