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ORIGINAL ARTICLE

# Risk stratifying the screening of Barrett's esophagus: An Asian perspective

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## Abstract

**Background and Aim:** Barrett's esophagus (BE) is a premalignant condition for esophageal adenocarcinoma. Although risk factors exist for screening patients in the West, we aimed to determine the factors in terms of demographics and symptoms for patients in an Asian setting.
**Methods:** We recruited 1378 patients over a 7-year period as part of an ongoing gastric cancer screening program. An appropriately designed questionnaire was utilized to determine the necessary risk factors and symptoms with endoscopic analysis and subsequent histological confirmation as the gold standard. We utilized the existence of intestinal metaplasia of the distal esophagus as the primary diagnostic pathology.
**Results:** We demonstrated that no symptoms were indicative of BE in an Asian setting. Age (odds ratio 1.081, 95% confidence interval 1.022–1.143) and male gender (odds ratio 4.808, 95% confidence interval 1.727–13.33) proved significant demographic factors for the presence of intestinal metaplasia (*P* 0.007, 0.003, respectively).
**Conclusions:** We advocate the utilization of increasing age and male gender as the primary risk factors for patients at risk of BE. We also recommend astute examination of the distal esophagus whilst patients undergo simultaneous gastric cancer screening.

## Introduction

Barrett's esophagus (BE) is a premalignant condition, which predisposes to the development of esophageal adenocarcinoma (EAC). Despite the low risk of progression to EAC per annum, estimated currently at 0.12%, the prognosis of EAC is poor, with an estimated 5-year survival of approximately 10–15%.[1,2]

Evidence highlights that screening for BE can help to detect associated neoplasia early and improve survival.[3]

Given the generally low prevalence of BE, endoscopic screening of the general population cannot be advocated for, as recommended by the current guidelines in the United Kingdom and United States.[2,3] Current Western guidelines have proposed targeting endoscopic screening for populations at risk of BE. Risk factors identified in the West include an age of more than 50 years, male gender, Caucasian race, obesity, smoking, positive family history of BE or EAC, and chronic gastroesophageal reflux disease (GERD).[3]

In Asia, research suggests that the presence of BE is on the rise. Shiota *et al*. undertook a systematic review and meta-analysis in an East Asian setting, and noted a prevalence of endoscopic BE of 7.8% across symptomatic and screening studies, with a subsequent histological confirmation of 1.3%. They demonstrated an increase in prevalence; however, the majority of pathology was short segment in nature.[4]

The aim of our study was to determine the risk factors and symptoms, which can help predict the presence of BE in an Asian population and risk-stratify patients accordingly. This will allow clinicians to target endoscopic screening of patients and enhance overall cost-effectiveness. This is particularly useful in an Asian setting where resources are limited.

## Methods

***Study population.*** Patients were prospectively enrolled in this study at the National University Hospital of Singapore from 2004 to 2011. They were invited to take part following written informed consent originally as part of an ongoing gastric cancer screening program—Gastric Cancer Epidemiology Clinical and Genetic Programme (GCEP).[5] The study was approved by the National Healthcare Group Domain Specific Review Board.

The inclusion criteria for our population comprised Chinese patients over the age of 50 years with one or more of the following additional criteria: history of dyspepsia for at least 4 weeks; family history of gastric cancer; and any medical condition for which an upper gastrointestinal (GI) endoscopic investigation was warranted.

Exclusion criteria included those with bleeding disorders, liver cirrhosis, a history of total or partial gastrectomy, and a severe comorbid disease, which required long-term non-steroidal anti-inflammatory therapy.

A total of 1378 patients were recruited over a 7-year period.

A separate group of subjects who underwent an esophagogastroduodenoscopy (EGD) during the same period for various indications, with no prior history of GERD, and who were found to have a normal looking esophagus at endoscopy, with minimal gastric pathology were recruited as controls. A 1:4 case-control ratio was employed in view of currently recommended statistical methods. Matching in reference to age, gender, and ethnicity was performed.

***Questionnaire.*** The questionnaire utilized to assess risk factors and symptoms was designed by two upper GI experts. Both have several decades of experience in upper GI research with chair positions in the Asia Pacific Barrett's consortium (KYH) and the Singapore Gastric Cancer Consortium (KGY).

The study was conducted by 10 research coordinators. The research coordinators were nonclinicians and hence had no bias towards a particular condition. They were rigorously trained and assessed in data collection by both KYH and KGY. The questionnaire was utilized once a patient who met the inclusion criteria had been recruited. Questions were appropriately translated to ensure patient understanding in view of the high proportion of Mandarin-speaking individuals (Table 1). Demographics and symptoms were recorded within a maximum of 6 months of endoscopy and stored on a secure password-protected database only accessible to the study members.

The demographics of patients were recorded at baseline, focusing on age, gender, body mass index (BMI), smoking status, alcohol consumption status, and family history of esophageal cancer. Both smoking and alcohol consumption status were trichotomized as "yes," "no," or "previous" for ease of analysis. Symptoms recorded were acid reflux, heartburn, dysphagia, nausea, vomiting, abdominal pain after meals, early satiety, bloating, loss of appetite, loss of weight, hematemesis, and melena. The presence of symptoms was dichotomized, and the impact of symptoms on activities of daily living (ADL) was noted.

Due to the possible Western language interpretation issues in an Asian setting, we provided an expanded explanation of various symptom assessments accordingly (Table 1).

**Table 1** Expanded symptom explanation for our Asian cohort

| | |
|---|---|
| Acid reflux | Notice a sour or acid tasting fluid at the back of your throat |
| Heartburn | Heartburn |
| Dysphagia | Difficulty swallowing |
| Nausea | Wanting to throw up |
| Vomiting | Throw up |
| Abdominal pain | Experience discomfort, distension or pain in the abdomen after meals |
| Early satiety | Over-filled soon after starting to eat out of proportion to the size of the meal |
| Bloating | Sensation of persistence of food in the stomach |
| Loss of appetite | Loss of appetite |
| Loss of weight | Loss of weight |
| Hematemesis | Vomit any red or dark brown material that looks like coffee grounds |
| Melena | Experience black, tarry stools |

***Diagnosis of Barrett's esophagus.*** Following recording of demographics and symptoms, patients underwent an upper GI endoscopy by experienced specialists. Endoscopy was conducted using the gold standard of white-light endoscopic analysis of the distal esophagus with a high resolution Olympus endoscope.

Endoscopists had been trained extensively by KYH in identifying the appropriate landmarks and the presence of pathology.[6] Biopsies were taken on the basis of pathological findings as per the Seattle protocol as required.

Histopathological assessment was conducted by two trained GI pathologists (SS/MT), looking specifically for columnar-lined epithelium (CLE) with goblet cells, namely intestinal metaplasia (IM).

Analysis of demographics and symptoms was performed in relation to the gold standard of histology.[2,3]

We chose the US definition of BE as a change from stratified squamous to CLE with goblet cells (IM) in view of the described increased risk of malignant progression.[2]

***Statistical analysis.*** Analysis of demographics and symptoms for IM was performed using IBM SPSS v 20.0 (IBM Corp., Armonk, NY, USA). A multinomial logistic regression was performed and significance was set at a $P$ value $<0.05$. Borderline significance was set at 0.10.

The primary outcome measure was the determination of the risk factors and symptoms for patients at risk of BE, namely IM, in an Asian setting.

## Results

With regard to the questionnaire, the research coordinators reported the ease of its administration. The histological break down, age, and BMI of the patient group are highlighted below. We initially grouped the CLE and IM patients as part of the general umbrella of Barrett's pathology and matched controls accordingly. However, in view of the malignant risk and hence clinical relevance as highlighted earlier, we chose to highlight IM as the primary pathology in this study.

- CLE $n = 65$ (13.2%), IM $n = 33$ (6.7%), control $n = 393$ (80%)

**Table 2** Characteristics of patients in both the Barrett's esophagus and control population

| | Histological diagnosis Intestinal metaplasia | Control |
|---|---|---|
| Gender | | |
| Female | | |
| *n* | 6 | 206 |
| % | 2.5 | 85.1 |
| Male | | |
| *n* | 27 | 187 |
| % | 10.8 | 75.1 |
| Alcohol | | |
| Yes | | |
| *n* | 1 | 37 |
| % | 2.2 | 80.4 |
| Previous | | |
| *n* | 5 | 19 |
| % | 16.7 | 63.3 |
| No | | |
| *n* | 27 | 337 |
| % | 6.5 | 81.2 |
| Smoking | | |
| Yes | | |
| *n* | 5 | 23 |
| % | 15.2 | 69.7 |
| Previous | | |
| *n* | 7 | 39 |
| % | 12.5 | 69.6 |
| No | | |
| *n* | 21 | 331 |
| % | 5.2 | 82.3 |
| Family history esophageal cancer | | |
| No | | |
| *n* | 33 | 388 |
| % | 6.8 | 79.8 |
| Yes | | |
| *n* | 0 | 5 |
| % | 0.0 | 100.0 |
| *Helicobacter pylori* | | |
| Negative | | |
| *n* | 31 | 386 |
| % | 6.5 | 81.1 |
| Positive | | |
| *n* | 2 | 7 |
| % | 13.3 | 46.7 |
| Use of anti-reflux medication | | |
| No | | |
| *n* | 23 | 325 |
| % | 5.8 | 81.3 |
| Yes | | |
| *n* | 10 | 68 |
| % | 11.0 | 74.7 |
| Proton pump inhibitor | | |
| No | | |
| *n* | 24 | 334 |
| % | 5.9 | 81.5 |
| Yes | | |
| *n* | 9 | 59 |
| % | 11.1 | 72.8 |
| Histamine H2 antagonist | | |
| No | | |
| *n* | 32 | 388 |
| % | 6.6 | 80.0 |
| Yes | | |
| *n* | 1 | 5 |
| % | 16.7 | 83.3 |
| Antacid | | |
| No | | |
| *n* | 33 | 385 |
| % | 6.9 | 80.0 |
| Yes | | |
| *n* | 0 | 8 |
| % | 0.0 | 80.0 |

- CLE mean age 59.52 years, IM 62.27 years, control 58.29 years
- CLE mean BMI 24.53 kg/m$^2$, IM 24.15 kg/m$^2$, control 23.25 kg/m$^2$
- IM segment length range 3–6 cm.

Our study highlighted a total of 65 (13.2%) columnar-lined esophagus patients and 33 (6.7%) IM patients. Our control population comprised 393 (80%) patients. The characteristics of patients in both the BE and control population along with symptom prevalence are noted in Tables 2 and 3.

As depicted in Tables 4 and 5, age (odds ratio [OR] 1.081, 95% confidence interval [CI] 1.022–1.143) and male gender (OR 4.808, 95% CI 1.727–13.33) proved significant factors for predicting the presence of IM (*P* 0.007, 0.003, respectively). No other factor was deemed significant.

We determined a risk-scoring platform based on previous work on colorectal cancer by the study authors. Noting age and male gender as the only significant risk factors, points in reference to the adjusted OR can be subsequently determined through numerical halving and rounding up accordingly. This would be 1 and 2.5, respectively. A stratification approach can then be assigned as average (0 risk factors), moderate (1 risk factor), and high (2 risk factors, a maximum of 3.5 points).[7]

## Discussion

The literature highlights the importance of screening at risk patients in order to better survey and ultimately treat Barrett's associated dysplasia and cancer.[2] This is in view of the fact that long-term survival of patients with EAC is bleak.[8]

Liu *et al*. undertook a prospective study to identify demographics and risk factors as a prescreening tool for BE in the West. Their findings highlighted demographics of age and gender, and symptoms namely heartburn, acid reflux, chest pain, abdominal pain, and medication, with an area under the curve of 0.61 and 0.64 for CLE and IM, respectively.[9]

In our study population in Asia, we observed that for patients at risk of developing IM, age and male gender proved significant (Tables 2–5). To the best of our knowledge, this study

**Table 3** Questionnaire responses in relation to symptoms associated with Barrett's esophagus

| | Histological diagnosis | |
|---|---|---|
| | Intestinal metaplasia | Control |
| Acid reflux | | |
| No | | |
| *n* | 27 | 323 |
| % | 6.8 | 81.0 |
| Yes | | |
| *n* | 6 | 70 |
| % | 6.5 | 76.1 |
| Heartburn | | |
| No | | |
| *n* | 24 | 312 |
| % | 6.2 | 80.8 |
| Yes | | |
| *n* | 9 | 81 |
| % | 8.6 | 77.1 |
| Dysphagia | | |
| No | | |
| *n* | 30 | 382 |
| % | 6.3 | 80.4 |
| Yes | | |
| *n* | 3 | 11 |
| % | 18.8 | 68.8 |
| Nausea | | |
| No | | |
| *n* | 33 | 365 |
| % | 7.2 | 79.5 |
| Yes | | |
| *n* | 0 | 28 |
| % | 0.0 | 87.5 |
| Vomiting | | |
| No | | |
| *n* | 33 | 383 |
| % | 6.9 | 80.0 |
| Yes | | |
| *n* | 0 | 10 |
| % | 0.0 | 83.3 |
| Abdominal pain | | |
| No | | |
| *n* | 24 | 229 |
| % | 8.1 | 77.6 |
| Yes | | |
| *n* | 9 | 164 |
| % | 4.6 | 83.7 |
| Early satiety | | |
| No | | |
| *n* | 33 | 359 |
| % | 7.3 | 79.2 |
| Yes | | |
| *n* | 0 | 34 |
| % | 0.0 | 89.5 |
| Bloating | | |
| No | | |
| *n* | 31 | 376 |
| % | 6.6 | 80.2 |
| Yes | | |
| *n* | 2 | 17 |
| % | 9.1 | 77.3 |
| Loss of appetite | | |
| No | | |
| *n* | 33 | 385 |
| % | 6.9 | 80.4 |
| Yes | | |
| *n* | 0 | 8 |
| % | 0.0 | 66.7 |
| Loss of Weight | | |
| No | | |
| *n* | 30 | 368 |
| % | 6.5 | 80.0 |
| Yes | | |
| *n* | 3 | 25 |
| % | 9.7 | 80.6 |
| Hematemesis | | |
| No | | |
| *n* | 33 | 389 |
| % | 6.8 | 80.0 |
| Yes | | |
| *n* | 0 | 4 |
| % | 0 | 80.0 |
| Melena | | |
| No | | |
| *n* | 33 | 381 |
| % | 6.9 | 79.9 |
| Yes | | |
| *n* | 0 | 12 |
| % | 0 | 85.7 |

is the first to demonstrate such risk factors in Asia. We sought to further validate our risk-stratification approach with a receiver operating characteristic curve, which demonstrated fair to good diagnostic accuracy (Fig. 1). Further work is, however, needed to help validate this risk-stratification approach.

In Asia, gastric cancer is more prevalent than BE despite studies noting an increasing trend for the latter. Given that the risk factors for gastric cancer also include age and male gender,[10] we therefore advocate that whilst patients are screened for gastric-based pathology, clinicians should also perform opportunistic screening for BE in these patients. At present, the focus is on the former but more emphasis on closer inspection of the distal esophagus should be made.

The debate continues as to the relevance of symptoms when screening Western patients at risk of BE. Rex *et al.* observed in their sample population that BE overall was not associated with heartburn.[11] Further work has also confirmed that despite the prevalence of reflux symptoms, their ability to predict BE is poor.[12] By and large, symptoms allied to gastroesophageal reflux also proved nonsignificant for BE in our Asian population. The poor discriminatory value of typical symptoms for diagnosing GERD among Asians is well known, and has previously been reported by the corresponding author.[13]

Limitations of our study do exist. First, this was a case-control analysis in reference to a gastric-based population. One

**Table 4** Adjusted odds ratio for risk factors and symptoms associated with Barrett's esophagus

| Risk factors and symptoms | Adjusted odds ratio | 95% confidence interval for adjusted odds ratio | | Adjusted *P* value |
|---|---|---|---|---|
| | | Lower bound | Upper bound | |
| Age | 1.081 | 1.022 | 1.143 | **0.007** |
| Body mass index | 1.071 | 0.946 | 1.212 | 0.278 |
| Male versus female | 4.808 | 1.727 | 13.333 | **0.003** |
| Taking alcohol versus not taking alcohol | 0.210 | 0.026 | 1.707 | 0.144 |
| Previously taking alcohol versus not taking alcohol | 0.810 | 0.208 | 3.155 | 0.762 |
| Smoker versus nonsmoker | 2.826 | 0.716 | 11.153 | 0.138 |
| Previous smoker versus nonsmoker | 1.565 | 0.544 | 4.500 | 0.406 |
| *Helicobacter pylori*: positive versus negative | 2.786 | 0.409 | 18.868 | 0.296 |
| Use of anti-reflux medication versus not using anti-reflux medication | 1.757 | 0.707 | 4.367 | 0.225 |
| Acid reflux | 0.957 | 0.307 | 2.985 | 0.940 |
| Heartburn | 1.372 | 0.475 | 3.968 | 0.559 |
| Dysphagia | 2.625 | 0.558 | 12.346 | 0.222 |
| Abdominal pain | 0.439 | 0.174 | 1.110 | **0.082** |
| Bloating | 3.077 | 0.550 | 17.241 | 0.201 |
| Loss of weight | 2.004 | 0.475 | 8.475 | 0.344 |

Significant/ borderline significant values are given in bold.

may argue that this cohort cannot be deemed pathologically normal. However, we aimed to minimize any anomalies by the utilization of a cohort with minimal pathology, namely minimal inflammation/reactive changes. Second, our symptom reporting was not based on a validated GERD questionnaire. Symptoms were initially aimed at capturing patients at risk of gastric pathology namely gastric IM/cancer. However, there is considerable symptom overlap with these conditions and hence we utilized these data accordingly. Our study was also confined to a Chinese population. Singapore is multiethnic with Malays and Indians present. Future work therefore should aim to focus on a multiethnic demographic.

**Table 5** β-coefficients and weights for risk factors and symptoms associated with Barrett's esophagus

| Histological diagnosis | β | Weight | Adjusted odds ratio | 95% confidence interval for adjusted odds ratio | | Adjusted *P* value |
|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | |
| Intestinal metaplasia | | | | | | |
| Age | 0.078 | 2 | 1.081 | 1.022 | 1.143 | 0.007 |
| Body mass index | 0.069 | 2 | 1.071 | 0.946 | 1.212 | 0.278 |
| Gender | | | | | | |
| Male | 1.570 | 36 | 4.808 | 1.727 | 13.333 | 0.003 |
| Female | 0 | 0 | 1 | | | |
| Alcohol | | | | | | |
| Taking alcohol | −1.559 | −35 | 0.210 | 0.026 | 1.707 | 0.144 |
| Previously taking alcohol | −0.210 | −5 | 0.810 | 0.208 | 3.155 | 0.762 |
| Not taking alcohol | 0 | 0 | 1 | | | |
| Smoking | | | | | | |
| Smoker | 1.039 | 24 | 2.826 | 0.716 | 11.153 | 0.138 |
| Previous smoker | 0.448 | 10 | 1.565 | 0.544 | 4.500 | 0.406 |
| Nonsmoker | 0 | 0 | 1 | | | |
| *Helicobacter pylori* | | | | | | |
| Positive | 1.024 | 23 | 2.786 | 0.409 | 18.868 | 0.296 |
| Use of anti-reflux medication | | | | | | |
| Yes | 0.564 | 13 | 1.757 | 0.707 | 4.367 | 0.225 |
| Acid reflux | −0.044 | −1 | 0.957 | 0.307 | 2.985 | 0.940 |
| Heartburn | 0.316 | 7 | 1.372 | 0.475 | 3.968 | 0.559 |
| Dysphagia | 0.966 | 22 | 2.625 | 0.558 | 12.346 | 0.222 |
| Abdominal pain | −0.822 | −19 | 0.439 | 0.174 | 1.110 | 0.082 |
| Bloating | 1.125 | 26 | 3.077 | 0.550 | 17.241 | 0.201 |
| Loss of weight | 0.694 | 16 | 2.004 | 0.475 | 8.475 | 0.344 |

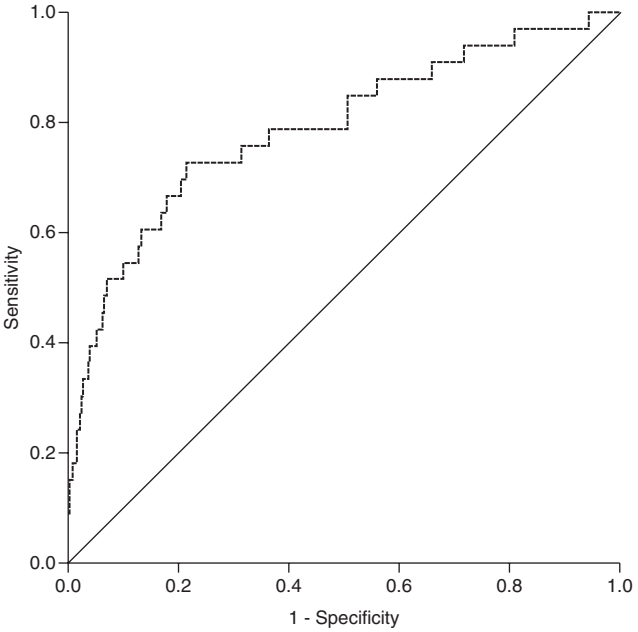


**Figure 1** Receiver operating characteristic curve for intestinal metaplasia. Area under the curve, 0.790 (95% confidence interval 0.698–0.882).

Despite these limitations, we conclude that an increasing age and male gender are risk factors for BE in an Asian population, and should be targeted for a screening EGD. Furthermore, symptoms are nonspecific in the diagnosis of BE in Asia, and are not helpful in stratifying the risk for screening BE. Finally, whilst patients undergo screening for gastric cancer, we advocate astute examination of the distal esophagus to examine for CLE, and judicious biopsy to determine the presence of IM.

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