Risk scoring systems to predict in-hospital mortality in patients with acute variceal bleeding due to hepatitis C virus-induced liver cirrhosis

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Abstract

This study was designed to validate and to compare accuracy of the prognostic scores; mainly Child Turcotte Pugh (CTP), creatinine-modified Child Turcotte Pugh (CTP-Cr), model for end-stage liver disease (MELD), albumin bilirubin score (ALBI), and AIMS65, for the predicting clinical outcomes in cirrhotic Egyptian patients presenting with acute variceal bleeding (AVB). Retrospective single center study involving 725 patients presenting with AVB due to liver cirrhosis and HCV infection either alone or mixed with HBV infection. In hospital mortality prognostic scores were calculated; mainly CTP, modified CTP-Cr, MELD, ALBI, AIMS65. The endpoint is either patient improvement or death. 725 patients were included over 1-year period, 547 (75%) survived and 178 (25%) died. Patients presented with hematemesis (515/71%), melena (120/16.5%) or hematemesis and melena (90/12.5%). Those with hematemesis for the first time were 241 (33%) and recurrent attacks were 484 (66.8%). The non-survivors had significantly more incidence of shock on presentation, more blood transfused units, history of NSAIDS intake, more ICU admission days and were more likely to be Childs C. Child, modified CTP-Cr, MELD, ALBI and AIMS65 scoring systems showed significant difference between survivors and non-survivors. Liver specific scores (Child, MELD) and gastrointestinal bleeding scoring systems (ALBI, AIMS65) are useful in predicting clinical outcomes of AVB in cirrhotic patients. CTP-Cr score had the highest prognostic capability of in hospital mortality. Presence of active bleeding at time of endoscopy, more complications, old age, shock and higher CPT-Cr score are additional independent predictors of in hospital mortality.

Introduction

Acute variceal bleeding (AVB) is one of the most dreadful complications of liver cirrhosis that occurs in 20-50% of patients. Despite the improvements in prognosis in the past decade, the mortality of patients with AVB remains high (24%) in cirrhotic patients.1 In Egypt, the commonest cause of upper GIT bleeding is bleeding esophageal varices due to liver cirrhosis either biliarhzal and/or hepatitis C; (51.6%).2,3

Estimation of prognosis is an essential element of managing patients with cirrhosis admitted to a hospital. Patients with cirrhosis and GI bleeding are classified as stage IV in Baveno IV consensus; with 1-year mortality risk of 57%.4 Moreover, half of these patients will die within the 6 weeks after their admission for GI bleeding.5 Although several risk-stratification tools have been formulated,6-7 accurate stratification model to estimate in-hospital mortality (IHm), in cirrhodics admitted with acute upper GI bleeding is not currently available.

Many prognostic models for liver disease have been developed.8,9 When cirrhotic patients are admitted to an ICU, the use of liver prognostic models, such as the Child Turcotte Pugh (CTP) and/or model for end-stage liver disease (MELD) scores, were found to be poor predictors of outcome. However, in patients with AVB, it still remains unclear if these models could do well in determining risk stratification among this group of patients.10

Modified CTP score was achieved by including creatinine into the score. The first analysis of creatinine-modified Child Turcotte Pugh (CTP-Cr) score was performed in 2003 by Angemay.11 Recent studies quite clearly confirm that creatinine modified CTP score contributed to improvement of the initial CTP score in assessment of survival.12

Albumin-bilirubin (ALBI) score is initially created to assess the severity of liver dysfunction in Japanese patients with hepatocellular carcinoma (HCC).13 It is superior to Child-Pugh and MELD scores for predicting the occurrence of hepatic events in patients with primary biliary cholangitis.14 The prognostic performance of the ALBI score was comparable with that of the CTP and MELD scores for predicting the IHM of AUGIB in liver cirrhosis.15

The AIMS65 score was retrospectively validated in 32,507 patients.16 It was developed to predict IHM in acute upper GI bleeding. These score uses only 5 elements that contribute equally to the score for ease of use and calculation. When more than two components of AIMS65 are present, the mortality risk is considered to be high.

The aim of this study is to validate and compare the accuracy of prognostic scores; mainly CTP, CTP-Cr, MELD, ALBI, and AIMS65, in predicting clinical outcomes in cirrhotic Egyptian patients presenting with AVB.

Materials and Methods

This is a retrospective cohort study that includes all adult cirrhotic patients presenting with AVB (hematemesis, melena and/or bloody fluids either as vomitus or drained by nasogastric tube) admitted to the ICU of Theodor Bilharz Research Institute Hospital over one-year period from 1/2016 to 1/2017. The ethical approval was obtained from the Ethical Committee Board of our hospital. Due to the retrospective nature of our study, the written informed consents were exempted.
Inclusion criteria

All cirrhotic patients presented by bleeding varices (esophageal, fundal or both).

Exclusion criteria

Patients with 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 vital signs, to all patients were recorded. Liver function and serum creatinine were assessed on admission and serially during hospitalization. Complete blood count, serum electrolytes, arterial blood gases, and number of units of blood received were recorded. All patients underwent abdominal ultrasonography and testing for HBsAg and anti-HCV.

All patients underwent upper endoscopy and therapy was initiated according to the endoscopic findings, all the endoscopic findings were described according to the Japanese research society for portal hypertension.17

All prognostic scores were calculated from the data collected on the 1st day of admission namely CTP, MELD, iMELD, United Kingdom Model for End Stage Liver Disease (UKELD), Updated MELD score, CTP-Cr, AIMS65 and ALBI scores.

Calculation of scores

1-CTP score (calculated according to the Pugh modification):8

2-ALBI score = \((\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)\).

In this equation, the unit of bilirubin is umol/L and that of albumin is g/L.

ALBI was classified into three grades: grade 1: ≤2.6; grade 2: >2.6, ≤1.39; grade 3: >1.39.13

3-MELD score = \(9.57 \times \ln \left[\text{creatinine (mg/dL)} + 3.78 \times \ln \left[\text{bilirubin (mg/dL)} + 11.2 \times \ln \left(\text{INR} + 6.43)\right]\right]\).

4-iMELD score = \{MELD + age (in years) \times 0.3\} – \([0.7 \times \text{Na (mmol/L)} + 100]\).18

5-UKELD score = \{5 \times [1.5 \times \ln (INR) + 0.3 \times \ln (\text{creatinine (mmol/L)}) + 0.6 \times \ln [\text{bilirubin (umol/L)} – 13 \times \ln (\text{Na (mmol/L)} + 70)]\}.19

6-Updated MELD score = \{\ln (1 + \text{creatinine (mg/dL)} + 0.94 \times \ln (1 + \text{bilirubin (mg/dL)}) + 1.66 \times \ln (1 + \text{INR})\}.20

7-AIMS65 score calculated according to Saltzman et al.16 i) Alb (mg/dL): < 3.0 (1 point); ii) INR > 1.5 s (1 point); iii) HE: < 14 (1 point); iv) Shock: < 90 (1 point); v) Age > 65 years (1 point).

8-CTP-Cr scores (numerical values 5–19) includes three categories as follow: 0 points are added to patients whose serum creat-
nine level does not exceed 1.3 mg/dL (114.92 μmol/L); 2 points are added to patients whose serum creatinine level is between 1.3–1.8 mg/dL (114.92–159.12 μmol/L); 4 points are added to patients whose serum creatinine level exceeds 1.8 mg/dL (159.12 μmol/L).

Statistical analysis
All statistical analyses were performed using the Med-Calc software version (11.4.2.0). Continuous data were expressed as the mean±standard error (SE). Areas under the receiving-operator characteristics curves (AUC) with 95% confidence intervals (CIs) were calculated and compared among using the DeLong tests. Then, sensitivity, specificity, positive predictive value, and negative predictive value with 95% CIs were reported. Subgroup analyses were performed in patients with only hepatitis B or C virus-related liver cirrhosis and in those treated with endoscopic therapy for AUGIB. P<0.05 was considered statistically significant.

The normality of data was tested by Kolmogorov-Smirnov test. For comparing two sets of data, in case of normal data distribution we used the t-test and if data distribution was not normal, the Mann-Whitney’s U-tests; between the groups were compared by using the chi-square (χ2) and test of proportion.

Results
A total of 725 patients (500 males and 225 females) were admitted to our department over a period of 1 year due to acute variceal bleeding. Their demographic and clinical data are shown in Table 1. Our endpoint is either patient improvement or transfer to the ward or patient death. 547 (75%) survived and 178 (25%) died. The etiology of liver cirrhosis was HCV in all patients (100%), however, 23 (3.2%) had in addition HBV infection. Survivors and those who died were similarly matched with regard to gender, age, ethnicity and etiology of cirrhosis. 515 (71%) patients presented with complications (>4D), age (>65Y), presence of active bleeding at endoscopy (Yes), shock (Yes), days (>2d), and CPT-Cr (>2) (Table 8).

Table 4. Complication of cirrhosis in survivors and non-survivors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivor</th>
<th>Non survivor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>338 (61.79%)</td>
<td>183 (91.57%)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>142 (25.90%)</td>
<td>99 (55.62%)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP</td>
<td>25 (4.5%)</td>
<td>37 (20.79%)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HRS</td>
<td>51 (9.32%)</td>
<td>65 (36.52%)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (n,%)</td>
<td>28 (5.12%)</td>
<td>61 (34.26%)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PVT</td>
<td>27 (4.94%)</td>
<td>15 (8.43%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**P<0.01 significant increase than survivor; *P<0.05 significant increase.

Table 5. Endoscopic finding of survivors and non-survivors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivor</th>
<th>Non survivor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIV</td>
<td>163 (29.80%)</td>
<td>49 (27.53%)</td>
<td>0.840</td>
</tr>
<tr>
<td>GIII</td>
<td>135 (24.68%)</td>
<td>34 (19.10%)</td>
<td>0.613</td>
</tr>
<tr>
<td>GII</td>
<td>106 (19.38%)</td>
<td>29 (16.29%)</td>
<td>0.412</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy</td>
<td>88 (16.09%)</td>
<td>77 (43.26%)**</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastric Ulcer (GU)</td>
<td>205 (37.48%)*</td>
<td>29 (16.29%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Active bleeding at time of endoscopy</td>
<td>281 (38.6%)</td>
<td>185 (14.5%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**P<0.01 significant increase, *P<0.05 significant decrease than survivors.

Table 6. Different scoring systems in survivors and non-survivors.

<table>
<thead>
<tr>
<th>Model</th>
<th>Survivor N=547</th>
<th>Non survivor N=178</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score</td>
<td>9.40±0.11</td>
<td>10.19±0.22***</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPT-Cr</td>
<td>10.42±0.13</td>
<td>11.10±0.24***</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MELD score</td>
<td>16.47±0.38</td>
<td>19.24±0.78**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>iMELD score</td>
<td>42.75±0.77</td>
<td>46.47±1.62**</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UDLE score</td>
<td>10.37±0.26</td>
<td>10.56±0.54</td>
<td>&gt;0.29</td>
</tr>
<tr>
<td>Updated MELD score</td>
<td>2.73±0.06</td>
<td>2.64±0.09</td>
<td>&gt;0.36</td>
</tr>
<tr>
<td>AIMS65</td>
<td>2.82±1.46</td>
<td>3.20±0.79</td>
<td>&gt;0.82</td>
</tr>
<tr>
<td>ALBI score</td>
<td>0.04±0.01</td>
<td>0.05±0.02</td>
<td>&gt;0.65</td>
</tr>
</tbody>
</table>

Child-Pugh, CPT-Cr, MELD, iMELD, Updated MELD, AIMS65, ALBI: Model for end-stage liver disease; ALBI: albumin-bilirubin; iMELD: Integrated score; UDLE: United Kingdom model for end stage liver disease. **P<0.01 very highly significant increase than survivor; *P<0.05 highly significant increase than survivor; *P<0.05 considered significant increase than survivor.
Discussion

Risk classifications that could help the physician to predict the risk of death a priori and to prioritize clinical care for high-risk patients are underexplored. Gastrointestinal bleeding scoring systems are useful for predicting clinical outcomes of AVB.21

The mean age in our study was 57.6 year and 58.1 year in the survivors and non-survivors group respectively. 75% were male and 25% were female in the survivors group while 49% were male and 51% were female in the non-survivors group. Taha et al. in 20163 reported the mean age in the low risk group was 41.07 years, 93.6% of them were <50 years, and 6.4% was >50 years, while in the high risk group the mean age was 49.1 years, 60% of them was <50 years, and 40% was >50 years. According to gender distribution in both groups, 63.1%, 42.8% were males and 36.9%, 57.2% were females in the low and high-risk groups respectively. In the study by Özlem et al.,22 the mean age was 58 years. 30.6% of the patients were females and 69.4% were males. Given, the distribution of the subjects according to their age groups, 51.9% of the patients were <60 years old, 41.3% were 60-79 years old and 6.9% were ≥80 years old. Mohammad and Morsy in 2016 (10) reported that older age was independently associated with hospital deaths.

In our study, mean value of hemoglobin concentration was 9.3 gm/dl and 8.8 gm/dl in survivors and non-survivors respectively with no statistical significance. Taha et al. in 20166 reported significantly decreased hemoglobin level in the high-risk group in comparison with the low risk group (8.4gm/dl, 13.2gm/dl respectively). This comparison with the low risk group, the independent predictor of adverse outcome was significantly associated with hospital deaths.

We have 25% IHM rate. In 1986, Chojkier and colleagues25 reported a bleeding-related mortality rate of 35%, whereas Afessa and Kubilis in the year 200024 reported IHM rate of 21% in bleeding cirrhosis. More recently, Chalasani et al.26 in a large study over 3 years reported the IHM to be 14.2%. Pauwels et al.27 showed that IHM in cirrhotic patients admitted with variceal bleeding has decreased by 50% over the past 15 years. This in contrary to other studies where the IHM rate 8.7% is consistent with the experience from other centers.28 Similar decline in the IHM rate has been reported in other studies.29 The variation of the IHM for cirrhotic patients with variceal hemorrhage is likely related to the degree of underlying liver dysfunction, the use of life support systems such as blood, vasoactive agents, and endotracheal intubation, and the subsequent development of clinical complications including renal insufficiency, cardiopulmonary complications, and infection. In our study, the high mortality rate could be explained as most of our patients had advanced liver disease as indicated by Child C grade; 379 (52%) and 250 (34.5%) patients were Child B.30

Although IHM in cirrhotic patients with GI bleeding is declining,31,32 it is still associated with significant morbidity and mortality.26,28 More than half of patients with GI bleeding have a comorbid disease mainly hypertension, diabetes mellitus, coronary artery diseases, and malignancies.31 Clinical guidelines published in 2008 in Scotland cited a mortality rate of 4% in GI bleeding patients without comorbidities, with the mortality rate increasing 1.8 times in cases with heart failure, 3.8 times in cases with malignancy, and 2.0 times in cases with liver disease.32 According to the NIH 2012 guidelines, patients with GI bleeding who also have chronic diseases are at a higher risk of death;33 Patients with DM and CAD, however, have significantly higher rates of ICU admission. Acute bleeding causes hemodynamic instability, and this condition worsens in the condition of CAD, particularly in patients with heart failure. Another factor underlying the higher ICU admission rate of patients with CAD was anticoagulant, antithrombotic and antplatelet therapy.34

Our patients were found to have DM in 243 (33.5 %) patients; 153 (28%) survivors and 90 (50.5%) non-survivors with significantly high value. DM is associated with gastroesophageal variceal bleeding in cirrhotic and increased risk of IHM. The risk of bleeding increases in patients with poor glycemic control.35 The higher mortality rate in patients with diabetes is not only due to the complications of DM but also to an increased risk of hepatocellular failure in long-term follow up.36 Hyperglycemia induces splanchnic hyperemia, increases portal pressure and may increase the risk of variceal bleeding.37 DM, active bleeding at endoscopy and bilirubin >3 mg/dL are bad prognostic factors for initial control of variceal bleeding, and recurrent bleeding in patients with cirrhosis.38

In a cohort study of patients with chronic hepatitis C, new-onset diabetes subsequently were found to have an increased risk of developing cirrhosis, or decompensation in those with established cirrhosis.39 HCV is associated with extra-hepatic diseases, including various types of glomerulonephritis. Soma et al.40 indicated that HCV infection leads to a rapid decline in the renal function of patients with diabetic nephropathy.

Uremic bleeding is a well-recognized complication in patients with renal failure, and it affects platelet aggregation and/or the coagulation cascade.41 In patients with chronic kidney disease, GI bleeding is also a common complication.42 Anand et al.43

Table 7. Predictive value of different scoring models.

<table>
<thead>
<tr>
<th>Model</th>
<th>AUROC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score</td>
<td>0.810±0.017</td>
<td>90.48</td>
<td>67.68</td>
<td>0.777-0.843</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPT-Cr</td>
<td>0.826±0.018</td>
<td>90.68</td>
<td>70.36</td>
<td>0.791-0.802</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MELD score</td>
<td>0.692±0.023</td>
<td>88.31</td>
<td>67.68</td>
<td>0.648-0.737</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Updated MELD score</td>
<td>0.558±0.025</td>
<td>70.36</td>
<td>74.59</td>
<td>0.509-0.608</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>UKELD score</td>
<td>0.479±0.025</td>
<td>70.92</td>
<td>69.90</td>
<td>0.431-0.527</td>
<td>0.386</td>
</tr>
<tr>
<td>ALBI score</td>
<td>0.527±0.04</td>
<td>73.21</td>
<td>65.91</td>
<td>0.449-0.605</td>
<td>0.513</td>
</tr>
<tr>
<td>AIMS65</td>
<td>0.525±0.024</td>
<td>63.97</td>
<td>68.75</td>
<td>0.478-0.572</td>
<td>0.309</td>
</tr>
<tr>
<td>iMELD score</td>
<td>0.539±0.03</td>
<td>71.20</td>
<td>67.37</td>
<td>0.466-0.612</td>
<td>0.338</td>
</tr>
</tbody>
</table>

[pag 16] [Gastroenterology Insights 2018; 9:7629]
showed that elevated serum creatinine levels are associated with increased rates of mortality and re-bleeding.

We check the performance of 8 prognostic scoring systems in cirrhotic patients with AVB. All of them showed good prognostic capability and can discriminate between survivors and non-survivors with AUC above 0.82. CTP-Cr score had the highest prognostic capability followed by CTP scores. Our results are in contrary with, Al-Freah et al.44 who 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. Peng et al. in 201545 found that both scoring systems; CTP and MELD, had good discriminative abilities for the IHM of acute UGIB in liver cirrhosis, and that the AUROC for MELD score might be slightly superior to that for Child-Pugh score, but with no statistically significant difference.

The significance of MELD score in predicting short-term survival is more superior to CTP score both in short and long-term (12-month and 36-month). The highest difference in the compared scores (CTP and MELD) is present in 6-week and 3-month periods of follow-up where MELD score is dominant. Although the difference is still on the side of MELD score, it is lower in 12-month and 36-month periods of follow-up.46

Patients with bleeding from esophageal varices who have CTP score and CTP-cr I score higher than 10.5 and CTP-cr II score higher than 11.5, have statistically significantly higher risk from mortality within one-month follow-up compared to patients with bleeding from esophageal varices who have lower numerical values of scores of the CTP group.12

Contrary to our results, Nakamura et al. found that the AIMS65 score is the best for predicting mortality among the mentioned five scores. It was previously reported to be a good predictor of the outcome of patients with acute upper gastrointestinal hemorrhage.47 Moreover, Hyett et al.48 found that the AIMS65 score was better than the Glasgow-Blatchford score for outcome prediction in those patients. Motola-Kuba et al. in 201621 found no differences in the accuracy between MELD and AIMS65 for predicting IHM, both of them with good calibration.

The more incidence of the complications; namely, SBP, hepatic encephalopathy, HCC, PVT, HR syndrome, the more worse the prognosis. This is in agreement with previous report.49

Our study has limitations. It was a retrospective design, the accuracy is just enough only to predict IHM, more data is necessary for other outcomes. Being a single-center observational study, confounding factors were relatively difficult to avoid. With the limitation of sample size and the relatively short follow-up period, additional well designed prospective studies with larger sample sizes are required. Our study was performed at a large urban hospital that may not be representative of the demographics of the other groups, and thus could potentially limit the generalizability of the study. Our study was also performed at a single-site, and thus biases in the severity of clinical disease, or the nature of clinical practice at this institution could be present. However, we suspect this to be unlikely, as outcomes were consistent with other published studies.

Conclusions

Liver specific scores (Child, MELD) and gastrointestinal bleeding scoring systems (ALBI, AIMS65) are useful in predicting clinical outcomes of AVB in cirrhotic patients. CTP-Cr score had the highest prognostic capability of in hospital mortality. Presence of active bleeding at time of endoscopy, more complications, old age, shock and higher CTP-Cr score are additional independent predictors of in hospital mortality.

Table 8. Logistic regression analysis of factors effecting mortality.

<table>
<thead>
<tr>
<th>Variable*</th>
<th>β**</th>
<th>OR</th>
<th>CI (OR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.429</td>
<td>1.536</td>
<td>1.270-1.857</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Complications</td>
<td>0.936</td>
<td>2.551</td>
<td>1.532-4.246</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Shock</td>
<td>-2.273</td>
<td>0.103</td>
<td>0.067-0.158</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Days</td>
<td>-0.163</td>
<td>0.849</td>
<td>0.736-0.980</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CPT-Cr</td>
<td>2.039</td>
<td>0.848</td>
<td>0.734-0.981</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.512</td>
<td>1.619</td>
<td>1.101-2.607</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Factors giving the best model are complications (>4D), age (>65Y), presence of active bleeding at endoscopy, shock, days (>2d), and CPT-Cr (>2).

References


