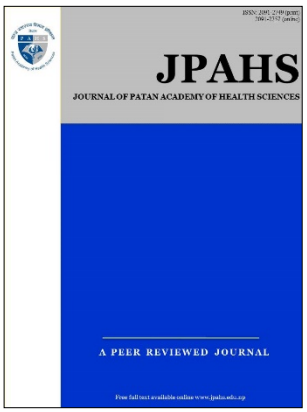

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Factors predicting early re-bleeding and in-hospital mortality after acute variceal hemorrhage in patients with cirrhosis

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Abstract

Introduction: Risk factors for early re-bleeding and in-hospital mortality following acute variceal hemorrhage (AVH) are incompletely understood. The aim of this study was to find out the risk factors for early re-bleeding within 5 days and in-hospital mortality after AVH in patients with cirrhosis.

Method: This was an analytical cross-sectional study conducted in Department of Medicine, Patan Hospital, Patan Academy of Health Sciences (PAHS), Nepal from July 2021 to June 2022. The ethical clearance was obtained from the Institutional Review Committee-PAHS. Informed consent was taken from the patients. Patients aged >18 y with diagnosed case of liver cirrhosis and endoscopy confirmed variceal bleeding were enrolled. All cases of early re-bleeding within 5 days and in-hospital outcome were recorded.

Result: In this study total 72 patients were enrolled. The mean age of our patients was 51.68 y. Sixty-seven (93%) of the patients improved, 3(4.16%) had early re-bleeding and 5(6.9%) died during the same hospital admission. Univariate analysis showed that early re-bleeding was significantly associated with the high PT/INR ($p<0.001$) and high Child-Turcotte Pugh (CTP) score ($p=0.032$), whereas in-hospital mortality of patients was significantly associated with low Protein ($p=0.044$), high CTP score ($p=0.041$), high Model for End-stage Liver Disease (MELD) score ($p=0.002$) and presence of gastric varices ($p=0.008$).

Conclusion: High PT/INR and high CTP score are the risk factors of early re-bleeding after AVH in cirrhotic patients. Low Protein, high CTP and MELD scores, and presence of gastric varices are the factors associated with in-hospital mortality in these patients.

Keywords: Cirrhosis, mortality, predictors, variceal hemorrhage

Introduction

Approximately half of patients with cirrhosis have esophageal varices, and one-third of all patients with varices will develop variceal hemorrhage (VH), which is a major cause of morbidity and mortality in patients with cirrhosis.[1,2] The risk of VH is increased in patients who have large varices and advanced stages of liver disease, as assessed on the basis of the Child-Pugh class.[3]

The immediate goal of therapy in these patients is to control bleeding, to prevent early recurrence (within 5 days) and prevent mortality.[3] The mortality rate for acute VH is highest during the first 5 days.[3] Despite advances in the management of variceal bleeding, mortality following VH has decreased by only 20%.[4,5]

Although some studies[6,7] have identified several risk factors associated with early re-bleeding and mortality in VH, risk factors specifically for re-bleeding have not been well-defined.

In a study done in Bir Hospital[8], predictors of in-hospital mortality of acute VH were evaluated; however, this study did not evaluate the risk factors for the re-bleeding. Whereas a Chinese study[9] reported moderate to severe ascites, number of bands placed, extent of varices and high prothrombin time to be the predictors of early rebleeding.

Research assessing various risk factors for acute VH in cirrhotic patients is important in an effort to identify the group of patients at high risk for re-bleeding and mortality, as it enables the immediate initiation of treatment.

Thus, the aim of this study was to identify factors predicting early re-bleeding and in-hospital mortality after acute VH in cirrhotic patients.

Method

This was an analytical cross-sectional prospective study conducted in the Department of Medicine, Patan Hospital, Patan Academy of Health Sciences (PAHS), Nepal from July 2021 to June 2022. The ethical clearance was obtained from the Institutional Review Committee of PAHS (Reference No. drs2106221542). Informed consent was taken from the patients or legal guardian of the patients if unable to give consent. Inclusion criteria were patients with age>18 years and diagnosed Liver Cirrhosis and endoscopy confirmed esophageal variceal bleeding. Exclusion criteria were non-cirrhotic portal hypertensive variceal bleeding, patients with Hepatocellular Carcinoma and patients who did not give consent.

Using the formula $N= (Za^2) (P) (Q)/d^2$, whereby estimated proportion in the population[10], confidence interval and margin of error were put at 5%, 95% and 5% respectively, the total minimum required sample size for the study was 72.

Consecutive patients diagnosed with liver cirrhosis and upper gastrointestinal (UGI) bleeding (hematemesis, coffee ground vomitus, hematochezia, or melena) were subjected to endoscopic evaluation after stabilization of hemodynamics.

Packed red cell transfusion was done according to restrictive transfusion strategy (to maintain the haemoglobin level between 7-9mg/dL). Platelet rich plasma and fresh frozen plasma were transfused in patients with significant coagulopathy (INR>2.5) and/or thrombocytopenia (platelets <50,000/μL) and required units were noted. Basic investigation reports of complete blood count, blood sugar, renal function and liver function tests were obtained to calculate Child Turcotte Pugh (CTP) and Model for End stage Liver Disease (MELD) scores.

CTP[11] score is the scoring system to assess the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5 to 6 is considered CTP Class A, 7 to 9 is Class B, and 10 to 15 is Class C, Table 1.

Table 1. Child-Pugh[11] or CTP Classification of severity of cirrhosis

Parameters	Points Assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	< 2 mg/dl	2-3 mg/dl	>3 mg/dl
Albumin	>3.5 g/dl	2.8-3.5 g/dl	<2.8 g/dl
Prothrombin time			
Seconds over control	<4	4-6	>6
INR (International Normalized Ratio)	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Model for End-Stage Liver Disease (MELD)[12] is a scoring system for assessing the severity of chronic liver disease. The MELD score was calculated by using following variables: International Normalized Ratio (INR), Bilirubin (mg/dl), Creatinine (mg/dl). Formula to calculate MELD score = 0.957 x Loge (creatinine mg/dL) + 0.378 x Loge (bilirubin mg/dL) + 1.120 x Loge(INR) + 0.6431

After stabilization, intravenous (iv) Pantoprazole 80mg loading dose followed by 8mg per hour was infused, iv Octreotide 50mcg loading dose followed by 50mcg per hour was infused for 5 days. All the patients also received antibiotic prophylaxis with iv Ceftriaxone 1g every 24 hours for a maximum of 7 days. All patients underwent UGI endoscopy followed by endoscopic variceal ligation for Esophageal Varices. Esophageal varices were graded based on the size of varix,[13] and red signs were also noted: Small- less than 5 mm in diameter and Large- greater than 5 mm in diameter

Re-bleeding was defined according to the Baveno criteria[3] as recurrence of bleeding after the first 24 h and within 5 d of admission for the bleeding episode after initial bleeding control evidenced by new melaena or haematemesis, requirement for >2 units of PRBCs in a 24-h time period, and haemodynamic instability. Patients with re-bleeding were subjected to second session of variceal ligation and rest of the pharmacotherapy was continued until bleeding was stopped. Patients were reassessed throughout the study, initially at least every 24 h for the first 5 days or until discharge. All cases of early re-bleeding within 5 days and final in-hospital outcome were recorded. The patients were categorized into 2 main categories for comparison; viz., re-bleeding versus no re-bleeding; and patient survived versus patient died.

All data were filled into a predesigned proforma and entered into Microsoft Excel. The data was uploaded and analyzed using Statistical Package for the Social Sciences version 16.0. Continuous variables like CTP score, MELD score, number of blood transfusions, AST and ALT levels etc. were expressed as mean, and categorical variables such as sex, age group, etiology of cirrhosis, presence of other complications of liver cirrhosis like ascites, hepatic encephalopathy etc. were expressed as count with percentage. Groups were compared using independent samples t-test for continuous variables like CTP score, MELD score, number of blood transfusions, laboratory parameters etc and χ^2 test for categorical variables like age, sex, etiology of cirrhosis, CTP class etc. All of these values were considered statistically significant if the p-value was ≤ 0.05.

Result

In our study, total 80 patients were assessed for the eligibility from July 2021 to June 2022. Eight patients were excluded because the etiology of GI bleeding was other than variceal hemorrhage. The mean age of the study patients was 51.68 y, with 56(77.8%) of men. Majority of patients (93%) had alcohol related liver cirrhosis, 2(2.8%) had non-alcoholic

steato-hepatitis (NASH) related cirrhosis, 2(2.8%) of patients had chronic Hepatitis B related liver cirrhosis and 1(1.4%) had no cause identified. The mean hemoglobin level at admission was 7.67g/dl, 37(51.4%) of patients had received a blood transfusion during the first 24h of hospitalization, with an average number of units transfused 1.36, Table 2.

Forty (55.6%) patients had Child C, 23(31.9%) had Child B and rest 9(12.5%) had Child A cirrhosis. Fifty-two (72.2%) patients had ascites and 8(11.1%) had Spontaneous Bacterial Peritonitis (SBP), and 20(27.8%) patients had hepatic encephalopathy (HE).

Table 2. Baseline characteristics of the patients presenting with acute variceal hemorrhage (N=72)

Age y, Mean±SD	**51.68±12.17**
Sex (Male,%)	56(77.8%)
Etiology	
Alcohol related	67(93%)
NASH	2(2.8%)
Chronic HBV	2(2.8%)
Other	1(1.4%)
Laboratory Parameters (Mean)	
Hemoglobin (g/dl)	7.67
Platelet (/L)	128368.06
Urea (mg/dl)	45.96
Creatinine (mg/dl)	1.36
Sodium (meq/L)	131.42
Potassium (meq/l)	4.39
Bilirubin (Total) (mg/dl)	4.43
AST (U/L)	120.4
ALT (U/L)	65.29
Protein (g/dl)	5.83
Albumin (g/dl)	2.571
PT/INR	1.54
CTP score (Mean±SD)	9.65±2.22
CTP Class	
A	9(12.5%)
B	23(31.9%)
C	40(55.6%)
MELD (Mean±SD)	17.61
Presentation	
Hematemesis	9(12.5%)
Malena	24(33.3%)
Both	39(54.2%)
Esophageal Varices with red color signs	70(97.2%)
Gastric varices	6(8.33%)
PHG	
Mild	51(70.8%)
Severe	21(29.2%)
Ascites	52(72.2%)
SBP	8(11.1%)
HE	20(27.8%)
Transfusion in first 24 hours	37(51.4%)
Average number of units transfused	1.36

Note: NASH- Nonalcoholic Steatohepatitis; AST- Aspartate Transaminase; ALT- Alanine Transaminase; PT/INR- Prothrombin; Time/International Normalized Ratio; CTP- Child Turcotte Pugh; MELD- Model for End-stage Liver Disease; PHG- Portal Hypertensive Gastropathy; SBP- Spontaneous Bacterial Peritonitis; HE- Hepatic Encephalopathy

Table 3. Predictors of early re-bleeding in study patients: univariate analysis

	Outcome		p-value
	Re-bleeding (n=3)	No re-bleeding (n=69)	
Age (Mean)	43.33	52.04	0.228
Hemoglobin(g/dl)	7.67	7.67	1
Platelets(/L)	142,333.33	127,760.87	0.718
Bilirubin(MG/dl)	7	4.32	0.512
ALT(U/L)	73.33	64.94	0.817
AST(U/L)	323.67	111.57	0.458
Protein	5	5.87	0.127
Albumin(gm/dL)	2.33	2.58	0.535
PT/INR	2	1.52	0.000
Creatinine(mg/dl)	0.67	1.39	0.372
Sodium(meq/L)	132.33	131.38	0.794
Ascites	3(100%)	49(71%)	0.273
SBP	1(33.33%)	7(10.14%)	0.211
HE	2(66.66%)	18(26.08%)	0.124
CTP score	12.33	9.54	0.032
MELD	21.33	17.45	0.239

Note: AST- Aspartate Transaminase; ALT- Alanine Transaminase; PT/INR- Prothrombin Time/International; Normalized Ratio; SBP- Spontaneous Bacterial Peritonitis; HE- Hepatic Encephalopathy; CTP- Child Turcotte Pugh; MELD- Model for End-stage Liver Disease

Table 4. Predictors of in-hospital mortality in study patients: univariate analysis

	Outcome		**p-value**
	Patients survived (n=67)	**Patients died (n=5)**	
Age (Mean)	51.8	50.2	0.78
Hemoglobin(g/dl)	7.73	6.8	0.415
Platelets(/L)	127,843.28	135,400.00	0.812
Bilirubin(MG/dl)	3.82	12.6	0.299
ALT(U/L)	65.78	58.8	0.806
AST(U/L)	114.4	200.8	0.588
Protein	5.9	5	0.044
Albumin(gm/dL)	2.58	2.4	0.56
PT/INR	1.52	1.8	0.261
Creatinine(mg/dl)	1.33	1.8	0.461
Sodium(meq/L)	131.25	133.6	0.415
Ascites	47(70.14%)	5(100%)	0.151
SBP	7(10.44%)	1(20%)	0.512
Gastric Varices	4(5.97%)	2(40%)	0.008
HE	18(26.86%)	2(40%)	0.527
CTP score	9.51	11.6	0.04
MELD	17.05	25	0.002
Blood Transfusion	35(52.23%)	2(40%)	0.597

AST- Aspartate Transaminase; ALT- Alanine Transaminase; PT/INR- Prothrombin Time/International Normalized Ratio; SBP- Spontaneous Bacterial Peritonitis; HE- Hepatic Encephalopathy; CTP- Child Turcotte Pugh; MELD- Model for End-stage Liver Disease

Sixty-six (91.66%) had esophageal varices (EV) alone, and 6(8.33%) had esophageal varices associated with gastric varices. All the patients in the study had large Esophageal Varices (EV) and majority (97.25%) had red color signs

Associated portal hypertensive gastropathy (PHG) was present in all patients, with 51(70.8%) and 21(29.2%) having mild and severe PHG respectively, Table 2.

Three (4.16%) patients in the study population had re-bleeding. Univariate analysis showed that re-bleeding was significantly associated with the high PT/INR (p<0.001) and high CTP score (p=0.032). Ascites was noted in all patients with re-bleeding (p=0.273) and SBP was present in 1(33.33%) of patients with re-bleeding. All patients with re-bleeding had Child C cirrhosis (p=0.286), Table 3.

Five (6.94%) patients died during the hospital stay, out of which 2 had re-bleeding within 5d, and in remaining cause of mortality was liver failure. Univariate analysis showed that early in-hospital mortality of patients was significantly associated with low Protein (p=0.044), high CTP (p=0.04), high MELD score (p=0.002) and presence of gastric varices (p=0.008), Table 4.

Stratification of patients according to MELD score (higher MELD≥18 points; lower MELD<18 points) revealed a significant increase in in-hospital mortality post-AVH between patients with higher compared with lower MELD scores (p=0.008).

In addition, variceal re-bleeding occurring within the first 5d after AVH was highly predictive of an increased in-hospital mortality (p=0.011).

Discussion

The rate of early re-bleeding in our study was 4.16%, this rate is lower than that reported by a study from United States (US)[7] which was 16% and much lower than the rate reported by study conducted in Morocco[14] (23%). The rate of re-bleeding was higher in other studies ranging from 35.8-44%.[15-16] This could be due to difference in severity of bleeding episodes, treatment methods and patient population. In one study[16] patients were treated by blood transfusions and vasoactive drugs, and if failure, sclerosis of esophageal varices was performed. And in the US study[7], endoscopic variceal band ligation was performed and if band ligation was not feasible or if band ligation failed to control bleeding, the bleeding oesophageal varices were treated with injection sclerotherapy. Whereas, in our study and in a study from Morocco[14], all patients were treated only by endoscopic band ligation. The comparison between these series allows us to conclude that endoscopic therapy is effective in acute variceal hemorrhage in cirrhotic patients.

In our study, high PT/INR and high CTP scores were significantly associated with early re-bleeding. In a study from Morocco[14] only a low rate of prothrombin was a predictor of recurrence, which is consistent with our study. This result implies that the severity of coagulopathy may play a critical role in re-bleeding. Whereas, a Chinese study[15] reported that low albumin levels, high white blood cell count, Child B and C, ascites, and encephalopathy were predictors of early re-bleeding in cirrhotic patients. Similarly, in the US study[7] MELD score and the presence of clot on a varix in the initial endoscopy were predictive of re-bleeding within 5 days.

In our study, in-hospital mortality rate of acute variceal hemorrhage was 6.94%, where majority of patients (80%) died within 5 days of AVH. Similarly, in US study[7] 5 days mortality after AVH was 5.6%, which is consistent with our study. Whereas in a Nepalese study[8] conducted in Bir Hospital between 2016-2017, in-hospital mortality rate was 12%. In a retrospective study[17] from India, in-hospital mortality rate was 8.7%. In contrast to another US study[18] in-hospital mortality rate was 14.2%. The mortality rate after variceal bleeding in our study was substantially lower than previously reported. Several studies[5,19] have also reported that in-hospital mortality in cirrhotic patients have decreased significantly over several years. This suggests that advances made in the management of variceal bleeding have improved outcomes after variceal bleeding.

The occurrence of re-bleeding during the first five days after the bleeding was significantly associated with early mortality in our study (p=0.011), which is also reported in the other studies.[7,14]

In our study, the highest mortality was observed in CTP-C which was 4(80%) followed by CTP- B having 1(20%) death. Similarly, in another Nepalese study[8], of the patients who died, 8(88.8%) were in CTP class-C followed by 1(11.1%) in CTP class-B. However, no mortality was seen in CTP-A in both studies. It suggests that the degree of liver dysfunction is an important predictor of variceal bleeding and it also reflects mortality.

Low serum protein, high CTP and MELD scores, and presence of gastric varices were predictive of in-hospital mortality in our study. Similarly, in a Nepalese study[8], high creatinine, high CTP and MELD scores were predictors of mortality. Whereas, US study[7] has reported MELD score, volume of PRBCs transfused within the first 24 h, AST level, serum sodium, presence of ascites, CTP class and active bleeding seen at the index endoscopy as the predictors of mortality. We found that high MELD (≥18) was associated with increase in-hospital mortality compared with lower MELD (<18) score (p=0.008) in our study, and this was consistent with the US study[7].

MELD score has been consistently found to be predictive of mortality across different series.[4,20] MELD score was reported to be a powerful predictor of early mortality after AVH in a Chinese study.[21] A multi-center study[22] also showed MELD is an accurate prognostic predictor in AVH and cirrhosis, and it is more efficient in selecting high risk patients who might benefit from more aggressive treatments.

Currently, there is no well-established model to accurately predict the survival of cirrhotic patients after AVH. One of the difficulties is that the prognosis for these patients is influenced not only by the severity of the bleeding episode itself, but also by the severity of the underlying liver disease. Since, MELD is a scoring system for assessing the severity of liver disease, so it can be a useful and accurate predictor of early re-bleeding and mortality in patients with AVH.

There are few limitations of our study. One, this was a single center study with small sample size. Second, only in-hospital morbidity and mortality were studied. Third, relatively few deaths occurred during the hospital stay in our study, which precluded us from performing a more detailed statistical analysis of the prognostic factors affecting in-hospital mortality after AVH. Our findings should be corroborated by a prospective investigation using a larger patient population. Finally, our study did not include physiological measurements of portal hypertension, such as Hepatic Venous Portal Gradient (HVPG) in the participants and we were not able to assess the predictive ability of HVPG in AVH re-bleeding and mortality. However, given that HVPG has been found to be predictive of poor outcomes among patients with variceal bleeding, it would be of interest to investigate the prognostic utility of MELD along with HVPG in patients of AVH and cirrhosis.

Conclusion

High PT/INR and high CTP score influenced the occurrence of early re-bleeding after acute variceal hemorrhage in cirrhotic patients. Low serum Protein, high CTP and MELD scores, and presence of gastric varices are the factors asscociated with in-hospital mortality in these patients. Patients with early re-bleeding had high in-hospital mortality.

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Conflict of Interest

None

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None

Author Contribution

Concept, design, planning: RS, SK, YRS; Literature review: RS; Data collection: RS, SK
Data analysis: RS, SK; Draft manuscript: RS; Revision of draft: YRS; Final manuscript: RS, SK,

YRS; Accountability of the work: RS, SK, YRS; Guarantor: RS.

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