Original Article

Histopathological Evolution of Barrett's Esophagus over a 12-Year Period: Insights from a Gastroenterology Clinic in Kashan, Iran

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ABSTRACT

Background: Barrett's esophagus (BE) is a premalignant condition that increases the risk of esophageal adenocarcinoma (EAC). Data on the natural history and histopathological changes of BE in Middle Eastern populations remain limited. This study aimed to evaluate the longitudinal course and prognostic factors of BE in an Iranian cohort over a 12-year period.

Materials and Methods: We conducted a retrospective cohort study of patients with histologically confirmed BE who attended the Gastroenterology Clinic of Shahid Beheshti Hospital, Kashan, between 2011 and 2023. Eligible patients had undergone at least two endoscopic evaluations with biopsy. We extracted demographic, clinical, and lifestyle data, and classified histopathology as short-segment BE (SSBE), long-segment BE (LSBE), low-grade dysplasia (LGD), high-grade dysplasia (HGD), or EAC. We categorized outcomes as regression, stability, or progression. Statistical analyses were performed using Chi-square, Fisher's exact test, and ANOVA.

Results: We included 87 patients (56.3% men; mean age 50.5 ± 18.6 years). At baseline, SSBE was more frequent than LSBE (70.1% vs. 29.9%). During follow-up, 16.1% of patients achieved complete regression, 34.5% showed overall improvement (complete or partial), 59.8% remained stable, and 5.7% progressed to LGD. Notably, all progressions occurred in LSBE, whereas no patient with SSBE developed dysplasia. *Helicobacter pylori (H. pylori*) infection was significantly associated with favorable outcomes (P=0.014), and longer surveillance intervals were linked to higher regression rates (P=0.014). Smoking and unhealthy diet were highly prevalent but not significantly associated with progression.

Conclusion: Most patients with BE remained stable during long-term follow-up, with regression observed predominantly in SSBE and progression confined to LSBE. These findings highlight the indolent nature of SSBE, the higher malignant potential of LSBE, and the possible protective role of *H. pylori*. Risk-based surveillance, particularly more intensive monitoring of patients with LSBE, remains essential. Prospective studies integrating molecular biomarkers are warranted to refine risk stratification and optimize patient management.

Keywords: Barrett's esophagus; Short-segment; Long-segment; Dysplasia; Esophageal adenocarcinoma; *Helicobacter pylori;* regression; progression

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INTRODUCTION:

Barrett's esophagus (BE) is a major premalignant condition characterized by replacement of the native squamous epithelium at the distal esophagus with columnar epithelium in the setting of gastroesophageal reflux disease (GERD) (1). This metaplastic change increases the risk of esophageal adenocarcinoma (EAC) a cancer with poor prognosis and rising global incidence (2). The canonical progression from BE to EAC typically follows a continuum from non-dysplastic intestinal metaplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and ultimately carcinoma (3). Accordingly, understanding the patterns and trajectory of histopathological change in BE is critical for early intervention and cancer prevention (4).

GERD is common across ages and sexes, with a global prevalence estimated at 8–33% and a substantial economic burden driven largely by proton-pump inhibitor (PPI) use of roughly 9–10 billion USD annually in the United States (5, 6). In Iran, the overall prevalence has been reported at approximately 5.6% (7). Clinical manifestations range from typical symptoms such as heartburn and regurgitation to atypical features including cough, asthma, chest pain, and fatigue (8, 9). The chronicity of GERD predisposes patients to complications such as esophagitis and BE, which occur in about 7–15% of cases (10, 11).

Guidelines define BE endoscopically by tongues of salmon-colored gastric-type mucosa extending into the pink esophageal mucosa, with histological confirmation of intestinal metaplasia (12). To optimize diagnostic yield, at least eight random biopsies are recommended; in short-segment disease (1–2 cm) where eight biopsies are impractical, a minimum of four-quadrant biopsies per centimeter of salmon-colored mucosa should be obtained (13, 14). In patients with suspected BE but no intestinal metaplasia on histology, repeat endoscopy within 1–2 years is advised to exclude missed BE (15).

Pathophysiologically, chronic exposure to acid and bile leads to repeated injury and inflammation of the esophageal epithelium, promoting an adaptive metaplastic transformation characterized by goblet cells and other columnar cell types within an epithelium that is normally squamous (16). While this adaptation may confer partial protection against acid, it heightens susceptibility to dysplastic change particularly in long-segment BE. Molecularly, progression to dysplasia and carcinoma has been linked to alterations in tumor-suppressor pathways (e.g., p53) and disruptions in cell-cycle regulation, apoptosis, and cellular proliferation. Established risk factors for progression include older age, male sex, Caucasian race, obesity, smoking, and a family history of EAC (4).

Given the malignant potential of BE, structured surveillance with periodic endoscopy and targeted biopsies is recommended to detect dysplasia at an early stage (17, 18). Nevertheless, grading dysplasia remains challenging and often benefits from review by expert gastrointestinal pathologists. Advances in imaging modalities and biomarker development aim to improve diagnostic accuracy and reproducibility and continue to be active areas of investigation (17, 18).

Multiple studies have demonstrated strong associations between the duration and severity of reflux and the extent of columnar metaplasia (19). Greater proximal extent of acid exposure correlates with BE development (20), and BE length has been associated with longer acid exposure times in both supine and upright positions more pronounced in long-segment than short-segment BE (21). Although short-segment BE is more prevalent in most series, the clinical implications of segment length and acid exposure remain central to risk stratification. Early endoscopic detection of BE may enable earlier EAC diagnosis in patients with prolonged reflux and improve outcomes (22). Still, some argue the cancer risk attributed to BE may be overestimated; notably, many patients with EAC have no prior BE diagnosis (23). Pragmatically, patients with persistent symptoms may be re-evaluated with endoscopy and esophageal physiologic testing to refine phenotyping and optimize therapy (24), and adherence to surveillance pathways reduces the risk of progression to carcinoma (25, 26).

Incidence estimates of BE vary internationally reported at 15–20.2% in Japan (27), 12.9% in Canada (28), 10–20% in the United States (29), and about 9.3% among Iranian patients with reflux (30). Factors such as male sex (31), higher age (31, 32), and smoking (32) have been implicated in BE development among GERD patients. However, longitudinal surveillance data from Iran are relatively limited and sometimes yield findings that diverge from international literature regarding determinants of BE and its progression (33). Because BE is often asymptomatic and detected incidentally during endoscopy for reflux symptoms, delays in recognizing dysplasia or early carcinoma may occur (34). Accurate identification and grading of dysplasia are therefore pivotal components of clinical management and surveillance (4).

To address these gaps and provide region-specific evidence, we conducted a 12-year retrospective evaluation (2011–2023) of temporal trends and patterns in histopathologic change among patients with GERD and BE presenting to a gastroenterology clinic in Kashan, Iran. We hypothesized that contemporaneous shifts in biopsy practices, surveillance intensity, and patient risk profiles would manifest as measurable changes in the proportions of non-

dysplastic BE, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and incident esophageal adenocarcinoma (EAC), thereby refining prognostication and informing locally optimized management strategies.

MATERIALS AND METHODS

Study Design

This retrospective cohort study was conducted at the Gastroenterology Clinic of Shahid Beheshti Hospital, Kashan, Iran. We reviewed data of consecutive patients with BE evaluated between March 2011 and March 2023.

Study Population and Setting

This study was conducted at the Gastroenterology Clinic of Shahid Beheshti Hospital, Kashan, Iran, and included all consecutive adults with BE evaluated between March 2011 and March 2023 who had available endoscopy and pathology records. Eligible participants were ≥18 years old, had a prior endoscopic diagnosis of BE confirmed by biopsy, and had undergone at least two upper gastrointestinal endoscopies within the study window (an index examination plus ≥1 follow-up) with pathology reports for both, while patients were excluded if they had esophageal varices, any prior esophageal or gastric surgery, dysplasia (low- or high-grade) or esophageal adenocarcinoma at the first presentation, non-diagnostic or indeterminate baseline biopsies, or a follow-up endoscopy performed less than 6 months after the index procedure.

Sampling Method

The study was designed as a census of all eligible cases. Accordingly, we included all patients with histologically confirmed BE who met the inclusion criteria during March 2011–March 2023 and reviewed all available records.

Data Collection

After protocol approval and ethics code issuance, the research team presented formal letters, obtained cooperation from the archive unit, and abstracted data on site from documented medical records and pathology/laboratory reports. Patients had previously undergone upper gastrointestinal endoscopy at public or private centers in Kashan; corresponding pathology reports were available in local pathobiology laboratories and were retrieved. A collaborating pathologist read or re-reviewed all pathology specimens.

Outcomes

Primary outcome: histologic trajectory on follow-up (complete IM, incomplete IM, low-grade dysplasia, high-grade dysplasia, adenocarcinoma).

Endoscopy and Biopsy Protocol

Upper gastrointestinal endoscopy was performed with video endoscopy after using topical lidocaine 10% and was reported by an endoscopy specialist. Biopsies were obtained from the gastroesophageal junction (Z-line) and suspected BE segments. Typically, we took 2–4 biopsies and, when feasible, one biopsy per quadrant. Each specimen was placed in a separate 10% neutral buffered formalin vial and sent to the hospital pathology laboratory. After fixation, staining, and microscopic examination, lesions were classified according to accepted international criteria. Pathologists were blinded to prior clinical/demographic information, index diagnosis, and endoscopic impressions whenever possible.

Histopathology Assessment

A single pathologist read or rechecked all slides, blinded to prior histology, demographics, index diagnosis, and endoscopic impression whenever possible. BE was confirmed by intestinal metaplasia; dysplasia was graded as low-grade or high-grade based on architectural and cytologic atypia. Incident EAC was recorded when present.

***Helicobacter pylori (H. pylori)* Testing and Eradication Status**

Per clinic protocol, antibiotics or bismuth were discontinued for ≥4 weeks and proton-pump inhibitors for ≥2 weeks before *H. pylori* testing whenever feasible. *H. pylori* status was determined from histology and/or rapid urease testing as documented in the records. When given, we recorded eradication therapy and documented post-treatment confirmation (follow-up endoscopy/pathology or rapid urease test) when available.

Data Management and Quality Control

Data were abstracted on-site (Medical Records Unit) into a pre-piloted checklist. Identifiers were removed and a study code assigned to preserve confidentiality. We clarified missing or ambiguous entries through chart review and, when necessary, phone contact, as documented.

Statistical Analysis

We conducted analyses using SPSS software version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± SD, and categorical variables as frequency (percentage). Categorical comparisons across outcome trajectory groups (improved, unchanged, worsened) used the Chi-square test or Fisher's exact test when expected counts were <5. We compared continuous variables (e.g., age, follow-up interval) using one-way ANOVA or independent-samples t tests, as appropriate. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

We included 87 patients with BE who met the eligibility criteria and underwent at least two endoscopic evaluations during the study period in the final analysis.

Table 1 presents the demographic and clinical characteristics of the study cohort. The majority were men (56.3%, n=49),

with a mean age of 50.5 ± 18.6 years (range: 19–87 years). Socioeconomic status was most frequently reported as good (40.2%), followed by excellent (25.3%), fair (18.4%), and poor (16.1%). The most common occupation was employee (35.6%), followed by self-employed (28.7%), retired (21.8%), and unemployed (13.8%). Cigarette smoking was documented in 29.9% of patients, and more than half (56.3%) reported an unhealthy dietary pattern. *H. pylori* infection was detected in 39.1% of cases. The mean interval between the first and last endoscopy was 50.9 ± 32.5 months (range: 6–117 months).

At the initial endoscopic assessment (Table 2), short-segment BE (SSBE) was observed in 70.1% (n=61), whereas long-segment BE (LSBE) accounted for 29.9% (n=26).

Table 3 summarizes changes in histopathology between baseline and the most recent endoscopy. Among patients with baseline SSBE, 21.3% (n=13) showed complete regression (no BE at follow-up), while 78.7% (n=48) remained unchanged; no cases progressed. In contrast, among those with baseline LSBE, 3.8% (n=1) achieved complete regression, 61.5% (n=16) regressed to SSBE, 15.4% (n=4) remained stable, and 19.2% (n=5) progressed to LGD.

Overall, at the end of follow-up, 14 patients (16.1%) had no evidence of BE, 64 (73.6%) had SSBE, 4 (4.6%) had persistent LSBE, and 5 (5.7%) had developed LGD. When categorized, 30 patients (34.5%) demonstrated improvement (complete or partial regression), 52 (59.8%) showed no change, and 5 (5.7%) experienced histologic progression. Importantly, all cases of progression occurred among patients with baseline LSBE, whereas no progression was observed in those with baseline SSBE.

Figure 1 illustrates the longitudinal histopathological trajectories of patients with BE. Among those with baseline SSBE, most remained stable, with a subset achieving complete regression. In contrast, patients with LSBE demonstrated both partial regression to SSBE and progression to dysplasia, with all cases of progression arising from the LSBE group.

Table 4 details associations between demographic/clinical variables and histologic outcomes. Sex, age, socioeconomic status, occupation, smoking, and dietary pattern were not significantly related to outcome trajectories (all P>0.05). In contrast, *H. pylori* infection was significantly associated with a favorable outcome (P=0.014). Regression or improvement occurred more frequently among *H. pylori*-positive patients. Additionally, the interval between the first and last endoscopy was significantly longer in patients with improvement compared with those who remained unchanged or progressed (P=0.014).

Table 1. Baseline demographic and clinical characteristics of patients with Barrett's esophagus (n=87)

Variable	Category	n (%) / Mean ± SD (range)
Sex	Male	49 (56.3)
	Female	38 (43.7)
Age (years)	50.5 ± 18.6 (19–87)	
Socioeconomic status	Poor	14 (16.1)
	Fair	16 (18.4)
	Good	35 (40.2)
	Excellent	22 (25.3)
Occupation	Employee	31 (35.6)
	Self-employed	25 (28.7)
	Retired	19 (21.8)
	Unemployed	12 (13.8)
Smoking	Yes	26 (29.9)
	No	61 (70.1)
Dietary pattern	Healthy	38 (43.7)
	Unhealthy	49 (56.3)
H. pylori infection	Positive	34 (39.1)
	Negative	53 (60.9)
Interval between index and last endoscopy (months)		50.9 ± 32.5 (6–117)

Table 2. Baseline severity of Barrett's esophagus (n=87)

BE type	n (%)
Short-segment	61 (70.1)
Long-segment	26 (29.9)

Table 3. Histopathologic changes from baseline to last follow-up

Baseline BE type	Follow-up outcome	n (%)
Short-segment BE (n=61)	Not seen	13 (21.3)
	Remained SSBE	48 (78.7)
	LSBE	0
	LGD	0
Long-segment BE (n=26)	Not seen	1 (3.8)
	Regressed to SSBE	16 (61.5)
	Remained LSBE	4 (15.4)
	LGD	5 (19.2)
Total (n=87)	Not seen	14 (16.1)
	SSBE	64 (73.6)
	LSBE	4 (4.6)
	LGD	5 (5.7)

Table 4. Association between demographic/clinical variables and patient outcomes

Variable	Improved n (%)	Stable n (%)	Worsened n (%)	p-value
Sex				0.534*
Male	16 (32.7)	29 (59.2)	4 (8.2)	
Female	14 (36.8)	23 (60.5)	1 (2.6)	
Age (years)	53.2 ± 20.1	49.2 ± 18.3	45.2 ± 21.3	0.563**
Socioeconomic status				0.408*
Poor	7 (50.0)	6 (42.9)	1 (7.1)	
Fair	7 (43.8)	8 (50.0)	1 (6.3)	
Good	7 (20.0)	26 (74.3)	2 (5.7)	
Excellent	9 (40.9)	12 (54.5)	1 (4.5)	
Occupation				0.929*
Employee	10 (32.3)	19 (61.3)	2 (6.5)	
Self-employed	8 (32.0)	15 (60.0)	2 (8.0)	
Retired/ Unemployed	12 (38.7)	18 (58.1)	1 (3.2)	
Smoking	Yes 8 (30.8)	17 (65.4)	1 (3.8)	0.749*
	No 22 (36.1)	35 (57.4)	4 (6.6)	
Dietary pattern	Healthy 14 (36.8)	22 (57.9)	2 (5.3)	0.916*
	Unhealthy 16 (32.7)	30 (61.2)	3 (6.1)	
H. pylori	Positive 18 (52.9)	15 (44.1)	1 (2.9)	0.014**
	Negative 12 (22.6)	37 (69.8)	4 (7.5)	
Interval (months)	54.3 ± 30.2	45.0 ± 33.0	29.1 ± 11.4	0.014**

* Chi-squared test/ ** ANOVA

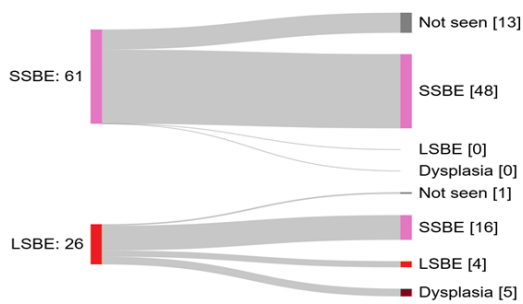


Figure 1. Sankey diagram showing histopathologic transitions from baseline to last follow-up in 87 patients with Barrett's esophagus. At baseline, 61 patients had short-segment BE (SSBE) and 26 had long-segment BE (LSBE). During follow-up, most SSBE cases remained stable or regressed, while LSBE cases demonstrated both regression to SSBE and progression to low-grade dysplasia. All dysplastic transformations occurred in the LSBE group.

DISCUSSION:

The present study provides a 12-year longitudinal perspective on the histopathologic course of BE in an Iranian cohort and offers important insights into demographic characteristics, disease trajectories, and prognostic factors. Consistent with international reports, we observed that BE was more frequent among middle-aged men with relatively good socioeconomic status, a finding consistent with Kuribayashi and colleagues (2021), who described a higher prevalence of BE among overweight, smoking males in their 5th and 6th decades of life (35). The male predominance may reflect differences in GERD prevalence, higher rates of tobacco use, and lifestyle behaviors among men (36). Although socioeconomic status did not significantly influence progression in our study, its importance has been highlighted elsewhere. Zhou and others (2023) reported that socioeconomic disparities may affect BE outcomes independent of race or ethnicity (37).

Most patients in our cohort presented with SSBE, while LSBE accounted for approximately one-third of cases. This distribution is similar to the findings of Tan and colleagues, who showed that SSBE was present in 73% of newly diagnosed patients in the United States (38). The predominance of SSBE may be related to earlier detection and surveillance, while LSBE represents a clinically significant subgroup at higher risk for progression and requiring closer follow-up. Notably, complete regression was observed in 16.1% of patients, predominantly in those with SSBE (21.3%), compared with only 3.8% of patients with LSBE. These results are in agreement with Bhat and others (2011), who demonstrated that patients with SSBE have higher rates of regression during long-term follow-up (39). Moreover, 61.5% of patients with LSBE experienced partial regression to SSBE, suggesting that medical therapy, particularly long-term proton pump inhibitors (PPIs), may play an important role in disease modification. This observation is consistent with the randomized trial by Shaheen and colleagues (2009), in which PPI therapy not only improved GERD symptoms but also led to endoscopic and histologic improvement of esophageal mucosa (40).

Despite these favorable outcomes, 5.7% of patients progressed to LGD, all of whom had LSBE at baseline, highlighting the higher malignant potential of LSBE compared with SSBE. None of the patients with SSBE in our cohort developed dysplasia during follow-up, which underscores the indolent nature of SSBE. These findings align with Weston and colleagues (2004), who identified segment length as a major determinant of progression to dysplasia and EAC (31). More than half of our patients (59.8%) remained stable, most of whom had SSBE, further

supporting the concept that SSBE typically follows a static course, whereas LSBE carries greater risk and requires intensified surveillance.

One of the most notable findings was the association between *H. pylori* infection and improved outcomes, as regression occurred more frequently in infected patients. Although this may seem paradoxical given the established role of *H. pylori* in gastric carcinogenesis, several studies have reported an inverse association between *H. pylori* and BE. Weston et al. and Wang et al. both described a protective effect of *H. pylori* against BE progression (37,38). Rubenstein and others (2013) also showed that infection with cagA-positive strains was inversely associated with BE prevalence (41). The hypothesized mechanism is a reduction in gastric acidity due to corpus-predominant gastritis in *H. pylori*–infected patients, thereby attenuating reflux-induced mucosal damage (42). Our findings are consistent with this evidence, suggesting that *H. pylori* may play a protective role in modifying the natural history of BE.

Another significant determinant was the interval between baseline and follow-up endoscopies, which was longer among patients who showed regression compared with those who remained unchanged or progressed. This observation underscores the potential reversibility of some histologic changes in BE under adequate therapy, particularly in SSBE, and highlights the importance of long-term follow-up. At the same time, patients with more severe or suspicious lesions may have undergone earlier repeat endoscopy, which might partially explain the shorter intervals in the non-regression group. This finding warrants further exploration in prospective designs.

Although smoking and unhealthy dietary patterns were highly prevalent in our cohort (29.9% and 56.3%, respectively), neither was statistically associated with progression. However, these factors remain well-established risk determinants for BE and EAC. A meta-analysis by Andrici and colleagues (2013) confirmed that smoking significantly increases BE risk (43), while diets rich in saturated fats and processed foods have been linked to chronic inflammation and epithelial abnormalities (44). The lack of statistical significance in our study may be due to limited sample size rather than the absence of a true effect.

Taken together, our findings underscore the need for individualized, risk-based management of BE. Patients with LSBE should undergo more frequent surveillance, ideally every 3 years, as recommended by the American College of Gastroenterology guidelines (45). Patients with SSBE without dysplasia may be monitored at longer intervals, such as every 5 years, provided that risk factors are controlled (45). Furthermore, the inverse association between *H. pylori* and disease progression highlights the need for mechanistic studies to clarify its protective role. Future research should also incorporate molecular biomarkers such as p53, Ki-67, and TP53 mutations, which have shown promise in identifying high-risk patients (46) as well as inflammatory cytokines such as IL-6 and IL-8 (47).

In conclusion, this study provides novel data on the natural history of BE in an Iranian population and demonstrates patterns largely consistent with international literature while offering region-specific insights. Although complete regression was limited, stability was common, particularly among patients with SSBE, whereas patients with LSBE carried a disproportionate risk of progression. These findings highlight the importance of early detection, risk-based surveillance, lifestyle modification, and regular pathologic evaluation to optimize BE management and reduce the burden of progression to dysplasia and carcinoma.

Strengths and limitations

This study has several strengths. It represents one of the few longitudinal analyses of BE in an Iranian cohort over a relatively long follow-up period (12 years), providing region-specific data that are scarce in the literature. Standardized pathology review by a single gastrointestinal pathologist, blinding to clinical information, and inclusion of both SSBE and LSBE cases enhance internal validity and reduce misclassification bias. In addition, the systematic assessment of demographic, lifestyle, and infection-related variables allowed for comprehensive evaluation of potential prognostic factors, including the novel observation of an association between *H. pylori* infection and improved outcomes.

Nevertheless, several limitations warrant acknowledgment. The retrospective design inherently carries the risk of incomplete or missing data, particularly regarding lifestyle variables such as smoking and dietary habits, which may have been underreported. The sample size, although sufficient for descriptive and exploratory analyses, limited the statistical power to detect modest associations, especially in subgroup comparisons.

The study did not assess molecular markers or advanced endoscopic imaging modalities, limiting mechanistic insight into progression pathways. Moreover, because the study was conducted at a single referral center, generalizability to broader populations should be interpreted with caution. Finally, surveillance intervals varied across patients, which may have influenced observed rates of regression and progression.

CONCLUSION:

In this 12-year retrospective cohort study of patients with BE in Kashan, Iran, most patients presented with short-segment BE, which generally showed a stable or regressive course, while long-segment BE was more prone to progression and accounted for all cases of dysplasia. *H. pylori* infection and longer surveillance intervals were associated with favorable outcomes, suggesting that certain histopathological changes in BE may be at least partially reversible with appropriate management. Although lifestyle factors such as smoking and unhealthy diet were highly prevalent, they did not reach statistical significance in predicting progression, likely due to limited sample size. Collectively, these findings emphasize the need for individualized, risk-based surveillance strategies, with closer monitoring of long-segment patients with BE and tailored preventive interventions. Future prospective studies integrating molecular biomarkers and advanced endoscopic techniques are warranted to refine risk stratification and improve clinical outcomes in this population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of Kashan University of Medical Sciences (Approval Code: IR.KAUMS.MEDNT.REC.1403.157). We obtained written informed consent from all participants before inclusion. The study was conducted in accordance with the Declaration of Helsinki.

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