

Prevalence, natural history, and management of suspected barrett's esophagus in patients with cirrhosis

Abstract

Background and Aims: Barrett's esophagus is a pre-malignant condition with increased risk of esophageal cancer in which metaplastic intestinal mucosa replaces the normal esophageal squamous mucosa. It is suspected during endoscopy when salmon colored mucosa is seen in the esophagus, but requires biopsy for confirmation. In the presence of cirrhosis, biopsies are often limited by coagulopathy, thrombocytopenia, and presence of esophageal varices, which makes the diagnostic and therapeutic options for Barrett's esophagus problematic. The purpose of this study is to look at the prevalence of suspected Barrett's esophagus in patients with cirrhosis, assess how often it was confirmed with biopsy, and evaluate its natural history and progression to adenocarcinoma. There have been no previous similar studies.

Methods: Our study involves a retrospective design to collect data of patients with cirrhosis who underwent upper endoscopy (EGD) at Saint Louis University and were found to have Barrett's esophagus, either suspected or confirmed. Data analysis was then completed to compare demographics, risk factors, natural history, and survival of the two groups.

Results: Our data suggests that the prevalence of Barrett's esophagus in patients with liver cirrhosis is increased compared to that found in the general population. Risk factors for the development and confirmation of Barrett's esophagus, along with survival data, were compared between groups and were not found to be statistically significant.

Conclusion: A higher prevalence of Barrett's esophagus is noted within a population of cirrhotics undergoing endoscopy. The estimated prevalence of Barrett's esophagus is 0.076-2% in the general population undergoing endoscopy whereas our study demonstrated a prevalence of over 10% of potential Barrett's patients (1.9% confirmed). It is important to recognize possible shared risk factors and the increased prevalence of Barrett's esophagus in this patient population.

Keywords: esophageal adenocarcinoma, premalignant condition, esophageal cancer, biopsies and clinical characteristics, intestinal metaplasia, alcohol consumption, data analysis, meld score, coagulopathy, thrombocytopenia, hepatocellular carcinoma, endoscopic surveillance, plasma vasoactive peptides, neurotensin, liver cirrhosis, hiatal hernia

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Abbreviations: IM, intestinal metaplasia; EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; LGD, low grade dysplasia; GAVE, gastric astral vascular ectasia; GERD, gastroesophageal acid reflux disease; PPI, proton pump inhibitor; HCC, hepatocellular carcinoma; ASGE, american society of gastrointestinal endoscopy; BE, barrett's esophagus; EGD: Esophagogastroduodenoscopy; NASH, non-alcoholic steatohepatitis

Introduction

Esophageal cancer is the sixth leading cause of cancer mortality worldwide.¹ While esophageal squamous cell carcinoma rates are declining, the incidence of esophageal adenocarcinoma has increased by six fold between 1975 to 2001.^{2,3} Barrett's esophagus (BE) is a premalignant condition that can lead to esophageal adenocarcinoma (EAC) in 0.018% of patients per year; recognizing and preventing its progression to esophageal adenocarcinoma has been a major focus to tackle increasing rates of esophageal cancer. The estimated

prevalence of BE is 0.076-2% in the general population undergoing endoscopy for any reason.⁴ Risk factors for the development of BE include long standing gastroesophageal reflux disease (GERD), male gender, obesity, and older age.⁵⁻⁷ Many of these risk factors are shared with cirrhotic patients. It is then not surprising that patients with cirrhosis are also at high risk of esophageal cancer, with a 2.6 to 7.5 fold increased incidence of developing esophageal cancer compared to controls.⁸⁻¹⁰ Furthermore, patients with cirrhosis and esophageal cancer have higher chemotherapy related toxicities when compared to patients without cirrhosis.¹¹ However, there is limited data in the literature on whether the risk of esophageal cancer in cirrhosis is due to adenocarcinoma or squamous cell carcinoma. In addition, prevalence, risk factors, and natural history of Barrett's esophagus have not been well defined in patients with cirrhosis. This may be due to potential difficulty in the diagnosis and surveillance of BE in cirrhotic patients due to factors such as esophageal varices, thrombocytopenia or coagulopathy.¹² Thus, we conducted a

retrospective, comparative cohort study of patients with cirrhosis who underwent esophagogastroduodenoscopy (EGD) for any indication in order to assess prevalence, management, and progression of BE in patients with cirrhosis.

Methods

Study design and data collection

Approval from the Institutional Review Board was obtained before conduction of this study. For this study we included patients with a history of cirrhosis, regardless of etiology, who underwent upper gastrointestinal endoscopy (EGD) at Saint Louis University from 1/1/2001 through 12/31/2008. We chose to halt data collection at the year 2008 to allow calculation of a 5 year survival rate after the first EGD that was documented at our institution.

Our cohort consisted of patients between 18-80years old, of both genders and all races. To identify patients with cirrhosis, we used billing codes for cirrhosis and CPT codes for EGDs done for any indication during our inclusion period. In order to validate our cohort, we further searched our endoscopy database for any EGD with indications of or findings suggestive of cirrhosis. Results of liver biopsies and clinical characteristics of all these patients were then collected. Patients were then excluded if they had no documented diagnosis of cirrhosis based on laboratory tests (such as serum albumin less than 3.0g/dL or blood platelet counts less than 150,000mm³), radiologic data, or pathologically by demonstration of cirrhosis on liver biopsy when performed.^{13,14}

We further divided our cohort in to two study groups including those with and without Barrett's. Among patients in the cohort described above, we searched our medical records for the earliest date of any suspected but not biopsied BE (SBE), confirmed Barrett's esophagus with intestinal metaplasia (IM), BE with dysplasia or esophageal adenocarcinoma (EAC). We also documented corresponding endoscopic findings on initial and subsequent endoscopies for the next 5years. EGD findings were collected also for cirrhotic patients with no evidence of BE or its complications, including dysplasia and adenocarcinoma. Finally, results of liver biopsies and clinical characteristics of patients were collected including date of liver transplantation if applicable.

Definitions

Barrett's esophagus (BE) was diagnosed when islands, tongues, or circular extension of salmon colored epithelium was seen above the gastroesophageal junction on EGD along with the presence of intestinal metaplasia with goblet cells on esophageal biopsies.¹⁵ Suspected but not biopsied BE (SBE) was defined as the presence of characteristic endoscopic findings as above without confirmatory biopsy for BE. We subdivided BE and SBE into long segment when it extended ≥ 3 cm above the GE junction and short segment (<3cm).

Study variables

Pathology findings that were recorded included the presence of intestinal metaplasia (IM), low grade dysplasia (LGD), high grade dysplasia (HGD), esophageal adenocarcinoma (EAC) with grade and stage, liver biopsy if available (grade, stage and etiology if available). We also documented corresponding endoscopic findings on initial and subsequent endoscopies for the next 5years. EGD findings included date of EGD, indication, presence of salmon colored mucosa, esophagitis, gastric astral vascular ectasia (GAVE), portal

hypertensive gastropathy (mild, moderate, severe), hiatal hernia, esophageal and/or gastric varices.

Clinical information collected included age, gender, race, height, weight, smoking status (defined as never, past or current), alcohol consumption (never, social, previously heavy or currently heavy), presence of heartburn or gastroesophageal acid reflux disease (GERD), proton pump inhibitor (PPI) use, aspirin use, etiology of cirrhosis, presence of ascites, presence of hepatocellular carcinoma (HCC), laboratory data in the 1year before and after EGD, liver transplant status and mortality.

Outcomes

The primary outcome evaluated in this study was the prevalence of suspected BE and biopsy proven BE in patients with cirrhosis undergoing EGD for any indication. Our secondary outcomes were to look at potential risk factors for the development of BE in cirrhosis, factors which might have influenced the decision of endoscopist not to confirm BE by biopsy or surveying BE as well as 5year survival rates of cirrhotic patients with and without BE.

Data analysis

Patient characteristics were summarized using frequencies (percents) for categorical data and means (standard deviation) for continuous variables. Data analysis was completed using SPSS version 23 (IBM Corp, 2015). Statistical significance was defined as $\alpha < .05$. Chi-square tests for categorical variables and independent samples t-tests or one-way analysis of variance (ANOVA) for continuous variables were used to examine differences between patients with and without BE, as well as differences between patients with suspected vs. confirmed BE. Cases with missing values on relevant variables were excluded from analysis. Kaplan-Meier survival analysis was conducted to examine differences in survival among those with BE compared to those without BE. Data were right-censored at last follow up date, which ranged from 0 to 180months from EGD date (Figure 1).

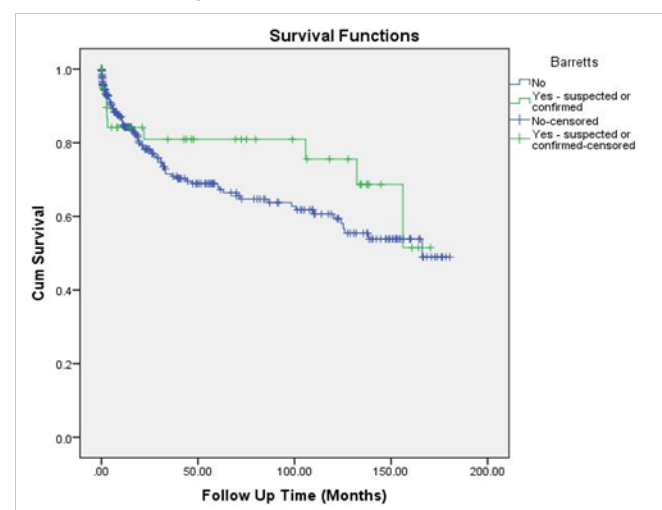


Figure 1 Survival Functions.

Kaplan-Meier survival analysis was conducted to examine differences in survival among those with BE compared to those without BE. Data were right-censored at last follow up date, which ranged from 0 to 180months from EGD date.

Results

There were a total of 885 patients in our cohort, 76(8.6%) of which had suspected BE and 17(1.9%) with confirmed BE. Four patients out of 885(0.004%) were found to have evidence of esophageal adenocarcinoma on EGD. Of the 17 patients with biopsied BE, 16(94.1%) were noted to have no dysplasia, 1(5.9%) with LGD, and none had HGD. None of our patients underwent ablation for the treatment of BE.

Basic demographics, specifically age, gender, and race, were similar between groups as shown in Table 1. The patients had diverse etiologies of cirrhosis with the most common being hepatitis C (51.3%), alcohol (18.7%), and non-alcoholic steatohepatitis (NASH) (8.8%) in all groups.

Table 1 Prevalence of suspected and confirmed Barrett's Esophagus versus no Barrett's

	Barrett's esophagus	No barrett's	p-value
Mean Age (SD)*	53.14(10.94)	53.73(10.63)	0.61
Gender, n(%)			
Male	55(59.1)	446(56.3)	0.86
Female	34(36.6)	287(36.2)	
Race, n(%)			
White	49(52.7)	423(53.4)	0.97
Black	21(22.6)	193(24.4)	
Other	11(11.8)	96(12.1)	

*Missing age for 5 patients

Table 2 Potential factors associated with Barrett's Esophagus

	Barrett's esophagus			p-value
	Suspected(n=76)	Confirmed(n=18)	No Barrett's(n=794)	
Mean Age (SD)*	53.00(11.72)	53.76(6.57)	53.73(10.63)	0.85
Gender				
Male	49(9.8)	6(1.2)	446(89.0)	0.16
Female	25(7.8)	9(2.8)	287(89.4)	
BMI, mean (SD)*	27.05(7.36)	34.78(7.95)	29.17(7.76)	0.15
Cirrhosis cause				
Alcohol	10(7.5)	1(0.7)	123(91.8)	
NASH	7(11.1)	2(3.2)	54(85.7)	
Hepatitis C	28(7.6)	8(2.2)	331(90.2)	
GERD/Heartburn, n(%)				
No	21(2.4)	4(0.45)	272(30.7)	0.73
Yes	10(1.1)	2(0.23)	98(11.1)	
Smoking, n(%)				
Never Smoker	11(7.6)	4(2.8)	129(89.6)	0.44
Past Smoker	10(7.9)	1(0.8)	113(91.1)	
Current Smoker	5(4.4)	1(0.9)	108(94.7)	
PPI, n (%)				
No	15(7.5)	4(2.0)	182(90.5)	0.99
Yes	16(7.4)	4(1.9)	196(90.3)	

Risk factors for the development of BE were compared between groups, shown in Table 2. In our cohort of patients with confirmed or suspected BE, 4(4.3%) patients reported social alcohol use, 9(9.6%) previous heavy use, and 10(10.7%) current heavy alcohol use. Although not statistically significant, BMI was numerically higher in patients with confirmed BE (mean 34.78) vs suspected BE (27.05) or no BE (29.17).

A MELD score of 12 was chosen as the score where patients began to progress to an advanced degree of cirrhosis with some evidence of clinical decompensation. In our study population, patients with a MELD score greater than 12 as opposed to a lower MELD score were more likely to have suspected BE than both confirmed BE or no BE.

We reviewed factors that might have prevented confirming BE with biopsies and found they were similar between suspected and confirmed BE groups (Table 3). These included coagulopathy, thrombocytopenia, presence of esophageal varices and presence of hepatocellular carcinoma, elevated MELD score, and transplant status. In our cohort of patients with BE (confirmed or suspected), 58 patients (62.3%) had esophageal varices, 48 patients (51.6%) of which were classified as small esophageal varices and 10(10.7%) as large varices. In addition, eight (8.7%) patients with suspected or confirmed BE had gastric varices. Coagulopathy, defined as an INR greater than 1.5, was present in 14(35.0%) patients with suspected BE and 4(30.8%) patients with confirmed BE.

In order to assess differences in survival in those with confirmed or suspected BE compared to those without BE, a Kaplan-Meier survival analysis was conducted. There was no significant difference in the groups using the log-rank test ($p=0.30$). Five year survival was 80.9% in the BE group compared to 68.9% in those without BE.

Table Continued....

Barrett's esophagus				
	Suspected(n=76)	Confirmed(n=18)	No Barrett's(n=794)	p-value
Aspirin use, n (%)				
No	24(7.2)	6(1.8)	302(91.0)	0.94
Yes	6(8.0)	1(1.3)	68(90.7)	
Hiatal Hernia, n (%)				
No	63(8.1)	16 (2.1)	700(89.9)	0.32
Yes	12(12.1)	1 (1.0)	86(86.9)	
MELD Score				
Less than or equal to 12	9(4.8)	4(2.1)	176(93.1)	0.1
Greater than 12	29(10.3)	6(2.1)	247(87.6)	

*Missing age for 5 patients, BMI missing for 710 patients

Table 3 Potential factors contributing to unconfirmed Barrett's esophagus

Barrett's esophagus			
	Suspected(n=76)	Confirmed(n=17)	p-value
INR, n (%)			
<1.5	26(34.2)	9(52.9)	0.78
>1.5	14(18.4)	4(23.5)	
Platelets, n (%)			
<50	6(7.9)	0 (0)	0.15
>50	37(48.6)	13(76.4)	
Esophageal Varices, n (%)			
None	29(38.2)	6(35.3)	0.83
Present	47(61.8)	11(64.7)	
HCC, n (%)			
No	32(42.1)	8(47.1)	0.53
Yes	8(10.5)	1(5.8)	
MELD Score, mean (SD)*	18.05(8.09)	13.60(6.40)	0.11
Transplant, n (%)			
No	35(46.0)	10(58.8)	0.46
Yes	13(17.1)	2(11.8)	

*Missing data on 45 patients

Discussion

Our study is the first to look at prevalence of BE and SBE in cirrhotic patients with longitudinal data. Our data suggests that the prevalence of BE in patients with liver cirrhosis is increased compared to that found in the general population. Historically, the estimated prevalence of Barrett's esophagus is 0.076-2% in the general population undergoing endoscopy whereas our study demonstrated a prevalence of over 10% of potential Barrett's in cirrhotic patients (1.9% confirmed). The mechanism of increased prevalence of BE in patients with liver cirrhosis has not been fully elucidated. As our results show, BE and EAC may have a higher prevalence in cirrhotic patients compared to the general population due to shared risk factors (gender, race, BMI). This may also be due in part to the development of esophageal motility disorders and decreased lower

esophageal sphincter pressure seen with varices leading to decreased esophageal clearance and increased contact time between acid and mucosa as well as the increased intra-abdominal pressure from ascites contributing to increase GERD.¹⁵⁻¹⁷ Some studies have also shown the levels of plasma vasoactive peptides and neurotensin, which are known to decrease the pressure of the lower esophageal sphincter, were markedly higher in patients with cirrhosis than in the normal population.¹⁸ This likely leads to increased acid exposure and increased development of BE. In addition, the number of cirrhotic patients undergoing routine endoscopy is higher than the general population due to recommendations for variceal screening and surveillance per American College of Gastroenterology (ACG) and American Society of Gastrointestinal Endoscopy (ASGE) guidelines.^{19,20} This may also have contributed in part to the elevated prevalence of BE and EAC. Given the increased prevalence, endoscopic surveillance following

transplant in cirrhotic patients undergoing liver transplantation should be considered.

BE was confirmed by biopsy in only 1.9% of our patients. We suspect this to be due to certain risk factors limiting confirmatory biopsy, including the presence of esophageal varices, thrombocytopenia, and coagulopathy. We did not find a statistical association between these factors and the performance of a biopsy for confirmation of BE. The concern of the endoscopist to biopsy a patient with underlying cirrhosis, regardless of varices or lab abnormalities, appears to have played a role in avoiding biopsy. As a result of these factors, cirrhotic patients may not be getting adequate surveillance of BE. The ACG guidelines suggest those patients with chronic GERD and two or more risk factors for BE or EAC: age >50, central obesity, family history, tobacco, etc qualify for screening for Barrett's.¹⁹ As shown, patients with liver dysfunction have higher risk of progression of BE and may in fact need more frequent surveillance. Further prospective studies are needed to confirm this association.

As this is a retrospective study, it has several limitations. Potential limitations of our study include a retrospective single institution chart review, along with limited number of patients with biopsy confirmed BE which in turn limited our evaluation of potential BE progression in a cirrhotic cohort. We do not have information regarding procedural complications. In addition, we initially identified patients with cirrhosis by billing codes. However, we did individually search our endoscopy data for cirrhosis and confirmed with clinical, laboratory, radiologic, or pathology data supporting a cirrhosis diagnosis. Although we have a large population of patients with cirrhosis with a robust number of surveillance endoscopies, our numbers of patients with cirrhosis and BE are small which may have limited our ability to assess statistical differences between patient population. Additionally given the large volume of short segment BE, there may have been a number of false positives leading to an over estimate of SBE.

Conclusion

In conclusion, a higher prevalence of Barrett's esophagus is noted within our population of cirrhotic patients undergoing endoscopy. Patients with cirrhosis often undergo endoscopy for cirrhosis related issues such as screening for varices or evaluation of gastrointestinal bleeding and surveillance of Barrett's esophagus may be missed. As patients with cirrhosis and Barrett's esophagus tend to have poorer outcomes and tolerate therapies for esophageal cancer less well, it is important to recognize possible shared risk factors and the increased prevalence of Barrett's esophagus and continue endoscopic surveillance in this patient population.²¹

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None.

Conflict of interest

Author declares that there is no conflict of interest.

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