AKI-CLIF-SOFA Score in Predicting Mortality of Critically Ill Cirrhotic Patients with Acute Kidney Injury

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a fatal complication of Chronic Liver Disease (CLD) and is a significant cause of mortality. Prognostication is vital in this setting because evidence-based decisions on the likely outcome might assist in decision making in relation to the delivery of critical care to patient groups most likely to benefit. The study aims at examining the diagnostic accuracy of AKI-CLIF-SOFA score in predicting 30 day and 90 day mortality of critically ill cirrhotic patients with acute kidney injury and to compare the novel AKI-CLIF-SOFA score with pre-existing scores.

Material and methods: This was a cross sectional – diagnostic accuracy study. The data of CLD patients admitted to the ICU with new onset renal failure were collected. The diagnostic accuracy of AKI-CLIF-SOFA score in predicting mortality was calculated and compared with the pre-existing prognostic scores – CHILD, MELD and CLIF-SOFA.

Results: A total of 50 patients were included in the study. The diagnostic accuracies are 82% and 76% in predicting 30 and 90 day mortality respectively. AKI-CLIF-SOFA score was compared with the pre-existing scores. For 30 day mortality, CLIF-SOFA is found to be superior followed by AKI-CLIF-SOFA, CHILD and MELD. For 90 day mortality, AKI-CLIF-SOFA is found to be superior followed by CLIF-SOFA, CHILD and MELD.

Conclusion: The novel score – AKI-CLIF-SOFA – has good diagnostic accuracy in predicting the mortality of critically ill Cirrhotic patients with acute kidney injury. The comparison with the already existing scores also shows superior discriminatory power of AKI-CLIF-SOFA score.

Keywords: Acute Kidney Injury, AKI-CLIF-SOFA Score, Chronic Liver Disease, Cirrhosis, Hepatorenal Syndrome

INTRODUCTION

Acute kidney injury (AKI) is a serious complication of Chronic Liver Disease (CLD) and is a significant cause of mortality. Patients with Chronic liver disease are susceptible to develop AKI because of the progressive vasodilatory state, reduced effective blood volume and stimulation of vasoconstrictor hormones. In a systematic review of 118 studies which evaluated survival predictors in cirrhosis, parameters of liver dysfunction (Child-Pugh score and its components) and parameters of renal failure (blood urea nitrogen/ azotaemia and creatinine) were both powerful predictors of death in decompensated CLD. Higher values of serum creatinine consistently lead to worse survival.[1]

The most common causes of AKI in cirrhosis are pre-renal azotaemia, hepatorenal syndrome (HRS) and acute tubular necrosis (ATN). Chronic glomerulonephritis and obstructive uropathy are rare causes of renal failure in cirrhotic patients. AKI is one of the last events in the natural history of chronic liver disease. Therefore, such patients should have an expedited referral for liver transplantation.[2] It is the only curative therapy for end stage liver disease, giving excellent long-term survival.

The mortality rate becomes very high when CLD patients require intensive care unit (ICU) admission.[3–5] Thus, the decision to initiate critical care is frequently questioned as these patients often progress to multi-organ failure.[5] Such admissions are costly, and in many countries there is shortage of ICU bed. Thus, it is necessary to identify those cirrhotic patients who may benefit most from continued ICU care. To aid in this, the clinical and laboratory variables which are associated predictively with mortality, need evaluation to see if objective scoring systems, providing accurate estimates for predicting outcomes, can be derived.[6] Till now there are many widely used liver-specific and general ICU prognostic models. CHILD and MELD are the widely used liver specific prognostic models. Acute Physiology and Chronic Health Evaluation III (ACPACHE III) scores, the Simplified acute physiology score (SAPS II) and SOFA score are the commonly used scoring systems used to assess the prognosis at ICU.[7,8]

Though there are many scores for estimating the prognosis of patients with Chronic Liver Disease, no accurate liver and renal specific scores were available for Cirrhotic patients developing acute kidney injury. In one study which was conducted by Sun et al, a novel prognostic score – AKI-CLIF-SOFA – was devised from 527 critically ill cirrhotic patients with acute kidney injury.[9] Acute kidney injury Chronic Liver Failure Sequential Organ Failure Assessment score (AKI CLIF SOFA) score demonstrated good discriminative power as compared to the pre-existing scoring systems. This objectives of the study are to examine the diagnostic accuracies of AKI-CLIF-SOFA score in predicting 30-day

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and 90-day mortality of critically ill cirrhotic patients with acute kidney injury. This study also compares the novel AKI-CLIF-SOFA score with the pre-existing scores.

MATERIALS AND METHODS

Selection and description of Participants

This is a cross sectional – diagnostic accuracy study conducted in the medical intensive care units of a tertiary care hospital in Kerala for a period of 2 years (August 2017- August 2019). 50 patients with Chronic Liver Disease admitted to the ICU with new onset renal failure were selected. Patients with pre-existing renal failure and with a history of liver transplantation were excluded. The diagnosis of CLD was based on clinical, biochemical and sonological evidence, as well as on liver histology, whenever a liver biopsy specimen was available. The definition of Acute Kidney Injury was based KDIGO criteria which is as follows:

(1) Increase in S.Cr by 0.3 mg/dL or more within 48 h; or
(2) Increase in S.Cr to 1.5 times baseline or more within the last 7 d; or
(3) Urine output less than 0.5 mL/kg per hour for 6 h

Sample size

Based on the results of sensitivity (53.1%) and specificity (80.32%) of AKI-CLIF-SOFA score for predicting mortality of critically ill Cirrhotic patients with Acute Kidney Injury observed in an earlier publication (AKI CLIF SOFA: a novel prognostic score for critically ill Cirrhotic patients with Acute Kidney Injury in AGING 2017, Vol.9, No.1) and with 20% precision and 95% confidence, the minimum sample size comes to 25 for sensitivity and 20 for specificity. In this study 50 cases have been included – randomly selected. With this sample size, the precision and confidence with respect to sensitivity will be 15% and 95% and with respect to specificity will be 15% and 99%.

Technical information

The patients' data including demographic, clinical and laboratory parameters were collected at the time of admission to ICU. The clinical parameters which included heart rate, SBP, DBP, MAP, use of inotropes, respiration, partial pressure of Oxygen (paO2) and mental status were derived from the data recorded in the in-patient file. The laboratory parameters including creatinine, bilirubin, platelet, PT INR, albumin, 24 hour serum creatinine were collected from the hospital information system. Lactate value was obtained from arterial blood gas analysis. Ascites was diagnosed by abdominal ultrasound. The start date was the patient's admission and the primary end points were defined at 30-days and 90-days for all-cause mortality. For all patients, AKI-CLIF-SOFA, CHILD, MELD and CLIF-SOFA scores were calculated. The variables included in AKI-CLIF-SOFA score are 24h creatinine, bilirubin, lactate, age and vasopressin used/not (0 or 1 for each variable, range 0-5 points). The cut-off of 24h creatinine, bilirubin, lactate and age are 1.45mg/dL, 5.20mg/dL, 2.55mg/dL and 64.5 years respectively. For values less than this cut-off, a point of 0 is given and for values above this, a point of 1 is given. Sensitivity and specificity

of AKI-CLIF-SOFA score in predicting the mortality at 30 and 90 days were calculated. This was compared with the pre-existing prognostic scores – CHILD, MELD and CLIF-SOFA.

STATISTICAL ANALYSIS

Statistical analysis was done using IBM SPSS 20.0 (SPSS Inc, Chicago, USA). For all the continuous variables, the results are given in Mean ± SD, and for categorical variables as percentage. To compare the mean difference of numerical variables between groups, independent two sample 't' test was applied for parametric data and Mann whitney u test for non parametric data. To obtain the association of morbidity and mortality with abnormalities with respect to various parameters, Chi square test was applied. ROC analysis was done to find out the prognostic efficiency of AKI-CLIF-SOFA score and other models for 30 day and 90 day mortality. Diagnostic accuracy was done for AKI-CLIF-SOFA score in predicting 30 day and 90 day mortality with validity parameters like Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and Accuracy was computed. A P-value < 0.05 was considered as statistically significant.

RESULTS

Of the 50 patients included in the study, 46 (92%) were males and 4 (8%) were females. Majority of the patients (34%) were in the age group of 50-59. The mean age of the study population was 59.10±10.30. The 30 day mortality was 66%. There were 4 patients with AKI-CLIF-SOFA score 1, all of whom survived(100%). 18 patients had AKI-CLIF-SOFA score 2, 11 (61.1%) patients survived and 7 (38.9%) did not survive. 13 patients had AKI-CLIF-SOFA score 3, of which only 1 (7.7%) survived and 12 (92.3%) did not survive. 12 patients had AKI-CLIF-SOFA score 4, of which there were 11 (91.7%) non survivors and 1 (8.3%) survivor. There were 3 (100%) patients with AKI-CLIF-SOFA score 5, none of them survived. There were 33 non survivors of which 26 (92.9%) patients had AKI-CLIF-SOFA score> 2 and 7 (31.8%) patients had AKI-CLIF-SOFA score≤2. 17 patients survived, of which 15(68.2%) had AKI-CLIF-SOFA score≤2 and 2 (7.1%) had score more than 2. AKI-CLIF-SOFA score was statistically significant with a p value of 0.180. The sensitivity and specificity of AKI-CLIF-SOFA score in predicting 30 day mortality were 78.8% and 88.2% respectively (Table 1). The positive predictive value (PPV) was 92.9%. Negative Predictive Value (NPV) was 68.2%. Diagnostic accuracy was 82%.

The 90 day mortality was 76%. There were 4(100%) patients with AKI-CLIF-SOFA score 1, all of whom survive. 18 patients had AKI-CLIF-SOFA score 2, 7(38.9%) patients survived and 11(61.1%) did not survive. 13 patients had AKI-CLIF-SOFA score 3, of which only 1(7.7%) survived and 12(92.3%) did not survive. 12 patients had AKI-CLIF-SOFA score 4, of which all the 12(100%) did not survive. There were 3(100%) patients with AKI-CLIF-SOFA score 5, none of them survived. There were 38 non survivors of

which 27(96.4%) patients had AKI-CLIF-SOFA score> 2 and 11(50.0%) patients had AKI-CLIF-SOFA score ≤2. 12 patients survived, of which 11(50.0%) had AKI-CLIF-SOFA score≤2 and 1(3.6%) had score more than 2. AKI-CLIF-SOFA score was statistically significant with a p value of 0.006. The sensitivity and specificity of AKI-CLIF-SOFA score in predicting 90 day mortality were 71.1% and 91.7% respectively (Table 2). The positive predictive value (PPV) was 96.4%, Negative Predictive Value (NPV) was 50% and Diagnostic accuracy was 76%.

The variables that were found statistically significant were Creatinine, Bilirubin, Lactate, INR and Mean Arterial Pressure (MAP) (Table 3). The mean values of Creatinine, Bilirubin, Lactate, INR and Mean Arterial Pressure (MAP) were 1.32 ±0.6, 4.66 ± 4.07, 2.58±1.99, 1.96±0.75 and 82.41±15.08 respectively for survivors. The mean values of Creatinine, Bilirubin, Lactate, INR and Mean Arterial Pressure (MAP) were 2.92±1.38, 9.72±8.00, 6.36±4.14, 2.59±0.94 and 59.82±17.95 respectively for non survivors. It is also found that the values of Creatinine, Bilirubin, Lactate and INR were significantly high among non survivors as compared to survivors. Mean Arterial Pressure (MAP) was low among non survivors as compared to survivors.

The mean AKI-CLIF-SOFA score for non survivors was 3.30 ± 0.92 and survivors were 1.94±0.75. It was statistically significant with a p value of <0.001. The mean Child Pugh Turcotte score for non survivors was 12.91±1.74and

survivors was 10.06±2.56. It was statistically significant with a p value of <0.001. The mean MELD score for non survivors was 30.88 ± 7.88 and survivors were 24.94 ± 6.13. It was statistically significant with a p value of 0.009. The mean CLIF SOFA score for non survivors was 313.58 ± 3.55 and survivors were 7.76±3.27. It was statistically significant with a p value of <0.001. The mean AKI-CLIF-SOFA, CLIF SOFA, Child Pugh Turcotte and MELD scores were more among non survivors as compared to survivors.
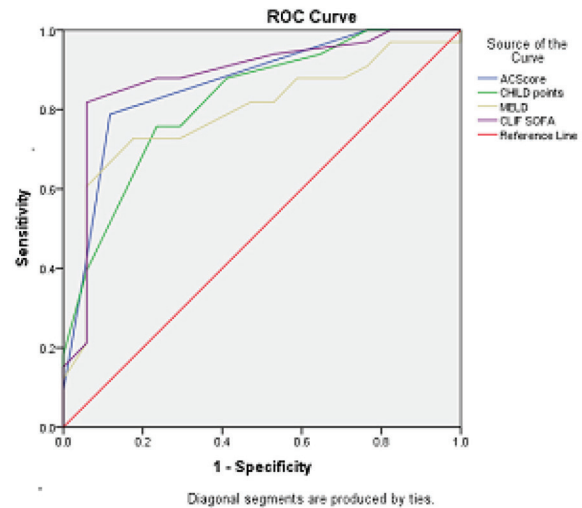

Figure-1: ROC analysis of the prognostic efficiency of AKI CLIF SOFA score and other models for 30 day mortality

AKI CLIF SOFA score	30 day mortality		P value
	Non Survivor n=33	Survivor n=17	
> 2	26 (92.9%)	2 (7.1%)	0.180
≤2	7 (31.8%)	15 (68.2%)	
Table-1: Accuracy of AKI CLIF SOFA score among 30 day mortality			

AKI CLIF SOFA score	90 day mortality		P value
	Non Survivor n=38	Survivor n=12	
> 2	27(96.4%)	1(3.6%)	0.006
≤2	11(50.0%)	11(50.0%)	
Table-2: Accuracy of AKI CLIF SOFA score among 90 day mortality			

Variables	Non Survivor (n=33)	Survivor (n=17)	P value
Age	59.33 ± 9.70	58.65 ± 11.69	0.826
Creatinine 24h	2.30 ± 0.82	2.14 ± 0.70	0.497
Creatinine	2.92 ± 1.38	1.32 ± 0.6	<0.001
Bilirubin	9.72 ± 8.00	4.66 ± 4.07	0.005
Lactate	6.36 ± 4.14	2.58 ±1.99	<0.001
Platelet	113.58 ± 80.48	124.24 ±60.67	0.634
INR	2.59 ± 0.94	1.96 ± 0.75	0.021
MAP	59.82 ± 17.95	82.41 ± 15.08	<0.001
Sodium	128.61 ± 10.21	131.35 ± 11.39	0.391
Potassium	4.49 ± 0.99	4.48 ± 0.92	0.697
Albumin	2.55 ± 0.55	2.79 ± 0.58	0.147
Table-3: Comparison of Characteristics of critically ill Cirrhotic patients with acute kidney injury			
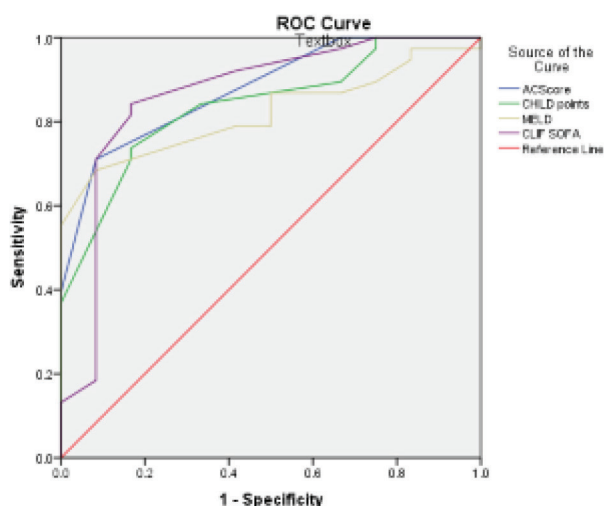
Figure-2: ROC analysis of the prognostic efficiency of AKI CLIF SOFA score and other models for 90 day mortality

The ability of different scores to predict mortality for critically ill Cirrhotic patients with acute kidney injury was illustrated by the area under ROC. For 30 day mortality, AUROC values were: CLIF SOFA 0.885, AKI-CLIF-SOFA 0.865, CHILD 0.823 and MELD 0.791 (Figure 1). CLIF SOFA is found to be superior followed by AKI-CLIF-SOFA, CHILD and MELD. For 90 day mortality, AUROC values were: AKI-CLIF-SOFA 0.878, CLIF SOFA 0.866, CHILD 0.839 and MELD 0.820 (Figure 2). AKI-CLIF-SOFA is found to be superior followed by AKI-CLIF-SOFA, CHILD and MELD.

DISCUSSION

To our knowledge, there are many studies which investigated the efficiency of different scoring systems for assessing the prognosis of critically ill CLD patients. However no specific score is commonly used to predict the prognosis of CLD patients developing Acute Kidney Injury. In one study which was conducted by Sun et al, a novel prognostic score - AKI-CLIF-SOFA – was devised from 527 critically ill cirrhotic patients with acute kidney injury.[9] The cut-off AKI-CLIF-SOFA score was 2. Those with score more than 2 had high risk of mortality as per the study conducted by Sun et al. The diagnostic accuracy of this score has not been investigated in any study previously. Our study is aimed at validation of this score in our population.

Epidemiological features of our patients show that their age range from 36 to 83 years and most number of patients were in the age group 50-59 years. This is in agreement with the studies done by Cherian et al[10] and Serag et al[11] who reported that the peak age of cirrhosis was at the fifth decade. Gender distribution in CLD patients in our study showed male preponderance with 92% of the patients being males. Similar result was found in the studies conducted by Jennifer Guy and Marion G. Peters in California and Ichiro Shimizu in Japan.[12,13]

The objective of the study is to examine the diagnostic accuracy of AKI-CLIF-SOFA score in predicting 30 and 90 day mortality of critically ill cirrhotic patients with acute kidney injury. As per the data, majority of patients included in the study did not survive. Mortality was 66% at 30 days and 76% at 90 days. The fact that acute kidney injury in Cirrhosis carries high risk of mortality is well established and is proved in the previous studies conducted by Gomes et al[14] and Scott et al.[15]

The study demonstrated an increasing trend of mortality with increasing AKI-CLIF-SOFA score. Patients with lower score had more chances of survival and patients with higher scores had increased risk of mortality. In our study, mortality was zero for patients with score 1 and 100% for patients with score 5. The sensitivity and specificity of AKI-CLIF-SOFA score in predicting 30 day mortality were 78.8% and 88.2% respectively. This was superior to the sensitivity (53.1%) and specificity(80.32%) obtained in the study conducted by Sun et al[9], in which the score was generated. The positive predictive value (PPV) was 92.9%. Negative Predictive Value (NPV) was 68.2%. Diagnostic accuracy was 82%. Therefore this new scoring system is proven to be highly effective in predicting the 30 day mortality of critically ill cirrhotic patients with acute kidney injury.

The results were similar in the prediction of 90 day mortality. The sensitivity and specificity of AKI-CLIF-SOFA score in predicting 90 day mortality were 71.1% and 91.7% respectively. The specificity of the score was higher in predicting 90 day mortality, however sensitivity was higher in predicting 30 day mortality. The positive predictive value (PPV) was 96.4%, Negative Predictive Value (NPV) was 50% and Diagnostic accuracy was 76% in predicting 90 day mortality.

Compared with the survival group, non survivors had significantly higher values of creatinine, bilirubin, lactate, PT INR and lower mean arterial pressure (MAP). In the study conducted by Sun et al[9] creatinine at 24 hours was found to be significant. However in our study, there was no significant difference in 24 hour creatinine between survivors and non survivors (p value 0.497). Bilirubin (p value 0.005), lactate (p value <0.001) and MAP were significant which was in agreement with the study conducted by Sun et al.[9] Bilirubin as a biomarker for short term mortality was established in the study done by Lopez Velazquez et al in Mexico.[16] The poor prognosis of high lactate levels in liver failure was shown in the study led by Gerry C. MacQuillin in Birmingham, England.[17] PT INR which was not significant in the previous study by Sun et al[9], was found to be significant in our study with a p value of 0.021.

The new AKI-CLIF-SOFA score was compared with the current gold standard scores such as Child Pugh score, MELD and CLIF SOFA. AuROC analysis was used for analysing this. AKI CLIF SOFA score (auROC 0.878) had the highest discriminatory power in predicting 90 day mortality in comparison with the other scores. This is in agreement with the study done by Sun et al.[9] CLIF SOFA score (auROC 0.866) was the next accurate followed by Child Pugh score (auROC 0.839) and MELD (auROC 0.820). In the studies conducted by Bao Q et al and Silva PE et al, CLIF SOFA score was found to be a strong predictor of mortality.[18,19]

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In our study, CLIF SOFA score was superior in predicting the 30 day mortality of critically ill Cirrhotic patients with acute kidney injury. AKI-CLIF-SOFA score was the next most accurate followed by Child Pugh and MELD scores. The auROC was 0.885 for CLIF SOFA, 0.865 for AKI-CLIF-SOFA score, 0.823 for Child Pugh score and 0.791 for MELD score.

Hence it is proven in our study that the novel score - AKI-CLIF-SOFA – has good diagnostic accuracy in predicting the mortality of critically ill Cirrhotic patients with acute kidney injury. The comparison with the already existing scores also shows superior discriminatory power of AKI-CLIF-SOFA score.

CONCLUSION

Renal failure is a serious complication of Chronic Liver Disease and is a major factor leading to mortality. AKI-CLIF-SOFA score was devised to assess the prognosis of critically ill CLD patients developing Acute Kidney Injury. It was found that patients with higher scores have increased risk of mortality. The study also compared AKI-CLIF-SOFA score with the pre-existing scores for assessing the prognosis of CLD patients. Child Pugh, MELD and CLIF-SOFA scores were calculated for all patients and was compared with AKI-CLIF-SOFA score. This showed better discriminative ability of the new scoring system in predicting 90 day mortality. However CLIF SOFA score was more accurate in predicting 30 day mortality, closely followed by AKI-CLIF-SOFA score. This is the first known study examining the diagnostic accuracy of the novel AKI-CLIF-SOFA score. The study shows better performance of the score as compared to the study conducted by Sun et al[9] for devising the score. Hence the new score can be recommended for accurately predicting the mortality of critically ill Cirrhotic patients with acute kidney injury in our population.

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