Delta model for end-stage liver disease and delta clinical prognostic indicator as predictors of mortality in patients with viral acute liver failure

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ABSTRACT

Objective: The objective of the study is to compare the model for end-stage liver disease (MELD) with clinical prognostic indicators (CPI) specifically the change in these parameters after 48 h of admission in predicting the mortality in patients with acute liver failure (ALF) due to acute viral hepatitis.

Materials and Methods: An open label, investigator-initiated prospective study was conducted that included 41 patients with acute viral hepatitis with ALF. The cases were followed prospectively till death or discharge. The MELD and CPI were calculated at admission and 48 h of admission.

Results: Patients having no change or worsening in CPI score, i.e., delta CPI more negative had a higher mortality over the next 48 h compared to patients having an improvement in their respective CPI score. Delta CPI predicted adverse outcome better than the presence of any three CPI on admission (P = 0.019). Patients having no change or a worsening in MELD score, i.e., delta MELD more negative, had a higher mortality in the next 48 h compared to the patients having improvement in their respective MELD score. However, MELD >33 on admission was superior to delta MELD in predicting the adverse outcome (P = 0.019).

Conclusion: Among the patients with ALF due to viral hepatitis, delta CPI was found to be superior to delta MELD in predicting the adverse outcome in patients with viral ALF (P < 0.0001).

Key Words: Acute liver failure, clinical prognostic indicator, model for end-stage liver disease, prognosis, viral hepatitis

INTRODUCTION

Acute liver failure (ALF) is a complex multi-system illness that results after a catastrophic insult to the liver, manifesting in the development of coagulopathy and encephalopathy within a short period. It carries a mortality rate in excess of 70%–80% and is responsible for an estimated 0.1% all deaths in the United States and perhaps, 6% of all liver-related deaths. Moreover, it accounts for about 7% of the liver transplants among adults. Therefore, the determination of prognosis for accurately predicting the outcomes in ALF is of immense value in establishing the need for referral to a specialist center. Among the prognostic criteria proposed, “Clichy Criteria” and the “King’s College Criteria” are used worldwide. The model for an end-stage liver disease (MELD) is a survival model based on a composite of three laboratory variables: serum

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creatinine, serum bilirubin, and international normalized ratio.\cite{6} Several newer prognostic scoring models have also come up recently, including clinical prognostic indicators (CPI),\cite{7} ALF in hospital mortality score,\cite{8} and scoring model for severe viral hepatitis.\cite{9} We conducted a study to compare MELD with CPI (age >50 years, jaundice-encephalopathy interval >7 days, presence of cerebral edema, creatinine >1.5 g/dl, prothrombin time >35 s), specifically the change in these parameters after 48 h of admission in predicting the outcomes in a cohort of patients with ALF due to acute viral hepatitis.

**MATERIALS AND METHODS**

Patients with ALF admitted to the emergency ward of a tertiary care hospital in Northern India between July 2006, and December 2007 were included in the study within 12 h of attending the emergency after taking a detailed consent. For the purpose of the study, ALF was defined according to the criteria of O’Grady et al.,\cite{1} i.e., onset of hepatic encephalopathy occurring within 12 weeks of onset of jaundice and further subclassifies into hyperacute (interval 0–7 days), acute (interval 8–28 days), and subacute (interval 29 days–12 weeks) liver failure.

Patients with evidence of underlying chronic liver disease or acute on chronic liver disease as evidenced by the presence of a shrunken liver, irregular surface, ascites, splenomegaly, collaterals on ultrasound, and history of excessive alcohol intake (>80 g/day in men or >30 g/day in women for 5 years or more) were excluded from the study.

A viral etiology was presumed when a history of exposure to drugs or toxins was absent, and a typical history of a prodromal illness was present. The diagnosis of acute viral hepatitis A, B, and E was made by the presence of anti-hepatitis A virus (IgM), hepatitis B surface antigen, anti-hepatitis B core antigen (IgM) and anti-hepatitis E virus (HEV) (IgM), respectively.

Hepatic encephalopathy was graded from grade 1 to 4 according to modified Parsons-Smith scale. The interval between detection of jaundice to the onset of hepatic encephalopathy was defined as “Jaundice-encephalopathy interval.”

The diagnosis of cerebral edema was based on the presence of bradycardia, hypertension (150/90 mmHg), increased muscle tone, unequal or abnormally reacting pupils, neurogenic hyperventilation, myoclonus, and spontaneous decerebrate posturing.

The patients were followed up to the point of discharge from hospital or death during this study. Univariate analysis was used to screen the variables on admission and after 48 h. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of CPI was calculated among survivors and nonsurvivors at admission and then again after 48 h. MELD score was calculated using the website calculator (http://www.unos.org/resources/meld-PeldCalculator.asp). Statistical analysis was performed by SPSS software for Windows, version 13.0, SPSS Inc., Chicago, IL, USA.

**RESULTS**

A total of 41 cases were included in the study after nearly twice as many were screened for inclusion and exclusion criteria. The cases were followed prospectively till death or discharge and grouped as survivors or nonsurvivors.

The patient cohort had a mean age of 27.83 ± 11.67 (range 12–64 years). There were 22 males (53.7%) and 19 females (46.3%). There were 38 patients (92.68%) with ALF and no patients with sub-ALF. Of the 38 patients with hyper-ALF, 13 (34.2%) survived as compared to none among the 3 patients with ALF. HEV (22 patients-53.65%), hepatitis A (10 patients-24.4%), and hepatitis B (6 patients-14.6%) were implicated to be the etiologies in the study group. Three patients had a dual infection with hepatitis A and hepatitis E.

The CPIs defined earlier adversely affected the outcome in our patients. The mean CPI score in the study population is shown in Table 1.

The presence of any three CPI was optimum in identifying survivors and nonsurvivors. The mortality increased with increasing number of adverse prognostic factors. Patients having no change or worsening in CPI score, i.e., delta CPI more negative had a higher mortality over the next 48 h compared to patients having an improvement in their respective CPI score. Delta CPI predicted adverse outcome better than the presence of any three CPI on admission (P = 0.019).

The mean MELD score is shown in Table 2. Mean MELD score at admission and at 48 h showed that there was a decrease (15.21%) in the mean MELD score in the survivor group during their course, whereas the mean MELD score raised (2.9%) in nonsurvivors on follow-up. Even though there was a considerable overlap in the values of MELD score among survivors and nonsurvivors, the value was significantly higher among nonsurvivors as compared to survivors.

Patients having no change or a worsening in MELD score, i.e., delta MELD more negative, had a higher mortality in the next 48 h compared to the patients having improvement in their respective MELD score. However,
MELD >33 on admission was superior to delta MELD in predicting the adverse outcome (P = 0.019).

Delta CPI was found to be superior to delta MELD in predicting the adverse outcome (P < 0.0001).

**DISCUSSION**

The etiology of ALF shows marked worldwide variation; viral causes predominate in the developing world, whereas drug-induced hepatotoxicity and seronegative hepatitis predominate the western world.[10‑15] The only definitive treatment option is liver transplant (orthotopic or living donor or auxiliary) along with supportive care. Mortality in centers with liver transplant facilities ranges between 21% and 41%.16] However, studies from our center, where liver transplant facilities only recently became available, showed a mortality up to 63.9%17 and it ranged in excess of 70% among other centers.18 This shows that early prognostication is necessary to identify the candidates that need an early liver transplant or referral to a center where it is available.

In this study, we have calculated delta MELD and delta CPI in our study group. Huo et al.[19] had shown that delta MELD of 2.5 was superior to the initial MELD score and CTP scores in predicting the outcome in patients with advanced cirrhosis. The idea underlying the study was clearly appealing: the worsening of death predictors should parallel the increase of death risk. However, the relationship between worsening predictor and increasing risk may be missed if death occurs before the second predictor measurement. Clearly, the design of the study was biased towards a more important prognostic role for delta MELD because of exclusion of patients dying after a single MELD, thus probably missing the most important prognostic information of initial MELD determination in this study.18 Bambha et al.[19] had shown similar results among patients of advanced cirrhosis listed for liver transplantation. Merion et al.[20] showed that mortality in patients with chronic liver disease who were on the transplant waiting list was directly increased by delta MELD score >5 over 30 days, independent of the absolute MELD score. However, in this study, patients with a higher MELD score were more medically ill, and hence, had undergone more frequent laboratory testing and subsequent reporting of higher delta MELD. Eliminating this bias of frequent laboratory testing, Northup and Berg[21] found no significant prediction of mortality by delta MELD after liver transplantation.

In all these above studies, delta MELD was calculated in patients with advanced cirrhosis or hepatocellular carcinoma. Delta MELD was calculated between initial MELD and MELD at 30 days. However, in our cohort of patients with ALF, it was logically not possible to wait for 30-day MELD calculation for calculation of delta MELD. To overcome this, we calculated delta MELD between the observation made at 48 h and assessed whether finding an early change in MELD can predict outcome. We found that patients having no change or worsening in the MELD score over 48 h, i.e., delta MELD more negative had an adverse outcome compared to those who had an improvement in the MELD over 48 h, i.e., delta MELD more positive. Similar observations have been made with delta CPI. However, initial MELD score on admission predicted mortality better than delta MELD (P = 0.019) in our study. Further, delta CPI was superior to any three CPI in predicting the mortality of patients (P = 0.019). However, some patients having a positive delta MELD, i.e., improvement in MELD score still died. In those patients, SIRS/sepsis was found to be the major cause of mortality. However, all the patients who had a negative delta CPI died, indicating the superiority of delta CPI over delta MELD in predicting the mortality (P < 0.0001).

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**Conflicts of interest**

There are no conflicts of interest.

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