STUDY OF ACUTE ESOPHAGEAL VARICEAL BLEEDING IN LIVER CIRRHOSIS PATIENTS

By

Qian Bi

A Dissertation Submitted to the Faculty of Harvard Medical School

in Partial Fulfillment of

the Requirements for the Degree of Master of Medical Sciences in Clinical Investigation (MMSCI)

Harvard University

Boston, Massachusetts

March, 2020

Area of Concentration: Gastroenterology

I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor: Dr. Marvin Ryou

ACKNOWLEDGEMENTS

This project would not have been possible without the support of many people. Many thanks to my primary mentor, Dr. Marvin Ryou, who read my numerous revisions and helped make some sense of the confusion. Many thanks to my adviser, Dr. Marwan S Abougergi, who gives us a lot of thoughtful ideas. Thanks Thomas Wang and Thomas McCarthy for helping me completing these projects. Also, thanks to my committee members, Ajay K. Singh, Finnian R. McCausland and Amil Shah, who offered guidance and support.

Thanks to Chinese PLA General Hospital by awarding me this two years' scholarship for study in Boston. Also, thanks to Harvard University for providing me with such a great opportunity to complete this project. And finally, thanks to my husband, my son Gary, daughter Lucy, parents, and numerous friends who endured this long process with me, always offering support and love.

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PREFACE

Liver cirrhosis and its associated complications is the fifth-leading cause of adult deaths in the United States and ranks eighth in economic cost among major health issues. Acute variceal hemorrhage (AVH) is one of serious complications of liver cirrhosis. It is a leading cause of death and major morbidity among patients with liver cirrhosis. Acute esophageal variceal hemorrhage's six-week mortality rate ranges between 15% and 25%.

Research using claims databases is instrumental in establishing the epidemiology of medical conditions as well as in resource allocation and policy making. The building blocks of such databases are the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) codes. Therefore, measuring the accuracy of ICD-10 CM codes in correctly and completely identifying the diagnoses and procedures they are intended to code for is a crucial first step in this type of research. The first part of our study was to determine the performance characteristics of the ICD-10 CM coding system in identifying both patients with acute esophageal variceal hemorrhage and those who had a band ligation procedure in the hospital setting.

Given the associated mortality, timing of Esophagogastroduodenoscopy (EGD) is crucial to providing both diagnostic and therapeutic benefit for patients presenting with AVH. Current guidelines suggested that upper endoscopy should be performed after fluid resuscitation and within 12 hours after a patient is admitted to hospital. However, the level of the evidence is relatively low.

Therefore, to better evaluate this consensus recommendation, in the second part of our study we performed a structured systematic review and meta-analysis to evaluate the impact of time to EGD on patients presenting to the hospital with AVH.

PAPER 1

Validation of ICD-10 CM and CPT codes for identification of acute esophageal variceal hemorrhage and esophageal varices band ligation among patients with liver cirrhosis

Thomas Wang, MD*[1], Qian Bi, MD*[2,3], Marvin Ryou, MD[2], Marwan S Abougergi, MD[4,5]

1. Department of Internal Medicine, Massachusetts General Hospital, Boston, MA, USA
2. Division of Gastroenterology Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
3. Liver Cirrhosis Diagnosis and Therapy Center, the Fifth Medical Center, the General Hospital of Chinese PLA, Beijing, China
4. Division of Gastroenterology, Department on Internal Medicine, University of South Carolina School of Medicine, Columbia, SC
5. Catalyst Medical consulting, Simpsonville, SC.

*Thomas Wang and Qian Bi contributed equally

Corresponding author: Dr. Marwan S Abougergi[1]

Division of Gastroenterology, Department on Internal Medicine, University of South Carolina School of Medicine, Columbia, SC

Short title: ICD-10 CM codes for esophageal variceal bleed

Conflict of interest: None of the authors has any conflict of interest to disclose

Abstract

Goals: We aimed to determine the performance characteristics of the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) and the current procedural terminology (CPT) coding systems in identifying patients with acute esophageal variceal hemorrhage and esophageal variceal band ligation.

Background: Claims databases are used ever more widely in medical research. The building blocks of such databases are the ICD-10 CM codes, which are used to identify study patients, exposures and procedures.

Study: Both liver cirrhosis and acute gastrointestinal hemorrhage were ascertained using manual electronical medical record review. The study patients' billing records were then obtained and searched for ICD-10 CM code I85.xx for esophageal variceal hemorrhage and 06L34CZ, 06L38CZ and CPT code 43244 for esophageal variceal band ligation.

Results: 1,231 patient encounters were included. Alcohol was the most common etiology for liver cirrhosis (62.3%), and hematemesis (40.5%) was the most common patient presentation. A principal diagnosis ICD-10 CM code of I85.xx was associated with high sensitivity (84.8%), specificity (88.6%), positive (PPV, 92.9%) and negative (NPV, 77.0%) predictive values for presence of esophageal varices. For esophageal variceal band ligation, the ICD-10 CM had lower sensitivity than the CPT codes (51% versus 77%, respectively). However, both systems had similar specificity (99% and

99%), positive (97% and 96%), and negative (86% and 93%) predictive values in this setting.

Conclusions: ICD-10 CM diagnostic code I85.xx and procedure codes 06L34CZ and 06L38CZ as well as CPT code 43244 accurately identified patients with acute esophageal variceal hemorrhage and esophageal variceal band ligation, respectively.

Keywords: ICD-10 CM; Acute esophageal variceal hemorrhage; Esophageal variceal band ligation; Validation

Introduction

Liver cirrhosis and its associated complications is the fifth-leading cause of adult deaths in the United States and ranks eighth in economic cost among major health issues.[1] The natural history of liver cirrhosis is to progress from a compensated to a decompensated stage. Decompensated liver cirrhosis stage starts with the occurrence of one or more of the following complications of portal hypertension: variceal hemorrhage, hepatic encephalopathy, ascites and jaundice. The onset of decompensation is associated with significantly worse prognosis: The 1-year mortality of patients with compensated liver cirrhosis is 5.4%, while it is 20.2% for patients with decompensated liver cirrhosis.[2]

Acute variceal gastrointestinal hemorrhage is a potentially fatal complication of portal hypertension. It is a leading cause of death and major morbidity among patients with liver cirrhosis[3]. Esophageal varices are the most common type of gastrointestinal varices. They are present in approximately 50% of patients with liver cirrhosis referred for esophageal variceal screening[4]. Small varices progress to large varices at a rate of 10% to 12% annually[5]. Esophageal variceal hemorrhage occurs at a rate of 10%-15% per year. Acute esophageal variceal hemorrhage's six-week mortality rate ranges between 15% and 25% [6,7].

Esophagogastroduodenoscopy (EGD) is the gold standard procedure used in the diagnosis and treatment of gastroesophageal variceal hemorrhage. Endoscopic variceal ligation (EVL) was first proposed as a treatment for esophageal varices by Van

Stiegmann et al in 1988 [8]. Since then, band ligation is the recommended first line treatment for the management of esophageal variceal hemorrhage [9].

Although prospective randomized controlled trials yield the highest quality of evidence in medical research, they might be difficult to implement for life-threatening conditions such as acute variceal hemorrhage. Retrospective studies conducted using claims databases can be the alternative to obtaining evidence in this setting. In addition, research using claims databases is instrumental in establishing the epidemiology of medical conditions as well as in resource allocation and policy making. The building blocks of such databases are the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) codes. Those are billing codes that are used to identify the diagnoses and procedures in claims databases-based research. George *et al*. found that the sensitivity and specificity of obesity coding were 34.5% and 96.0%, while that of morbid obesity were 32.5% and 96.7%, respectively[10]. Singh H *et al.* found that sensitivity of ICD-10 CDI code in discharge abstracts was 72.8% among those with inflammatory bowel disease(IBD) and 70.8 among those without IBD.[11] The inaccuracy of coding will may lead to inadequate reimbursements, and may also overestimate the effect of disease. Therefore, measuring the accuracy of ICD-10 CM codes in correctly and completely identifying the diagnoses and procedures they are intended to code for is a crucial first step in this type of research. The purpose of this study was to determine the performance characteristics of the ICD-10 CM coding system in identifying both patients with acute esophageal variceal hemorrhage and those who had a band ligation procedure in the hospital setting. Materials and Methods

Study design and setting:

This was a retrospect cohort study using medical record chart review to identify the cirrhosis patients who admitted to hospital because of acute upper gastrointestinal hemorrhage. And then evaluate the performance characteristics of different ICD-10 CM codes for esophageal varices hemorrhage in a large medical database. Data was extracted from the Research Patient Data Registry (RPDR) of a large hospital and physician network in Massachusetts. This database has complete electronic medical records as well as billing information on all patients treated in any of the facilities in the network. The study period was from September 1st, 2015 to April 30th, 2019. This study was reviewed and approved by the hospital organization's institutional review board (IRB).

Study population and case confirmation:

The inclusion criteria were: 1) patient's age of 18 years or older, 2) a personal history of liver cirrhosis, and 3) hospitalization for an acute upper gastrointestinal hemorrhage. Patients were excluded if they did not have an in-hospital EGD or if the EGD performed did not have a clear indication of upper gastrointestinal hemorrhage. Both liver cirrhosis and acute gastrointestinal hemorrhage were ascertained using electronical medical record review. The diagnosis of liver cirrhosis was established using either liver biopsy results showing grade IV fibrosis and/or small nodular liver with heterogeneous enhancement on CT, MRI, or ultrasound scan of the abdomen. The presence of esophageal varices was ascertained through upper endoscopy reports, which clearly stated that at least 2 columns of esophageal varices of any size were present in the distal esophagus. After we identified these cirrhosis patients with acute upper gastrointestinal hemorrhage by going through patients' chart review. The billing records for the study patients were then obtained and searched for ICD-10 codes I85.xx as well as K92.0-92.2. The first x in I85.xx can be either 0 or 1, in which 0 signifies esophageal varices, and 1 signifies secondary esophageal varices. The second x can be 0 for varices without bleeding and 1 for varices with bleeding. K92.0-92.2 code for hematemesis, melena and gastrointestinal hemorrhage, unspecified and served as a control population to calculate the specificity of the codes I85.xx in identifying the presence of esophageal varices. Two medical chart reviewers, both physicians who are also co-authors on this study, performed all chart reviews using a standardized data collection tool. Cases that were ambiguous in their classification were further discussed, sometimes with a third more senior physician, until consensus was obtained.

<u>Patient Characteristics and study outcomes</u>

The patient characteristics collected were as follows: Patient age, sex, race, ethnicity, in- or out-of-state location, insurance type, cirrhosis etiology, presence of hepatocellular carcinoma, and nature of initial presentation. The primary outcome was the performance characteristics of the I85.xx ICD-10 CM codes in identifying esophageal variceal hemorrhage. Secondary outcomes were 1) performance characteristics of the I85.xx ICD-10 CM code in identifying esophageal varices when they are the most likely source of the hemorrhage 2) presence of signs of active/recent hemorrhage from the esophageal varices, and 3) performance characteristics of the ICD-10 CM procedure codes and CPT codes in identification of esophageal variceal band ligation.

Statistical Analysis

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals (CI) were calculated using a 2 x 2 contingency table. Statistical analysis was performed with SAS 9.4 Software (Cary, NC).

Results

1231 patient encounters for 876 patients were included in the study. They were cirrhosis patients who admitted to hospital because of acute upper gastrointestinal hemorrhage and had at least one EGD during hospitalization. Figure 1 shows the inclusion diagram **[Figure 1]**. **Table 1** summarizes the demographic characteristics of the patient population. The average patient's age was 59.3 years, and almost two-thirds were male. The majority of patients were Caucasian and resided in Massachusetts, with only 12% residing out-of-state. About half of the patients had Medicare and/or Medicaid, and about a third had private insurance. Alcoholic cirrhosis was the most common etiology of liver cirrhosis (62%), and hematemesis (41%) and melena (39%) was the most common patient presentation.

Upper endoscopy findings:

Table 2 outlines relevant upper endoscopy findings. Total number of 1371 EGD was analyzed. Esophageal varices were found in two thirds of all EGDs (64%). Around one-third of patients (37%) who had esophageal varices had signs of active or recent hemorrhage (red wale or nipple sign). The vast majority (93%) of patients with active/recent esophageal variceal hemorrhage received endoscopic treatment with variceal band ligation. Gastric varices were present concomitantly with esophageal varices for 14% of patients.

Performance characteristics of ICD-10 CM I85.xx

The ICD-10 CM code I85.xx was the principal diagnosis in 58% of all encounters. A principal diagnosis ICD-10 CM code of I85.xx was associated with high sensitivity (85%), specificity (89%), positive predictive value (93%) and negative predictive value (77%) for the presence of esophageal varices **[Figure 2]**. On subgroup analysis, a principal diagnosis ICD-10 CM code of I85.x0 (without bleeding) had a sensitivity of 73%, specificity of 74%, positive predictive value of 65% and negative predictive value of 80% for the presence of esophageal varices [**Figure 3]** while code I85.x1 (with bleeding) had a sensitivity of 58%, specificity of 91%, PPV of 66%, and NPV of 91% for the presence of esophageal varices [**Figure 4].** Of note, 10 of the 31 patients (32%) with gastric varices but without esophageal varices had a principal diagnosis ICD-10 CM code of I85.xx . However, this only constituted 20% (10/51) of all false positives for the presence of esophageal varices.

<u>Most common ICD-10 CM procedure codes and CPT codes for esophageal varices band ligation and their performance characteristics:</u>

Control of esophageal hemorrhage occurred during 32% of all upper endoscopies. **Table 3** outlines the most frequently encountered ICD-10 CM procedure codes and CPT codes used to code for control of esophageal hemorrhage in the study population. The ICD-10 CM codes 06L34CZ and 06L38CZ and the CPT code 43244 were the most common codes for esophageal variceal band ligation. The two ICD-10 codes had a combined specificity of 99%, sensitivity of 51%, positive predictive value of 97% and a negative predictive value of 86% for detecting esophageal variceal band ligation. The CPT code had similar specificity (99%), positive (96%) and negative (93%) predictive value as the ICD10- CM codes but a higher sensitivity of 77%. The combination of both ICD10-CM and CPT codes had the best performance characteristics (83%, 99%, 95%, 95% for sensitivity, specificity, positive and negative predictive values, respectively) **[Figure 5]**.

Discussion

We demonstrate that a principal diagnosis ICD-10 CM code of I85.xx was associated with high sensitivity, specificity, positive and negative predictive values for the presence of esophageal varices. On subgroup analysis, I85.x0 (without bleeding) had lower performance characteristics compared with code I85.xx while I85.x1 (with bleeding) had lower sensitivity and positive predictive value but similar specificity and higher negative predictive value compared with the same code. Both the ICD-10 CM codes 06L34CZ and 06L38CZ and the CPT code 43244 had excellent specificity, negative and positive predictive value in detecting esophageal variceal band ligation. However, the CPT code had a higher sensitivity compared with the ICD-10 CM codes in this setting.

The ICD-10 CM coding system contains more than 65,000 codes compared with around 16,000 codes for the ICD-9 system. Whether this increase in the number of codes and associated administrative burden translate into better coding accuracy was uncertain to this date. To our knowledge, this is the first study to completely validate the ICD-10 codes specific for both esophageal variceal hemorrhage and esophageal varices band ligation. Previously, Mapakshi S *et al*. used a 325-patient group from the national Veterans Affairs (VA) Corporate Data Warehouse and showed that the positive predictive value for the combination of codes I85.xx and I84.6 (gastric varices) for the detection of varices was 90.2%, respectively[12]. Unlike the current study, the authors did not calculate sensitivity or specificity, did not analyze neither esophageal and gastric varices separately nor the individual codes for esophageal varices, and did not study the performance of ICD-10 CM or CPT codes for esophageal band ligation procedure.

Our study confirms the high positive predictive value for I85.xx, and expand Mapakshi S *et al's* results as above to a patient population derived from hospitals of small, medium and large sizes, both teaching and non-teaching.

We tested and compared three coding strategies to identify esophageal variceal hemorrhage: I85.xx, I85.x0 and I85.xx. One challenge encountered by coders and billers (including physicians) is the choice of codes to use when non-bleeding esophageal varices are encountered in a patient without other etiology for the upper gastrointestinal hemorrhage. In an attempt to avoid billing errors and possibly fraud, some physicians enter code I85.x0 in this setting since the varices were not actively hemorrhaging at the time of endoscopy. Other physicians use code I85.x1 since the esophageal varices, although not bleeding at the time of endoscopy, are the only possible source for the hemorrhage. We believe this is the reason why code I85.x1 has a sensitivity of only 58% but a specificity of 91%. We show that using all codes for esophageal varices (I85.xx) increases the sensitivity to 85% while maintaining the same high specificity (89%). Based on these findings, we recommend using codes I85.xx preferentially in this setting.

To our knowledge the current study is also the first to identify and examine the performance characteristics of the most commonly used codes for esophageal variceal band ligation. Since CPT codes are used for billing in the United States and ICD-10 CM procedural codes are not, our hypothesis was that CPT codes are more accurate than ICD-10 CM codes. Consistent with our hypothesis, we found that both coding systems had similar specificity, positive and negative predictive value, but that CPT codes were more sensitive. Thus, in databases where both coding systems are available, we recommend using the CPT codes preferentially. However, multiple large databases including the Agency for Healthcare Research and Quality's (AHRQ) Healthcare cost and Utilization Project (HCUP) Databases contain ICD-10 CM codes exclusively. Those codes are still highly specific; however, they may underreport procedures due to the lower sensitivity. HCUP databases are frequently used in epidemiological research, and since 2015, the HCUP database Nationwide Emergency Department Sample (NEDS) included CPT codes for procedure performed in the Emergency Department. Although the combination of both systems has the best performance characteristics, rare are the databases that contain both coding system for the same procedure.

Our study has some limitations. First, we included hospitals and patients from Massachusetts, which might not be representative of the other states. However, we included both teaching and non-teaching hospitals, as well as small, medium and large hospitals and both tertiary care centers and community hospitals. It would be better if we have other states or different healthcare system data to further validate the accuracy of ICD-10 CM code. Second, and along the same line, all hospitals participating in the study had the same electronic healthcare record, which assists physicians in coding. However, professional coders and billers reviewed all medical charts and generated the final codes entered in the files. Third, the ICD-10 codes are updated every third quarter of the year. Therefore, the codes we validated for esophageal varices and esophageal variceal band ligation might change in the future. However, the ICD-9 CM codes for esophageal varices did not change, and we expect the ICD-10 CM codes to be the same. Fourth, we may have classification bias. We identify the cohort patients using “term search” strategy to identify the target patients and then obtain their ICD-10 CM codes and CPT codes. Some excluded patients may have wrong codes, and these patients not included in our study. Fifth, we start collect patients’ data from the first day ICD-10 codes were using, there might be some transition period “mistakes” leading to high inaccuracy during the first few month or year.

Our study has several advantages too. It included patients from hospital with all sizes, teaching status and designations (peripheral versus tertiary care centers). In addition, we included patients with all insurance types including uninsured patients. We also have calculated the complete performance characteristics of the coding algorithms we present. All the above help our results be generalizable to a wide range patients and treatment settings.

In conclusion, we have compared several algorithms to identify esophageal variceal hemorrhage and esophageal band ligation using ICD10-CM codes and CPT codes. We identified I85.xx to have the best performance characteristics in this setting, with very high sensitivity, specificity, positive and negative predictive values. For esophageal variceal band ligation, the CPT coding system had a higher sensitivity to detect the procedure compared with the ICD10-CM system, but both had very high specificity, positive and negative predictive values. Research using administrative databases can provide answers to questions when randomized clinical trials cannot be done for ethical or financial reasons. In addition, they give a real-world picture of both treatment outcomes and resource utilization. Using the coding algorithm will improve patient selection in this setting.

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Table 1. Basic Patient Characteristics on Presentation of Acute Upper Gastrointestinal Hemorrhage

Patient Characteristics	Number of Patients (n=876)
Age, mean ± SD	59.3 ± 13.1
Sex, Female, n (%)	312 (35.6)
Race, n (%)	
Caucasian/White	701 (80.0)
African American/Black	61 (7.0)
Asian/Pacific Islander/Native	27 (3.1)
Other/Not Documented	87 (9.9)
Ethnicity, n (%)	
Hispanic	33 (3.8)
Non-Hispanic	816 (93.2)
Unknown	27 (3.1)
Home Location, n (%)	
In-state, Massachusetts	772 (88.1)
Out-of-state	104 (11.9)
Northeast	80 (9.1)
Midwest	2 (0.2)
South	12 (1.4)
West	3 (0.3)
U.S. Territory or Abroad	7 (0.8)

Insurance Type, n (%)	
Public	435 (49.7)
Medicare	151 (17.2)
Medicaid	241 (27.5)
Medicare/Medicaid	43 (4.9)
Private/Commercial	271 (30.9)
Private + Public	34 (3.9)
None/Not Documented	136 (15.5)
Liver Cirrhosis Etiology, n (%)	
Type	
Alcohol	546 (62.3)
NAFLD/NASH	126 (14.4)
Hepatitis C	195 (22.3)
Hepatitis B	36 (4.1)
Autoimmune	40 (4.6)
Other	89 (10.2)
More Than One Etiology Present	149 (17.0)
Is HCC present?	64 (7.3)
Initial Presentation of Gastrointestinal Hemorrhage	
Hematemesis	355 (40.5)
Coffee Ground Emesis	53 (6.1)
Hematochezia/BRBPR	103 (11.8)

Melena	340 (38.8)
Drop in Hemoglobin, Unexplained	188 (21.5)

Table 1. SD = standard deviation, NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, HCC = hepatocellular carcinoma, BRBPR = bright red blood per rectum

Table 2. Primary and Secondary Outcomes:

	Number of EGDs, (n=1371), n (%)
Presence of Esophageal Varices	873 (63.7)
Presence of Gastric Varices	195 (14.2)
Active /Signs of Recent Hemorrhage	320 (23.3)
Band Ligation Procedure Performed	334 (24.4)

Table 2. EGD = esophagogastroduodenoscopy, SD = standard deviation

Table 3. Prevalence of EGD Associated CPT or ICD-10 Codes in the Study Population

CPT/ICD-10 code	Description	Number of EGDs (n=1371), n (%)
43244	Esophagogastroduodenoscopy, flexible, transoral; with band ligation of esophageal/gastric varices	269 (19.6)
43255	esophagogastroduodenoscopy, flexible, transoral; with control of bleeding, any method	150 (10.9)
Any CPT		412 (30.1)
06L34CZ	Occlusion of Esophageal Vein with Extraluminal Device, Percutaneous Endoscopic Approach	74 (5.4)
06L38CZ	Occlusion of Esophageal Vein with Extraluminal Device, Via Natural or Artificial Opening Endoscopic	100 (7.3)
Any 06L-		174 (12.7)
0W3P8ZZ	Control Bleeding in Gastrointestinal Tract, Via Natural or Artificial Opening Endoscopic	86 (6.3)
0DL58ZZ	Occlusion of Esophagus, Via Natural or Artificial Opening Endoscopic	1 (0.1)
0DQ18ZZ	Repair Upper Esophagus, Via Natural or Artificial Opening Endoscopic	2 (0.2)
0DQ28ZZ	Repair Middle Esophagus, Via Natural or Artificial Opening Endoscopic	4 (0.3)

0DQ38ZZ	Repair Lower Esophagus, Via Natural or Artificial Opening Endoscopic	9 (0.7)
0DQ48ZZ	Repair Esophagogastric Junction, Via Natural or Artificial Opening Endoscopic	1 (0.1)
Any ICD-10		277 (20.2)

Table 3. EGD = esophagogastroduodenoscopy, CPT= current procedural terminology, ICD-10 = International Classification of Diseases, tenth revision

LIST OF FIGURES

Figure 1. Screening Algorithm in Identifying Final Cohort of Patients and Upper Gastrointestinal Endoscopies

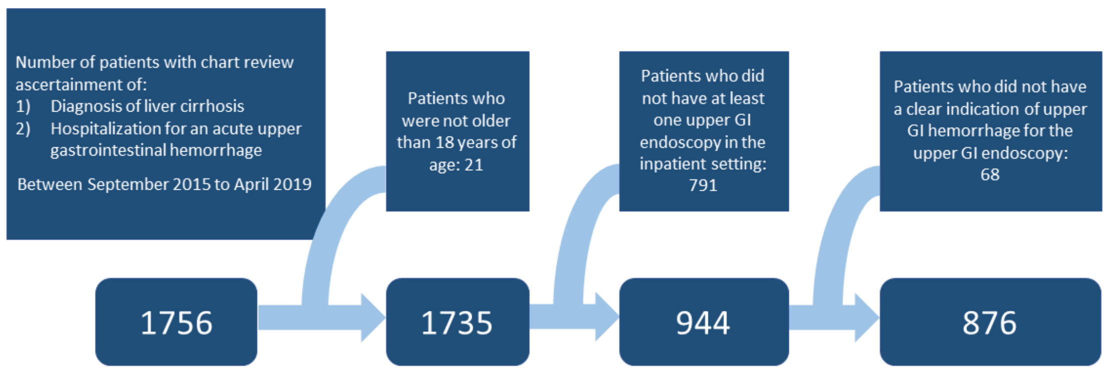

Figure 1. Outline of inclusion and exclusion criteria for identifying patients for the study. The left most number indicates the initial number of patients manually screened in with subsequent removal of patients per indicated criteria towards building the final cohort of patients (far right).

Figure 2. Sensitivity, Specificity, and Predictive Value of the I85.xx Diagnosis Code for the Presence of Esophageal Varices

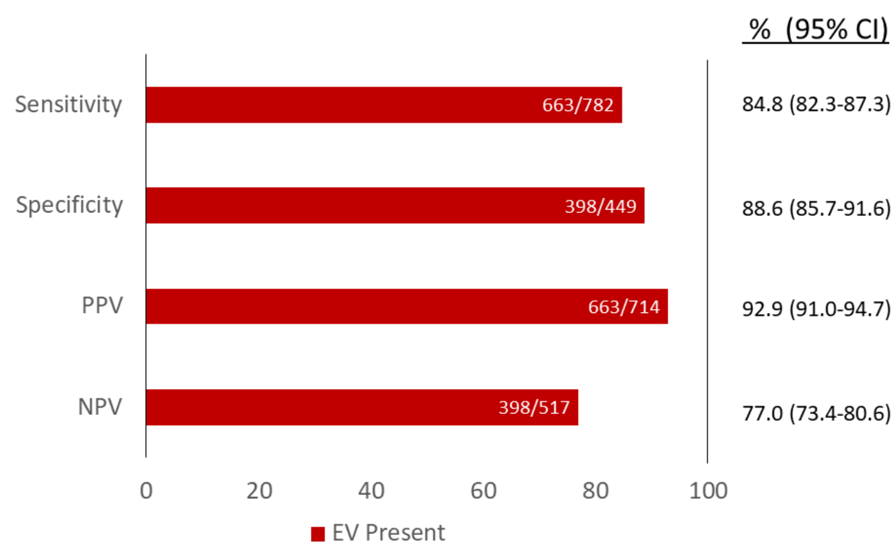

Figure 2. PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval, EV = esophageal varices

Figure 3. Sensitivity, Specificity, and Predictive Value of the I85.x0 Diagnosis Code for the Presence of Esophageal Varices Without Bleeding

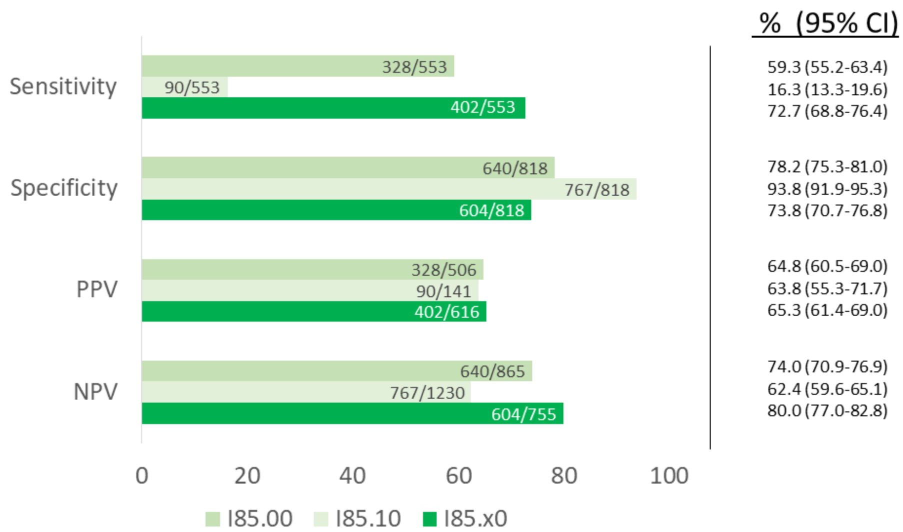

Figure 3. PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval

Figure 4. Sensitivity, Specificity, and Predictive Value of the I85.x1 Diagnosis Code for the Presence of Esophageal Varices with Bleeding

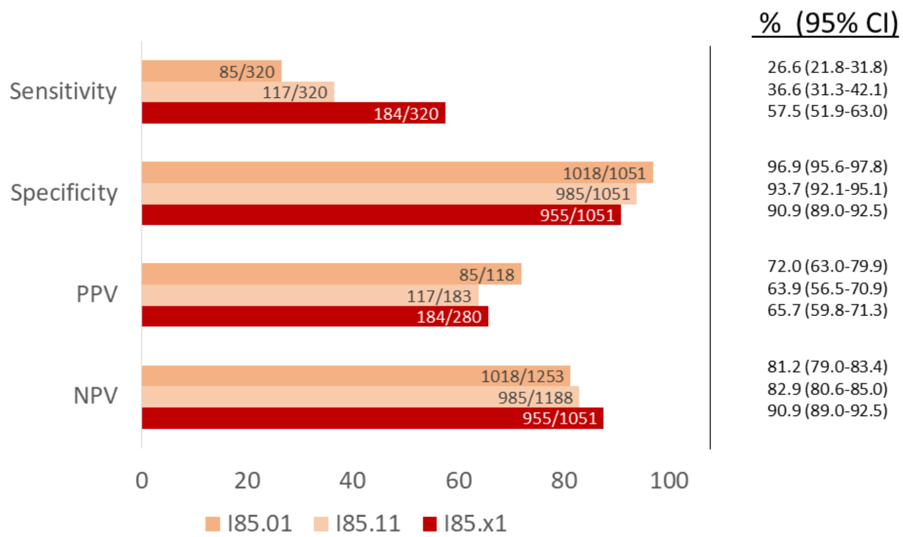

Figure 4. PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval

Figure 5. Sensitivity, Specificity, and Predictive Value of CPT and ICD-10 Diagnosis Codes Associated with Band Ligation of Esophageal Varices

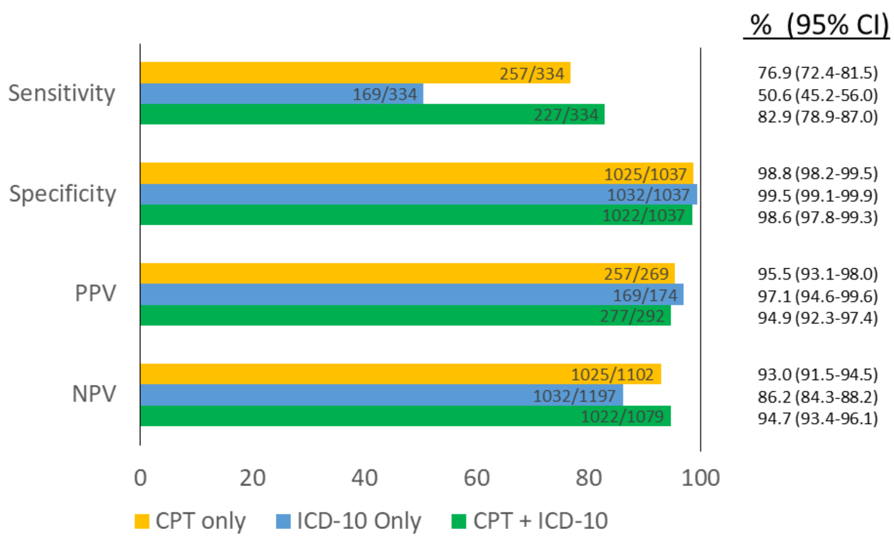

Figure 5. CPT= current procedural terminology. The CPT code 43244 is associated with esophageal variceal band ligation. ICD-10 = International Classification of Diseases, tenth revision. ICD-10 codes associated with esophageal variceal band ligation include 06L34CZ and 06L38CZ. PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval.

PAPER 2

Urgent endoscopy timing in acute variceal hemorrhage patient: a systematic review and meta-analysis

Qian Bi [1,2], Thomas R McCarty[1], Thomas Wang[3], Marvin Ryou[1]

1. Division of Gastroenterology Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
2. Liver Cirrhosis Diagnosis and Therapy Center, the Fifth Medical Center, the General Hospital of Chinese PLA, Beijing, China
3. Department of Internal Medicine, Massachusetts General Hospital, Boston, MA, USA

Corresponding author: Dr. Marvin Ryou

Division of Gastroenterology Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Conflict of interest: None of the authors has any conflict of interest to disclose

Keywords: Systematic review, acute variceal bleeding, Meta-analysis, Mortality, Endoscopic intervention

Abstract

Background: Acute variceal bleeding (AVB) is a very serious condition with clinical guidelines recommending upper endoscopy within 12 hours. Despite these recommendations based upon expert opinion, present literature remains limited and controversial.

Aims: To perform a systematic review and meta-analysis of the relationship between the endoscopy timing and clinical outcomes in patients presenting with AVB.

Methods: This study was prospectively submitted in PROSPERO. Systematic searches of PubMed, EMBASE, Web of Science, and the Cochrane Library databases were performed from available literature from inception through February 29, 2020. All full-text manuscripts and published abstracts on human studies investigating impact comparing mortality between urgent endoscopy timing (<12 hours) versus non-urgent endoscopy timing (>12 hours) on acute variceal bleeding was included. The pooled rates were estimated using random effects models and presented as point estimates (rates) with 95% confidence intervals. Risk of bias and quality of observational studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale and JADAD score for quality of randomized trials. Heterogeneity was assessed for the individual meta-analyses using the chi squared test and the I^2 statistic. A funnel plot was created for publication bias.

Results: Four observational cohort studies (n=1047 patients) were included. Urgent endoscopy was not associated with in-hospital mortality [OR 1.56 (95% CI, 0.96 to 2.54; I^2=0.00%; *P*=0.074)], rate of rebleeding [OR 1.16 (95% CI, 0.71 to 1.91; I^2=54.95%; *P*=0.546)] and death at 6-week follow-up [OR 1.82 (95% CI, 0.47 to 1.43; I^2=14.66%; *P*=0.4822)].

Conclusions: Urgent endoscopy is not associated with in-hospital mortality, rebleeding rate and mortality at 6-week follow-up in acute variceal hemorrhage patients.

Introduction

Variceal hemorrhage is a serious and life-threatening condition. Among all patients with cirrhosis, approximately 30-70% will develop esophageal varices [13]. While many patients with underlying liver disease are found to have esophageal varices at the time of diagnosis, once esophageal varices are identified, the annual rate of first variceal bleeding episode is approximately 12%. [14]If bleeding occurs, the associated 6-week mortality is 15-25%, thus underscoring the importance of prophylactic strategies and early identification and treatment for acute variceal bleeding (AVB) [15].

Based upon consensus guidelines, the immediate goal of therapy in patients presenting with AVB is to achieve hemostasis, to prevent early recurrence (typically defined as rebleeding within 5-7 days) and decrease 6-week mortality[16], Along with appropriate triage and validated risk classification scores as well as early resuscitation efforts, timing of esophagogastroduodenoscopy (EGD) remains pivotal. Upper endoscopy, or EGD procedure, allows for proper identification of bleeding site, further risk classification of rebleeding and treatment response, control of active hemorrhage, and prevention of the first and recurrent bleeding in cirrhotic patients with AVB.

Given the associated mortality, timing is crucial to providing both diagnostic and therapeutic benefit for patients presenting with AVB. Current guidelines suggested that upper endoscopy should be performed after fluid resuscitation and within 12 hours after a patient is admitted to hospital[17]. However, these recommendations are based largely upon expert opinions or anecdotal evidence with limited data and no current randomized trials (Baveno VI consensus: weakest-grade recommendation based on lowest level of evidence). Based upon the Baveno VI consensus, the main benefit of early endoscopy (defined as < 12 hours) is a proposed reduction in 6-week mortality.[16] However, again, the level of the evidence is relatively low.

There are some studies addressing the association between the timing and outcomes in patients of AVB, however, some conflicts existed in the literatures. Yoo J *et al.* reviewed 274 patients with AVB, found no significant difference of the 6-week mortality between urgent endoscopy (i.e. ,≤ 12 h after admission), and nonurgent endoscopy (> 12 h after admission)[18]. Chen PH *et al.* found that early endoscopy (≤12 h) is associated with a better outcome in hematemesis patients, after reviewed 101 patients with AVB[19]. However, Huh CW *et al.* showed urgent endoscopy is significantly associated with a poorer outcome in patients with AVB, especially in low-risk patients[20]. Additionally, in different studies, the timing comparison varied, Azab M *et al.* compared groups of endoscopy within 6 hours, and ones between 6-24 hours[21]. While Hsu YC *et al.* suggested 15 hours should be used to define delayed or non-delayed endoscopy. In conclusion, it is difficult to reach a consistent conclusion from the literature.[22]

Therefore, to better evaluate this consensus recommendation, we performed a structured systematic review and meta-analysis to evaluate the impact of time to EGD on patients presenting to the hospital with AVB.

Methods

Literature Search

Individualized literature search strategies were developed in order to identify full-text manuscripts and published abstracts evaluating the impact of endoscopy timing on acute variceal gastrointestinal hemorrhage. Systematic searches of PubMed, EMBASE, Web of Science, and the Cochrane Library databases were performed from available literature from inception through February 29, 2020. The following medical subject heading (MESH) terms included: *endoscopy AND variceal bleeding*. For articles related to *endoscopy AND variceal bleeding*, subject heading search terms and title and abstract were reviewed for: *timing of endoscopy*, *hemostasis*, *rebleeding*, and, *mortality*.

All relevant English language full-text articles or published abstracts regardless of year of publication were included in this systematic review and meta-analysis. From the initial search results, duplicate articles were first extracted, and then the titles and abstracts of all potentially relevant studies were screened for eligibility according to PRISMA methodology. The reference lists of studies of interest were then manually reviewed for additional articles by cross checking bibliographies as shown in the flow diagram. Two reviewers (TRM and BQ) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. In the case of studies with incomplete information, contact was attempted with the principal authors to obtain additional data.

Study Selection Criteria

This study was prospectively submitted in PROSPERO, an international database of prospectively registered systematic reviews in health and social care. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines for reporting systematic reviews and meta-analyses was used to report findings – **Appendix 1** and **Appendix 2**.[23,24] Full-text manuscripts and published abstracts were included in this analysis. Only human studies investigating impact of timing for endoscopy on acute variceal bleeding was included. Non-variceal bleeding etiologies (i.e., peptic ulcer, gastritis, esophagitis, Mallory Weiss, or other etiologies) were excluded. A study was also excluded if deemed to have insufficient data with inability to calculate pooled proportions, as were review articles, editorials, and correspondence letters that did not report independent data. Case series and reported studies with <10 patients were excluded to minimize selection bias. Multiple published work from similar authors was evaluated for overlapping enrollment times to preserve independence of observations.

Outcome Measures

For AVB patients EGD plays an important role in early diagnosis and treatment. However, if EGD treatment fail, patients will have second prophylaxis for variceal bleeding, such as propranolol, TIPS, liver translation etc. These will all affect patient's mortality in the long run. In-hospital mortality and 6-week mortality can be more accurate to reflect whether the timing of EGD will affect patients' survivals. In-hospital mortality varied from 8.1% to 12.6% according to literatures[18,19,25], and only 2 studies used 6-week mortality. Above all, we choose in-hospital mortality as our primary outcome. The primary outcome measurement in this study was assessment of timing of endoscopy (defined as <12 hours versus ≥12 hours) in relationship to in-hospital mortality. All included studies were required to report in-hospital mortality as an outcome to be included in this analysis. Secondary outcome measures of interest included rate of initial hemostasis, rate of rebleeding, and 6-week mortality, Secondary reported characteristics included baseline patient characteristics including time to endoscopy, etiology of liver disease, MELD and Child-Turcotte-Pugh score, history of previous esophageal band ligation therapy, validated Glasgow-Blatchford and Rockall scores for upper gastrointestinal hemorrhage, initial hemoglobin (mg/dL), number of red cell transfusions required, and total length of hospital stay.

Statistical Analysis

This systematic review and meta-analysis were performed by calculating pooled proportions. After appropriate studies were identified through systematic review, the individual study proportion was transformed into a quantity using the Freeman–Tukey variant of the arcsine square root transformed proportion. Then the pooled proportion was calculated as the back transform of the weighted mean of the transformed proportions, DerSimonian–Laird weights for the random effects model[26–29]. The pooled rates were estimated using random effects models and presented as point estimates (rates) with 95% confidence intervals[30–32]. In contrast to fixed effect models, which are used to estimate a common effect, random effect models estimate an average effect, and the variability of the effects represented by their average may have clinical implications. All calculated *P* values were 2-sided, and $P<0.05$ was considered statistically significant. Tabular and graphical analyses were performed using Comprehensive Meta-Analysis software, version 3 (BioStat, Englewood, NJ). Combined weighted proportions were determined by use of the Stata 15.0 software package (Stata Corp LP, College Station, TX).

Risk of Bias and Quality Assessment

Risk of bias and quality of observational studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale and JADAD score for quality of randomized trials.[33,34] In this study, high quality was defined as a Newcastle-Ottawa Quality Assessment Scale score of ≥4 or a JADAD score of ≥3. Two authors (TRM and BQ) independently extracted data and assessed the risk of bias and study quality for each of the articles. Any disagreements were resolved by discussion and consensus between the two authors.

Investigations of Heterogeneity

Heterogeneity was assessed for the individual meta-analyses using the chi squared test and the I^2 statistic.[32] Significant heterogeneity was defined as $P<0.05$ using I^2 >50%, with values >50% indicating substantial heterogeneity. Further quantification of heterogeneity was categorized based upon I^2 with values of 25%, 50%, and 75% indicating low, moderate, and high amounts of heterogeneity, respectively.

Publication Bias

A funnel plot was created and visually inspected for asymmetry and quantitatively using Egger regression testing to assess for publication bias.[35,36] If evidence of publication bias, then the trim and fill method was used to correct for funnel plot asymmetry and provide an adjusted effect.[37] The classic fail-safe test was also applied to assess risk of bias across studies.

Results

Baseline Study Characteristics

A total of 4 studies (n=1076 patients) were included in this meta-analysis[18,20,25]. A PRISMA flow chart of search results is shown in **Figure 1**. All studies were from 2008 to 2020. All studies were retrospective, observational studies. No randomized controlled trials or prospective studies were included. One study was a published abstract with the remaining studies being full-text manuscripts. One study was from the United States, two from South Korea, and one from Canada. A complete summary of baseline study, patient, and bleeding characteristics is highlighted in **Table 1**.

Patient and Variceal Bleeding Characteristics

Mean age of all patients was 55.63 ±2.06 years with older patients undergoing non-urgent endoscopy (56.12 ±2.59 versus 53.40 ±1.69; $P<0.001$) – **Table 2**. Seventy-one percent of patients were male with no difference between cohorts. Percent of patients with prior banding was also not statistically different between the urgent endoscopy and the non-urgent endoscopy group ($P=0.120$). However, MELD and Child-Turcotte-Pugh scores were higher among patients in the non-urgent endoscopy group [14.49 ±2.25 versus 13.78 ±1.64; $P<0.001$ and 8.30 ±0.20 versus 8.20 ±0.00; $P<0.001$, respectively].

Despite lower MELD and Child-Turcotte-Pugh scores, patients in the urgent endoscopy group had a higher Rockall score (P<0.001) and lower initial hemoglobin level on presentation (P<0.001). Glasgow-Blatchford score was reported in only one study (urgent endoscopy: 9.1 versus non-urgent endoscopy 9.2). Initial hemoglobin was decreased in the urgent endoscopy group compared to the non-urgent group (8.85 ±0.56 versus 8.73 ±0.18 mg/dL; P<0.001). Patients who underwent endoscopy in <12 hours also required more transfusions (3.99 ±0.53 versus 3.14 ±0.32 units pRBC; P<0.001) and required a longer hospital stay (8.74 ±3.20 versus 7.98 ±2.92 days; P<0.001).

Impact of Timing on Initial Hemostasis, Rebleeding, and Mortality

Rate of initial hemostasis was reported in 3 studies and demonstrated no difference between urgent versus non-urgent endoscopy [OR 0.84 (95% CI, 0.56 to 1.28; I^2=0.00%; P=0.423)] – **Figure 2**. With regards to rate of rebleeding which was reported in all studies, again there was no difference between groups [OR 1.16 (95% CI, 0.71 to 1.91; I^2=54.95%; P=0.546] – **Figure 3**. For the primary study outcome, urgent endoscopy was not associated with a significantly higher in-hospital mortality [OR 1.56 (95% CI, 0.96 to 2.54; I^2=0.00%; P=0.074)] – **Figure 4**. Rate of death at 6-week follow-up was also reported in 2 studies with no difference noted [OR 1.82 (95% CI, 0.47 to 1.43; I^2=14.66%; P=0.4822)] – **Figure 5**.

Risk of Bias Assessment

All studies were evaluated using the Newcastle-Ottawa Quality Assessment Scale. Quality assessment for each study was determined to be of high quality (Newcastle-Ottawa Quality Assessment Scale scores ≥4) and demonstrated in **Table 1**. Publication bias was also assessed for the primary outcome of in-hospital mortality. Visual inspection of the funnel plot demonstrated that smaller and statistically insignificant studies appeared to be missing likely due to publication bias – **Figure 6A**. With the Duval and Tweedie's trim and fill method, urgent endoscopy was not associated with an increased odd of in-hospital mortality [adjusted OR 1.48 (95% CI, 0.94 to 2.33)] – **Figure 6B**.

Discussion

Our study is the first systematic review and comprehensive meta-analysis to investigate the correlation between endoscopic time and mortality in patients with AVB. According to current clinical guidelines, urgent upper endoscopy, defined as < 12 hours from hospital admission, had been adopted as the recommended timing for EGD among patients presenting with AVB.[16] Yet despite this expert opinion summary, in this systematic review and meta-analysis, we found there was no statistically significant difference in outcomes for patients undergoing urgent versus non-urgent EGD for AVB.

Despite these findings, it is important to note the two cohorts of patients were heterogeneous and different at baseline. Patients who underwent urgent endoscopy were younger, had less advanced underlying liver disease (i.e., lower MELD and Child-Turcotte-Pugh scores), higher Rockall scores, and presented with lower hemoglobin and required more transfusion therapy. The mechanism of these factors influencing the outcome of AVB patients warrants further investigations. The statistics we could do is meta-regression. However due to the low number of articles we included, it is really hard for us to do this meta-regression. Last not least, we should keep this in mind when we look at the conclusion. Further studies are needed to stressed what is best timing strategy of EGD for AVB patients, considering benefits for both patients and cost-efficiency of medical resources.

While these two groups may not be entirely comparable, the lack of significant difference in rates of initial hemostasis, rebleeding, in-hospital mortality, and 6-week mortality may suggest a shift in focus away from time to upper endoscopy, and towards appropriate resuscitation efforts. While this was not examined in the present meta-analysis, appropriate resuscitation prior to endoscopy is pivotal and can independently impact mortality [38]and certainly has become a critical early treatment focus in recent guidelines for optimal management of acute non-variceal upper gastrointestinal bleeding (NVUGIB)[39,40]. Furthermore, this meta-analysis did not examine use of standard adjunctive therapies for AVB such as use of proton-pump inhibitor therapy, octreotide, and antibiotics with or without vasopressor support.

Specific limitations to this systematic review and meta-analysis include moderate heterogeneity of included studies, including differences in patient population, outcome event reporting, and variable hospital and institution practice and triage patterns. Furthermore, there is no randomized studies were published. We only have small, retrospective observational studies in our analysis. Some studies not included in our analysis. Like Azab M *et al.* compared groups of endoscopy within 6 hours, and ones between 6-24 hours[21]. While Hsu YC *et al.* suggested 15 hours should be used to define delayed or non-delayed endoscopy.[22] These studies all had important findings regarding the timing of EGD for AVB patients. Due to different time cut, we could not include them in our meta-analysis.

Publication bias was also assessed and present in a meta-analysis; however, correction of such did not significantly alter our findings.

Despite these limitations, this study has several strengths. Most importantly, our meta-analysis methodologically summarizes all available literature to evaluate the impact of time to EGD among patients presenting with AVB. Additionally, measured outcomes as collected in this meta-analysis reflect current guideline-based recommendations and clinically significant markers during hospitalization. We hope these findings provide an important assessment of the current literature and perhaps allow for further examination of the importance of time to EGD among patients presenting with AVB. Future research and well-designed randomized trials may impact future clinical decision and be possible given our current findings.

In conclusion, time to upper endoscopy (defined as urgent versus non-urgent EGD) did not impact rate of initial hemostasis, rate of rebleeding, in-hospital mortality, or 6-week mortality among patients presenting to the hospital with AVB. Based on the results of this systematic review and meta-analysis, there does not appear to be an association between urgent endoscopic time and mortality in cirrhosis patients with AVB. Additional literature is needed to determine the true impact of these findings; however, a shift with emphasis towards appropriate resuscitative efforts may benefit patients more than a 12-hour marker to perform upper endoscopy.

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Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart of Literature Search Results

Urgent Endoscopy (<12 hours)

Author	Year	Country of Study	Manuscript Type	Study Type and Design	No of Patients	Mean Age in years	No of Males	Time to Endoscopy (hours)	Etiology of Liver Disease	MELD Score	Child-Turcotte-Pugh Score	Prior Banding	Glasgow-Blatchford Score	Rockall Score	Initial Hgb (mg/dL)	Transfusions Required (units pRBC)	Hospital LOS	Hemostasis	Rebleeding Rate	In-Hospital Mortality	6-Week Mortality	Quality Assessment*
Yoo et al	2018	South Korea	Full-Text	Retrospective Cohort	173	57.62 ±12.09	128	4 (2.1-6.8)	EtOH 43; HBV 86; HCV 16; Other 8	15.4 ±6.9		110/173	9.2 ±3.3	4.0 ±1.4	9.0 ±2.5		4.0 (2.0-9.0)		35/173	14/173	39/173	5
Huh et al	2019	South Korea	Full-Text	Retrospective Cohort	317	53.9 ±11.6	226	4.9 ±3.0	EtOH 181; HBV 86; HCV 19; Other 27	12.3 ±7.1	8.2 ±2.4				8.6 ±2.4	4.4 ±4.0	11.9 ±10.6	229/317	98/317	40/317		5
Cheung et al	2008	Canada	Full-Text	Retrospective Cohort	134			<12 hours								3.7 ±3.0	8.4 ±6.6	129/134	28/134	15/134		5
Bi et al	2020	United States	Abstract	Retrospective Cohort	90	56.4 ±13.3	58	6.1±2.6	EtOH 59; HBV 5; HCV 17; Other 15	15.9±6.1	8.2±2.0	83/90		4.2 ±0.9	8.7±2.1	3.0±3.2	7.2±5.2	71/90	13/90	8/90	9/90	4.5

Non-Urgent Standard Endoscopy (≥ 12 hours)

Author	Year	Country of Study	Manuscript Type	Study Type and Design	No of Patients	Mean Age in years	No of Males	Time to Endoscopy (hours)	Etiology of Liver Disease	MELD Score	Child-Turcotte-Pugh Score	Prior Banding	Glasgow-Blatchford Score	Rockall Score	Initial Hgb (mg/dL)	Transfusions Required (units pRBC)	Hospital LOS	Hemostasis	Rebleeding Rate	In-Hospital Mortality	6-Week Mortality	Quality Assessment
Yoo et al	2018	South Korea	Full-Text	Retrospective Cohort	101	58.77 ±12.22	79	19.5 (15.0-35.5)	EtOH 26; HBV 51; HCV 9; Other 15	16.9 ±9.2		6/101	9.1 ±3.9	3.6 ±1.5	9.6 ±2.5		4.0 (3.0-11.0)		25/101	8/101	30/101	5
Huh et al	2019	South Korea	Full-Text	Retrospective Cohort	94	52.6 ±10.6	65	32.7 ±41.7	EtOH 59; HBV 22; HCV 9; Other 4	11.5 ±6.4	8.5 ±2.4				8.47 ±2.1	3.1 ±2.7	11.8 ±6.4	73/94	17/94	7/94		5
Cheung et al	2008	Canada	Full-Text	Retrospective Cohort	76			>12 hours								3.6 ±2.6	9.1 ±8.5	74/76	12/76	5/76		5
Bi et al	2020	United States	Abstract	Retrospective Cohort	91	56.8±14.3	66	31.4±4.8	EtOH 53; HBV 5; HCV 33; Other 17	14.9±6.9	8.1±2.3	84/91		4.0 ±0.8	8.4±2.6	2.8±2.9	7.5±6.6	70/90	16/91	4/91	7/91	4.5

pRBC: packed-red blood cell

LOS: Length of Stay

*Quality assessment for each study was determined to be of high quality (Newcastle-Ottawa Quality Assessment Scale scores ≥4 for prospective and retrospective observational studies)

Table 2. Baseline Characteristics Between Urgent versus Non-Urgent Endoscopy Groups

Variables	Total	Urgent Endoscopy (<12 Hours)	Non-Urgent Endoscopy (≥12 hours)	*P* value
No of Patients (n)	1076	714	342	
Mean Age in years (SD)	55.63 (2.06)	55.40 (1.69)	56.12 (2.59)	<0.001
No of Males (%)	71.82%	71.03%	73.43%	0.462
Prior Banding Performed (%)	76.04%	79.69%	73.38%	0.120
Mean Time to Endoscopy in Hours (SD)	12.35 (11.29)	4.91 (0.67)	25.91 (4.66)	<0.001
MELD Score (SD)	14.02 (1.89)	13.78 (1.64)	14.49 (2.25)	<0.001
Child-Turcotte-Pugh Score (SD)	8.23 (0.12)	8.20 (0.00)	8.30 (0.20)	<0.001
Glasgow-Blatchford Score (SD)	9.16 (0.05)	9.2 (0.00)	9.1 (0.00)	NA
Rockall Score (SD)	3.95 (0.20)	4.07 (0.10)	3.79 (0.20)	<0.001
Initial Hemoglobin in mg/dL (SD)	8.77 (0.36)	8.73 (0.18)	8.85 (0.56)	<0.001
Transfusions Required in pRBC (SD)	3.72 (0.62)	3.99 (0.53)	3.14 (0.32)	<0.001
Length of Hospital Stay in days (SD)	8.48 (3.13)	8.74 (3.20)	7.98 (2.92)	<0.001

LIST OF FIGURES

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart of Literature Search Results

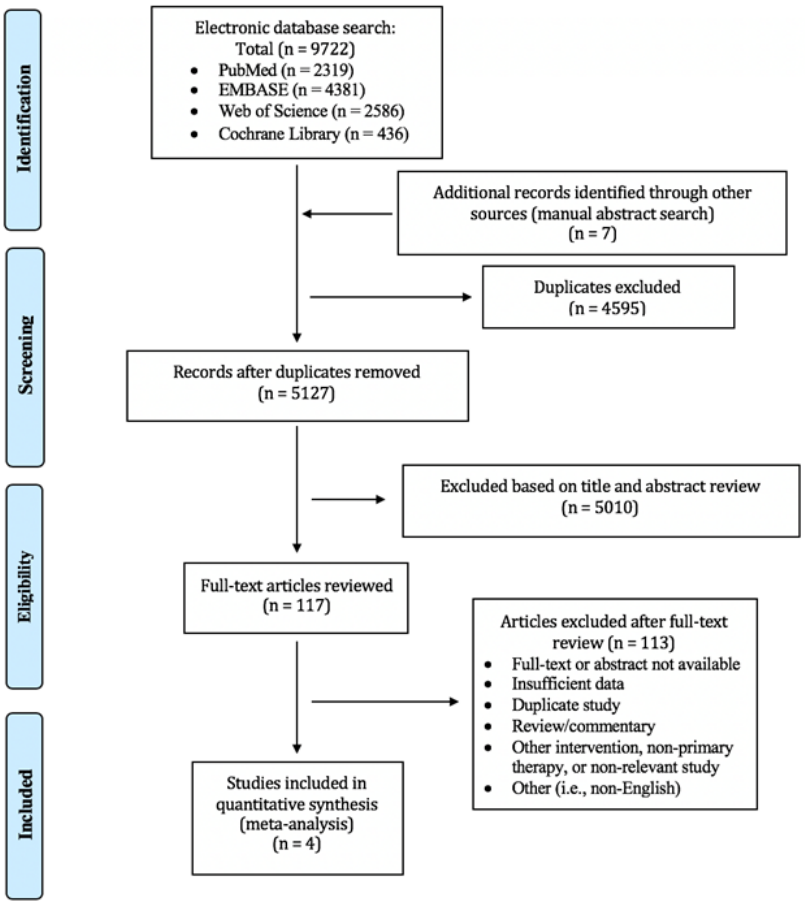
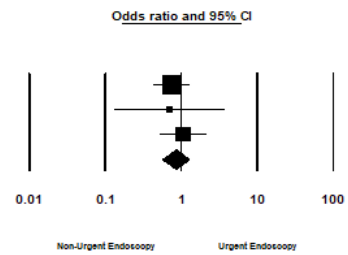


Figure 2: Rate of Initial Hemostasis: Urgent vs Non-Urgent Endoscopy

Rate of Initial Hemostasis: Urgent vs Non-Urgent Endoscopy

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Huh et al 2019	0.7486	0.4345	1.2898	-1.0431	0.2969
Cheung et al 2008	0.6973	0.1320	3.6840	-0.4245	0.6712
Bi et al 2020	1.0677	0.5252	2.1703	0.1809	0.8564
	0.8430	0.5550	1.2802	-0.8013	0.4230



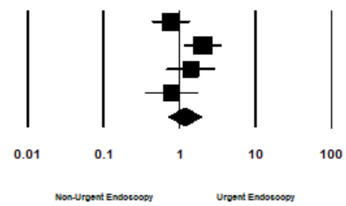
Meta Analysis

Figure 3: Rate of Rebleeding: Urgent vs Non-Urgent Endoscopy

Rate of Rebleeding: Urgent vs Non-Urgent Endoscopy

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Yoo et al 2018	0.7710	0.4297	1.3835	-0.8718	0.3833
Huh et al 2019	2.0269	1.1386	3.6082	2.4010	0.0163
Cheung et al 2008	1.4088	0.6695	2.9647	0.9029	0.3666
Bi et al 2020	0.7808	0.3514	1.7350	-0.6073	0.5436
	1.1652	0.7090	1.9149	0.6031	0.5464

Odds ratio and 95% CI

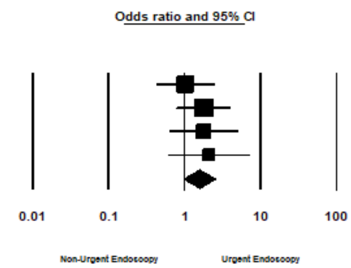


Meta Analysis

Figure 4: In-Hospital Mortality: Urgent vs Non-Urgent Endoscopy

In-Hospital Mortality: Urgent vs Non-Urgent Endoscopy

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Yoo et al 2018	1.0236	0.4139	2.5316	0.0505	0.9598
Huh et al 2019	1.7947	0.7761	4.1504	1.3673	0.1715
Cheung et al 2008	1.7899	0.6239	5.1351	1.0826	0.2790
Bi et al 2020	2.0976	0.6084	7.2322	1.1730	0.2408
	1.5610	0.9580	2.5435	1.7877	0.0738

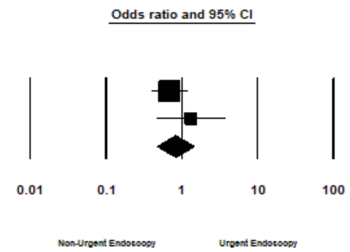


Meta Analysis

Figure 5: 6 Week Mortality: Urgent vs Non-Urgent Endoscopy

6 Week Mortality: Urgent vs Non-Urgent Endoscopy

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Yoo et al 2018	0.6888	0.3950	1.2013	-1.3138	0.1889
Bi et al 2020	1.3175	0.4684	3.7054	0.5226	0.6013
	0.8178	0.4668	1.4329	-0.7028	0.4822



Meta Analysis

Figure 6A: Funnel Plot of Publication Bias and Eggers Regression Test for Included Studies to Assess In-Hospital Mortality

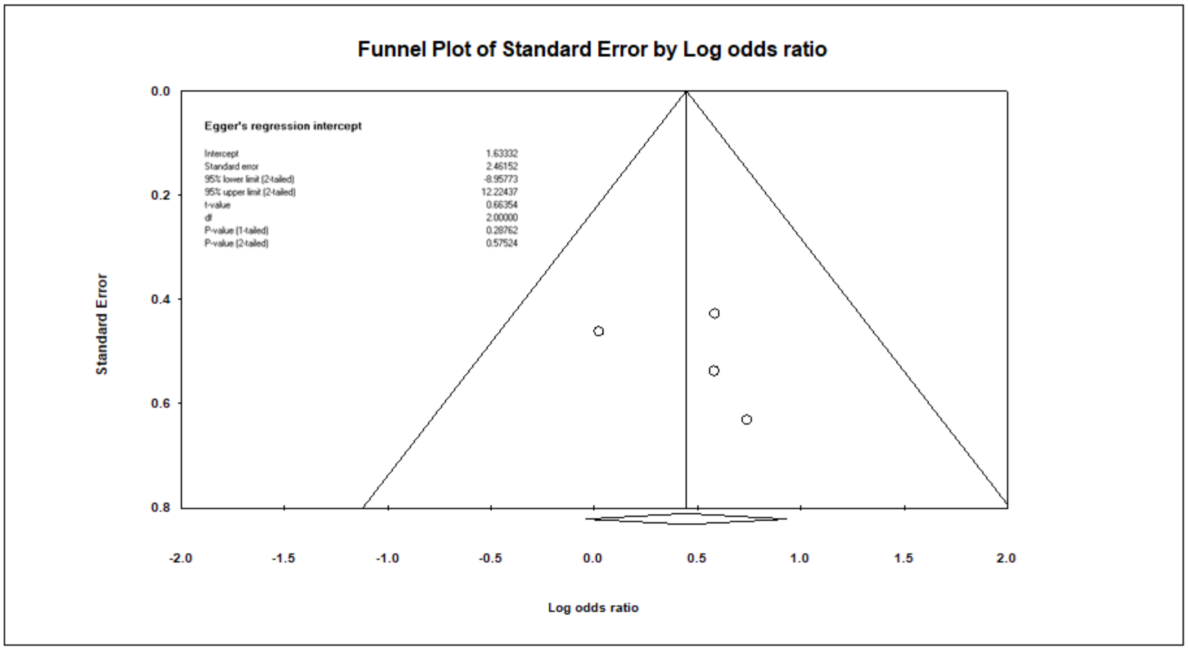
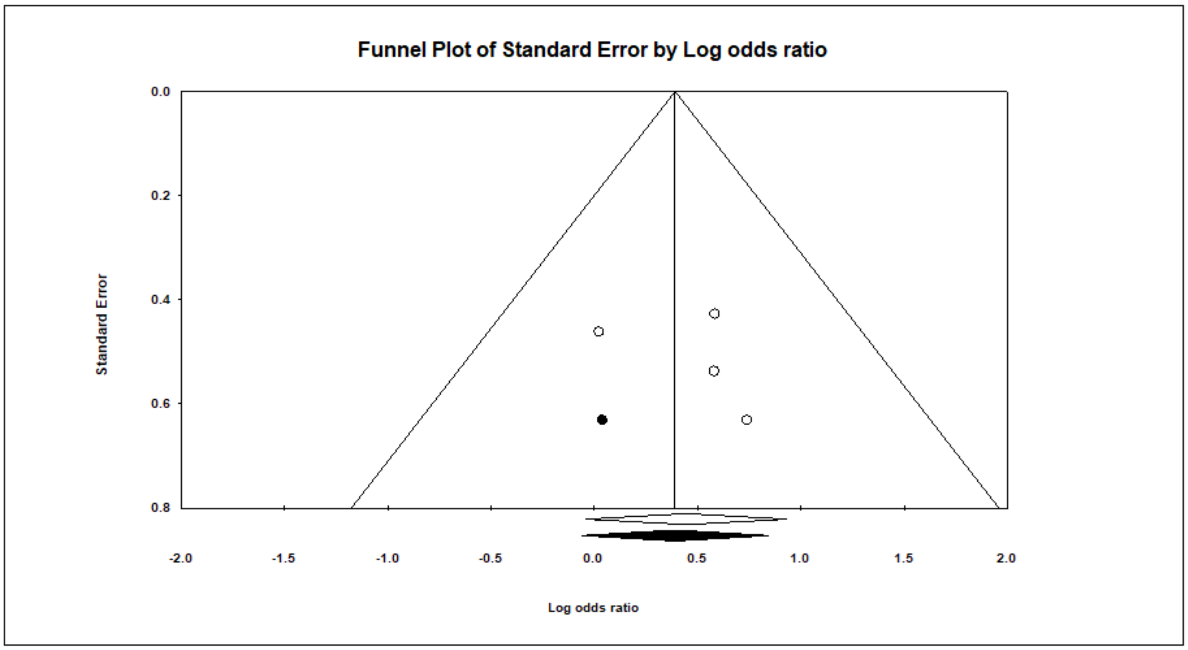


Figure 6B: Funnel Plot of Publication Bias with Duval and Tweedie's Trim and Fill Method.



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SUMMARY

From the first study, we have compared several algorithms to identify esophageal variceal hemorrhage and esophageal band ligation using ICD10-CM codes and CPT codes. We identified I85.xx to have the best performance characteristics in this setting, with very high sensitivity, specificity, positive and negative predictive values. For esophageal variceal band ligation, the CPT coding system had a higher sensitivity to detect the procedure compared with the ICD10-CM system, but both had very high specificity, positive and negative predictive values. Research using administrative databases can provide answers to questions when randomized clinical trials cannot be done for ethical or financial reasons. In addition, they give a real-world picture of both treatment outcomes and resource utilization. Using the coding algorithm will improve patient selection in this setting.

From second study, time to upper endoscopy (defined as urgent versus non-urgent EGD) did not impact rate of initial hemostasis, rate of rebleeding, in-hospital mortality, or 6-week mortality among patients presenting to the hospital with AVB. Based on the results of this systematic review and meta-analysis, there does not appear to be an association between urgent endoscopic time and mortality in cirrhosis patients with AVB. Additional literature is needed to determine the true impact of these findings; however, a shift with emphasis towards appropriate resuscitative efforts may benefit patients more than a 12-hour marker to perform upper endoscopy.