

Original Article

Correlation between the type of esophagogastric junction and refractory reflux esophagitis

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Abstract: Objective: To investigate the correlation between refractory gastroesophageal reflux disease (RGERD) and the esophagogastric junction (EGJ), as well as to assess their effect on the efficacy of acid suppression therapy. Methods: This prospective cohort study (ChiCTR2500101077) enrolled 81 patients with reflux esophagitis (RE) at Pingxiang People's Hospital from April 2023 to September 2024. Participants underwent high-resolution manometry (HRM) to classify EGJ subtypes (I-III) and received an 8-week course of vonoprasen fumarate therapy. Refractory reflux esophagitis (RRE) was defined as the persistence of GERD-Q symptoms following treatment. Patients diagnosed with RRE underwent 24-hour pH-impedance monitoring to evaluate the efficacy of acid suppression. Results: The EGJ subtypes were classified as Type I (n=44), Type II (n=21), and Type III (n=16). After treatment, 37 patients were diagnosed with RRE, including 13 cases of Type I, 12 cases of Type II, and 12 cases of Type III, with significant differences observed among the three groups ($P<0.004$). The EGJ subtype negatively correlated with LES pressure ($r=-0.626$, $P<0.001$). 24 h-pH impedance monitoring demonstrated significant differences in reflux metrics, including total reflux episodes ($P<0.001$), acid exposure percentage ($P<0.001$), prolonged reflux episodes ($P<0.003$), and DeMeester score ($P<0.001$) among the EGJ subtypes, with correlation coefficients of 0.800, 0.787, 0.489, and 0.800, respectively. Conclusion: EGJ type significantly influences the development of RRE, with Type III EGJ exhibiting the strongest association. An abnormal EGJ structure reduces LES pressure and increases acid exposure, thereby diminishing the efficacy of acid suppression.

Keywords: Refractory reflux esophagitis, EGJ type, high-resolution esophageal manometry, 24-hour esophageal pH monitoring

Introduction

Gastroesophageal reflux disease (GERD) is a prevalent disorder of the digestive system [1]. Refractory reflux esophagitis (RRE) refers to reflux esophagitis (RE) that continues to present clinical symptoms despite 8 weeks of double-dose standard acid suppression therapy [1]. As the number of patients diagnosed with GERD increases, debates persist regarding its pathogenesis. The prevailing theories suggest that either the aggressive factors contributing to esophageal reflux have intensified or the defensive factors of the anti-reflux barrier have decreased [2]. In the anatomic context, the anti-reflux mechanism is situated at the esophagogastric junction (EGJ), which encompasses the lower esophageal sphincter (LES), the phrenoesophageal ligament, the crura of the diaphragm, and the angle of His [2, 3]. The EGJ

comprises both the LES and the crural diaphragm (CD), functioning as a complex LES [4]. The diaphragm serves as an external sphincter, while the LES functions as an internal sphincter [2, 3]. The integrity of EGJ function and the preservation of its anatomic structure serve as the primary defenses against GERD [2, 5]. High-resolution manometry (HRM) is capable of classifying the morphology of the EGJ into three distinct types [6, 7]. Nevertheless, the relationship between EGJ type and RRE remains ambiguous. This study aims to investigate the association between EGJ type and RRE, as well as its implications for acid suppression therapy.

Materials and methods

General data and research methods

This study employed a prospective cohort design. From April 2023 to September 2024, we

enrolled patients with reflux esophagitis who visited the People's Hospital of Pingxiang City. The inclusion criteria were as follows: 1) Patients exhibiting gastroesophageal reflux symptoms who were diagnosed with reflux esophagitis via esophagogastroduodenoscopy (EGD); 2) All patients provided informed consent for HRM and 24-hour gastroesophageal pH monitoring; 3) Age 18-75 years. The exclusion criteria included: 1) Disorders of gastrointestinal motility; 2) Poor cardiac, pulmonary, or cerebral function, the presence of active peptic ulcers, hypertension, coronary heart disease, or other conditions that would hinder cooperation with treatment; 3) Presence of psychiatric or neurological disorders, or patients exhibiting excessive anxiety or depression; 4) Pregnant or breastfeeding women; 5) Individuals deemed ineligible by the investigators for safety reasons. Eligible participants were administered 20 mg of Vonorasen fumarate (manufactured by Takeda Pharmaceuticals, approval number: National Medicine Standard J20200015, dosage form: 20 mg/tablet) orally once daily for an 8-week course. After treatment, participants were assessed by the investigators using the GERD-Q questionnaire to categorize them into refractory and non-refractory reflux esophagitis groups based on symptom relief [1]. For patients with RRE who did not respond adequately to treatment, a 24-hour esophageal pH impedance test was performed to evaluate differences in acid suppression effectiveness. This study was approved by the Ethics Committee of Pingxiang City (Ethics Approval Number: SW-2023Z071-HS02) and was registered at the Chinese Clinical Trial Center (Registration Number: ChiCTR2500101077, URL: <https://www.chictr.org.cn>).

Examination method

High-resolution esophageal manometry: Participants fasted for 8 hours prior to the examination. A Solar GI 24-channel high-resolution manometry system (MMS, the Netherlands) was used. Patients were instructed to discontinue prokinetic agents, sedatives, and other related medications for at least 5 days before the procedure. They were positioned in a supine manner, and the manometry catheter was inserted through the nostril into the stomach and secured. Following a 2- to 3-minute acclimation period, resting pressure was measured for 30 seconds without swallowing. Patients then performed 10 wet swallows of 5 ml of water at

30-second intervals. The morphology of the EGJ was analyzed based on the graphical output. The EGJ morphology was classified into three types: (1) Type I, characterized by complete overlap between the LES and the diaphragm, with no separation or a separation of less than 1 cm between the lower edge of the LES and the diaphragm; (2) Type II, characterized by partial overlap between the LES and the diaphragm, with a separation greater than 1 cm and less than 2 cm; (3) Type III, indicative of a hiatal hernia, with a separation greater than 2 cm between the LES and the diaphragm [4, 8].

24-hour esophageal pH monitoring: To evaluate the therapeutic efficacy of acid suppressants, we conducted 24-hour esophageal pH monitoring on the day of the procedure, during which the administration of acid suppressants was temporarily suspended. The monitoring was carried out using an Orion portable pH monitor (MMS, the Netherlands). Following the acquisition of informed consent, the pH electrode catheter was carefully inserted through the nostril and positioned approximately 5 cm above the LES. Patients were instructed to maintain a comprehensive 24-hour activity log, documenting meal times, changes in posture (e.g., lying down or standing), and the occurrence of any discomfort symptoms, including heartburn, acid regurgitation, and chest pain [9]. The monitoring results encompassed several measures, including acid exposure time percentage (AET), total reflux minutes, the number of reflux episodes, the number of prolonged reflux episodes, the longest reflux duration, and the DeMeester score. The diagnostic criteria for gastroesophageal acid reflux were established as follows [9, 10]: (1) AET >4%; (2) DeMeester score ≥ 14.7 ; (3) total number of reflux episodes >54; (4) symptom index (SI) >50% and symptom association probability (SAP) >95%. A positive result in any one of these four criteria was deemed indicative of positive esophageal acid reflux.

Gastroscopy: Esophagitis grading was performed using the Los Angeles (LA) classification system during endoscopy, as follows: LA-A: Presence of one or more mucosal breaks with a length ≤ 5 mm, without fusion across the tops of two mucosal folds. LA-B: Presence of one or more mucosal breaks with a length >5 mm, without fusion across the tops of two mucosal folds. LA-C: Presence of one or more mucosal breaks with fusion across ≥ 2 mucosal folds,

Morphology of EGJ and reflux esophagitis

Table 1. General statistics of patients with reflux esophagitis

| | n | Male | Age (mean \pm SE, yr) | LA-A | LA-B | GERD-Q score (pre) | GERD-Q score (post) |
|---------|----|-------|-------------------------|-------|------|--------------------|---------------------|
| EGJ I | 44 | 27 | 50.87 \pm 10.12 | 25 | 19 | 13.55 \pm 1.98 | 7.18 \pm 1.85 |
| EGJ II | 21 | 13 | 53.00 \pm 13.99 | 12 | 9 | 14.33 \pm 1.79 | 7.86 \pm 1.88 |
| EGJ III | 16 | 11 | 58.34 \pm 14.45 | 6 | 8 | 15.86 \pm 1.78 | 10.19 \pm 2.04 |
| X2/F | | 0.288 | 2.257 | 0.919 | | 8.582 | 14.822 |
| P | | 0.866 | 0.111 | 0.631 | | 0.001*** | 0.001*** |

Note: ***, **, * represent 1%, 5%, 10%. Stratification of EGJ type using Chicago Classification v4.0 criteria was performed in 81 participants through HREM. Subjects diagnosed with RE underwent standardized endoscopic evaluation with Los Angeles Classification grading. GERD-Q scores were systematically recorded at baseline and following 8-week proton pump inhibitor therapy.

Table 2. Proportion of refractory esophagitis and LES pressure in three groups

| | n | RRE | LES pressure (X \pm S) |
|---------|----|----------|--------------------------|
| EGJ I | 44 | 13 | 15.21 \pm 5.23 |
| EGJ II | 21 | 12 | 10.67 \pm 3.21 |
| EGJ III | 16 | 12 | 6.69 \pm 3.30 |
| X2/F | | 11.271 | 23.415 |
| P | | 0.004*** | 0.001*** |

Note: ***, **, * represent 1%, 5%, 10%. Among the 81 enrolled participants, 37 were identified as having refractory esophagitis following the therapeutic intervention. Statistical analysis stratified by EGJ subtype revealed significant differences in both RRE and lower LES.

involving <75% of the esophageal circumference. LA-D: Presence of one or more mucosal breaks with fusion involving \geq 75% of the esophageal circumference.

Statistical analysis

Statistical analyses were conducted utilizing SPSS version 23.0. Continuous data were expressed as mean \pm standard deviation (X \pm S), whereas categorical data were evaluated using the chi-square test. In the comparison of differences among three groups, both Pearson's chi-square test and one-way analysis of variance (ANOVA) were applied. To evaluate the correlation between variables, Pearson correlation analysis and Spearman rank correlation analysis were employed. A *p*-value < 0.05 was considered significant.

Results

Comparison of general information and GERD-Q score of each EGJ subtype

A total of 81 patients with reflux esophagitis were enrolled and categorized by EGJ type: 44

with Type I, 21 with Type II, and 16 with Type III. No significant differences in age (*P*=0.866) or gender (*P*=0.111) were observed among the groups. Similarly, no significant differences were noted in the pre-enrollment LA classification of RE (*P*=0.631). Pre-treatment GERD-Q scores revealed significant differences among the groups (*P*<0.001), indicating an association with EGJ type. After 8 weeks of acid suppression therapy, post-treatment GERD-Q scores indicated that patients with EGJ Type III had significantly higher scores compared to those with Type I and II (*P*<0.001), with no significant differences between Type I and II (*P*=0.128). These findings suggest that acid suppression therapy was least effective in patients with EGJ Type III (**Table 1**).

Correlation analysis of EGJ type with LES pressure and refractory esophagitis

HREM was conducted on patients diagnosed with RE, demonstrating a significant correlation between LES pressure and EGJ type (**Table 2**). The distance between the LES and the CD exhibited an inverse relationship with LES pressure. Further analysis utilizing Spearman correlation revealed a negative correlation between EGJ type and LES pressure (*r*=-0.626, *P*<0.001; **Table 4**). Based on post-treatment GERD-Q scores, patients were classified into refractory and non-refractory esophagitis groups, with the distribution as follows: 13 patients with Type I, 12 with Type II, and 12 with Type III. Chi-square analysis indicated significant differences among these groups (*P*<0.004, **Table 2**). Additionally, further Spearman correlation analysis yielded a correlation coefficient of 0.41 (*P*<0.001), suggesting an association between EGJ morphology and refractory esophagitis.

Table 3. Analysis of 24-hour esophageal pH in patients with refractory esophagitis

| | n | Total number of reflux episodes | AET | Prolonged reflux episodes | DeMeester score |
|---------|----|---------------------------------|-----------|---------------------------|-----------------|
| EGJ I | 13 | 28.16±8.60 | 2.77±0.57 | 1.08±0.86 | 9.07±2.07 |
| EGJ II | 12 | 48.75±16.97 | 3.87±0.94 | 2.50±1.17 | 13.98±3.56 |
| EGJ III | 12 | 72.83±16.61 | 6.18±2.27 | 2.42±1.17 | 19.41±7.17 |
| F | | 29.314 | 18.259 | 7.016 | 15.138 |
| P | | 0.001*** | 0.001*** | 0.003*** | 0.001*** |

Note: ***, **, * represent 1%, 5%, 10%. 24-hour esophageal pH monitoring was performed in 37 subjects with RRE. Comprehensive analysis of reflux measures included: (1) total number of reflux episodes, (2) percentage time of acid exposure (pH <4), (3) number of prolonged reflux episodes (>5 minutes), and (4) Demeester score.

Table 4. EGJ typing and Spearman correlation coefficient

| | Spearman correlation coefficient |
|---------------------------|----------------------------------|
| RRE | 0.41 (0.001***) |
| LES pressure | -0.626 (0.001***) |
| total reflux episodes | 0.8 (0.001***) |
| AET% | 0.787 (0.001***) |
| prolonged reflux episodes | 0.489 (0.002***) |
| DeMeester score | 0.8 (0.001***) |

Note: ***, **, * represent 1%, 5%, 10%. Spearman's rank correlation analysis was performed to assess the associations between EGJ subtypes and the following data: (1) RRE, (2) LES pressure, (3) total number of reflux episodes, (4) acid exposure time percentage (AET%) (pH <4), (5) number of prolonged reflux episodes (>5 minutes), and (6) Demeester score.

Analysis of related measures between EGJ type and refractory esophagitis

24 h-esophageal pH monitoring was conducted in patients diagnosed with RRE. The analysis included the total number of reflux episodes, acid exposure time (AET), the number of prolonged reflux episodes, and the DeMeester score. The results revealed significant differences among these data (see **Table 3**). Additionally, a Spearman correlation analysis was performed to assess the relationship between these data and EGJ type. The correlation coefficients obtained were as follows: total reflux episodes (0.800, $P<0.001$), AET (0.787, $P<0.001$), prolonged reflux episodes (0.489, $P<0.001$), and DeMeester score (0.800, $P<0.001$) (refer to **Table 4**). These findings suggest a significant correlation between the total number of reflux episodes, AET, prolonged reflux episodes, DeMeester score, and EGJ morphology.

Discussion

Acid suppression therapy is considered the primary treatment for GERD. However, despite the optimized administration of PPIs, over 30% of patients continue to experience inadequate acid suppression and subsequently develop RRE [11]. Therefore, the early identification of RRE is of paramount importance. In this study, we observed a positive correlation between EGJ typing and GERD-Q questionnaire scores among patients with RE, suggesting that higher EGJ typing correlates with more severe reflux symptoms and a diminished response to acid suppression therapy. This finding aligns with the research conducted by Akimoto and Ferrari [12, 13], which demonstrated that in cases of esophageal acid reflux that type 1 < type 2 < type 3, with a significantly higher incidence of esophagitis observed in patients classified as type 3 compared to those classified as types 1 and 2. Morphologic abnormalities of the EGJ may serve as indicators of impaired barrier function. Our study revealed significant differences in the mean LES pressure across various EGJ types, indicating that alterations in EGJ morphology may influence LES pressure. Spearman correlation analysis demonstrated a significant association between EGJ typing and LES pressure, whereby greater separation between the LES and the CD is linked to lower LES pressure. Hyoju Ham's investigation into antireflux barrier indices found that in patients with reflux esophagitis, the EGJ compliance index (EGJ-CI) pressure varied according to EGJ subtype and was lower than that observed in healthy individuals [14]. This reduction in LES pressure compromises the anti-reflux barrier. When the separation between the LES and CD exceeds 2 cm, a diagnosis of hiatal hernia can be established, which is significantly correlated

with RRE [14]. Furthermore, both the EGJ-CI and distal contraction integral (DCI) decrease in the presence of EGJ morphologic abnormalities, thereby adversely affecting the anti-reflux barrier and the acid clearance function of the esophagus [15].

To further investigate the relationship between EGJ type and treatment outcomes in RRE, a 24-hour esophageal pH monitoring study was conducted following an 8-week course of acid suppression therapy. Patients were instructed to discontinue acid-suppressing medications on the day of testing. The results indicated that patients classified as EGJ Type 3 exhibited significantly higher percentages of acid exposure, total reflux episodes, and Demeester scores compared to those with the other two types. Specifically, in patients with EGJ Type 3 diagnosed with RRE, the Demeester score exceeded 14.72, suggesting the presence of pathologic acid reflux and a poor response to acid suppression therapy. Correlation analysis demonstrated that the mean esophageal acid exposure time, total reflux episodes, total reflux minutes, and Demeester score were all significantly correlated with EGJ typing, exhibiting high correlation coefficients. This finding implies that EGJ typing substantially influences the efficacy of acid suppression therapy, resulting in persistent symptoms of reflux esophagitis due to pathologic acid reflux. Previous studies have corroborated these findings, indicating that patients with Type III reflux esophagitis have higher mean esophageal AET, total reflux episodes, and symptom association probability (SAP) compared to those with Type I and II [12, 16]. The separation distance between the LES and the CD was positively correlated with AET, total reflux episodes, symptom association probability, and Demeester score during esophageal pH monitoring. Additionally, a significant relationship was observed between EGJ contraction pressure and EGJ type [14, 15, 17]. These results align with our study; however, the extent to which EGJ typing influences treatment efficacy and contributes to refractory esophagitis remains uncertain. Our research indicated that EGJ typing does affect the treatment efficacy of reflux esophagitis, and Spearman correlation analysis revealed a significant association between EGJ typing and RRE. The underlying mechanism may involve the separation of the LES from the CD, which compromises the anti-reflux barrier and conse-

quently increases the frequency and duration of reflux episodes [12, 15, 17]. Additionally, impaired esophageal peristalsis and diminished clearance function may further reduce the effectiveness of acid suppression therapy [18], ultimately leading to more RRE symptoms in patients.

Thus, individualized approaches are needed for patients with morphologic abnormalities of the EGJ in order to prevent ineffective treatment and the associated economic burden. Treatment options may vary based on the underlying reasons for the lack of therapeutic response and include lifestyle modifications, increasing the dosage of proton pump inhibitors (PPIs), substituting PPIs with alternative medications, and incorporating H₂-receptor antagonists, prokinetics, antacids, alginates, and adsorbents [19]. If conservative treatment is ineffective, it is possible to consider alternative methods, such as surgical treatment [20]. In the efficacy of surgical treatment for RRE revealed that the preoperative classification of EGJ type 3 was significantly correlated with the severity of postoperative recurrence of gastroesophageal reflux symptoms [21]. Therefore, the assessment of abnormal EGJ type is crucial for preoperative evaluation and aids healthcare professionals and patients in developing more effective clinical strategies.

This study has several limitations. Due to clinical constraints, 24-hour esophageal pH monitoring was not performed before acid suppression treatment, potentially affecting the analysis. However, in patients with RRE, post-treatment acid exposure levels in EGJ Type III were significantly higher than in the other types, supporting the research conclusions preliminarily.

Conclusion

This study identified significant associations between EGJ type and RRE, with particular emphasis on the predisposition of type III EGJ to RRE. Structural anomalies of the EGJ were shown to decrease LES pressure and increase acid exposure, thereby undermining the efficacy of acid suppression. The interplay between anatomic and functional aspects of EGJ dysfunction emerged as a crucial mechanism in the pathogenesis of RRE and its resistance to treatment. The integration of high-resolution manometry-based EGJ classification with 24 h-

pH-impedance monitoring provides essential insight for personalized clinical management, so that therapy can be optimized in refractory cases.

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Disclosure of conflict of interest

None.

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