

# **Prevalence, clinical characteristics, and risk** factors of Barrett esophagus in Vietnamese patients with upper gastrointestinal symptoms

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#### Abstract

The current barrier for investigation of Barrett esophagus (BE) in Asia is diagnostic standardization, which is a challenge to identify its true risk factors. This study aimed to investigate the prevalence, clinical characteristics and risk factors of BE in Vietnamese patients with upper gastrointestinal symptoms.

A cross-sectional study was conducted on consecutive outpatients who underwent upper gastrointestinal endoscopy. Endoscopically suspected esophageal metaplasia (ESEM) which was clearly visible at least 1 cm above the gastroesophageal junction at endoscopy was taken biopsy. At least 1 biopsy per 2 cm in tongues of ESEM and 4 biopsies per 2 cm of circumferential ESEM were taken. The diagnostic criterion for BE was replacement of the normal squamous epithelial lining by columnar epithelium confirmed by histology.

A total of 1947 patients were recruited. Forty-seven out of 58 patients with ESEM were histologically confirmed BE. The prevalences of BE and hiatal hernia (HH) were 2.4% (95% confidence interval [CI], 1.7–3.1%) and 2.3% (95% CI, 1.6–2.9%), respectively. Heartburn and/or regurgitation presented in only 61.7% (95% CI, 46.4–75.5%) of patients with BE. In multivariate analysis, the only 2 factors significantly associated with BE were HH (OR 7.53; 95% CI, 3.13–18.11; P < .001) and typical reflux symptom (OR 2.07; 95% CI, 1.12–3.83; P=.020).

BE is not uncommon in Vietnamese patients with upper gastrointestinal symptoms. In addition, typical reflux symptoms and HH are the risk factors for BE in Vietnamese.

**Abbreviations:** BE = Barrett esophagus, CI = confidence interval, EAC = esophageal adenocarcinoma, EGD = esophagogastroduodenoscopy, ESEM = endoscopically suspected esophageal metaplasia, HH = hiatal hernia, OR = odds ratio.

Keywords: Barrett esophagus, hiatus hernia, prevalence, risk factor, Vietnamese

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### 1. Introduction

Barrett esophagus (BE) is a precursor for the development of esophageal adenocarcinoma (EAC). The risk of EAC was about 30-fold or higher among patients with BE compared to that of the general population.<sup>[1]</sup> The increasing prevalence of BE in Western countries over the last 30 years has contributed to the dramatically increasing incidence of EAC in this part of the world.<sup>[2]</sup> In Asia, the prevalence of BE is still lower than that in the West but its increasing trend has been also observed over the past 3 decades.<sup>[3]</sup> There is community-based data showing that the demographic distribution of BE differs markedly by race and is comparable to that of EAC.<sup>[4]</sup> Whether the natural history of BE in Asia will mirror that in the West is an important issue. Currently, the most challenging barrier for further investigations of BE in Asia is diagnostic standardization.<sup>[5]</sup> Endoscopic criteria, biopsy protocols and histologic criteria have been used significantly different across Asian studies. Consequently, there is substantially variability in the reported BE prevalence in the region and the true risk factors might not be correctly identified.<sup>[5,6]</sup> At present, the updated Asia-Pacific consensus defines BE as the replacement of the normal distal squamous epithelial lining by columnar epithelium, which must be clearly visible endoscopically  $\geq 1 \text{ cm}$  above the gastroesophageal junction, and be confirmed by histology. In addition, the Prague C and M classification is recommended for documenting BE in clinical practice.<sup>[7]</sup> However, there have been few studies on

prevalence and risk factors of BE in Asia applying this recommendation; and most of these studies were conducted more than 10 years ago.<sup>[3]</sup> This study was conducted to assess the prevalence, clinical characteristics and risk factors of BE in Vietnamese patients with upper gastrointestinal symptoms using the recommendation of the updated Asia-Pacific consensus.<sup>[7]</sup>

#### 2. Materials and methods

#### 2.1. Study participants

This is a prospective study conducted in out-patients ≥18 years of age who presented with upper gastrointestinal symptoms (e.g., nausea, vomiting, acid regurgitation, heartburn, epigastralgia, and abdominal fullness) and underwent esophagogastroduodenoscopy (EGD) at the University Medical Center at Hochiminh City from August 2017 to March 2018. Patients were excluded if having one or more of the following conditions: prior history of esophageal cancer or gastrectomy, history of bleeding tendency, suspected symptoms of active upper gastrointestinal bleeding within one week, use of anticoagulants or antiplatelets within one week before EGD; detection of esophageal varices, esophageal, gastric, or duodenal cancer during EGD; whom rapid urease test was not performed; or whom not being able to tolerate EGD under topical anesthesia for a thorough endoscopic examination.

Informed consent was obtained from all participants. The Board of Ethics in Biomedical Research of University of Medicine and Pharmacy at Ho Chi Minh City approved the study protocol (ID number: 271/DHYD-HD, signed on August 4, 2018).

#### 2.2. Pre-endoscopic evaluation

Before patients underwent EGD, the patients' symptoms, history of smoking and alcohol consumption were recorded. The typical reflux symptoms (i.e., heartburn and regurgitation) were carefully described to every patient by 2 investigators (QTTP and TLTT). All recruited patients then filled out the gastro-esophageal reflux disease questionnaire (GERDQ).<sup>[8]</sup> The Vietnamese version of this questionnaire has been previously validated. Waist and hip circumference were measured in every patient following instructions of the World Health Organization (WHO) Expert Consultation report.<sup>[9]</sup> The body mass index and waist–hip ratio were calculated for all patients. All of the above-mentioned clinical information were kept blinded to the endoscopists who performed EGDs.

#### 2.3. Endoscopic examination

The EGDs were performed under topical anesthesia by experienced endoscopists (VNTH, LQD, NDTN, DNLB, LNQ) using Olympus scopes GIF-160 or GIF-Q180 (Olympus Co Ltd, Tokyo, Japan). All of these endoscopists have experienced with at least 5000 EGD procedures over the last 5 years and attended 2 local training workshops on BE assessment according to the Prague C and M classification. These workshops were organized 4 weeks apart at the Department of Endoscopy, University Medical Center at Hochiminh City before patient recruitment. The trainer was a senior endoscopist (QDT) who was also a core member of the Asia-Pacific Barrett Consortium (ABC). The materials used for the training were video clips provided by ABC, which had been used for multicenter training workshop across Asia and shown an excellent agreement among Asian endoscopists.<sup>[10]</sup> In addition, these endoscopists have also attended previous local training workshops on the assessment of gastroesophageal flap valve and hiatal hernia (HH) as described in our previous report.<sup>[11]</sup>

In this study, sliding HH was diagnosed when the apparent separation between the squamocolumnar junction, which was defined as the top of gastric folds, and the diaphragmatic impression was  $>2 \text{ cm.}^{[12]}$  Patients were considered *Helicobacter pylori* infection when local validated rapid urease test, which has been confirmed to have the same accuracy as PyloriTek (Serim Research Corp, Elkhart, IN), was positive within 1 hour.<sup>[13]</sup>

A standard protocol for documenting BE using the Prague C and M criteria at endoscopy was applied in all patients.<sup>[14]</sup> The proximal margin of the gastric folds was considered as the endoscopic landmark for gastroesophageal junction. Endoscopically suspected esophageal metaplasia (ESEM) which was clearly visible  $\geq 1$  cm above the gastroesophageal junction at endoscopy was rated according to the Prague C and M criteria.<sup>[14]</sup> Extent of the lesion was recorded as CxMy (with x and y stands for values of circumferential and maximum extent, respectively). At least 1 biopsy per 2 cm in tongues of endoscopic suspected BE, and 4 biopsies per 2 cm of circumferential suspected BE were taken for histologic examination.<sup>[14,15]</sup> Additional target biopsies were also taken if local lesion was identified endoscopically.

# 2.4. Histologic examination

Biopsy specimens were fixed in formalin 10%. Sections were cut at 5 µm and stained with Giemsa and hematoxylin and eosin. The diagnostic criterion for BE was replacement of the normal distal squamous epithelial lining by columnar epithelium.<sup>[7]</sup> Dysplasia, when present and definite, was graded as low grade or high grade according to the Vienna classification.<sup>[16]</sup> All of the specimens were histologically examined by experienced gastrointestinal pathologists at the Department of Surgical Pathology, University Medical Center at Hochiminh City. A senior gastrointestinal pathologist (HML) re-checked all the specimens and made the final conclusion.

# 2.5. Statistical analysis

Continuous and categorical variables were expressed as mean  $\pm$  standard deviation and 95% confidence interval (95% CI), respectively. Continuous variables were analyzed using Student *t* test or 1-way analysis of variance as appropriate. Categorical variables were analyzed using Pearson Chi-squared test. Univariable and multivariable analyses using logistic regression were performed to identify the risk factors for BE. All tests were 2-sided and performed at the 5% level of significance. All statistical calculations were performed with SPSS version 20.0 for Windows software (SPSS, Chicago, IL).

# 3. Results

There were 1947 patients fulfilling the criteria and undergoing upper gastrointestinal endoscopy (Fig. 1). Fifty-eight patients had ESEM and all were taken biopsy for histologic examination. There were 2 patients in whom the number of biopsy specimens were less than recommended but BE were histologically diagnosed in both cases. Totally, histologic examination confirmed BE in 47 patients. The prevalences of BE in the whole population and in patients with ESEM were 2.4% (95% CI, 1.7–3.1%) and 81.0% (95% CI, 68.6–90.1%), respectively.



Figure 1. Flowchart for patients recruited into the study. BE=Barrett esophagus, EGD=esophagogastroduodenoscopy, ESEM=endoscopically suspected esophageal metaplasia.

The demographic and clinical characteristics of patients in the study are presented in Table 1. The mean age of patients with BE was  $45.34 \pm 11.44$ . Male was slightly predominant with the male-to-female ratio of 1.7:1. The prevalences of typical reflux symptoms (i.e., heartburn or regurgitation) were 40.5% (95% CI, 38.3-42.7%) in the whole population, and 61.7% (95% CI, 46.4-75.5%) in patients with BE. However, heartburn and regurgitation were chief complaints in only 10.6% (95% CI, 3.5-23.1%) and 19.1% (95% CI, 9.1-33.3%) of patients with BE, respectively. The prevalences of BE in subgroups of patients with and without typical reflux symptoms were 3.7% (95% CI, 2.4-5.0%) and 1.6% (95% CI, 0.8-2.3%), respectively.

The endoscopic findings of patients in this study are presented in Table 2. Histologically, there were 8 (17.0%) BE with intestinal metaplasia and 39 (83.0%) with columnar metaplasia. Two (4.2%) patients with BE had low-grade dysplasia, 1 with intestinal metaplasia and the other with cardiac metaplasia. Both patients were endoscopically classified as C $\leq$ 1M1 and did not have co-existent reflux esophagitis. The prevalences of intestinal-type BE in the whole population and in patients with ESEM were 0.4% (95% CI, 0.1–0.7%) and 13.8% (95% CI, 6.1–25.4%), respectively. In the subgroup of patients presenting with typical reflux symptoms, the prevalence of BE was 3.7% (95% CI, 2.4–5.0%) and there were no patients with intestinal-type BE.

In univariate analysis, there were significant associations between BE and male, smoking, HH, reflux esophagitis, typical reflux symptoms, and GERDQ score (Table 3). In multivariate analysis, only the associations between BE and HH and typical


#### Demographic and clinical characteristics of patients in the study.

	Total	Patients with Barrett esophagus	Patients without Barrett esophagus
Characteristics	n = 1947	n=47	n=1900
Age (mean $\pm$ SD)	42.47 ± 12.00	$45.34 \pm 11.44$	$42.40 \pm 12.00$
Sex			
Male (n, %)	890 (45.7)	30 (63.8)	17 (36.2)
Female (n, %)	1057 (54.3%)	17 (36.2)	1040 (54.7)
Body mass index (mean $\pm$ SD)	$22.34 \pm 3.03$	$22.82 \pm 2.75$	22.34 ± 3.04
Waist circumference	$79.72 \pm 9.02$	$82.23 \pm 9.24$	79.66±9.01
Waist-to-hip ratio	0.84 <u>+</u> 0.07	$0.86 \pm 0.06$	$0.84 \pm 0.07$
Smoking (ex- or current) (n, %)	440 (22.6)	19 (40.4)	421 (22.2)
Alcohol usage (n, %)	565 (29.0)	16 (34.0)	549 (28.9)
Chief complaints			
Heartburn (n, %)	69 (3.5)	5 (10.6)	64 (3.3)
Regurgitation (n, %)	233 (12.0)	9 (19.1)	224 (11.8)
Epigastric pain (n, %)	929 (47.7)	16 (34.1)	913 (48.0)
Early satiety (n, %)	297 (15.3)	9 (19.2)	288 (15.2)
Belching (n, %)	126 (6.5)	1 (2.1)	125 (6.6)
Nausea/vomiting (n, %)	132 (6.8)	3 (6.4)	129 (6.8)
Typical reflux symptoms (n, %)	788 (40.5)	29 (61.7)	759 (39.9)
GERDQ (mean $\pm$ SD)	5.39 ± 2.15	$6.11 \pm 2.44$	5.37 ± 2.14
Helicobacter pylori infection (n, %)	644 (33.1)	17 (36.2)	627 (33.0)

GERDQ = gastro-esophageal reflux disease questionnaire, SD = standard deviation.

reflux symptoms remained significant with the odd ratios of 7.530 (95% CI, 3.130–18.117) and 2.074 (95% CI, 1.122–3.832), respectively (Table 4).

# 4. Discussion

This study is the 1st report on the prevalence and risk factors of BE in Vietnamese. A recent meta-analysis found that the prevalence of BE in Asia has increased from 0.8% for 1991 to 1999 to 2.2% for 2010 to 2014, especially in Eastern Asian countries.<sup>[3]</sup> Our study, which recruited patients in Vietnam from 2017 to 2018, found a compatible prevalence of 2.4% (95% CI,

1.7–3.1%). The prevalence of BE in Asia has been reported with remarkably wide range: 0.06% to 43% for endoscopic BE and 0.06% to 6% for histologic BE.<sup>[3]</sup> But most of the studies which reported high prevalence of BE included patients with ESEM <1 cm in length.<sup>[17–19]</sup> There is strong evidence that the endoscopic assessment of such a short ESEM is not reliable. One study, which recruited 29 expert endoscopists with a special interest in BE from 14 countries, reported a reliability coefficient of only 0.22.<sup>[14]</sup> Another study, which recruited 34 endoscopists from 7 Asian cities, confirmed the low interobserver reliability in Asia.<sup>[10]</sup> In contrast, both studies reported excellent agreement in the diagnosis and grading of BE in subjects with ESEM ≥1 cm using

# Table 2

Endoscopic characteristics of patients in the study.

	Total	Patients with Barrett esophagus	Patients without Barrett esophagus	
Characteristics	N=1947	N=47	N=1900	
ESEM				
C≤1M1 (n, %)	50 (86.2)	41 (87.2)	9 (81.8)	
C≤1M2 (n, %)	7 (12.1)	5 (10.6)	2 (18.2)	
C5M5 (n, %)	1 (1.7)	1 (2.2)	0 (0)	
Reflux esophagitis (n, %)				
LA-A (n, %)	190 (9.8)	4 (8.5)	186 (9.8)	
LA-B (n, %)	41 (2.1)	5 (10.6)	36 (1.9)	
LA-C (n, %)	1 (0.1)	1 (2.1)	0 (0)	
LA-D (n, %)	0	0	0	
GEFV				
Type I (n, %)	93 (4.8)	0	93 (4.9)	
Type II (n, %)	1704 (87.5)	41 (87.2)	1663 (87.5)	
Type III (n, %)	128 (6.6)	2 (4.3)	126 (6.6)	
Type IV (n, %)	22 (1.1)	4 (8.5)	18 (1.0)	
Hiatal hernia (n, %)	44 (2.3)	8 (17.0)	36 (1.9)	
Gastric ulcer (n, %)	37 (1.9)	1 (2.1)	36 (1.9)	
Duodenal ulcer (n, %)	40 (2.1)	1 (2.1)	39 (2.1)	
Gastric cancer (n, %)	5 (0.3)	1 (2.1)	4 (0.2)	

ESEM = endoscopically suspected esophageal metaplasia, GEFV = gastroesophageal flap valve.

Table 3Risk factors for Barrett esophagus: univariate analysis.

Characteristics	Odds ratio	95% CI	Р
Male	2.134	1.169-3.896	.014
Age	1.020	0.996-1.045	.098
Body mass index	1.053	0.960-1.156	.275
Waist circumference	1.031	1.000-1.064	.054
Waist-to-Hip Ratio	28.408	0.381-2118	.128
Smoking	2.384	1.318-4.311	.004
Alcohol	1.270	0.689-2.341	.443
Typical reflux symptoms	2.422	1.336-4.392	.004
GERDQ score	1.160	1.024-1.313	.019
Reflux esophagitis	2.043	1.002-4.165	.049
GEFV type III/IV	1.785	0.745-4.274	.194
Hiatal hernia	10.621	4.635-24.336	.000
Helicobacter pylori infection	1.151	0.630-2.102	.648

CI = confidence interval, GEFV = gastroesophageal flap valve, GERDQ = gastro-esophageal reflux disease questionnaire.

the Prague C and M criteria. Currently, the guidelines on diagnosis and management of BE worldwide recommend to exclude subjects with ESEM <1 cm in length; and histologic assessment is required for every subject with ESEM  $\geq$ 1 cm to confirm the BE diagnosis.<sup>[7,15,20]</sup> However, there are still few studies in Asia following this recommendation.<sup>[3]</sup> The result of our study, therefore, would shed further light on the understandings of BE in Asia.

In our study, less than two-third of patients with BE had typical reflux symptoms and very few had these symptoms as chief complaints. The same finding has been reported world-wide.<sup>[3,15,21]</sup> In addition, our study found that the prevalence of BE in the subgroup patients presenting with typical reflux symptoms was only slightly higher than the whole population (3.7% vs 2.4%, respectively), and there were no patients with intestinal-type BE in the former group. This was much lower than that reported in Western studies, which found a prevalence of BE of 10% to 12% (intestinal-type BE, 6–6.7%) among patients with reflux symptoms.<sup>[21]</sup> Therefore, typical reflux symptoms are probably not sensitive to identify subjects with BE in Vietnamese. Focussing on only reflux symptoms would lead to miss a significant proportion of BE and better risk markers are needed.

Out of 47 patients with histologic BE in our study, there were only 1 (2.1%) patient with long-segment BE and 2 (4.3%) patients with low-grade dysplasia. These results were identical to those reported in a recent meta-analysis, which found that <20% of BE in Asia was long-segment and the rate of low-grade dysplasia in BE was 6.9% (95% CI, 4.2–11.3%).<sup>[3]</sup> Notably, both of the 2 cases with low-grade dysplasia in our study were

Risk factor	s for Barrett econhagus, multivariable analysis
Table 4	

Characteristics	Odd ratio	95% CI	Р
Male	1.299	0.571-2.955	.532
Age	1.020	0.993-1.048	.142
Waist circumference	1.027	0.967-1.090	.390
Waist-to-hip ratio	0.024	0.000-159.9	.406
Smoking	1.776	0.821-3.843	.145
Typical reflux symptoms	2.074	1.122-3.832	.020
Reflux esophagitis	1.290	0.597-2.786	.517
Hiatal hernia	7.530	3.130-18.117	.000

endoscopically classified as C0M1 and had no visible lesions. Therefore, all ESEMs, irrespective of length, should be biopsied to confirm the BE diagnosis as well as to assess the risk level of EAC development.

Previous studies reported several risk factors for BE in Asia, which included old age, male gender, smoking, abdominal obesity, reflux symptoms, and HH.<sup>[3,7]</sup> However, the reported factors were somewhat different across Asian studies, which might be explained by some reasons. First, the ethnicity of recruited patients was different among Asian studies. A study conducted in Malaysia, a multiethnic Asian country, found that BE was significantly more common in Indians than in Chinese and Malays.<sup>[22]</sup> Second, the criteria for BE diagnosis, especially the inclusion of BE <1 cm in length and the histologic criteria for BE diagnosis, were also different among studies.<sup>[3]</sup> Our study, which strictly applied the currently recommended biopsy protocol and diagnostic criteria, found that there were no significant associations between BE and age, sex, smoking, and abdominal obesity in Vietnamese patients with upper gastrointestinal symptoms. HH and typical reflux symptoms were the only 2 independent factors significantly associated with BE in multivariable analysis; and the former was the more predominant risk factor compared to the later (odds ratio [OR] = 7.5 and OR = 2.1, respectively). As the former is an endoscopic finding and the later has low sensitivity, opportunistic screening is probably better than clinical ground as screening tool for BE in Vietnamese.

The impact of HH on the development and the characteristics of BE is of great interest. One meta-analysis, which comprised 457,147 patients from 51 original studies in Asia also found that HH is the most predominant risk factor of BE (OR = 4.9).<sup>[3]</sup> Another meta-analysis, which comprised 4390 BE patients from 33 original studies, found that HH was associated with 2.9- and 12.7-fold increase in odd for short-segment and long-segment BE, respectively.<sup>[23]</sup> Interestingly, a follow-up study in Japan found that the presence of HH, along with typical reflux symptoms, was a positive predictor BE elongation.<sup>[24]</sup> In Asia, the reported prevalence of HH was generally much lower than that reported by Western studies (2.9–6.9% vs over 15%, respectively).<sup>[25]</sup> Our study also found that the prevalence of HH was only 2.3% in Vietnamese patients with upper gastrointestinal symptoms. The results of our study, along with the findings from previous studies, suggested that HH is the most important risk factor of BE; and it might be the key to explain the difference in BE prevalence and proportion of long-segment BE between the East and the West.

Our study has some limitations. First, this is a single-center, hospital-based study in patients with upper gastrointestinal symptoms. Therefore, we were not able to assess the prevalence of BE in asymptomatic Vietnamese subjects. Second, there were only 1 method for *H pylori* diagnosis in this study; and patients with prior history of *H pylori* eradication were not excluded. Therefore, the association between *H pylori* infection and BE could not be concluded due to potential bias. As recent meta-analyses reported inconsistent finding regarding this association,  $[^{3,26]}$  the issue remains debatable.

In summary, we reported for the 1st time the prevalence, clinical characteristics, and risk factors of BE in Vietnamese patients with upper gastrointestinal symptoms. Less than twothird of patients with BE had typical reflux symptoms, and very few had these symptoms as chief complaints. HH and typical reflux symptom were independently associated with BE in Vietnamese.

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## **Author contributions**

Quach DT initiated the study conception, designed the research study and supervised the study. Quach DT served as the local trainer and Ho KY and Sharma P served as advisors for the local endoscopic training workshops. Pham Q, Tran T, Vu N, Le Q, Nguyen D, Dang N, Le N and Le HM contributed on the data acquisition. Quach DT and Pham Q performed the statistical analysis and interpretation of data. Quach DT wrote and critically revised the manuscript. All authors approved the final version of the draft. Quach DT submitted the study.

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