Albumin-bilirubin Score for Predicting the In-hospital Mortality of Variceal Bleeding in Children with Liver Cirrhosis

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ABSTRACT

Background: Liver cirrhosis is an end stage liver damage. Biliary atresia (BA) and inherited syndromes of intrahepatic cholestasis are the most frequent causes of liver cirrhosis in children especially in the first year of life.

Objective: To compare the prognostic value of albumin-bilirubin grade (ALBI), an alternative predictor of mortality in cirrhotic adults, with Child-Pugh and Pediatric End-Stage Liver Disease (PELD) scores in cirrhotic children with variceal bleeding.

Methods: We analyzed the patients' data using MedCalc software, and calculated area under the curves (AUC) of receiving-operator characteristic (ROC).

Results: All scores were higher in expired compared to survived patients ($p<0.001$). The AUC values for predicting mortality in all patients were 0.879±0.04 for Child-Pugh and PELD scores and 0.733±0.06 for ALBI. The prognostic values in two subgroups of BA and those with other underlying diseases (non-BA) showed that in BA group, ALBI score with AUC of 0.607±0.102, $p<0.29$, had no significant difference between survived and non-survived patients. ALBI in non-BA group, with AUC of 0.863±0.063 showed closer value to other scores (0.954), and was differed between survived and non-survived groups ($p<0.001$).

Conclusion: Our results suggested that ALBI might be useful in predicting mortality in non-BA patients.

KEYWORDS: Cirrhosis; ALBI; Child-Pugh; PELD; Biliary atresia

INTRODUCTION

Liver cirrhosis is an end stage liver damage. Biliary atresia (BA) and inherited syndromes of intrahepatic cholestasis are the most frequent causes of liver cirrhosis in children especially in the first year of life. Also, genetic metabolic diseases such as α-1-antitrypsin deficiency, galactosemia, tyrosinemia and Wilson are among the most important causes of liver cirrhosis in young children. In older children cirrhosis is usually caused by chronic viral and autoimmune hepatitis [1]. In a study reported by Dehghani *et al.* on a number of transplanted patients , BA, cryptogenic cirrhosis, autoimmune hepatitis, Wilson and tyrosinemia were the most common underlying diseases, respectively [2]. The major predictors of early mortality due to variceal bleeding in cirrhotic adults are included hepatic encephalopathy, Child-Pugh score, MELD (Model for End Stage of Liver

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Table 1: Demographic, hematological and biochemical features of cirrhotic children with variceal bleeding.

Variables	Total (n=70)	Male (n=37)	Female (n=33)
Age (months)	36.7±37.8	38.9±37.04	34.2±39.2
WBC ($\times10^3/\mu L$)	12.8±8.95	13.1±8.5	12.5±9.5
Hemoglubin (g/dL)	7.3±2.2	7.3±2.3	7.3±2.1
MCV (fL)	87.1±8.4	86.8±7.9	87.4±9.1
Platelet ($\times10^3/\mu L$)	165±146	163±176	166±105
Albumin (mg/dL)	3±0.73	2.96±0.76	3.01±0.7
Total bilirubin (mg/dL)	16.6±16.3	15.4±12.2	18±20
INR (mg/dL)	3.7±3.6	3.7±3.6	3.7±3.8
AST (IU/L)	234±242	237±222	231±266
ALT (IU/L)	122±120	128±127	115±113
Na^+ (mEq/L)	135±7	136±7.2	134±6.7
Creatinine (mg/dL)	0.29±0.26	0.28±0.19	0.31±0.32
Encephalopathy			
Negative	37 (52.9)	17	20
Grade 1	11 (15.7)	7	4
Grade 2	13 (18.5)	9	4
Grade 3	7 (10)	3	4
Grade 4	2 (2.9)	1	1
Ascites			
Negative	14 (20)	7	7
Mild	22 (31.4)	12	10
Moderate	22 (31.4)	10	12
Severe	12 (17.2)	8	4
SBP			
Negative	57 (81.4)	31	26
Positive	13 (18.6)	6	7
Hepatorenal syndrome			
Negative	47 (67.1)	25	22
Positive	23 (32.9)	12	11
Hepatopulmonary syndrome			
Negative	55 (78.6)	27	28
Positive	15 (21.4)	10	5
Infection			
Negative	43 (61.4)	22	21
Positive	27 (38.6)	15	12
Mortality			
Expired	24 (34.3)	16 (43.2)	8 (24.2)
Survived	46 (65.7)	21 (56.8)	25 (75.8)

Data are presented as number (%). SBP, spontaneous bacterial peritonitis.

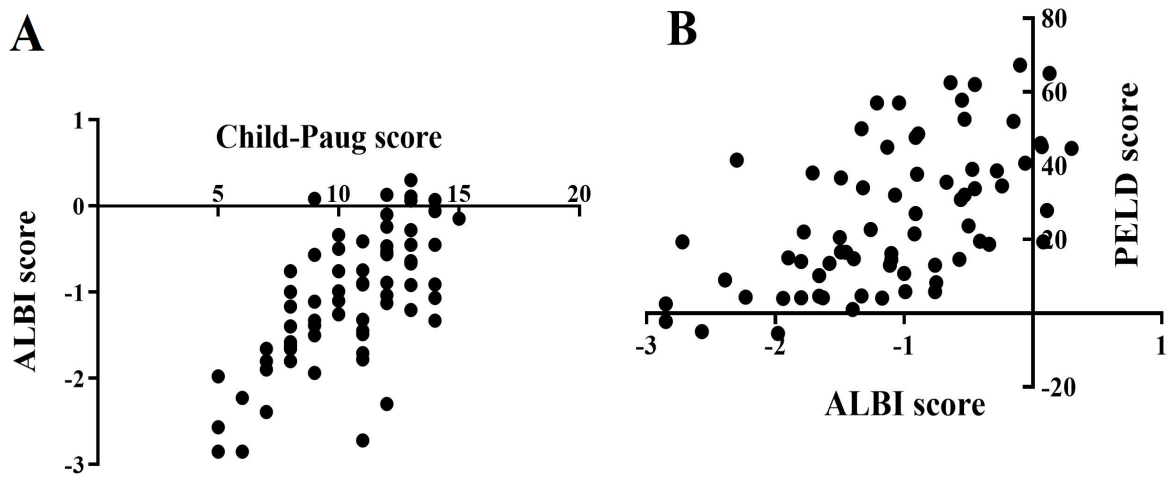

Figure 1: Correlation between ALBI score with Child-Pugh (r=0.65) and PELD (r=0.59) scores in all patients (p<0.001).

Disease) score, shock, renal failure, infection, portal vein thrombosis, and hepatocellular carcinoma (HCC) [3, 4].

Child–Pugh score is widely used to determine the severity of liver dysfunction. It was firstly proposed by Child and Turcotte to predict the operative risk in patients undergoing portosystemic shunt surgery for variceal bleeding and included ascites, hepatic encephalopathy, nutritional status, total bilirubin and albumin [5]. Then, Pugh *et al.* modified the primary version by adding prothrombin time or international normalized ratio (INR) and removing nutritional status [6].

MELD was designed to determine the complication risks in patients with transjugular intrahepatic portosystemic shunts (TIPS) [7]. This score comprises three biochemical parameters including serum total bilirubin, INR and serum creatinine [8]. In children younger than 12 years old, Pediatric End Stage Liver Disease (PELD), is used instead. Beside parameters in MELD except for serum creatinine, age, status of growth and serum albumin are contributed in PELD. These methods are used to prioritize liver transplant candidates.

In 2015, a new grading system was designed by Johnson *et al.* named albumin-bilirubin grade (ALBI) and was primarily used to assess liver function in large population of adults suffering from HCC. ALBI grade was calculated using only two objective parameters; serum bilirubin and albumin concentration. Besides, this model had a comparable prognostic value with Child-Pugh score; it was a more simple, objective and discriminatory method which eliminate the need for subjective variables such as encephalopathy and ascites [9].

Most of the studies about ALBI grade have been performed on adult patients with HCC and while no data is available on the efficacy and predictive value of ALBI in cirrhotic children [10-13]. Therefore, we aimed to design a retrospective unicenter study to assess ALBI score in pediatric patients with cirrhosis due to acute variceal bleeding. Since BA was the most common underlying disease, the prognostic value of ALBI was also investigated in two subgroups of patients with BA and those with other underlying diseases (non-BA). We compared the predicting value of ALBI score for mortality, with Child-Pugh and PELD/MELD scores in the patients.

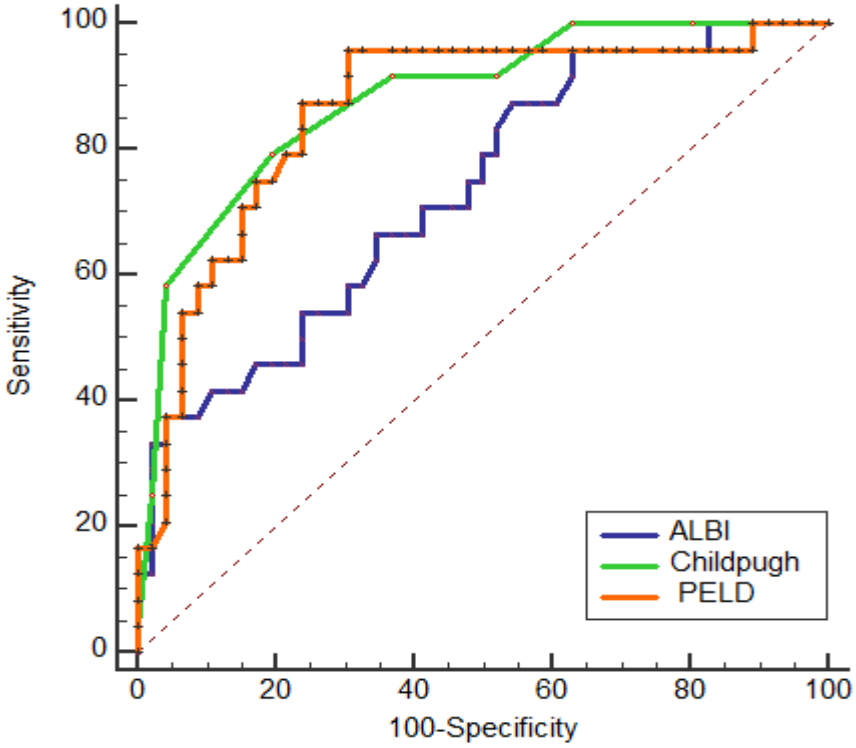

Figure 2: Differences between the Child-Pugh, PELD and ALBI scores for predicting mortality in all cirrhotic children with variceal bleeding using receiver operating characteristic curve (ROC) analysis.

MATERIALS AND METHODS

The patients were children aged less than 18 years old with confirmed cirrhosis based on any underlying cause who were complicated with acute variceal bleeding and were admitted in Pediatric Gastroenterology Ward in Nemazee Hospital affiliated with Shiraz University of Medical Sciences.

History of liver diseases, clinical manifestations, imaging studies, such as ultrasound, computed tomography (CT) scan and/or magnetic resonance imaging (MRI), and liver biopsy were used for the diagnosis of liver cirrhosis. Patients with HCC or other malignancies were excluded. Repeated admissions were not excluded.

Patients' records were studied retrospectively and the following data were collected: age, sex, etiology of liver disease, and laboratory tests [red blood cell count, white blood cell (WBC) count, platelet, total bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, prothrombin time (PT), INR, ascites and encephalopathy]. In-hospital death data and its causes were also collected.

Child-Pugh class/score, PELD/MELD scores, and ALBI were calculated for patients. Child-Pugh score was measured using five variables: encephalopathy, ascites, albumin, total bilirubin, and prothrombin time. Each parameter obtains a point and based on total obtained points, Child-Pugh score was classified to three classes. Class A: Point 5 to 6, Class B: 7 to 9, and Class C: 10 to 15 [14].

MELD score = 3.78 × ln [serum bilirubin (mg/dl)] + 11.2 × ln [INR] + 9.57 × ln [serum creatinine (mg/dl)] + 6.43; for children

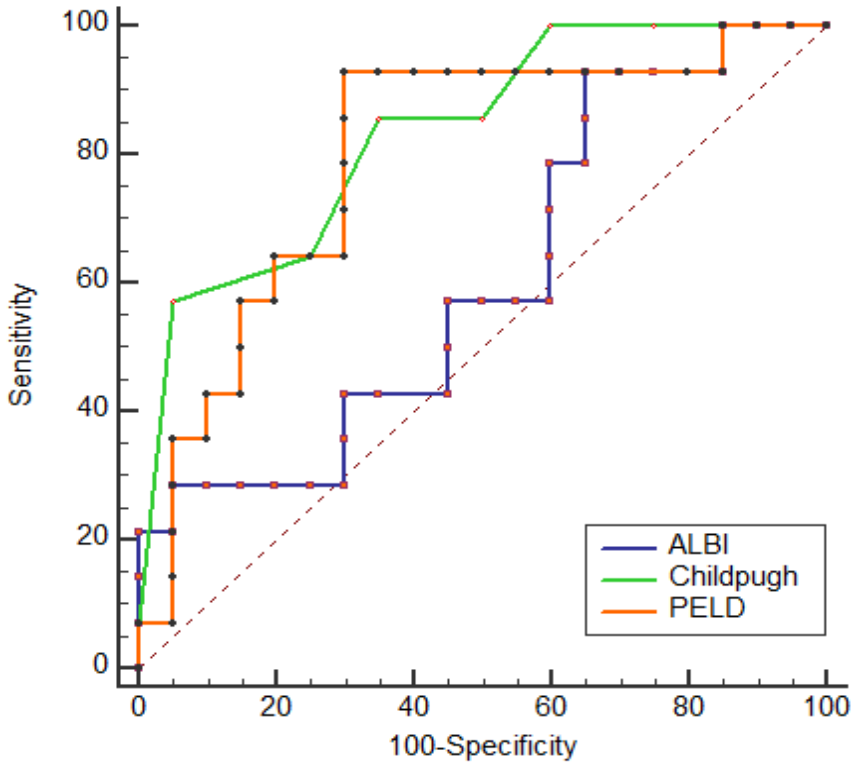

Figure 3: Differences between prognostic value of Child-Pugh, PELD and ALBI scores for mortality in cirrhotic children with variceal bleeding and BA as the underlying disease.

age≥ 12 years

PELD score = 4.80 × ln [serum bilirubin (mg/dl)] + 18.57 × ln [INR] - 6.87 × ln [albumin (g/dl)] + 4.36 (<1 year old) + 6.67 (growth failure); for children age> 12 years [15]

ALBI is classified into three grades: Grade 1: ≤-2.6, Grade 2: >-2.6, ≤-1.39, and Grade 3: >-1.39 [9].

ALBI score = -0.085 × [albumin (g/L)] + 0.66 × log10 [bilirubin (umol/L)].

Ethical Considerations

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences and were in accordance with the ethical standards of the Helsinki Declaration.

Statistical Analysis

Data were analyzed using SPSS software version 19 and GraphPad prism version 7. Continuous variables were presented as mean ± standard deviation and median (range). Categorical variables were presented as frequency (percentage). We used Mann-Whitney U test and Kruskal-Wallis to evaluate quantitative values differences between every two or more than two groups, respectively. Any correlation between two quantitative variables was assessed using Pearson's correlation test. Chi-square was used to compare qualitative variables among the groups. P value< 0.05 was considered as statistically significant.

The statistical analyses for prognostic values and differences between the scores were performed by MedCalc software version 11.4.2.0. Areas under the receiving-operator characteristic curve (AUROC) with 95% confidence intervals (CIs) were calculated to evaluate the

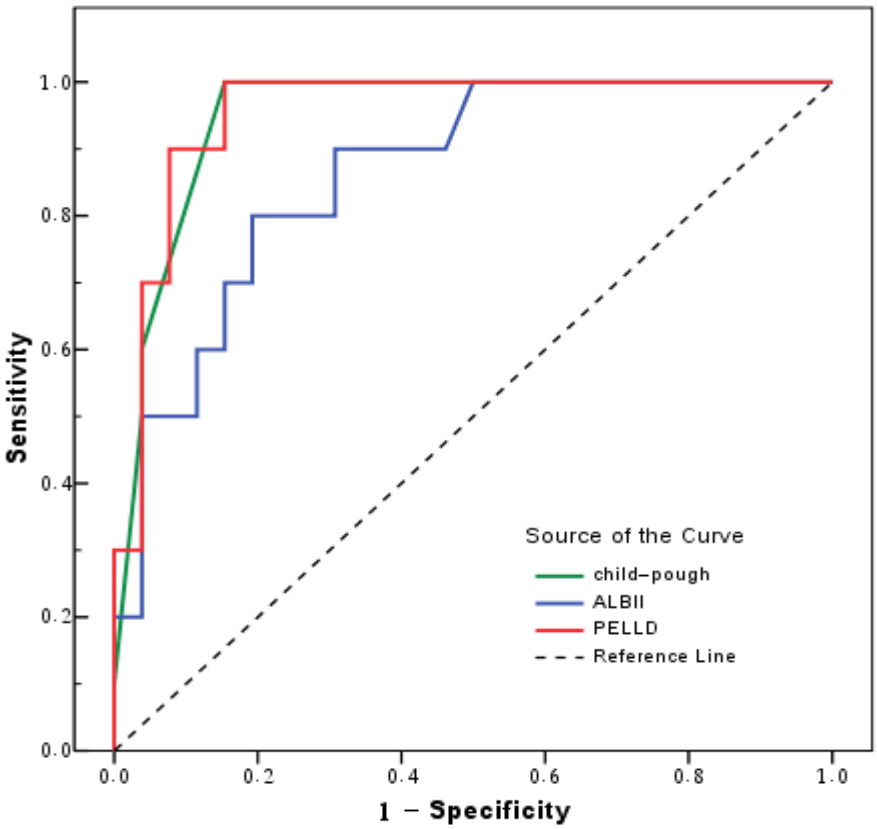

Figure 4: The ROC curves for Child-Pugh, PELD and ALBI scores for predicting mortality in cirrhotic children with variceal bleeding and other underlying diseases.

discriminative abilities of three scores. We compared the AUROCs of these scores in predicting the in-hospital mortality of patients by De-Long tests. These data were presented as mean ± standard error and p value<0.05 was statistically significant. We narrowed our analysis in two subgroups, a subgroup of patients with BA as a cause of liver cirrhosis and a subgroup of other underlying causes (non-BA). AUC of ROC with 95% CIs were calculated for three scores in each subgroup and then they were compared.

RESULTS

A total of 70 cirrhotic children with acute variceal bleeding were enrolled in this study. Of patients, 37 (52.9%) were male with mean age of 38.9±37.04 months and 33 (47.1%) were female with mean age of 34.2±39.2 months. The most common underlying disease was BA (34 patients, 48.6%). Of patients with other underlying diseases, 13 patients had unknown cause and the rest had neonatal hepatitis (6 patients), progressive intrahepatic familial cholestasis (PFIC, 4 patients), tyrosinemia (4 patients), autoimmune hepatitis (3 patients) and Wilson (2 patients). Demographic, hematological and biochemical characteristics of the patients are shown in Table 1. As shown, WBC and platelet number of patients were 12.8±8.95 $\times 10^3/\mu L$ and 165±146 $\times 10^3/\mu L$, respectively. Patients' hemoglobin was in the range of 2 - 12.6 g/dL and MCV range was 62.5 - 113 fL. The mean serum level of albumin in all patients was 3±0.73 mg/dL (range, 1.4 - 4.7) and total bilirubin was 16.6±16.3 mg/dL (range, 0.4 - 85).

In Table 1, the clinical manifestations of the

patients are shown too. Of patients, 48% showed encephalopathy and the rest were negative for this manifestation. The patients are divided according to the severity of ascites to those who had no ascites (20%), and those with mild (31.4%), moderate (31.4%) and severe (17.1%) ascites. Spontaneous bacterial peritonitis (SBP) occurred in 37 (18.6%) of patients. Twenty-three patients showed hepatorenal impairment and 27 patients (38.6%) showed infections (mostly pneumonia, sepsis, SBP). Analysis of these data showed no significant differences in clinical manifestations including encephalopathy (p=0.36), ascites (p=0.6), SBP (p=0.6), hepatorenal (p=0.9) and hepatopulmonary (p=0.2) syndrome, and infection (p=0.7) between male and female patients.

During the hospital course, 24 patients (34.3%) died of which 16 (66.7%) were male and 8 (33.3%) were female (p<0.09).

Of patients, 7.1% were in class A, 27.1% in class B and 65.7% in class C. The majority of patients were in ALBI grade 3 (65.7%).

ALBI value of patients in different classes of Child-Pugh were -2.5±0.4 in class A, -1.4±0.56 in class B and -0.8±0.63 in class C (p<0.001), demonstrating a significant difference in ALBI score of patients with different Child-Pugh classes. A significant correlation between these two scores in all patients (p<0.001) (Fig 1A) male (p<0.001) and female patients (P<0.001) was found.

Patients showed a PELD score of 26.3±19.3 (range 1 - 67) and ALBI score of -1.08±0.76 (range -2.85 - 0.3). A significant correlation between these two scores in all patients (Fig 1B, p<0.001), male (p<0.001) and female patients (P<0.001) was found.

The values of Child-Pugh (12.5±1.5 vs 9.41±2.2), PELD (42.3±15.6 vs 17.9±15.3) and ALBI scores (-0.66±0.63 vs -1.3±0.73) between died and live patients showed significant higher values in non-survived group than survived patients (p<0.001).

In order to find the prognostic value of ALBI score compared to PELD and Child-Pugh scores in all the patients, the ROC curve analysis was performed. These scores were assessed by measuring the AUC values for Child-Pugh, PELD and ALBI scores in regard to mortality rate. The AUC value for Child-Pugh score was 0.879±0.04 (95% confidence interval, CI, 0.779 - 0.944, P<0.0002), for ALBI was 0.733±0.06 (95% CI, 0.614-0.832, P<0.0001) and for PELD score was 0.879±0.05 (95% CI, 0.779-0.944, P<0.0001). These results showed that all methods significantly predicted mortality (Fig 2). The difference between Child-Pugh and PELD scores was not significant (p=0.62), but ALBI score showed significant differences with Child-Pugh (p=0.004) and PELD (p=0.026) scores. These results indicated a similar prognostic value of Child-Pugh and PELD scores. Although, ALBI may be an alternative index for predicting the mortality in these patients, but its prognostic value was less than two other scores in all patients regardless of their underlying disease.

In BA group, determination of Child-Pugh, PELD and ALBI scores in survived and non-survived patients showed that ALBI score unlike two other sores, had no significant difference between survived and non-survived patients. The ROC curve analysis showed that Child-Pugh with AUC of 0.834±0.068, CI, 0.667-0.939 (P<0.0001) was superior to PELD (AUC, 0.796±0.081, CI, 0.624-0.915, p<0.0003) and ALBI (AUC, 0.607±0.102, CI, 0.425-0.77, P<0.29) scores for predicting mortality in BA patients. Child-Pugh and PELD scores has no significant difference in predicting mortality of these patients (p=0.527), but ALBI showed significant differences with Child-Pugh (p=0.0013) and PELD (p = 0.045) scores. These results indicated that ALBI might not be an alternative index for predicting mortality, and may have no important prognostic value in this group of patients (Fig 3).

In non-BA group, ALBI score showed a significant difference between survived and non-survived groups (p<0.001). The AUC for Child-Pugh (0.95±0.34, CI, 0.883 to 1.017, P<0.0001) was similar to PELD (0.954±0.033,

CI, 0.889-1.018, P<0.0001) and AUC for ALBI was 0.863±0.063, CI, 0.740-0.987. These results showed that ALBI significantly predicted mortality (p<0.001). Comparison of these scores showed that Child-Pugh and PELD scores had no significant difference in predicting mortality in this group. ALBI value was very close to Child-Pugh and PELD scores (Fig 4).

DISCUSSION

The ALBI, is a newly defined index with at least equal efficacy and significance in predicting the outcome and prognosis of patients with HCC in comparison to other previous scoring systems such as Child-Pugh and MELD/PELD [16-18]. Also, few studies evaluated the effectiveness of this score in cirrhotic patients [19,20] and cirrhotic adults with variceal bleeding [21-23). Although many articles support the nobility of this score in adults, data on effectiveness of ALBI in children is lacking and the validity of this score in children is an area of uncertainty.

Child-Pugh and MELD/PELD scores have been used to assess the severity of liver diseases for years. They also were used for prioritizing patients for liver transplantation in end-stage liver diseases. Several studies have been performed to compare eligibility of these two scores in end stage liver diseases. In 2016 a systematic review and meta-analysis was published in which 119 papers were reviewed to analyze the value of these scores for assessment of prognosis in liver cirrhosis. The overall analysis showed similar prognostic value of these two scores, though the researchers suggested that each of these scores have better efficacy in special conditions and situations [5].

In another side, limitations of previous scores such as Child-Pugh score, especially in patients with conditions such as HCC who are not necessarily cirrhotic has been reported [9]. For example, the appropriateness of Child-Pugh score in patients with HCC with a range of liver damage from mild injuries to advanced fibrosis is not clear [9]. Another weak point of Child-Pugh score is that variables such as amount of ascites and encephalopathy are subjective and there are no criteria for mild, moderate and severe ascites. Also, in Child-Pugh score for example serum bilirubin 5 mg/dL has the same impact as 50 mg/dL and also albumin 2.7 g/dL and 1.5 g/dL, while it seems that they show different levels of liver dysfunction. Due to these limitations researchers have investigated other scores such as ALBI which is calculated by using two objective parameters, serum albumin and bilirubin.

All together it seems that ALBI score has overcome some of these limitations and we aimed to assess this score in cirrhotic children with variceal bleeding. Based on our search in literature there was no study about the ALBI score and its prognostic value in children with cirrhosis. In this study, we collected the demographic, hematological, biochemical and clinical data of 70 patients with different underlying causes of liver cirrhosis complicated with acute variceal bleeding in a period of 7 years (2012-2019). In these patients Child-Pugh, PELD and ALBI scores were calculated and their prognostic values were compared. Because near 50% of our patients had liver cirrhosis on the basis of BA, we also analyzed these three scores in subgroups of patients with BA and non-BA.

In the assessment of acute variceal bleeding and liver dysfunction, the lowest hemoglobin was 2 g/L, the lowest serum albumin was 1.4 mg/dL and the highest serum bilirubin was 85 mg/dL. SBP was the most common infection among patients and 18.6% of patients had SBP. Approximately one third of patients had hepatorenal syndrome and 21% of patients had hepatopulmonary disturbance.

Based on our results 34% of cirrhotic patients with acute variceal bleeding who were admitted in hospital were eventually expired in their admission. Of note, we excluded dead on arrivals and also a group of patients who were severely ill and were expired in few hours, before laboratory assessment could be completed, due to lack of data. More than half of the patients were male and less female. We found no sig-

nificant difference in demographic, clinical and paraclinical data between male and female patients.

Near 67% of patients were in Child-Pugh stage C and ALBI grade 3. Mean value of ALBI score among grade B and C Child-Pugh score was -1.4 and -0.8, respectively. The patients with ALBI grade 3 were mostly distributed in stage B and C of Child-Pugh score. As we expected the study showed strong significant correlation of ALBI with PELD and Child-Pugh score in all patients and also in male and female patients. This data was in line with the previous reports on adult patients with cirrhosis [24-26].

We calculated the values of each score in patients who expired and or survived. The mean value of each score among non-survived patients were ALBI, -0.66; Child-Pugh, 12.5 and PELD, 42.3. Comparison of these values with the same values in survived patients showed strong significance differences.

In order to compare prognostic values, we used AUC values under ROC curves for each score. Values for Child-Pugh and PELD scores were very close. These two scores had the greatest AUC 0.879. ALBI with AUC 0.733 showed significant differences with these scores. It is concluded that although ALBI had significant value in prediction of mortality in all the patients but Child-Pugh and PELD with greater AUC remained as better prognostic scores.

In BA patients, we found significant differences for the values of Child-Pugh and PELD scores between survived and non-survived groups. AUC for Child-Pugh, PELD and ALBI scores were 0.834, 0.796 and 0.607, respectively. These data indicated that Child-Pugh score followed by PELD score had significant values for predicting mortality in BA patients and there were no significant difference between these two scores. However, we found significant differences between ALBI score with both scores, suggested that ALBI might not be an alternative index for predicting mortality, and have no important prognostic value in this group of patients. This result is different from the results obtained by researchers on adult patients with liver cirrhosis [24-26].

We also studied the prognostic value of the ALBI score compared to Child-Pugh and PELD scores in the rest of the patients (non-BA). All three scores were significantly different between non-survived and survived patients in this group. Moreover, AUC for ALBI was 0.863 which was closer to Child-Pugh and PELD scores. It is concluded that although ALBI had significant value in prediction of mortality in all the patients but Child-Pugh and PELD with greater AUC remained as better prognostic scores.

In conclusion, our study showed that Child-Pugh and PELD scores have almost the same or close prognostic value among cirrhotic children with variceal bleeding. ALBI score, though with lesser extent than Child-Pugh and PELD, significantly predicted mortality in all patients. However, we found that the efficacy of ALBI score was different according to the underlying disease; non-significant in BA group and significant in non-BA group. As the non-BA group consisted of various diseases such as neonatal hepatitis, PFIC, autoimmune hepatitis, Wilson and tyrosinemia, further studies on different subgroups of etiologies in larger group of patients to clarify the eligibility of ALBI score in each disease in children with cirrhosis.is suggested.

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