ORIGINAL ARTICLE

MELD Score: Utility and Comparison with King's College Criteria in Non-Acetaminophen Acute Liver Failure

Om Parkash, Khalid Mumtaz, Saeed Hamid, Syed Hasnain Ali Shah and S.M. Wasim Jafri

ABSTRACT

Objective: To compare Model for End-stage Liver Disease Score (MELD Score, MS) and King's College Hospital (KCH) criteria for finding correlation of mortality in non-acetaminophen induced acute liver failure (NAI-ALF).

Study Design: An analytical cross-sectional study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from 2005 to 2007.

Methodology: The study included patients with NAI-ALF. KCH criteria were labelled as good and bad prognosis groups. MELD score were calculated by using the MELD calculator. ROC was plotted and sensitivity analysis was done. ETA was used to see correlation between MELD and KCH.

Results: Ninety-one patients with mean age of 32.5 ± 16.3 years were studied; 49 were males (54%). Out of these, 57 patients died (63%); two leading causes of non-acetaminophen induced acute liver failure (NAI-ALF) were hepatitis hepatitis B virus (HBV) (n = 30, 33%) followed by hepatitis E virus in (n = 23, 25.3%). According to King's College Hospital (KCH) criteria, 50 patients (88%) who died had bad prognosis and 24 patients (70.6%) who survived had good prognosis. The ROC determined MELD score of 32 was the best predictor of mortality with sensitivity and specificity of 79% and 71%, respectively and positive predictive value (PPV) and negative predictive values (NPV) of 82% and 67% respectively. There was significant association between mortality and bad prognosis according to KCH criteria ($p < 0.001$). Overall mean MELD score (MMS) was 35.35 ± 8.64. MMS on admission was 38 ± 7.32 in patients who died and 30.7 ± 8.77 in those who survived ($p = < 0.001$). MMS correlated equally with KCH criteria (ETA = 0.52).

Conclusion: The admission MELD score has an excellent utility and correlates equally with KCH criteria for mortality in NAI- ALF.

Key words: *MELD score. KCH criteria. Non-Acetaminophen induced acute liver failure.*

INTRODUCTION

Acute liver failure (ALF) is an uncommon clinical syndrome characterized by sudden loss of liver function in apparently normal person with no pre-existing history of liver disease.[1] Previously labelled as fulminant hepatic failure (FHF), it causes high mortality as well as morbidity due to cerebral oedema, bleeding and infections.[2] ALF can be determined by the presence of deranged coagulation (INR > 1.5), hepatic encephalopathy and duration of illness ≤ 24 weeks. This syndrome has a variety of causes like viral aetiology, drug and toxin induced, metabolic errors, ischaemia and some rare causes.[1] The aetiology of ALF varies worldwide, for example very high rate of suicidal acetaminophen overdose in the United Kingdom (UK) and hardly any case of acetaminophen induced liver injury from developing countries.[3,4] Viral hepatitis is most common cause for ALF in the last three decades of the 20th century and among the viral aetiology most common are hepatitis B virus (HBV), hepatitis A virus (HAV) and in tropical countries hepatitis E (HEV) as well.

The prognosis and severity of ALF is of utmost importance because this would guide the physician to transfer these patients to intensive care unit (ICU) earlier and to an institute where desired management including liver transplantation is available. In the pre-liver transplant era, ALF had significantly high mortality i.e. > 80% of patients with ALF died without liver transplant.[5,6]

There are multiple prognosis scores and criteria available for ALF, but two score have been used popularly i.e. the King's College Hospital Criteria (KCHC) and Clichy's criteria.[7] Among these two prognostic criteria, KCHC has been used more extensively for ALF.[5] Utility of these scores has been checked in European Union (EU) and North America.[5,8,9] There are certain limitations of KCHC such as low sensitivity, few subjective parameters like duration between hepatic encephalopathy (HE) and jaundice and grade of HE; moreover, there is a delay in detection of severity of disease requiring transplantation.[10,11] Hence, there is growing interest to determine better prognostic criteria/scores for early detection of severity of ALF i.e. even before the development of HE in order to arrange

Department of Medicine, The Aga Khan University Hospital, Karachi.

***Correspondence:** Dr. Om Parkash, Gastroenterologist and Senior Instructor, The Aga Khan University Hospital, Stadium Road, Karachi.*
E-mail: om.parkash@aku.edu

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for either early shift to intensive care unit or referral to a liver transplant unit.[10]

The Model for End-stage Liver Disease (MELD) scoring system was originally designed for the assessment of short-term prognosis in patients with chronic liver disease undergoing a transjugular intrahepatic portosystemic shunts (TIPS) to reduce portal pressure.[12] MELD score is based on three biochemical parameters; total serum bilirubin, prothrombin time and creatinine. Now-a-days its use has been expanded to predict survival in end stage chronic liver disease in general. It has been applied as a disease severity index in organ allocation decisions for liver transplantation in patients with liver cirrhosis and also for short-term mortality (3 months) in patients waiting for liver transplantation.[13,14]

Recently MELD score has also been used to determine the prognosis in patients with acetaminophen and non-acetaminophen induced ALF in many studies.[10,15-17]

MELD was implemented in US in 2002 by UNOS for allocation of liver in patients with chronic liver disease, waiting for transplant.[15,17]

This study was conducted to determine the utility of MELD score and its correlation with KCH in predicting prognosis in patients with non-acetaminophen induced acute liver failure (NAI-ALF) and determine the correlation between MELD and KCH as well as that of bad prognosis with mortality.

METHODOLOGY

This analytical cross-sectional study was conducted at the Aga Khan University Hospital (AKUH), Karachi, from 2005 to 2007.

The diagnosis of ALF was based on the definition proposed by O'Grady and colleagues,[18] (deranged coagulation (INR >1.5), hepatic encephalopathy and duration of illness < 24 weeks). Initially ALF was defined by an interval between the onset of illness and appearance of encephalopathy of 8 weeks or less.[1,19]

Medical records of consecutive adult patients aged ≥ 14 years, coded as acute liver failure or fulminant hepatic failure (FHF) were included in this study. Patients with acute on chronic liver failure were excluded. A data collection form including demographics, aetiology, clinical features, laboratory parameters, and outcome was designed. The data was obtained from the Health Information Management System (HIMS) department of the hospital. All patients were offered standard management, including protein restriction, bowel decontamination, lactulose, rehydration and acid suppression by proton pump inhibitor or H2 antagonist. All patients were admitted to the special care unit (SCU) and shifted to intensive care unit (ICU) in case they needed mechanical ventilation. History was obtained from the patient's attendants, and a detailed clinical examination was performed at admission. A uniform management protocol was implemented in each case, which included monitoring and correction of blood sugar levels, inotropic support to maintain mean arterial pressure above 60 mmHg, and mechanical ventilation in grade III encephalopathy with cerebral oedema; intravenous mannitol was used to control cerebral oedema. Prophylactic antibiotics were started at presentation in all cases (such as ceftriaxone). Antibiotic therapy was modified based on culture reports. Antibiotics were continued till neurological recovery and resolution of evidence of infection was ensured. Haemodialysis was used whenever required. Neither liver transplantation nor liver support device were available at the centre, and each patient was followed-up until recovery or death.

All patients were categorized in two groups based on King's College Hospital criteria i.e. good and bad prognosis as shown in Table I. Hepatic encephalopathy (HE) grade I and II were categorized as early HE while grade III and IV were categorized as advanced HE.

Modified End-stage Liver Disease (MELD) score was calculated with the help of MELD calculator available online from United Network of Organ Sharing (UNOS) (http://www.unos.org/resources/meld-PeldCalculator.asp).

Based on MELD score, patients were divided into group 1 with MELD score < 32 and group 2 with MELD score > 32, based on previously reported value of MELD for grouping of ALF patients.[10,15] This study was approved by Ethic Review Committee of the hospital.

Statistical analysis was performed on Statistical Package for Social Sciences (SPSS version 16) for windows. Data were summarized as means ± standard deviation (SD) for continuous variables and as percentage for categorical variables. Median with inter-quartile range (IQR) was used for variables which did not have normal distribution. Student t-test was used for continuous variables and chi-square test was used for categorical variables (dichotomous variable). Receiver operating characteristic (ROC) analysis was used for determination of threshold values that had discriminated between KCHC and MELD score. In this analysis, a score with an area under curve (AUC) between 0.7 and 0.9 is considered to be clinically useful. Best value of MELD score was determined by ROC. Sensitivity and specificity of mortality was calculated for MELD score and for KCHC. Negative and positive predictive values for mortality were also determined for MELD score and KCHC. Correlation between the KCHC and MELD score was determined by ETA. P-value of ≤ 0.05 was considered as significant.

RESULTS

A total of 91 patients with NAI- ALF were included in the study. There were 49 males (54%) and median age was

Table I: King's College criteria for acute liver failure (1,3).

Acetaminophen group
• PH < 7.30 (Irrespective of grade of encephalopathy)
Or
• Prothrombin time > 100 seconds (INR > 6.5)
• Serum creatinine > 3.4 mg/dl (> 300 Mmol/L) in patients with grade III/IV encephalopathy
Non acetaminophen group
• Prothrombin time > 100 seconds (INR > 6.5; irrespective of grade of encephalopathy)
Or
Any three of following variables
• Age < 10 years or > 40 years
• Cause:
Non-A, non-B hepatitis
Drug induced
Idiosyncratic reactions
• Duration of jaundice before onset of encephalopathy > 7 days
• Prothrombin time > 50 seconds (INR 3.5)
• Serum bilirubin 17.6 mg/dl (> 300 mmol)

Table II: Demographic, clinical features and laboratory parameters of cohort with NAI-ALF (patients, n=91).

Variables	Values
Complete blood count	
• Haemoglobin (gm/dl)	13.09 gm/dl ± (2.5)^
• TLC (cmm)	14/cmm (11-18)*
• PLT (cmm)	194/cmm (125-310)*
Bleeding diathesis	
• PT in seconds	49 seconds (27-78)*
• INR	4.8 (IQR 2.7-7)*
Liver Function Test	
• Bilirubin (mg/dl)	16mg/dl(10-24)*
• SGPT (IU/L)	1267 IU/L (428-2663)*
• SGOT (IU/L)	796 IU/L (345-1774)*
• GGT (IU/L)	47 IU/L (30-94)*
• SAP (IU/L)	164 IU/L (128-224)*
Renal Function	
• S.Cr (mg/dl)	1.48 mg/dl± (0.86)^
• Arterial pH	7.37 (0.4)^

** Median with interquartile range (IQR); ^ Mean ± Standard deviation (SD).*

26 years (IQR 22-40 years). There were 70 patients (77%) below 40 years of age. Laboratory parameters of all patients with NAI-ALF are shown in Table II. Fifty-two patients (57%) had advanced (grade > II) HE at time of admission while in grade-I 12 (13/5) and 27 (30%) had grade-II. There were 86 patients (95%) who developed HE within 7 days of development of jaundice (hyperacute liver failure). All 91 patients (100%) had jaundice. NAI-ALF was caused by hepatitis B virus in 30 (33%), hepatitis E virus in 23 (25%), unknown aetiology in 19 (21%), drug induced in 11 (12%) and rest were miscellaneous including (HAV n=2, fatty liver of pregnancy, n=2, CMV n=2, HBV/HDV, n=2). Median hospital stay for all patients was 6 days (IQR 4-11). A total of 57 patients died (63%) and among them 50 (88%) were falling in the bad prognosis based on KCH criteria. Among those survived, 24/34 (77%) had good prognosis according to KCH criteria. There was a significantly higher mortality in bad prognosis group (n=60, p < 0.001) as compared to good prognosis (n=31). There was significant association between mortality and bad prognosis according to KCH criteria (p < 0.001).

Overall mean MELD score was 35.35 ± 8.64. Mean MELD score at the time of admission was significantly higher in patients (n=57) who died (38±7.32) as compared to patients (n=34) who survived (30.7 ± 8.77, p < 0.001). The ROC was developed to determine the best predictive value of MELD score shown in Figure 1; comparison between MELD and KCH is shown in Figure 2. Mean MELD score fairly correlates with KCH criteria (ETA=0.52).

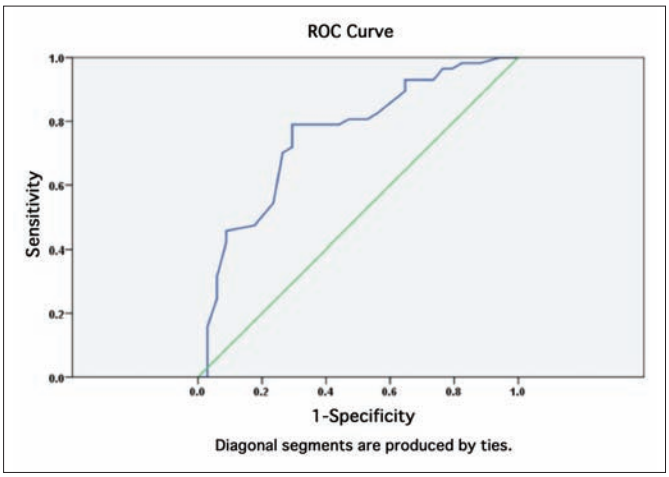

Figure 1: ROC curve of MELD for mortality in NAI-ALF patients.

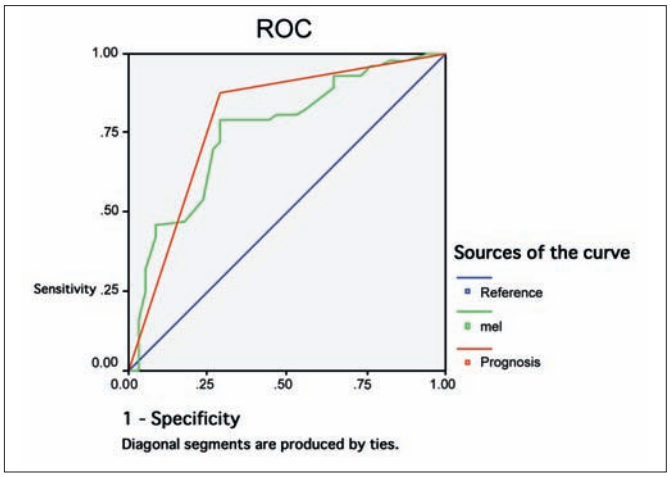

Figure 2: ROC comparing MELD with KCH criteria for mortality in NAI- ALF.

DISCUSSION

This is the first study from South Asia assessing the role of MELD score in ALF as prognostic marker. This study has shown excellent validity of MELD score (> 32 score) for death in terms of high sensitivity and specificity.

Similarly, there was a high positive predictive value for MELD score (> 32 score) as well as for bad prognosis of KCH criteria for death. Therefore, one can suggest bad outcome in ALF when MELD score exceeds 32.

Previously, MELD score has been validated as a good measuring tool to predict mortality in liver cirrhosis for 3 months.[13] It has already been used as a predictor of liver failure and death in acetaminophen induced liver failure in European studies. Schmidt *et al*. has not found MELD score useful in predicting death in acetaminophen induced ALF than isolated value of INR or KCH criteria; on the contrary they found it a useful predictor of ALF in acetaminophen induced liver injury.[10] There is very scant data regarding the use of MELD score in NAI-ALF; a recent report had suggested that MELD score can be used as a complement to other prognostic model especially in NAI-ALF.[20]

In a recent study on assessment of MELD score at listing for predicting survival of pre-transplant and post-transplant patients with ALF on waiting list of United Network for Organ Sharing (UNOS) as status 1. This study had suggested that patients who belonged to NAI-ALF group had poor survival, if liver transplant not received at 30 days and having negative correlation with MELD score. Hence, MELD was significantly predicting survival in NAI-ALF.[17] Contrary to this, this study has shown that MELD score of 32 and KCH criteria has excellent validity for mortality. Another study from India also reported that MELD score of 33 is better discriminator between survival and deaths as depicted by ROC which is in line with our MELD score cut off.[16]

Meaningful interpretation of MELD score in ALF is very critical because it is dependent on bilirubin, creatinine and prothrombin time (PT). ALF is a dynamic condition which mainly affects these three major systems. Therefore, continuous MELD score monitoring is more practical than KCH criteria. Moreover, theoretically different cut-offs can be used for different stages of disease, different populations and different indications.[10] Hence, MELD score can be used in patients with severe acute hepatitis before the onset of HE for proper triage to deliver better care and for possible liver transplant where facilities are available. Different cut-offs of MELD score were used to determine best prognostic value for mortality, which would have best sensitivity as well as specificity. This study has shown higher validity scores at a MELD score of 32 as compared to the study by Schmidt *et al*. who has reported lower validity score i.e. sensitivity of 58%, specificity of 54%, PPV 59% and NPV of 53%. Similarly, for KCH criteria, Schmidt *et al*. study reported lower validity as compared to this study. The sensitivity as well as specificity for KCH criteria in Schmidt *et al*. study is 67% and 79% respectively and lower values for NPV and PPV (68 and 79% respectively). This also confirms that the patients with NAI-ALF had more severe disease in which MELD score can do better in predicting prognosis.

There were significant differences among the MELD score of dead (MMS = 38) and survived (MMS = 30) patients as compared to Schmidt *et al*. (MMS = 32 vs. 30). This is important as it can be used as a predictor of mortality at the time of admission. Recently, another study by Yantorono *et al*. has reported that MELD score of 30 is an excellent prognosis indicator in patients with ALF both in adults and children.[21] They reported NPV of 100% and PPV of 91% while the present study had reported NPV of 67% and PPV of 82% which is much lower. Katoonizadeh *et al*. had shown higher NPV 91% as compared to 67% in this study and lower PPV (56%) as compared to much higher value (82%) in this study.[15]

Survival in the present study was 37% which is comparable with 34% reported by Schmidt *et al*.[10] Shakil *et al*. had reported higher specificity and PPV of KCH for poor outcome as compared to this report.[5] Contrary to Shakil *et al*. findings where 96% cases fulfilling KCH criteria died, mortality was 88% in this study.

There was a significant contribution of viral aetiology in ALF i.e. > 50% in this cohort as compared to Western studies in which viral aetiology is lower.[5,22] Aetiology of ALF was indeterminate in a significant proportion of this group as compared to in Western reports;[1] 21% in this cohort as compared to 14% by Lee *et al*. has unknown aetiology of ALF.[1] Dhimen *et al*. reported higher (50%) hepatitis B related ALF,[16] while hepatitis E virus was the causative factor in 25% of our patients. Interestingly indeterminate group (21%) is slightly higher as compared to the 19% by Dhiman *et al*.[16] This difference in aetiological agents from two developing countries has no scientific explanation, but could be related to a higher prevalence of hepatitis B in India as compared to Pakistan.

The patients who survived were younger (p=0.023). Dhiman *et al*. also reported similar significant difference for age in survivors of ALF;[16] besides age, the mortality in two studies were also similar.

Based on the results of sensitivity, specificity and predictive values of this study and due to a significant correlation between the MELD score and KCH, it can be proposed that MELD score can be used for predicting mortality in NAI-ALF.

The prognosis of ALF depends on many factors like hepatic regeneration, hepatic failure, brain oedema and multi-organ failure. There are practical limitations for MELD because of the dependence on creatinine, INR and bilirubin. These factors can be corrected with artificial measures like replacement therapy and plasma exchange or transfusion. Therefore, this correction could lead to decreased MELD score leading to seemingly better score and should be interpreted with caution.[10]

CONCLUSION

MELD score can be used complementary to other prognostic criteria for ALF especially in non-acetaminophen induced acute liver failure (NAI-ALF). Due to subjective parameters in KCH criteria, MELD score can replace it for predicting high risk of death due to NAI-ALF.

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