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CLINICAL DETERMINANTS AND ENDOSCOPIC CORRELATES OF BARRETT'S ESOPHAGUS IN PATIENTS WITH CHRONIC GASTROESOPHAGEAL REFLUX DISEASE: A COHORT-BASED ANALYSIS

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Barrett's esophagus (BE) is a premalignant condition associated withchronic gastroesophageal reflux disease (GERD) and an increased risk of esophageal adenocarcinoma. Although GERD is highly prevalent, only a subset of patients develops intestinal metaplasia, indicating that additional demographic, structural, and endoscopic determinants likely contribute to disease progression. The objective of our paper was to evaluate the prevalence and clinical predictors of intestinal metaplasia consistent with Barrett's esophagus in patients with chronic GERD symptoms. This observational cohort study was conducted at the Clinic of Gastroenterology, University Clinical Center Niš, Serbia, between January and December 2024. A total of 518

consecutive patients with chronic reflux symptoms underwent upper gastrointestinal endoscopy. After applying predefined inclusion and exclusion criteria, 148 patients were included in the final analysis. Demographic, clinical, and endoscopic variables were compared between patients with and without intestinal metaplasia. Intestinal metaplasia was identified in 24 patients (16.2%). Patients with metaplasia were significantly older than those without metaplasia (62 ± 14 vs. 51 ± 13 years, p = 0.003). Hiatal hernia was more prevalent in the metaplasia group (87.5% vs. 56.1%, p = 0.032), and long-segment columnar-lined esophagus was strongly associated with intestinal metaplasia (56.3% vs. 6.1%, p = 0.004). Heartburn was less frequently reported in patients with metaplasia (20.0% vs. 67.1%, p = 0.008), whereas regurgitation was more common (68.8% vs. 29.3%, p = 0.012). These were key determinants of Barrett's esophagus. These findings support a risk-oriented rather than symptom-oriented approach to identifying patients who may benefit from diagnostic endoscopy and surveillance.

Key words: Barrett's Esophagus, Intestinal Metaplasia, Gastroesophageal Reflux Disease, Hiatal Hernia, Columnar-Lined Esophagus

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KLINIČKI PARAMETRI I ENDOSKOPSKA KORELACIJA BARETOVOG EZOFAGITISA KOD PACIJENATA SA HRONIČNOM GASTROEZOFAGEALNOM REFLUKSNOM BOLEŠĆU: ANALIZA KOHORTE

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Barrettov jednjak (BE) predstavlja premaligno stanje povezano sa hroničnom gastroezofagealnom refluksnom bolešću (GERB) i povećanim rizikom od adenokarcinoma jednjaka. Iako je GERB veoma čest, kod određenog broja pacijenata dolazi do razvoja intestinalne metaplazije, što ukazuje na značaj dodatnih demografskih, strukturnih i endoskopskih faktora u progresiji bolesti.Cilj rada bio je da se proceni prevalenca i klinički prediktori intestinalne metaplazije u skladu sa Barrettovim jednjakom kod pacijenata sa hroničnim simptomima GERB-a. Ova opservaciona kohortna studija sprovedena je na Klinici za gastroenterologiju Univerzitetskog kliničkog centra Niš, Srbija, u periodu od januara do decembra 2024. godine.

Ukupno 518 uzastopnih pacijenata sa hroničnim refluksnim simptomima podvrgnuto je gornjoj endoskopiji digestivnog trakta. Nakon primene unapred definisanih kriterijuma za uključivanje i isključivanje, u konačnu analizu uključeno je 148 pacijenata. Demografske, kliničke i endoskopske varijable upoređene su između pacijenata sa i bez intestinalne metaplazij. Intestinalna metaplazija identifikovana je kod 24 pacijenta (16,2%). Pacijenti sa metaplazijom bili su značajno stariji od pacijenata bez metaplazije (62 ± 14 naspram 51 ± 13 godina, p=0,003). Hijatalna hernija bila je češća u grupi sa metaplazijom (87,5% naspram 56,1%, p=0,032), a dugačak segment cilindričnog epitela jednjaka bio je snažno povezan sa intestinalnom metaplazijom (56,3% naspram 6,1%, p=0,004). Gorušica je bila ređe prijavljivana kod pacijenata sa metaplazijom (20,0% naspram 67,1%, p=0,008), dok je regurgitacija bila češća (68,8% naspram 29,3%, p=0,012). Ovi parametri bili su ključne determinante Barrettovog jednjaka. Ovi nalazi podržavaju pristup zasnovan na proceni rizika, a ne samo na simptomima, u identifikaciji pacijenata koji mogu imati korist od dijagnostičke endoskopije i nadzora.

Ključne reči: Barrettov jednjak, intestinalna metaplazija, gastroezofagealna refluksna bolest, hijatalna hernija, cilindrični epitel jednjak

Introduction

Gastroesophageal reflux disease (GERD) is a chronic and increasingly prevalent gastrointestinal disorder characterized by the retrograde movement of gastric contents into the esophagus, leading to troublesome symptoms and/or mucosal injury [1]. It represents a major healthcare burden due to its frequency, chronicity, impact on quality of life, and association with long-term complications. Global epidemiologic analyses have shown substantial geographic variation in GERD prevalence, with increasing rates reported in many regions over recent decades [2].

Among the most clinically relevant complications of GERD is Barrett's esophagus (BE), a condition in which the normal stratified squamous epithelium of the distal esophagus is replaced by specialized columnar epithelium with intestinal differentiation. BE is widely recognized as the only known premalignant lesion for esophageal adenocarcinoma, a malignancy whose incidence has risen markedly in Western populations over the last several decades [3]. Although the absolute annual risk of malignant progression in nondysplastic BE is relatively low, the consequences of a missed diagnosis may be substantial, as neoplastic progression may remain clinically silent until advanced stages [4].

The pathophysiology of BE is multifactorial and is believed to result from prolonged exposure of the distal esophagus to acid and bile reflux, leading to chronic inflammation, epithelial injury, repair, and metaplastic transformation [5]. However, only a proportion of patients with longstanding GERD develop BE, suggesting that symptom burden alone is not sufficient to explain disease evolution. Epidemiologic and clinical studies have identified several factors associated with increased risk, including older age, male sex, central obesity, smoking, hiatal hernia, and the extent of reflux-related mucosal exposure [6].

The prevalence of BE varies according to the population studied and the diagnostic criteria used. It has been estimated at approximately 1–2% in the general population and 5–15% among patients with GERD symptoms undergoing endoscopic evaluation [7]. Despite this, screening strategies remain imperfect because many patients with BE do not report severe or typical reflux symptoms, while many symptomatic GERD patients do not harbor intestinal metaplasia [8]. This discrepancy has encouraged a shift toward more refined risk-based screening approaches [9]. In addition, the endoscopic phenotype of BE is clinically important.

The length of the columnar-lined segment has been associated with the likelihood of intestinal metaplasia, dysplasia, and neoplastic progression, underscoring the importance of careful endoscopic characterization for diagnosis and surveillance planning [10]. Hiatal hernia, as a structural abnormality of the gastroesophageal junction, may further facilitate chronic reflux exposure and contribute to metaplastic transformation [11].

The aim of the present study was to evaluate demographic, clinical, and endoscopic determinants associated with intestinal metaplasia in patients with chronic GERD symptoms treated at a tertiary gastroenterology clinic. By comparing patients with and without intestinal metaplasia, we sought to identify clinically relevant features that may improve the detection of Barrett's esophagus in routine practice.

Material and Methods

Study design and setting: This observational cohort study was conducted at the Clinic of Gastroenterology, University Clinical Center Niš, Serbia, from January 2024 to December 2024. The study was designed to evaluate the relationship between clinical presentation, endoscopic findings, and histologically confirmed intestinal metaplasia in patients referred for endoscopic evaluation because of chronic reflux symptoms.

Study population*:* During the study period, 518 consecutive patients with chronic symptoms suggestive of GERD underwent upper gastrointestinal endoscopy. Following application of predefined inclusion and exclusion criteria, 148 patients with complete clinical, endoscopic, and histopathological data were included in the final analytic cohort. The exclusion of 370 patients (71.4%) reflected standard clinical practice, with the primary reasons being incomplete endoscopic documentation (n=125), prior esophageal surgery (n=98), insufficient biopsy material (n=87), and other exclusion criteria (n=60).

Chronic reflux symptoms were defined as recurrent heartburn and/or regurgitation occurring at least twice weekly over a prolonged period [12, 13]. Patients were considered eligible if they had persistent reflux symptoms warranting endoscopic evaluation and if biopsy material was available for histopathological interpretation.

Inclusion and exclusion criteria: Patients were included if they: were adults (≥18 years) with chronic reflux symptoms; underwent upper gastrointestinal endoscopy during the study period; had complete documentation of endoscopic findings; and had a biopsy-based histopathological assessment of suspected columnar-lined mucosa.

Patients were excluded if they had: prior esophageal or gastric surgery; known esophageal malignancy; severe esophageal motility disorders; incomplete endoscopic or histological documentation; or insufficient biopsy material for definitive histopathological analysis.

Endoscopic assessment: All patients underwent upper gastrointestinal endoscopy in accordance with standard clinical practice using high-definition endoscopes. The gastroesophageal junction was identified based on the proximal extent of the gastric folds. Columnar-lined esophagus (CLE) was defined as the presence of columnar mucosa extending at least 1 cm above the gastroesophageal junction.

The extent of the endoscopically suspected Barrett's segment was classified according to segment length. Patients were categorized as having:

- short-segment CLE, when the columnar segment measured < 3 cm; or
- long-segment CLE, when the segment measured ≥ 3 cm.

The presence of erosive reflux disease (ERD), non-erosive reflux disease (NERD), and hiatal hernia was recorded based on endoscopic findings. All endoscopic procedures were performed by experienced endoscopists.

Histopathological evaluation: Biopsy samples were obtained systematically from abnormal-appearing distal esophageal mucosa and analyzed histopathologically by experienced pathologists. The diagnosis of Barrett's esophagus required the presence of specialized intestinal metaplasia with goblet cells [17]. Patients were then stratified into two groups: those without intestinal metaplasia and those with intestinal metaplasia.

Clinical variables: The following variables were analyzed: age, sex, heartburn, regurgitation, NERD, ERD, hiatal hernia, short-segment CLE, and long-segment CLE.

Statistical analysis: Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as percentages with 95% confidence intervals (95%

CI). Continuous variables were compared using Student's t-test, and categorical variables using the chi-square test. A two-tailed p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS software version 25.0 (IBM Corporation, Armonk, NY).

Results

Study cohort

A total of 518 patients with chronic GERD symptoms underwent endoscopic evaluation during the study period. After application of the predefined selection criteria, 148 patients were included in the final analysis. Of these, 24 patients (16.2%; 95% CI: 10.4–23.1%) had histologically confirmed intestinal metaplasia consistent with Barrett's esophagus, while 124 patients had no evidence of intestinal metaplasia.

Baseline demographic characteristics

Patients with intestinal metaplasia were significantly older than those without metaplasia (62 ± 14 vs. 51 ± 13 years; p = 0.003). There were no statistically significant differences in sex distribution between the two groups. These findings suggest that age, rather than sex alone, was the more prominent differentiating characteristic in this cohort.

Table 1. Baseline demographic characteristics of the study population

Characteristic	No intestinal metaplasia (n = 124)	Intestinal metaplasia (n = 24)	p-value
Age (years)	51 ± 13	62 ± 14	0.003
Male sex (%)	79.3%	81.3%	0.85
Female sex (%)	20.7%	18.7%	0.85

Clinical characteristics and symptom profile

Analysis of symptoms demonstrated an interesting pattern. Heartburn was significantly less common in patients with intestinal metaplasia than in those without metaplasia (20.0% vs. 67.1%; p = 0.008). In contrast, regurgitation was significantly more frequent in the metaplasia

group (68.8% vs. 29.3%; p = 0.012). Regarding endoscopic reflux phenotype, NERD was more common than ERD in both groups, particularly among patients with intestinal metaplasia. Most importantly, hiatal hernia was significantly more prevalent in patients with intestinal metaplasia (87.5% vs. 56.1%; p = 0.032).

These data indicate that typical symptom burden, especially heartburn, may not adequately reflect the likelihood of intestinal metaplasia, whereas structural abnormalities such as hiatal hernia may be more informative.

Table 2. Clinical characteristics and symptom profile

Variable	No intestinal metaplasia (n = 124)	Intestinal metaplasia (n = 24)	p-value
Heartburn (%)	67.1%	20.0%	0.008
Regurgitation (%)	29.3%	68.8%	0.012
NERD (%)	72.0%	87.5%	0.038
ERD (%)	28.0%	12.5%	0.038
Hiatal hernia (%)	56.1%	87.5%	0.032

Endoscopic findings

The extent of columnar-lined esophagus was strongly associated with intestinal metaplasia. Short-segment CLE was more common in patients without metaplasia, while long-segment CLE was markedly more frequent in patients with metaplasia. Specifically, long-segment CLE was present in 56.3% (95% CI: 39.8–71.5%) of patients with metaplasia, compared with only 6.1% (95% CI: 2.3–12.5%) of those without metaplasia (p = 0.004). These results indicate that segment length is an important endoscopic correlate of intestinal metaplasia and may serve as a clinically useful marker of increased risk.

Table 3. Endoscopic characteristics of columnar-lined esophagus (CLE)

CLE characteristic	No intestinal metaplasia (n = 124)	Intestinal metaplasia (n = 24)	p-value
Short-segment (<3 cm)	56.1% (95% CI: 47.2–64.7%)	31.3% (95% CI: 13.9–53.3%)	0.016
Long-segment (≥3 cm)	6.1% (95% CI: 2.3–12.5%)	56.3% (95% CI: 39.8–71.5%)	0.004
No CLE	37.8% (95% CI: 29.3–46.8%)	12.4% (95% CI: 3.1–28.0%)	0.009

Discussion

The present study evaluated demographic, clinical, and endoscopic determinants of intestinal metaplasia in patients with chronic GERD treated at a tertiary gastroenterology clinic. Several findings are clinically relevant. First, older age was strongly associated with intestinal metaplasia. Second, a hiatal hernia was significantly more frequent among patients with metaplasia. Third, a long-segment columnar-lined esophagus showed a strong association with intestinal metaplasia. Finally, symptom burden alone, particularly heartburn, did not reliably identify patients at increased risk.

The cross-sectional design of the study limits causal inference, and the observed relationships should be interpreted as associations rather than predictors of disease development. One of the strengths of this study is the relatively large screened cohort of 518 patients evaluated in routine clinical practice. Although the final analysis included only 148 patients, the broader initial pool enhances the real-world relevance of the findings and reflects standard clinical selection criteria in endoscopic practice. The 71.4% exclusion rate reflects rigorous application of inclusion criteria to ensure data quality and histopathological validation.

Age emerged as a significant factor associated with Barrett's esophagus in our cohort. Patients with intestinal metaplasia were older than those without, consistent with prior studies showing that the prevalence of Barrett's esophagus increases with age [5,14]. This is likely related to cumulative exposure to refluxate and progressive mucosal injury over time [6, 15, 16]. More

recent epidemiologic and review literature has reinforced the central role of age in risk stratification models for Barrett's esophagus [7].

A particularly important observation in our study was the inverse relationship between heartburn and intestinal metaplasia. Although this finding may appear counterintuitive, it supports previous evidence that symptom severity does not reliably correlate with the presence of Barrett's esophagus [8]. Reduced symptom perception may occur in patients with longstanding disease due to altered esophageal sensitivity or mucosal adaptation. Contemporary review articles emphasize that Barrett's esophagus may remain clinically silent or present with atypical symptoms, which limits the effectiveness of symptom-based screening strategies [9,17,18].

Regurgitation, in contrast, was more frequently reported in patients with intestinal metaplasia (68.8% vs. 29.3%, $p = 0.012$). While this finding may indicate differences in reflux phenotype, it further supports the notion that symptom profile alone is insufficient for risk stratification. The predominance of NERD over ERD in both groups (72.0% and 87.5%, respectively) suggests that endoscopic mucosal breaks do not distinguish patients with advanced metaplasia. Recent literature increasingly supports a shift toward risk-based screening approaches that integrate demographic, clinical, and structural factors rather than relying solely on symptom severity [10,18,19].

The strong association between hiatal hernia and intestinal metaplasia observed in this study ($p = 0.032$) confirms its role as a key structural factor in GERD pathophysiology [11]. Hiatal hernia disrupts the normal anatomy of the gastroesophageal junction, facilitating prolonged exposure of the esophageal mucosa to refluxate. This association has been consistently reported in both earlier and more recent review studies, in which hiatal hernia is identified as a major determinant of Barrett's esophagus development [12].

The segment length of the columnar-lined esophagus was another critical determinant. Long-segment CLE was significantly associated with intestinal metaplasia, with 56.3% of metaplasia patients exhibiting long-segment disease compared to only 6.1% of those without metaplasia ($p = 0.004$). This strong association is consistent with previous studies showing that longer segment length correlates with a higher risk of dysplasia and neoplastic progression [13]. Recent reviews further confirm that segment length remains an essential parameter for both diagnosis and surveillance planning [13,18,19].

Recent literature also highlights a transition toward more refined screening strategies. Traditional symptom-driven approaches have shown limited sensitivity, leading to underdiagnosis

of Barrett's esophagus. Modern strategies emphasize targeted screening in patients with multiple risk factors, including older age, male sex, obesity, hiatal hernia, and chronic reflux exposure [15]. In this cohort, patients with combined risk factors (age >60 years, hiatal hernia, and long-segment CLE) represent a high-risk group warranting routine surveillance.

Despite its strengths, this study has several limitations. It was conducted at a single tertiary center, which may limit generalizability to primary care populations. The high exclusion rate (71.4%) due to incomplete documentation or prior surgery may introduce selection bias. Additionally, some relevant risk factors, such as obesity (BMI), smoking status, and family history of esophageal cancer, were not included in the analysis and may have further refined risk stratification. The cross-sectional design precludes assessment of progression to dysplasia or malignancy during follow-up [16].

Our findings support a multifactorial model of Barrett's esophagus development. Age, hiatal hernia, and segment length of columnar-lined esophagus were the strongest determinants of intestinal metaplasia in this cohort, while symptom-based assessment alone proved insufficient. These results are consistent with contemporary literature and support the adoption of integrated, risk-based approaches to screening and surveillance [17].Furthermore, recent studies highlight the importance of integrated risk stratification models and advances in screening strategies for Barrett's esophagus and esophageal adenocarcinoma [18–20].

Conclusion

In conclusion, Barrett's esophagus remains a clinically significant complication of chronic GERD and an important target for early detection strategies. In this cohort, advanced age, hiatal hernia, and greater segment length of columnar-lined esophagus were independently associated with intestinal metaplasia. In contrast, symptom burden alone did not reliably identify high-risk patients. These findings support the use of combined clinical and endoscopic risk profiling in patients with chronic reflux symptoms and may improve selection for diagnostic endoscopy and surveillance. Future prospective studies with broader clinical characterization and longitudinal follow-up are needed to better define causal pathways and progression risk.

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