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ORIGINAL ARTICLE

Hiatal Hernia Associated with Higher Odds of Dysplasia in Patients with Barrett's Esophagus

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Abstract

Background Patients with Barrett's esophagus (BE) are more likely to have associated hiatal hernia (HH) compared to the general population. Studies show that HH are typically longer and wider in patients with BE.

Aims To determine whether patients with HH have associated increased odds of coexistence of BE by examining inpatient prevalence, as well as determining other inpatient outcomes.

Methods This was a case–control study using the NIS 2016, the largest public inpatient database in the USA. All patients with ICD10CM codes for BE were included. None were excluded. The primary outcome was determining the association between BE and HH in hospitalized patients, stratified by grade of dysplasia. Secondary outcomes included measuring use of endoscopic ablation in patients with BE and HH compared to patients with BE and no HH, determining the degree of association between HH and esophagitis in patients with or without BE, as well as the association between esophagitis and dysplasia in patients with BE and HH.

Results A total of 118,750 patients with BE were identified, of which 24,030 had associated HH. Adjusted odds of having associated BE in patients with HH was 10.9 ($p < 0.01$) compared to patients without HH. Patients with HH also displayed significantly higher odds of both low-grade dysplasia (aOR 34.5, $p < 0.01$) and high-grade dysplasia (aOR 14.7, $p < 0.01$). For secondary outcomes, the odds of undergoing ablation for BE was higher 4.77 ($p < 0.01$) in patients with HH.

Conclusions Patients with HH have significantly higher odds of having associated BE, regardless of the level of dysplasia. Furthermore, the odds of undergoing ablation are much higher, likely reflecting higher odds of dysplasia. This highlights the importance of BE in patients with HH, and potentially consider these patients as higher risk.

Keywords Barrett's esophagus · Hiatal hernia · Dysplasia · Radiofrequency ablation

Introduction

Barrett's esophagus (BE) is an acquired condition in which normal squamous epithelium in the distal esophagus is replaced by metaplastic columnar epithelium. It is thought to be a result of long-standing gastroesophageal reflux disease (GERD) [1–3]. Evidence suggests that male sex, Caucasian race, obesity, and smoking may also increase risk for developing BE [4–6]. Family history of BE in a 1st degree relative also increases risk, with some studies suggesting possible significant genetic factor influence [7]. Current US guidelines state that BE is diagnosed when at least 1 cm of metaplastic columnar epithelium replaces the squamous epithelium at the gastroesophageal junction (GEJ) [8]. Barrett's esophagus can be further classified as short-segment BE if the intestinal metaplasia is < 3 cm above the GEJ, or long-segment BE if it extends ≥ 3 cm above the GEJ [9].

In the literature, BE has also been associated with hiatal hernias (HH). Hiatal hernias refer to herniation of elements of the abdominal cavity, typically the stomach, through the esophageal hiatus into the mediastinum [3]. These hernias are thought to be caused by widening of the muscular hiatal tunnel and circumferential laxity of connective tissue ligaments anchoring the esophagus to the diaphragm at the GE junction. In prior studies, HH were found in 76–100% of patients with endoscopically and histologically proven BE [10–15] Furthermore, in

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a meta-analysis of 33 studies comprising 4390 patients with BE, HH were associated with an increased risk of BE of any length (odds ratio 3.94; 95% CI 3.02–5.13). The strongest association was seen between HH and long-segment BE (odds ratio 12.67; 95% CI 8.33–19.25) [16].

An increase in HH length is also associated with the presence of BE. A study of 167 patients examined during endoscopy showed that HH length was increased at 3.95 cm in patients with BE compared to 2.77 cm in controls with GERD but without BE or esophagitis [15]. These patients with BE also showed wider hiatal openings with a mean maximal hiatal width of 3.52 cm compared to 2.21 in controls. Another study showed a correlation between HH length and BE length: HH were significantly longer in those with long-segment BE (3.4 cm ± 0.5 cm) than in those with short-segment BE (1.5 cm ± 0.4 cm), with a correlation coefficient of $r = 0.62$ ($p < 0.01$) [17]. These results suggested that patients with longer HH are likely to have longer segments of BE. However, no prior literature has directly observed associations of HH and the degree of dysplasia found in BE.

The aim of this study was to investigate whether patients with HH have increased odds of developing BE by examining inpatient prevalence using data from a large national database. Furthermore, we observe associations between the presence of HH and degree of histological dysplasia seen in BE. Lastly, we observed the odds of undergoing ablation in the inpatient setting.

Methods

Study Design and Data Source

All data were abstracted from the latest version of the Nationwide Inpatient Sample (NIS) for the year 2016, which is the largest publically available, inpatient, all-payer database in the USA. Each year of data contains more than 7 million hospital stays, which are a 20% stratified sample of over 4000 non-federal acute care hospitals of more than 44 states of the USA, and after applying discharge weights provided by the Healthcare Cost and Utilization Project (HCUP) makes the data representative of 95% of hospital discharges nationwide. A principal diagnosis, defined as the primary discharge diagnosis, as well as 29 other secondary diagnoses are included in the dataset. The dataset also includes codes for up to 15 procedures performed during the hospital stay. It also allows determining length of hospital stay, and total hospitalization charges, as well as desired outcome measures such as calculations of inpatient disease prevalence.

Study Population

All patients in the NIS dataset for 2016 with an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) with any diagnostic code for BE (K22.7XX) were included in the study. Patients with ICD-10 codes for HH (K44.9) were also identified within the database. No patients were excluded. Propensity scores were used to match the BE cohort with a diagnosis of HH to a cohort of patients with BE and no HE, as described in the statistical section.

Variable Definition

The degree of BE dysplasia was classified as "no dysplasia," "low-grade dysplasia," and "high-grade dysplasia," according to respective ICD-10 diagnostic codes (K22.70, K22.71, and K22.711, respectively). Patient general characteristics included demographics such as age, gender, ethnicity, body mass index (BMI), long-term nonsteroidal anti-inflammatory drugs (NSAID), long-term aspirin use, median income in zip code, and insurance type. Hospital characteristics included hospital region, teaching status, number of hospital beds, and hospital location. The HCUP divides the USA into four geographical locations known as "census regions." Each patient's vital status at the conclusion of hospital stay, total days of hospitalization, and total hospitalization charges were also abstracted from the database. To account for patient comorbidities, the Deyo adaptation of the Charlson Comorbidity Index was used, which is a validated tool for large database analysis [18].

Aims

The primary aim was to determine the relative frequency of BE in patients with HH compared to patients without HH.

Secondary outcomes were determining the association with the different degrees of dysplasia in patients with BE and HH, and was compared to patients with BE who did not have associated HH. The association between HH and a diagnosis of esophagitis was also explored and compared in patients with and without BE, as well as the association between esophagitis and dysplasia. In addition, the association between esophagitis and dysplasia in patients with BE and HH was also explored. Lastly, the association with endoscopic ablation in patients with BE and HH was also examined and compared to patients with BE and no HH. Resource utilization was measured by total hospitalization charges and hospital costs.

Statistical Analysis

Discharge-level weights published by the HCUP were used to estimate the number of patients with BE and HH. Fisher's exact test was used to compare proportions and analysis of variance was utilized to compare means. Propensity score matching was used to construct two matching populations with age, gender, BMI, and Charlson Comorbidity Index as matching covariates with a caliper distance of 0.01. Subsequently, a hybrid multivariate logistic regression model was used to adjust for other covariates of interest and obtain adjusted odds ratios to determine association between variables. The variables included in the multivariate model were median income in patient zip code, insurance carrier, ethnicity, hospital region, hospital urban/rural location, and number of hospital beds. All statistical analyses were conducted by a team member with formal biostatistical training (PTK) using STATA, Version 14 (StataCorp LP, College Station, TX, USA).

Results

A total of 118,750 patients with BE were identified, of which 24,030 also had a HH and 94,720 patients did not have HH, which were subjected to propensity score matching for selected covariates. The mean age was 68 years, and 44% were female. Table 1 displays the basic characteristics of all patients with BE stratified by the presence of HH. All patients with an associated diagnosis of BE were stratified into two cohorts based on the presence or absence of associated HH diagnosis. When comparing the baseline patient characteristics of the two cohorts, the cohort with associated HH was proportionately comprised of more female patients, Hispanic ethnicity, with less comorbidity burden, as evaluated by the Charlson Comorbidity Index, when compared to patients without HH. Proportionately more patients with BE and HH were taking long-term NSAIDs. There were no significant differences in BMI and proportion of patients taking long-term aspirin. The two cohorts differed in some hospital characteristics at baseline. The patient cohort with associated HH was comprised of proportionately more patients from the southern region of the USA. Although the two cohorts differed at a statistically significant level in other aspects, these differences were not felt to be clinically relevant. These results are reflected in Table 1.

Overall, all inpatients with any diagnostic code for HH had increased odds of having associated BE (adjusted OR: 10.89, $p < 0.01$) when compared to patients without HH. Of the patients with BE and coexisting HH, a total of 23,664 (98.5%) did not have dysplasia, while 166 (0.69%) had low-grade dysplasia and 202 (0.84%) had high-grade dysplasia. Of the patients with BE that did not have coexisting HH, 93,934 (99.2%) did not have dysplasia, while 199 (0.21%) had low-grade dysplasia and 578 (0.61%) had high-grade dysplasia. The unadjusted

Table 1 Baseline characteristics of patients with Barrett's esophagus with and without associated hiatal hernia

Characteristics of Patients with Barrett's Esophagus	Without Hiatal Hernia	With Hiatal Hernia ($n = 24{,}030$)	p value
Mean age (years)	66.9	67.6	0.31
Female gender (%)	39.7%	43.8%	< 0.01
Ethnicity			
Caucasian	90.1%	86.5%	< 0.01
African American	3.2%	3.9%	
Hispanic	3.9%	6.2%	
Other	2.8%	3.4%	
Body mass index category			
Underweight	4.5%	4.7%	0.94
Normal/Overweight	78.8%	78.8%	
Obesity	8.8%	8.7%	
Morbid obesity	7.9%	7.9%	
Long-term aspirin use	16.0%	15.7%	0.60
Long-term NSAID use	1.03%	1.79%	< 0.01
Insurance carrier			
Medicare	65.4%	65.0%	< 0.01
Medicaid	8.4%	9.2%	
Private	22.0%	20.5%	
Out-of-pocket	1.6%	2.3%	
Other	2.6%	4.0%	
Income in zip code			
$1–$37,999	21.7%	24.5%	< 0.01
$38 K–47,999	25.8%	27.1%	
$48 K–63,999	27.9%	25.9%	
> $64,000	24.7%	22.5%	
Charlson score			
0	20.5%	23.1%	< 0.01
1	22.4%	24.7%	
2	17.8%	17.4%	
3 or more	39.4%	34.8%	
Hospital region			
Northeast	25.3%	20.6%	< 0.01
Midwest	28.8%	26.1%	
South	29.4%	34.0%	
West	16.5%	19.3%	
Urban location	92.1%	92.1%	0.94
Teaching hospital status	66.2%	63.0%	< 0.01
Weekend admission	19.3%	19.8%	0.46
Hospital bed size			
Small	19.3%	19.9%	0.59
Medium	28.7%	28.9%	
Large	52.0%	51.2%	

NSAID nonsteroidal anti-inflammatory drugs

Table 2 Dysplasia status in patients with Barrett's esophagus with and without coexisting hiatal hernia

Dysplasia status	Patients without HH N = 94,720	Patients with HH N = 24,030	*p* value
No dysplasia	99.17%	98.47%	< 0.01
Low-grade dysplasia	0.21%	0.69%	
High-grade dysplasia	0.61%	0.84%	

HH hiatal hernia

Table 3 Adjusted odds ratios, 95% confidence intervals, and p values for degrees of dysplasia in patients with Barrett's esophagus and coexisting hiatal hernia compared to patients with Barrett's esophagus and no hiatal hernia

Dysplasia status	Adjusted OR	95% confidence interval	*p* value
Overall dysplasia	14.7	11.72–18.42	< 0.01
Low-grade dysplasia	34.5	20.69–57.53	< 0.01
High-grade dysplasia	14.7	10.03–21.66	< 0.01

OR odds ratio

differences between both groups reached statistical significance ($p < 0.01$). Table 2 displays the differences in dysplasia status among patients with BE with and without coexisting HH.

These findings were confirmed in the multivariate model, as patients with BE and HH displayed increased adjusted odds ratio (aOR) of overall dysplasia (aOR 14.7, $p < 0.01$). Upon stratifying for degree of dysplasia, patients with BE and coexisting HH had increased odds of low-grade dysplasia (aOR 34.5, $p < 0.01$) and high-grade dysplasia (aOR 14.7, $p < 0.01$) when compared to patients with BE and no HH. Table 3 displays all adjusted odds ratios, 95% confidence intervals, and p values.

For the secondary outcome, a total of 104 patients (0.11%) with BE and no HH underwent ablation, while 120 (0.5%) patients with BE and associated HH underwent ablation ($p < 0.01$). This was confirmed on multivariate analysis, as patients with BE and HH had increased adjusted odds of ablation (aOR 4.77, $p < 0.01$) when compared to patients with BE and no HH. Both patients with and without BE who had HH had increased associated odds of esophagitis (aOR 2.76, 95% CI [2.37–3.22], $p < 0.001$) and aOR: 17.88 [95% CI 17.09–18.71], $p < 0.001$, respectively) compared to patients with and without BE without HH. For patients with BE and HH, there was no statistically significantly different odds of dysplasia in patients with or without esophagitis (aOR 1.11, [95% CI 0.27–4.55], $p = 0.88$).

Discussion

The results of this study not only suggest that patients with HH are more likely to have associated BE, but that patients with BE and coexisting HH have significantly higher occurrence and odds of dysplasia (both low and high grade) when compared to patients with BE and no HH. Furthermore, patients with BE and HE had higher rates and odds of undergoing ablation, likely being secondary to the associated increased odds of dysplasia in this cohort when compared to patients with BE and no HH. In addition, although patients with BE had associated higher odds of esophagitis in the presence of a coexisting HH diagnosis, the presence of esophagitis was not associated with statistically different odds of dysplasia in patients with BE compared to patients without esophagitis.

Five main complications are associated with BE and outline its clinical significance: complications of GERD, strictures, ulcerations/perforations, bleeding, and adenocarcinoma [1]. Early epidemiological studies reported that the presence BE predicts a 30- to 40-fold increased risk for esophageal adenocarcinoma (EAC) [19]. A more recent study reported a more modest relative risk of 11.3 in developing EAC in the presence of BE compared to the general population [20]. Another study involving a prospective multivariate analysis of 550 patients with BE found that large size hiatal hernias were a significant risk factor associated with the index diagnosis of high-grade dysplasia (HGD) and cancer [21]. Another study of 131 patients found the same conclusion [22]. One can speculate that this is secondary to the increased associated prevalence of GERD in patients with HH, which in turn increases the risk of metaplasia and eventually dysplasia. There are several mechanisms by which HH can promote reflux, including impaired clearance of acid from the esophagus due to trapping in the hernial sac, as well as widening of the esophageal hiatus that may impair the ability of the crural diaphragm to function as a sphincter [23, 24]. Along with acid reflux, bile salt reflux has also been associated with hiatal hernias [25]. Some studies have suggested that bile salt reflux may act synergistically with acid reflux in worsening dysplasia and progression of BE [26].

Current treatment options of EAC are limited and odds of survival remain low. Therefore, surveillance and reduction of risk factors remain the best method of approach. Regarding current guidelines, the American Gastroenterological Association states that "HH has been demonstrated to be a risk factor in BE, and hernia size is correlated with the length of BE" [19]. This is consistent with the findings in our study which showed patients with HH have a higher likelihood of BE (Fig. 1). The AGA recommends endoscopic screening patients of with multiple risk factors

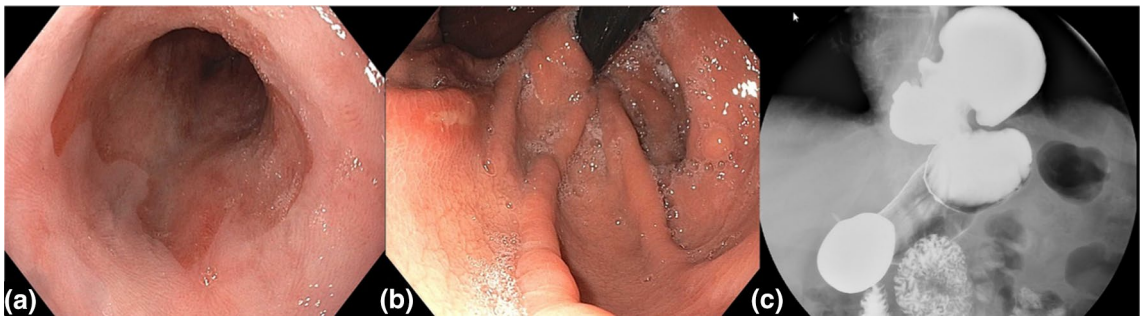

Fig. 1 Images for an 80-year-old patient with biopsy-proven Barrett's esophagus without dysplasia and a hiatal hernia. **a**. Upper endoscopy demonstrating a 4-cm-long salmon-colored mucosa consistent with Barrett's esophagus classified C3-M4 per Prague criteria, along with LA grade B esophagitis. **b**. Endoscopic view in retroflexion within the hiatal hernia sac with the visible site of the paraesophageal gastric protrusion, as well as a Cameron's lesion. **c**. Contrast esophagram demonstrating a type III paraesophageal hernia with 30% of the stomach above the hiatus. The patient ultimately underwent a Nissen's fundoplication and is currently asymptomatic at four months post-procedure

of BE, of which includes HH. The American College of Gastroenterology guidelines do not overtly acknowledge HH as a risk factor in BE, but do state that the "presence of a large hiatal hernia can increase the risk of recurrence of metaplasia after endoscopic therapy" [8]. The American Society for Gastrointestinal Endoscopy, British Society of Gastroenterology, and European Society of Gastrointestinal Endoscopy guidelines on BE do not comment on the presence of HH in patients with BE [8, 27–29] Given the findings in this study, as well as the evidence outlined in prior studies included in the introduction, we hope to persuade these other Gastroenterological societies in considering HH a significant risk factor associated with BE. Furthermore, no guidelines currently include HH in the consideration of endoscopic surveillance in patients with known Barrett's esophagus. Surveillance guidelines are typically based on the degree of dysplasia seen on initial endoscopic biopsy. As HH has been associated with higher likelihood of both low and high-grade dysplasia in patients with BE, this brings up the question of whether the presence of a HH should be a consideration on the frequency of endoscopic surveillance.

Because of the large body of data supporting its safety, efficacy, and effectiveness, radiofrequency ablation (RFA) has quickly become the preferred therapy for dysplastic BE [8, 30]. There is evidence that the presence of HH impacts the success of RFA. For instance, a study of 67 patients with BE after RFA, patients who had unsuccessful eradication after initial ablation had larger HH (7 cm) compared to those who did have successful therapy (2 cm, $p = 0.01$). These patients also required an increased number of repeated ablations to achieve successful therapy [31]. This association has also been observed in other studies [32, 33]. The presence of large HH can also affect the method of ablation used, as it is often suggested to use a focal catheter device such as the HALO-90 or HALO-60 during the procedure. This may be due to the fact that the widening of the distal esophagus into a HH may make it challenging to bring the electrode of the ablative device into good contact with the mucosa at the GEJ [34]. The results of our study show that patients with BE and HE had higher rates and odds of undergoing ablation, and this may be due to the increased odds of dysplasia in this cohort. However, we acknowledge that this finding may also be a reflection of how these patients may need several repeated ablations to achieve successful eradication.

The limitations of this study stem primarily from the nature of the dataset itself. Despite attempting to control for bias with propensity score matching, the retrospective characteristics of this study exposes it to selection bias. Since the NIS is a dataset dependent on coding, it is inherently exposed to mis-coding bias. Importantly, the administrative nature of this coding-dependent dataset is that it is unable to differentiate between type of hiatal hernia (i.e., sliding, paraesophageal, or mixed). More specifically, since a sizeable proportion of sliding hiatal hernias are underdiagnosed and there is no gold standard for its diagnosis, it is also likely that the number of patients accounted for in the dataset with these HH do not represent the true prevalence. Thus, the associations reported in this study may serve more as a qualitative (and not quantitative) gauge. The NIS's baseline unit of information is the "hospital discharge," for one is unable to track individual patients within the dataset. Therefore, patients requiring to be readmitted multiple times would be seen as separate discharges. As its name implies, the NIS includes only inpatient cases and no outpatient cases, which is associated with selection bias. Other limitations associated with the data itself include the inability to determine the precise time of diagnosis of BE, the length of the BE segment (i.e., short vs. long segment), or the characteristics of the HH. Data on HH size would have been useful to stratify the magnitude of the association of each size with BE.

There is also inability to assess for medication use (i.e., proton-pump inhibitor therapy), laboratory data, testing results (e.g., manometric studies), or specific histological interpretations beyond "no dysplasia," "low-grade dysplasia," or "high-grade dysplasia."

In conclusion, inpatients with HH have greater association with BE compared to inpatients without HH. Furthermore, the presence of a HH in patients with BE was associated with greater odds of low- and high-grade dysplasia compared to patients with BE alone. This study further highlights the importance of awareness of HH in patients with BE. Despite the fact that clinical decisions should not be based on studies evaluating correlation between variables, this study does reinforce the need for prospective, special studies further investigating this aspect. Only then will it be possible to determine whether patients with BE and HH truly are at greater risk of dysplasia and therefore esophageal adenocarcinoma.

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Compliance with Ethical standards

Conflict of interest The authors certify that we have no financial arrangements (e.g., consultancies, stock ownership, equity interests, patent-licensing arrangements, research support, honoraria, etc.) with a company whose product figures prominently in this manuscript or with a company making a competing product.

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