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ORIGINAL ARTICLE

Prediction of outcomes of acute variceal hemorrhage in cirrhotic patients using platelet albumin bilirubin (PALBI) score.

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ABSTRACT… Objective: To determine the predictive ability of "platelet albumin bilirubin (PALBI)" scores in assessing outcomes among acute variceal hemorrhage (AVH) patients. **Study Design:** Cross-sectional study. **Setting:** Department of Gastroenterology, Liaquat National Hospital. **Period:** September 2022 to September 2023. **Methods:** Cirrhotic patients with upper gastrointestinal bleed of either gender of age at least 18 years were included. Patients with malignancies and unwilling to participate were excluded. Patients were enlisted with their written informed consent. Data was analyzed using IBM-SPSS version 26. **Results:** Total 300 patients were enrolled into the study with mean age of 59.9 ± 10.4 years and majority were males (73.7%). According to endoscopic findings, small, medium and large esophageal varices (EV) were seen in 9%, 28% and 63% patients respectively. Rebleeding was seen in 27.7%. On multivariable model, none of the score including "Child-Turcotte-Pugh (CTP)" score, "Model of End-stage Liver Disease (MELD)" score, "albumin-bilirubin (ALBI)" score and PALBI score were found to be associated with rebleeding. During the study in-hospital mortalities were seen in 10.3% cases. In multivariable regression analysis, when adjusted for confounders, prediction score MELD and PALBI were found to be linked with in-hospital mortality. **Conclusion:** The present study found that PALBI predicting in-hospital mortality even after adjusting other confounders. However, PALBI was not a promising marker for prediction of re-bleeding.

Key words: Cirrhosis, Child-Pugh Classification, MELD Score, PALBI Score, Variceal Bleeding, Variceal Hemorrhage.

INTRODUCTION

One of the most challenging complication in case of liver cirrhosis with portal hypertension is acute variceal hemorrhage (AVH) with prevalence of 20-50% and contributes higher burden of morbidity as well as mortality. AVH stands as leading death cause in cirrhotic populace. The mortality associated with AVH remains higher (24%) regardless of betterment in prognosis.[1] Majority of cirrhotic patients some at some point in time develops varices; however nearly one-third of them exhibit bleeding.

Estimated 30-50% mortalities occur within initial six weeks in liver cirrhosis patients because of AVH episode.[2] Incidence of AVH episodes sharply increase rebleeding and death rate in initial six weeks which later on stabilize.[3] Rebleeding rate is ranges from 24-30% in first six weeks.[4] The ideal practices for managing AVH currently includes rapid vasoactive medication administration, prophylactic antibiotic administration, and endoscopic band ligation therapy or sclerotherapy for gastric varices.[5]

The most significant algorithms for determining the likelihood of upper gastrointestinal bleeding survival and evaluating the degree of liver dysfunction are the "Model of End-stage Liver Disease (MELD)" scores and "Child-Turcotte-Pugh (CTP)". Researchers also forecast the patient's chance of mortality and rebleeding while still in the hospital.[6] Among cases of chronic liver disease awaiting transplantation of hepatic, MELD score is reported to be a more accurate indicator of hepatic illness severity than the CTP score. Additionally, the MELD score reliably predicts the patients' three-month mortality.[7]

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The subjective evaluation of encephalopathy and ascites volume are the boundaries in CTP score in evaluating hepatic functioning in individuals with upper "gastrointestinal tract (GIT)" haemorrhage. According to a recent study, mortality in cirrhotic cases with AVH can be accurately predicted by a model of MELD that only takes into account objective characteristics. MELD scores greater than 19 indicated a death rate greater than 20%, while scores less than 11 indicated a mortality rate less than 5%.[1]

"The albumin-bilirubin (ALBI)" score was proposed which based on albumin and bilirubin and does not include CTP class. The results are given as three classes at distinctive thresholds.[8] In order to account for portal hypertension, Roayaie et al. suggested include the platelet count into the ALBI score.[3] In the past, the PLABI score has been utilized to forecast the prognosis following a variceal haemorrhage.[8] As per our discerment, no local evidence is published yet on the significance of PLABI score in Pakistani settings. Therefore, we planned the present study to determine the predictive ability of PALBI scores in assessing outcomes among AVH patients.

METHODS

This cross-sectional study was performed in Gastroenterology Department during September 2022 to September 2023 after taking approval from hospital ethics committee (App# 0817-2022LNH-ERC). Cirrhotic patients with upper gastrointestinal bleed of either gender of age at least 18 years were included. Patients with malignancies and unwilling to participate were excluded. Patients were enlisted with their written informed consent.

A previously conducted study reported that frequency of in-hospital mortality and re-bleeding was 21.9% and 3.12% respectively.[8] Using 95% confidence interval and 5% precision, a sample of 263 is required for estimating in-hospital mortality whereas with the same confidence interval limit but a precision of 2.3%, a sample of 220 patients is required for re-bleeding. Hence, a larger sample of 263 was enrolled into the study. Sample size estimation was performed online available calculator Open-Epi. Patients were enlisted through non-probability consecutive sampling technique.

Diagnosis of was acute upper gastrointestinal bleeding was establish with occurrence one or more episodes of bloody vomiting or coffee ground vomiting, melena and presence of blood in nasogastric tube. On incidence of active bleeding from gastric varix or esophageal varix, the diagnosis of variceal hemorrhage was made. The study outcomes are inhospital mortality and rebleeding. Re-bleeding was considered with re-onset of melena or hematemesis after initital episode of bleeding which is controlled by successful endoscopic therapy that occurred after 24 hours or more from point of 24 hours vital signs and hemoglobin.[9]

Laboratory investigations performed at the time of admission were used to compute MELD, CTP class, ALBI and PALBI scores. MELD score was computed as: $0.378\times$ log (bilirubin) $+0.957\times$ loge (creatinine) $+$ 1.1 $20\times$loge (INR) $+$ 0.643(11) n.[10] CTP scores was based on "international normalized ratio (INR)", albumin, bilirubin, encephalopathy and ascites presence. CTP was classified as A, B, C for score of 5-6, 7-9 and 10 or higher respectively.[11] Score for ALBI was computed as: -0.085 albumin (g/L) $+0.66$ $\log_{10}$ bilirubin (µmol/L).[12] Equation for PALBI score is: $2(0.37\times\log10$ bilirubin $2.02)\log_{10}$ bilirubin-0.04albumin-$3.48\log_{10}$ platelets $+2.02$(Log10 platelets) where bilirubin, albumin and platelet counts were expressed in µmol/L, g/L, and 1000/µL respectively.[13]

Data was analyzed using SPSS version 26. Frequencies and percentages were computed for non-numerical variables. Numerical variables were conveyed as mean $\pm$ standard deviation. "Receiver operating characteristic (ROC)" curve was plotted and "area under the curve (AUC)" was computed to find out predictive ability of PALBI and other scores in forecasting rebleeding and in-hospital mortality.[14] Binary logistic regression was applied to determine predictors of rebleeding and in-hospital mortality. Parameters with p-value

<0.25 in univariate analysis were put up in a final regression model. P-value ≤0.05 was taken statistically significant.

RESULTS

Total 300 patients were enrolled into the study with mean age of 60 ± 10.4 years and majority were males (73.7%). HBV and HCV was positive in 14% and 43% patients respectively. Ascites were present in nearly half of patients (49.7%). Among 149 (49.7%) patients with ascites, mild, moderate and severe ascites were present in 52.3%, 29.5% and 18.1% respectively. Hepatic encephalopathy was present in 4% patients. According to endoscopic findings, small, medium and large EV were seen in 9%, 28% and 63% patients respectively. Gastric varices were present in 13.3% patients. Treatment modality included band ligation (90.3%) and histoacryl injection (12.3%). Table-I patients' demographic and clinical features.

Variables	Number (%) / Mean ± SD
Age	59.9 ± 10.4
Gender (male)	79 (26.3)
Diabetes	92 (30.7)
Hypertension	87 (29)
Hepatitis B virus positive	42 (14)
Hepatitis C virus positive	129 (43)
Systolic blood pressure (mm Hg)	111.3 ± 12.1
Diastolic blood pressure (mm Hg)	76.4 ± 10.2
Heart rate (beats/minute)	94.1 ± 16.0
Hemoglobin (g/dl)	7.7 ± 2.0
White blood cells (10^9/L)	7.3 ± 3.4
Platelets (10^9/L)	149.5 ± 639.5
Total bilirubin (umol/L)	1.9 ± 1.8
Alanine Aminotransferase (U/L)	56.2 ± 45.3
Alkaline phosphatase (IU/L)	144.4 ± 112.1
Gamma-glutamyl transferase (IU/L)	101.6 ± 93.0
Aspartate aminotransferase (U/L)	76.7 ± 47.6
Albumin (g/dl)	2.8 ± 0.5
Prothrombin time/international normalized ratio (seconds)	1.4 ± 0.30
Model of End-stage Liver Disease score	15.1 ± 6.2
Albumin-bilirubin score	-1.5 ± 0.6
Platelet albumin bilirubin score	0.3 ± 0.6

Table-I. Summary of patients' demographic and clinical features.

Rebleeding was seen in 27.7%. Figure-1 displays ROC curve of PALBI score, ALBI score, MELD score and CTP score for prediction of rebleeding with AUC of 0.613 (95% CI: 0.54-0.68), 0.665 (95% CI: 0.60-0.74), 0.634 (95% CI: 0.56-0.71) and 0.650 (95% CI: 0.58-0.72) respectively.

Table-II displays univariate and multivariable association of patients' features with rebleeding.

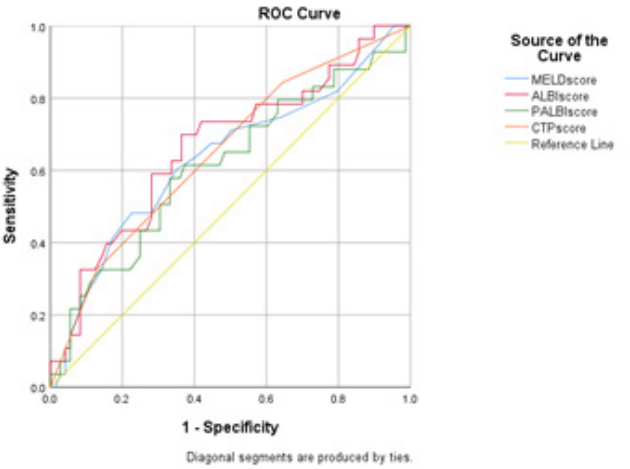

Figure-1. ROC curve of PALBI, ALBI, CTP score, and MELD score for prediction of acute variceal hemorrhage.

In univariate analysis, esophageal varices, WBC, platelet, bilirubin, ALT, albumin, CTP class, MELD score, ALBI score and PALBI score were associated with rebleeding. On multivariable model, after adjusting the model with other covariates none of the score including CTP score, MELD score, ALBI score and PLABI score were found to be associated with rebleeding.

During the study in-hospital mortalities were seen in 10.3% cases. Figure-2 depicts ROC curve of PALBI score, ALBI score, MELD score and CTP score for prediction of mortality. AUC for PALBI score, ALBI score, MELD score and CTP score was 0.690 (95% CI: 0.57-0.80), 0.795 (95% CI: 0.71-0.88) and 0.807 (95% CI: 0.73-0.87), 0.710 (95% CI: 0.61-0.81) respectively.

In univariate model, WBC, total bilirubin, ALT, akbumin PT/INR, CTP class, MELD score, ALBI score and PALBI score were associated with mortality. In multivariable regression analysis, when adjusted for confounders prediction score MELD and PALBI were found to be linked with in-hospital mortality (Table-III).

Variables	OR (95% CI)	P-Value	aOR (95% CI)	P-Value
Age	1.013(0.989-1.039)	0.289	-	-
Gender (male)	1.077(0.604-1.922)	0.802	-	-
Diabetes	0.891(0.512-1.552)	0.684	-	-
Hypertension	1.078(0.619-1.875)	0.791	-	-
Hepatitis B virus positive	1.054(0.511-2.171)	0.888	-	-
Hepatitis C virus positive	1.021(0.613-1.702)	0.936	-	-
Hepatic encephalopathy	0.867(0.229-3.283)	0.833	-	-
Ascites	1.287(0.775-2.137)	0.330	-	-
Small esophageal varices	22.24(6.417-77.083)	*<0.001	61.994(15.326-250.757)	*<0.001
Medium esophageal varices	0.334(0.156-0.716)	*0.005	0.379(0.15-0.957)	*0.040
White blood cells (10^9/L)	1.113(1.035-1.196)	*0.004	1.151(1.044-1.268)	*0.005
Platelet (10^9/L)	1.007(1.002-1.011)	*0.003	1.001(0.993-1.009)	0.782
Total bilirubin (umol/L)	1.273(1.096-1.478)	*0.002	1.142(0.881-1.48)	0.315
Alanine Aminotransferase (U/L)	1.006(1.001-1.012)	*0.021	1.011(1.003-1.018)	*0.005
Alkaline phosphatase (IU/L)	0.998(0.996-1.001)	0.226	-	-
Gamma-glutamyl transferase (IU/L)	0.999(0.996-1.002)	0.507	-	-
Aspartate aminotransferase (U/L)	1.001(0.996-1.006)	0.707	-	-
Albumin (g/dl)	0.373(0.223-0.626)	*<0.001	0.988(0.232-4.203)	0.987
Prothrombin time/international normalized ratio (seconds)	1.999(0.875-4.57)	0.101	0.4(0.087-1.842)	0.240
Child-Turcotte-Pugh A	0.175(0.079-0.386)	*<0.001	0.313(0.075-1.307)	0.111
Child-Turcotte-Pugh B	0.398(0.211-0.751)	*0.004	0.521(0.19-1.431)	0.206
Model of End-stage Liver Disease score	1.074(1.031-1.118)	*0.001	1.018(0.93-1.115)	0.700
Albumin-bilirubin score	3.021(1.874-4.871)	*<0.001	3.384(0.748-15.307)	0.113
Platelet albumin bilirubin score	1.722(1.158-2.563)	*0.007	0.562(0.229-1.383)	0.210

Table-II. Univariate and multivariable association of patients' features with rebleeding.
CI: Confidence interval, OR: Odds ratio, aOR: Adjusted odds ratio, *Significant at p<0.05

Variables	OR (95% CI)	P-Value	aOR (95% CI)	P-Value
Age (in years)	1.007	0.689	-	-
Gender (male)	0.860	0.719	-	-
Hypertension	4.238	*0.020	4.827	*0.048
Hepatitis B virus positive	2.926	*0.014	6.563	0.029
Hepatitis C virus positive	0.821	0.611	-	-
Hepatic encephalopathy	3.095	0.104	1.069	0.953
Ascites	0.944	0.880	-	-
Small esophageal varices	0.736	0.487	-	-
Medium esophageal varices	1.290	0.243	-	-
White blood cells (10^9/L)	1.183	*<0.001	1.155	0.038
Platelets (10^9/L)	1.000	0.855	-	-
Total bilirubin (umol/L)	1.400	*<0.001	1.241	0.136
Alanine Aminotransferase (U/L)	1.010	*0.004	1.006	0.220
Alkaline phosphatase (IU/L)	1.001	0.335	-	-
Gamma-glutamyl transferase (IU/L)	1.003	0.066	1.007	*0.007
Aspartate aminotransferase (U/L)	0.997	0.521	-	-
Albumin (g/dl)	0.098	<0.001	0.537	0.594
Prothrombin time/international normalized ratio (seconds)	43.971	*<0.001	4.054	0.211
Child-Turcotte-Pugh A	0.092	*<0.001	1.326	0.799
Child-Turcotte-Pugh B	0.244	*0.001	2.439	0.227
Model of End-stage Liver Disease score	1.206	*<0.001	1.161	*0.025
Albumin-bilirubin score	5.262	*<0.001	2.703	0.418
Platelet albumin bilirubin score	3.197	*0.001	0.216	*0.024

Table-III. Association of patients' features with in-hospital mortality on regression analysis

CI: Confidence interval, OR: Odds ratio, aOR: Adjusted odds ratio, *Significant at p<0.05

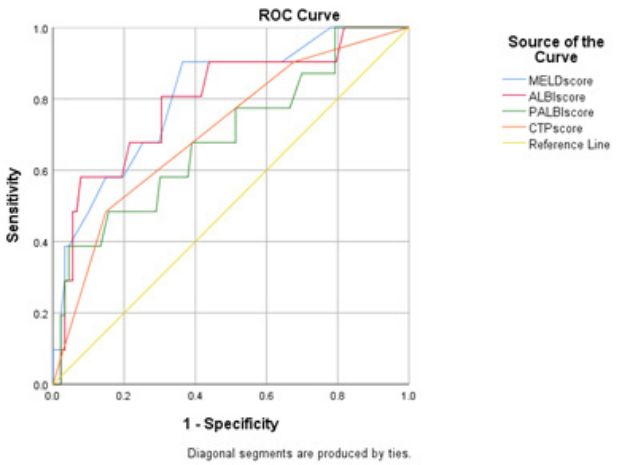

Figure-2. ROC curve of the PALBI, ALBI, CTP score, and MELD for prediction of mortality.

DISCUSSION

Patients with cirrhosis commonly present with AVH due to underlying portal hypertension. Given the unfavorable outcomes and poor prognosis associated with variceal bleeding, it is imperative to manage these patients and implement appropriate risk stratification.[15] In the present study, we assessed the mortality and rebleeding rates with AVH using several scoring systems including CTP, MELD, ALBI, and PALBI.

Cirrhotic patients experiencing variceal hemorrhage pose an elevated mortality risk and rebleeding.[15] The mortality rate within our current study cohort was recorded at 10.3%. Comparable results have been observed in studies conducted in Pakistan and China, with mortality rates reported as 8.8% and 10.6%, respectively.[15,16] A recent article published in the Journal of Population Therapeutics & Clinical Pharmacology explored that mortality often arises from uncontrolled rebleeding, infections, or kidney failure in these patients.[15]

It has been noted that rebleeding within the initial 6 weeks is a common occurrence in cirrhotic patients after initial management, often peaking within the first 5 days.[17] Our study monitored the patients for 5 days, revealing rebleeding in 27.7% of cases. This aligns with findings demonstrated by Mohammed et al. and Wang et al., who revealed rebleeding rates of 25% and 20.3%, respectively[16,18] Additionally, in a multi-center clinical audit encompassing 212 UK hospitals, a similar rebleeding rate of 26% was reported.[19] Research shows that patient-related factors contributing to rebleeding include decreased hemoglobin levels, presence of ascites, severity of varicose veins and coagulation dysfunction.[18,20]

Recurrent bleeding in a cirrhotic patient may be attributed to underlying conditions. Our study findings indicate no significant association between rebleeding and patient comorbidities, including ascites, hepatic encephalopathy, or HBV and HCV positivity. These study findings are consistent with previous literature that found no positive correlation between rebleeding and patient hepatitis status and hepatic encephalopathy.[21] However, coexisting diseases such as diabetes and the presence of ascites may contribute to rebleeding in some patients.[18,21] It is understandable that these variations in results may arise due to differences in patient demographics, characteristics, and study locations.

The literature demonstrates that CTP and MELD scores are valuable clinical tools used for evaluating risk and survival probability in AVH cases. Prior study findings have established a significant association between rebleeding and increasing MELD and CTP scores.[21-23] Our study results indicate a correlation of MELD and CTP scores with both rebleeding and mortality in univariate analysis. However, upon conducting multivariable analysis, only the MELD score was found to forecast mortality in patients. This finding was similar to that obtained from earlier studies showing an association of the MELD score with mortality in subgroup analysis but not with rebleeding.[15,20] One possible reason for the lack of association with rebleeding could be that the MELD score incorporates creatinine, which may be temporarily influenced during GIT bleeding.[23]

In our study, multivariate analysis did not reveal CTP as a predictor of mortality or rebleeding after controlling for the effects of other confounders. This contradicts previous findings regarding CTP's association with mortality.[24] It is essential to recognize that these scoring systems were

not originally intended to foresee survival in AVH patients. Therefore, there is a possibility that the CTP and MELD prognostic scores currently employed might not precisely capture the risk associated with acute variceal bleeding.[15]

Tantai and colleagues have reported that PLABI outperforms the ALBI scoring system in predicting rebleeding and mortality in patients. While the ALBI score, initially established by Johnson et al.[25], is based on two variables, bilirubin and albumin, PLABI, an altered version of ALBI proposed by Roayaie et al.[26], incorporates platelet count as well. This addition reveals the influence of portal hypertension, a primary cause of AVH.[23]

In our study, both ALBI and PLABI scores exhibited a moderate level of predictive ability for rebleeding and mortality in univariate analysis. However, in multivariable analysis, only the PALBI score was found to be predictive of mortality, with no significant association observed for either factor with rebleeding. In contrast to the findings reported by Elshaarawy et al., who concluded that both PLABI and ALBI effectively predicted in-hospital mortality and rebleeding among variceal hemorrhage patients, our study yielded different results.[23] This disparity may be attributed to the larger cohort size in their study compared to the present one (N=1517 vs N=300).

All four scoring markers exhibited a relationship on the ROC curve; however, AUC was determined to be less significant for all variables. The ALBI score showed the highest predictive value for rebleeding (AUC=0.665), followed by the CTP score (AUC=0.650), MELD score (AUC=0.634), and PALBI score (AUC=0.613). According to other research, the PALBI score outperformed the ALBI, MELD score, and CTP classification in the total analysis.[23] The current study's improved ALBI performance was most likely brought about by removing the subjective criteria (encephalopathy and ascites) from the CTP score.

Our study has several limitations. In our inclusion criteria, not all recruited patients could be diagnosed with liver cirrhosis using the gold standard hepatic biopsy. However, in outpatient settings, it is a practice to rely on clinical criteria involving radiological and examination findings, along with laboratory values, to diagnose patients with liver cirrhosis.[27]

CONCLUSION

The present study found that PALBI predicting in-hospital mortality even after adjusting other confounders. However, PALBI was not a promising marker for prediction of re-bleeding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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1	Salimah Anwar Jussa	Conceptualized the study, Designed the study protocol initial, Manuscript writing, Data collection, Manuscript revision.	
2	Mansoor Ul Haq	Designed the study, Protocol Critical review & revision of initial manuscript draft.	
3	Adeel Rahat	Designed the study protocol statistical analysis initial manuscirpt writing.