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Determinants of Re Bleeding and Mortality in Cirrhotic Patients after Variceal Bleeding

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Abstract

Background: Variceal bleeding (VB) is the most serious complication of liver cirrhosis and carries a high mortality rate.

Methods: The retrospective analysis on 263 cirrhotic patients with variceal bleeding in Taipei Medical University Shuang Ho hospital from 2012 to 2018.

Aim: determine determinants of re-bleeding and mortality.

Results: Patients' characters were median age (56 years), male (73.4%), HCC (28.1%), ascites (53.2%), portal vein thrombosis (PVT, 6.4%), mean MELD score (17.5); mean Child-Tourette-Pugh score (CTP=8.2) and active bleeding at endoscopy (44.8%). Variceal re-bleeding occurred 4.1% at day-five, 11.0% at week-six and 28.1% at year-one. CTP score>7, MELD score>16, bilirubin>30mg/dL, hepatic encephalopathy and HCC predicted early and late re-bleeding. Old age, renal injury, active bleeding, albumin<2.8 g/dL, ascites, bacterial infection and PVT determined early re-bleeding. The mortality after first VB was 3.8%, 14.1% and 25.8% at day-5, week-6 and year-1 respectively. Old age, CTP>7, MELD>16, renal injury, ascites, hepatic encephalopathy, bacterial infection and HCC were determined early and late mortality. Early variceal re-bleeding was associated with early mortality. Use of non-selective beta-blocker or variceal ligation reduced mortality at year-1 (Odds Ratio; OR 0.03 and OR 0.3) and combination therapy reduced early re-bleeding (OR 7.5).

Conclusion: Re-bleeding and mortality rate after VB were substantially high in hepatic decompensation, renal injury, presence of HCC, PVT and infection. Early identification of variceal bleeding patients who are at substantially high risk would probably benefit from early trans-jugular intrahepatic portosystemic shunt or liver transplantation.

Keywords: Cirrhosis, Variceal Bleeding, Re bleeding, Mortality

Introduction

Approximately 50% of patients with cirrhosis have gastroesophageal varices and variceal bleeding (VB) from varices occurs in 30% of those patients. The rate of bleeding with known varices is 12 to 15% per year and VB is only 5–11% of all gastrointestinal bleeding[1,2] but it is 60–65% of bleeding episodes in cirrhotic patients. Baveno VI consensus conference[3] recommended following hemodynamic resuscitation, endoscopic variceal ligation or tissue adhesive should be undergone within 12h of presentation and vasoactive drugs should be started as soon as possible, before endoscopy. Antibiotic prophylaxis is an integral part of therapy for cir-

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rhotic patients presenting with upper gastrointestinal bleeding but it may be voided in CTP class A patients as very low risk of bacterial infection and mortality. Vasoactive drugs (terlipressin, somatostatin, octreotide) should be used in combination with endoscopic therapy to improve outcomes following variceal bleeding.[4] VB is a major cause of mortality and morbidity in cirrhotic patients.[5,6] The risk of re-bleeding within 1 year is approximately 60%.[7] Mortality rate from each episode of VB is approximately 15 to 20%[8,9] in the past and 10 20% at 6 weeks mortality in the previous study.[10] Thus, it is extremely important that patients who survive an initial VB start on prophylactic therapy to prevent future bleedings.

Several factors may increase the risk of bleeding such as the size of the varices, presence at endoscopy of red wale markings, the severity of liver disease and active alcohol use.[11] Several factors have been identified as predictors of mortality after VB, including bacterial infection, hepatic venous pressure gradient (HVPG) >20 mmHg measured shortly after admission, active bleeding at initial endoscopy, severity of initial bleeding, presence of portal vein thrombosis(PVT), hepatocellular carcinoma (HCC), alcoholic liver disease, early re-bleeding, serum bilirubin and albumin levels, Child-Turcotte-Pugh (CTP) class B or C, and Model for End-stage Liver Disease (MELD) score.[12-14]

With our hospital data-base, we will analyse patient characters (age, sex, aetiology of cirrhosis, CTP score, MELD score, portal vein thrombosis, ascites), association with HCC and PVT; and different characters of alcoholic cirrhotic patients. We evaluate clinical outcomes including non-controlled bleeding, re-bleeding and mortality at day-5, week-6 and 1-year. Moreover, we identify the risk factors of re-bleeding and mortality of cirrhotic patients after initial variceal bleeding.

Materials and Methods

Retrospective analysis on cirrhotic patients admitted with variceal bleeding to Taipei Medical University-Shuang Ho hospital from January 2012 to December 2018. Data were obtained from medical records, endoscopy and laboratory databases. Stage of liver disease was determined by CTP score and Model of End Stage Liver Disease (MELD-Na) scores within 24 hours of bleeding onset. Follow-up was maintained until the patient's death or the end of the observation period (December, 2018). Re-bleeding and survival were assessed at day-5, week-six, and year-one. The study was approved by the Institutional Review Board (protocol number N201905130) of Taipei Medical University. The study was conducted according to the criteria set by the declaration of Helsinki.

Statistical Analysis

Descriptive statistics included the mean+standard deviation (SD) for quantitative variables and the number (percentage) for qualitative values. Comparisons between groups were assessed using Student's *t* test for quantitative variables and the Chi-square test or Fisher's extract test for quantitative variables. Factors associated with survival were assessed to univariate and multivariate analysis.

Results

Patient characteristics

Out of 263 enrolled cases of variceal bleeding, sources of bleeding were esophageal varices (238 patients, 90.5%) and gastric varices (25 patients, 9.5%) respectively. Etiology of cirrhosis were alcohol (46.8%) including alcohol + viral hepatitis (13.7%); viral hepatitis B virus (HBV) (36.4%), hepatitis C virus (HCV) (22.1%), co-infection of HBV+HCV (7 patients, 5.0%), autoimmune hepatitis (3.5%) and other etiology (32.8%). The characters of patients were, male (73.4%), mean age (57.9 years), ascites (53.2%), HCC (28.1%), portal vein thrombosis(6.4%), bacterial infection (24.3%), hepatic encephalopathy (28.1%), active variceal bleeding at endoscopy (44.8%), mean MELD score (17.5) and mean CTP score (8.2); CTP class A 25.9%, class B 46.0%, and class C 28.1%). At inclusion, mean blood tests were haemoglobin (8.9mg/dL), Platelet count (120.4 x 10^3/μL), bilirubin (3.6mg/dL), albumin (2.9g/dL) and prothrombin time (17.7 seconds). Among them, 17.1% patients were using non-selective beta-blocker (NSBB), and 4.5% patients had prior VB. All the patients were received endoscopic treatment within 12-hours of presentation and vasopressor use (84.8%). Treatment modalities included band-ligation in 239 patients, and cyanoacrylate injection in 24 patients respectively. Half of patients received secondary prevention after VB; NSBB alone (20.1%), EVL alone (20.9%) and combinations of NSBB & EVL(6.4%) Table 1.

Outcomes

The outcomes at day-5, week-6 and year-1 are displayed Table 2-5.

Non-controlled bleeding and re bleeding

Two patients (0.7%) experienced non-control of bleeding between inclusion and day-five. Re-bleeding rate was 4.1% (n=11) at day-5, 11.0% (n=29) at week-6 and 28.1% (n=74) at year-1 respectively. These proportions did not differ with etiology of cirrhosis. Nevertheless, re-bleeding occurred higher in CTP class C patients (RR 6.9 at week-6 and RR 2.0 at year-1) and CTP class B patients (RR 1.9 at year-1) with P<0.04 Table 2,3.

The parameters associated with re-bleeding at week-6 were old age>60 years (OR 2.3); CTP score>7 (OR 3.8); MELD score>16 (OR 3.0); renal injury (creatinine>1.5mg/dL) (OR 2.4); albumin less than 2.8g/dL (OR 5.8); bilirubin>3mg/dL (OR 3.9); ascites (OR 6.0); hepatic encephalopathy (OR 2.3); active bleeding at endoscopy (OR 5.8); bacterial infection (OR 4.5); HCC (OR 3.7) and portal vein thrombosis (OR 3.7) with P value<0.05. The parameters asso-

ciated with re-bleeding at year-1 were CTP score>7 (OR 2.9); MELD score>16 (OR 2.6); albumin<2.8g/dL (OR 1.9); bilirubin>3mg/dL (OR 3.4), active bleeding (OR 5.1), ascites (OR 3.1), bacterial infection (OR 2.0); PVT (OR 4.4) with P value<0.035. Alcohol use, thrombocytopenia and non-selective beta-blocker use were not determinants of re-bleeding Table 4.

Table 1: Patients' characteristics.

Variables	All patients (n = 263)	Alcoholic patients (n = 123) (46.8%)	Non-alcoholic patients (n = 140) (53.2%)	p-value
Age (years) Median (range)	56 (27 - 99)	48 (27 - 81)	64 (30 - 99)	<0.0001
Mean + SD	57.9 + 14.4	49.7 + 10.2	62.3 + 13.7	<0.0001
Male Sex, n (%)	193 (73.4)	113 (91.8)	80 (57.1)	<0.0001
Cause of bleeding				
Oesophageal varices, n (%)	**238 (90.5)	113 (91.9)	125 (89.3)	0.4736
Gastric varices, n (%)	25 (9.5)	10 (8.1)	15 (10.7)	0.4736
Viral hepatitis infection				
Viral hepatitis B, n (%)	73 (27.8)	22 (17.9)	51 (36.4)	-
Viral hepatitis C, n (%)	44 (16.7)	13 (10.6)	31 (22.1)	-
Both viral hepatitis B and C, n (%)	9 (3.4)	2 (1.6)	7 (5.0)	-
Prior variceal haemorrhage, n (%)	12 (4.5)	9 (7.3)	3 (2.1)	0.0435
NSBB use at inclusion, n (%)	45 (17.1)	27 (21.9)	18 (12.8)	0.0507
Bacterial infection at inclusion, n (%)	64 (24.3)	26 (21.1)	38 (27.1)	0.2585
Encephalopathy at inclusion, n (%)	74 (28.1)	41(33.3)	33(23.6)	0.0815
Ascites at inclusion*, n (%)	140 (53.2)	57 (46.3)	83 (59.2)	0.0368
Haemoglobin at inclusion (g/dL), mean + SD	8.9 + 2.4	8.8 + 2.4	8.9 + 2.3	0.7306
Platelet at inclusion (x 10^3/µL), mean + SD	120.4 + 75.0	110.2 + 57.3	129.4 + 86.6	0.0376
Bilirubin at inclusion (mg/dL)*, mean + SD	3.6 + 5.2	4.3 + 5.0	3.1 + 5.2	0.06
Albumin at inclusion (g/dL)*, mean + SD	2.9 + 6.4	2.9 + 0.7	2.9 + 0.6	0.8767
Prothrombin time at inclusion (sec), mean + SD	17.7 + 9.3	19.6 + 12.7	16.1 + 3.6	0.0018
Hepatocellular carcinoma, n (%)	74 (28.1)	20 (16.3)	54 (38.6)	0.0001
Portal vein thrombosis, n (%)	17 (6.4)	7 (5.7)	10 (7.1)	0.2002
CTP score, mean + SD	8.2 + 2.4	8.6 + 2.0	7.9 +2.5	0.0136
MELD score, mean + SD	17.5 + 6.9	18.5 + 7.2	16.6 + 6.5	0.0221
Active bleeding at inclusion, n (%)	118 (44.8)	67 (54.5)	51 (36.4)	0.0033
NSBB use alone, post-VB, n (%)	53 (20.1)	27 (21.9)	26 (18.5)	0.4962
EVL alone, post-VB, n (%)	55 (20.9)	23 (18.7)	32 (22.857)	0.4091
EVL plus NSBB use, post-VB, n (%)	17 (6.4)	8 (6.5)	9 (6.428)	0.9811
Rebleeding: At Day-5, n (%)	11 (4.1)	5 (4.0)	6 (4.3)	0.9359
At Week-6, n (%)	29 (11.0)	10 (8.1)	19 (13.57)	0.1582
At Year-1, n (%)	74 (28.1)	32 (26.0)	42 (30.0)	0.4725
Death: At Day-5, n (%)	10 (3.8)	4 (3.2)	6 (4.3)	0.6416
At Week-6, n (%)	37 (14.1)	13 (10.6)	24 (17.1)	0.131

SD: Standard deviation; n: number; CTP: Child Tourette Pugh; MELD: Model for End stage Liver Disease; EVL: esophageal variceal ligation; VB: variceal bleeding; NSBB: non-selective beta-blocker

Normal reference values: Cr < 1.30mg/dL; platelet count 130 to 400 x 10^3/µL; total bilirubin < 1.5 mg/dL; albumin 3.8 to 5.3g/dL; prothrombin time 11.0 to 14.5 sec

*Some data were missing for some patients. The number of patients missing data never exceed 4.9% for Bilirubin and 13.6% for albumin; 4.5% for ascites

**2 patients had both oesophageal and gastric variceal bleeding

Table 2: Outcome of the post variceal bleeding patients with different CTP classes.

	Total (n=263)	CTP class A (n=68)	CTP class B (n=121)	CTP class C (n=74)
Outcome on Day-5				
Rebleeding, n (%)	11 (4.1)	0	5 (4.1)	6 (8.1)
Death, n (%)	10 (3.8)	0	4 (3.3)	6 (8.1)
Outcome at week-6				
Rebleeding, n (%)	29 (11.0)	2 (2.9)	12 (9.9)	15 (20.2)
Death, n (%)	37 (14.1)	2 (2.9)	9 (7.4)	26 (35.1)
Outcome at year-1				
Rebleeding, n (%)	74 (28.1)	11 (16.1)	38 (31.4)	25 (33.7)
Death, n (%)	68 (25.8)	6 (8.8)	26 (21.5)	36 (48.6)

CTP: Child Tourette Pugh

Table 3: Multivariate logistic regression of mortality of CTP class B and CTP class C compared with CTP class A patients.

Outcomes	CTP class A (n= 68)	CTP class B (n= 121)			CTP class C (n = 74)		
		No	RR (95% CI)	p-value	No	RR (95% CI)	p-value
Re-bleeding at Week-6	2	12	3.3 (0.77 – 14.6)	104	15	6.9 (1.63 -29.03)	0.008
at Year-1	11	38	1.9 (1.06 -3.54)	0.03	25	2.0 (1.11 -3.91)	0.021
Death at week-6	2	9	2.7 (0.61 -12.3)	0.185	26	11.9 (2.94 -48.4)	0.0005
at Year-1	6	26	2.4 (1.05 -5.62)	0.037	36	5.5 (2.47 -12.2)	<0.0001

CTP: Child Tourette Pugh; RR: Relative Ratio; 95%CI; 95% Confidence interval

Table 4: Multivariate analysis- Parameters associated with re-bleeding at week-6 and Year-1.

Variables	Rebleeding at Week-6				Rebleeding at Year-1			
	Yes n=29	No* n=207	Odds Ratio (95% CI)	p- value	Yes n=74	No* n=152	Odds Ratio (95% CI)	p-value
Age > 60 years	17	78	2.3 (1.06 to 5.16)	0.0348	31	58	1.1 (0.66 to 2.05)	0.5899
Alcoholic	10	103	0.5 (0.23 to 1.19)	0.1274	32	78	0.7 (0.41 to 1.26)	0.2553
CTP score > 7	26	143	3.8 (1.13 to 13.3)	0.0309	62	97	2.9 (1.45 to 5.90)	0.0027
MELD > 16	22	105	3.0 (1.25 to 7.45)	0.0143	45	72	2.6 (1.41 to 4.90)	0.0024
Creatinine > 1.5mg/dL	12	46	2.4 (1.10 to 5.54)	0.0283	19	30	1.4 (0.72 to 2.70)	0.3105
Albumin < 2.8g/dL**	17	46	5.8 (2.37 to 14.5)	0.0001	27	31	1.9 (1.06 to 3.76)	0.0323
Bilirubin > 30mg/dL**	15	47	3.9 (1.73 to 9.05)	0.0473	31	27	3.4 (1.81 to 6.41)	0.0001
Platelet < 80x10^3/µL	6	64	0.5 (0.22 to 1.50)	0.2632	22	31	1.6 (0.87 to 3.11)	0.122
Active bleeding	23	82	5.8 (2.28 to 14.9)	0.0002	53	50	5.1 (2.80 to 9.45)	<0.0001
Ascites **	23	96	6.0 (2.01 to 18.1)	0.0013	52	65	3.1 (1.69 to 5.75)	0.0003
Encephalopathy	12	48	2.3 (1.04 to 5.23)	0.039	24	35	1.6 (0.86 to 2.97)	0.1325
Bacterial infection	14	35	4.5 (2.03 to 10.3)	0.0002	22	26	2.0 (1.06 to 3.94)	0.0312
HCC	15	46	3.7 (1.68 to 8.33)	0.0012	23	32	1.6 (0.90 to 3.16)	0.101
Portal vein thrombosis	5	11	3.7 (1.18 to 11.6)	0.024	8	4	4.4 (1.30 to 15.4)	0.0172
Combination of EVL plus NSBB use	2	2	7.5 (1.026 to 56.1)	0.047	20	27	1.6 (0.84 to 3.13)	0.1482
Preventive EVL alone	0	1	2.3 (0.092 to 58.6)	0.6065	9	5	4.7 (1.313 to 12.6)	0.015
NSBB use alone	4	48	0.5 (0.17 to 1.59)	0.2596	20	29	1.5 (0.81 to 3.01)	0.1755

CTP: Child Tourette Pugh; MELD: Model for End stage Liver Disease; HCC: hepatocellular carcinoma; NSBB: non selective beta blocker; EVL: preventive oesophageal variceal ligation

*control groups excluded patients expired within those periods

**Some data were missing for some patients. The number of patients missing data never exceed 4.9% for Bilirubin and 13.6% for albumin; 4.5% for ascites.

Survival

Mortality rate after episode of variceal bleeding was 3.8% (n=10 patients) at day-5, 14.1% (n=37) at week-6 and 25.8% (n=68) at year-1, respectively. More than half of year-1 mortality was within 6 weeks (54.1%) and 88.2% occurred within 6 months. The mortality rate differed among CTP classes: CTP class A (0%, 2.9% and 8.8%), CTP-B (3.3%, 7.4% and 21.5%), and CTP-C (8.1%, 35.1% and 48.6%) at day-5, week-6 and 1-year, respectively Table 2. In multivariate logistic regression analysis, mortality was higher in CTP-class C patients (RR 11.9 at week-6 and RR 5.5 at year-1); and CTP-class B patients (RR 2.4 at year-1) with P value<0.04 Table 3.

The parameters associated with mortality at week-6 were age>60 years (OR 2.3), CTP score>7 (OR 7.3), MELD score >16 (OR 4.9), renal injury (OR 4.9), albumin<2.8g/dL (OR 4.7), bilirubin>3 mg/dL (OR 5.2), ascites (OR 6.9), encephalopathy (OR 2.8), bacterial infection (OR 7.4), HCC (OR 4.6), and variceal re-bleeding (OR 4.1) with P value<0.035.

Alcohol use, active bleeding at endoscopy, and portal vein thrombosis were not influence 6-week mortality.

The parameters associated with mortality at year-1 were age older than 60 years (OR 2.3), CTP score>7 (OR 4.9), MELD score>16 (OR 2.8), renal injury (OR 3.2), albumin<2.8g/dL (OR 3.7), bilirubin>3mg/dL (OR 3.2), ascites (OR 3.2), bacterial infection (OR 4.9), HCC (OR 6.3), and PVT (OR 3.5) with P value<0.013. Hepatic encephalopathy, low platelet count and active bleeding at endoscopy, were not related with mortality at year-1. Non-selective beta-blocker-use reduced both week-6 and year-1 mortality (OR 0.09, 95% CI 0.01 to 0.69, P =0.020 and OR 0.3, 95% CI 0.12 to 0.74, P =0.009) Table 5.

Table 5: Multivariate analysis: Parameters associated with Mortality at week-6 and at Year-1.

Variables (n)	Mortality at Week-6				Mortality at Year-1			
	Yes n=37	No n=226	Odds Ratio (95% CI)	p-value	Yes n=68	No n= 195	Odds Ratio (95% CI)	p-value
Age > 60 years	22	88	2.3 (1.13 to 4.67)	0.0212	39	71	2.3 (1.33 to 4.12)	0.0029
Alcohol use	13	110	0.5 (0.27 to 1.17)	0.1293	22	101	0.4 (0.24 to 0.79)	0.0063
CTP score > 7	35	159	7.3 (1.72 to 31.54)	0.007	62	132	4.9 (2.02 to 12.0)	0.0004
MELD score > 16	31	115	4.9 (2.00 to 12.41)	0.0006	50	96	2.8 (1.56 to 5.25)	0.0007
Creatinine > 1.5mg/dL	19	40	4.9 (2.36 to 10.2)	<0.0001	29	36	3.2 (1.79 to 5.99)	0.0001
Albumin < 2.8g/dL*	24	54	4.7 (2.24 to 9.93)	0.0358	36	42	3.7 (2.02 to 6.78)	<0.0001
Bilirubin > 3mg/dL*	23	54	5.2 (2.51 to 10.87)	<0.0001	34	44	3.2 (1.80 to 5.85)	0.0001
Platelet < 80 x 10^3/µL	10	69	0.8 (0.38 to 1.83)	0.6667	39	60	0.8 (0.47 to 1.60)	0.6615
Active bleeding	21	97	1.7 (0.86 to 3.52)	0.1197	32	86	1.1 (0.64 to 1.96)	0.6731
Ascites*	32	108	6.9(2.62 to 18.59)	0.0001	50	90	3.2 (1.75 to 6.20)	0.0002
Encephalopathy	18	56	2.8 (1.41 to 5.86)	0.0036	25	49	1.7 (0.96 to 3.12)	0.0678
Bacterial infection	23	41	7.4 (3.51 to 15.62)	<0.0001	33	31	4.9 (2.70 to 9.19)	<0.0001
HCC	22	54	4.6 (2.26 to 9.63)	<0.0001	40	36	6.3 (3.45 to 11.5)	<0.0001
Portal vein thrombosis	4	13	1.9 (0.61 to 6.45)	0.2541	9	8	3.5 (1.31 to 9.65)	0.0124
Combination of EVL and NSBB use	0	2	1.1 (0.05 to 25.4)	0.908	1	16	1.6 (0.02 to 1.28)	0.0854
Preventive EVL alone	0	6	0.4 (0.02 to 8.19)	0.5915	7	48	0.3 (0.15 to 0.82)	0.0156
NSBB use alone	1	52	0.09 (0.01 to 0.69)	0.0206	6	47	0. 3 (0.12 to 0.74)	0.0097
Re-bleeding	13	26	4.1 (1.89 to 9.17)	0.0004	23	51	1.4 (0.79 to 2.61)	0.2272

CTP: Child Tourette Pugh score; MELD: Model for End-stage Liver Disease; HCC: Hepatocellular carcinoma; NSBB: non-selective beta-blocker
*Some data were missing for some patients. The number of patients missing data never exceed 4.9% for Bilirubin and 13.6% for albumin; 4.5% for ascites.

Discussions

The current study showed that variceal bleeding was more frequent from esophageal varices than from gastric varices (90.5% versus 9.5%). Variceal bleeding was more frequent in male patients (73.4%), and was similar to those shown in the previous literature.[15] Alcoholic cirrhosis was 46.8% of variceal bleeding patients which was lower than those reported in other studies.[16,17] In our study, alcoholic patients were significant male predominant (91.8% VS 57.4%), younger age (49.7 years VS 62. years), higher CTP score

(8.6 VS 7.9), and higher MELD score (18.5 Vs 16.6) in compare to non-alcoholic cirrhotic patients, P < 0.025.

The early re-bleeding rate in the current study was 4.1% at day-5 and 11.0% at week-6 which is similar to previous study[18] and much lower than the rates reported in previous studies (range, 8%-46%).[19-22] It has been reported that the presence of active bleeding at endoscopy, CTP class C, ascites, and encephalopathy contributes to the re-bleeding rate.[2] Our study found that variceal re-bleeding was contributed by active bleeding at endoscopy, CTP-class C, presence of ascites, and HCC but alcoholic etiology and thrombocytopenia were not predictors of re-bleeding. The risk of variceal rupture increases with the increased severity of liver disease and the mortality of patients with variceal bleeding is closely related to the CTP classes.[23,24] In this study, the majority of patients were CTP class B and C (74.1%); CTP class C was significantly related with bleeding (RR 6.9 at week-6 and RR 2.0 at year-1, P<0.03) and mortality (RR 11.9 at week-6 and RR 5.5 at year-1, *P*< 0.001); this result was similar to findings in other studies.[25,18] We also found that CTP class B was related with re-bleeding and mortality at year-1 (RR 1.9 and RR 2.4, P<0.04). One study stated that MELD score of ≥18 and hepatic vein pressure (HVPG)≥20, were associated with 6-week mortality. HVPG independently predicts short-term prognosis in patients with VB, but HVPG measurements are poorly reproducible, difficult to perform in bleeding patients[26] and lack of local expertise, our study was to evaluate mortality using non-invasive variables instead of HVPG measurement.[27] In the present study, MELD score >16 was a risk of re-bleeding (OR 3.0 at week-6 and OR 2.6 at year-1, P<0.03) and mortality (OR 4.9 at week-6 and OR 2.8 at year-1, P<0.001) but not predict variceal re-bleeding. Similar to Krige study,[9] our study showed that old age>60 years, CTP score>7, MELD score>16, creatinine>1.5mg/dL, albumin<2.8g/dL, bilirubin>3mg/dL, ascites, encephalopathy, bacterial infection, and HCC were related with short-term mortality. Hepatocellular carcinoma has been reported as a significant predictive factor for death in decompensated cirrhosis and early rebleeding.[28] Our analysis also showed HCC contributed 28.1% of patients. Presence of HCC predicted early re-bleeding (OR 3.7, P=0.001) and mortality (OR 4.6 at week-6 and OR 6.3 at year-1, P<0.001). Portal vein thrombosis was related with re-bleeding (OR 3.7 at week-6 and 4.4 at year-1, P<0.03) and morality at year-1 (OR 3.5, P=0.012).

Active bleeding at endoscopy was an independent predictor of early re-bleeding, but not of mortality,[29] similarly in our study, active bleeding predicted re-bleeding at both week-6 and year-1 (OR 5.8 and OR 5.1, P<0.002) but did not affect survival. Bacterial infections are frequent and well-recognized complication of cirrhosis that may occur along the course of cirrhosis associated with gastrointestinal bleeding, and adversely affect both bleeding control and mortality.[30,31] In our study, the patients with bacterial infection had risk of re-bleeding (OR 4.5 at week-6 and 2.0 at year-1, P<0.04) and mortality (OR 7.4 at week-6 and OR 4.9 at year-1, P<0.001).

High mortality rate of variceal bleeding was well described in the Baveno IV consensus conference: 57% at year-1 and nearly half of these deaths occur in week-6.[32] In our study, the overall mortality rates were 3.8%, 14.1% and 25.8% at day-5, week-6, and year-1 respectively. Many studies have reported decreasing incidence and mortality rates of variceal bleeding by the progress of treatment modalities.[33] This is also applicable to our study.

After first variceal bleeding, using non-selective beta-blockers (NSBB) plus endoscopic variceal ligation (EVL) reduced re-bleeding and mortality.[34] In a meta-analysis of eight trials, EVL plus NSBB use resulted in greater risk reduction for re-bleeding compared with EVL alone or pharmacologic intervention alone.[35] However, combination therapy is only marginally more effective than drug therapy alone, with a tendency for an increased survival with drugs alone in a recent meta-analysis.[36] This suggests that pharmacological therapy is the cornerstone of combination therapy. In our study, NSBB use alone reduced mortality at week-6 and year-1 (OR 0.09, P=0.02 and OR 0.3, P<0.01, respectively). Preventive EVL alone reduced bleeding and mortality at year-1(OR 4.7 and OR 0.3, P<0.02). However, there were some limitations for preventive intervention, old age (>60 years, 44.1%), presence of associated chronic illness (50.2%), ascites (53.2%) and poor patients' adherent to regular follow-up (34.2%). Hence, small proportions of our patients accepted preventive measurements, i.e. NSBB alone (20.1%), EVL alone (20.9%) and combination therapy (6.4%).

If the patients are not tolerated or have complications from beta blockers or EVL, transjugular intrahepatic porto-systemic shunt (TIPS) should be considered, particularly if the patient has another complication (e.g., ascites). TIPS placement using a covered stent reduces the risk of re-bleeding, but without a survival benefit, compared with endoscopic and pharmacologic strategies.[37] The Baveno VI consensus meeting concluded that an early TIPS must be considered in high risk cirrhotic patients presenting with VB (CTP class B plus active bleeding at endoscopy or CTP class C10-13 patients. In a large multi-center real life study, the actuarial probability of survival at one-year was significantly increased in early TIPS patients and the severity of liver disease was the only parameter independently associated with one-year survival. However, one-third of the cirrhotic patients admitted for VB fulfilled the criteria for early-TIPS placement and TIPS was restricted to patients displaying less severe cirrhosis.[38] In addition, TIPS placement within a short duration is not available in all centers because this treatment requires expert interventional radiologists and the necessary technical equipment. Liver transplantation provides successful long-term management of variceal bleeding and other complications of portal hypertension.[39] However, the value of transplantation as a preventive inter-

vention is limited by the frequently long waiting period before a donor liver is available.

In conclusion, effective preventive endoscopic and pharmacologic intervention could improve mortality but substantially high mortality in cirrhotic patients with old age, liver decompensation (CTP >7 and MELD >16), renal injury, infection, HCC and PVT. Those determinants can be used as stratified factors to discern high-risk patients and make a decision to proceed to TIPS or liver transplantation earlier.

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Conflicts of Interest

Authors declares that there is no conflicts of interest.

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