Histomorphology of Gastroesophageal Junction Lesions (GEJ) and their Malignant Potential in Gastroesophageal Reflux Disease (GERD): A Study of 145 Cases in a Tertiary Level Hospital in Bangladesh

*Zabin SG,[1] Dewan RK,[2] Jinnah SA,[3] Jeba R,[4] Sultana T,[5] Rahman LY,[6] Khan ZB[7]

Abstract

Background: Gastroesophageal reflux disease (GERD) is a common disease and the incidence of GERD is rising worldwide. The histomorphological diagnosis of gastroesophageal reflux disease is generally believed to be an important tool. Early diagnosis of gastroesophageal reflux disease is crucial because chronic reflux esophagitis is a key risk factor for the development of Barrett´s esophagus, which predisposes to esophageal adenocarcinoma. These reflux-induced changes of the squamous epithelium are mainly related to the diagnosis of acute and/or active reflux. The chronic consequences of gastroesophageal reflux disease are mainly characterized by metaplastic mucosal replacement.

Objective: To evaluate the histomorphological variants of different lesions occurring at gastroesophageal junction.

Methods: The study was a descriptive cross sectional type and carried out at Dhaka Medical College from July 2016 to June 2018. The patients with symptoms of GERD (both male and female) attended at Department of Gastroenterology, Dhaka medical College Hospital were selected. Biopsies were taken from gastroesophageal junction of these patients and all relevant information were recorded systematically in a predesigned data collection sheet. A total of 145 cases were included in this study and histopathological evaluations were done in all cases.

Result: In this study, there were positive association between smoking and betel chewing with lesions occurring at GEJ. No significant association was found between GEJ lesions and history of intake of Aspirin/NSAID/Cyclo oxygenase 2 or use of PPI/H2RA /Antacid. More than one third patients showed recurrent moderate heart burn, more than half came with recurrent moderate regurgitation and one fourth came with recurrent moderate dysphagia. In histopathological evaluation two third patients had reflux esophagitis in group-I, three fourth patients had Barrett's esophagus negative for dysplasia in group II and almost two third patients had adenocarcinoma in group III.

Conclusion: The study revealed a positive association between gastroesophageal junction lesions with smoking and betel chewing. Reflux esophagitis was the most common histopathological finding in group I, Barrett's esophagus was most common in group II, and adenocarcinoma was more frequent in group III.

[Journal of Histopathology and Cytopathology, 2020 Jul; 4 (2):101-110]

Keywords: Gastroesophageal reflux disease, histomorphological diagnosis, Barrett´s esophagus, esophageal adenocarcinoma, squamous epithelium.

1. **Dr. Shirin Gull Zabin, Pathologist, Department of Pathology, Dhaka Medical College, Dhaka. gullzabin23@gmail.com*
2. *Professor Dr. Md. Rezaul Karim Dewan, Head of the Department of Pathology, Dhaka Medical College, Dhaka*
3. *Dr. Shahed Ali Jinnah, Associate Professor, Department of Pathology, Dhaka Medical College, Dhaka*
4. *Dr. Ruksana Jeba, Associate Professor, Department of Pathology, Dhaka Medical College, Dhaka*
5. *Dr. Tahmina Sultana, Lecturer, National Institute of Cancer Research and Hospital (NICRH)*
6. *Dr. Labiba Yesmin Rahman, Specialist, Ancillary Service, Square Hospital Ltd.*
7. *Dr. Zubaida Bahroon Khan, Assistant Professor, Department of Pathology, Dhaka Medical College, Dhaka*

**For correspondence*

Introduction

The incidence and prevalence of gastro-esophageal reflux disease (GERD) have increased remarkably worldwide over the past decades.[1] The approximate prevalence of GERD is 10%-20% in Europe and USA and less than 5% in Asia. Symptoms of GERD are among the most common complaints encountered by general physicians.[2] GERD is defined as a condition that develops when reflux of stomach contents cause troublesome symptoms and/or complications.[3] GERD summarizes the whole spectrum of reflux disease of the gastro-esophageal junction. It includes intermittent symptoms like heart burn or acid regurgitation to endoscopic reflux esophagitis and Barrett's esophagus.[4]
A complex set of mechanism determines GERD manifestations and its complications. These include- characteristics and composition of refluxate, dysfunction of antireflux barrier, impairment of mucosal defense, visceral motility and esophageal clearance.[5]

Gasto-esophageal junction (GEJ) is the junction of esophagus with stomach where the protective stratified squamous epithelium of esophagus abruptly changes to glandular epithelium.[6] Due to abrupt transitional changes of lining epithelium and continuous exposure to gastric acid reflux, GEJ is frequently subjected to inflammation (for example gastric carditis, esophagitis), BE, dysplasia and carcinoma.

Barrett's esophagus is the most important complication of GERD, is a premalignant condition that affect 1.3 % to 2% of adult population.[7] Patients with BE have 10 to 55 fold increased risk of developing esophageal adenocarcinoma.[8] Most esophageal adenocarcinoma (EAC) seems to arise from specialized columnar metaplastic epithelium which is mostly related to the intestinal type of metaplasia. GERD is considered to play a major role in the development of these histologic changes.[9]

Unless detected early, EAC is a lethal cancer with mortality greater than 85% and an average 5 year survival of 18.4%.[10] Worldwide, EAC is eighth most common incidental cancer and sixth most common cause of cancer mortality.[11]

Squamous dysplasia is a histologic lesion confined to epithelium and is characterized by cytologic and architectural abnormalities. This condition is regarded as premalignant condition for esophageal squamous cell carcinoma.

ESCC most commonly occurs in the middle third of the esophagus and less commonly in the lower third. Small cell carcinoma is extremely rare in the esophagus.[12]

It is worth noting that identification of premalignant lesions in patients with GERD may help the clinicians to give therapeutic guideline. A very few studies have so far been carried out on the GEJ lesions in Bangladesh. Therefore, the present study was aimed to describe the histomorphological pattern of GEJ lesions in patients with GERD, making an early diagnosis of premalignant lesions and most importantly to reduce the number of invasive adenocarcinoma.

Methods

Study population

The study was a descriptive type and carried out at Dhaka Medical College from July 2016 to June 2018. The patients with symptoms of GERD (both male and female) who were attended at Gastroenterology Department as new cases were selected. After clinical examination patients who advised for endoscopy were referred to endoscopy department. From these selected patients with GERD biopsy was taken from GEJ and a total

of 145 cases were included in this study and histopathological evaluation was done in all cases.

Five (5) of them revealed no histomorphological lesion and were excluded. The rest of the 140 patients were categorized into 3 groups. Group-I includes non-neoplastic disease, premalignant conditions were Group-II and malignant lesions were considered as Group-III.

Sample processing and forwarding
Samples from GEJ were taken with biopsy instrument. After collection, specimens were immersed in 10% buffered formalin. Samples were fixed for 12 hours which were required for proper H & E stain. Tissue processing and routine H & E staining were done on all 145 cases at the department of pathology, DMC.

Data collection procedure
During the collection of specimens all relevant information were recorded systematically in a predesigned data collection sheet. All cases were numbered chronologically and the same number was given to histopathologic slides.

Ethical Implication
Ethical issue was discussed with the patients; regarding the study and informed written consent were obtained. The research protocol was approved by the Institutional Review Board (IRB) of DMC, Dhaka.

Procedure of data analysis
Statistical analysis was carried out by using the Statistical Package for Social Sciences (SPSS) version 20.0 for windows. The mean values were calculated for continuous variables.

Results
A total of 145 patients were biopsed. 5 of them revealed no histomorphological lesion and were excluded. The rest of the 140 patients were grouped into 3 groups. Group-I includes non-neoplastic disease, premalignant conditions are grouped as Group-II and malignant lesions grouped as Group-III.

Table I: shows the mean age, history of smoking and history of betel chewing were statistically significant ($p<0.05$) among three groups. Sex, history of Aspirin/ non steroidal anti-inflammatory drugs (NSAID) intake and history of taking proton pump inhibitor (PPI)/ H2 receptor antagonist (H2RA) were almost alike among three groups.

Table II shows mean age of most common histopathological findings in three groups. The mean age for reflux esophagitis (most common condition in G-I) was 48.1±15.62, Barrett's esophagus (most common premalignant disease in G-II) was 50.97±14.49 and adenocarcinoma (most common malignancy in G-III) was 60.83±11.24.

Table III shows association between age in years and most common histopathological findings in the study population, it was observed that most of the patients were in 51-70 years, among them 13 were with reflux esophagitis, 26 patients with Barrett's esophagus and 14 were with adenocarcinoma.
Table IV shows association between sex and most common histopathological findings in study population, it was observed that majority of patients had reflux esophagitis in group I among them 18 were male and 10 were female, most of the patients had Barrett's esophagus in group II among them male were 24 and female 20, majority of patients had adenocarcinoma in group III among them male were 26 and female 9. The difference was statistically not significant ($p>0.05$) between two groups.

Table I: Distribution of the study patients by age, sex and personal habits (n=140)

	Group I (n=42)		Group II (n=49)		Group III (n=49)		P value
Age in years (mean±SD)	47.67	±19.06	49.84	±15.67	56.24	±10.92	[a]0.012[s]
Sex n(%)							
Male	21(50.0)		35(71.4)		29(59.2)		[b]0.109[ns]
Female	21(50.0)		14(28.6)		20(40.8)		
H/O smoking n(%)							
Yes	10(23.8)		25(51.0)		19(38.8)		[b]0.029[s]
No	32(76.2)		24(49.0)		30(61.2)		
H/O betel chewing n(%)							
Yes	16(38.1)		15(30.6)		27(55.1)		[b]0.042[s]
No	26(61.9)		34(69.4)		22(44.9)		
H/O Aspirin/NSAID n(%)							
Yes	14(33.3)		23(46.9)		15(30.6)		[b]0.205[ns]
No	28(66.7)		26(53.1)		34(69.4)		
H/O PPI/ H2RA n(%)							
Yes	25(59.5)		36(73.5)		32(65.3)		[b]0.365[ns]
No	17(40.5)		13(26.5)		17(34.7)		

s= significant, ns= not significant, [a]p value reached from one way ANOVA test, [b]p value reached from Chi-Square test

Table II: Mean age of the most common disease in G-I, G-II and G-III

Disease	Age (in years) Mean±SD
Reflux esophagitis	48.1±15.62
Barrett's esophagus	50.97±14.49
Adenocarcinoma	60.83±11.24

Table III: Association between age (in years) and most common histopathological findings in the study population

Histological Findings	Age in Years			
	<30	30-50	51-70	>70
Reflux esophagitis	3	11	13	
Barrett's esophagus	6	11	26	
Adenocarcinoma	5	15	14	

Table IV: Association between sex and in most common histopathological findings the study population

Histological Findings	Sex			P value
	Male	Female	M:F	
Reflux esophagitis	18	10	1.8:1	0.193[ns]
Barrett's esophagus	24	20	1.2:1	
Adenocarcinoma	26	9	2.9:1	

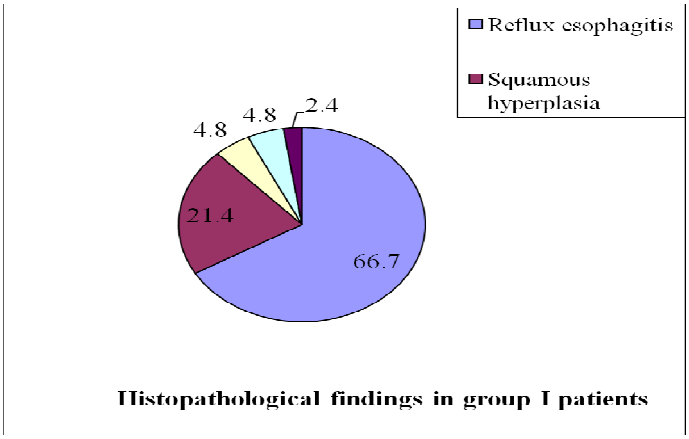

Figure 1. Pie chart showing categorization of study subjects in group I according to histopathological findings

This pie chart shows about 66.7% patients had reflux esophagitis and 21.4% patients had squamous hyperplasia in G-I.

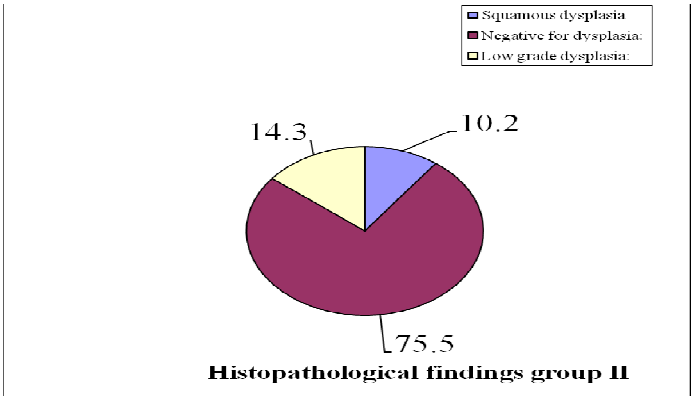

Figure 2. Pie chart showing categorization of study subjects in group II according to histopathological findings

This pie chart shows 75.5% patients had Barrett's esophagitis without dysplasia and 14.3% patients had Barrett's esophagitis with low grade dysplasia in G-II.

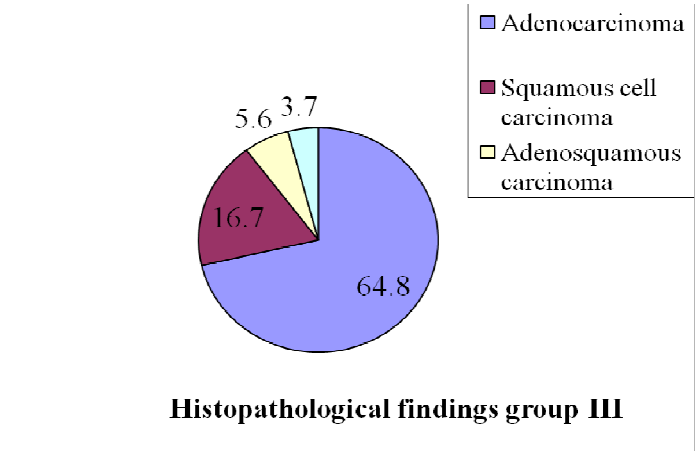

Figure 3. Pie chart showing categorization of study subjects in group III according to histopathological findings

This pie chart shows adenocarcinoma (64.8%) was the commonest histopathological finding and squamous cell carcinoma was the second common finding.

Table V shows association between Barrett's esophagus with smoking status. It was observed that among 44 patients with Barrett's esophagus almost two third (61.4%) patients were smoker and 17(38.6%) were non smoker. The difference was statistically significant ($p<0.05$) between smoker and non smoker in patients with Barrett's esophagus.

Table V: Association between Barrett's esophagus with smoking status (140)

Barrett's esophagus	Smoker		Non smoker		P value
	n	%	n	%	
Present (44)	27	61.4	17	38.6	0.001^s
Absent (96)	27	28.1	69	71.9	

s= significant
p value reached from Chi-Square test

Table VI shows association between adenocarcinoma with smoking status. It was observed that among 35 patients with adenocarcinoma more than half (57.1%) patients were smoker and 15(42.9%) were non smoker. The difference was statistically significant ($p<0.05$) between smoker and non smoker in patients with adenocarcinoma.

Table VI: Association between adenocarcinoma with smoking status (140)

Adenocarcinoma	Smoker		Non smoker		P value
	n	%	n	%	
Present (35)	20	57.1	15	42.9	0.009^s
Absent (105)	34	32.4	71	67.6	

s= significant
p value reached from Chi-Square test

Table VII shows distribution of the study patients by histopathological findings, it was observed that 28(66.7%) patients had reflux esophagitis in group I and not found in others groups, 2(4.1%) patients had mild and 2(4.1%) patients had moderate squamous dysplasia in group II, 37(75.5%) patients had Barrett's esophagus (negative for dysplasia) in group II and 35(64.8%) patients had adenocarcinoma in group III.

Table VII: Distribution of the study patients by histopathological findings (n=140)

Histopathological findings	Number of patients	Percentage
Group I (n=42)		
Reflux esophagitis	28	66.7
Squamous hyperplasia	9	21.4
Chronic non-specific ulcer	2	4.8
Inflammatory polyp	2	4.8
Chronic gastritis	1	2.4
Group II (n=49)		
Squamous dysplasia		
Mild	2	4.1
Moderate	2	4.1
Severe	1	2.0
Barrett's esophagus:		
Negative for dysplasia:	37	75.5
Low grade dysplasia:	7	14.3
High grade dysplasia	0	0.0
Group III (n=49)		
Adenocarcinoma	35	64.8
Squamous cell carcinoma	9	16.7
Adenosquamous carcinoma	3	5.6
Small cell carcinoma	2	3.7

Discussion

Gastroesophageal reflux disease (GERD) includes an entire spectrum of reflux diseases of the gastroesophageal junction. GERD complications include reflux esophagitis and Barrett's esophagus (BE).[3] Furthermore; GERD is categorized according to endoscopy as reflux esophagitis and non-erosive reflux disease (NERD).[13]

This descriptive study was carried out to determine the morphology of gastroesophageal junction lesions (GEJ) and their malignant potential in gastroesophageal reflux disease (GERD) in a tertiary level hospital.

In this study, the mean age was found 47.67±19.06 in group-I, 49.84±15.67 in group-II and 56.24±10.92 in group-III. The mean age difference is statistically significant among these three groups. Therefore, it could be assumed that progression of severity of disease is associated with GERD occur with advanced age.

This study revealed that the mean age of reflux esophagitis was 48.1±15.62. Wu et al.[1] found that the mean age was 56.0±10.4 years in patients with reflux esophagitis. Moreover, Noh et al.[14] found that the mean age of RE was 42.8±8.4. Both results are comparable with the present study.

The mean age of Barrett's esophagus (BE) was 50.97±14.49 in this study. Cook et al.[15] reported that the mean age was 59±12 years in BE, which is in accordance with this study. The mean age of EAC was 60.83±11.24 in this study. Drahos et al.[16] found that the mean age for EAC was 69.2 which is consistent with the present study.

In this study, maximum number of patients with BE was found in 51-70 years of age. Authors also reported that the prevalence of BE was higher in patients aged above 50 years.[16]

In this current study, it was observed that 61.4% patients were male and 38.6% patients were female and male to female ratio was 1.46:1 Moreover, it was observed that 50.0% patients were male in non - neoplastic group (group I), 71.4% in premalignant group (group II) and 59.2% in malignant group (group III). In all groups male patients were predominant. Similarly male predominance was also observed by authors.[1,17]

Regarding the association between Barrett's esophagus with smoking status, it was observed that among 44 patients with Barrett's esophagus almost two third (61.4%) patients were smoker and 17(38.6%) were non smoker. The difference was statistically significant ($p<0.05$) between smoker and non smoker in patients with Barrett's esophagus.

Cook et al.[15] stated that cigarette smoking is a risk factor for Barrett's esophagus. The association appears to strengthen with increased exposure to cigarette smoking. In another study Cook et al.[8] found the association between smoking and increased risk of BE and EAC. Increasing pack-years of smoking increased the risk for Barrett's esophagus. There was evidence of a synergy between ever-smoking and heartburn or regurgitation; the attributable proportion of disease among individuals who ever smoked and had heartburn or regurgitation was estimated to be 0.39 (95% CI: 0.25–0.52).[19]

Regarding the association between adenocarcinoma with smoking status, it was observed that among 35 patients with adenocarcinoma more than half (57.1%) patients were smoker and 15(42.9%) were non smoker and the difference was statistically significant ($p<0.05$) between smoker and non smoker in patients with adenocarcinoma. In agreement with our study, Anderson et al.[19] also found positive association between smoking and EAC.

Among 140 patients, 58 (41.4%) had positive history of betel chewing and 38.1% patients belonged to G-I, 30.6% in G-II and 55.1% in G-III. The difference is statistically significant among three groups. But no comparable data are available in this regard.

In this study, 52(37.1%) patients had positive H/O Aspirin/NSAID/Cyclo oxygenase 2 intake. It was observed that 33.3% in G-I, 46.9% in G-II and 30.6% in G-III. The difference was not statistically significant among three groups. A large case-control study by Nguyen et al.[20] indicated that using of non steroidal anti-inflammatory drugs NSAID/Aspirin therapy in patients with BE might reduce the risk of developing EAC. Furthermore, a study found that the incubation of isolated cells from mucosal biopsies of BE metaplasia with aspirin and omeprazole together induced a significantly greater reduction in proliferative activity than that induced separately by any of the two drugs, and suggesting a synergistic effect of the two drugs.[21] A chemo preventive effect has been observed for aspirin, nonsteroidal anti-inflammatory drugs, and possibly for the more specific cyclooxygenase-2 inhibitors. Aside from laboratory evidence, a review of 3 case-control trials suggests that aspirin may be an effective chemo preventive.[22] A meta-analysis of observational studies evaluating both aspirin and nonsteroidal anti-

inflammatory drugs suggests a protective effect for any use of these drugs and esophageal cancer (squamous and adenocarcinoma).[23]

In this study, it was observed that 66.4% patients had history of use of PPI/H2RA/ Antacid and 33.5% patients had no history of use of PPI/H2RA /Antacid. On the other hand, it was observed that 59.5% patients with positive history are in non-neoplastic group, 73.5% in premalignant group and 65.3% in malignant group. The difference was statistically not significant ($p>0.05$) among three groups. Kim et al.[24] reported that the H_2 blocker can promote bacterial proliferation by neutralizing gastric pH; the bacteria may in turn facilitate the formation of carcinogenic nitrosamines.

Regarding the complaints, it was observed that all patients came with complaints of heart burn and regurgitation. 52.1% patients came with dysphagia. It was also found that 45.2% patients had recurrent moderate heart burn in group I, 53.1% had recurrent severe heart burn in group II and 51.0% patients in group III had recurrent severe heart burn.

The proportions that reported recurrent (weekly or greater) heartburn and/or recurrent regurgitation were greatest in the EAC group and lowest amongst the controls; anti-gastro esophageal reflux medications displayed a similar pattern.[25] This analysis indicates that the association between heart burn/regurgitation symptoms and EAC is strong and increases with increased duration and/or frequency, and is consistent across major risk factors. High heterogeneity was also observed in a meta-analysis of gastro esophageal reflux and EAC.[26] It is conceivable that GERD may vary in its carcinogenic potency in different populations for reasons such as genetic background (i.e., gene-environment interactions) and diet. For example, the composition of refluxate can affect symptom perception as well as the capacity for mucosal damage and this may differ geographically.[27]

Researchers reported that the risk of esophageal adenocarcinoma was increased nearly eightfold among persons in whom heartburn, regurgitation, or both occurred at least once weekly compared to persons without these symptoms.[28] They noted that the risk of esophageal adenocarcinoma was three times higher among patients who used medication for symptoms of reflux compared to those who did not use any antireflux medication.

It was observed in this study that in non-neoplastic group 66.7% patients had reflux esophagitis, 21.4% squamous hyperplasia, 4.8% chronic non-specific ulcer, 4.8% inflamatory polyp and 2.4% patients had chronic gastritis. Among premalignant group there are two conditions; squamous dysplasia and Barrett's esophagus. In patients with squamous dysplasia-mild, moderate and severe dysplasia were 4.1%, 4.1% and 2% respectively. In Barrett's esophagus cases, 75.5% patients had Barrett's esophagus negative for dysplasia, 14.3% had low grade dysplasia. In malignant cases, 64.8% patients had adenocarcinoma, 16.7% squamous cell carcinoma, 5.6% adenosquamous carcinoma and 3.7% patients had small cell carcinoma.

Miao et al.[29] reported that the most common histologic types of EGJ cancer are adenocarcinoma and squamous cell carcinoma. Esophageal squamous cell carcinoma (ESCC) is the most common histological type of esophageal cancer and is identified as the world's sixth leading cause of cancer death.[30-31] The incidence of esophageal adenocarcinoma (EAC) is rapidly increasing in industrialized countries (e.g., Australia, USA, and Northern Europe) and

appeared as the most prevalent histological type in these countries.[32-33] EAC occurs after the normal squamous epithelium undergoes metaplasia, into a specialized columnar epithelium, which can eventually progress to subsequent malignancy.[34]

In this study, among malignancy other than EAC, nine were SCC (16.7%). Esophageal SCC is common in middle third and less common in lower third. There were three cases of adenosquamous carcinoma (5.6%), which shows both squamous and glandular differentiation. Two cases were small cell carcinoma (3.7%). In accordance the present study, researchers also reported that small cell carcinoma is extremely rare in esophagus.

Conclusion

In this study positive association between GEJ lesions with smoking and betel chewing was found. RE was the most common histopathological finding in group I, Barrett's esophagus was most common in group II and adenocarcinoma was more frequent in group III.

Limitations

1. The study population was selected from Dhaka Medical College Hospital, which is referral based hospital in Dhaka city. The advanced and referred cases like adenocarcinoma and BE are more in number in this study. So the data of the study may not reflect the scenario of all over the country.
2. Small sample size and short study period.

Recommendations

- GERD is a common problem among general population. Patients with recurrent H/O of regurgitation and heart burn should be advised for endoscopy, histopathological evaluation and proper follow up instructed by physician. By this way Barrett's esophagus and adenocarcinoma like severe complications can be prevented.
- Large sample size, multicentric study with longer duration could provide more representative information.

References

1. Wu YW, Tseng PH, Lee YC, Wang SY, Chiu HM, Tu CH, Wang HP, Lin JT, Wu MS, Yang WS. Association of esophageal inflammation, obesity and gastroesophageal reflux disease: from FDG PET/CT perspective. PloS one. 2014 Mar 18; 9(3):e92001.
2. Locke GR, Zinsmeister AR, Talley NJ. Can symptoms predict endoscopic findings in GERD? Gastrointestinal endoscopy. 2003 Nov 1; 58(5):661-70.
3. Vakil N, Van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. The American journal of gastroenterology. 2006 Aug; 101(8):1900.
4. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: a systematic review. Journal of neurogastroenterology and motility. 2011 Jan;17(1):14.
5. Martinucci I, de Bortoli N, Russo S, Bertani L, Furnari M, Mokrowiecka A, Malecka-Panas E, Savarino V, Savarino E, Marchi S. Barrett's esophagus in 2016: From pathophysiology to treatment. World journal of gastrointestinal pharmacology and therapeutics. 2016 May 6; 7(2):190.
6. Young B, Woodford P, O'Dowd G. Wheater's Functional Histology E-Book: A Text and Colour Atlas. Elsevier Health Sciences; 2013 Oct 9.
7. Ford AC, Forman D, Reynolds PD, Cooper BT, Moayyedi P. Ethnicity, gender, and socioeconomic status as risk factors for esophagitis and Barrett's

esophagus. American journal of epidemiology. 2005 Sep 1; 162(5):454-60.
8. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Pandeya N. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. Journal of the National Cancer Institute. 2010 Sep 8;102(17):1344-53.
9. Conio, M., Blanchi, S., Lapertosa, G., Ferraris, R., Sablich, R., Marchi, S., D'onofrio, V., Lacchin, T., Iaquinto, G., Missale, G. and Ravelli, P., 2003. Long-term endoscopic surveillance of patients with Barrett's esophagus. Incidence of dysplasia and adenocarcinoma: a prospective study. The American journal of gastroenterology, 98(9), p.1931.
10. Jain, S. and Dhingra, S., 2017. Pathology of esophageal cancer and Barrett's esophagus. Annals of cardiothoracic surgery, 6(2), p.99.
11. Zhang, Y., 2013. Epidemiology of esophageal cancer. World journal of gastroenterology: WJG, 19(34), p.5598.
12. Chen WW, Wang F, Zhang DS, Luo HY, Wang ZQ, Wang FH, Qiu MZ, Ren C, Wei XL, Wu WJ, Li YH. Primary small cell carcinoma of the esophagus: clinicopathological study of 44 cases. BMC cancer. 2014 Dec; 14(1):222.
13. Kim N, Lee SW, Cho SI, Park CG, Yang CH, Kim HS, Rew JS, Moon JS, Kim S, Park SH, Jung HC. The prevalence of and risk factors for erosive oesophagitis and non-erosive reflux disease: a nationwide multicentre prospective study in Korea. Alimentary pharmacology & therapeutics. 2008 Jan; 27(2):173-85.
14. Noh YW, Jung HK, Kim SE, Jung SA. Overlap of erosive and non-erosive reflux diseases with functional gastrointestinal disorders according to Rome III criteria. Journal of neurogastroenterology and motility. 2010 Apr; 16(2):148.
15. Cook MB, Shaheen NJ, Anderson LA, Giffen C, Chow WH, Vaughan TL, Whiteman DC, Corley DA. Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. Gastroenterology. 2012 Apr 1; 142(4):744-53.
16. Drahos J, Li L, Jick SS, Cook MB. Metabolic symdrome in relation to Barrett's esophagus and esophageal adenocarcinoma: Results from a large population-based case-control study in the Clinical Practice Research Datalink. Cancer epidemiology 2016; 42:9-14.
17. Xiong LS, Cui Y, Wang JP, Wang JH, Xue L, Hu PJ, Chen MH. Prevalence and risk factors of Barrett's esophagus in patients undergoing endoscopy for upper gastrointestinal symptoms. Journal of digestive diseases. 2010 Apr;11(2):83-7.
18. Wong A, Fitzgerald RC. Epidemiologic risk factors for Barrett's esophagus and associated adenocarcinoma. Clinical Gastroenterology and Hepatology. 2005 Jan 1;3(1):1-0.
19. Smith KJ, O'Brien SM, Green AC, Webb PM, Whiteman DC, Study of Digestive Health. Current and past smoking significantly increase risk for Barrett's esophagus. Clinical Gastroenterology and Hepatology. 2009 Aug 1;7(8):840-8.
20. Anderson LA, Watson RP, Murphy SJ, Johnston BT, Comber H, Mc Guigan J, Reynolds JV, Murray LJ. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. World journal of gastroenterology: WJG. 2007 Mar 14; 13(10):1585.
21. Nguyen DM, Richardson P, El–Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients

with Barrett's esophagus. Gastroenterology. 2010 Jun 1; 138(7):2260-6.
22. Richter JE, Penagini R, Pohl D, Dvorak K, Goldman A, Savarino E, Zentilin P, Savarino V, Watson JT, Wong RK, Pace F. Barrett's esophagus: proton pump inhibitors and chemoprevention II. Annals of the New York Academy of Sciences. 2011 Sep; 1232(1):114-39.
23. Bosetti C, Talamini R, Franceschi S, Negri E, Garavello W, La Vecchia C. Aspirin use and cancers of the upper aerodigestive tract. British journal of cancer. 2003 Mar;88(5):672.
24. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology. 2003 Jan 1;124(1):47-56.
25. Kim JH, Rhee PL, Lee JH, Lee H, Choi YS, Son HJ, Kim JJ, Rhee JC. Prevalence and risk factors of Barrett's esophagus in Korea. Journal of gastroenterology and hepatology. 2007 Jun; 22(6):908-12.
26. Cook MB, Corley DA, Murray LJ, Liao LM, Kamangar F, Ye W, Gammon MD, Risch HA, Casson AG, Freedman ND, Chow WH. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). PloS one. 2014 Jul 30;9(7):e103508.
27. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Alimentary pharmacology & therapeutics. 2010 Nov; 32(10):1222-7.
28. Woodland P, Sifrim D. The refluxate: the impact of its magnitude, composition and distribution. Best practice & research Clinical gastroenterology. 2010 Dec 1; 24(6):861-71.
29. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. New England journal of medicine. 1999; 340(11):825-31. Miao Y, Liu R, Pu Y, Yin L. Trends in esophageal and esophagogastric junction cancer research from 2007 to 2016: a bibliometric analysis. Medicine. 2017 May; 96(20).
30. Miao, Y., Liu, R., Pu, Y. and Yin, L., 2017. Trends in esophageal and esophagogastric junction cancer research from 2007 to 2016: a bibliometric analysis. Medicine, 96(20).
31. Lam AK. Molecular biology of esophageal squamous cell carcinoma. Critical reviews in oncology/hematology. 2000 Feb 1;33(2):71-90.
32. Chen J, Kwong DL, Cao T, Hu Q, Zhang L, Ming X, Chen J, Fu L, Guan X. Esophageal squamous cell carcinoma (ESCC): advance in genomics and molecular genetics. Diseases of the Esophagus. 2015 Jan 1;28(1):84-9.
33. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Annals of oncology. 2012 Jul 30;23(12):3155-62.
34. Bollschweiler E, Wolfgarten E, Gutschow C, Hölscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2001 Aug 1; 92(3):549-55.
35. Eads CA, Lord RV, Wickramasinghe K, Long TI, Kurumboor SK, Bernstein L, Peters JH, DeMeester SR, DeMeester TR, Skinner KA, Laird PW. Epigenetic patterns in the progression of esophageal adenocarcinoma. Cancer research. 2001 Apr 15; 61(8):3410-8.