Pediatric End-stage Liver Disease Score in Acute Liver Failure to Assess Poor Prognosis

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See ''To Transplant or Not to Transplant: Certainly One of the Questions'' by Shneider on page 164.

ABSTRACT

Background and Aim: Although establishing accurate prognosis in acute liver failure (ALF) is of paramount importance, prognostic scoring systems still fail to achieve success. The pediatric end-stage liver disease (PELD) score has been used as a predictor of mortality in children with chronic liver disease listed for liver transplantation (LT); however, experience with the PELD score in ALF is limited. The goal of the present study was to investigate the prognostic accuracy of the PELD score in children with ALF.
Patients and Methods: PELD score was calculated based on results of blood tests obtained at hospital admission from June 1999 to January 2009, in 40 consecutive patients younger than 18 years who presented with ALF. Poor outcome was defined as LT or death.
Results: Mean (±SD) age of patients was 5.3 ± 4.4 years (range 6 months–17 years); 52.5% were girls (n = 21). Etiologies of ALF were hepatitis A in 42.5% (17), indeterminate in 35% (14), autoimmune hepatitis in 17.5% (type 1 12.5% [n5], type 2 5% [n2]), and toxic in 5% (2). Mean PELD score was 34.92 ± 10.48 (range 6–55). PELD scores obtained on admission were significantly higher among nonsurvivors (39.8 ± 9.5) and recipients of an LT (39 ± 7.1) compared with those who survived without LT (31.3 ± 3) ($P < 0.001$). A cutoff of 33 in PELD score using receiver operating characteristic curves showed 81% specificity and 86% sensitivity for poor outcome (positive predictive value 92% and negative predictive value 69%; area under curve 0.88 95% confidence interval 0.77–1.0; $P < 0.0001$).
Conclusions: PELD score obtained upon admission may be of help to establish the optimal timing for LT evaluation and listing. Further validation in larger and more diverse populations is needed.

Key Words: acute liver failure, children, PELD score

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Acute liver failure (ALF) is characterized by an acute and diffuse liver lesion, with severe deterioration of liver function (1,2), responsible for a complex and multisystemic disorder. ALF is one of the most dramatic conditions in medicine occurring in healthy individuals and has a high risk of mortality. Coagulopathy and encephalopathy are classic indicators of liver insufficiency. In young children, encephalopathy can present with subtle mood changes, which may be difficult to detect. Encephalopathy is not considered essential for diagnosis (3).

Despite new therapies and support measures, survival continues to be low, ranging between 10% and 40% (4). After the introduction of liver transplantation (LT) as a therapeutic option for patients with ALF, survival rate reached 60% to 80% (5–7). The challenge consists in identifying early enough patients with ALF for whom chances of survival without LT are null to avoid developing severe complications that may contraindicate it. When to list a patient is critical for the success of LT. Knowledge of sensitive prognostic markers could also determine whether there is a possibility for recovery without LT. Transplantation implies surgical risks and permanent immunosuppression in a patient with a potentially reversible disease. LT must be indicated whenever chances for survival are lower without rather than with transplantation (8). Numerous prognostic models have been investigated mainly in adults with varying success. The goal of the present study was to investigate the prognostic accuracy of the PELD (pediatric end-stage liver disease)-MELD (model for end-stage liver disease) score in children with ALF admitted to our LT center.

PATIENTS AND METHODS

The retrospective analysis included a total of 50 consecutive patients younger than 18 years with ALF who were admitted to the pediatric intensive care unit of the Hospital Italiano, from June 1999 to January 2009. ALF was defined according to the Pediatric Acute Liver Failure Study Group criteria as the biochemical evidence of liver injury with absence of previously known history of chronic liver disease, coagulopathy not corrected by the use of vitamin K, and an international normalized ratio (INR) >1.5 in patients with encephalopathy or >2 in those without (9). Each PELD score was calculated based on blood tests results obtained at hospital admission. Poor outcome was defined as LT or death within 16 weeks of admission.

Studied Variables

Laboratory test results collected at admission included serum bilirubin, albumin, creatinine, and INR. In addition, age, sex, weight, height, and etiology of ALF were recorded. The stage of encephalopathy was also registered at the time of admission, using the West-Hevan criteria (10). The PELD score was calculated from clinical parameters (failure to thrive: tables by sex based on weight and height for age) and the first laboratory results obtained upon hospital admission in children younger than 12 years. The MELD score was calculated based on first laboratory data in children older than 12 years, using the Internet calculator *www.unos.org/resources/meld-PeldCalculator.asp* (11). The King's College Hospital (KCH) criteria were calculated upon admission. All of the

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patients received standard therapy in the pediatric intensive care unit. Placing of an intracranial pressure monitor was indicated in those who progressed to stage 3 to 4 hepatic encephalopathy. Follow-up PELD scores were not established because several patients received fresh frozen plasma before placement of intracranial pressure monitors or undergoing other invasive procedures. Liver support devices were not used in the present study. LT was indicated in patients with stage 4 hepatic coma and in those with progression or lack of improvement of encephalopathy and/or coagulopathy during hospitalization. LT was contraindicated whenever irreversible brain damage, multiorgan failure, and uncontrolled infection developed (12,13). Medical care and criteria for listing and LT remained mostly unchanged throughout the last 10 years. The study was approved by the institutional review board of the Hospital Italiano.

Data Analysis

Mean and standard deviation (range) were calculated for numeric variables and counts and percentages for categorical variables. The population was divided according to outcome during hospitalization into 2 groups: group I: survivors and group II: patients with poor prognosis, defined as LT or death. Comparisons between groups for numerical variables were performed by Student t test. $P < 0.05$ was considered statistically significant.

Statistical Analysis

Receiver operating characteristic (ROC) curves were calculated for the PELD-MELD score results according to outcome. ROC curves are indicators of diagnostic precision and provide unifying criteria in test evaluation processes. The area under the ROC curve (AUC) >0.8 indicates an excellent diagnostic accuracy, and a model with an AUC >0.7 may be considered clinically useful (14). Variables calculated to describe the prognostic value in ALF included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for both KCH and PELD-MELD score criteria. The Bayes theorem was applied to determine the posttest probability of LT or death. Statistical analyses were done with STATA software 8.0 (StataCorp, College Station, TX).

RESULTS

Of the total of 50 patients who were diagnosed as having ALF, 10 were excluded from analysis because of lack of complete laboratory data to calculate the PELD-MELD score. A total of 40 children with ALF were analyzed. Demographics, etiology, and clinical variants are shown in Table 1. Clinical variants of ALF, as defined by the interval between jaundice and encephalopathy and days in the transplant waiting list, did not differ between groups. Eleven (27.5%) survived with medical therapy, 6 (15%) died without LT, and 23 (57.5%) received an LT. Among the 11 patients who survived with medical treatment, only 7 were listed for LT. The remaining 4 patients significantly improved or resolved hepatic encephalopathy within 48 to 72 hours of hospitalization and therefore were not listed. Of the 6 patients who died without LT, 1 had a contraindication for the procedure on admission and 5 died while on the waiting list. Twelve (30%) developed stage 3 to 4 encephalopathy upon admission (Table 2). Mean PELD score was 34.92 ± 10.48 (range 6–55). PELD scores obtained on admission were significantly higher among nonsurvivors (39.8 ± 9.5) and patients receiving transplants (39 ± 7.1) compared with those who survived without LT (31.3 ± 3) ($P < 0.001$). Mean PELD score was significantly higher among patients with stage 0 to 2 encephalopathy who received LT or died within 16 weeks of admission ($P < 0.0002$) (Table 3).

TABLE 1. Characteristics on admission of children with acute liver failure

Variable	SV, n = 11	LT, n = 23	Non-SV, n = 6	P
Sex (%)				
Male	4 (36.4)	9 (39.1)	5 (83.3)	
Female	7 (63.6)	14 (60.8)	1 (16.7)	
Age	5.15 (8 mo–14 y)	5.25 (6 mo–17 y)	5.3 (28 y)	
Original indication LT (%)				
Hepatitis A	4 (36.4)	11 (47.8)	2 (33.6)	
Indeterminate	1 (9.1)	9 (39.1)	4 (66.4)	
Autoimmune hepatitis 1	3 (27.3)	2 (8.6)	—	
Autoimmune hepatitis 2	2 (18.2)	—	—	
Toxic	1 (9.1)	1 (4.3)	—	
Clinical variants of ALF (%)				
Hyperacute	—	2 (8.6)	1 (16.6)	
Acute	11 (100)	17 (74)	3 (50)	
Subacute	—	4 (17.4)	2 (33.4)	
Encephalophathy (%)				
Grade 0–2	8 (72.8)	18 (78.2)	2 (33.3)	
Grade 3–4	3 (27.2)	5 (21.8)	4 (66.7)	
Serum bilirubin, mg/dL	19.4 ± 10.8	26.8 ± 6.5	22 ± 7.8	<0.09
INR	4.6 ± 1.7	5.5 ± 3.3	4.8 ± 3.1	ns
Albumin, g/dL	2.8 ± 1.3	2.7 ± 0.9	2.4 ± 1.6	ns
Days on waiting list	3.9 ± 2.1	4.6 ± 4.1	4.8 ± 3.9	ns
PELD-MELD	31.1 ± 10.3	39.6 ± 7.1	39.8 ± 9.5	<0.001

ALF = acute liver failure; INR = international normalized ratio; LT = liver transplantation; MELD = model for end-stage liver disease; PELD = pediatric end-stage liver disease; SV = survivors.

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TABLE 2. Stage of hepatic encephalopathy and outcome in 40 children with acute liver failure

Clinical features	All, n = 40	SV, n = 11	LT/Non-SV, n = 29
No encephalopathy (%)	13 (32.5)	6 (54.5)	7 (24.1)
Encephalophathy (%)			
Grade 1	2 (5)	—	2 (6.9)
Grade 2	13 (32.5)	2 (18.1)	11 (37.9)
Grade 3	10 (25)	3 (27.4)	7 (24.2)
Grade 4	2 (5)	—	2 (6.9)

LT = liver transplantation; SV = survivors.

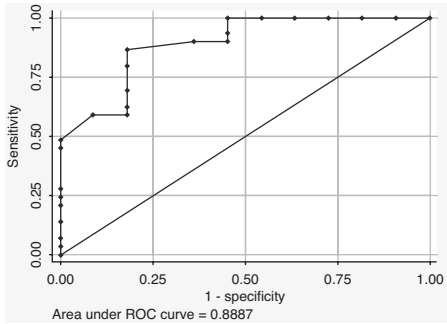

FIGURE 1. ROC curve of PELD score in 40 children with acute liver failure.

A cutoff of 33 in PELD score using the ROC curve showed a specificity of 81% and a sensitivity of 86% for poor outcome (PPV 92% and NPV 69%, AUC 0.88 95%, confidence interval [CI] 0.77–1.0, $P < 0.0001$) (Fig. 1). The KCH criteria analysis provided a sensitivity of 88%, a specificity of 72%, a PPV of 88%, and an NPV of 61%, lower than what was calculated with the PELD-MELD score (Table 4). The pretest probability of a poor prognosis of 70% increased to 91% in those patients with a PELD score of 33 or higher (LR+ 4.52). In patients with a PELD score <33, the posttest probability decreased to 28% (LR− 0.17). The odds ratio between patients with positive and negative scores was 3.93 (CI 1.75–8.86, $P = 0.000866$).

DISCUSSION

In the present retrospective study, we evaluated the prognostic accuracy of the PELD-MELD score upon hospital admission in a cohort of pediatric patients with ALF. Using the ROC curve, it was determined that a PELD-MELD cutoff value of 33 or higher presented an accurate specificity and sensitivity to discriminate patients with poor outcome, a value identical to that found by Dhiman et al (8) in a study that compared the prognostic value of the MELD score versus the KCH criteria in adult patients. These results suggest that the PELD-MELD score obtained at admission in pediatric patients could be helpful in establishing the optimal moment for LT evaluation and inclusion in the emergency waiting list because it can significantly discriminate patients with poor prognosis. When patients with stage 0 to 2 encephalopathy are evaluated, the use of the PELD score may contribute to identify those patients with poor outcome despite absence of encephalopathy.

KCH criteria reported by O'Grady et al (15) and the Clichy criteria reported by Bernuau and Benhamou (16) and Bernuau et al (17) are considered to be the most valuable tools to assess prognosis. Several studies have reported a PPV of 70% to 100% and a NPV of 25% to 94%, with acceptable specificity but low sensitivity. Yantorno et al (18) concluded that Clichy criteria were more useful in children and that the MELD-PELD score was superior to that of the KCH and Clichy, with a diagnostic accuracy of 95% (C-statistic 0.96). Compared to the KCH and Clichy criteria, the MELD score was a better death predictor (KCH: PPV 71%, NPV 84%; Clichy: PPV 91%, NPV 72%; MELD >30: PPV 91%, NPV 100%). Renal failure developed in 45% of those who died while on the waiting list. This represents an additional advantage of MELD over KCH and Clichy because its calculation does not include serum creatinine as a prognostic variable.

TABLE 3. Stage of hepatic encephalopathy grade 0–2 and mean PELD-MELD score

	Group I, n = 8	Group II, n = 20	*P*
PELD-MELD	24.09 ± 10.9	37.9 ± 6.2	0.0002

Group I = survivors; group II = liver transplant/non-survivors; MELD = model for end-stage liver disease; PELD = pediatric end-stage liver disease.

The Pediatric Acute Liver Failure Study Group was created in 1999 and developed a database with the purpose of facilitating the comprehension of all of the aspects of ALF in children. By logistic regression analysis, it was shown that serum bilirubin values ≥5 mg/dL, INR ≥2.5, and hepatic encephalopathy were predictive factors of death or LT (9), both variables which are included in the PELD-MELD score. A study of 210 patients made in 2 pediatric LT centers in Argentina concluded that the most significant indicators of death or need for LT were prothrombin time and stage 3 to 4 encephalopathy (19). During the last 2 decades, many static and dynamic scores have been proposed to assess prognosis in patients with ALF such as the liver injury units score (20) and the acute physiology and chronic health evaluation (21); however, none of these models offered advantages over the existing ones. Several other studies suggested different clinical, biochemical, radiological, and histological prognostic markers (prothrombin time (22), factor V and factor VIII (23), serum bilirubin (24), α-fetoprotein (25), serum phosphate (26,27), lactate (28), galactose elimination capacity (29), ammonia (30), and vitamin D–binding protein (31)), images (residual liver value <700 cm^3), necrosis extension obtained by transjugular biopsy (32,33), and others such as age, etiology, and encephalopathy stage (16,20). None of the aforementioned has been validated in prospective studies including a large enough cohort of pediatric patients.

Combining in the same group of analysis patients with LT with those that died could introduce a bias because it implies that every patient with LT would have otherwise died under medical treatment. Another limitation was the fact that 10 patients were excluded from the analysis because of the lack of complete laboratory reports to calculate the PELD-MELD score. Clinical characteristics of these 10 patients did not differ from the rest of the studied group. As opposed to chronic patients, the accessory variables of PELD over MELD in terms of weight and height by age would have no value in the acute presentation in which they would not be modified. Age could be of importance, however, because (as seen with the KCH criteria) young patients could present a higher risk of death. In addition, hepatitis A is an infrequent cause of ALF in most countries. Although the

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TABLE 4. Sensitivity, specificity, PPV, NPV of King's College, and PELD-MELD score in patients with LT and those who died

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
KCH criteria	82	72	88	61
PELD-MELD	86	81	92	69

KCH = King's College Hospital; MELD = model for end-stage liver disease; NPV = negative predictive value; PELD = pediatric end-stage liver disease; PPV = positive predictive value.

predominant cause of ALF in the present study was hepatitis A, we found a high percentage of indeterminate hepatitis (35%), similar to what was described in other geographical areas, and a surprisingly high percentage of autoimmune hepatitis (AIH) (17.5%). Finally, the absence of acetaminophen toxicity limits the generalization of the results.

Determining prognosis in ALF is critical for both LT indication and organ assignment. Future studies to improve these score systems will allow for a better assessment and evaluation, and optimize the organs and resources in adults and children.

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