EJGH15787 R2

Effect of acute upper gastrointestinal bleeding manifestations at admission on the in-hospital outcomes of liver cirrhosis: Hematemesis versus melena without hematemesis

Running title: Effect of AUGIB manifestations on cirrhosis

Yingying Li[1,2#], Hongyu Li[1#], Qiang Zhu[3], Emmanuel Tsochatzis[4], Ran Wang[1], Xiaozhong Guo[1]*, Xingshun Qi[1]*

[1] Department of Gastroenterology, General Hospital of Northern Theater Command (formerly General Hospital of Shenyang Military Area), Shenyang, 110840, P.R. China.

[2] Postgraduate College, Jinzhou Medical University, Jinzhou 121001, P.R. China.

[3] Department of Gastroenterology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China.

[4] University College London Institute for Liver and Digestive Health, Royal Free Hospital, Pond Street NorthWestern3 2QG, London.

[#]**Co-first authors**

***Correspondence to:**

Dr. Xingshun Qi, Prof. Xiaozhong Guo, Department of Gastroenterology, General Hospital of Northern Theater Command (formerly General Hospital of Shenyang Military Area), No. 83 Wenhua Road, Shenyang, 110840 Liaoning Province, China.

Tel: 86-24-28897603; Fax: 86-24-28851113;

Email: xingshunqi@126.com (XQ); guo_xiao_zhong@126.com (XG)

Authors' emails:

270308577@qq.com (YL)

13309887041@163.com (HL)

zhuqiang@medmail.com.cn (QZ)

e.tsochatzis@ucl.ac.uk (ET)

wangran891017@163.com (RW)

guo_xiao_zhong@126.com (XG)

xingshunqi@126.com (XQ)

Authors' Contributions:

Y. Y. L. reviewed and searched the literature, wrote the protocol, collected the data, performed the statistical analysis and quality assessment, interpreted the data, and drafted the manuscript.

R. W. collected the data.

E. T. and Q. Z. gave critical comments and revised the manuscript.

H. Y. L. and X. Z. G. checked the data and gave critical comments.

X. S. Q. conceived the work, reviewed and searched the literature, wrote the protocol, performed the statistical analysis, interpreted the data, and revised the manuscript.

All authors read and approved the final manuscript.

Financial support: None.

Conflict of interest: The authors declare that there is no conflict of interest in this study.

Figures: 3

Tables: 3

Supplementary Figures: 2

Supplementary Tables: 5

List of abbreviations in the order of appearance: AUGIB, acute upper gastrointestinal bleeding; INR, international normalized ratio; MELD, model for end-stage liver disease; PPIs, proton pump inhibitors; ORs, odd ratios; CI, confidence interval; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

Abstract

Background and Aims: Patients with acute upper gastrointestinal bleeding (AUGIB) often manifest as hematemesis and/or melena. Theoretically, hematemesis will carry worse outcome of AUGIB. However, there is little real-world evidence. We aimed to compare the outcomes of hematemesis versus no hematemesis as a clinical manifestation of AUGIB at admission in cirrhotic patients.

Methods: All cirrhotic patients with AUGIB who were consecutively admitted to our hospital from January 2010 to June 2014 were considered in this retrospective study. Patients were divided into hematemesis with or without melena and melena alone without hematemesis at admission. A 1:1 propensity score matching analysis was performed. Subgroup analyses were performed based on systemic hemodynamics (stable and unstable) and Child-Pugh class (A and B+C). Sensitivity analyses were conducted in patients with moderate and severe esophageal varices confirmed on endoscopy. Primary outcomes included 5-day rebleeding and in-hospital death.

Results: Overall, 793 patients were included. Patients with hematemesis at admission had significantly higher 5-day rebleeding rate (17.4% versus 10.1%, P=0.004) and in-hospital mortality (7.9% versus 2.4%, P=0.001) than those without hematemesis. In the propensity score matching analyses, 358 patients were included with similar Child-Pugh score (P=0.227) and MELD score (P=0.881) between the two groups; 5-

day rebleeding rate (19.0% versus 10.6%, P=0.026) and in-hospital mortality (8.4% versus 2.8%, P=0.021) remained significantly higher in patients with hematemesis. In the subgroup and sensitivity analyses, the statistical results were also similar.

Conclusions: Hematemesis at admission indicates worse outcomes of cirrhotic patients with AUGIB, which is useful for the risk stratification of AUGIB.

Key words: liver cirrhosis, acute upper gastrointestinal bleeding, hematemesis, melena, outcomes.

1. Introduction

Acute upper gastrointestinal bleeding (AUGIB) is a common and lethal complication of liver cirrhosis with a mortality of 10-15%[1, 2]. It often manifests as hematemesis and/or melena, even hemorrhagic shock with pallor, weakness, light-headedness, or syncope[3]. Such clinical manifestations can potentially reflect the severity of blood loss[4, 5], which is useful for risk stratification of AUGIB[4]. It has been conventionally supposed that hematemesis is more severe than melena[6]. Hematemesis often occurs when the volume of blood promptly accumulated in the stomach reaches 250-300 ml; by contrast, melena occurs when the volume of blood lost reaches 50-70 ml[7]. Studies indicated that hematemesis carried a significantly higher risk of rebleeding and mortality than melena without hematemesis among patients with nonvariceal AUGIB[8, 9]. Recently, a large multinational prospective observational study also confirmed that hematemesis had a significantly higher mortality than melena among patients with AUGIB regardless of liver cirrhosis[10]. However, there is scanted data with regards to the effect of manifestations of AGUIB at admission on the outcome of cirrhotic patients. Therefore, we conducted a retrospective study to compare 5-day rebleeding rate and in-hospital mortality of patients with liver cirrhosis and AUGIB presenting with versus without hematemesis at admission.

2. Methods

2.1. Study design

We reviewed the electronic medical records of cirrhotic patients with AUGIB who were admitted to the General Hospital of Northern Theater Command from January 2010 to June 2014. Patients would be eligible if they met the following inclusion criteria: (1) a diagnosis of liver cirrhosis, (2) a diagnosis of AUGIB, and (3) hematemesis and/or melena at admission. Exclusion criteria were as follows: (1) malignancies, and (2) only positive fecal occult blood at admission. Age and sex were not limited. The source of bleeding and the underlying cause of liver disease were not limited. Repeated admission was not restricted. The Medical Ethical Committee of our hospital approved this study with the ethical approval number of k (2018) 48.

2.2. Data collection

The following data was collected: demographic data (i.e., age and gender), etiology of liver disease, presence of hematemesis and/or melena and hemodynamics (i.e., heart rate and systolic blood pressure) at admission, and laboratory tests (i.e., red blood cell, hemoglobin, white blood cell, platelet count, total bilirubin, direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, blood urea nitrogen, creatinine, potassium, sodium, prothrombin time, activated partial thromboplastin time, and international normalized ratio [INR]). The severity of esophageal varices was reviewed based on the Chinese

endoscopic criteria[11]. Briefly, linearly or slightly tortuous esophageal varices without red-color sign were regarded as mild; linearly or slightly tortuous esophageal varices with red-color sign or serpentine esophageal varices without red-color sign were regarded as moderate; serpentine esophageal varices with red-color sign or beaded, nodular, and mass-like esophageal varices with or without red-color sign were regarded as severe. The Child-Pugh score and model for end-stage liver disease (MELD) score were calculated[12, 13].

The treatment of AUGIB included blood transfusion (i.e., red blood cell), somatostatin and/or octreotide, proton pump inhibitors (PPIs), endoscopic therapy (i.e., band ligation, sclerotherapy, and histoacryl), Sengstaken Blackmore tube, and surgery (i.e., splenectomy combined with pericardial devascularization, which is a common surgical procedure for portal hypertension related upper gastrointestinal bleeding in China[14, 15]). Generally, a restrictive transfusion strategy was adopted [16].

The primary outcomes included 5-day rebleeding rate and in-hospital mortality.

2.3. Definitions and classifications

AUGIB was defined as a fresh bleeding episode presenting with hematemesis and/or melena within 120 hours (5 days) before our admission[17]. Hematemesis was defined as vomiting fresh blood or coffee ground emesis[10]. Melena was defined as black tarry-

ground stool[18]. The patients were divided into hematemesis with or without melena and melena without hematemesis according to their clinical manifestations at admission. Tachycardia was defined as heart rate >100 beats per min. Unstable hemodynamics were defined as heart rate >100 beats per min and/or systolic blood pressure <90 mmHg. Five-day rebleeding was defined as the recurrence of hematemesis and/or fresh melena within 5 days after the initial bleeding episode was completely controlled[19].

2.4. Statistical analyses

Continuous variables were expressed as mean±standard deviation and median (range). Categorical variables were expressed as frequency (percentage). The non-parametric Mann-Whitney U test was used for continuous variables and Chi-square test was used for categorical variables when the difference between patients with and without hematemesis was compared. A 1:1 propensity score matching analysis was performed. Matching factors included gender, age, systolic blood pressure <90 mmHg, source of bleeding, Child-Pugh score, and MELD score. Subgroup analyses were conducted based on the systemic hemodynamics (stable and unstable) and Child-Pugh class (A and B+C). Binary logistic analysis was used to evaluate the role of hematemesis for predicting the risk of 5-day rebleeding rate and in-hospital mortality. Odd ratios (ORs) with 95% confidence interval (CI) were calculated. Sensitivity analyses were conducted in patients who underwent endoscopy and were regarded as

variceal bleeding (i.e., moderate and severe esophageal varices on endoscopy). A two-tailed $P<0.05$ was considered statistically significant. All statistical analyses were performed with IBM SPSS 20.0 statistical package and Stata/SE 12.0 (Stata Corp, College Station, TX) software.

3. Results

3.1. Overall analyses

A total of 826 patients were diagnosed with AUGIB and liver cirrhosis. Among them, 33 patients presented with positive fecal occult blood without hematemesis or melena at admission. Finally, 793 patients were included in our study (**Figure 1**).

Patients' characteristics at our admission are shown in **Table 1**. Median age was 55.60 years (range: 6.28-95.13 years) and 542 (68.3%) were male. Alcohol abuse alone (n=209, 26.3%) was the most common etiology of liver diseases followed by hepatitis B virus alone (n=200, 25.2%). Four hundred and sixty-six (58.8%) patients had hematemesis with or without melena. Median heart rate was 80 beats per min (range: 54-162 beats per min). Median systolic blood pressure was 115 mmHg (range: 60-185 mmHg). Among them, 587 patients underwent endoscopy during hospitalizations.

The severity of esophageal varices was assessed by endoscopy in 502 patients. A majority of patients had Child-Pugh class B (389/745, 52.2%) and C (135/745, 18.1%). Median MELD score was 6.35 (range: -7.52-37.65).

Blood transfusion was given in 520 (65.6%) patients, of whom 496 (62.5%) received red blood cell transfusion with a median amount of 4 units (range: 1.00-29.50). Somatostatin and/or octreotide were given in 728 (91.8%) patients. PPIs were given in

784 (98.9%) patients. Endoscopic treatment was performed in 491 (61.9%) patients. Sengstaken Blakemore was performed in 20 (2.5%) patients. Surgery was performed in 9 (0.9%) patients.

The 5-day rebleeding rate was 14.4% (n=114). The in-hospital mortality was 5.7% (n=45). The causes of death included uncontrolled AUGIB (n=18), liver failure with hepatic encephalopathy (n=2), uncontrolled AUGIB with hepatic encephalopathy (n=4), end-stage liver disease with multiple organ failure (n=20), and cardiogenic shock (n=1).

Compared with patients without hematemesis at admission, patients with hematemesis at admission were significantly older, had a smaller proportion of male, lower red blood cell, platelet count, albumin, and alkaline phosphatase, a larger proportion of tachycardia, and higher heart rate, white blood cell, total bilirubin, direct bilirubin, aspartate aminotransferase, blood urea nitrogen, serum creatinine, prothrombin time, INR, Child-Pugh score, and MELD score (**Table 2**).

Compared with patients without hematemesis at admission, patients with hematemesis at admission had significantly higher probability of receiving blood transfusion, red blood cell transfusion, somatostatin and/or octreotide, PPIs, and Sengstaken Blakemore (**Table 2**).

Compared with patients without hematemesis at admission, patients with hematemesis at admission had significantly higher 5-day rebleeding rate (17.4% versus 10.1%, P=0.004) and in-hospital mortality (7.9% versus 2.4%, P=0.001) (**Table 2**).

3.2. Propensity score matching analyses

A total of 358 patients were included after propensity score matching. Compared with patients without hematemesis at admission, patients with hematemesis at admission had significantly lower systolic blood pressure, albumin, and alkaline phosphatase and higher heart rate and white blood cell (**Table 3**).

Compared with patients without hematemesis at admission, patients with hematemesis at admission had significantly higher probability of receiving somatostatin and/or octreotide, PPIs, and Sengstaken Blakemore (**Table 3**).

Compared with patients without hematemesis at admission, patients with hematemesis at admission had significantly higher 5-day rebleeding rate (19.0% versus 10.6%, P=0.026) and in-hospital mortality (8.4% versus 2.8%, P=0.021).

3.3. Subgroup analyses

Subgroup analyses based on systemic hemodynamics. Among the 657 patients with stable hemodynamics, patients with hematemesis at admission had significantly higher 5-day rebleeding rate (18.1% versus 10.0%, P=0.004) and in-hospital mortality (6.1% versus 1.4%, P=0.003) than those without hematemesis (**Supplementary Table 1**). Logistic regression analyses demonstrated that hematemesis was a significant risk factor for 5-day rebleeding (OR=2.00, 95%CI=1.25-3.19) and in-hospital mortality (OR=4.51, 95%=1.54-13.20) (**Figures 2 and 3**).

Among the 136 patients with unstable hemodynamics, no significant difference was observed in 5-day rebleeding rate (14.4% versus 10.9%, P=0.561) and in-hospital mortality (15.6% versus 8.7%, P=0.264) between patients with hematemesis at admission and without hematemesis (**Supplementary Table 2**). Logistic regression analyses demonstrated that hematemesis was not a significant risk factor for 5-day rebleeding (OR=1.38, 95%CI=0.46-4.15) or in-hospital mortality (OR=1.93, 95%=0.60-6.25) (**Figures 2 and 3**).

Subgroup analyses based on Child-Pugh class. Child-Pugh class was available in 745 patients. Among the 221 patients with Child-Pugh class A, patients with hematemesis at admission had significantly higher 5-day rebleeding rate (14.2% versus 5.2%, P=0.024) than those without hematemesis. Patients with hematemesis at admission had higher in-hospital mortality than those without hematemesis (2.8%

versus 0%), but the difference was not statistically significant between the two groups (P=0.069) (**Supplementary Table 3**). Logistic regression analyses demonstrated that hematemesis was a significant risk factor for 5-day rebleeding (OR=3.00, 95%CI=1.12-8.03) (**Figure 2**).

Among the 524 patients with Child-Pugh class B and C, patients with hematemesis at admission still had significantly higher 5-day rebleeding rate (19.1% versus 11.8%, P=0.028) and in-hospital mortality (9.4% versus 3.1%, P=0.006) than those without hematemesis (**Supplementary Table 4**). Logistic regression analyses demonstrated that hematemesis remained a significant risk factor for 5-day rebleeding (OR=1.77, 95%CI=1.06-2.96) and in-hospital mortality (OR=3.28, 95%CI=1.34-8.00) (**Figures 2 and 3**).

3.4. Sensitivity analyses

The information regarding severity of esophageal varices by endoscopy was available in 502 patients. Among them, 445 patients had moderate and severe esophageal varices. Patients with hematemesis at admission had significantly higher 5-day rebleeding rate (18.0% versus 8.4%, P=0.004) and in-hospital mortality (4.9% versus 1.1%, P=0.031) than those without hematemesis (**Supplementary Table 5**).

4. Discussion

Our study demonstrated that hematemesis was associated with higher 5-day rebleeding rate and in-hospital mortality in cirrhotic patients with AUGIB in the overall analyses. Such findings were further confirmed by the propensity score matching analyses after adjusting age, gender, systolic blood pressure of <90 mmHg, source of bleeding, Child-Pugh score, and MELD score and sensitivity analyses of patients with variceal bleeding confirmed on endoscopy. Furthermore, subgroup analyses demonstrated that hematemesis was associated with higher 5-day rebleeding rate and in-hospital mortality in patients with stable hemodynamics at admission, but not in patients with unstable hemodynamics at admission. In addition, hematemesis was associated with higher 5-day rebleeding rate and in-hospital mortality regardless of Child-Pugh class.

Traditionally, as for general patients with liver cirrhosis, regardless of its complications, their outcomes are often evaluated by several scoring systems that can reflect the severity of liver and renal dysfunction. Among them, Child-Pugh and MELD scores are the most commonly used prognostic parameters in clinical practice[12, 13, 20]. As for cirrhotic patients with AUGIB, Child-Pugh score, MELD score, and severity of esophageal varices are the risk factors associated with early rebleeding and mortality[21, 22]. Recently, ALBI score was confirmed a favorable index for predicting rebleeding and in-hospital mortality in liver cirrhosis[23]. Meanwhile, other

scoring systems, such as AIMS65 score, acute physiology and chronic health evaluation II (APACHE II) score, and sequential organ failure assessment (SOFA) score, have been increasingly employed for prognostic assessment[24, 25]. In such population, hematemesis is an easy-to-access clinical index, but rarely used for prognostic stratification.

The value of hematemesis for predicting the risk of rebleeding in patients with acute gastrointestinal bleeding has been reviewed. As for nonvariceal bleeding, hematemesis was significantly associated with rebleeding[26-28]. As for variceal bleeding, a cohort study of 101 patients with active esophageal variceal bleeding indicated that 6-week rebleeding rate was marginally higher in the hematemesis group than the non-hematemesis group (28.8% versus 17.9%, P=0.107)[29]. It was worth noting that hepatocellular carcinoma was not excluded in the study and a relatively longer duration of rebleeding (6 weeks) was observed. By comparison, our study excluded patients with malignancy and focused on early rebleeding (5 days).

Among the patients with AUGIB regardless of source of bleeding, hematemesis seemed to be associated with higher mortality (**Supplementary Figure 1**)[10, 29-31]. Kim et al. conducted a retrospective study including patients hospitalized with AUGIB regardless of source of bleeding and found that in-hospital mortality was significantly higher in patients with hematemesis than those without hematemesis (7.7% versus

5.3%, P=0.03)[30]. Laine et al. conducted a multinational prospective observational study including patients with AUGIB secondary to peptic ulcers or suspected varices and found that mortality was significantly lower in patients with melena without hematemesis than those with hematemesis (OR=0.55, 95%CI=0.35-0.84)[10]. However, considering that mortality seemed to be marginally higher in patients with acute variceal bleeding than those with acute nonvariceal bleeding (**Supplementary Figure 2**)[19, 32-35], further assessment should focus on patients with variceal bleeding. To our knowledge, one cohort study included patients with active esophageal variceal bleeding alone and indicated that 6-week mortality was significantly higher in the hematemesis group than the non-hematemesis group (39.7% versus 10.7%, P=0.007)[29]. Indeed, patients with advanced liver cirrhosis are more likely to develop hematemesis as a result of drastically increased portal pressure and its secondary variceal rupture. Similarly, our sensitivity analyses which included patients with moderate and severe esophageal varices also indicated that in-hospital mortality was significantly in patients with hematemesis than those without hematemesis.

Several limitations should not be neglected. First, not all included patients had Child-Pugh or MELD score due to the lack of some laboratory data. Second, not all included patients underwent endoscopy. Indeed, in a large multicenter prospective study, 31.4% (934/2977) of included patients did not receive endoscopy yet[10]. Finally, the potential bias in evaluating the events by reviewing the medical charts due to the retrospective

nature of this study could not be ignored.

In conclusion, hematemesis at admission is an important predictor for 5-day rebleeding and in-hospital death in cirrhotic patients with AUGIB. Risk stratification of AUGIB based on the clinical presentations at admission (with or without hematemesis) is readily available and warranted.

Figure Legends

Figure 1: Flow chart of patient inclusion.

Figure 2: Subgroup analyses with regards to the effect of hematemesis on 5-day rebleeding.

Figure 3: Subgroup analyses with regards to the effect of hematemesis on in-hospital mortality.

Supplementary Figure 1: Prior studies with regards to the mortality of AUGIB: hematemesis versus no hematemesis.

Supplementary Figure 2: Prior studies with regards to the mortality of AUGIB: variceal bleeding and nonvariceal bleeding. “Mixed” refers to patients with bleeding from various sources.

Acknowledgment:

This work was partially presented as a poster presentation at the Asian Pacific Association for the Study of Liver (APASL) Single Topic Conference 2018 held in Beijing on December 6, 2018.

References

1. Carbonell N, Pauwels A, Serfaty L, et al. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 2004;40:652-9.
2. Tandon P, Bishay K, Fisher S, et al. Comparison of clinical outcomes between variceal and non-variceal gastrointestinal bleeding in patients with cirrhosis. J Gastroenterol Hepatol 2018;33:1773-9.
3. Meltzer AC, Klein JC. Upper gastrointestinal bleeding: patient presentation, risk stratification, and early management. Gastroenterol Clin North Am 2014;43:665-75.
4. Sarin SK, Kumar A, Angus PW, et al. Diagnosis and management of acute variceal bleeding: Asian Pacific Association for Study of the Liver recommendations. Hepatol Int 2011;5:607-24.
5. Cappell MS, Friedel D. Initial management of acute upper gastrointestinal bleeding: from initial evaluation up to gastrointestinal endoscopy. Med Clin North Am 2008;92:491-509, xi.
6. Wara P, Stodkilde H. Bleeding pattern before admission as guideline for emergency endoscopy. Scand J Gastroenterol 1985;20:72-8.
7. Srygley FD, Gerardo CJ, Tran T, et al. Does this patient have a severe upper gastrointestinal bleed? Jama 2012;307:1072-9.
8. Telaku S, Kraja B, Qirjako G, et al. Clinical outcomes of nonvariceal upper gastrointestinal bleeding in Kosova. Turk J Gastroenterol 2014;25 Suppl 1:110-5.
9. Blatchford O, Davidson LA, Murray WR, et al. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. Bmj 1997;315:510-4.
10. Laine L, Laursen SB, Zakko L, et al. Severity and Outcomes of Upper Gastrointestinal Bleeding With Bloody Vs. Coffee-Grounds Hematemesis. Am

J Gastroenterol 2018;113:358-66.

11. Chinese Society of Gastroenterology CSoH, Chinese Society of Endoscopy, Association CM. Consensus on prevention and treatment for gastroesophageal varices and variceal hemorrhage in liver cirrhosis. Zhong hua gan zang bing za zhi 2008;16:564-70.
12. Peng Y, Qi X, Dai J, et al. Child-Pugh versus MELD score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis. Int J Clin Exp Med 2015;8:751-7.
13. Peng Y, Qi X, Guo X. Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. Medicine (Baltimore) 2016;95:e2877.
14. Liu B, Deng MH, Lin N, et al. Evaluation of the effects of combined endoscopic variceal ligation and splenectomy with pericardial devascularization on esophageal varices. World J Gastroenterol 2006;12:6889-92.
15. Chen H, Yang F, Li TT, et al. Comparison of Efficacy of Laparoscopic and Open Splenectomy Combined With Selective and Nonselective Pericardial Devascularization in Portal Hypertension Patients. Surg Laparosc Endosc Percutan Tech 2018;28:401-403.
16. Bai Z, Guo X, Li H, et al. Should red blood cell transfusion be immediately given to a cirrhotic patient with active upper gastrointestinal bleeding? AME Medical Journal 2018;3:83-83.
17. de Franchis R, Baveno VF. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762-8.
18. Jairath V, Thompson J, Kahan BC, et al. Poor outcomes in hospitalized patients with gastrointestinal bleeding: impact of baseline risk, bleeding severity, and process of care. Am J Gastroenterol 2014;109:1603-12.
19. Ardevol A, Ibanez-Sanz G, Profitos J, et al. Survival of patients with cirrhosis

and acute peptic ulcer bleeding compared with variceal bleeding using current first-line therapies. Hepatology 2018;67:1458-71.

20. Bambha K, Kim WR, Pedersen R, et al. Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut 2008;57:814-20.
21. Hunter SS, Hamdy S. Predictors of early re-bleeding and mortality after acute variceal haemorrhage. Arab J Gastroenterol 2013;14:63-7.
22. Poordad FF. Presentation and complications associated with cirrhosis of the liver. Curr Med Res Opin 2015;31:925-37.
23. Zou D, Qi X, Zhu C, et al. Albumin-bilirubin score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis: A retrospective study. Turk J Gastroenterol 2016;27:180-6.
24. Al-Freah MA, Gera A, Martini S, et al. Comparison of scoring systems and outcome of patients admitted to a liver intensive care unit of a tertiary referral centre with severe variceal bleeding. Aliment Pharmacol Ther 2014;39:1286-300.
25. Mohammad AN, Morsy KH, Ali MA. Variceal bleeding in cirrhotic patients: What is the best prognostic score? Turk J Gastroenterol 2016;27:464-9.
26. Kim JS, Kim BW, Park SM, et al. Factors Associated with Rebleeding in Patients with Peptic Ulcer Bleeding: Analysis of the Korean Peptic Ulcer Bleeding (K-PUB) Study. Gut Liver 2018;12:271-7.
27. Joo I. Risk factors for rebleeding after angiographically negative acute gastrointestinal bleeding. World Journal of Gastroenterology 2009;15:4023.
28. Rotondano G, Cipolletta L, Koch M, et al. Predictors of favourable outcome in non-variceal upper gastrointestinal bleeding: implications for early discharge? Dig Liver Dis 2014;46:231-6.
29. Chen PH, Chen WC, Hou MC, et al. Delayed endoscopy increases re-bleeding and mortality in patients with hematemesis and active esophageal variceal

bleeding: a cohort study. J Hepatol 2012;57:1207-13.

30. Kim JJ, Sheibani S, Park S, et al. Causes of bleeding and outcomes in patients hospitalized with upper gastrointestinal bleeding. J Clin Gastroenterol 2014;48:113-8.

31. Silverstein FE, Gilbert DA, Tedesco FJ, et al. The national ASGE survey on upper gastrointestinal bleeding. II. Clinical prognostic factors. Gastrointest Endosc 1981;27:80-93.

32. D'Amico G. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology 2003;38:599-612.

33. Halland M, Young M, Fitzgerald MN, et al. Characteristics and outcomes of upper gastrointestinal hemorrhage in a tertiary referral hospital. Dig Dis Sci 2010;55:3430-5.

34. Lahiff C, Shields W, Cretu I, et al. Upper gastrointestinal bleeding: predictors of risk in a mixed patient group including variceal and nonvariceal haemorrhage. Eur J Gastroenterol Hepatol 2012;24:149-54.

35. Minakari M, Badihian S, Jalalpour P, et al. Etiology and outcome in patients with upper gastrointestinal bleeding: Study on 4747 patients in the central region of Iran. Journal of Gastroenterology and Hepatology 2017;32:789-96.