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Evaluation of Mortality Risk in Liver Cirrhosis with Albumin-Bilirubin (ALBI), Platelet-Albumin-Bilirubin (PALBI), and Fibrosis-4 (FIB-4) Scores

DA Sindhughosa[1], IK Mariadi[2], IDN Wibawa[2]*, IGA Suryadarma[2], N Purwadi[2], G Somayana[2] and CI Yuliandari[2]

[1]Internal Medicine Resident, Faculty of Medicine of Udayana University, Sanglah Hospital, Denpasar, Bali, Indonesia.
[2]Gastroenterohepatology Division, Internal Medicine Department, Faculty of Medicine of Udayana University/Sanglah Hospital, Denpasar, Bali, Indonesia.
*Corresponding author E-mail: agusbobwibawa@yahoo.com

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The model for end stage liver disease (MELD) score considered as a reliable predictor of survival for advanced liver diseases patients. Among several chemistry laboratorium examinations, albumin, bilirubin and platelet reflect the function of the liver. To investigate the correlation of albumin-bilirubin (ALBI), platelet-albumin-bilirubin (PALBI), and fibrosis-4 (FIB-4) scores with mortality risk based on MELD score and evaluate their role in predicting cirrhosis mortality risk. The analytic cross-sectional study design recruited adults with liver cirrhosis of any etiology during the period of November 2018 through January 2019. Descriptive and correlative analyses were done before proceeding to diagnostic ability analysis. Sixty-two patients with mean age of 52.95 ± 12.05 were included in the analysis. The ALBI, PALBI, and FIB-4 scores were significantly correlated with higher mortality risk based on MELD score. The three scores significantly predicted higher mortality risk with varying sensitivity and specificity. Positive correlation between ALBI, PALBI, and FIB-4 scores with MELD score was found. ALBI (=-1.26), PALBI (=-2.05), and FIB-4 (=5.84) values higher than the threshold could predict mortality risk in cirrhosis.

Keywords: ALBI; FIB-4; Liver Cirrhosis; Mortality Risk; PALBI.

Cirrhosis is characterized by distorted liver architecture and nodules formation which indicates end-stage hepatic fibrosis. Liver cirrhosis is clinically classified into compensated and decompensated cirrhosis depending on the evidence of overt clinical pictures.[1] In the United States alone, the incidence is estimated to be 360 per 100,000 population, and more than 40% are asymptomatic. The global increase in mortality due to liver cirrhosis was reported by Global Burden of Disease (GBD) from 676,000 deaths in 1980 to more than a million deaths in 2010.[2]

Scoring methods have been widely applied to predict liver cirrhosis prognosis. Child-Turcotte-Pugh (CTP) classification includes the parameters: serum bilirubin and albumin, prothrombin time, ascites severity, and the degree of encephalopathy. Model for end-stage liver

disease (MELD) estimates patients survival based on serum bilirubin and creatinine values and international normalized ratio (INR). The score is also proven to be a useful predictor of outcomes in other settings such as presurgical assessment of cirrhosis, alcoholic hepatitis, or fulminant hepatic failure.[3]

The role of non-invasive markers, such as albumin-bilirubin (ALBI), platelet-albumin-bilirubin (PALBI), and fibrosis-4 (FIB-4), in assessing chronic liver disease severity is extensively studied to reduce liver biopsy requirement. These are simple and objective assessment systems using scores obtained from laboratory tests of peripheral blood.[4] Several studies on the role of the three markers in patients with liver disease have been carried out and most of them show promising results as prognostic markers in chronic liver disease.[4-6] The study aimed to determine the correlation between ALBI, PALBI, and FIB-4 scores with the mortality risk in cirrhosis patients calculated using MELD scores. The secondary objective is to evaluate the predictive ability of each score for high risk of mortality.

METHODS

The analytic cross-sectional study design used consecutive sampling method to recruit participants during November 2018 through January 2019. Patients aged e"18 years diagnosed with liver cirrhosis regardless of the etiology were included. The history of sepsis, acute infection, hypertension, diabetes mellitus, coronary heart disease, chronic heart failure, chronic kidney disease, malignancy, chemotherapy, systemic lupus erythematosus, steroid use in the past month, and platelet transfusion (within five days) constituted the exclusion criteria. The study protocol was approved by local ethical committee board and all study participants provided written consent.

The equation to calculate for ALBI, PALBI, FIB-4, and MELD score were obtained from calculation with formula. ALBI was calculated with the following formula: [($\log_{10}$ bilirubin x 0.66) + (albumin x [-0.085]). While PALBI with 2.02 x $\log_{10}$ bilirubin – 0.37 x ($\log_{10}$ bilirubin)^2 – 0.04 x albumin – 3.48 x $\log_{10}$ platelet + 1.01 x ($\log_{10}$ platelets)^2. The value of FIB-4 calculated with the following formula: (age (years) × AST (UD L))/ (Platelet (10^9D L))× "(ALT (UD L)). MELD score measured with the formula of (0.957 x ln (Serum Cr) + 0.378 x ln (Serum Bilirubin) + 1.120 x ln (INR) + 0.643) x 10.

Compiled data was analyzed with Statistics Program for Social Science (SPSS) for Windows version 23.0. Appropriate central tendency and dispersion for was opted based on the data distribution. The correlation was analyzed with either Pearson's test or Spearman's correlation test

Table 1. Basic characteristics of patients

Characteristic	Total patient n = 62
Age (years), mean ± SD	52.95 ± 12.05
Platelet (1000/µL), median (min-max)	92.58 (22.08-554.5)
Total bilirubin (µmol/L), median (min-max)	22.91 (4.28-615.26)
AST (U/L), median (min-max)	46.05 (17.1-498.8)
ALT (U/L), median (min-max)	32 (6-200)
INR, median (min-max)	1.4 (0.9-2.3)
Creatinine serum (mg/dL), median (min-max)	0.97 (0.62-1.328)
Albumin (g/L), mean ± SD	33 (17-51)
PALBI, mean ± SD	-2.16 ± 0.52
ALBI, mean ± SD	1.94 ± 0.81
FIB-4, median (min-max)	5.17 (0.59-26.12)
MELD, median (min-max)	12.22 (6.43-37.52)

*AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: International Normalized Ratio, PALBI: platelet-albumin-bilirubin, ALBI: albumin-bilirubin, FIB-4: Fibrosis-4, MELD: model for end stage liver disease

depending on data distribution. Either independent T-test or Mann-Whitney was utilized to evaluate the difference of each variable in high (MELD >15) and low mortality risk. Receiver Operating Characteristic (ROC) curve analysis was done to determine the optimal cut-off values representing the best indices of accuracy.

RESULTS

The study involved 62 samples, consisting of 49 subjects (79%) male and 13 subjects (21%) female. The basic characteristics of the research subjects can be seen in table 1. The mean PALBI was -2.16 ± 0.52, ALBI -1.94 ± 0.81, and FIB-4 6.13 ± 5.25.

The result shown that ALBI (r = 0.789; p <0.001), PALBI (r = 0.785; p <0.001), and FIB-4 (r = 0.691; p <0.001) were positively correlated with cirrhosis mortality risk generated from MELD scores (Table 2, Figure 1).

ALBI, PALBI and FIB-4 scores in the high and low risk group were significantly different (-1.27 ± 0.6 vs -2.34 ± 0.63, p <0.001; -1.72 ± 0 , 35 vs -2.43 ± 0.41, p <0.001, and 10.04 ± 6.36 vs. 3.84 ± 2.49, p <0.001) (Table 3).

Table 2. Correlation of ALBI, PALBI, and FIB-4 with the mortality risk in cirrhosis patients calculated using MELD

Variables	r	*p* value
ALBI	0.789	< 0.001
PALBI	0.785	< 0.001
FIB-4	0.691	< 0.001

*PALBI: platelet-albumin-bilirubin, ALBI: albumin-bilirubin, FIB-4: Fibrosis-4, MELD: model for end stage liver disease** All data were analyzed using Spearman correlation

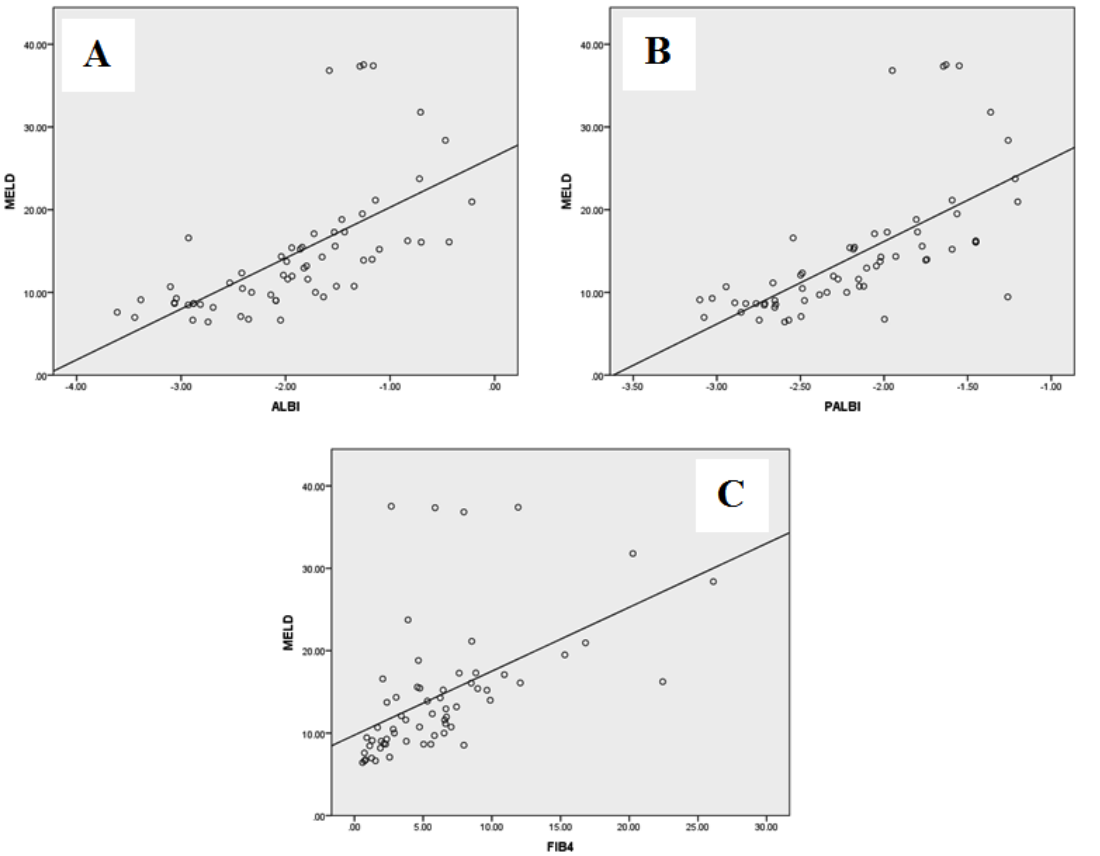

Fig. 1. Scatter diagram of correlation plot between A). ALBI with MELD (r = 0.789; p <0.001), B). PALBI with MELD (r = 0.785; p <0.001), C). FIB-4 with MELD (r = 0.691; p <0.001)

All scores significantly predict high mortality risk in liver cirrhosis. Selected ALBI cut-off value of -1.26 yielded the lowest sensitivity (47.8) and specificity (52.2) with area under the curve (AUC) of 0.897 (p <0.001). The cut-off value of 5.84 for FIB-4 had sensitivity (73.9) and specificity (74.4), whilst the cut-off value of -2.05 for PALBI had the highest sensitivity (78.3) and specificity (79.5) among the three scores (AUC 0.896, p <0.001) as seen on Figure 2 and Table 4.

DISCUSSION AND CONCLUSIONS

Cirrhosis of the liver is often accompanied by portal hypertension. Portal hypertension (PH) is the leading cause for liver cirrhosis complications

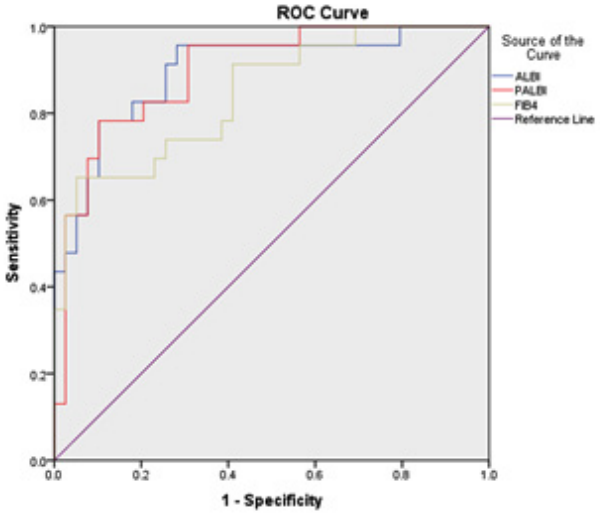

Fig. 2. ROC analysis of ALBI, PALBI and FIB-4 to predict the high mortality risk (MELD> 15) in liver cirrhosis patients (cut-off for ALBI: -1.26, sensitivity 47.8, specificity 52.2, AUC: 0.897, p <0.001. Cut-off for PALBI: -2.05, sensitivity 78.3, specificity 79.5, AUC: 0.896, p <0.001. Cut-off for FIB-4: 5.84, sensitivity 73, 9, specificity 74.4, AUC: 0.844, p <0.001)

Table 3. Bivariate analysis between patients with high and low mortality risk

Characteristics	Mortality risk		*p* value
	High (n = 23)	Low (n = 39)	
Age (years), mean ± SD	55.43 ± 9.73	51.49 ± 13.13	0.216[a]
Platelet (1000/µL), median (min-max)	66 (22.08-181.5)	115.6 (34.86-554.5)	< 0.001[b]
Total bilirubin (µmol/L), median (min-max)	59.85 (15.9-615.26)	14.88 (4.28-84.99)	< 0.001[b]
AST (U/L), median (min-max)	51 (23.9-498.8)	36.9 (17.1-168.7)	0.007[b]
ALT (U/L), median (min-max)	35 (9.5-200)	29.8 (6-146.1)	0.126[b]
INR, median (min-max)	1.82 (1.24-2.3)	1.29 (0.9-1.65)	< 0.001
Creatinine serum (mg/dL), median (min-max)	1.1 (0.72-1.33)	0.9 (0.62-1.15)	0.215[b]
Albumin (g/L), mean ± SD	29.17 ± 5.87	36.67 ± 6.57	< 0.001[a]
PALBI, mean ± SD	-1.72 ± 0.35	-2.43 ± 0.41	< 0.001[a]
ALBI, mean ± SD	-1.27 ± 0.6	-2.34 ± 0.63	< 0.001[a]
FIB-4, median (min-max)	8.54 (2.06-26.12)	3.03 (0.59-9.88)	< 0.001[b]

*AST: aspartat aminotransferase, ALT: alanine aminotransferase, INR: International Normalized Ratio, PALBI: platelet-albumin-bilirubin, ALBI: albumin-bilirubin, FIB-4: Fibrosis-4, MELD: model for end stage liver disease[a]Independent t test analysis[b]Mann-Whitney analysis

Table 4. Sensitivity and specificity values of ALBI, PALBI, and FIB-4 from several intersections points to predict high mortality risk (MELD> 15)

	Cut-off	Sensitivity	Specificity	AUC	*p* value
ALBI	-1.3166	56.5	43.5	0.897	< 0.001
	-1.2771	52.2	47.8		
	-1.2597	47.8	52.2		
	-1.2539	47.8	52.2		
	-1.2134	43.5	56.5		
PALBI	-2.1129	82.6	76.9	0.896	< 0.001
	-2.0807	82.6	79.5		
	-2.0517	78.3	79.5		
	-2.0350	78.3	82.1		
	-2.0215	78.3	84.6		
FIB-4	5.6162	73.9	69.2	0.844	< 0.001
	5.7450	73.9	71.8		
	5.8452	73.9	74.4		
	6.0544	69.6	74.4		
	6.3480	69.6	76.9		

PALBI: platelet-albumin-bilirubin, ALBI: albumin-bilirubin, FIB-4: Fibrosis-4, MELD: model for end stage liver disease

and mortality.[5] The largest proportion of deaths from liver cirrhosis in the world is found at 50-64 years. Mortality due to liver cirrhosis rose significantly over the year 1980-2010 across multiple continents, particularly in the Caribbean, with a rapid increase from 600,000 to one million. In Asia, the highest incidence of liver cirrhosis is found in Thailand.[2]

Although it has been used frequently, CTP and MELD scores have some disadvantages. Weaknesses in the CTP score are, first, their limited discrimination capacity and does not adequately separate patients with progressive abnormal laboratory results. For example, patients with serum bilirubin 20 mg/dl will be given the same number of points as patients who have serum bilirubin 3.5 mg/dl, whereas very high serum bilirubin has a major effect on prognosis. Second, the CTP score imposes the same burden on each parameter. Third, two of the five parameters (ascites and encephalopathy) must be interpreted subjectively. Fourth, several other prognostic factors such as serum creatinine and varicose bleeding are not included in the scoring system.[3,6,7] Compared to CTP, MELD has the advantage that all three parameters are laboratory results that are objective, stable, and easily interpreted but there are variations between laboratories regarding the results of INR. There are also reported misclassification rates by the MELD method of up to 10 to 20%[8]. Another weakness is that other pathological conditions can cause an increase in INR or creatinine[3]. CTP is easier to calculate while MELD generally requires access to the MELD calculator.[7,9]

ALBI score calculation uses serum bilirubin and serum albumin data without using subjective parameters or invasive methods. Patients were then classified into grades 1-3 based on the following thresholds, respectively: <"2.60, >"2.60-1.39, and >"1.39. The PALBI model was prepared by entering the number of platelets into the ALBI grade previously described. Fibrosis-4 (FIB-4) is calculated based on age, AST, platelet and ALT data with the formula.[5]

In this study, it was found that the lower ALBI, PALBI, and FIB-4 scores had a positive correlation with the MELD score. Besides, the ALBI, PALBI, and FIB-4 scores in cirrhosis patients with a high mortality risk have a higher value than those with hepatic cirrhosis patients with low mortality risk. ALBI, PALBI, and FIB-4 values can be used to predict high mortality risk. However, the ALBI score has a low sensitivity and specificity value.

Several studies have proven the application of ALBI, PALBI, and FIB-4 scores in cases of liver

cirrhosis. ALBI was shown to be comparable to CTP and MELD scores in predicting mortality during hospitalization in acute gastrointestinal bleeding complicating liver cirrhosis.[6] ALBI score had the best AUC in predicting short-term mortality and FIB-4 index over 8.4 was associated with decreased survival[5]. A study by Lei *et al*[4] showed that ALBI scores were higher in HBV-ACLF patients, which had the most severe liver damage, compared with patients HBV-LC or HBV-HCC. Prospective cohort studies in patients with a previous history of decompensated liver cirrhosis showed that ALBI and PALBI grades were strongly correlated with transplant-free survival according to Kaplan-Meier analysis. FIB-4 was also able to identify patients with severe cirrhosis in chronic hepatitis C.[10]

The ALBI score has the advantage because it only requires two parameters to calculate the score. Overall analysis from various studies also shows the ability of the ALBI model to be comparable to CTP and MELD scores in assessing mortality during hospitalization.[11] The ALBI score serves as short-term mortality predictor in high-risk subjects, thus complementing the MELD score.[5] PALBI has the better discriminatory ability in early and slow mortality than CTP scores and is comparable to MELD scores in cohort studies.[12]

In conclusion, ALBI, PALBI, and FIB-4 scores are positively correlated with MELD scores and are associated with risk of death. ALBI, PALBI, and FIB-4 values can be used to predict higher mortality risk. However, the ALBI score has a low sensitivity and specificity value.

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Conflict of Interest

All author declare no conflict of interest exist in regards to this article.

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Authors' Contribution

DAS designed the research, collect material and clinical data, analyzed the data, and writing the manuscript; IKM designed the research, collect material and clinical data, writing the manuscript; IDNW collect material and clinical data, analyzed the data, revised the manuscript; NP designed the research, analyzed the data, and writing the manuscript. IGAS collect material and clinical data, analyzed the data, revised the manuscript. GS designed the research, collect material and clinical data and writing the manuscript. CIY collect material and clinical data, analyze data and writing the manuscript All authors read and approved the final manuscript.

Statement of Informed Consent

All study participants provided written consent.

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