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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

Editorial article to: Animal experimental study on magnetic anchor technique-assisted endoscopic submucosal dissection of early gastric cancer

Enrico Fiori, Antonietta Lamazza, Daniele Crocetti, Antonio V Sterpetti

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Abstract

In this editorial we comment on the article published in the recent issue of the *World Journal of Gastrointestinal Endoscopy* 2023; 15 (11): 634-680. Gastric cancer (GC) remains the fifth most common malignancy and the fourth leading cause of cancer-related death worldwide. The overall prevalence of GC has declined, although that of proximal GC has increased over time. Thus, a significant proportion of GC cases and deaths can be avoided if preventive interventions are taken. Early GC (EGC) is defined as GC confined to the mucosa or submucosa. Endoscopic resection is considered the most appropriate treatment for precancerous gastrointestinal lesions improving patient quality of life, with reduced rates of complications, shorter hospitalization period, and lower costs when compared to surgical resection. Endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD) are representative endoscopic treatments for EGC and precancerous gastric lesions. Standard EMR implies injection of a saline solution into the sub-mucosal space, followed by excision of the lesion using a snare. Complete resection rates vary depending on the size and severity of the lesion. When using conventional EMR methods for lesions less than 1 cm in size, the complete resection rate is approximately 60%, whereas for lesions larger than 2 cm, the complete resection rate is low (20%-30%). ESD can be used to remove tumors exceeding 2 cm in diameter and lesions associated with ulcers or submucosal fibrosis. Compared with EMR, ESD has higher en bloc resection rates (90.2% *vs* 51.7%), higher complete resection rates (82.1 *vs* 42.2%), and lower recurrence rates (0.65% *vs* 6.05%). Thus, innovative techniques have been introduced.

Key Words: Gastric cancer; Early gastric cancer; Endoscopic resection; Endoscopic

mucosal resection; Endoscopic sub-mucosal dissection

Core Tip: Endoscopic resection (ER) is considered the most appropriate treatment for precancerous gastrointestinal lesions improving patient quality of life, with reduced rates of complications, shorter hospitalization period, and lower costs when compared to surgical resection. Complete ER rates and recurrence rates after procedure vary depending on the size and severity of the lesion. Innovative techniques could improve endoscopic rate and clinical outcomes.

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INTRODUCTION

Gastric cancer (GC) remains the fifth most common malignancy and the fourth leading cause of cancer-related death worldwide. The overall prevalence of GC has declined, although that of proximal GC has increased over time. There are important differences in epidemiology, pathology, diagnosis, and treatment strategy worldwide: Several factors influence the prevalence, development of GC as well as its recurrence after resection[1-4].

The high prevalence of autoimmune gastritis in low-income populations is the probable reason for the increased prevalence of GC in specific regions and group of patients. The age standardized mortality rates related with GC differ from country to country. The higher survival rates are documented in Korea and in Japan 5-year survival rates of 65%[5,6], whereas in the rest of the world the 5-year survival rate is around 20%. These differences may be the consequence of specific initiatives implemented in East Asia for the higher prevalence of GC, including early detection of GC through screening programs and diffusion of treatments to eradicate *Helicobacter pylori* infection. Eradication of *Helicobacter pylori* infection has been associated with reduction of more than 30% of the prevalence of GC[7-10].

The better survival rates Easy Asia countries after diagnosis of GC support the importance and effectiveness of preventive measures and interventions in this specific clinical setting. Furthermore, the age standardized mortality rate of early-onset GC in China showed a decreasing trend from 2000 to 2019. Early GC (EGC) is defined as GC confined to the mucosa or sub-mucosa. Endoscopic resection (ER) is considered the most appropriate treatment for precancerous gastric lesions[11,12]. The 10-year observed survival rate for patients with EGC rate was similar between ER (81.9%) and surgery (84.9%)[12].

Moreover, ER implies a significant reduced operative trauma in comparison with surgical resection, with shorter hospital stay and complications rates: These factors lead to better early and late patient quality of life. ER is associated with reduced costs in comparison with surgical resection, which is an important factor to be considered, namely in regions with high prevalence of the disease.

Extensive clinical experience has brought to specific guidelines: High grade dysplasia is better treated with ER, considering that the lesion has a high probability for degeneration in carcinoma. ER should be extended also to low-grade dysplasia for patients who present specific risk factors for progression of low-grade dysplasia to high grade dysplasia and carcinoma. Recognized risk factors which support ER also in patients with low grade dysplasia are tobacco and alcohol abuse, and presence of *Helicobacter pylori* infection. These conditions favor local inflammation, acidosis, hypoxia with consequent production of growth factors and inflammatory cytokine which trigger cell proliferation and differentiation. Other anatomic and pathological factors which seem to determine progression and degeneration of low-grade dysplasia include larger lesions (lesions with dimension more than 10 mm), presence of ulceration, located in the distal portion of the stomach.

This evidence has brought to a steady trend to extend indications for ER even to more advanced lesions. The Japanese Gastric Cancer Association[13] has extended the use of ER, analyzing the absence of lymph node metastases in patients who underwent gastrectomy with extended lymph node removal for patients with differentiated carcinoma, with dimension inferior to 2 cm, absence of ulceration and cancer confined to the mucosa. A retrospective study of more than 5000 patients who underwent gastrectomy showed absence of lymph node metastases in case of intra-mucosal differentiated carcinoma, less than 2 cm in size and no ulceration.

ENDOSCOPIC SUBMUCOSAL DISSECTION OF EGC

The most common methods for removal of high degree dysplasia and EGC are endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD). Standard EMR implies injection of a saline solution into the sub-mucosal space, followed by excision of the lesion using a snare. Standard EMR seems to be appropriate and valid for lesions less than 1

cm in dimension. EMR allows a complete resection in about 60%-70% of patients with lesions 1 cm or less in dimension; however, standard EMR fails to achieve complete resection in almost 70%-80% of patients with lesions 2 cm in size. Thus, several effective innovative techniques have been introduced. One of these is cap-mounted pan-endoscopic EMR[14]. The endoscope is provided with a cap mounted at its end. The lesion is aspirated into the plastic cap. The operator can cut the lesion under direct vision with a snare. Another widely used technique implies to circumferential cutting the lesion as first step; then, EMR completes a detailed dissection of the regions surrounding the removed lesion. These endoscopic techniques are very effective, with improved rates of complete resection for lesions less than 2 cm in size. They have resulted less valid for patients with larger lesions and presence of mucosal ulceration. For this reason, there has been a significant interest in developing ESD, using several type of technical details and knives.

ESD implies removal also of the sub-mucosa. ESD is effective in anatomic conditions where the accepted EMR methods commonly fail to achieve complete resection, like lesions with more than 2 cm in size, and tumors with ulceration and high degree of inflammation. Compared with EMR, ESD has higher en bloc resection rates (90.2% *vs* 51.7%), higher complete resection rates (82.1% *vs* 42.2%), and lower recurrence rates (0.65% *vs* 6.05%)[12]. However, often it is difficult to obtain sufficient tension and good field, with possibility for of adverse events, bleeding, and perforation[15]. The improved techniques for ER have brought to important results: The 5-year survival rate for patients with EGC meeting expanded criteria was similar to the 5-year survival rate of patients with standard indications for ER (94.8%-99.5%). A recent prospective study confirmed the effectiveness of ER in EGC with an overall 5-year survival rate of 89.0%[16,17]. Thus, ER should be considered a valid from of treatment for patients with EGC. *Helicobacter pylori* eradication therapy should be performed after ER.

EXPERIMENTAL STUDY

In this *ex vivo* animal experimental prospective controlled group study, Pan *et al*[18] introduce an innovative technique to perform a more extended ESR. Conceptually, their proposed technique allows a more precise and extended sub-mucosal resection, applying traction on the gastric mucosa, with a good visualization of the area to excise. Bleeding can be more easily prevented and controlled. This is a very important advantage of the proposed technique considering the high percentage of patients taking anti-platelets drugs. The study is at its initial step, and a more extensive applications on patients are required, also considering the difference between the healthy mucosa and healthy muscle layer of the stomach of the experimental animals and the mucosa and muscle layer surrounding an EGC, often associated with inflammation and easier tendency for bleeding. The authors used explanted stomach to experiment their technique. Inevitably, in this condition, every form of experiment is easier to be performed, and the probable difficulties to perform a delicate endoscopic technique like the one proposed by the authors are less evident.

CONCLUSION

We encourage the authors to continue their studies addressing several important points: (1) To perform the experiments *in vivo*, without sacrificing the experimental animals to be able to determine the difficulties to perform the technique and to ascertain the possibilities of early and medium-term complications; (2) To perform the technique in experimental animals treated with anti-platelets agents, considering that most patients who require ER are taking anti-platelets agents; and (3) The obvious final step is to assess the feasibility and appropriateness of the technique in patients. The technique described by the authors can be extended to treat also colorectal lesions[19-21].

FOOTNOTES

Author contributions: Fiori E, Lamazza A, Crocetti D, and Sterpetti AV contributed to this paper; Fiori E designed the overall concept and outline of the manuscript; Lamazza A and Crocetti D contributed to the discussion and design of the manuscript; Sterpetti AV contributed to the writing, editing the manuscript, and review of literature.

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ORIGINAL ARTICLE

Retrospective Study

Association between triglyceride-glucose index and colorectal polyps: A retrospective cross-sectional study

Ya-Jie Teng, Ying-Xue Yang, Jing-Jing Yang, Qiu-Yan Lu, Jia-Yi Shi, Jian-Hao Xu, Jie Bao, Qing-Hua Wang

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Abstract

BACKGROUND

Colorectal polyps (CPs) are frequently occurring abnormal growths in the colorectum, and are a primary precursor of colorectal cancer (CRC). The triglyceride-glucose (TyG) index is a novel marker that assesses metabolic health and insulin resistance, and has been linked to gastrointestinal cancers.

AIM

To investigate the potential association between the TyG index and CPs, as the relation between them has not been documented.

METHODS

A total of 2537 persons undergoing a routine health physical examination and colonoscopy at The First People's Hospital of Kunshan, Jiangsu Province, China, between January 2020 and December 2022 were included in this retrospective cross-sectional study. After excluding individuals who did not meet the eligibility criteria, descriptive statistics were used to compare characteristics between patients with and without CPs. Logistic regression analyses were conducted to determine the associations between the TyG index and the prevalence of CPs. The TyG index was calculated using the following formula: Ln [triglyceride (mg/dL) × glucose (mg/dL)/2]. The presence and types of CPs was determined based on data from colonoscopy reports and pathology reports.

RESULTS

A nonlinear relation between the TyG index and the prevalence of CPs was identified, and exhibited a curvilinear pattern with a cut-off point of 2.31. A significant association was observed before the turning point, with an odds ratio

(95% confidence interval) of 1.70 (1.40, 2.06), $P < 0.0001$. However, the association between the TyG index and CPs was not significant after the cut-off point, with an odds ratio (95% confidence interval) of 0.57 (0.27, 1.23), $P = 0.1521$.

CONCLUSION
Our study revealed a curvilinear association between the TyG index and CPs in Chinese individuals, suggesting its potential utility in developing colonoscopy screening strategies for preventing CRC.

Key Words: Triglyceride-glucose index; Colorectal polyps; Colorectal cancer; Insulin resistance; Cross-sectional study

Core Tip: This study represents the first exploration of the association between the triglyceride-glucose (TyG) index and colorectal polyps in a Chinese population. The results showed a curvilinear relation, with a significant association observed before a cut-off point of 2.31. Beyond this cut-off point the association was no longer significant. These results provide valuable insights for future research in this area. Importantly, monitoring the TyG index and managing insulin resistance could potentially aid in identifying individuals at a higher risk of developing colorectal polyps, and implementing timely interventions to prevent their progression to colorectal cancer. This study contributes novel perspectives and avenues for preventing colorectal cancer.

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INTRODUCTION

Colorectal polyps (CPs) are common abnormal growths and protrusions on the surface of the colon and rectum[1]. There are various types, including adenomatous polyps and hyperplastic polyps, and they are recognized as the most common precursors of colorectal cancer (CRC)[2]. Adenomatous polyps are the most frequently observed premalignant lesions preceding the development of CRC, and CRC is the most commonly diagnosed cancer and the second most common cause of cancer death after lung cancer[3,4]. The incidence of CPs and CRC has been steadily increasing worldwide in recent decades, making them a significant public health concern[5]. Early detection and removal of CPs are crucial for preventing the development of CRC[6]. Identifying risk factors associated with CPs can help in developing effective screening strategies and implementing preventive measures[7]. Several risk factors have been identified for the development of CPs, including age, family history of CRC, genetic predisposition, dietary factors, and lifestyle choices such as smoking and alcohol consumption[8]. However, there is still a need to explore additional risk factors that may contribute to the development of CPs.

The triglyceride-glucose (TyG) index is a novel marker that has gained significant attention in recent research. It is a composite index that combines the levels of fasting plasma glucose and fasting triglycerides, and provides a comprehensive assessment of metabolic health[9]. Recently, the TyG index has become a popular method for assessing insulin resistance (IR), a forerunner of type 2 diabetes[10]. Studies have demonstrated that an elevation of the TyG index correlates with cardiovascular diseases, depression, erectile dysfunction, and gastrointestinal cancers[11-14]. However, its association with CPs is not clear.

Accumulating evidence has shown that IR may increase the risk of CPs. Qin *et al*[15] reported a significant correlation between IR and the occurrence of CPs and adenomatous polyps. Furthermore, Keku *et al*[16] conducted a comprehensive study involving 239 patients with colorectal adenoma and 517 adenoma-free persons, and the results suggested that IR is significantly associated with an elevated risk of developing adenomatous polyps. Additionally, the study revealed a decrease in apoptosis within the normal rectal mucosa among individuals with IR. Similarly, Flood *et al*[17] found that patients with elevated levels of insulin and glucose have a higher risk of recurrence of adenomatous polyps. Notably, patients with increased glucose levels exhibited an even greater increase in the risk of recurrent advanced adenomatous polyps.

Therefore, the purpose of this study was to investigate the potential association between the TyG index and CPs in a Chinese population. Understanding this association may provide valuable insights into the pathogenesis and early detection of CPs, leading to improved screening strategies and better prevention of CRC.

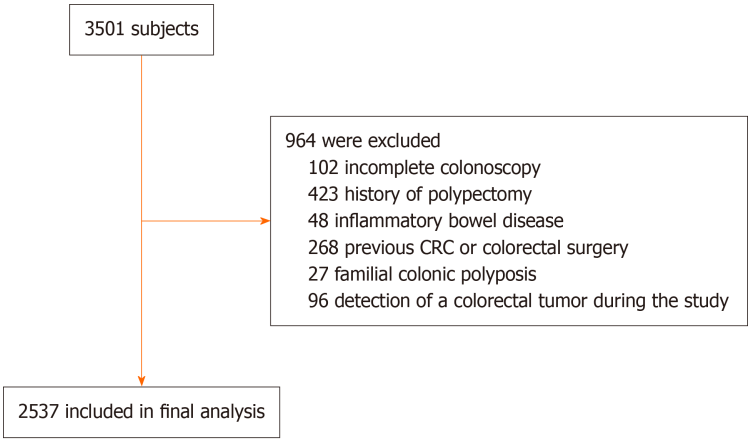

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Figure 1 Flow diagram of patient inclusion and exclusion. CRC: Colorectal cancer.

MATERIALS AND METHODS

Study population

The study included asymptomatic individuals who underwent colonoscopy as part of a comprehensive health screening program at The First People's Hospital of Kunshan, China, between January 2020 and December 2022. The retrospective review included patients between 18 and 79 years of age. Exclusion criteria consisted of incomplete colonoscopy results, history of polypectomy, inflammatory bowel disease, previous CRC or colorectal surgery, familial colonic polyposis, and detection of a colorectal tumor during the examination. The total number of patients included in this study was 2537 (Figure 1). The ethical committee of The First People's Hospital of Kunshan, China, approved the study, and the requirement for informed consent was waived due to its retrospective nature and the use of de-identified secondary data.

Biochemical analyses

After a 12-h overnight fasting period, blood samples were obtained from each participant. Biochemical analysis of the blood samples was performed using routine enzymatic methods on the VITROS 5600 Integrated System. The blood samples were tested for serum levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), and uric acid (UA). Additionally, the concentrations of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined using previously described methodologies. The TyG index was calculated as Ln [triglycerides (mg/dL) × fasting glucose (mg/dL)/2][18].

Colonoscopy and pathological examination

Prior to colonoscopy, all patients underwent a bowel preparation involving the use of polyethylene glycol electrolyte powder. The colonoscopies were performed using an ELUXEO 7000 endoscope system (FUJIFILM, Japan) by highly skilled gastroenterologists with a minimum of 5 years of experience in performing colonoscopies. Each endoscopist had performed over 1000 colonoscopies, and performed 6 or more colonoscopy examinations per day. Successful completion of the colonoscopy examination was defined as traversal of the colonoscope to the cecum, which was achieved in 97% of cases.

Pertinent colonoscopy features recorded included the presence or absence of polyps, which were subsequently biopsied or removed. The CPs included adenomatous and non-adenomatous polyps, and patients with polyps diagnosed as malignant were excluded from the study. The histological assessment of the polyps followed the established criteria outlined by the World Health Organization, and was conducted by experienced pathologists. Based on the combined colonoscopy and pathological findings, the patients were categorized into 2 distinct groups: A polyp-free group and a colorectal polyps group (one or more polyps). A subgroup analysis was also performed on the group with adenomatous polyps.

Statistical analysis

All statistical analyses were performed with R (version 3.5.3) software. Demographic data and risk factors associated with CPs were reported as mean ± SD, or count (percentage). The Kruskal-Wallis test was used to compare continuous variables, while Fisher's exact test was used to compare categorical variables. Multivariate logistic regression was conducted to identify risk factors associated with both adenomatous and non-adenomatous polyps. The consistency of relation was inspected through the use of linear trend tests. Generalized Additive Models (GAMs) and smooth curve fittings were used to examine potential non-linear associations. From the smoothing curve, the turning point was calculated using a recursive algorithm before being subjected to a 2-piecewise linear regression model. A value of $P < 0.05$ was considered statistically significant.

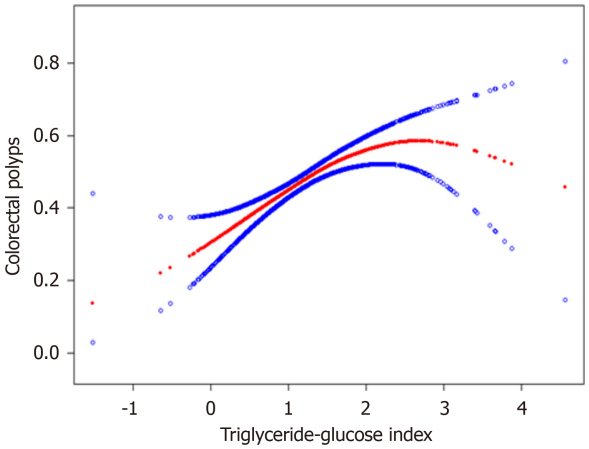

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Figure 2 The association between triglyceride-glucose index and colorectal polyps. Age, sex, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were adjusted.

RESULTS

Baseline characteristics

The general characteristics of the study population in relation to colonoscopic findings are summarized in Table 1. In comparison to the polyp-free group, patients with CPs were older and predominantly male. The polyp-free group had lower levels of AST, and higher levels of TGs, TC, LDL-C, HDL-C, UA, and FPG, and a higher TyG index (Table 1).

Association between TyG index and CPs

A positive correlation between the TyG index and the risk of CPs was identified (Table 2). The association remained significant after adjusting for different variables. In Model I, no covariates were adjusted; in Model II, age and sex were adjusted; and in Model III adjustment was made for age, sex, TC, LDL-C, and HDL-C. The positive association persisted in Model III [odds ratio (OR) = 1.56; 95% confidence interval (CI): 1.03–1.86; $P < 0.0001$]. These results indicate that each unit increase in the TyG index was associated with a 56% higher risk of CPs. Stratifying the data by age or sex revealed consistent positive associations similar to those observed without stratification (Table 2).

The relation between the TyG index and the prevalence of CPs was non-linear, as evidenced by the GAM and smoothing curve analyses (Figure 2). Specifically, a curvilinear pattern with a cut-off point at 2.31 was identified. A significant association was detected before the cut-off point (OR = 1.70; 95%CI: 1.40–2.06; $P < 0.0001$). However, after the cut-off point the association was no longer significant (OR = 0.57; 95%CI: 0.27-1.23; $P = 0.1521$) (Table 3).

DISCUSSION

In this cross-sectional study conducted within a Chinese population, we examined the correlation between the TyG index and CPs. We observed a persistent positive association, even after adjusting for variables such as sex, age, TC, HDL-C, and LDL-C. The relation was non-linear, with a significant turning point at 2.31. Notably, prior to the turning point each unit increase in the TyG index was associated with a 56% higher risk of CPs. This study is the first to investigate the association between the TyG index and CPs in a Chinese population. It is also the first study to uncover a non-linear association between the TyG index and CPs, and subsequently conduct a threshold effects analysis to further examine the non-linear relation.

Our results showed a critical threshold at 2.31 in the non-linear relation between the TyG index and CPs. Specifically, our results suggest that increasing TyG index values are significantly associated with an increased risk of developing CPs up to the turning point of 2.31. Beyond this threshold the relation was no longer statistically significant. It is well established that the magnitude of the TyG index is positively associated with IR. Recently, the TyG index has been verified as a simple and dependable estimate of IR, and it is comparable to the euglycemic-hyperinsulinemic clamp method, which is considered the gold standard for evaluating IR[19]. Therefore, we postulate that treatment and management of IR might be beneficial to prevent the occurrence and progression of CPs and CRC.

Previous research has established a significant association between the TyG index and the development of CRC. It has also suggested that the TyG index should be considered an important factor in determining the need for screening colonoscopy. Okamura *et al*[20] conducted a historical cohort study involving 27944 participants (16454 men and 11490 women) to examine the impact of the TyG index on incident CRC. They used a Cox proportional hazard model and adjusted for covariates, and revealed a hazard ratio of 1.38 (95%CI: 1.00-1.91; $P = 0.049$) for the TyG index. Their covariate-adjusted receiver operating characteristic (ROC) curve analysis identified a cut-off value of 8.27 for the TyG index in relation to incident CRC [area under the ROC curve (AUC) = 0.687, 95%CI: 0.637-0.737, sensitivity = 0.620, specificity =

Table 1 Demographic and clinical characteristics of the subjects according to colonoscopic findings

	Polyp-free	Colorectal polyps	*P* value *vs* polyp-free	Adenomatous polyps	*P* value *vs* polyp-free
n (%)	1349 (53.17)	1188 (46.83)		276	
Male	680 (50.41)	772 (64.98)	< 0.001	170 (14.31)	< 0.001
Age (yr)	52.92 ± 15.49	55.87 ± 11.91	< 0.001	53.62 ± 12.70	< 0.449
WBC (× 10^9/L)	5.74 ± 2.00	5.74 ± 1.53	0.940	5.68 ± 1.43	0.235
ALT (U/L)	27.37 ± 50.07	24.96 ± 20.08	0.122	27.27 ± 20.16	< 0.001
AST (U/L)	25.12 ± 36.33	22.62 ± 11.14	0.023	23.24 ± 9.16	0.008
TG (mmol/L)	1.44 ± 1.25	1.64 ± 1.12	< 0.001	1.71 ± 1.37	0.001
TC (mmol/L)	4.29 ± 1.07	4.67 ± 0.96	< 0.001	4.59 ± 1.01	< 0.001
LDL-C (mmol/L)	2.62 ± 0.82	2.88 ± 0.77	< 0.001	2.82 ± 0.81	< 0.001
HDL-C (mmol/L)	1.33 ± 0.36	1.40 ± 0.31	< 0.001	1.39 ± 0.31	0.009
UA (mmol/L)	306.95 ± 90.30	332.52 ± 89.48	< 0.001	330.76 ± 88.24	< 0.001
GLU (mmol/L)	5.35 ± 1.32	5.46 ± 1.14	< 0.001	5.47 ± 1.06	0.002
TyG index	1.15 ± 0.62	1.32 ± 0.61	< 0.001	1.31 ± 0.69	< 0.001

ALT: Alanine aminotransferase; AST: Aspartate transaminase; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; UA: Uric acid; GLU: Glucose; TyG: Triglyceride-glucose.

0.668, $P < 0.001$]. These results suggest that the TyG index has predictive ability for the development of CRC. A prospective cohort study by Liu *et al*[21] investigated 93659 cancer-free participants in Northern China, and assed the TyG index and the TG/HDL-C ratio. The results showed an increased risk of developing CRC in adults with an elevated TyG index and TG/HDL-C ratio. The aforementioned studies support an association between and elevated TyG index and the development of CRC. Given that CPs have been shown to be associated with the development of CRC, it is imperative to delve further into the relation between CPs and the TyG index. Such investigation would provide novel evidence for the prevention of CRC.

The exact mechanisms underlying the relation between the TyG index and CRC development are not fully understood. However, there is substantial evidence linking IR to CRC, and the TyG index is a validated surrogate marker for IR, comparable to the commonly used Homeostatic Model Assessment of IR index[22]. Thus, it is biologically plausible to consider an elevated TyG index as a risk factor for CRC.

Previous studies have shown that IR is a significant risk factor for the development of CRC. Insulin and insulin-like growth factor (IGF) may contribute to CRC development through their anti-apoptotic and mitogenic effects[23]. In a Mendelian randomization analysis conducted by Murphy *et al*[24] that used blood samples from nearly 400000 persons in the United Kingdom Biobank, an association between circulating levels of IGF1 and CRC was demonstrated. Using genetic data from over 52000 patients with CRC and 46000 persons without CRC, they observed that genetically determined higher levels of IGF1 were associated with an increased risk of CRC. These findings suggest that the interaction of various processes, directly or indirectly regulated by IGF-1, may contribute to CRC development.

Previous studies have also shed light on the role of insulin/IGF-1 in CRC. It has been shown that insulin/IGF-1 activate signaling pathways such as PI3K/Akt/mTORC and Raf/MAPK, thereby promoting cancer progression. In addition, insulin/IGF-1 activation leads to the activation of glucose transporters like GLUT1 and key glycolytic enzymes including LDHA, LDH5, HK II, and PFKFB3. Moreover, abnormal expression of oncogenes such as *MYC* and *KRAS*, as well as overexpression of signaling proteins like HIF-1, TGF-β1, PI3K, ERK, Akt, and mTOR, have been observed in CRC [25-29].

Our study has several limitations which we would like to acknowledge. First, while missing data of covariates were assumed to be missing randomly and the sample size was adequately large to draw a conclusion, we did not use multiple imputation to account for the missing data, which may potentially affect the accuracy of the results. Second, since this was a cross-sectional study, causality between the TyG index and the risk of CPs cannot be determined. Third, this study was conducted at a single center, and therefore multi-center studies should be carried out to verify our findings.

CONCLUSION

In summary, the TyG index, as a surrogate measure of IR, may potentially mediate the association between insulin-related factors, such as IGF1, and the risk of CRC. Our results clearly demonstrate an association between the TyG index and the development of CPs, providing new evidence in support of colonoscopy screening. Despite the limitations of our study, our findings suggest the need for further research to evaluate the potential role of the TyG index in assessing the

Table 2 Adjusted ORs and 95%CIs for the occurrence of colorectal polyps in relation to triglyceride-glucose index based on multinomial logistic regression

Variable	Model I		Model II		Model III	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Colorectal polyps						
TyG index	1.57 (1.37, 1.78)	< 0.0001	1.43 (1.25, 1.64)	< 0.0001	1.56 (1.30, 1.86)	< 0.0001
Sex						
Male	1.52 (1.29, 1.80)	< 0.0001	1.53 (1.29, 1.81)	< 0.0001	1.80 (1.42, 2.28)	< 0.0001
Female	1.45 (1.18, 1.78)	0.0005	1.36 (1.10, 1.68)	0.0050	1.32 (1.01, 1.76)	0.0457
Age (yr)						
< 50	1.81 (1.45, 2.27)	< 0.0001	1.62 (1.29, 2.04)	< 0.0001	1.66 (1.19, 2.30)	0.0027
> 50	1.37 (1.17, 1.61)	0.0001	1.33 (1.13, 1.57)	0.0006	1.37 (1.11, 1.70)	0.0037
Adenomous polyps						
TyG index	1.48 (1.21, 1.80)	< 0.0001	1.42 (1.16, 1.74)	0.0006	1.84 (1.34, 2.52)	0.0002
Sex						
Male	1.49 (1.16, 1.91)	0.0016	1.50 (1.17, 1.92)	0.0015	2.04 (1.42, 2.92)	0.0001
Female	1.32 (0.94, 1.84)	0.1097	1.33 (0.94, 1.89)	0.1028	1.33 (0.84, 2.11)	0.2258
Age (yr)						
< 50	1.94 (1.40, 2.70)	< 0.0001	1.85 (1.31, 2.60)	0.0004	2.26 (1.40, 3.64)	0.0008
> 50	1.24 (0.96, 1.60)	0.0963	1.22 (0.95, 1.58)	0.1197	1.40 (0.99, 1.97)	0.0578

Model I is non-adjusted. Model II is adjusted for age and sex. Model III is adjusted for age, sex, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol. TyG: Triglyceride-glucose.

Table 3 Threshold effect analysis of triglyceride-glucose index on for the occurrence of colorectal polyps using a two-piecewise linear regression model

Colorectal polyps	Odds ratio (95%CI)	*P* value
TyG index		
Fitting by standard linear model	1.55 (1.30, 1.86)	< 0.0001
Fitting by two-piecewise linear model		
Inflection point	2.31	
< 2.31	1.7 (1.40, 2.06)	< 0.0001
> 2.31	0.57 (0.27, 1.23)	0.1521
Log-likelihood ratio	0.009	

Age, sex, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were adjusted. TyG: Triglyceride-glucose.

risk for CPs and identifying patients who would benefit from colonoscopy screening.

ARTICLE HIGHLIGHTS

Research background

Colorectal polyps (CPs) are widely recognized as precursors to colorectal cancer (CRC), posing a significant global health concern. The triglyceride-glucose (TyG) index, an emerging biomarker, has shown associations with metabolic health and insulin resistance, making it a subject of interest in gastrointestinal cancer research.

Research motivation

The increasing incidence of CPs and CRC worldwide underscores the need for effective screening strategies. This study aims to fill the gap in knowledge by exploring the potential link between the TyG index and CPs in a Chinese population. Understanding this relationship could have implications for developing preventative measures and screening strategies.

Research objectives

The primary objective is to investigate the association between the TyG index and CPs, marking a pioneering exploration in a Chinese demographic. The study endeavors to identify a potential turning point in this relationship, offering valuable insights for future research and interventions.

Research methods

The retrospective cross-sectional study involves 2537 participants undergoing health examinations and colonoscopies. Thoroughly described methods include participant selection criteria, TyG index calculation, and statistical analyses. By employing logistic regression and a comprehensive approach, the study aims to reveal the nuances of the TyG index's association with CPs.

Research results

The study unveils a non-linear relationship between the TyG index and CP prevalence, delineating a significant turning point at 2.31. The analysis indicates a heightened risk of CPs before this threshold, while the association diminishes beyond it. The results contribute to the understanding of the TyG index's role in colorectal health, with potential implications for risk assessment and screening strategies.

Research conclusions

This study's novel findings confirm a curvilinear association between the TyG index and colorectal polyps, with a critical cut-off point at 2.31. The persistent positive association before this point highlights the potential utility of the TyG index in identifying individuals at risk. This study's conclusion emphasizes the relevance of these findings in shaping colonoscopy screening strategies for CRC prevention.

Research perspectives

The study prompts further investigation into the mechanisms linking the TyG index, insulin resistance, and colorectal health. Advocating for multi-center studies, the research perspectives underscore the importance of validating findings across diverse populations. The TyG index's potential role in informing future screening guidelines and its broader applicability for assessing colorectal polyp risk remain promising avenues for future research.

FOOTNOTES

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Author contributions: Teng YJ, Yang YX, Yang JJ, Bao J, Shi JY, Xu JH and Wang QH participated in literature search, study design; Teng YJ, Yang YX, Yang JJ participated in data acquisition and wrote the manuscript; Teng YJ, Yang YX, Lu QY participated in interpretation of data; all authors read and approved the final manuscript.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data.

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ORIGINAL ARTICLE

Retrospective Study

Retrospective analysis of discordant results between histology and other clinical diagnostic tests on *helicobacter pylori* infection

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Abstract

BACKGROUND

A reliable test is essential for diagnosing *Helicobacter pylori* (*H. pylori*) infection, and crucial for managing *H. pylori*-related diseases. Serving as an excellent method for detecting *H. pylori* infection, histologic examination is a test that clinicians heavily rely on, especially when complemented with immunohistochemistry (IHC). Additionally, other diagnostic tests for *H. pylori*, such as the rapid urease test (CLO test) and stool antigen test (SA), are also highly sensitive and specific. Typically, the results of histology and other tests align with each other. However, on rare occasions, discrepancy between histopathology and other *H. pylori* diagnostic tests occurs.

AIM

To investigate the discordance between histology and other *H. pylori* tests, the underlying causes, and the impact on clinical management.

METHODS

Pathology reports of gastric biopsies were retrieved spanning August 2013 and July 2018. Reports were included in the study only if there were other *H. pylori* tests within seven days of the biopsy. These additional tests include CLO test, SA, and *H. pylori* culture. Concordance between histopathology and other tests was determined based on the consistency of results. In instances where histology re-

sults were negative while other tests were positive, the slides were retrieved for re-assessment, and the clinical chart was reviewed.

RESULTS

Of 1396 pathology reports were identified, each accompanied by one additional *H. pylori* test. The concordance rates in detecting *H. pylori* infection between biopsy and other tests did not exhibit significant differences based on the number of biopsy fragments. 117 discrepant cases were identified. Only 20 cases (9 with CLO test and 11 with SA) had negative biopsy but positive results in other tests. Four cases initially stained with Warthin-Starry turned out to be positive for *H. pylori* with subsequent IHC staining. Among the remaining 16 true discrepant cases, 10 patients were on proton pump inhibitors before the biopsy and/or other tests. Most patients underwent treatment, except for two who were untreated, and two patients who were lost to follow-up.

CONCLUSION

There are rare discrepant cases with negative biopsy but positive in SA or CLO test. Various factors may contribute to this inconsistency. Most patients in such cases had undergone treatment.

Key Words: *Helicobacter pylori*; Discordance; Gastric biopsy; Histology; Rapid urease test; Stool antigen test; *Helicobacter pylori* culture

Core Tip: The concordance between histopathology and rapid urease test (CLO test) or stool antigen test (SA) for detecting *Helicobacter pylori* (*H. pylori*) detection is excellent. The agreement between histology and *H. pylori* culture is good. Concordance between histopathology and other tests shows no significant differences based on the number of biopsy fragments. Occasionally, there are rare cases where histology is negative for *H. pylori*, while the CLO test or SA is positive. The causes of such discrepancies may be multifactorial, necessitating a separate analysis for each case with clinical correlation. Most of these cases were subsequently treated for *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is directly associated with chronic gastritis, gastric/duodenal ulcer, MALT lymphoma, and gastric adenocarcinoma[1-4]. It is crucial to diagnose *H. pylori* infection accurately and promptly for the clinical management of associated diseases[1]. Various methods for *H. pylori* detection, both invasive and noninvasive, have been developed[1,5]. Invasive tests include histological examination, rapid urease test (CLO test), and *H. pylori* culture. Noninvasive tests include urease breath test (UBT), stool antigen test (SA), and serology testing for *H. pylori* antibody[1,5].

Each diagnostic method has its advantages and disadvantages. No single test is universally acknowledged as a gold standard for detecting *H. pylori* infection[4]. A well accepted approach is combining two or more detection methods[4]. The selection of diagnostic tests depends on various factors, including test availability, sensitivity, specificity, cost, and turnaround time. Although non-invasive tests like UBT offer high sensitivity and specificity for detecting *H. pylori*, upper gastrointestinal (GI) endoscopy with biopsy remains the preferred method, particularly for individuals over 60 or those with alarming symptoms, as recommended by the American College of Gastroenterology[6]. In our hospital, the initial evaluation for symptomatic patients typically involves gastric biopsy and another method. Commonly employed other tests include SA, CLO test, and *H. pylori* culture. Clinicians place particular emphasis on the morphological assessment of gastric biopsy, especially when combined with immunohistochemistry (IHC), considering it one of the most accurate methods. While the results of other clinical tests generally align with biopsy findings, occasional rare discrepancies may pose challenges for clinicians, especially in cases where biopsy results are negative but other clinical tests are positive.

This study aims to clarify and characterize the discrepancies between various diagnostic tests and histological interpretations. A retrospective study is conducted to compare the results of gastric biopsy diagnoses with other *H. pylori* diagnostic tests. Additionally, ancillary tests used for the histologic diagnosis of *H. pylori*-associated gastritis are evaluated.

Table 1 Gastric biopsy cases with ancillary stains

Ancillary stains	Total cases	*H. pylori* positive	*H. pylori* negative
WS only	1199	333	866
IHC only	81	20	61
WC/IHC	60	13	47
H&E only	56	26	30
Total	1396	392	1004

WS: Warthin-Starry stain; IHC: Immunohistochemistry stain; *H. pylori*: *Helicobacter pylori*; H&E: Hematoxylin and eosin stain.

MATERIALS AND METHODS

Data collection

The research received approval from the Institutional Review Board of the hospital (2016-6957). Pathology reports of gastric biopsies were extracted from the hospital's in-house database using Clinical Looking Glass (version 4.4.2) spanning from August 2013 to July 2018. Reports were chosen based on specimens originating from the stomach, with comments indicating the presence or absence of *H. pylori* organism. Inclusion criteria mandated the presence of other *H. pylori* diagnostic tests conducted within seven days of the biopsy. Other clinical tests included in the study were: (1) Rapid urease test (CLO test); (2) stool antigen test (SA); and (3) *H. pylori* culture. In instances of multiple tests within a two-week window, the result closest to the biopsy date was considered. Data extracted from the reports included the number of stomach biopsy fragments collected during endoscopy, procedure dates, *H. pylori* status, and the stains used for histologic diagnosis. Test results were considered concordant when both biopsy and clinical tests provided the same diagnosis for *H. pylori* infection; otherwise, they were labeled as discordant. In cases where a negative biopsy with a positive clinical test were identified, histologic slides were retrieved for re-assessment, and the patient's chart was reviewed.

Statistical analysis

The inter-test agreement between histology and another diagnostic test (CLO test, *H. pylori* culture, or stool test) for detecting *H. pylori* infection was assessed utilizing the kappa statistic. An excellent agreement was defined as a kappa value ≥ 0.75, fair to good agreement as a kappa value between 0.4 and 0.75, and poor agreement as a kappa value < 0.4. Concordance referred to the alignment between histology and another diagnostic test on *H. pylori* detection, with the concordance rate calculated as the number of concordant cases divided by the total number of cases. Differences in concordance rates among various diagnostic tests with histology in detecting *H. pylori* infection were assessed using chi-square tests. Statistical analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC, United States), and p-values of 0.05 or less were deemed statistically significant.

RESULTS

A total of 1396 pathology reports were identified. The majority of biopsies (n = 1199) were stained solely with Warthin-Starry (WS) stain. Only a small number of cases were reported with *H. pylori* IHC stain only (n = 81), both WS and IHC stains (n = 60), or no special stain used (n = 56) (Table 1). Among them, 392 cases tested positive for *H. pylori* through morphological examination, with WS stain, and/or with IHC. Each biopsy was accompanied by only one additional *H. pylori* test (CLO test, SA, or *H. pylori* culture). Both CLO test and *H. pylori* culture were invasive, conducted on the day of the biopsy. SA was performed within seven days of the biopsy. The summary of additional test results (CLO test, SA, or *H. pylori* culture) is presented in Table 2.

The overall concordance rate between histology and other diagnostic tests was high (n = 1279; 91.6%). CLO test and stool antigen tests demonstrated significantly higher concordance rates with biopsy in detecting *H. pylori* infection compared to *H. pylori* culture (95.6% for CLO test *vs* 92.2% for SA *vs* 87.5% for culture; P < 0.001) (Table 2). The estimated kappa statistic for assessing agreement in identifying *H. pylori* infection between histology and other diagnostics were 0.86 for CLO test (95%CI: 0.81–0.92; Table 3), 0.77 for stool antigen test (95%CI: 0.68–0.86; Table 4), and 0.72 for culture (95%CI: 0.66–0.78; Table 5) respectively.

The correlation between concordance rates and the number of biopsy fragments was also examined (Figure 1). The number of biopsy fragments exhibited considerable variation across cases, ranging from 1 to 6 or more: 83 cases (1 fragment), 321 cases (2 fragments), 229 cases (3 fragments), 262 cases (4 fragments), 132 cases (5 fragments), and 364 cases (6 fragments and above). Additionally, 5 cases lacked information on fragment numbers. Notably, the concordance rates in detecting *H. pylori* infection between biopsy and other clinical diagnostic tests did not differ significantly by the number of fragments (88.0% *vs* 93.5% *vs* 92.1% *vs* 92.7% *vs* 93.2% *vs* 89.2%, P = 0.268; Figure 1).

The majority of cases exhibiting discordance were those with a positive biopsy but negative results in other *H. pylori* tests (97 cases). Among these cases, a significant proportion involved bacterial culture (70 cases). Additionally, there were

Table 2 Concordance rate between histology and three other *Helicobacter pylori* tests

Other *H. pylori* test	CLO test	SA test	*H. pylori* culture
Total cases	528	306	562
H. pylori positive cases	104	66	145
H. pylori negative cases	424	240	417
H. pylori positivity rate	19.8%	21.5%	25.8%
Concordance cases	505	282	492
Discordance cases	23	24	70
Concordance rate with histology	95.6%	92.1%	87.5%

H. pylori: *Helicobacter pylori*; CLO test: Campylobacter-like organism (rapid urease test); *H. pylori* culture: *Helicobacter pylori* culture.

Table 3 Assessment of concordance between histology and rapid urease test

	CLO test positive	CLO test negative	Total
Histology positive	95	14	109
Histology negative	9	410	419
Total	104	424	528

CLO test: Campylobacter-like organism (rapid urease test).

Table 4 Assessment of concordance between histology and stool antigen test

	SA positive	SA negative	Total
Histology positive	55	13	68
Histology negative	11	227	238
Total	66	240	306

SA: Stool antigen test.

Table 5 Assessment of concordance between histology and *Helicobacter pylori* culture

	H. pylori Culture positive	*H. pylori* Culture negative	Total
Histology positive	145	70	215
Histology negative	0	347	347
Total	145	417	562

H. pylori culture: *Helicobacter pylori* culture.

14 instances of negative CLO tests and 13 cases with negative SA tests, despite a positive histological diagnosis. Conversely, there were only 20 cases with negative biopsy results but positive results in other tests (SA or CLO test; Tables 3-5). All 20 cases were reported to exhibit chronic inactive inflammation on histological examination, with one case also displaying focal active gastritis. No atrophy was observed in any case. Sixteen cases were available for reassessment, with IHC staining performed on those cases not previously tested. In this reevaluation, four cases were found to be positive for *H. pylori* by IHC, despite previous reports indicating negativity. A review of the original H&E slides and WS stains for these four cases revealed the presence of rare and/or morphologically atypical *H. pylori* organisms. Among them, all four cases showed inactive chronic gastritis, and one exhibited focal chronic active gastritis. Additionally, it was observed that three of these patients were under proton pump inhibitor (PPI) treatment at the time of biopsy. Consequently, these four cases were excluded from subsequent assessment. Among the remaining 16 'true' discrepant cases, only four cases had four or more fragments from gastric biopsy, while 12 had three fragments or fewer submitted for histologic examination.

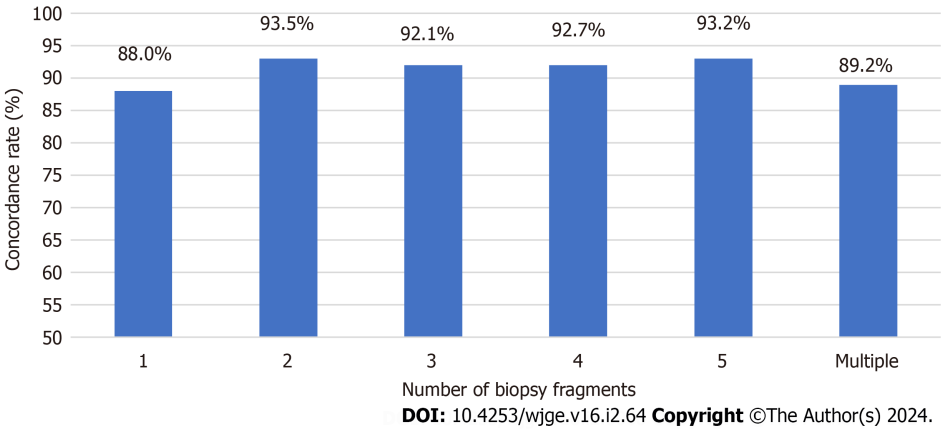

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Figure 1 Concordance rate between histology and other *Helicobacter pylori* tests based on numbers of biopsy fragments. Multiple: 6 fragments and up. Concordance rate is labeled on top of each column.

Ten cases were on PPI either when biopsied and/or tested for SA (Table 6); six were on PPI when biopsied but not tested for SA; three were on PPI when biopsied and tested; while one was on PPI only when tested for SA but not biopsied. Additionally, three cases (case 8, 9, and 15) were on antibiotics in addition to PPI when biopsied, as the treatment (triple or quadruple therapy) was initiated after a positive SA result a few days before the biopsy procedure. The majority of patients received treatment for *H. pylori* infection, with the exception of two patients who were untreated, and two patients who were lost to follow-up (Table 6). According to the clinical chart, the decision for treatment was determined by various factors, including clinical presentation, endoscopy findings, pathology results other than *H. pylori* infection status, and occasionally repeated biopsy or other *H. pylori* tests (as observed in cases 13 and 15).

DISCUSSION

While histology is commonly regarded as the preferred method for symptomatic patients[6,7], other *H. pylori* diagnostic tests are equally crucial, often being more convenient, less invasive, and cost-effective, yet maintaining high sensitivity and specificity[4]. Discrepancies between biopsies and the results of other *H. pylori* diagnostic tests can occasionally arise. No single test is considered the gold standard alone[4]. Nevertheless, clinicians prioritize the morphological assessment of gastric biopsies, especially when augmented with immunohistochemistry, considering it as one of the most accurate approaches. Negative clinical test results may be deemed false negatives when the corresponding biopsy is positive. However, the discrepancy between a negative biopsy and a positive clinical test result can pose a challenge for physicians. This study's objective is to elucidate and characterize the discordance between histopathology and other clinical diagnostic tests in determining *H. pylori* status.

The CLO test, SA test, and *H. pylori* bacterial culture were selected for comparison with histology, as they are the most employed tests in conjunction with upper GI endoscopy at our hospital. Both the CLO test and SA test exhibit high sensitivity and specificity, while *H. pylori* culture has nearly 100% specificity with slightly lower sensitivity[4]. Our findings indicate excellent agreement between histology and the CLO test and stool antigen test (with Kappa values exceeding 0.75). *H. pylori* culture demonstrates a slightly lower but still commendable concordance rate (Kappa value of 0.72) mainly due to its higher false negative rate.

The sensitivity and diagnostic accuracy of *H. pylori* are impacted by the sampling during biopsy. It is recommended by the Sydney protocol[8] to submit four biopsy samples for *H. pylori* detection: Two from the antrum and two from the body. An additional sample from incisure angularis is advised for gastritis characterization[3,8]. In our study, most cases have less than five biopsy fragments submitted (Figure 1), and there is no available data regarding the origin of these fragments. Interestingly, the number of gastric samples obtained during each endoscopy did not significantly influence the concordance rate between histological diagnosis and other *H. pylori* tests in our study. However, it is essential to note that concordance does not equate to test accuracy, as concordant results can be either false positives or false negatives. Treatment status at the time of testing is unknown, and both results could be affected by PPI or antibiotics, even if they are concordant.

Most cases have WS stain for histologic diagnosis, as WS stains were automatically ordered from 2013 to 2015 at our hospital. WS stain was preferred over *H. pylori* IHC stain due to its lower cost and quicker turnaround time. Recent studies indicate that ancillary stains provide little additional benefits to H&E stains for *H. pylori* detection[2,9], particu-larly in cases without inflammation. Since 2016, there have been no further automated orders for special stains on GI biopsy in our laboratory, informed by both literature findings and our own experiences. In our investigation of discrepant cases, four biopsy cases initially reported as negative for *H. pylori* later revealed *H. pylori* organisms through IHC. All four cases exhibited inactive chronic gastritis with one displayed focal active chronic gastritis. Upon re-examination of the H&E slides and WS stains, rare and/or morphologically atypical *H. pylori* organisms were identified. Notably, three patients were noted to be on PPI, potentially altering bacterial appearance and making identification challenging with H&E and

Table 6 Discrepant cases with negative histology but positive rapid urease test or stool antigen test

Cases #	No. of biopsy specimens	Histology test results		Clinical tests		Treated for *H. pylori*
		WS/IHC	On PPI/Antibiotics when biopsied	Pos. Clinical Tested	On PPI/Antibiotics when tested	
1	3	Neg/Neg	NA	CLO	NA	Yes
2	2	Neg/Neg	NA	CLO	NA	Yes
3	3	Neg/Neg	NA	CLO	NA	NA
4	2	Neg/Neg	NA	CLO	NA	NA
5	2	Neg/Pos	No	CLO	No	No
6	2	Neg/Neg	Yes[1]	SA	Yes[1]	Yes
7	1	Neg/Neg	No	SA	Yes[1]	Yes
8	M	NP/Neg	Yes[2]	SA	No	Yes
9	3	Neg/Neg	Yes[2]	SA	No	Yes
10	M	Neg/Pos	Yes[1]	SA	Yes[1]	Yes
11	4	Neg/Pos	Yes[1]	SA	Yes[1]	Yes
12	3	NP/Neg	No	SA	No	No
13	M	Neg/Neg	Yes[1]	SA	No	No
14	2	NP/Neg	Yes[1]	SA	No	Yes
15	1	NP/Neg	Yes[2]	SA	No	Yes
16	2	Neg/Pos	Yes[1]	SA	No	Yes

[1]PPI only.

[2]PPI and antibiotics.

WS: Warthin-Starry stain; IHC: Immunohistochemistry; *H. pylori*: *Helicobacter pylori*; CLO: Campylobacter-like organism (rapid urease test); SA: Stool antigen test; PPI: Proton pump inhibitor; NA: Not available; Neg: Negative; Pos: Positive; M: Multiple (6 fragments and up).

special stains[10,11]. In this case, immunohistochemistry would help identify rare and/or morphological atypical *H. pylori* organisms in cases with other evidence of *H. pylori* and inflammatory mucosa.

There are 16 discrepant cases, excluding 4 instances where *H. pylori* was detected by IHC after initially being negative by H&E and WS. Several factors may contribute to the disparity between a negative biopsy and a positive CLO test or SA test. Firstly, the presence of organisms may be reduced or absent due to medications such as PPI and/or antibiotics[12]. Additionally, these medications can alter the appearance of bacteria, making recognition challenging[3,11]. Among the patients, 10 were on PPI before the biopsy procedure and/or other *H. pylori* tests, with the majority (6 cases) only taking PPI before biopsy, not before other *H. pylori* tests. For these 6 cases, results from other *H. pylori* tests are more likely reliable than histology. Secondly, sampling may contribute to the discrepancy, with 12 out of 16 cases having three fragments or fewer. Although the overall number of gastric samples does not significantly affect the concordance rate, as discussed previously, this may differ when patients are on PPI, particularly if they were on PPI for one test but not for another. Lastly, some results could be false positives from CLO test or SA tests, as both can yield false positive results[13-16].

It is important to note that despite conflicting results presented to clinicians, most patients received treatment without additional testing, except in two cases. This could be attributed to multiple factors, including limited test availability, insurance coverage constraints, challenges in discontinuing medications to minimize testing interference, or delays in treatment. The choice to pursue treatment is influenced by various factors, including clinical symptoms, endoscopic observations, pathology findings other than *H. pylori* infection status, and occasionally the repetition of biopsies or other *H. pylori* tests.

CONCLUSION

Our findings demonstrated that both CLO test and SA tests exhibit high concordance rates with histological diagnoses. The concordance rate between histology and *H. pylori* culture is slightly lower, primarily attributed to the lower sensitivity of the *H. pylori* culture assay. Importantly, the concordance rate shows no significant difference by the number of fragments obtained during the biopsy procedure. There are rare instances of discrepancies, where *H. pylori* diagnosis is negative by histology but positive by CLO test or stool antigen test. Multiple factors may contribute to these discrep-

ancies. Even though histological examination showed negative results for *H. pylori* in these cases with discrepancies, most patients still received treatment. Correlating with clinical history, past laboratory results, and follow-up testing may assist in clinical management.

ARTICLE HIGHLIGHTS

Research background

Determining *Helicobacter pylori* (*H. pylori*) status is essential in the management of *H. pylori*-related diseases. No single test is universally recognized as the gold standard alone. Typically, symptomatic patients at our hospital undergo upper GI endo-scopy with biopsy, often accompanied by an additional *H. pylori* test. The results generally align with each other, although discrepancies arise occasionally.

Research motivation

The clinician places particular emphasis on gastric biopsy results, especially when supplemented with immunohisto-chemistry (IHC), often considering it the most accurate. Rare cases where biopsy results are negative while other clinical tests show positivity can present challenges for clinicians.

Research objectives

The goal of this retrospective study is to examine the discordance between histopathology and alternative *H. pylori* tests, explore the underlying causes, and assess the implications for clinical management.

Research methods

Pathology reports of gastric biopsies were retrospectively retrieved from August 2013 to July 2018. Inclusion in the study required the presence of other *H. pylori* tests within seven days of the biopsy, including rapid urease test (CLO test), stool antigen test (SA), and *H. pylori* culture. The concordance between histopathology and other tests was evaluated based on result consistency. In cases where histology was negative while other tests showed positivity, the slides underwent reassessment, and the clinical chart was examined.

Research results

1396 pathology reports were identified, each accompanied by one additional *H. pylori* test. The concordance rates between biopsy and other tests did not show significant differences based on the number of biopsy fragments. 117 discrepant cases were identified. Only 20 cases (9 with CLO test and 11 with SA) had negative biopsy but positive results in other tests. Four cases initially stained with Warthin-Starry stain turned out to be positive for *H. pylori* with subsequent IHC staining. Among the remaining 16 true discrepant cases, 10 patients were on proton pump inhibitors before the biopsy and/or other tests. Most patients underwent treatment, except for two who were untreated, and two patients who were lost to follow-up.

Research conclusions

Our findings reveal that both SA and CLO test demonstrate high concordance rates with histological diagnoses. The concordance rate between histology and *H. pylori* culture is slightly lower, mainly due to the lower sensitivity of the *H. pylori* culture assay. Importantly, the concordance rate remains consistent regardless of the number of gastric biopsy fragments. Rare instances of discrepancies exist, where *H. pylori* diagnosis is negative by histology but positive by SA or CLO test. Multiple factors may contribute to the discordance. Despite histological examination showing negative results for *H. pylori* in these cases with discrepancies, most patients still received treatment. Correlation with clinical history, past laboratory results, and follow-up testing may aid in clinical management.

Research perspectives

This retrospective study was conducted at a singular tertiary medical center. It would be intriguing to conduct similar retrospective research in other hospitals to compare discordance rates between histology and other *H. pylori* tests and variations in clinical management.

FOOTNOTES

Co-first authors: Xiaohua Qi and Kevin Kuan.

Author contributions: Qi X and Kuan K contributed equally to this work; Fang Y and Liu Q designed the research study; Qi X and Kuan K performed the data extraction; Kuan K, Qi X, Jabbour T, Liu Y, and Fang Y performed the data analysis and interpretation of the results; Fang Y, Kuan K, and Qi X wrote the manuscript, Lo Y is a Biostatistics professor and performed the statistical analysis; Fang Y, Kuan K and Qi X revised the manuscript; and all authors read and approved the final version.

Institutional review board statement: This study was reviewed and approved by the Albert Einstein College of Medicine Institutional Review Board (IRB No: 2016-6957).

Informed consent statement: This is a retrospective study with a focus on quality assurance (QA). The institutional review board (IRB) granted a waiver of consent.

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

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ORIGINAL ARTICLE

Retrospective Study

Comparative efficacy and safety between endoscopic submucosal dissection, surgery and definitive chemoradiotherapy in patients with cT1N0M0 esophageal cancer

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Abstract

BACKGROUND

Endoscopic submucosal dissection (ESD) and surgical resection are the standard of care for cT1N0M0 esophageal cancer (EC), whereas definitive chemoradiotherapy (d-CRT) is a treatment option. Nevertheless, the comparative efficiency and safety of ESD, surgery and d-CRT for cT1N0M0 EC remain unclear.

AIM

To compare the efficiency and safety of ESD, surgery and d-CRT for cT1N0M0 EC.

METHODS

We retrospectively analyzed the hospitalized data of a total of 472 consecutive patients with cT1N0M0 EC treated at Sun Yat-sen University Cancer center between 2017-2019 and followed up until October 30th, 2022. We analyzed demographic, medical recorded, histopathologic characteristics, imaging and endoscopic, and follow-up data. The Kaplan-Meier method and Cox proportional hazards modeling were used to analyze the difference of survival outcome by treatments. Inverse probability of treatment weighting (IPTW) was used to minimize potential confounding factors.

RESULTS

We retrospectively analyzed patients who underwent ESD (n = 99) or surgery (n = 220) or d-CRT (n = 16) at the Sun Yat-sen University Cancer Center from 2017 to 2019. The median follow-up time for the ESD group, the surgery group, and the d-CRT group was 42.0 mo (95%CI: 35.0-60.2), 45.0 mo (95%CI: 34.0-61.75) and 32.5 mo (95%CI: 28.3-40.0), respectively. After adjusting for background factors using IPTW, the highest 3-year overall survival (OS) rate and 3-year recurrence-free survival (RFS) rate were observed in the ESD group (3-year OS: 99.7% and 94.7%

and 79.1%; and 3-year RFS: 98.3%, 87.4% and 79.1%, in the ESD, surgical, and d-CRT groups, respectively). There was no difference of severe complications occurring between the three groups ($P \geq 0.05$). Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with OS and RFS.

CONCLUSION

For cT1N0M0 EC, ESD had better long-term survival and lower hospitalization costs than those who underwent d-CRT and surgery, with a similar rate of severe complications occurring.

Key Words: Retrospective study; cT1N0M0; Esophageal squamous cell carcinoma; Endoscopic submucosal dissection; Surgery; Definitive chemoradiotherapy

Core Tip: This is a first retrospective study to compare overall survival, recurrence-free survival and complication rates of endoscopic submucosal dissection (ESD), surgery and definitive chemoradiotherapy (d-CRT). In this study, we found that ESD attained better survival benefits and lower hospitalization costs than surgery and d-CRT, and they had similar complication rates. This study provides a more comprehensive analysis of the efficacy and safety of current cT1N0M0 esophageal cancer (EC) treatment patterns and provides new evidence for the use of ESD in cT1N0M0 EC.

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INTRODUCTION

Esophageal cancer (EC) is an aggressive and poorly prognostic gastrointestinal tumor and one of the common causes of cancer death[1]. Over the past few decades, the proportion of patients with cT1N0M0 EC has increased due to improvements in endoscopic techniques and increased awareness of disease prevention. Approximately 90% of EC are squamous cell carcinoma (SCC) and vary by geographical region, with SCC being more common in Central Asia and China[2]. According to the depth of infiltration, cT1N0M0 EC is classified as mucosal carcinoma (T1a) and submucosal carcinoma (T1b), regardless of lymph node status.

In the European Society of Endoscientific Oncology and the National Comprehensive Cancer Network guidelines, endoscopic resection is recommended for mucosal (T1a) lesions, surgical resection is recommended for patients with submucosal (T1b) lesions, and definitive chemoradiotherapy (d-CRT) is recommended for patients who are unable or unwilling to undergo surgery[3,4]. Endoscopic resection can accurately stage the patients, reduce the surgical complications, and achieve the effect of curative resection[5-7], but carries a higher risk of recurrence (especially for large lesions). And radical esophagectomy is usually associated with postoperative complications, including anastomotic fistula, vocal cord paralysis, and pneumonia[8].

d-CRT is the standard treatment for patients with locally unresectable esophageal squamous cell carcinoma (ESCC) and an alternative treatment option for locally resectable ESCC[9-13]. However, in clinical practice, d-CRT is often selected as an alternative therapy for cT1N0M0 EC patients, depending on the comorbidities, tumor localization, and widespread expansion. Few reports have described the use of d-CRT in patients with stage I ESCC. A parallel group controlled trial conducted in Japan found that the survival of CRT in cT1bN0M0 ESCC was comparable to surgery and had acceptable toxicity[14]. However, the trial was conducted in Japan, and it was not clear about the generalizability of the evidence to different countries, while elderly patients and those not medically fit for surgery were excluded or underrepresented in the trial, and the study mainly included thoracic EC, thus questioning the generalizability of the results. Given the lack of sufficient evidence for the comparative efficacy of different treatments in cT1N0M0 EC, especially the role of d-CRT, we conducted this first retrospective study to compare the efficacy and complications of endoscopic submucosal dissection (ESD), surgery and d-CRT.

MATERIALS AND METHODS

Patient selection

We retrospectively analyzed patients with cT1N0M0 EC treated with ESD, surgery and d-CRT between January 2017 and December 2019 at the Cancer Center of Sun Yat-sen University. The inclusion criteria were as follows: (1) All patients met the diagnostic criteria for cT1N0M0 EC: the tumor tissue was limited to the esophageal mucosa or submucosa without

lymph node or distant metastasis (cT1N0M0), and the diagnosis was made by endoscopy, pathological biopsy and imaging evaluation; (2) Patients with histology of SCC or precancerous lesions; (3) Patients without other concomitant malignancies; and (4) Patients with complete clinical medical records.

The study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the institutional review board of the Sun Yat-sen University Cancer Center.

Preoperative and postoperative evaluation

The preoperative and postoperative evaluations mainly included endoscopic, imaging and histopathological examinations. Endoscopic examinations were performed by physicians with more than 6 years of endoscopic experience in the Department of Endoscopy of Sun Yat-sen University Cancer Center. Endoscopic examinations generally included conventional endoscopy with white light imaging for all lesions; magnifying endoscopy with narrow-band or blue laser imaging (commonly referred to as ME-NBI/BLI) using a GIF-H260Z (Olympus Corporation, Tokyo, Japan) or EG-L590ZW gastroscope (Fujifilm Corporation, Tokyo, Japan) for suspicious lesions; ultrasound endoscopy utilizing 7.5 MHz, 10 MHz, or 12 MHz radical scanning probes (SU 9000, EG-530UR2, Fujifilm; EU-ME2, Olympus) or a 20-MHz miniature probe (UM-DP20-25R, Olympus) was applied for identifying the depth of tumor infiltration or metastasis of lymph nodes. Preoperative enhanced computed tomography (CT), magnetic resonance or positron emission tomography/CT were performed to assist in the diagnosis of esophageal carcinoma. Postoperative follow-up examinations were started 1-2 mo after the end of treatment, once every 3 mo during the initial 2 years, once every 6 mo from 2 to 5 years, and once a year after 5 years. R0 resection was defined as complete resection of the tumor, and histopathology showed a negative resection margin and no tumor residue after ESD or surgery therapy. Complete response (CR) was defined as the disappearance of the primary tumor and the absence of irregular erosive lesions, ulcerative lesions, or apparently elevated lesions as observed during endoscopy and/or the absence of malignant cells in biopsy specimens after d-CRT therapy[15].

ESD, surgery and d-CRT

ESD was performed by endoscopists with extensive experience. All inpatients were placed in the left lateral position with general anesthesia under tracheal intubation. The esophageal lesion was stained with Lugol solution, and the resection margin was marked with adenomatous polyposis coli or high-frequency electrocoagulation. A mixed liquid (0.9% NS: Sodium hyaluronate = 4:1) was injected into the submucosa, the submucosa was dissected on the surface of the intrinsic muscular layer after circumferential incision outside the marked points, and the lesion was completely excised. Finally, the specimen was laid flat, fixed on a cork board with pins, soaked in formalin and sent for pathological examination. The intrinsic muscular layer of the esophagus was carefully examined endoscopically for any additional damage or residual tumor at the resection margin. The decision to add other additional treatments was made after a thorough evaluation based on the pathological findings and the therapeutic wishes of the patient and their family. In this study, 2 patients underwent radical EC resection after ESD because of the positive resection margin of the pathological specimen.

Surgery was performed by experienced surgeons in our hospital. After general anesthesia was stabilized, the patients were placed in a supine position. After routine disinfection, surgeons removed the esophageal tumors, dissected the peripheral lymph nodes *via* thoracotomy or thoracoscopy and reconstructed the digestive tract using a laparotomy or laparoscopic approach. In this study, the pathological examination of 1 patient after esophagectomy indicated that tumor cells were visible at the resection margin of the specimen, so an extended surgical procedure was implemented.

The d-CRT regimen was discussed and decided by physicians with extensive experience in the medical oncology and radiotherapy departments of our hospital. d-CRT consisted of 5 courses of albumin paclitaxel (45-60 mg/m^2) and cisplatin (20-25 mg/m^2) on Day 1 every week along with concurrent radiotherapy by the intensity-modulated radiotherapy technique. Radiation therapy was delivered using megavoltage equipment (≥ 6 MV). The patients were treated 5 d per week at 1.8 to 2.0 Gy/d for a total dose of 60 Gy. The target volume of radiotherapy was individualized according to the primary tumor site and metastasis. The clinical target volume of mid-thoracic EC was defined as the gross tumor volume with a 3 cm margin for upper and lower extents and the lymph node target volume (gross tumor volume-nd) with a 0.5 to 1 cm margin for three-dimensional extents. The planned target volume was decided according to the actual positional error and was generally formed by a 0.5 cm margin for three-dimensional outward extents based on the clinical target volume and a 0.3 cm margin for cervical or upper thoracic EC fixed by head, neck and shoulder mesh.

Statistical analysis

The statistical methods used in this study included Student's *t* test (or Mann-Whitney *U* test) and Fisher's exact test (or Pearson's chi-square test). The mean ± standard deviation for normally distributed measures was expressed by *t* test and the median and interquartile range [M (P25, P75)] for nonnormally distributed measures were expressed by rank sum test; the count data were expressed as percentages (%) and compared by chi-square test (χ^2 test). To account for selection bias and potential cofounding factors between groups in comparisons of outcome, we performed weighted propensity score analysis to control for differences in baseline characteristics between patients who underwent ESD, surgery and d-CRT. The propensity model was generated using the inverse probability treatment weighting (IPTW) method. Each patient was weighted by inverse probability with the goal of balancing observable features. The Bonferroni correction was needed as a conservative method for probability thresholding to control the occurrence of false positives. The 3-year overall survival (OS) and recurrence-free survival (RFS) were calculated and expressed as months. OS was right censored if the patient was alive at study termination or was lost to follow-up, and patient death was considered an event. In RFS analysis, the recurrence of EC after eradication therapy was considered an event. The follow-up period was calculated from treatment, and the cutoff date was October 30, 2022. Follow-up ended when patients died or were lost to follow-up

and cause of death and cause of loss analysis was analyzed. Time to recurrence was calculated from the time of treatment to the time of the most recent endoscopic evaluation at our facility or another hospital. The survival curves were plotted using the Kaplan-Meier method, and OS and RFS rates of therapeutic groups were compared by log-rank test. Cox proportional hazards modeling was used to assess the hazard ratios (HRs) and 95% confidence intervals (CIs). All data were analyzed by SPSS version 25.0 (IBM Corp., Armonk, NY, United States) and R version 4.3.1. All tests were two-sided with a significance level of $P < 0.05$.

RESULTS

Patient characteristics and complications

A total of 3911 patients with EC were treated in our hospital between January 2017 and December 2019, including 75 patients with precancerous esophageal lesions and 472 patients with cT1N0M0 EC. After exclusion, we retrospectively analyzed cT1N0M0 EC patients who underwent ESD (n = 99) or surgery (n = 220) or d-CRT (n = 16) at our hospital. Tables 1 and 2 show the baseline characteristics and complications of patients in the ESD, surgery and d-CRT groups before and after IPTW adjustment.

Before IPTW adjustment, patients in the d-CRT group were older than those in the ESD and surgery groups. In the d-CRT group, there were 6 patients with clinical stage T1a (cT1a: M1-2), of whom 4 (66.7%) achieved CR, and 10 patients with clinical stage T1b (cT1b: M3-SM1-3), of whom 8 (80.0%) achieved CR. Among the cT1a patients, an 87-year-old patient developed more serious radiotherapy toxic side effects such as radiation pneumonia and finally died despite achieving CR, while 1 patient who did not achieve CR died of EC and severe complications of radiotherapy. Among the cT1b patients, severe complications were observed in 4 patients who achieved CR and survived, including 3 patients with esophageal stricture and 2 patients with radiation pneumonia. In contrast, 1 patient who did not achieve CR died after receiving additional treatments because of lymph node metastasis. Patients in the surgery and d-CRT groups had more complications than those in the ESD group. Esophageal stricture was the main postoperative complication (surgery *vs* ESD *vs* d-CRT: 17.7% *vs* 4.1% *vs* 18.8%, $P = 0.004$).

While after IPTW adjustment, the covariate balance in the three groups was improved; the number of background factors with P value above 0.05 was increased from 1 to 7. Complication rates were similar in the three groups, with all P values > 0.05.

Hospitalization costs and follow-up

Table 3 shows the hospitalization costs and remedies after recurrence or metastasis in the ESD, surgery and d-CRT groups. The median follow-up time was 42.0 mo (95%CI: 35.0-60.2) in the ESD group, 45.0 mo (95%CI: 34.0-61.75) in the surgery group and 32.5 mo (95%CI: 28.3-40.0) in the d-CRT group. The ESD group had the lowest hospitalization costs, while the d-CRT group had the highest hospitalization costs among the three groups. One patient died of EC in the ESD group. In the surgery group, 16 patients died of progression or metastasis of EC (84.2%), 2 patients died of postoperative multiorgan failure, and 2 patient died of severe respiratory disease. Two patients died of EC, and one patient died of severe complications of radiation therapy in the d-CRT group. During the follow-up period, 4 patients developed recurrence or metastasis (4.0%), and 3 patients underwent surgical resection of the lesions in the ESD group, while 38 patients in the surgery group developed recurrence or metastasis (17.3%), and 31 patients underwent salvage treatments. Additionally, 1 patient in the d-CRT group was treated with palliative chemoradiotherapy after recurrence or multiple metastases.

Survival analysis

To compare 3-year OS and RFS in the ESD, surgery and d-CRT groups, the survival analysis was performed with IPTW adjustment and using Bonferroni correction to control the occurrence of false positives. Figure 1 shows the Kaplan-Meier survival curves before and after IPTW adjustment. The 3-year OS and RFS of ESD were superior to those of surgery and d-CRT (OS: ESD: 99.7%, surgery: 94.7%, d-CRT: 79.1%; RFS: ESD 98.3%, surgery: 87.4%, d-CRT: 79.1%).

We further investigated the risk factors for OS and RFS in the different treatment modalities. Figure 2 shows the results of the Cox proportional hazards model for OS and RFS after IPTW adjustment. Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with OS and RFS.

DISCUSSION

Many studies have compared the outcomes of ESD and surgery, or surgery and CRT in the treatment of cT1N0M0 EC, but there is a lack of studies directly comparing the efficacy and safety between ESD, surgery and d-CRT. After analyzing our included patients' clinical data before and after IPTW adjustment, we found that ESD yielded better OS, RFS rates and lower hospitalized costs than surgery and d-CRT. Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with OS and RFS, and it was similar to the previous study[16].

We explored the reasons for the difference in 3-year OS and RFS between the three treatments. We found that the depth of infiltration was more superficial in patients in the ESD group and that the local oncological control rate with ESD or surgery was higher, so patients could achieve tumor-free status to a greater extent. Patients in the d-CRT group were generally older and had high-grade and larger tumors, so EC was more likely to progress to an advanced stage and could

Table 1 Baseline patient characteristics before and after inverse probability of treatment weighting adjustment of patients treated by endoscopic submucosal dissection, surgery and definitive chemoradiotherapy

Characteristic		Unmatched				IPTW			
		d-CRT	ESD	Surgery	*P* value	d-CRT	ESD	Surgery	*P* value
		16	99	220		9	157	207	
Sex	Female	5 (31.2)	39 (39.4)	53 (24.1)	0.02	1 (11.1)	24 (15.3)	61 (29.5)	0.228
	Male	11 (68.8)	60 (60.6)	167 (75.9)		8 (88.9)	133 (84.7)	146 (70.5)	
Age	< 60	11 (68.8)	44 (44.4)	79 (35.9)	0.02	8 (88.9)	102 (65.0)	29 (38.2)	0.17
	≥ 60	5 (31.2)	55 (55.6)	141 (64.1)		1 (11.1)	55 (35.0)	128 (61.8)	
Tumor location	Cervical	0	3 (3.0)	0	< 0.001	0	1 (0.6)	0	0.047
	Upper thoracic	4 (25.0)	13 (13.1)	14 (6.4)		0	5 (3.2)	12 (5.8)	
	Middle thoracic	4 (25.0)	42 (42.4)	111 (50.5)		1 (10.5)	27 (17.2)	99 (47.8)	
	Lower thoracic	5 (31.2)	39 (39.4)	87 (39.5)		7 (77.4)	121 (77.1)	87 (42.0)	
	Multiple sources	3 (18.8)	2 (2.0)	8 (3.6)		1 (8.5)	4 (2.5)	9 (4.4)	
Tumor's longest diameter in cm	< 3	5 (31.2)	66 (66.7)	93 (42.3)	< 0.001	1 (11.1)	31 (19.7)	93 (44.9)	0.077
	≥ 3	11 (68.8)	33 (33.3)	127 (57.7)		8 (88.9)	126 (80.3)	114 (55.1)	
Circumference ratio	< 3/4	12 (75.0)	97 (98.0)	178 (80.9)	< 0.001	8 (88.9)	136 (86.6)	176 (85.0)	0.902
	≥ 3/4	4 (25.0)	2 (2.0)	42 (19.1)		1 (11.1)	21 (13.4)	31 (15.0)	
Depth of infiltration	M1	4 (25.0)	87 (87.9)	49 (22.3)	< 0.001	2 (22.2)	59 (37.6)	85 (41.1)	0.072
	M2	2 (12.5)	4 (4.0)	9 (4.1)		6 (66.7)	3 (1.9)	9 (4.3)	
	M3-SM1	2 (12.5)	3 (3.0)	18 (8.2)		0	8 (5.1)	14 (6.8)	
	SM2-3	8 (50.0)	5 (5.1)	144 (65.5)		1 (11.1)	87 (55.4)	99 (47.8)	
Histology	Precancerous	11 (68.8)	89 (89.9)	51 (23.2)	< 0.001	3 (33.3)	61 (38.9)	88 (42.5)	0.422
	Well-differentiated SCC	0	1 (1.0)	7 (3.2)		0	0	5 (2.4)	
	Moderately-differentiated SCC	5 (31.2)	6 (6.1)	108 (49.1)		6 (66.7)	88 (56.1)	77 (37.2)	
	Poorly-differentiated SCC	0	3 (3.0)	54 (24.5)		0	8 (5.0)	37 (17.9)	
R0 resection or CR	No	4 (25.0)	8 (8.1)	147 (66.8)	< 0.001	1 (11.1)	88 (55.9)	101 (48.8)	0.544
	Yes	12 (75.0)	91 (91.9)	73 (33.2)		8 (88.9)	69 (44.1)	106 (51.2)	
Complication	No	9 (56.2)	93 (93.9)	143 (65.0)	< 0.001	7 (77.8)	54 (34.4)	151 (72.9)	0.039
	Yes	7 (43.8)	6 (6.1)	77 (35.0)		2 (22.2)	103 (65.6)	56 (27.1)	
Lymph node metastasis	N0	14 (87.5)	96 (97.0)	196 (89.1)	0.059	9 (100.0)	155 (98.7)	189 (91.3)	0.002
	N1-2	2 (12.5)	3 (3.0)	24 (10.9)		0	2 (1.3)	18 (8.7)	

Data are *n* (%). CR: Complete response; d-CRT: Definitive chemoradiotherapy; ESD: Endoscopic submucosal dissection; IPTW: Inverse probability of treatment weighting; M1: Epithelium; M2: Lamina propria mucosa; M3: Muscularis mucosae; SCC: Squamous cell carcinoma; SM: Submucosa.

not achieve CR. Our study showed that the rates of CR and severe complications for patients who received d-CRT were 75.0% and 43.8%, respectively, a relatively lower curative rate and higher complication rate than ESD and surgery. Those factors were perhaps associated with the significant difference in 3-year OS and RFS between the ESD, surgery and d-CRT groups.

Besides, the severe complications were similar among patients treated by these therapies. But we found that esophageal stricture was the major complication of the three treatment methods. Several previous studies have shown that the circumferential extent of the tumor and infiltration depth were independent risk factors for esophageal stricture [17-19]. Currently, clinical measures for the prevention and treatment of postoperative esophageal stenosis include esophageal dilatation, esophageal stent placement, mucosal injection or oral steroid hormone[20-22]. Meanwhile, some

Table 2 Complications before and after inverse probability of treatment weighting adjustment of patients treated by endoscopic submucosal dissection, surgery and definitive chemoradiotherapy

Complication		Unmatched				IPTW			
		d-CRT	ESD	Surgery	*P* value	d-CRT	ESD	Surgery	*P* value
		16	99	220		9	157	207	
Radiation pneumonitis	No	15 (93.8)	99 (100.0)	220 (100.0)	< 0.001	9 (100.0)	157 (100.0)	207 (100.0)	0.783
	Yes	1 (6.2)	0	0		0	0	0	
Aphonia	No	16 (100.0)	99 (100.0)	218 (99.1)	0.591	9 (100.0)	157 (100.0)	206 (99.5)	0.745
	Yes	0	0	2 (0.9)		0	0	1 (0.5)	
Pneumothorax	No	16 (100.0)	99 (100.0)	214 (97.3)	0.203	9 (100.0)	157 (100.0)	203 (98.1)	0.537
	Yes	0	0	6 (2.7)		0	0	4 (1.9)	
Dysphagia	No	15 (93.8)	99 (100.0)	219 (99.5)	0.01	9 (100.0)	157 (100.0)	206 (99.5)	0.439
	Yes	1 (6.2)	0	1 (0.5)		0	0	1 (0.5)	
Anastomotic ulcer	No	16 (100.0)	99 (100.0)	215 (97.7)	0.265	9 (100.0)	157 (100.0)	204 (98.5)	0.58
	Yes	0	0	5 (2.3)		0	0	3 (1.5)	
Pulmonary infection	No	16 (100.0)	99 (100.0)	206 (93.6)	0.022	9 (100.0)	157 (100.0)	197 (95.2)	0.308
	Yes	0	0	14 (6.4)		0	0	10 (4.8)	
Anastomotic fistula	No	16 (100.0)	99 (100.0)	192 (87.3)	< 0.001	9 (100.0)	157 (100.0)	187 (90.3)	0.133
	Yes	0	0	28 (12.7)		0	0	20 (9.7)	
Anastomotic or esophageal stenosis	No	13 (81.2)	95 (96.0)	181 (82.3)	0.004	9 (100.0)	132 (84.1)	178 (86.0)	0.734
	Yes	3 (18.8)	4 (4.0)	39 (17.7)		0	25 (15.9)	29 (14.0)	
MOF	No	16 (100.0)	99 (100.0)	213 (96.8)	0.154	9 (100.0)	157 (100.0)	202 (97.6)	0.489
	Yes	0	0	7 (3.2)		0	0	5 (2.4)	

Data are *n* (%). d-CRT: Definitive chemoradiotherapy; ESD: Endoscopic submucosal dissection; IPTW: Inverse probability of treatment weighting; MOF: Multiple organ failure.

Table 3 Incidence of hospitalization costs and salvage treatments after recurrence or metastasis before inverse probability of treatment weighting adjustment

Parameter	ESD, *n* = 98	Surgery, *n* = 220	d-CRT, *n* = 16
Follow up time	40.0 (35.0-48.0)	43.0 (34.0-53.75)	32.5 (28.3-40.0)
Total cost	25	100	130
Death toll	1 (1.0)	19 (8.6)	3 (18.8)
Recurrence	4 (4.0)	3 8(17.3)	4 (25.0)
Salvage measures after recurrence or metastasis	Surgery (*n* = 3)	Surgery (*n* = 5)	Neoadjuvant chemo-radiotherapy (*n* = 1)
	No treatment (*n* = 1)	Neoadjuvant radiotherapy (*n* = 4)	
		Neoadjuvant chemotherapy (*n* = 8)	
		Neoadjuvant chemo-radiotherapy (*n* = 15)	
		No treatment (*n* = 7)	

Data are *n* (%). d-CRT: Definitive chemoradiotherapy; ESD: Endoscopic submucosal dissection.

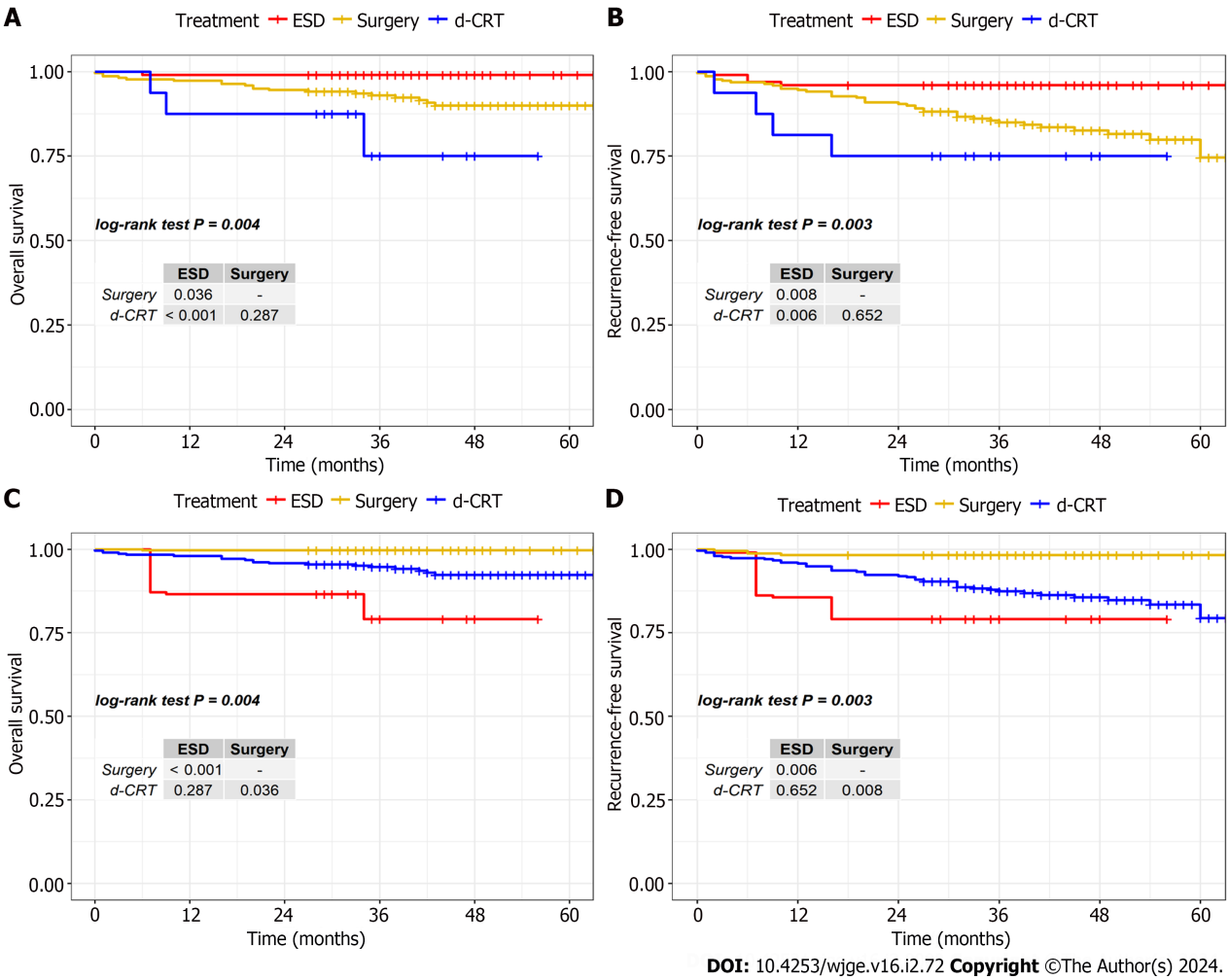

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Figure 1 Overall survival and recurrence-free survival of endoscopic submucosal dissection, surgery and definitive chemoradiotherapy before and after inverse probability of treatment weighting analysis. The small table in the figure represents the results obtained from a two-by-two comparison of the survival rates of the three groups. A: Survival curves of overall survival (OS) for patients before inverse probability of treatment weighting (IPTW) adjustment; B: Survival curves of recurrence-free survival (RFS) for patients before IPTW adjustment; C: Survival curves of OS for patients after IPTW adjustment; D: Survival curves of RFS for patients after IPTW adjustment. d-CRT: Definitive chemoradiotherapy; ESD: Endoscopic submucosal dissection. *P* value was calculated by the log-rank test.

novel techniques are being investigated by other scholars[23,24]. However, the effectiveness of these methods requires more clinical evidence and there is no ideal therapy in current clinical practice, so we are also conducting relevant research on this aspect.

By comparing the efficiency and complication rate between ESD, surgery and d-CRT, we summarize the experience of our center: for early EC with infiltration to M1 or M2, no lymph node metastasis, no distant metastasis, and circumferential extent of tumor < 3/4, ESD was the preferred therapy. In particular, for patients with cervical or upper thoracic esophageal carcinoma, ESD is better than surgery. d-CRT should be attempted for patients who are of advanced age, frail, contraindicated to surgery and have an upper and circumferential extent of ≥ 3/4.

In this study, we firstly conducted a retrospective study with a large sample size to compare the efficacy of early EC treated with ESD, surgery and d-CRT, providing some useful suggestions. However, there are some limitations in our study. First, the sample size of our study was still not large enough, especially because the number of patients in the d-CRT group was insufficient. Second, the study was a single-center retrospective study, which has considerable limitations. Last, the data were obtained mainly from the medical records and follow-up, so there was a certain rate of missing visits and missing data. Therefore, multicenter prospective studies with larger sample sizes or randomized controlled studies are needed to supplement the evidence of our study.

CONCLUSION

This is a first retrospective study to compare OS, RFS and complications of ESD, surgery and d-CRT. In this study, we found that ESD attained better survival benefits and lower hospitalization costs than surgery and d-CRT, and they had similar complications rates. This study provides a more comprehensive analysis of the efficacy and safety of current

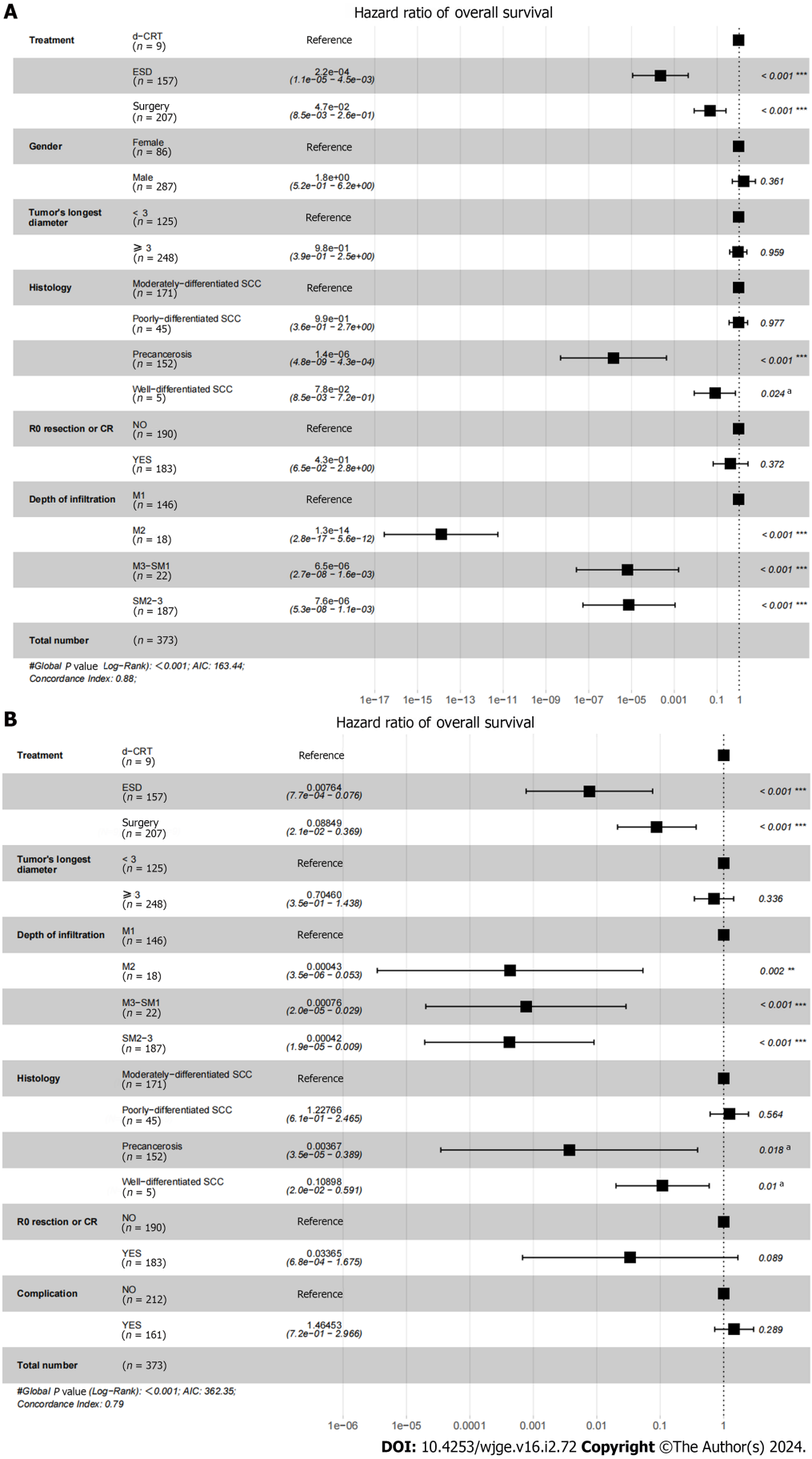

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Figure 2 Cox regression estimates of overall survival and recurrence-free survival after inverse probability of treatment weighting

analysis among patients with cT1N0M0 EC who underwent endoscopic submucosal dissection, surgery and definitive chemoradiotherapy. A: Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with overall survival; B: Multivariate analysis showed that treatment method, histology and depth of infiltration were independently associated with recurrence-free survival (RFS). CR: Complete response. (*) represents the significant difference, and the more the number of "a", the greater the difference.

cT1N0M0 EC treatment patterns and provides new evidence for the use of ESD in cT1N0M0 EC.

ARTICLE HIGHLIGHTS

Research background

For cT1N0M0 esophageal cancer (EC), the current study has mainly focused on surgery and endoscopic submucosal dissection (ESD), while definitive chemoradiotherapy (d-CRT) is a complementary treatment for cT1N0M0 EC. Studies on estimating the therapeutic effect and safety of d-CRT, surgery and ESD are not sufficient, so this study is important.

Research motivation

Early-stage EC is currently increasing year by year, and its treatment methods are also changing rapidly. It is very important to choose the treatment methods with good prognosis and fewer complications, while some patients have the dilemma of treatment choice due to age, cost and other reasons. It is very important to summarize and compare the advantages and disadvantages of the existing treatment methods, which is very important for the health management of patients with EC.

Research objectives

By comparing the efficiency and safety of ESD, surgery and d-CRT for cT1N0M0 EC, to provide a clinical basis for the treatment selection of cT1N0M0 EC and to achieve better prognosis and quality of survival for EC.

Research methods

We retrospectively analyzed the medical records, pathology, imaging and endoscopic findings, and follow-up results of the cT1N0M0 EC. We met the inclusion criteria and adjusted the effects of confounding factors using the inverse probability of treatment weighting method to conduct survival analysis, Cox proportional risk regression analysis, collected complications and costs, rescue measures after recurrence, and finally evaluated the efficacy and safety of cT1N0M0 EC patients receiving ESD, surgery and d-CRT.

Research results

Results showed that ESD had better survival outcomes, lower hospital costs and more acceptable occurrences of complications. This study provides a more comprehensive analysis of the efficacy and safety of current cT1N0M0 EC treatment patterns and provides new evidence for the use of ESD in cT1N0M0 EC. To our knowledge, our study is the first to compare the effects of all three treatments for cT1N0M0 EC. In addition, there are relatively few studies on d-CRT for cT1N0M0 EC patients, and our study can provide relevant evidence of d-CRT for cT1N0M0 EC, so it has a certain new innovation.

Research conclusions

This is a first retrospective study to compare overall survival, recurrence-free survival and complication rates of ESD, surgery and d-CRT, and show that ESD attained better survival benefits and lower hospitalization costs than surgery and d-CRT, and they had similar complication rates. This study provides a more comprehensive analysis of the efficacy and safety of current cT1N0M0 EC treatment patterns and provides new evidence for the use of ESD in cT1N0M0 EC.

Research perspectives

In the future, we will conduct a subgroup analysis of survival outcomes for the three therapies in cT1N0M0 EC patients, and investigate methods to reduce the occurrence of complications.

FOOTNOTES

Co-first authors: Shu-Ai Luo and Yu-Ying Sun.

Author contributions: Huang CY designed and performed the research and supervised the report; Luo SA performed the research, collected the data, wrote the paper and contributed to the analysis; Sun YY supervised the report, wrote the paper and revised the paper; Zeng YT contributed to the analysis and provided clinical advice. Luo SA and Sun YY have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Sun Yat-sen University Cancer Center.

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Data sharing statement: The raw data used to support the findings of this study could be obtained by getting in touch with the corresponding author.

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ORIGINAL ARTICLE

Clinical Trials Study

Coca-Cola consumption *vs* fragmentation in the management of patients with phytobezoars: A prospective randomized controlled trial

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Abstract

BACKGROUND

Gastric phytobezoars (GPBs) are very common in northern China. Combined therapy involving carbonated beverage consumption and endoscopic lithotripsy has been shown to be effective and safe. Existing studies on this subject are often case reports highlighting the successful dissolution of phytobezoars through Coca-Cola consumption. Consequently, large-scale prospective investigations in this domain remain scarce. Therefore, we conducted a randomized controlled trial to examine the effects of Coca-Cola consumption on GPBs.

AIM

To evaluate the impact of Coca-Cola on GPBs, including the dissolution rate, medical expenses, ulcer rate, and operation time.

METHODS

A total of 160 consecutive patients diagnosed with GPBs were allocated into two groups (a control group and an intervention group) through computer-generated randomization. Patients in the intervention group received a Coca-Cola-based regimen (Coca-Cola 2000-4000 mL per day for 7 d), while those in the control group underwent emergency fragmentation.

RESULTS

Complete dissolution of GPBs was achieved in 100% of the patients in the intervention group. The disparity in expenses between the control group and intervention group (t = 25.791, P = 0.000) was statistically significant, and the difference in gastric ulcer occurrence between the control group and intervention

group (χ^2 = 6.181, P = 0.013) was also statistically significant.

CONCLUSION
Timely ingestion of Coca-Cola yields significant benefits, including a complete dissolution rate of 100%, a low incidence of gastric ulcers, no need for fragmentation and reduced expenses.

Key Words: Coca-Cola; Bezoars; Solubility; Lithotripsy; Gastroscopy

Core Tip: The timely and sufficient ingestion of Coca-Cola by patients with phytobezoars yields significant benefits, including a high rate of complete dissolution, a low incidence of gastric ulcers, no need for surgery, and reduced medical expenses.

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INTRODUCTION

Gastric bezoars are defined as foreign objects that develop within the gastrointestinal tract due to the accumulation of ingested material[1]. Specifically, gastric phytobezoars (GPBs) were consisted of indigestible cellulose, tannin, and lignin derived from the consumption of persimmons, hawthorn fruits, or date plum persimmons. Tannin undergoes polymerization, resulting in a coagulum that includes protein, pepsins, cellulose, and hemicellulose, forming bezoars[2]. In recent years, a combined therapy approach involving litholysis with carbonated beverages and endoscopic lithotripsy has emerged as an effective and safe treatment for GPBs[3]. However, despite the excellent outcomes, this therapeutic approach causes significant discomfort and has high costs and a prolonged operation time[4]. Notably, in 2013, Ladas *et al*[5] proposed the consumption of Coca-Cola as a first-line treatment option, highlighting its ability to effectively dissolve GPBs. Coca-Cola consumption has been recognized as a particularly safe, cost-effective, and well-tolerated intervention [6]. While case reports documenting the successful dissolution of phytobezoars exist, large-scale clinical studies in this domain are scarce. Therefore, we conducted a randomized controlled trial to evaluate the impact of Coca-Cola consumption on GPBs, including the dissolution rate, medical expenses, ulcer rate, and operation time.

MATERIALS AND METHODS

Study design and sample estimation

This meticulously designed study followed a prospective, single-blinded approach with balanced randomization at a 1:1 ratio. Ethical approval for the study was obtained from the Institutional Review Board of the Affiliated Hospital of Qingdao University (QYFYWZLL 26293), and the study was registered in the ClinicalTrial.gov Protocol Registration System with the registration number NCT05645263. The study was conducted at the Affiliated Hospital of Qingdao University from January 1st, 2018, to December 1st, 2022. All participants who expressed willingness to take part in the study provided digital informed consent. The study strictly adhered to the principles outlined in the World Medical Association Declaration of Helsinki.

The sample size was calculated using the following website: http://riskcalc.org:3838/samplesize/. Ultimately, a total of 160 patients (2 arms) were enrolled in the study and randomly allocated to the control or intervention group at a 1:1 ratio.

Participants

The study employed specific inclusion and exclusion criteria to ensure the selection of appropriate participants. The inclusion criteria encompassed the absence of contraindications (such as severe heart diseases, suspected shock, or digestive tract perforation), suspected mental diseases, or infectious diseases of the digestive tract that could hinder gastroscopy. Additionally, participants were required to have a bezoar history of no more than 14 d, no history of peptic ulcer diseases and an age range between 14 and 80 years. The exclusion criteria comprised individuals who had history of upper gastrointestinal surgery, underwent previous therapies before enrollment or individuals who did not consent to random allocation.

Equipment and consumables

The following instruments and materials were used in this study: CV-290 (Olympus Co. Ltd), GIF-Q260J (Olympus Co. Ltd), the WF-DTH fragmentation kit (Wilson Shanghai Co. Ltd), disposable snares (Micro-Tech Nanjing Co. Ltd), and Coca-Cola.

Method

A total of 160 consecutive patients were enrolled in the study by doctors in the outpatient department and randomly assigned at a 1:1 ratio to either the control group, which underwent emergency fragmentation with gastroscopy, or the intervention group, which consumed Coca-Cola in the endoscopy center. The enrollment period spanned from January 1, 2018, to December 1, 2022. Randomization was conducted by the investigator using a web-based computer-generated random number system (www.randomization.com). In the intervention group, patients consumed Coca-Cola to treat GPBs. The amount consumed was 250 mL-500 mL every 2 h until bedtime, tailored to individual health conditions and lifestyle habits. Close attention was given to the patients' bowel movements to assess the excretion of bezoars (which are usually harder than normal stool and not scattered by flushing water). The duration of Coca-Cola ingestion was 7 d for the intervention group. Upon completion of the Coca-Cola therapy, patients underwent another endoscopy because endoscopy can observe the mucosa of the stomach directly and further intervention if fragmentation was necessary. The endoscopist recorded all images for every patient. The volume of GPBs was estimated under endoscopy and the evaluation for gastric ulcer was performed in the first endoscopy. Prior to endoscopy, all patients provided digital informed consent.

Statistical analysis was performed using SPSS version 22 (IBM, Inc. Armonk, NY, United States). Continuous variables are presented as the mean and standard deviation (SD). Independent samples *t* test was utilized for continuous variable analysis. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A significance level of $P < 0.05$ was considered statistically meaningful.

RESULTS

The CONSORT 2010 Flow Diagram is illustrated in Figure 1. Atypical images pertaining to the study findings are shown in Figures 2 and 3. The images of Figures 2 and 3 are all from the intervention group. The patient in Figure 2 has a GPB history of 7 d and the patient in Figure 3 has a GBPs history of 14 d. The former 2 images of Figure 2 shows the GPBs in the stomach and an ulcer which is shallow and bleeding located in the angulus in the first endoscopy and the last image shows nothing anomaly except the ulcer in the second endoscopy after Coca-Cola therapy. The former 2 images of Figure 3 shows the GPBs in the stomach and a deep ulcer located in the angulus in the first endoscopy and the last image shows nothing anomaly except the shallower ulcer in the second endoscopy after Coca-Cola therapy.

General data

Data on age, bezoar volume and medical expenses are presented in Table 1. There were no statistically significant differences in age or bezoar volume between the 2 groups, but there was a significant difference in medical expenses.

Dissolution rate

Remarkably, a complete dissolution rate of 100% was achieved in the intervention group, highlighting the effectiveness of the intervention in treating GPBs.

Medical expenses

Table 1 provides information regarding the medical expenses incurred during the study. The statistical analysis revealed significant differences in the medical expenses between the control and intervention groups (1540.01 ± 250.81 RMB *vs* 27.59 ± 7.96 RMB, $t = 25.971$, $P = 0.000$).

Operation time

The gastric fragmentation time of the control group was 31.23 ± 9.62 min; however, no patients had gastric fragmentation in the intervention group.

Gastric ulcer rate

Information on the occurrence of gastric ulcers between the control and intervention groups is presented in Table 2. The rate of gastric ulcer occurrence was 86.25% in the control group and 70.0% in the intervention group. Notably, a statistically significant difference was observed between the control group and intervention group in terms of gastric ulcer occurrence ($\chi^2 = 6.181$, $P = 0.021$). The results shed light on the varying rates of gastric ulcer occurrence associated with different treatment approaches.

DISCUSSION

GPBs often arise from the ingestion of persimmons, hawthorn fruits, or date plums on an empty stomach. They can also

Table 1 Comparisons between the control group and intervention group

Group	*n*	Age (yr)	Volume of bezoar (cm × cm)	Expenses (RMB)
Control group	80	53.80 ± 11.76	18.07 ± 8.16	1540.01 ± 520.381
Intervention group	80	50.79 ± 12.95	18.38 ± 8.31	27.59 ± 7.96
t value		1.54	-0.233	25.791
P value		0.327	0.487	0.000

Table 2 Comparison of the gastric ulcer rate between the control group and intervention group

Group	*n*	Ulcer	No ulcer	χ^2	*P* value
Control group	80	69	11	6.181	0.013
Intervention group	80	56	24		

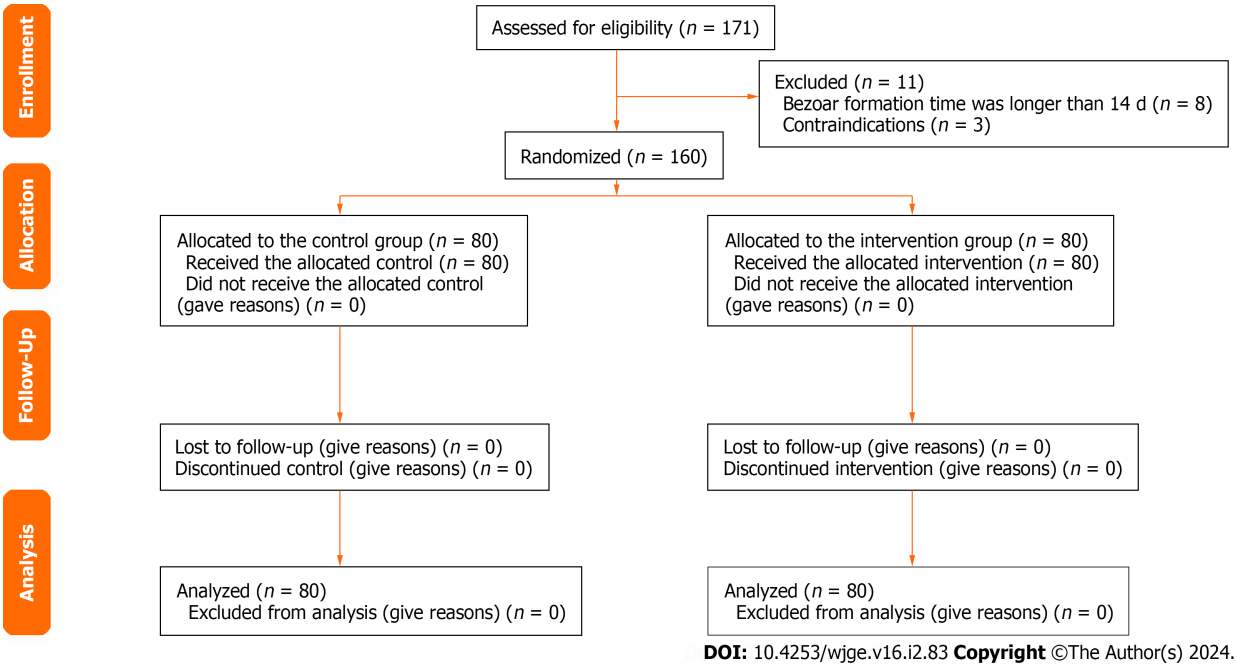

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Figure 1 CONSORT 2010 flow diagram.

be associated with conditions such as diabetic gastroparesis[7] and endoscopic sclerotherapy, which can lead to delayed gastric emptying[8,9]. In the present study[10], patients were successfully treated using a combination of endoscopic fragmentation and pharmacotherapy. While this combined therapy has been indicated to be effective, it involves high costs, discomfort, and long operation time.

A significant milestone in the use of Coca-Cola for phytobezoar treatment was the publication of the article "Gastric phytobezoars may be treated by nasogastric cola lavage" in 2002 by Ladas *et al*[11]. This study documented complete success in the treatment of five phytobezoar patients using Coca-Cola lavage. In a systematic review conducted by Ladas *et al*[5] in 2013, it was concluded that Coca-Cola can effectively dissolve GPBs and could be considered a first-line treatment option, with a complete dissolution rate of 50% and a favorable outcome observed in 91.3% of patients. It has been reported that the consumption of 3 Liters of Coca-Cola every 12 h has a satisfactory effect on bezoar lysis[5,12,13]. Our study demonstrated a complete phytobezoar dissolution rate of 100%, which aligns with previous findings.

The article "In Vitro Analysis of Gastric Phytobezoar Dissolubility by Cola, Cola Zero, Cellulose and Papain" reported that Coca-Cola exhibited the highest phytolytic activity, with an 18.5% ± 5.8% decrease in weight, while Coke Zero also demonstrated substantial phytolytic action (16.1% ± 0.4%). In patients who consumed carbonated beverages, bezoars were easily broken when grasped with forceps, which was not observed in patients who consumed water, cellulose or papain. These findings provide scientific evidence supporting the efficacy of Coca-Cola in bezoar lysis[14]. Although the exact mechanism of the dissolution of bezoars by Coca-Cola has not been fully explained, it may be attributed to the low acidity. The pH of Coca-Cola is 1.9, which is more acidic than that of 0.010 mol/L hydrochloric acid (pH 2.0). Furthermore, the pH of Coca-Cola remains relatively stable (2.0) even after 3 h of exposure to room air[12]. The dissolution effect

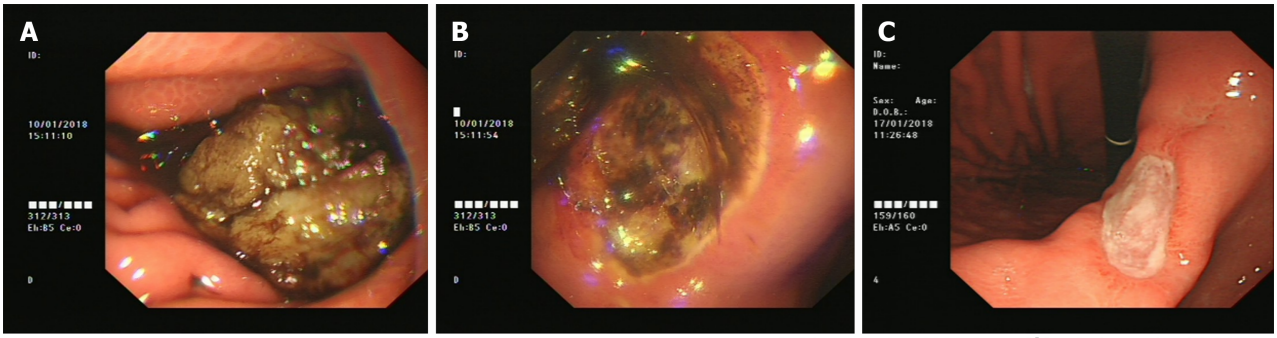

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Figure 2 Image of gastric phytobezoars in a patient with a gastric phytobezoars history of 7 d. A: Gastric phytobezoars (GPBs) located in the stomach; B: The gastric ulcer, which is shallow and bleeding located in the angulus of the stomach; C: No GPBs or bleeding in the stomach was observed after Coca-Cola therapy.

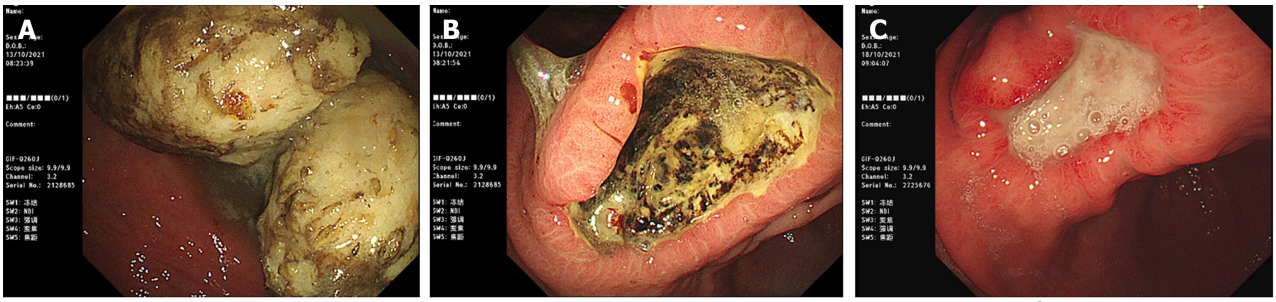

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Figure 3 Image of gastric phytobezoars in another patient with a gastric phytobezoars history of 14 d. A: Gastric phytobezoars (GPBs) located in the stomach; B: A deep gastric ulcer is located in the angulus of the stomach; C: No GPBs was observed and the gastric ulcer became smaller and shallower after Coca-Cola therapy.

of Coca-Cola on bezoars may be attributed to carbonic and phosphoric acids, which are believed to be important for fiber digestion[7,12,13,15]. Acetic acid (CH_3COOH) reacts with calcium phosphate to form calcium acetate [$Ca(CH_3COO)_2$][2] and phosphoric acid, both of which are water-soluble[16]. Additionally, the mucolytic effect of $NaHCO_3$ and the presence of CO_2 bubbles may contribute to the mechanism of dissolution[12]. The consumption of a large volume of Coca-Cola can enhance gastrointestinal motility, leading to the rapid decomposition and elimination of phytobezoars. "Cola lysis" serves as a clinically appropriate term to describe the mechanism of phytobezoar dissolution, signifying the dissolution and lysis of the accumulated mass[7].

In terms of adverse effects, short-term Coca-Cola therapy may cause temporary bloating, reflux, and gastritis. However, the long-term use of Coca-Cola can lead to tooth decay and osteoporosis[17,18]. These issues should be taken into account when utilizing Coca-Cola as a therapeutic intervention for GPBs. The participants in our study had no obvious side effects because of the short regimen.

Intestinal obstructions caused by phytobezoars are a rare occurrence in adults with normally functioning intestinal tracts[19]. However, in cases where ileus is present or when patients have refractory bezoars, surgical removal becomes necessary[20]. Avoiding severe complications associated with phytobezoars poses a challenge for medical professionals. Partially dissolved bezoars have the potential to pass through the pylorus and obstruct the small bowel, particularly in the presence of ankylosis, enterostasis, or poor gastric motility[13,21-27]. Therefore, it is crucial for patients receiving Coca-Cola therapy to be vigilant about their stool and monitor symptoms of ileus. Once a patient is confident that the bezoar has been discharged in the stool, they can discontinue the Coca-Cola diet to prevent small bowel obstruction. The duration of Coca-Cola consumption can be prolonged as necessary without any set limitations. Additionally, a low-fiber diet during Coca-Cola therapy is recommended to support the treatment process.

GPBs as foreign bodies located in the stomach, can cause mechanical friction and/or compression, leading to erosion, ulceration, or bleeding of the gastric mucosa[2]. The incidence of gastric ulcers associated with phytobezoars is approximately 80%[28]. The presence of a gastric bezoar can result in gastric mucosal injury, but as the bezoar dissolves, the gastric mucosa becomes less affected. In our study, the gastric ulcer occurrence rate in the intervention group (70.00%) was lower than that in the control group (86.25%). This lower rate of gastric ulcers in the intervention group may be attributed to the consumption of Coca-Cola. Coca-Cola softens bezoars[29], and the gastric mucosa becomes less irritated once bezoars are softened. Gastric ulcers can manifest as single or multiple lesions located in various regions of the stomach, including the angulus, body, or antrum. The overall occurrence of gastric ulcers in our study was 78.13%, which aligns with previous findings. The timely administration of Coca-Cola appears to yield better outcomes, as the occurrence rate of gastric ulcers decreases with the dissolution of bezoars.

CONCLUSION

Treating GPBs with Coca-Cola consumption offers a practical, cost-effective, and effective approach. Patients with GPBs should consume Coca-Cola at the earliest opportunity to minimize the occurrence of gastric ulcers, making it a routine practice in clinical settings. However, the optimal dosage and duration of Coca-Cola ingestion for treating GPBs have not been definitively established through large-scale experimental studies. Therefore, further extensive research is warranted to investigate and establish guidelines regarding the appropriate dose and duration of Coca-Cola consumption in the treatment of GPBs.

ARTICLE HIGHLIGHTS

Research background

With the publication of Ladas SD's article (Systematic review: Coca-Cola can effectively dissolve gastric phetobezoars as a first-line treatment), Coca-Cola dissolution therapy in patients with gastric phytobezoars (GPBs) is gradually being accepted in clinical practice. However, existing studies on this subject are often case reports highlighting the successful dissolution of phytobezoars using Coca-Cola. Consequently, large-scale prospective investigations in this domain remain scarce. Therefore, we conducted a randomized controlled trial to examine the effects of Coca-Cola administration on GPBs.

Research motivation

This study evaluated the intervention treatment of patients with Coca-Cola dissolution therapy, including the complete resolution rate, gastric ulcer rate, medical expenses and endoscopic operation time. Additionally, this study aimed to find a treatment plan that can attain the expected results and minimize the side effects.

Research objectives

The aim was to evaluate the impact of Coca-Cola on GPBs, including the dissolution rate, medical expenses, ulcer rate, and operation time.

Research methods

In this study, a total of 160 consecutive patients diagnosed with GPBs were allocated into two groups (a control group and an intervention group) through computer-generated randomization. Patients in the intervention group were receive a Coca-Cola-based regimen (Coca-Cola 2000-4000 mL per day for 7 d), while those in the control group underwent emergency fragmentation.

Research results

Complete dissolution of GPBs was achieved in 100% of the patients in the intervention group. The disparity in expenses between the control group and intervention group (t = 25.791, P = 0.000) was statistically significant, and the difference in the gastric ulcer occurrence rate between the control group and intervention group (χ^2 = 6.181, P = 0.013) was also statistically significant.

Research conclusions

Timely ingestion of Coca-Cola yields significant benefits, including a complete dissolution rate of 100%, a low incidence of gastric ulcers, no need for fragmentation and reduced expenses.

Research perspectives

This treatment is beneficial for relieving patients' pain, reducing the need for emergency gastroscopy, decreasing medical expenses and lowering the gastric ulcer rate. Therefore, Coca-Cola dissolution therapy for GPBs is a safe, feasible, simple and effective method that is worthy of clinical application and promotion.

FOOTNOTES

Author contributions: Liu FG designed the study and reviewed the manuscript. Liu Y and Shen X collected the data; Meng DF analyzed the data. Meng D and Zhang LY wrote and drafted the manuscript; all authors have read and approve the final manuscript.

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Clinical trial registration statement: The study was registered in the ClinicalTrial.gov Protocol Registration System, registration No. NCT05645263.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and

medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors declare that they have no conflicts of interest regarding this work.

Data sharing statement: All data available from the corresponding author at zhanglingyun@qdu.edu.cn

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CASE REPORT

Treatment of benign rectal stricture caused by repeated anal insertion by endoscopy and balloon dilation: A case report

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Abstract

BACKGROUND

Benign rectal strictures can be categorized as primary (disease-related) and secondary (surgical anastomosis-related). Secondary strictures arise from surgical complications, whereas primary strictures have diverse etiologies, including various inflammatory conditions. Benign strictures are usually managed by surgery and endoscopy. We present an unusual etiology of benign rectal stricture caused by the repeated insertion of foreign objects into the rectum for sexual purposes, resulting in rectal injury and subsequent chronic inflammation.

CASE SUMMARY

A 53-year-old man presented to the outpatient clinic of the Colorectal Surgery Department with symptoms of chronic constipation and bloody stools. The patient previously experienced rectal injury due to foreign object insertion for sexual purposes. Colonoscopy revealed benign circumferential narrowing of the rectum. He underwent treatment by endoscopic argon plasma coagulation and balloon dilation and follow-up as an outpatient for 4 months. A colonoscopy at the end of the follow-up period revealed no evidence of rectal stricture relapse.

CONCLUSION

A history of rectal injury, followed by chronic inflammation, should be considered in patients with benign rectal strictures. Management with endoscopic argon plasma coagulation and balloon dilation can prevent the need for surgical resection of benign rectal strictures.

Key Words: Chronic rectal inflammation; Colonoscopy; Benign rectal stricture; Foreign body insertion; Rectal injury; Case report

Core Tip: The etiologies of benign rectal stricture are primarily associated with chronic inflammation and post-surgical complications. We describe an unusual etiology caused by repeated insertion of foreign objects into the rectum for sexual purposes, resulting in rectal injury and subsequent chronic inflammation. Initiating treatment with endoscopic management and then considering surgical resection, if unsuccessful, might be the most suitable therapeutic strategy. Endoscopic argon plasma coagulation combined with balloon dilation is beneficial for treating benign rectal stricture.

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INTRODUCTION

Benign strictures of the rectum are classified as primary (disease-related) and secondary (surgical anastomosis-related) [1]. Secondary strictures arise from anastomotic dehiscence or ischemia, stapling devices, postoperative pelvic infections, or postoperative radiation-induced proctitis[2]. Etiological factors of primary strictures include nonsteroidal anti-inflammatory drug use[3], chronic proctitis (prevalent in inflammatory bowel disease)[4], tuberculosis[5], and complicated diverticulitis[6]. These factors primarily affect patients who have undergone recent surgery or have underlying inflammatory diseases. Proctitis is an inflammatory condition that affects the anal canal and/or rectum. It can result from inflammatory bowel disease, infectious proctitis due to sexually transmitted infections through genital-anal mucosal contact, or traumatic proctitis caused by digital contact or the use of foreign objects[7]. Benign strictures are usually managed surgically and endoscopically. However, an optimal approach to treating benign rectal strictures has not been established. We posit that initial endoscopy rather than surgical resection can improve patient satisfaction with more favorable postoperative outcomes. Here we describe a case of a homosexual male with an unusual rectal stricture. Although he denied receptive anal intercourse with men, he inserted toys or household items into the rectum *via* the anal canal for sexual eroticism. The rectum was damaged, chronically inflamed, and constricted. We applied a novel therapeutic approach comprising argon plasma coagulation (APC) and balloon dilation.

CASE PRESENTATION

Chief complaints

A 53-year-old Chinese man presented to the outpatient department of Tri-Service General Hospital, Songsang Branch with bloody stools.

History of present illness

The patient reported experiencing discomfort and difficulty passing stools for approximately 6 months that were not relieved by laxatives. He recalled having persistent anal pain and bleeding for approximately 2 wk after inserting anal toys and household items approximately 1 year before presentation; however, he did not seek medical assistance at that time.

History of past illness

The patient had no history of chronic diseases or surgeries.

Personal and family history

The personal and family history of the patient was unremarkable.

Physical examination

Abdominal and digital rectal findings were not specific.

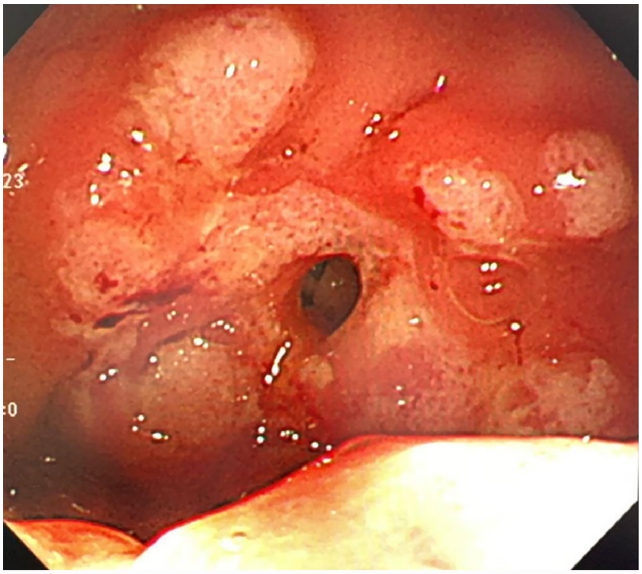

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Figure 1 Colonoscopy shows an apparently benign, circumferential rectal narrowing 6 cm above the anal verge.

Laboratory examinations

Laboratory serum examinations revealed no significant abnormalities.

Imaging examinations

Colonoscopy revealed an apparently benign, circumferential rectal stricture 6 cm above the anal verge (Figure 1) through which the colonoscope could not pass. A biopsy of the stricture revealed adenomatous hyperplasia with fibroblast proliferation.

FINAL DIAGNOSIS

Colonoscopy indicated a benign rectal stricture.

TREATMENT

A colonoscopy with APC for tissue ablation at the stricture edge was performed after the initial diagnosis was confirmed (Figure 2). One week later, balloon dilation using a Foley catheter was performed. The balloon was inflated with 15 mL of water, and the diameter of the inflated balloon was approximately 25 mm. The stenosis improved, as evidenced by the smooth passage of a 25-mm anal dilator (Figure 3). Improvement in the patient's symptoms was limited after 6 wk of follow-up. Therefore, the patient underwent a repeat colonoscopy with APC that achieved complete resolution of luminal narrowing (Figure 4).

OUTCOME AND FOLLOW-UP

No complications developed during the management. Four months after treatment, a repeat colonoscopy revealed no evidence of rectal stricture relapse (Figure 5). The patient's symptoms were completely resolved thereafter.

DISCUSSION

Rectal strictures typically form in an area of muscle that contracts over time and narrows or blocks the intestinal passage. These strictures have various underlying causes and are broadly categorized as benign or malignant. Benign rectal strictures often manifest as the outcome of an inflammatory cascade, leading to the development of hyperplastic scars and tissue fibrosis[8]. They can greatly affect the quality of life of patients, which leads to changes in bowel habits. They sometimes manifest as medical emergencies when they obstruct the bowel.

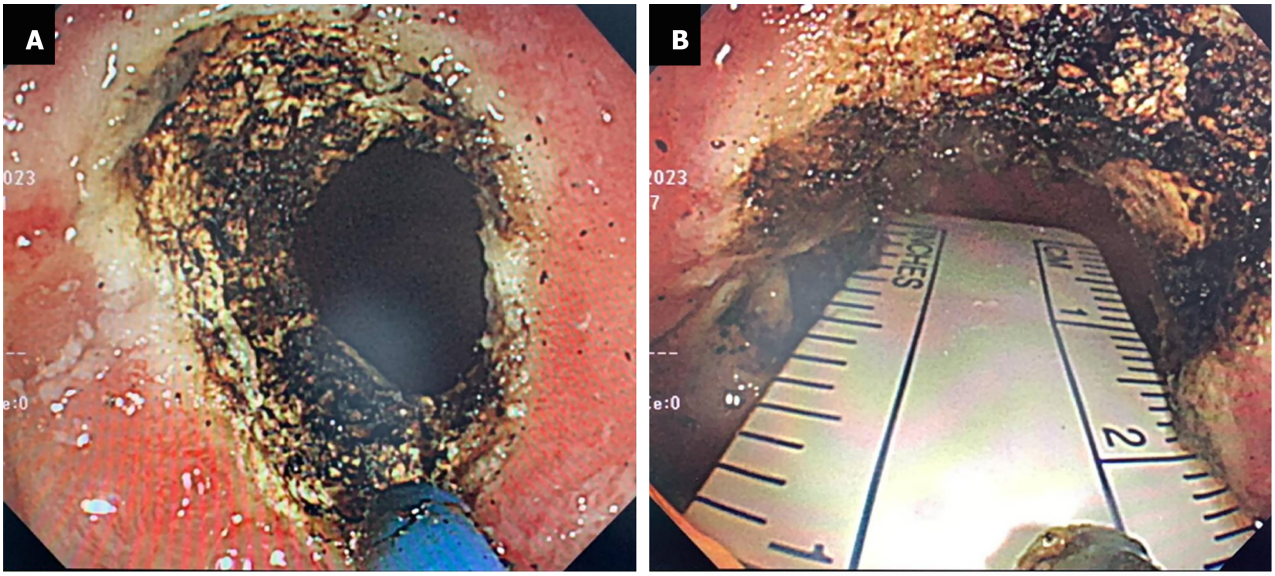

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Figure 2 First endoscopic stricturotomy using argon plasma coagulation. A: Tissue ablation at stricture edge using argon plasma coagulation; B: The diameter of the stricture increased.

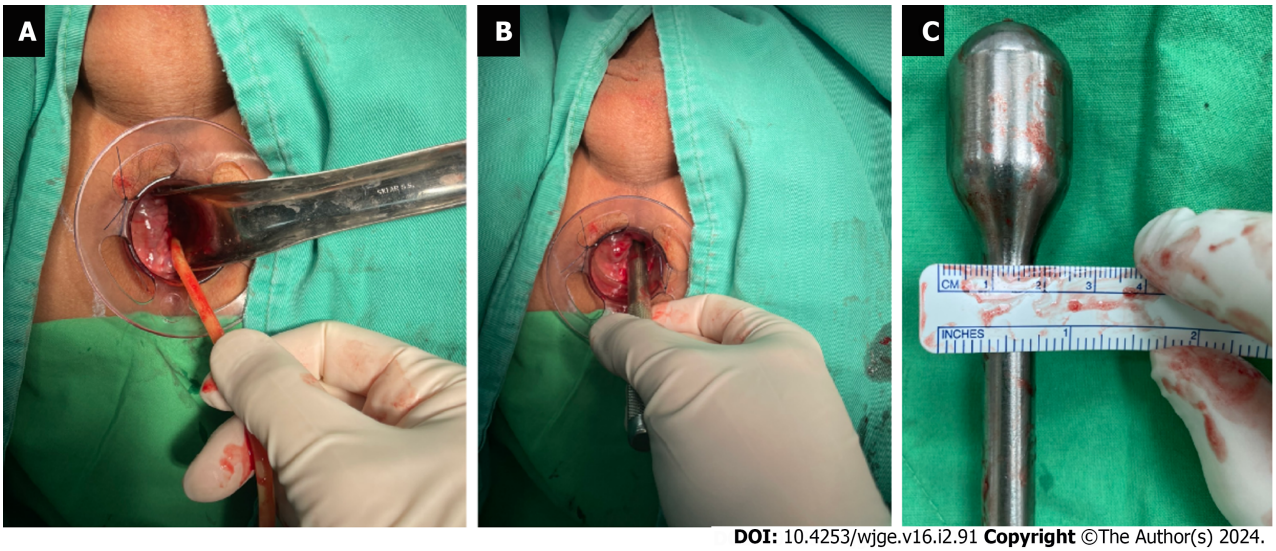

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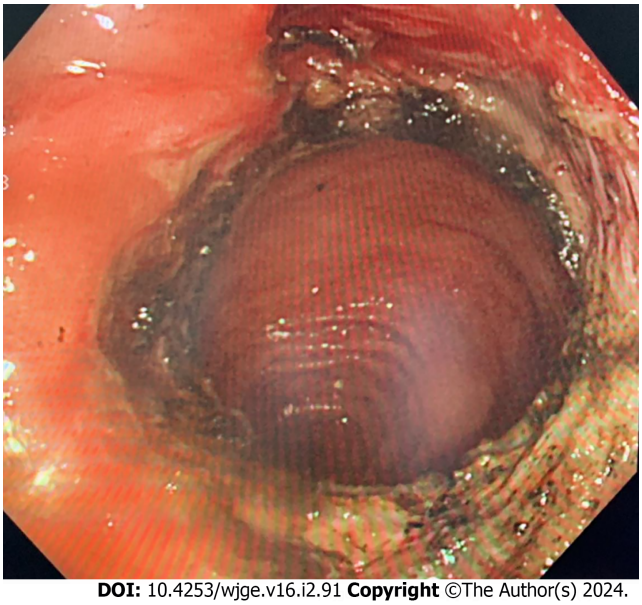
Figure 3 Ballon dilation using Foley catheter. A: Stricture site dilation to 25 mm with Foley balloon (15 mL water); B and C: A 25 mm anal dilator passes through smoothly.

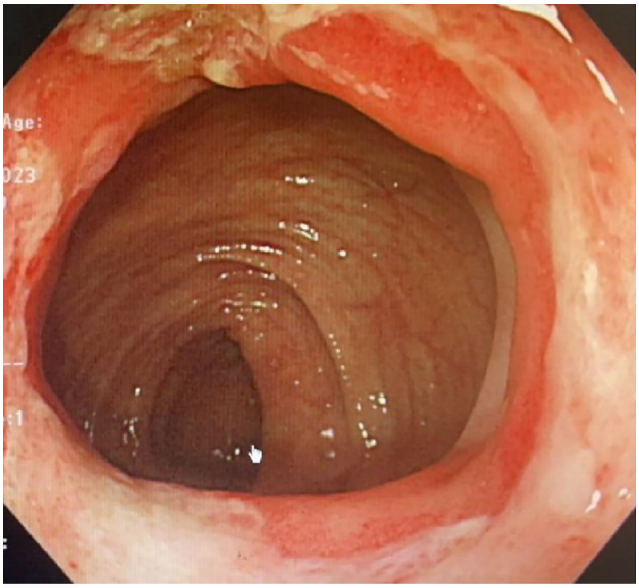
Anastomotic strictures associated with colorectal surgery were ruled out because the patient had not undergone any procedures. He had no history of drug use. Inflammatory bowel disease was unlikely as the patient did not have diarrhea. Endoscopic findings revealed no erosions, ulcers, edema, mucosal granularity, and friability[9]. Although rectal strictures are rarely associated with foreign bodies, one case report has described a rectal stricture caused by a chicken bone that had been retained for two years[10]. Rectal stricture can result from chronic inflammation caused by foreign body insertion. We inferred that repeated insertion of a foreign body over the long term caused the rectal injury in this patient. Rectal strictures can also occur due to burn injuries associated with hot water or coffee enemas[11,12]. All these causes similarly indicate that rectal injury can lead to strictures because of chronic inflammation. To the best of our knowledge, similar reports of rectal stricture caused by repeated foreign object insertion have not been published in the literature.

Various therapeutic approaches include the mechanical dilation of rectal strictures, electrocautery, manual widening, transanal mechanical stapling devices, endoscopic, and surgical methods[13]. Surgical procedures, such as resection and stricturoplasty, are more efficient than endoscopic approaches in addressing colorectal strictures. However, surgical resection and stricturoplasty are linked to a notably higher incidence of postoperative complications, which can require further diverting stoma and a greater likelihood of stricture recurrence[14,15]. Endoscopic methods such as implanted stents, electrocautery incision, balloon dilation, or combined management, are minimally invasive, simple procedures



DOI: 10.4253/wjge.v16.i2.91

Figure 4 Second endoscopic stricturotomy with argon plasma coagulation. Complete resolution of the rectal stricture.



DOI: 10.4253/wjge.v16.i2.91

Figure 5 Follow-up colonoscopy after endoscopic treatment. The luminal narrowing resolved completely without evidence of recurrent rectal stricture four months after the endoscopic treatment.

that can delay the need for surgery by an average of 6.5 years[16].

We avoided surgical resection for our patient because incontinence, frequency, and urgency, which are collectively described as low anterior resection syndrome would have adversely affected his quality of life[17]. The resolution of one issue would lead to the development of another. Stent placement was not selected because this can lead to complications over the long term such as stent dislodgment and obstruction due to fecal impaction[18]. We applied radial incisions using endoscopic electrocautery with APC to ensure that hyperplastic tissues were thoroughly cleaned within the incisions. An APC technique for benign colorectal strictures has been established[19]. The success rate of balloon dilation to treat surgical anastomotic and inflammatory disease-related strictures is approximately 97% and the incidence (< 3%) of major complications is low[20]. We used a Foley balloon instead of an endoscopic balloon because of the short length of the stricture. The Foley balloon could adequately cover the narrow area, which was close to the anus. Although recommendations for managing benign colorectal strictures have not been officially established, the outcome of treating our patient with APC combined with balloon dilation was successful. Nonetheless, long-term and regular colonoscopic surveillance is critically important to assess recurrence in patients with rectal strictures.

CONCLUSION

Benign rectal strictures are primarily associated with chronic inflammation and postoperative complications. Our patient had an unusual etiology that developed from the prolonged insertion of foreign objects into the rectum for pleasure, resulting in rectal injury and subsequent chronic inflammation. A standardized approach to treating this type of benign rectal stricture has not been established. However, initiating treatment with endoscopy and considering surgery if unsuccessful might be the most suitable strategy under such circumstances. We treated the rectal stricture using endoscopic APC in combination with balloon dilation, which avoided surgical resection of the rectum.

FOOTNOTES

Author contributions: Liu SH and Kang JC drafted the manuscript; TW Pu revised the final draft of the manuscript; Lin KS contributed to data acquisition; Chen CY and Hu JM contributed to the investigation and interpretation of the data; All authors have read and approved this version of the manuscript.

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