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Impact of Gender on Gastroesophageal Reflux Disease Complications: Analysis of 27 Million Hospitalizations

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ABSTRACT

Background & Aims: Previous studies have reported gender differences in patients with gastroesophageal reflux disease (GERD). These studies have also reported differences based on gender in the rates of complications. In this study, we aim to identify gender disparities in the rates of GERD complications in the United States.
Methods: We queried the 2016-2020 National Inpatient Sample database to identify patients with GERD. Patients with eosinophilic esophagitis or missing demographics were excluded. We compared patient demographics, comorbidities and complications based on gender. Multivariate logistic regression analysis was used to identify the impact of gender on complications of GERD.
Results: 27.2 million patients were included in the analysis. Out of them, 58.4% of the hospitalized patients with GERD were female. Majority of the women were White (75%), aged>65 years (57.5%) and were in the Medicare group (64%). After adjusting for confounders, females were noted to have lower odds of esophagitis (aOR=0.85, 95%CI: 0.84-0.86, p<0.001), esophageal stricture (aOR=0.95, 95%CI: 0.93-0.97, p<0.001), Barrett's esophagus (aOR=0.58, 95%CI: 0.57-0.59, p<0.001) and esophageal cancer (aOR=0.22, 95%CI: 0.21-0.23, p<0.001).
Conclusions: Our study confirms the findings of previous literature that females, despite comprising the majority of the study population, had a lower incidence of GERD related complications. Further studies identifying the underlying reason for these differences are required.

Key words: gender – GERD - National Inpatient Sample – complications – Barrett's esophagus – esophageal cancer – stricture.

Abbreviations: BE: Barrett's esophagus; EAC: esophageal adenocarcinoma; ECI: Elixhauser comorbidities index; GERD: gastroesophageal reflux disease; ICD-10 CM: The International Classification of Diseases 10th Version, Clinical Modification; OSA: obstructive sleep apnea; PPI: proton pump inhibitor.

INTRODUCTION

Gastroesophageal reflux disease (GERD) occurs due to the loss of lower esophageal sphincter tone, resulting in the reflux of acid from the stomach into the esophagus. Patients usually present with symptoms of acid reflux, dyspnea, and dysphagia [1]. Complications of untreated GERD include anemia, esophagitis, Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC) [2]. The prevalence of GERD in the United States (US) has been estimated to be between 18-27.8% [3]. Gastroesophageal reflux disease is associated with a significant healthcare burden with one study reporting GERD to account for more than 4.3 million office visits and 317,000 emergency department visits. Medical costs of GERD have been estimated to be between $15-20 billion per year with resource utilization increasing in advanced stages of the disease [4]. A study by Howden et al. [5] reported that patients with refractory GERD have substantially higher healthcare costs than those without refractory GERD. Thus, it is essential to identify patients which are at higher risk of progressing to advanced stages of the disease.

Previous studies have linked gender as a risk factor for GERD, as it has been noted to occur more frequently in females compared to males [6-8]. Although the exact mechanism underlying this association remains unclear, estrogen has been hypothesized to play a significant role in the development of GERD. Studies have shown that female sex hormones can relax the lower esophageal

sphincter, which may be contributing to higher symptomatic burden in women [9]. Although the prevalence of GERD is higher in females, studies have found the rate of GERD complications to be higher in males. Sharma et al. [10] reported that male patients have higher rates of non-dysplastic BE and BE-related neoplasia than female patients (56.1% vs 76.8%). This might be linked to the role of estrogen in maintaining epithelial integrity. A systematic review by Kim et al. [11] similarly found that the prevalence of complications of GERD was higher in men compared to women. Estrogen has also been reported to have an anti-inflammatory role with studies suggesting women to have BE and EAC in later stages of life than males, potentially due to the loss of protective effects of estrogen after menopause [9].

Although there are numerous studies that have shown gender disparities in the risk of developing complications of GERD, there have been no studies using US national data to evaluate this association. In this study, we collected data from 27 million hospitalizations to assess if female gender is protective against the development of complications in patients with GERD.

METHODS

Data Source

The Healthcare Cost and Utilization Project (HCUP) maintains the National Inpatient Sample (NIS), the largest database of inpatient hospital stays [12]. It reliably estimates illness burden and outcomes using data from a 20% stratified sample of hospitals in the United States from 37 states. Every hospitalization is de-identified and kept as a unique entry in the National Inpatient Sample. As a result, the study did not require IRB approval.

Study Population

The International Classification of Diseases 10th Version, Clinical Modification (ICD-10 CM) diagnosis codes were used to identify all patients with a diagnosis of GERD between 2016-2020. We excluded patients who were less than 18 years old, missing demographics or had a diagnosis of eosinophilic esophagitis. In total, 27,282,960 patients met the inclusion criteria. Patients were further stratified into two groups based on gender. The inclusion process is presented in Fig. 1.

Study Variables and Complications

We collected additional information on patient demographics such as age, gender, race, primary insurance, and median income quartile. We further collected information on comorbidities such as tobacco use, obstructive sleep apnea (OSA), hyperlipidemia, diabetes, chronic pulmonary disease, obesity, alcohol misuse, drug use, psychoses, liver disease, peptic ulcer disease and depression. We used Elixhauser comorbidities index (ECI), a well-validated index based on ICD 10-CM codes meant to be used in large administrative data to reliably estimate the comorbidity burden [13]. We also collected information on the common complications of GERD such as esophageal stricture, BE and EAC.

Statistical Analysis

Hospital-level discharge weights were used to generate national estimates. To compare categorical variables, Chi-square test was used, while an independent sample t-test was used for continuous variables. Univariate logistic regression analysis was performed to identify association between various confounding factors and complications of GERD. Only factors that had a p value<0.1 were included in the multivariate logistic regression model. We adjusted for patient demographics, comorbidities and Elixhauser comorbidity index. The unadjusted and adjusted odds ratios were calculated with a 95% confidence interval (95%CI). A type I error of 0.05 was considered to be statistically significant. STATA 17.0 (Texas) was used to analyze the data.

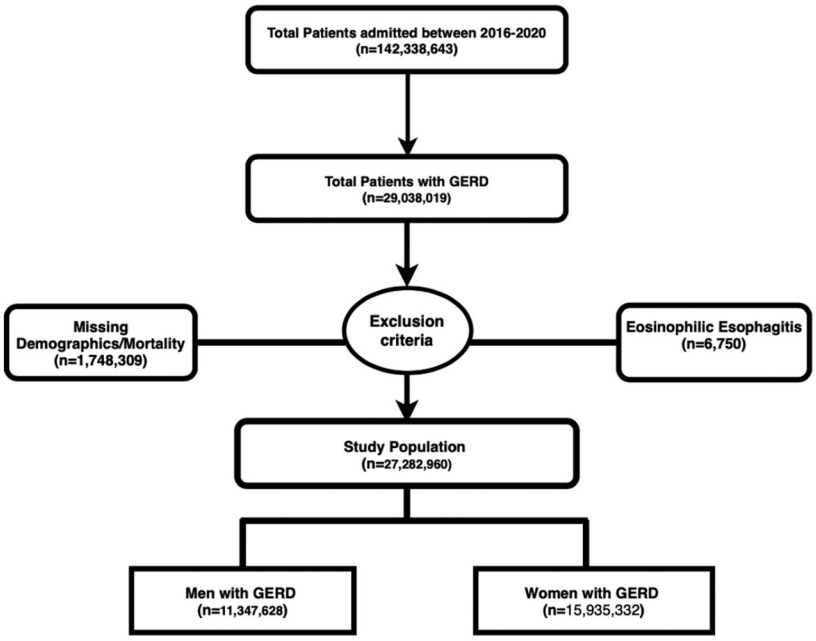

Fig. 1. Inclusion process for the study.

RESULTS

Patient Demographics

A total of 27,282,960 patients were included in the study. Females accounted for 58.4% of the study population. The majority of the women admitted were >65 years (57.5%) of age. The majority of the women admitted with GERD were White (75%) followed by African-Americans (13.8%). Majority of the patients with GERD were in the Medicare group (64%). A complete list of patient demographics is presented in Table I.

Table I. Patient demographics, stratified by gender

	Males, n (%)	Females, n (%)	p
	11,347,628	15,935,332	
Age Categories			<0.001
18-44	1,072,350 (9.5)	2,046,169 (12.8)	
45-65	3,904,755 (34.5)	4,717,894 (29.6)	
>65	6,37,0523 (56)	9,171,268 (57.5)	
Race			<0.001
White	8,823,018 (77.7)	11,940,182 (75)	
African American	1,281,185 (11.29)	2,183,655 (13.8)	
Hispanic	768,210 (6.8)	1,143,310 (7.1)	
Asian/Pacific islander	180,105 (1.6)	262,800 (1.6)	
Native American	58,745 (0.5)	85,125 (0.5)	
Other	236,365 (2.1)	320,260 (2.1)	
Insurance			<0.001
Medicare	6,998,608 (61.7)	10,195,693 (64)	
Medicaid	1,203,055 (10.6)	1,870,139 (11.7)	
Private	2,444,555 (21.5)	3,315,270 (20.)	
Uninsured	276,535 (2.4)	270,675 (1.7)	
Income			<0.001
Lowest quartile	2,278,814 (29.8)	4,887,354 (30.7)	
Second quartile	3,081,810 (27.2)	4,329,434 (27.2)	
Third quartile	2,710,544 (23.9)	3,790,199 (23.8)	
Highest quartile	2,176,460 (19.2)	2,928,344 (18.3)	

Comorbidities in Patients with GERD

Females had a lower incidence of hyperlipidemia, diabetes, psychosis and peptic ulcer disease than males. The incidence of chronic pulmonary disease and depression was noted to be higher in females than males. There was a lower proportion of females with 3 or more Elixhauser comorbidities than males. A complete list of etiologies is present in Table II.

Complications

Esophagitis

A total of 3.3% of the study population had esophagitis. Esophagitis was noted in 3.7% of males and 3% of females. The results of GERD outcomes stratified by gender are presented in Table III. On multivariate analysis, women had a statistically significant decrease in the odds of developing esophagitis compared to males (aOR=0.85, 95%CI: 0.84-0.86, p<0.001). The results of multivariate logistic regression model are presented in Table IV.

Table II. Comorbidities in patients with GERD, stratified by gender

	Males, n (%)	Females, n (%)	p
OSA	1,678,875 (14.8)	1,709,655 (10.8)	<0.001
Smoking	5,668,099 (50)	5,808,754 (36.4)	<0.001
Hyperlipidemia	5,600,559 (49.3)	6,885,714 (43.2)	<0.001
Diabetes	4,033,939 (35.5)	5,014,849 (31.4)	<0.001
COPD	3,476,039 (30.6)	5,642,314 (35.4)	<0.001
Alcohol Abuse	1,095,535 (9.6)	511,240 (3.2)	<0.001
Drug abuse	709,075 (6.2)	678,025 (4.2)	<0.001
Psychosis	361,375 (3.1)	394,800 (2.4)	<0.001
Depression	2,072,465 (18.3)	4,228,560 (26.5)	<0.001
Liver disease	956,215 (8.4)	953,850 (6)	<0.001
Obesity	2,066,965 (18.2)	3,913,720 (24.6)	<0.001
Peptic ulcer disease	158,345 (1.4)	212,025 (1.3)	<0.001
NSAIDs use	140,940 (1.2)	229,130 (1.4)	<0.001
Elixhauser Comorbidities			<0.001
0	311,815 (2.7)	1,397,780 (4.0)	
1	936,540 (8.2)	1,397,780 (8.8)	
2	1,547,360 (13.6)	2,193,379 (13.8)	
3 or more	8,551,913 (75.4)	11,719,523 (73.4)	

GERD: gastroesophageal reflux disease; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea; NSAID: nonsteroidal anti-inflammatory drug.

Table III. Outcomes in patients with GERD, stratified by gender

	Males, n (%)	Females, n (%)	p
Esophagitis	424,200 (3.7)	472,400 (3)	<0.001
Esophageal stricture	90,195 (0.7)	119,075 (0.5)	<0.001
Barrett's esophagus	192,050 (1.7)	147,945 (1.0)	<0.001
Esophageal cancer	50,445 (0.4)	14,480 (0.1)	<0.001

For abbreviations see Table II.

Esophageal Stricture/Obstruction

A total of 7.7% of the study population had esophageal stricture. Esophageal stricture was documented in 0.7% of males and 0.5% of females. On multivariate analysis, women had a statistically significant decrease in the odds of developing esophageal stricture compared to males (aOR=0.95, 95%CI: 0.93-0.97, p<0.001). The results of multivariate logistic regression model are presented in Table IV.

Table IV. Results of multivariate logistic regression model identifying association between gender and outcomes using males as reference

	aOR	95% CI	p
Esophagitis	0.85	0.84-0.86	<0.001
Esophageal stricture	0.95	0.93-0.97	<0.001
Barrett's esophagus	0.58	0.57-0.59	<0.001
Esophageal cancer	0.22	0.21-0.23	<0.001

aOR: adjusted odd ratio; CI: confidence interval.

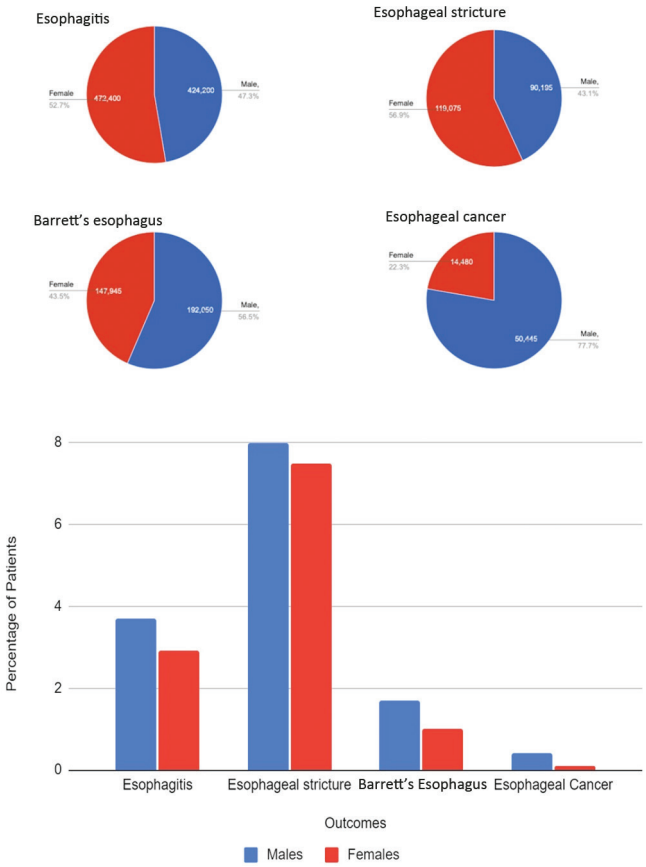

Fig. 2. Outcomes of GERD, stratified by gender.

Barrett's Esophagus

A total of 2.7% of the study population developed BE; it was documented in 1.7% of males and 1% of females. On multivariate analysis, women had a statistically significant decrease in the odds of developing BE compared to males (aOR=0.58, 95%CI: 0.57-0.59, p<0.001).

Esophageal Cancer

A total of 0.5% of the study population developed esophageal cancer; it was documented in 0.4% of males and 0.1% of females. On multivariate analysis, women had a statistically significant decrease in the odds of developing esophageal cancer compared to males (aOR=0.22, 95%CI: 0.21-0.23, p<0.001).

DISCUSSION

Our study found that 58.4% of patients with GERD were females, which is consistent with previous studies that have reported GERD to be predominant among women [14]. Well-documented risk factors for GERD include advanced age, presence of hiatal hernia, obesity, smoking and alcohol consumption [1]. Additionally, gender has also been reported as a risk factor for the development of GERD. It has been suggested that estrogen has a relaxing effect on lower esophageal sphincter muscle, which can result in increased reflux of stomach contents into the esophagus leading to GERD [15]. This is a common finding in pregnancy and young females. Studies have also noted that after menopause, the risk of developing GERD is higher. A study by Infantino et al. [16] reported that post-menopausal women were 2.9 times more likely to have GERD than perimenopausal patients. One possible explanation for this finding is the development of post-menopausal adiposity which can lead to increased intra-abdominal pressure and higher reflux rates [17]. Additionally, studies have shown that estrogen may upregulate esophageal tight junction proteins such as occludin, which in turn increases the barrier resistance of the esophageal mucosa [18]. A decreased amount of estrogen in male gender or post-menopausal status may account for increased susceptibility to developing GERD.

Symptomatic GERD is categorized into erosive and non-erosive GERD based on the endoscopic pathology [18]. Our study shows that women were at 15% lower odds of esophagitis compared to males. A recent meta-analysis of 28 studies by Cook et al. shows that among patients with erosive esophagitis, the pooled male/female sex ratio was 1.57/1 [19]. Several animal model studies have provided important insights into the protective role of estrogen on esophageal mucosa [20]. It has been reported that 17 beta estradiol, which is the active form of estrogen hormone, inhibits the expression of proinflammatory transcription factor p65/RelA leading to downregulation of the inflammatory response [21]. Furthermore, 17 Beta estradiol upregulates the expression of tight junction protein occludin responsible for maintaining the mucosal integrity of the esophageal wall while being exposed to acid [18].

Our study noted that females were at 5% and 42% lower odds of developing esophageal stricture and BE compared to males. Our results are consistent with the findings of Cook et al. [19], who reported males to have 1.96 times risk of BE compared to females (1.96:1). Their study also reported that the male:female ratio in the United States is 2.33:1 while in the United Kingdom male:female ratio is 1.54:1. This was attributed to the variability in the definition of BE in the different regions of the world. In the United States, the diagnosis of BE requires the presence of intestinal metaplasia, while in the United Kingdom, the presence of intestinal metaplasia is not required. This geographic variation might explain the discrepancy in the incidence of BE. There is also variation in the risk factors, especially rates of obesity and genetic variation within these regions. Interestingly, a similar geographic gender variation has been noted in the rates of EAC [22].

Our study shows that females have 78% lower odds of developing esophageal cancer compared to males. The pathophysiology of esophageal cancer can be explained as a continuum from erosive esophagitis to BE to high-grade dysplasia leading to esophageal cancer. Traditional risk factors for esophageal cancer such as smoking and alcohol consumption are higher in males compared to females, which may contribute to these findings [22]. Additionally, estrogen might be playing a protective role against the development of esophageal cancer. Estrogen has an anti-inflammatory effect by inhibiting TNF alpha expression by mast cells seen in reflux esophagitis. [23-25]. This may slow the progression of GERD to malignancy among female patients. Another factor that plays a significant role in the progression of reflux to BE to esophageal cancer, especially adenocarcinoma is visceral obesity [17]. However, in our study, females had a lower rate of esophageal cancer despite having higher rates of obesity. Males and post-menopausal females have higher visceral fat

which produces adipose-mediated hormones including TNF alpha, insulin like growth factor, interleukin-6, and adipokines (i.e. leptin) which are known to promote carcinogenesis in various cancers including esophageal adenocarcinoma [26-29]. Another possible explanation for the differences in the rates of esophageal cancer between males and females could be the differences in proton pump inhibitor (PPI) use. Due to the nature of the database, we cannot ascertain the proportion of patients who were on PPI in both groups. However, given that the majority of females with GERD are symptomatic, it is likely that these patients were initiated on PPI earlier in their disease course which might have contributed to decreased rates of complications in females [30-32]. Male patients are more commonly asymptomatic than female patients, and therefore likely initiated PPI therapy later in their disease course.

Other limitations of our study include a lack of data regarding pathologic biopsy of reflux esophagitis, BE, EAC and the method of diagnosis for BE. Our study relies on ICD-10 codes, so coding errors cannot be ruled out. In addition, the inclusion of only the inpatient population can affect the generalizability of the results as only hospitalized patients are included in the analysis. The major strength of the study is that the data is obtained from a large database representative of the US population and is free from regional bias.

CONCLUSIONS

Our study emphasizes the importance of gender variation seen in the continuum of pathologic states of GERD from esophageal stricture to BE leading to EAC. Our study confirms the findings that male gender is associated with an increased rate of complications of the disease. Women comprised a higher proportion of patients with GERD, but had lower rates of esophageal stricture, BE and esophageal cancer. Our findings suggest that male patients with GERD should be followed more diligently to identify complications of GERD in order to reduce morbidity and mortality. Further studies examining the role of estrogen in the development of GERD complications is warranted.

Conflicts of interest: None to declare.

Authors' contribution: K.B and H.I. were involved in the conception, design, analysis, and interpretation of data, drafted the article and revised it critically for important intellectual content, and approved the final version to be published. A.A., M.D., I.S., and I.K. reviewed the literature and helped drafting the manuscript. H.C., D.D., and A.S. interpreted the data, drafted the manuscript, and revised it for important intellectual content. J.Y revised the data for important intellectual content and was involved in the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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