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Variceal bleeding in cirrhotic patients: What is the best prognostic score?

LIVER

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Original Article

ABSTRACT

Background/Aims: To find the most accurate, suitable, and applicable scoring system for the prediction of outcome in cirrhotic patients with bleeding varices.

Materials and Methods: A prospective study was conducted comprising 120 cirrhotic patients with acute variceal bleeding who were admitted to Tropical Medicine and Gastroenterology Department in Sohag University Hospital, over a 1-year period (1/2015 to 1/2016). The clinical, laboratory, and endoscopic parameters were studied. Child–Turcotte–Pugh (CTP) classification score, Model for end-stage liver disease (MELD) score, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, and AIMS65 score were calculated for all patients. Univariate and multivariate analyses were performed for all the measured parameters and scores.

Results: Of the 120 patients (92 male) admitted during the study period, eight patients (6.67%) died in the hospital. Advanced age, the presence of encephalopathy, rebleeding, and higher serum bilirubin were independent factors associated with higher hospital mortality. The largest area under the receiver operator curve (AUROC) was obtained for the AIMS65 score and SOFA score, followed by the MELD score and APACHEII score, then CTP score, all of which achieved very good performance (AUROC>0.8). AIMS65 score showed the best sensitivity, specificity, and negative and positive predictive values. Although the AIMS65 score was not significantly different from the MELD, SOFA, and APACHEII scores, it was the optimum among them in terms of the prediction of mortality.

Conclusion: AIMS65 score is the best simple and applicable scoring system for independently predicting mortality in cirrhotic patients with acute variceal bleeding.

Keywords: AIMS65, liver cirrhosis, variceal bleeding

INTRODUCTION

Bleeding from the upper part of the gastrointestinal tract (UGIB) covers any bleeding originating from the esophagus to the ligament of Treitz at the duodenojejunal flexure (1). Acute upper gastrointestinal (GI) bleeding is a frequent cause of hospital emergency admissions worldwide (2). The causes of UGIB may be variceal (esophageal or gastric varices) or nonvariceal (erosive gastritis, gastric or duodenal ulcer, reflux esophagitis, etc.). Emergency upper gastrointestinal endoscopy is recommended for both the diagnosis and treatment of UGIB (3). Acute variceal hemorrhage (AVH) is the most dangerous complication of portal hypertension as it is associated with significantly higher morbidity and mortality (4). The prognosis for cirrhotic patients is associated with liver disease severity (5). In the Child–Turcotte–Pugh (CTP) classification used to assess the severity of liver disease, higher scores significantly affect the survival time. The mortality rate after the first episode of bleeding ranges from 15% to 80% and is higher with Child's classes B and C (60%–80%) than with class A (15%) (6). Many factors have been studied and found to be associated with increased risk of mortality in patients with bleeding varices (7). When cirrhotic patients are admitted to an intensive care unit, the use of liver prognostic models, such as the Child–Pugh and MELD scores, were found to be poor predictors of outcome (8). However, in patients with acute variceal hemorrhage, it still remains unclear if these models could do well in determining risk stratification among this group of patients.

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The aim of the present study was to evaluate the outcome of patients who presented to our tertiary referral center with acute variceal bleeding and to determine which was the best prognostic model for the prediction of this outcome.

MATERIALS AND METHODS

This prospective study included all adult cirrhotic patients admitted to Sohag University Hospital, Tropical Medicine and Gastroenterology Department, with acute variceal bleeding (in the form of hematemesis, melena, and or bloody fluids, either as vomitus or drained by a nasogastric tube) from 1/2015 to 1/2016. The study was approved by the local ethics committee in Sohag School of Medicine.

Inclusion criteria

Cirrhotic patients presenting with bleeding varices (esophageal, fundal, or both).

Exclusion criteria

Patients diagnosed to have other causes of upper GIT bleeding (such as peptic ulcer disease, reflux esophagitis, erosions, antral vascular ectasia) previously or at endoscopy after admission.

A complete history, thorough physical examination, and monitoring of the vital signs of all patients were performed.

Liver function and serum creatinine were assessed on admission and serially during hospitalization. Complete blood count, serum electrolytes, arterial blood gases, and the number of units of blood received were recorded.

All the patients underwent upper endoscopy, and therapy was initiated according to the endoscopic findings. All endoscopic findings were described according to the Japanese research society for portal hypertension (9).

Urine analysis, chest X-ray, and ascitic fluid analysis were performed to detect the sources of infection.

All the patients underwent abdominal ultrasonography and were tested for the surface antigen of the hepatitis B virus (HBsAg) and hepatitis C virus antibodies (HCV Abs).

Prognostic scores were calculated from the data collected on the first day of admission. The Child–Turcotte–Pugh (CTP) score, the model for end-stage liver disease (MELD) score, the acute physiology and chronic health evaluation II (APACHE II) score, and the sepsis-associated organ failure assessment (SOFA) score were calculated according to the Pugh modification (10), United Network of Organ Sharing adjustments (11), Knaus et al. (12), and Vincent et al. (13) respectively.

The AIMS65 score was calculated according to the recently developed method by Saltzman et al. (14). This risk score predicts in-hospital mortality, length of stay, and costs for patients with acute UGIB. The new score was composed from the following parameters: level of albumin <3.0 g/dL (A), international normalized ratio (INR) >1.5 (I), mental status alteration (M), systolic blood pressure ≤90 mm Hg (S), and age >65 years (65). When more than two components of AIMS65 are present, the mortality risk is considered to be high.

Hypovolemic shock was defined as the presence of a decrease in systolic blood pressure to <90 mmHg; tachycardia >100 beats/minute; and a decreased central venous pressure or jugular venous pressure (15).

Rebleeding is the recurrent vomiting of blood, and/or melena with shock and/or a decrease of at least 2 g/d L in hemoglobin concentration after initial treatment, resuscitation, and indicated endoscopic therapy (16).

Transfusion requirements refer to the whole number of blood units and/or blood products needed to the admitted to the patient on day 1 of admission or after 5 days (17).

Blood transfusions are initiated when the hemoglobin count is <7 g/dL when there is no associated illness; our aim is to reach a level of ≥7 g/dL. However, in patients presenting with UGIB and suffering from coronary artery disease, we needed to reach a hemoglobin level ≥9 g/dL in order to avoid adverse events of significant anemia. Fresh frozen plasma (FFP) or platelets were transfused to patients with coagulopathy or uncontrolled bleeding and/or a severe thrombocytopenia (<50,000 per µL) (18).

An esophageal balloon tamponade was used when bleeding was rapid with hemodynamic instability before endoscopy.

Statistical analysis

The Chi-squared test or Fisher's exact test were used to analyze the data as appropriate. Univariate and multivariate analysis were performed using logistic regression models. The data was analysed using Statistical Package for Social Sciences (SPSS) version 16.0 for Windows (SPSS Inc.; Chicago, IL, USA).

RESULTS

A total of 120 patients (92 males) were admitted to our department over a period of 1 year due to acute upper GIT bleeding, with the bleeding attributed to gastroesophageal varices (GEV). Their demographic, clinical, laboratory, and endoscopic data are shown in Table 1.

The etiology of liver cirrhosis was HCV in 95 patients (79.17%), HBV in 5 patients (4.17%), infection with HBV and HCV in 2 patients (1.67%), and unknown in 18 patients (15%).

Sixteen patients had infections, including chest infection, spontaneous bacterial peritonitis (SBP), and bed sores. Hepatic encephalopathy was found in 28 patients, while rebleeding occurred in 8 patients, and portal vein thrombosis (PVT) in 7 patients from the 23 patients diagnosed with hepatocellular carcinoma (HCC).

Table 1. Comparison of the demographic, clinical, laboratory, and endoscopic findings in survivors and nonsurvivors

Parameter	Survivors 112 (93.33%)	Nonsurvivors 8 (6.67%)	p
Age Mean (SD)	56.94 (9.20)	64.75 (16.69)	0.03*
Male	85 (75.89%)	7 (87.50%)	0.68
Female	27 (24.11%)	1 (12.5%)	
Hypovolemic shock at admission	16 (14.29%)	3 (37.50%)	0.11
Melena	95 (84.82%)	8 (100%)	0.60
Presence of encephalopathy	20 (17.86%)	8 (100%)	<0.0001*
Need for balloon tamponade	57 (50.89%)	5 (62.50%)	0.72
Presence of infection	11 (9.82%)	5 (62.50%)	0.001*
Rebleeding	4 (3.57%)	4 (50.00%)	0.001*
No. of transfused blood units Mean (SD)	1.18 (1.57)	0.88 (0.83)	0.99
HCC	22 (19.64%)	1 (12.50%)	1.00
Etiology of cirrhosis			
HCV	89 (79.46%)	6 (75.00%)	
HBV	5 (4.46%)	0	0.77
HBV and HCV	2 (1.79%)	0	
Unknown	16 (14.29%)	2 (25.00%)	
Comorbidity			
No	73 (65.18%)	5 (62.50%)	
DM	32 (28.57%)	2 (25.00%)	
DM, HTN	2 (1.79%)	1 (12.50%)	0.43
DM, HTN, COPD	1 (0.89%)	0	
HTN	4 (3.57%)	0	
Albumin Mean (SD)	2.72 (0.55)	2.23 (0.25)	0.01*
Bilirubin Mean (SD)	1.85 (1.48)	4.94 (2.87)	0.001*
INR Mean (SD)	1.38 (0.21)	1.56 (0.14)	0.02*
Prothrombin time Mean (SD)	15.71 (2.39)	17.58 (1.24)	0.03*
Prothrombin concentration Mean (SD)	64.39 (12.81)	52.56 (5.52)	0.01*
Mean (SD)	1.25 (0.53)	1.79 (0.66)	0.02*
S. creatinine Mean (SD)	1.25 (0.53)	1.79 (0.66)	0.02*
Size of varices			
F1	9 (8.04%)	1 (12.50%)	
F2	68 (60.71%)	4 (50.00%)	
F3	26 (23.21%)	3 (37.50%)	
Esophagus F1-Gastric F1	2 (1.79%)	0	
Esophagus F1-Gastric F2	2 (1.79%)	0	0.98
Esophagus F2-Gastric F2	2 (1.79%)	0	
Esophagus F3-Gastric F1	2 (1.79%)	0	
Esophagus F3-Gastric F2	1 (0.89%)	0	
Endoscopic intervention			
Band ligation	99 (88.39%)	8 (100%)	
Histoacryl injection	9 (8.04%)	0	0.59
Both	4 (3.57%)	0	

*Statistically significant.
SD: standard deviation; HCV: hepatitis C virus; HBV: hepatitis B virus; DM: diabetes mellitus; HTN: hypertension; COPD: chronic obstructive pulmonary disease; INR: international normalized ratio; F: form (shape and size)

As regard the endoscopic findings**,** esophageal varices were found in 105 patients, while 6 had gastric varices and 9 had both gastric and esophageal varices. Also, 107 patients had band ligation, nine had histoacryl injection, and four patients had both band ligation and histoacryl injection.

In our study, eight patients (6.67%) died. The clinical characteristic of the studied population in survivors and nonsurvivors is shown in Table 1.

Here, it can be seen that there was a significant difference between survivors and nonsurvivors as regard the presence of encephalopathy (p<0.0001), infection (p=0.001), and rebleeding (p=0.001) (Table 1).

Upon studying the laboratory and endoscopic characteristics in survivors and nonsurvivors, we found that: The nonsurvivors had significantly lower albumin levels [2.23(0.25) vs. 2.72(0.55) mg/dL, p=0.01] and higher bilirubin [4.94(2.87) vs. 1.85(1.48) mg/dL, p=0.001], with higher INR [1.56(0.14) vs. 1.38(0.21), p=0.02] and a more prolonged prothrombin time (p=0.03) and decreased prothrombin concentration (p=0.01).

The site, size of varices, and type of endoscopic therapy did not influence mortality (Table 1).

Hospital mortality was significantly higher with Child C compared to survival rates (87.5% vs. 26.79%), p=0.001, while the MELD score>18 (p=0.0003), APACHE II score>14 (p=0.0006), SOFA score>7 (p=0.0001), and AIMS65 score>2 (p=0.0001) (Table 2).

Table 2. Comparison of the prognostic scores of the studied population in survivors and nonsurvivors

Parameter	Survivors	Nonsurvivors	p
Child's score			
A	29 (25.89%)	0	
B	53 (47.32%)	1 (12.50%)	0.001*
C	30 (26.79%)	7 (87.50%)q	
MELD score			
Mean (SD)	13.96 (4.38)	21.88 (4.99)	0.0003*
APACHE II score			
Mean (SD)	9.91 (2.63)	17.5 (5.37)	0.0006*
SOFA score			
Mean (SD)	4.84 (1.68%)	9 (1.41)	<0.0001*
AIMS65 score			
Mean (SD)	1.09 (0.89)	3.13 (0.35)	<0.0001*

*Statistically significant.
SD: standard deviation; MELD: model for end-stage liver disease; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; AIMS65: albumin, INR, Mental state, systolic blood pressure, age>65

By multivariate analysis we found that advanced age, presence of encephalopathy, rebleeding, and higher serum bilirubin were all independent factors for the prediction of hospital mortality (Table 3).

We analyzed the prognostic risk stratification models for predicting hospital mortality (Table 4); The AIMS65 score and SOFA score were found to have the largest area under the receiver operator curve (AUROC), followed by the MELD score and APACHEII score, then the CTP score, all of which achieved very good performance (AUROC>0.8).

A pair-wise comparison of the AUROC showed no significant difference between AIMS65, MELD, SOFA, and APACHEII scores ($p<0.05$); however, the AIMS56 score was superior to the best AUROC score ($p>0.05$) (Table 4, Figure 1).

After evaluation of the performance of each model, the AIMS65 score showed the best performance in the prediction of mortality in patients with variceal bleeding and had the higher sensitivity (100%) and negative predictive value (100%), but the APACH II score had the highest specificity (98.2%), and positive predictive value (75.0%) (Table 5).

DISCUSSION

Gastrointestinal bleeding is a major complication of liver cirrhosis and portal hypertension and is responsible for high morbidity and mortality (19).

Table 3. Final multivariate model of the risk factors for in-hospital mortality

Parameter	Odds ratio (95% confidence interval)	p
Age	1.14 (1.01–1.28)	0.03*
Presence of infection	18.97 (1.41–254.85)	0.03*
Rebleeding	23.40 (1.87–293.25)	0.02*
S. bilirubin	2.15 (1.29–3.63)	0.003*
Hepatic encephalopathy	Cannot be calculated as it is present in all deaths	

*Statistically significant.

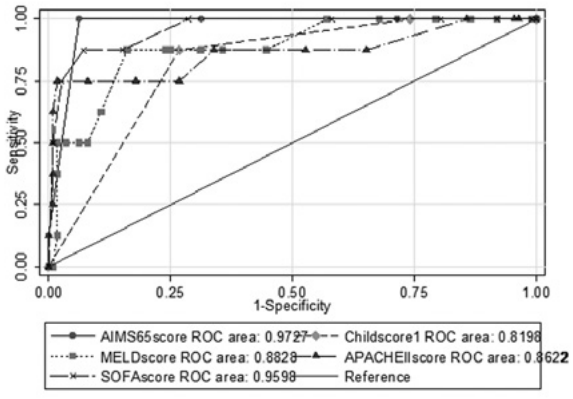

Figure 1. Comparison between the receiver operating curves (ROC) of different scores in the prediction of mortality in patients admitted to intensive care unit with AVH

In recent years, improvements in patient management, including the use of terlipressin, prophylactic antibiotics, endoscopic intervention modalities, and TIPSS, have resulted in an improved prognosis and decrease in in-hospital mortality (20-22).

In this study, we studied the factors associated with mortality in patients admitted to our hospital with AVH and liver cirrhosis and herein report the outcomes of those patients. Our in-hospital mortality (HM) rate of 7.67% is consistent with the experience from other centers, although this may be attributed to the relatively small sample size and the inclusion only of patients who had an endoscopic intervention in our study. In 1998, Pauwels et al. (23) showed that in-hospital mortality in cirrhotic patients presenting with acute variceal bleeding had decreased by 50% over the preceding 15 years. Chalasani et al. (24), in a large study over 3 years long, reported that in-hospital mortality was 14.2%. In another large series involving 403 cirrhotic patients and variceal bleeding, Del Olmo et al. (25) reported a mortality rate of 7.4%.

In our study, older age was independently associated with hospital deaths following AVH; this was also previously reported by Das et al. (8) and Du Cheyron et al. (26).

Our results revealed that increased serum bilirubin, the presence of hepatic encephalopathy, and rebleeding after endoscopy were independent predictors of mortality. These results are in line with Afessa and Kubilis (27) and Chojkier et al. (28).

Magliocchetti et al. (29) further showed that the Child–Pugh score, albumin level, encephalopathy, and GEV hemorrhage were correlated with survival.

In our study, the type of endoscopic therapy (either band ligation, histoacryl injection, or both) and the etiology of liver cirrhosis did not influence mortality, and this correlates with the findings of Hassanien et al. (30) However, the presence of HCC and PVT were found also not to influence mortality, but this does not correlate with the present study.

In a large retrospective study of 403 cirrhotics with variceal bleeding, renal failure with raised serum creatinine, post-gastroscopy rebleeding, and the presence of HCC and hepatic encephalopathy were found to be independent predictors of mortality (31). The occurrence of rebleeding was significantly associated with mortality, a factor also reported in the series of Bambha et al. (7).

Portal vein thrombosis has no statistically significant difference between survivors and nonsurvivors in our study. These findings are in accordance with those of Hassanien et al. (30), although tumor infiltration to the portal vein seemed to increase the portal pressure and may increase the risk of uncontrolled bleeding.

The increased requirement for blood /blood product transfusion was significantly associated with mortality, this finding cor-

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Table 4. Comparison of the receiver operator characteristics of hospital mortality for the various prognostic models measured

Variable	AUROC	95% CI	p	AUROC Difference	S.E.	95% CI	p
AIMS65 score	0.97	0.93–0.99	<0.0001*				
SOFA score	0.96	0.91–0.99	<0.0001*	0.01	0.03	–0.04–0.07	0.65
MELD score	0.88	0.81–0.93	<0.0001*	0.09	0.06	–0.03–0.21	0.14
APACHE II score	0.86	0.79–0.92	0.0002*	0.11	0.10	–0.08–0.30	0.25
Child score	0.82	0.74–0.88	<0.0001*	0.15	0.05	0.05–0.25	0.003*

*Statistically significant.
AUROC: area under the receiver operator curve; AIMS65: albumin, INR, Mental state, systolic blood pressure, age>65; SOFA: sequential organ failure assessment; MELD: model for end-stage liver disease; APACHE: acute physiology and chronic health evaluation; S.E.: standard error; CI: confidence interval

Table 5. Performance of the scoring system in the prediction of mortality in patients with acute variceal bleeding

Variable	Youden Index	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
AIMS65 score	0.94	>2	100 (63.1—100)	93.8 (87.5–97.5)	53.3 (26.6:78.7)	100 (96.5–100)
SOFA score	0.80	>7	87.5 (47.3–99.7)	92.9 (86.4–96.9)	46.7 (20.5:74.3%)	99.0 (94.8–100)
MELD score	0.71	>18	87.5 (47.3–99.7)	83.9 (75.8–90.2)	28.0 (12.1:49.4)	98.9 (94.3–100)
APACHE II score	0.73	>14	75.0 (34.9–96.8)	98.2 (93.7–99.8)	75.0 (34.9:96.8)	98.2 (93.7–99.8)
Child score	0.61	>2	87.5 (47.3–99.7)	73.2 (64.0–81.1)	18.9 (8.0:35.2)	98.8 (93.4–100)

AIMS65: area under the receiver operator curve; AIMS65: albumin, INR, Mental state, systolic blood pressure, age>65; SOFA: sequential organ failure assessment; MELD: model for end-stage liver disease; APACHE: acute physiology and chronic health evaluation; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value

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relates with that of Al-Freah et al. (17), who reported that there was a 7% rise in hospital mortality with every unit increase in Packed RBCs transfusion on the day of admission. However, increased requirements for blood transfusion were reported to be a poor prognostic indicator with other researchers, which is consistent with our finding (4,7).

We found that the AIMS65 score is the best for predicting mortality among the mentioned five scores, as it has the highest area under the curve. It was previously reported to be a good predictor of the outcome of patients with acute upper gastrointestinal hemorrhage by Nakamura et al. (32). Moreover, Hyett et al. (33) found that the AIMS65 score was better than the Glasgow-Blatchford score for outcome prediction in those patients. Also, we found that the SOFA score is superior to the MELD score, APACHEII score, and Child's score in the prediction of mortality with the Child's (CP) score having the least area under the curve.

Cholongitas et al. (34) also reported that the SOFA score had a better predictive value compared to the APACHE II and CP scores. The Child-Pugh score had the worst performance, possibly due to it not including the kidney functions in its parameters (34). However, this does not correlate with the findings of Afessa and Kubilis (27), who compared the prognostic performances of APACHE II and the Child–Pugh score in 111 cirrhotic patients hospitalized for upper GI bleeding, where they did not find significant differences between the two scoring systems. In a single center cohort of ICU-admitted patients presenting with acute upper gastrointestinal bleeding from varices, Al-Freah et al. (17) found that MELD had the best performance as the best liver prognostic model but did not significantly differ from other ICU scoring models as predictors of outcome.

There are some limitations to this study including: first, it was performed in a single institution; second, it involved a relatively small sample size; third, the calculation of mortality only referred to during hospital admission, and further follow-up of the patients for 30 and 60 days is required. Finally, we only included patients who had an endoscopic intervention in our study.

In conclusion, older age, the presence of sepsis, serum bilirubin levels, the presence of hepatic encephalopathy, and rebleeding after gastroscopy were independent predictors of mortality in our patients with liver cirrhosis and variceal bleeding. The AIMS65 score was a simple and applicable scoring system to independently predict mortality in patients with variceal bleeding and achieved high performance.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sohag School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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