Research Article

Acute on chronic liver failure: causative factors and comparison of prognostic scores

Abstract

Background: Acute-on-chronic Liver failure (ACLF) is a distinct entity, different from patients with cirrhosis and de compensation. However, despite being a devastating syndrome with inordinately high mortality, the precipitating factors or prognostic scoring systems remain ill defined. We studied the precipitating factors, role of various factors on outcome and compared prognostic scores in predicting short term (7days) outcome. Methods: 100 patients with ACLF were enrolled. All patients were worked up for possible etiologies of underlying CLD & acute precipitating events & were classified in various categories of ACLF accordingly. APACHE II, SOFA, CTP & MELD scores were compared in terms of AUROC values for predicting short term mortality.

Results: The etiology of underlying cirrhosis was alcohol in majority of patients (59%) with alcoholic hepatitis being the most common acute precipitating event, occurring in 43% of patients. The short term mortality was 55%. There was a significant difference in the values of Mean arterial pressure (p=0.044), Heart rate (p=0.042), Platelet count (p=0.001), S. Bilirubin (p=<0.001), S. Sodium (p=<0.001), S. Creatinine (p=0.076), S. Albumin (p=<0.001) & INR (p=<0.001) of survivors & Non survivors. The short term mortality was comparatively higher in patients with SBP (93%, p=0.001) & UGI bleed (100%, p=0.003) as their precipitating causes while it was comparatively lower in patients with Acute viral hepatitis & Hepatitis B virus flare/Autoimmune hepatitis flare (13%, p=<0.001). Overall APACHE II had a higher AUROC than SOFA, MELD, CTP (0.938 vs 0.782 for SOFA vs 0.780 for MELD and 0.669 for CTP).

Conclusion: APACHE II scoring system is superior to other prognostic scores in predicting short term mortality.

Keywords: cirrhosis, precipitating factor, apache ii, alcoholic hepatitis

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Abbreviations: ACLF, acute-on-chronic liver failure; ROC, receiver operating characteristic curve; AUROC, area under the roc curve; SBP, spontaneous bacterial peritonitis

Introduction

Acute on chronic liver failure (ACLF) is defined as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[1] ACLF is a distinct entity, different from patients with cirrhosis and de compensation in two key elements. First the development of liver failure and end organ dysfunction in ACLF is much faster. Second (and may be of more importance), in ACLF, there is still a chance of recovery of liver function. Patients may revert back to the basic clinical status if the acute event and clinical consequences recover.[2]

Patients with ACLF have a high short-term mortality. The mortality rate is directly proportional to the number of organ failures observed.[3] The treatment modalities are limited in patients with ACLF, therefore it is important to make prognosis for these patients. Assessment of prognostic criteria of ACLF will allow us to incorporate it as a possible new indicator of high urgency allocation of patients to ICU and also help in determining various other treatment protocols. Hence we did this study to evaluate the performance of various prognostic scores in prediction of short term mortality in patients with ACLF.

Methods

Definition and inclusion criteria

The study included 100 consecutive patients with ACLF admitted in the Medicine Wards in Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi from Nov 2013 to Dec 2014. Written and informed consent was taken from all the subjects participating in the study. Ethical clearance was taken from ethical committee of the institute before conducting the study.

ACLF was diagnosed according to the Asian-Pacific Association for the study of the Liver (APASL) criteria. Acute insult was defined as serum bilirubin >5mg/dl and liver failure as INR≥1.5 or pro thrombin activity <40%, complicated within 4weeks by ascites and/or encephalopathy occurring in a patient with known or unknown CLD.[1]

CLD was defined as either the presence of cirrhosis or chronic hepatitis of any etiology. Cirrhosis was defined as diffuse process in the liver characterized by development of extensive fibrosis and replacement of normal liver architecture by structurally abnormal nodules of fibrotic tissue.[4] Chronic hepatitis B was defined as ongoing injury to the cells of liver with persistence of HBsAg in serum for at least 6months.[4] Diagnosis of Cirrhosis was based on clinical findings, biochemical findings (low serum albumin, AST: ALT ratio >1), imaging findings (USG findings of heterogeneous echotexture of liver with irregular outline, altered liver size depending on the etiology, portosystemic collaterals).

All patients were worked up thoroughly for the possible etiologies of their underlying CLD and acute precipitating events, and were then classified in the various categories of ACLF accordingly. Based on the type of acute insult, patients were divided into three types: Type I (Infectious etiology), Type II (Non infectious etiology), Type III (Unknown hepatotoxic etiology).[1] They were also divided into Type I (non-hepatic injury) and Type II (hepatic injury) according to whether hepatic or non hepatic cause was the acute precipitating event. SBP, various infections (like LRTI, UTI, Cellulites etc.) leading to sepsis/ MODS, acute variceal bleed, surgical interventions were classified as non hepatic insults precipitating ACLF. In the hepatic causes, acute viral hepatitis, drugs/toxins, alcoholic hepatitis, HBV flare were considered.[5] Sepsis was considered as acute precipitating event only after common hepatic acute events including acute viral hepatitis, viral or autoimmune hepatitis flare and exposure to drugs and toxins were excluded by appropriate history and investigations.

Clinical manifestations and prognostic scores

History included asking the patients for Jaundice, abdominal distension, drowsiness/altered sensorium, fever, haematemesis or malena, alcohol consumption and other related symptoms. A detailed physical examination was also done. All routine blood investigations including those required for the calculation of various prognostic scores were obtained. All patients were evaluated for various prognostic scores after all the required parameters were available within 48hours of the patient's admission including APACHE II, SOFA, CTP and MELD, as per the standard definitions. All patients were followed up during the hospital stay. Short term mortality was defined as patients in hospital death and death within 1month after leaving the hospital.

Statistical analysis

The data was expressed as median (25-75% IQR). To study the causative factors and their outcome on the mortality comparisons were made between survivors and non survivors. Chi square test (for qualitative variables) and student t test (for quantitative variables) were used. The Mann-Whitney U-test was used to compare the prognostic scores between the survivors and non-survivors. The performance of prognostic scores on the prediction of short term mortality was assessed by the receiver operating characteristic (ROC) curve. The area under the ROC curve (AUROC) was calculated for APACHE-II, SOFA, CTP and MELD scores in all patients. Sensitivity, specificity, positive predictive value and negative predictive value for the prediction of the short term mortality were determined. Measurement of agreement was based on kappa statistics. Statistical analysis was performed using SPSS version 21.0. p value <0.05 was taken as level of statistical significance.

Results

Baseline clinical and biochemical characteristics

Out of the 100 patients studied, the mean age was 52.37years ranging from 35-65years and the median age was 53years. 80 patients were males and 20 were females. Jaundice was present in all the cases and ascites with encephalopathy was the clinical presentation in 64% of the cases (Table 1).

Etiology of CLD and acute insults

The etiology of underlying cirrhosis was alcohol in 59(59%), alcohol plus virus (HBV or HCV) in 6(6%), HBV in 12(12%), HCV in 9(9%), AIH in 3(3%), Wilson's in 2(2%), NASH/cryptogenic in 9(9%) of patients (Table 1). Alcoholic hepatitis was the overall most common acute precipitating event followed by Spontaneous bacterial peritonitis (SBP) (Table 2).

Table 1 Baseline characteristics, etiology of liver cirrhosis and clinical presentations in patients with acute-on-chronic liver failure (N=100)

Baseline characteristics	
Age, (years median [25–75% IQR])	53 (35-65)
Sex, n (M : F)	80:20:00
Etiology of cirrhosis (n)	
Alcohol	59
Alcohol plus virus infection (HBV/HCV)	6
HBV	12
HCV	9
AIH	3
NASH/cryptogenic	9
Wilson's disease	2
Clinical presentation (n)	
Jaundice	100 (100%)
Ascites	95 (95%)
Encephalopathy alone	64 (64%)
Fever	26 (26%)

Table 2 Etiology of acute events

Etiology	Patients(n)
Infectious etiology	41
Hepatotropic viruses	14
Reactivation of Hep B or Hep C	2
Other infectious agents afflicting the liver	25
Non infectious etiology	58
Alcohol : active drinking within last 4 weeks	43
Hepatotoxic drugs	2
Flare of AIH or Wison's	3
Surgical intervention	0
Variceal bleed	10
Unknown hepatotoxic etiology	1

Short-term mortality

Out of the 100 patients, 48 patients died during the hospital stay and 7patients left the hospital against medical advice with a very sick status and were confirmed to have died via telephone contact with the family. Hence the overall short-term mortality in our study came out to be 55%.
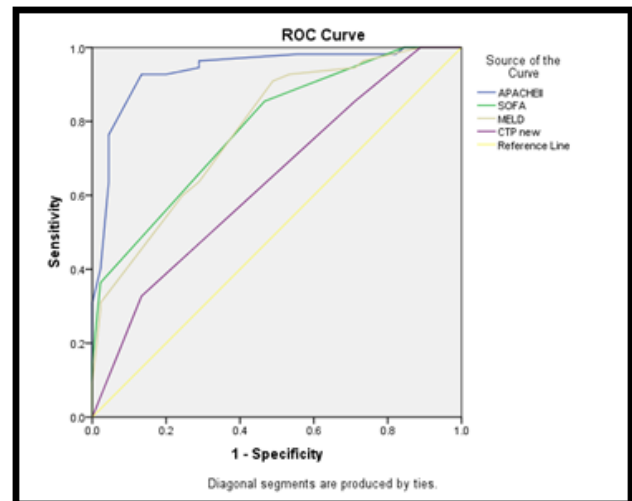
Comparison of prognostic scores and other factors

There was a significant difference in the values of MAP (p=0.044), Heart rate (p=0.042), Platelet count (p=<0.001), S. bil (p=<0.001), S. Sodium (p=<0.001), S. Creatinine (p=0.076), S. Albumin (p=<0.001)

and INR (p=<0.001) of survivors and non-survivors (Table 3a) (Table 3b).

Table 3a Etiology and types of ACLF

Etiology and type of ACLF	Patients(n)
Type I (non hepatic insult)	35
SBP	15
Cellulitis	2
UTI	3
LRTI	3
Sepsis/other sites of infection	2
UGI bleed	10
Post surgery decompensation	0
Type II (hepatic insult)	64
Type II A	
Acute viral hepatitis	14
Type II B	
Drug induced	2
Type II C	
Alcoholic hepatitis	43
AIH flare	3
HBV flare	2
Unknown etiology	1

Figure 1 Comparison of various prognostic scores.

The short-term mortality is high in ACLF with the mortality comparatively higher in patients with UGI bleed, SBP and various other causes of sepsis/infection as the cause of precipitating event. All the patients with UGI bleed in our study presented with low MAP, hematocrit and required urgent packed cell transfusions. Patients with ACLF who died had significantly higher CTP, MELD, APACHE II and SOFA scores than survivors. (p=0.001). APACHE II had a higher AUROC than SOFA, MELD, CTP (0.938 vs 0.782 for SOFA, 0.780 for MELD and 0.669 for CTP). This shows the superiority of APACHE II in relation to other scores for predicting short-term mortality (Table 4).

Table 3b Comparison of various biochemical & hemodynamic factors between survivors and non-survivors: [data represented in median (Inter quartile range)]

Variables	Non survivors[n=55]	Survivors[n=45]	P-value
MAP (mmHg)	70 (65.0-70.0)	83 (80-85)	0.044
HR (/min)	98 (88.0-110.0)	84 (80-90)	0.042
RR (/min)	24 (24.0-26.0)	18 (16-20)	0.112
Hct	35.8 (28.9-39.2)	39 (34.7-42.8)	0.124
TLC	9700 (7800-12900)	9400 (7730-10250)	0.128
Platelet count (×10³)	102 (78-148)	178 (118-214)	0.001
S. Sodium	125 (118-130)	139 (135.5-143)	0.001
S. Potassium	4.4 (3.8-4.8)	4.1 (3.8-4.8)	0.142
S.bil	22.7 (18.8-26.4)	11.8 (10.8-13.7)	0.001
S. Creat	1.2 (0.8-1.3)	0.8 (0.6-1.1)	0.076
S.albumin	2.4 (2.2-2.6)	2.9 (2.6-3.0)	0.001
INR	2.6 (2.1-2.9)	1.6 (1.6-1.9)	0.001

Table 4 Comparison of prognostic scores in patients with acute-on-chronic liver failure (ACLF) in predicting short-term Mortality

Scores	AUROC(95% CI)	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
APACHE II	0.94 (0.889-0.987)	92.7	86.7	89.5	90.7
SOFA	0.78 (0.694-0.87)	85.5	53.3	69.1	75
MELD	0.78 (0.69-0.869)	90.9	51.1	69.4	82.1
CTP	0.67 (0.561-0.778)	81.8	51.2	67.2	69.7

Discussion

Patients with ACLF usually present with multi-organ failure with poor overall survival. There was a short term mortality of 55% in our study. This is similar to the data published from various studies worldwide.[3,6,7]

Alcohol was the most common cause of underlying cirrhosis in our study (in 59%) with alcoholic hepatitis as the most common acute precipitating event (in 43%). Hepatitis B as an etiological factor of CLD in our study is less. In the Relief trial done in European countries, the etiology of liver disease was alcohol in 78% of the patients.[8] Similar results were shown in a study by Karavellas et al.[9]

In our study, a total of 35patients had type I ACLF (non hepatic insult), 65 had type II (hepatic insult). Considering these etiologies under infectious and non infectious causes as classified by APASL working committee, in our study, infectious causes amounted to 41% of the causes and non-infectious causes to 58%. Similar results are shown by few recent studies done in India on patients who strictly meet the criteria of ACLF according to APASL definition. Duseja et al.[5] concluded that Non hepatic insults are common acute precipitants in patients with Acute on Chronic Liver failure (ACLF). Out of 100 patients studied, 62patients had non hepatic cause, mostly SBP as a precipitant of Jalan et al.[10] concluded that non hepatic insults like gastrointestinal bleeding or sepsis may start a cascade of events that culminate in end-organ dysfunction and liver failure in a patient with stable cirrhosis. They postulated the cytokine burst and profound disturbance in systemic hemodynamics and their interplay as the major pathogenesis in these patients.[10]

The early short term mortality was higher in patients who had UGI bleed & sepsis. These clinical observations are supported by the fact that patients with sepsis & SBP have defects in neutrophil functions in the form of defective neutrophil locomotion, chemotaxis, phagocytosis and bactericidal capacity.[11,12]

Our study shows the superiority of APACHE II in relation to other scores for predicting short-term mortality. In critically ill cirrhotic patients admitted to an ICU, some studies have demonstrated that APACHE II and SOFA performed better than CTP in predicting in-hospital mortality.[13,14] In a study done by Zauner et al.[15] APACHE III was found to be the most reliable scoring system to separate survivors and non survivors. Yu et al.[16] in concluded that the APACHE III scoring system is superior to CTP and MELD scoring systems for prognosticating in-hospital mortality among decompensated cirrhotic patients.

Limited studies have been published on the usefulness of prognostic scores in patients defined strictly as ACLF. Garg et al.[6] studied the predictors of mortality in patients of ACLF. The CTP had AUROC of 0.667 whilst all three remaining scores MELD, SOFA and APACHE II had AUROCs of >0.8 which was significantly higher (p<0.05) than that of CTP. Krishna et al.[17] concluded that MELD scoring system was a better predictor of 3-month outcome than CTP score. Duseja et al.[7] assessed the performance of various prognostic scores in predicting short-term mortality in patients with ACLF. They concluded that short-term mortality is high in patients with ACLF. Overall, the area under the receiver operating characteristic curve of APACHE II score (0.74) was higher than that of SOFA (0.65), MELD (0.67) and CTP score (0.61).[7]

The CTP scoring system has been widely used to risk stratify cirrhotic patients and assess the efficiency of various therapeutic procedures, but is not ideal tool for predicting mortality or resource utilization in cirrhotic patients with multiple organ failure due to failure to assess extrahepatic prognostic factors such as cardiovascular, renal and pulmonary functions. APACHE II accurately risk stratifies critically ill patients with cirrhosis because it explains many of the factors known to influence prognosis. APACHE II incorporates parameters that measures the pulmonary, cardiac, electrolyte, acid-base and neurologic status of the patient. Hence the ultimate prognosis of patients with ACLF is significantly influenced by the degree of acute physiological derangements reflected by the acute physiology score of the APACHE model.[17]

There is scarcity of data on liver transplant in ACLF. Orthotropic liver transplantation remains the only definitive therapy for patients who do not improve with supportive measures to sustain life. Developing effective methods of liver support or other alternatives for transplantation and better prognostic scoring systems remains key goals to further improve overall survival rates for the condition.[18,19] Liver transplantation should be performed according to prognostic scores suggesting death within the next 3 months. It should be considered earlier if HRS develops.[1] Long-term results from chronic hepatitis-B-related liver disease are satisfactory.[18,19]

Given the limited treatment and limited medical resources, physicians require a reliable tool to risk stratify and monitor patients of ACLF. The use of various prognostic scores in patients with ACLF may help in categorizing patients to limited ICU resources and evolving therapies. So the early mortality can be predicted by applying APACHE II scoring system.

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None

Conflict of interest

Author declares that there is no conflict of interest.

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