European Review for Medical and Pharmacological Sciences 2022; 26: 5884-5889

Barrett esophagus frequency and predictors of dysplasia or cancer in Barrett esophagus

N.T. KUCUKMETIN[1] A. TIFTIKCI[2], B. CICEK[3]

[1]Department of Gastroenterology, Faculty of Medicine, Namik Kemal University Tekirdag, Turkey
[2]Department of Gastroenterology, Faculty of Medicine, Mehmet Ali Aydinlar University, Istanbul, Turkey
[3]Department of Gastroenterology, Acibadem Maslak Hospital, Istanbul, Turkey

Abstract. – OBJECTIVE: Identificating factors associated with an increased risk for dysplasia and cancer development among patients with Barrett esophagus would aid better patient care and improve risk stratification approaches. This study aimed at examining the frequency of Barrett esophagus and factors predicting the presence of dysplasia and cancer among patients with Barrett esophagus.

PATIENTS AND METHODS: Adult patients that underwent upper gastrointestinal endoscopic examination for gastroesophageal complaints were screened in this retrospective, cross-sectional study; and patients diagnosed with Barrett esophagus were included in the analysis. Frequency of dysplasia/cancer and its predictors were examined.

RESULTS: Among 10,404 endoscopic examinations performed during the study period, 143 patients (1.4%) were diagnosed with Barrett esophagus. Among patients with Barrett esophagus, the frequency for high-grade dysplasia, low grade dysplasia, and adenocarcinoma was 2.8%, 2.1%, and 1.4%, respectively. On multivariate analysis, age ≥55 years (OR, 11.1 [95%CI: 2.0-61.4], *p*=0.006) and long segment Barrett esophagus (OR, 5.7 [95%CI: 1.2-27.8], *p*=0.031) emerged as significant independent predictors for dysplasia/cancer.

CONCLUSIONS: Frequency of Barrett esophagus in our population seems to be different than figures reported from different geographical regions. Advanced age and long Barrett segment on endoscopic examination are associated with the presence of concomitant dysplasia/cancer on pathological examination. Larger studies with prospective methodology are warranted.

Key Words:
Barrett esophagus, Dysplasia, Esophageal cancer, Upper gastrointestinal endoscopy.

Introduction

Chronic gastroesophageal reflux disease (GERD) is already known as an established risk factor for the development of Barrett esophagus, along with obesity, advanced age, male gender, and Caucasian ethnicity[1]. Barrett esophagus is defined as the presence of metastatic columnar epithelium in distal esophagus to any extent, instead of its normal stratified squamous epithelial lining[2].

The presence of Barrett esophagus with intestinal metaplasia is the only histological type that has been clearly linked to esophageal cancer[2]. Esophageal cancer is still associated with poor survival, necessitating close surveillance for Barrett esophagus[2,3].

It is hard to identify the true prevalence of Barrett esophagus; therefore, it is unclear. A screening study identified 6.8% frequency among patients that underwent colonoscopy simultaneously with screening upper gastrointestinal endoscopy[4]. On the other hand, figures from Turkey for patients with dyspeptic complaints or reflux symptoms are far lower and data for cancer prevalence are lacking[5-7]. There may be geographical differences in epidemiology and course of Barrett esophagus.

Identification of the factors associated with increased risk for dysplasia and cancer development would not only aid better and individualized patient care and follow-up, but also improve the understanding of the disease process and risk stratification algorithms. So far, several studies[8-13] with different methodologies have examined the predictors for unfavorable progression of Barrett esophagus, and identified longer segment, advanced age, mucosal irregularities, male gender, longstanding GERD, increased hiatal hernia size, nodularity and visible endoscopic lesions, lifestyle, medications, molecular markers, abdominal obesity, caffeine intake, smoking, and presence of esophagitis as potential predictors. However, these findings need to be validated and confirmed with the data of patient groups from different geographical regions.

Corresponding Author: Nurten Turkel Kucukmetin, MD; e-mail: nturkel@hotmail.com

This study aimed at examining the frequency of Barrett esophagus among patients that underwent upper gastrointestinal endoscopy for dyspeptic complaints, and frequencies of dysplasia and cancer among patients diagnosed with Barrett esophagus as well as factors predicting presence of dysplasia and cancer.

Patients and Methods

Study Design

Adult patients that underwent upper gastrointestinal endoscopic examination between January 2010 and September 2018 for dyspeptic complaints, epigastric pain, or symptoms suggestive of GERD were screened for this retrospective cross-sectional study, and the patients diagnosed with Barrett esophagus were included in the analyses. Patients younger than 18 years, pregnant women, and patients with known malignant disease or patients who were diagnosed with squamous cell carcinoma of esophagus or other gastric cancers during the endoscopic examination were excluded.

Endoscopic and Pathological Examination

A diagnosis of Barrett esophagus was made with both endoscopic examination and pathological examination findings. Endoscopic examinations were done using Exera-II CV 180 series or Exera-II CV 190 series devices (Olympus, Japan). Under white light endoscopic examination, a salmon color change was considered characteristic appearance of Barrett esophagus. Barrett esophagus was suspected when squamocolumnar junction was located ≥ 1 cm proximal to the gastroesophageal junction and optical chromoendoscopy was performed with narrow band imaging. A Barrett esophagus segment of ≥ 3 cm and < 3 cm was defined as long segment and short segment Barrett esophagus, respectively. Multiple biopsies were obtained from suspected regions. No biopsy was taken from apparently normal Z line or irregular Z line extending < 1 cm to the esophagus.

Statistical Analysis

Statistical Package for Social Sciences version 21.0 (SPSS, IBM Corp., Armonk, NY, USA) was used for data analysis. To test the normality of continuous variables, hypothesis tests and graphical methods were used; and Student's *t*-test or Mann-Whitney U test was used for intergroup comparisons of continuous data, where appropriate. For intergroup comparisons of dichotomous data, Pearson's Chi-square test or Fisher's Exact test was used, where appropriate. Logistic regression was used for multivariate analysis of the potential predictors for cancer or dysplasia on pathological examination. Receiver Operating Characteristic (ROC) curves were used to identify optimal cut-off values for age to be incorporated in multivariate analysis. A p-value < 0.05 was considered statistically significant.

Results

A total of 10,404 endoscopic examinations were performed during the study period. Among them, 143 (1.4%) were diagnosed with Barrett esophagus; in addition, 4 (0.04%) had high grade dysplasia, 3 (0.03%) had low-grade dysplasia, and 2 (0.02%) had adenocarcinoma. The frequency for high grade dysplasia, low grade dysplasia, adenocarcinoma was 2.8%, 2.1%, and 1.4%, respectively, among patients diagnosed with Barrett esophagus.

Table I compares Barrett esophagus patients with or without dysplasia/cancer based on pathological examination in terms of demographical and clinical characteristics. An optimal cut-off point of 55 years was found through ROC analysis (AUC: 0.671, p=0.087) with 0.78 sensitivity and 0.72 specificity. Figure 1 shows Receiver Operating Characteristics (ROC) curve for age to predict the presence of dysplasia/cancer on pathological examination. Dysplasia/cancer was more frequent among patients ≥ 55 years of age (p=0.004); however, the difference did not reach statistical significance for gender, Barrett length (short or long segment), or hernia presence (p > 0.05 for all).

On multivariate analysis, age ≥ 55 years (OR, 11.1 [95%CI: 2.0-61.4], p=0.006) and a long segment Barrett esophagus (OR, 5.7 [95%CI: 1.2-27.8], p=0.031) emerged as significant independent predictors of dysplasia/cancer on pathological examination, among patients with Barrett esophagus.

Follow-up of Patients with Dysplasia/Cancer

Table II summarizes the characteristics of nine patients diagnosed with dysplasia/cancer. All patients were male and intestinal metaplasia was the

only type identified in Barrett esophagus patients diagnosed with dysplasia/cancer.

Discussion

This study demonstrated a relatively low frequency of Barrett esophagus among patients who received upper gastrointestinal endoscopic examination for dyspeptic complaints, and Barrett length and advanced age emerged as significant independent predictors of dysplasia/cancer on pathological examination. This study is among the few examples of its kind[11] examining the predictors of dysplasia/cancer with a cross-sectional design.

A previous study by Anandasabapathy et al[11] with a similar retrospective cross-sectional design with the present study, examined 109 patients who were diagnosed with Barrett esophagus and demonstrated the risk factors for the presence of high/low grade dysplasia and adenocarcinoma on pathological examination; and identified duration of reflux symptoms (≥ 20 years), longer Barrett segment (≥ 3 cm), hernia size and male gender as indicators for higher pathological grade. Similarly, Barrett length emerged as a significant predictor for unfavorable pathological findings in the present study. On the other hand, the present study is inconsistent with the study of Anandasabapathy et al[11] in the fact that age did not emerge as a predictor; however, that study did not perform an analysis with an age cut-off value. In our study, although age did not emerge as a predictor when included as a continuous variable, the optimal cut-off point identified (55 years) emerged as a significant predictor. This finding actually may be considered in line with the findings of that previous study, which found the duration of GERD as a significant predictor.

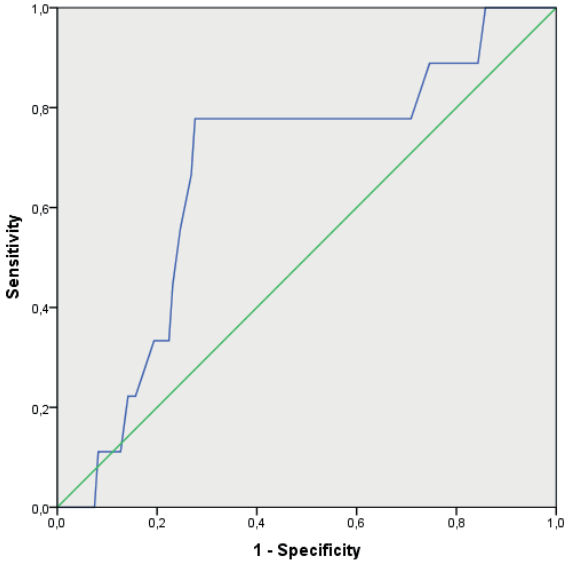

Figure 1. Receiver Operating Characteristics (ROC) curve for age to predict presence of dysplasia/cancer on pathological examination.

To date, several studies have examined the predictors for progression of Barrett esophagus to higher pathological grades over time[8-10,14-17]. A recent study[10] with 518 patients diagnosed with Barrett esophagus identified longer Barrett's esophagus segment, increased age (≥ 60 years), and the presence of mucosal irregularities as independent predictors for progression to higher pathological grades. Again, another study[15] included 318

Table I. Comparison between the period March/April 2020 (Group 1A) and the same period in 2019 (Group 1B).

	Dysplasia/Cancer present (n=9)	Dysplasia/Cancer absent (n=134)	*p*
Age, years (mean±SD)	55.3±12.1	47.4±13.6	0.087
Age group			
Age≥55 (n=44)	7 (15.9%)	37 (84.1%)	0.004
Age<55 (n=99)	2 (2.0%)	97 (98.0%)	
Gender			
Male (n=107)	9 (8.4%)	98 (91.6%)	0.112
Female (n=36)	0 (0.0%)	36 (100.0%)	
Barrett length			
Short (n=95)	3 (3.2%)	92 (96.8%)	0.061
Long (n=48)	6 (12.5%)	42 (87.5%)	
Hernia			
Absent (n=99)	7 (7.1%)	92 (92.9%)	0.772
Present (n=44)	2 (4.5%)	42 (95.5%)	

Unless otherwise stated, data presented as n (%).

Table II. Summary of nine patients diagnosed with dysplasia/cancer.

Pt. No.	Age/Sex	Barret length	Hernia	Diagnosis	Course
1	57/M	Short	Absent	LGD	No intervention, lost to follow-up.
2	33/M	Long	Present	LGD	RF, alive without disease.
3	58/M	Long	Absent	LGD	No intervention, lost to follow-up.
4	56/M	Long	Absent	HGD	EMR resulted in cure, lost to follow-up.
5	69/M	Long	Present	HGD	RFx2, progressed to stage IV disease, died.
6	66/M	Short	Absent	HGD	RFx4 resulted in cure, alive without disease.
7	62/M	Short	Absent	HGD	EMR identified intramucosal Adeno Ca, RFx2 resulted in cure, alive without disease.
8	59/M	Long	Absent	Adenocarcinoma	Surgical resection, alive without disease.
9	38/M	Long	Absent	Adenocarcinoma	Surgical resection, lost to follow-up.

M, male; LGD, low grade dysplasia; HGD, high grade dysplasia; RF, radiofrequency ablation; EMR, endoscopic mucosal resection.

non-dysplastic Barrett esophagus patients and 301 patients with Barrett esophagus accompanied with low grade dysplasia, and patients were followed for a mean duration of 5.3 years. In that study, Barrett esophagus length, presence of nodularity, and low-grade dysplasia at baseline emerged as significant predictors for progression to esophageal carcinoma[15]. Another recent retrospective study[13] on 460 patients identified age, caffeine intake, and low-grade dysplasia as risk factors for progression to high grade dysplasia or esophageal cancer but also demonstrated that statin or SSRI usage reduced the risk. A 2018 meta-analysis with 20 studies[17], more than 1,200 events, and almost 75,000 patients, identified advanced age, male sex, current or past smoking, higher Barrett segment length, and low-grade dysplasia as predictors for progression; and use of proton pump inhibitors or statins emerged as protective factors. In several small-sized studies, few biomarkers, such as aneuploidy and p53 loss of heterozygosity, were found to be associated with progression[14]. Although several factors such as Barrett length, age, and low-grade dysplasia consistently found to be associated with poor outcomes over time, other potential predictors vary across studies owing to the use of different methodologies and assessments. Based on such findings, algorithms and even computer models have been developed using clinical, endoscopic, and molecular predictors for progression; however, they all need further development and validation[12,14].

GERD is a common and ever-increasing problem in the Western world[18,19]. A 2014 meta-analysis[19] found that GERD prevalence was estimated between 18.1-27.8% and 8.8-25.9%, in North America and Europe, respectively[19]. On the other hand, rates in East Asia were relatively lower (2.5-7.8%). However, such rates may be underestimated given the fact that many people use over-the-counter GERD medications[18]. Previous studies[21,22] showed a similar population prevalence in Turkey; thus, it can be considered as a high prevalence country. Prevalence of GERD was estimated to be 20% in a study conducted by Bor et al[20] in Izmir region. Another nation-wide population-based study estimated 19.1% GERD prevalence in Turkey[21].

Barrett esophagus is a clinically imported complication of GERD; however, there are variations in the reported figures for its prevalence, possibly due to differences in methodologies[6]. For example, some studies[6] were conducted in patients with GERD symptoms or any dyspeptic symptoms, and some were done with healthy individuals. In Western countries with estimated high prevalence of GERD, the reported[6,22] prevalence estimates of Barrett esophagus are also relatively high among individuals with gastrointestinal complaints, mostly ranging between 8.6-50%, although a figure as low as 0.08% has also been reported from Spain[22]. In contrast, the present study found a low prevalence rate (1.4%) among patients with dyspeptic complaints in a country that can be considered to have high prevalence of GERD. This is in line with the figures previously reported from Turkey. In a study by Yilmaz et al[7], a low prevalence of Barrett esophagus (0.4%) was found among 18,766 patients who underwent upper gastrointestinal endoscopy for general symptoms. In another study by Bayrakci et al[5], Barrett esophagus rate was 2% among 160 patients who underwent endoscopy for GERD symptoms. Such a difference between Turkey and Western countries may be explained by differences in certain risk factors such as eating habits, obesity prevalence, and *H. pylori* prevalence.

In the present study, adenocarcinoma rate was 1.4% among patients diagnosed with Barrett esophagus and 0.02% among whom had endoscopy for dyspeptic symptoms. This study also provided the dysplasia rates among these patients. Previously, no data were present regarding the frequency of Barrett-related dysplasia and adenocarcinoma in Turkish population[6].

Findings of this study underscore the differences between various geographical locations in terms of the progression and course of upper gastrointestinal conditions from simple gastrointestinal complaints to the development of Barrett esophagus and possible dysplasia and cancer. Such information may give clues for developing more accurate algorithms to predict serious upper gastrointestinal conditions; possibly including certain geographical factors may result in improvements. In addition, our findings support current evidence on the prognostic role of Barrett length and age – or indirectly the duration of GERD symptoms – in the development of higher pathological grades including cancer.

Limitations

The main limitation of the present study is its retrospective and cross-sectional design, and findings do not give an idea about the timely course of pathological changes. Another limitation may be considered the relatively small sample size.

Conclusions

Our findings demonstrate a difference in the frequency of Barrett esophagus in our geographical location when compared to Western societies. In addition, Barrett length and advanced age appears to be important indicators for the presence of dysplasia/cancer among patients with Barrett esophagus. Further large-scale studies will shed light on the course of these upper gastrointestinal conditions.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval

The study was performed according to the principles of the Declaration of Helsinki and the protocol was approved by the local ethics committee (Acibadem Mehmet Ali Aydinlar University, Ethics Committee for the Evaluation of Medical Studies; No. 2022-06/38; date: March 25, 2022).

Informed Consent

Informed consent was not required since the study was retrospective; all information is presented anonymously, and no private data of patients are presented in the manuscript. However, an informed consent for the intervention (not for the study) had been received from the patient at the time of intervention.

Authors' Contributions

All authors contributed to the study conception and design. Statistical analysis was designed and performed by Nurten Turkel-Kucukmetin. Material preparation and data collection were performed by all authors. The first draft of the manuscript was written by Nurten Turkel-Kucukmetin, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study was not funded.

ORCID ID

Nurten Turkel Kucukmetin: 0000-0002-0015-614X; Arzu Tiftikci: 0000-0002-6735-0799; Bahattin Cicek: 0000-0002-8415-5047.

References

1) Winberg H, Lindblad M, Lagergren J, Dahlstrand H. Risk factors and chemoprevention in Barrett's esophagus--an update. Scand J Gastroenterol 2012; 47: 397-406.
2) American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology 2011; 140: 1084-1091.
3) Wang KK, Sampliner RE, Practice Parameters Committee of the American College of G. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2008; 103: 788-797.
4) Rex DK, Cummings OW, Shaw M, Cumings MD, Wong RK, Vasudeva RS, Dunne D, Rahmani EY, Helper DJ. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. Gastroenterology 2003; 125: 1670-1677.
5) Bayrakci B, Kasap E, Kitapcioglu G, Bor S. Low prevalence of erosive esophagitis and Barrett

esophagus in a tertiary referral center in Turkey. Turk J Gastroenterol 2008; 19: 145-151.

6) Bor S, Saritas Yuksel E. How is the gastroesophageal reflux disease prevalence, incidence, and frequency of complications (stricture/esophagitis/Barrett's esophagus/carcinoma) in Turkey compared to other geographical regions globally? Turk J Gastroenterol 2017; 28: S4-S9.
7) Yilmaz N, Tuncer K, Tuncyurek M, Ozutemiz O, Bor S. The prevalence of Barrett's esophagus and erosive esophagitis in a tertiary referral center in Turkey. Turk J Gastroenterol 2006; 17: 79-83.
8) Sikkema M, Looman CW, Steyerberg EW, Kerkhof M, Kastelein F, van Dekken H, van Vuuren AJ, Bode WA, van der Valk H, Ouwendijk RJ, Giard R, Lesterhuis W, Heinhuis R, Klinkenberg EC, Meijer GA, ter Borg F, Arends JW, Kolkman JJ, van Baarlen J, de Vries RA, Mulder AH, van Tilburg AJ, Offerhaus GJ, ten Kate FJ, Kusters JG, Kuipers EJ, Siersema PD. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. Am J Gastroenterol 2011; 106: 1231-1238.
9) Anaparthy R, Sharma P. Progression of Barrett oesophagus: role of endoscopic and histological predictors. Nat Rev Gastroenterol Hepatol 2014; 11: 525-534.
10) Alnasser S, Agnihotram R, Martel M, Mayrand S, Franco E, Ferri L. Predictors of dysplastic and neoplastic progression of Barrett's esophagus. Can J Surg 2019; 62: 93-99.
11) Anandasabapathy S, Jhamb J, Davila M, Wei C, Morris J, Bresalier R. Clinical and endoscopic factors predict higher pathologic grades of Barrett dysplasia. Cancer 2007; 109: 668-674.
12) Chakraborty S, Iyer PG. Predictors of Progression in Barrett's Esophagus. Curr Treat Options Gastroenterol 2019; 17: 18-31.
13) Kambhampati S, Tieu AH, Luber B, Wang H, Meltzer SJ. Risk Factors for Progression of Barrett's Esophagus to High Grade Dysplasia and Esophageal Adenocarcinoma. Sci Rep 2020; 10: 4899.
14) Prasad GA, Bansal A, Sharma P, Wang KK. Predictors of progression in Barrett's esophagus: current knowledge and future directions. Am J Gastroenterol 2010; 105: 1490-1502.
15) Solanky D, Krishnamoorthi R, Crews N, Johnson M, Wang K, Wolfsen H, Fleischer D, Ramirez FC, Katzka D, Buttar N, Iyer PG. Barrett Esophagus Length, Nodularity, and Low-grade Dysplasia are Predictive of Progression to Esophageal Adenocarcinoma. J Clin Gastroenterol 2019; 53: 361-365.
16) Weston AP, Badr AS, Hassanein RS. Prospective multivariate analysis of clinical, endoscopic, and histological factors predictive of the development of Barrett's multifocal high-grade dysplasia or adenocarcinoma. Am J Gastroenterol 1999; 94: 3413-3419.
17) Krishnamoorthi R, Singh S, Ragunathan K, Visrodia K, Wang KK, Katzka DA, Iyer PG. Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018; 16: 1046-1055.
18) Patti MG. An Evidence-Based Approach to the Treatment of Gastroesophageal Reflux Disease. JAMA Surg 2016; 151: 73-78.
19) El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014; 63: 871-880.
20) Bor S, Mandiracioglu A, Kitapcioglu G, Caymaz-Bor C, Gilbert RJ. Gastroesophageal reflux disease in a low-income region in Turkey. Am J Gastroenterol 2005; 100: 759-765.
21) Mungan Z. Prevalence and demographic determinants of gastroesophageal reflux disease (GERD) in the Turkish general population: a population-based cross-sectional study. Turk J Gastroenterol 2012; 23: 323-332.
22) Alcedo J, Ferrandez A, Arenas J, Sopena F, Ortego J, Sainz R, Lanas A. Trends in Barrett's esophagus diagnosis in Southern Europe: implications for surveillance. Dis Esophagus 2009; 22: 239-248.