Acute-on-chronic liver failure: MELD score 30-day mortality predictability and etiology in a Pakistani population.

Original Article

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ABSTRACT

Background: Cirrhosis is a pathological condition that ultimately leads to liver failure. Acute on chronic liver failure (ACLF) has a high short term mortality rate. Viral hepatitis is the most common cause of liver failure in our local population. We carried out this study to identity the 30-day mortality and etiology of patients presenting with ACLF using Model for End-Stage Liver Disease (MELD) score predictability.

Methodology: This was a descriptive case series, conducted at Sheikh Zayed Hospital, Lahore, Pakistan from January 31, 2018 to July 30, 2018. One hundred and eighty five patients who met the inclusion criteria were enrolled using 95% confidence level and 4% margin of error. Data was entered and analyzed with SPSS version 23.0. Numerical variables including age was presented by Mean ± S.D. Categorical variables i.e. gender, etiology of acute-on-chronic liver failure and 30-day mortality were presented by frequency and percentage. Data was stratified for age, gender, duration of chronic liver disease and MELD grade to address the effect modifiers. Post-stratification chi-square test was calculated using 95% significance ($p \leq 0.05$).

Results: Majority of the enrolled patients were male (74.6%) while only 25.4% of the patients were female. One hundred and thirty patients (70.3%) had underlying viral hepatitis while twelve patients (6.5%) and forty three patients (23.2%) presented with alcoholic liver disease and drug-induced ACLF, respectively. Eighty patients (43.2%) died within 30 days of admission.The 30-day mortality with respect to MELD grade was statistically significant ($p<0.001$) with the highest mortality noted in grade-IV and thirty five patients (43.8%) dying within 30 days of admission ($p<0.001$). Grade-II and III MELD scores also contributed to the 30-day mortality with twenty three patients (28.8%) and nineteen patients (23.8%) dying within 30 days of admission ($p<0.001$).

Conclusion: MELD scores are able to accurately predict the short-term mortality in patients with ACLF and viral hepatitis was the most common etiology in our population. Early detection and use of appropriate prognostic models may alleviate mortality and morbidity in paitents with ACLF.

Keywords: *Acute-on-chronic liver failure, model for end-stage liver disease, cirrhosis, etiology, short-term mortality.*

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INTRODUCTION

Cirrhosis is a pathological condition defined by diffuse fibrosis, disruption of the intrahepatic arterial and venous flow, portal hypertension and leading to liver failure. Two phases of cirrhosis have been identified, compensated and decompensated.[1] While compensated cirrhosis is asymptomatic, decompensated cirrhosis manifests with ascites, variceal haemorrhage and/or hepatic encephalopathy with a mean survival of approximately 3-5 years.[1]

Unless contraindications are present, patients may need to be evaluated for liver transplant. Depending on the underlying etiology, the decompensated cirrhosis may be reversed, such as due to alcohol abuse, obesity or chronic viral hepatitis.[1]Acute on chronic liver failure (ACLF) is defined as acute decomposition of cirrhosis associated with organ failure and high short-term 28-day mortality.[2] This is a separate entity when compared to decompensated hepatic cirrhosis due to occurrence of

organ failure, systemic inflammation, specific precipitating factors and high risk mortality.[3] In the Indian population, frequently-identified etiologies in patients presenting with ACLF include alcoholism followed by viral hepatitis and drugs.[4-7] The 30-day mortality in patients with ACLF ranged from 42.6% till 55% in the Indian Population.[4,5] However, the 30-day mortality in the Bangladeshi population was much lower at 16.67%.[8] In the Pakistani population, the most frequent etiology of ACLF was viral hepatitis (33.3%) followed by drugs (23.6%) while alcoholic liver disease was identified in only 8.3% of the patients. In the same cohort, the 30-day mortality was 39.3% in patients presenting to the Sindh Institute of Urology and Transplantation (SIUT), Karachi.[9] Patients with higher Model for End-Stage Liver Disease (MELD) scores had a higher frequency of mortality (66.7% vs. 33.3%; p=0.001) using MELD<30 vs. MELD ≥30. There are wide variations globally regarding the frequency of mortality with limited data in the Pakistani population.[9] In Pakistan, viral hepatitis has been identified as the most common underlying etiology for ACLF.[9] However, there are considerable geographic differences regarding the prevalence of viral hepatitis across Pakistan.[10-12] The following study aims to identity the 30-day mortality and etiology of patients presenting with ACLF to a tertiary care hospital using Model for End-Stage Liver Disease (MELD) score predictability.

SUBJECTS AND METHODS

This was a descriptive case series, conducted at department of gastroenterology, Sheikh Zayed Hospital, Lahore, Pakistan from January 31st 2018 to July 30th 2018.

Operational Definitons

a) Acute-on Chronic Liver Failure (ACLF): Liver cirrhosis was diagnosed with the following 2 criteria on ultrasonography:

1) coarse shrunken liver and 2) dilated portal vein (>50 x normal).

Diagnosed cases of liver cirrhosis for duration of disease of ≥1 year who presented with jaundice (total bilirubin >5 mg/dl) and coagulopathy (international normalised ratio ≥1.5) were then selected with a diagnosis of acute-on chronic liver failure.

b) Model for End-Stage Liver Disease (MELD) Grading: Patients diagnosed with ALCF within the last 24 hours who were included in the study and were graded per Model for End-Stage Liver Disease (MELD):

a. Grade-I: 6-10
b. Grade-II: 11-18
c. Grade-III: 19-24
d. Grade-IV: 25-40

c) Etiological spectrum:

a. **Viral Hepatitis:** Patient diagnosed with Hepatitis A, B, C and E by ELISA.
b. **Alcoholism:** Patients presenting with history of alcoholism in ≤6 months with gamma glutamyl transferase (γGGT) ≥50 IU/lit[15] in serum.
c. **Drug Induced:** Patients presenting with history of one or more of the following medication in the preceding 2 weeks:
    i. General anesthesia
        1. Halothane
        2. Chloroform
        3. Isoflurane, Enflurane, Desflurane
        4. Nitrous oxide
    ii. Interferon therapy
    iii. Anti-Tuberculous Therapy
    iv. Homeopathic medication
    v. Herbal medication

d) 30-day Mortality: Death of enrolled patients within 30 days of presentation to the hospital.

Sample Size

Sample size of 185 was calculated with 95% confidence level and 4% margin of error while estimating expected percentage of drug induced hepatitis as 8.3% in patients with ACLF.[9] The subjects were selected by non-probability consecutive sampling.

Inclusion Criteria

Adult patients of either gender, aged 20-60 years and diagnosed with acute-on-chronic liver failure (as per operational definition) in the last 24 hours.

Exclusion Criteria

Patients with chronic renal disease (serum creatinine levels ≥1.5 mg/dl), heart failure (ejection fraction ≤60%), respiratory failure (SpO2/FiO2<214) and/or cancer (diagnosed cases as preclinical record).

Data Collection

One hundred and eighty five patients presenting to the emergency department of Gastroenterology at Sheikh Zayed Hospital, Lahore who met the inclusion criteria were enrolled into our study. Detailed history and written informed consent to participate in the study was taken from each patient. The patients' age and gender were noted and they were evaluated for ACLF as per operational definitions. The patients were managed as per standard departmental protocols. The 30-day mortality was recorded as well as demographic details and etiology in the attached proforma. Laboratory testing was acquired at Sheikh Zayed hospital and the patients were managed by a single medical team to minimize bias. Confounding variables were controlled by exclusion.

Data Analysis

Data was entered and analyzed using SPSS version 23.0. Numerical variables including age was presented by Mean ± S.D. Categorical variables i.e. gender, etiology of acute-on-chronic liver failure and 30-day mortality were presented by frequency and percentage. Data was stratified for age, gender, duration of chronic liver disease and MELD grade to address the effect modifiers. Post-stratification chi-square test was calculated using 95% significance ($p \leq 0.05$).

RESULTS

Majority of the enrolled patients were male (74.6%) while only 25.4% of the patients were female [Table 1].

Seventy six patients were >50 years (41.1%) while sixty patients (32.4%) and forty nine patients (26.5%) were between 36-50 and 20-35 years, respectively [Table 2].

The duration of cirrhosis was 1-3 years in sixty seven patients (36.2%), 3-5 years in sixty one patients (33%) and >5 years in fifty seven patients (30.8%) [Table 3].

Thirty seven patients (20.0%) had MELD grade-I, while forty six patients (24.9%), fifty three patients (28.6%) and forty nine (26.5%) patients presented with MELD grades-II, III and IV respectively [Table 4].

One hundred and thirty patients (70.3%) had underlying viral hepatitis while twelve patients (6.5%) and forty three patients (23.2%) presented with alcoholic liver disease and drug-induced ACLF, respectively [Table 5].

Eighty patients (43.2%) died within 30 days of admission [Table 6].

The 30-day mortality with respect to MELD grade was statistically significant ($p<0.001$) with the highest mortality noted in grade-IV with thirty five patients (43.8%) dying within 30 days of admission ($p<0.001$) (Table 7). Grade-II and III MELD scores also contributed to the 30-day mortality with twenty three patients (28.8%) and nineteen patients (23.8%) dying within 30 days of admission ($p<0.001$) [Table 7].

There was no statistical significance of gender-based etiology ($p<0.770$) and gender-based 30-day mortality ($p<0.210$). Additionally, no statistical significance was observed for gender-based etiology ($p<0.770$), gender-based 30-day mortality ($p<0.210$), age-based etiology ($p<0.170$) and age-based 30-day mortality ($p<0.801$). The etiology of ACLF ($p<0.437$) and 30-day mortality ($p<0.605$) with respect to duration of disease was not statistically significant ($p<0.437$). The etiology of ACLF with respect to MELD score was also insignificant ($p<0.389$).

DISCUSSION

This is a novel study as it assesses the role of MELD score in ACLF as a prognostic marker in our local Pakistani population. Acute-on-chronic liver failure (ACLF) is prevalent in the South-Asian population due to high burden of viral hepatitis.[9] However, no prognostic models have been developed with specific data in this target population.[13] ACLF presents with multiple complications and has a short-term mortality rate of 50-90%.[14] While the most effective treatment modality is liver transplantation, there is a dearth of liver donors and the cost of procedures are high.[15] It is crucial to diagnose and determine the prognosis of patients with ACLF in order to categorize patients in need of liver transplantation or only intensive medical care.[16] The most commonly used model for its prognostic potential in ACLF is the model for end-stage liver disease (MELD) scoring system and it was established to determine the short-term prognosis in patients with liver cirrhosis who were undergoing transjugular intrahepatic portosystemtic shunts as well as to categorize the urgency of patients requiring liver transplantation by the United Network for Organ Sharing (UNOS).[16] MELD is based on three easily attainable biochemical variables including serum bilirubin, serum creatinine, and international normalized ratio (INR) of prothrombin time. The modified MELD scoring system incorporates the measurement of serum sodium levels.[17] In January 2016, the Organ Procuerment and Transplantation Network Policy 9.1 was updated to include serum sodium in the MELD score grading system. The model has been shown to accurately predict the short-term mortality of patients independent of etiology and complications such as portosystemic encephalopathy and spontaneous baceterial peritonitis.[18] Previous data indicates the validation of MELD score in predicting the 3-month mortality in cirrhotic patients.[19] However, these models may not be ideal for use in the Pakistani population and their potential to predict outcomes of patients in non-transplantation setting is not entirely clear. The prognosis of ACLF is dependent on multiple factors including multi-organ failure and brain oadema. Since MELD scores rely on serum markers including creatininem, INR and bilirubin, it is likely that correction of these measures via methods including plasma exchange or replacement therapy may negatively skew the MELD scores.[20] It is important to interpret MELD scores with precaution since better scores may not be representative of the severity of disease in the patients. Our study reports a high short-term 30-day mortality rate, 43.2%, in patients admitted due to ACLF. The MELD scoring system was used to categorize the severity of ACLF and the results are statistically significance for predicting the 30-day mortality with respect to MELD

Gender	Frequency	Percent
Male	138	74.6
Female	47	25.4
Total	185	100.0

Table 1: Frequency distribution of gender.

Age groups	Frequency	Percent
20-35 years	49	26.5
36-50 years	60	32.4
>50 years	76	41.1
Total	185	100.0

Table 2: Frequency distribution of age groups.

Duration of disease	Frequency	Percent
1-3 years	67	36.2
3-5 years	61	33.0
>5 years	57	30.8
Total	185	100.0

Table 3: Frequency distribution of duration of disease

MELD grade	Frequency	Percent
Grade-I	37	20.0
Grade-II	46	24.9
Grade-III	53	28.6
Grade-IV	49	26.5
Total	185	100.0

Table 4: Frequency distribution of MELD grade.

Etiology of ACLF	Frequency	Percent
Viral hepatitis	130	70.3
Alcoholic liver disease	12	6.5
Drugs	43	23.2
Total	185	100.0

Table 5: Frequency distribution of etiology of ACLF.

30-days mortality	Frequency	Percent
Yes	80	43.2
No	105	56.8
Total	185	100.0

Table 6: Frequency distribution of 30-days mortality.

MELD grade	30-days mortality		Total	p-value
	Yes	No		
Grade-I	3	34	37	<0.001
	3.8%	32.4%	20.0%	
Grade-II	19	27	46	
	23.8%	25.7%	24.9%	
Grade-III	23	30	53	
	28.8%	28.6%	28.6%	
Grade-IV	35	14	49	
	43.8%	13.3%	26.5%	
Total	80	105	185	
	100.0%	100.0%	100.0%	

Table 7: Stratification of 30-days mortality with respect to MELD grade.

scores. This study has shown strong validity of MELD scores for prediction of short-term mortality with regards to its sensitivity and specificity. However, there are concerns regarding the use of the MELD grading system. Of primary concern is whether the MELD prognostic model takes into account complications including esophageal varices, spontaneous bacterial peritonitis and other related complications.

CONCLUSION

The prospective study presents data for 30-day mortality and etiology of patients admitted with acute-on-chronic liver failure in a tertiary care hospital. The MELD score grading system is able to accurately predict the short-term mortality in patients with ACLF. Viral hepatitis was the most common etiology of cirrhosis in our population. These findings are consistent with previous studies that were conducted to validate the MELD score grading system as a liver disease severity index. While our study did not compare other prognostic models, application of the MELD score grading system needs to be scrutinized for use in the South-Asian population before being used for its predictive potential in short-term mortality of patients with ACLF.

LIMITATIONS

Our study has a few limitatations. First, we collected data from a single center that may introduce bias. Second, our sample size was small and we used a single MELD score instead of serial delta scores. Third, we did not compare MELD scores with other prognostic models. Last, the cut-offs used for the MELD scores in our study have not been validated by other studies in the South-Asian population. It may be of use to identify and validate accurate scoring systems for the South-Asian population which may lead to better survival in the population. Appropriate cut-points help isolate patients at risk of high mortality further prompting aggressive and correct management.[21]

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CONFLICT OF INTEREST

The Authors declared no conflicts of interest.

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