LIVER TRANSPLANTATION 13:822-828, 2007

ORIGINAL ARTICLE

MELD Is Superior to King's College and Clichy's Criteria to Assess Prognosis in Fulminant Hepatic Failure

Silvina E. Yantorno,[1] Walter K. Kremers,[2] Andrés E. Ruf,[1] Julio J. Trentadue,[1] Luis G. Podestá,[1] and Federico G. Villamil[1]

[1]*Liver Unit, Fundación Favaloro, Buenos Aires, Argentina;* [2]*William J. von Liebig Transplant Center, Mayo Clinic, Rochester, MN*

Assessment of prognosis in fulminant hepatic failure (FHF) is essential for the need and appropriate timing of orthotopic liver transplantation (OLT). In this study we investigated the prognostic efficacy of King's College criteria, Clichy's criteria, Model for End-Stage Liver Disease (MELD), and Pediatric End-Stage Liver Disease (PELD) in 120 consecutive patients with FHF. Survival with medical therapy (18%), death without OLT (15%), and receipt of a liver transplant were similar in adults (n = 64) and children (n = 56). MELD scores were significantly higher in patients who died compared to those who survived without OLT, both in adults (38 ± 7 vs. 26 ± 7, $P = 0.0003$) and children (39 ± 7 vs. 23 ± 6, $P = 0.0004$). Using logistic regression analysis in this cohort of patients, concordance statistics were significantly higher for MELD (0.95) and PELD (0.99) when compared to King's College (0.74) and Clichy's criteria (0.68). When data was analyzed in a Cox model including patients receiving transplants and censoring the time from admission, the concordance statistic for MELD (0.77) and PELD (0.79) remained significantly higher than that of King's College criteria but not higher than that of Clichy's criteria. In conclusion, this study is the first to show that MELD and PELD are superior to King's College and Clichy's criteria to assess prognosis in FHF. However, because data was generated from a single center and included a rather low number of patients who survived or died without OLT, further confirmation of our findings is required. ***Liver Transpl 13:822-828, 2007.*** © **2007 AASLD.**

Received August 22, 2006; accepted December 19, 2006.

See Editorial on Page 786

Fulminant hepatic failure (FHF) is the most severe and dramatic of all liver diseases. Reported mortality rates with supportive medical therapy range from 60 to 90%.[1,2] The advent of orthotopic liver transplantation (OLT) significantly improved outcome for adults and children with FHF. However, major benefits provided by OLT are limited by its relatively low applicability, either due to development of contraindications such as irreversible brain damage or multiorgan failure or the unavailability of an organ donor in a timely fashion.[3,4] Castells et al.[3] showed that among 49 patients with FHF meeting criteria for OLT, 17 developed contraindications, 4 died on the waiting list, and only 28 (57%) received transplants. Similarly, applicability of OLT was 66% in a multicenter study of 308 consecutive patients with FHF reported by Ostapowicz et al.[4] Accurate assessment of prognosis early after referral is a key factor for the appropriate timing of OLT and the outcome of FHF. Effective prognostic markers should allow the differentiation of patients likely to survive with medical therapy, and thus with no need for OLT, from those with poor prognosis in whom OLT should not be delayed. At present, the King's College criteria reported by O'Grady et al.[5] and the Clichy's criteria reported by Bernuau and Benhamou[6] and Bernuau et al.[7] are considered to be the most valuable tools to assess progno-

Abbreviations: FHF, fulminant hepatic failure; OLT, orthotopic liver transplantation; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease.

Supported in part by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (DK 34238) and from Fundación para la Docencia e Investigación de las Enfermedades del Hígado (FUNDIEH).

Address reprint requests to Professor Federico G. Villamil, Liver Unit, Fundacion Favaloro, Avenida Belgrano 1782 (C1093AAS), Piso 5, Buenos Aires, Argentina. Telephone: 54 11 4378 1366; FAX: 54 11 4378 1392; E-mail: fvillamil@ffavaloro.org

DOI 10.1002/lt.21104
Published online in Wiley InterScience (www.interscience.wiley.com).

sis in patients with FHF. The Model for End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) have been found to be excellent predictors of 3-month mortality in adults and children with chronic liver disease listed for OLT.[8-10] However, experience with MELD and PELD in FHF is limited. Kremers et al.[11] recently investigated the ability of MELD to predict pre- and post-OLT survival in 720 patients listed as status 1 in the Organ Procurement and Transplantation Network/United Network for Organ Sharing. This study showed that patients with nonacetaminophen FHF had statistically significant lower survival rates while awaiting OLT than those with primary nonfunction or hepatic artery thrombosis and that the risk of death correlated significantly with MELD scores. In addition, the group with nonacetaminophen FHF had the greatest survival benefit with OLT. The goal of the present study was to investigate the prognostic accuracy of the King's College criteria, Clichy's criteria, MELD, and PELD in adults and children with FHF.

PATIENTS AND METHODS

The study included 120 consecutive patients with FHF who were referred to our institution between June 1995 and August 2004. Of these, 64 (53%) were adults and 56 (47%) were children. Among the pediatric group, only 5 patients (8.7%) were aged 11 to 16 yr. Due to the low number of cases, prognosis of FHF in adolescents was not analyzed either as a separate subgroup or in combination with adults. FHF was defined as the acute onset of coagulopathy and hepatic encephalopathy within 8 weeks of initial symptoms in patients with no previous history of liver disease.[12] Clinical variants of FHF were defined according to the criteria reported by Bernuau and Benhamou[6] and O'Grady et al.[13] King's College criteria, Clichy's criteria, and MELD score were calculated based on the results of blood tests obtained on hospital admission and compared to each other in 40 of 120 patients (33%) who either survived or died without OLT. Patients who underwent OLT were excluded from the analysis of prognosis, except for the Cox model which included the entire cohort. PELD was evaluated only in the pediatric population. Follow-up MELD and PELD scores were not analyzed because several patients received transfusions of fresh frozen plasma before placement of intracranial pressure monitors or other invasive procedures. All data was collected prospectively and analyzed retrospectively. Indicators of poor outcome of the King's College criteria for patients with nonacetaminophen FHF are either an international normalized ratio of prothrombin >6.5 or presence of at least 3 of 5 variables including age (<10 or >40 yr), interval from jaundice to encephalopathy >7 days, indeterminate or drug-induced etiologies, international normalized ratio of prothrombin >3.5, or serum bilirubin >300 μmol/L.[5] Clichy's criteria indicate a poor prognosis when hepatic encephalopathy is associated with factor V concentrations <20% for patients aged <30 yr or <30% for those older than 30 yr.[6,7] Of note, these prognostic variables were derived only from patients with FHF of viral etiology. MELD and PELD scores were calculated according to United Network for Organ Sharing.[14] One patient with chronic renal failure on hemodialysis developed fulminant hepatitis B and died on the waiting list. Otherwise, no patient with FHF required renal replacement therapy for acute renal dysfunction. FHF was considered of indeterminate etiology in patients with no previous exposure to hepatotoxic drugs and with negative immunoglobulin M antibodies to hepatitis A virus, immunoglobulin M antibodies to hepatitis B core antigen, hepatitis B surface antigen, hepatitis C virus ribonucleic acid by qualitative polymerase chain reaction, autoantibodies, and metabolic markers. Fulminant autoimmune hepatitis was diagnosed in patients with no history of chronic liver disease, acute onset with coagulopathy and encephalopathy, detectable autoantibodies, and massive or submassive hepatic necrosis in the explant or liver biopsy. In this series, there were no cases of FHF due to acetaminophen toxicity. All patients received standard medical therapy in the intensive care unit. Intracranial pressure monitoring was indicated in those who progressed to stage 3-4 hepatic encephalopathy. Liver support devices were not utilized in this study. OLT 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. Medical care and criteria for listing and OLT remained mostly unchanged throughout the 9-yr study period. The study was approved by the Institutional Review Board.

Statistical Methods

Data were summarized using means ± standard deviation (range) for numeric variables, and counts and percents for categorical variables. Group comparisons for numerical variables are based upon a *t*-test, binomial variables based upon a Fisher's exact test, and other categorical variables based upon a chi-squared test. Positive and negative predictive values, diagnostic accuracy, and concordance statistic are used to describe the predictive and discriminative value of the predictors of survival. Concordance between mortality for the 30-day period since FHF onset and predictors of mortality were derived both from the logistic model to allow comparison with earlier studies of survival in patients with end-stage liver disease,[9,15] as well as for the Cox model,[16,17] which accounts for the variable follow-up due to transplantation. For the logistic model, concordance only took into consideration those patients who survived 30 days or who died within 30 days of FHF onset (n = 41) and does not use information on those individuals who were transplanted within 30 days. One patient with sub-FHF underwent OLT beyond 30 days of admission and was therefore included in the logistic model. For the Cox model, concordance is essentially the fraction of patient pairs in which the model correctly identifies which patient died first. Cox analysis included the entire cohort of patients with FHF. Differences in concordance for the prognostic

TABLE 1. Characteristics on Admission of Adults and Children With Fulminant Hepatic Failure

Variable	Adults (n = 64)	Children (n = 56)	*P*-value
Median age (yr)	35 (18–65)	4 (0.6–16)	
Etiology of fulminant hepatic failure			0.0001
Hepatitis A	8 (12%)	27 (48%)	
Hepatitis B	7 (11%)	0	
Autoimmune hepatitis	12 (19%)	2	
Drug-induced hepatotoxicity	11 (17%)	1	
Pregnancy	5 (8%)	0	
Wilson's disease	2	3	
Giant-cell hepatitis	0	1	
Indeterminate	19 (30%)	22 (39%)	
Clinical variants of acute liver failure			
Fulminant	36 (56%)	40 (71%)	
Subfulminant	28 (44%)	16 (29%)	0.09
Hyperacute	23 (36%)	13 (23%)	
Acute	28 (44%)	31 (55%)	0.35
Subacute	13 (20%)	12 (22%)	
Serum bilirubin (mg/dL)	24.5 ± 13.6	26.6 ± 12.9	0.39
INR	3.2 ± 2.0	4.7 ± 2.8	0.002
Stage 3–4 hepatic coma	36 (56%)	24 (43%)	0.20
MELD	32.5 ± 8.1	34.2 ± 7.7	0.26
PELD	NA	38 ± 13.1	NA

Abbreviations: NA, not analyzed; INR, international normalized ratio.

TABLE 2. Outcome of Adults and Children With Fulminant Hepatic Failure

Outcome	Adults (n = 64) (%)	Children (n = 56) (%)	All patients (n = 120) (%)
Survived without OLT	11 (17)	11 (20)	22 (18)
Listed	2	2	4
Died without OLT	11 (17)	7 (12)	18 (15)
Listed	6	3	9
Contraindication	5	4	9*
Underwent OLT	42 (66)	38 (68)	80 (67)

Abbreviation: OLT, orthotopic liver transplantation.
*Multiorgan failure = 6, brain death = 3.

scores were assessed using the jackknife method. A *P* value <0.05 was considered statistically significant.

RESULTS

Demographics, etiology, clinical variants, and severity of liver failure in adults and children with FHF are described in Table 1. Hepatitis A was the most frequent identifiable etiology in the pediatric group (48%) and autoimmune hepatitis (19%) and drug-induced hepatotoxicity (17%) among adults. FHF was classified as of indeterminate etiology in approximately one-third of both adults and children. Clinical variants of FHF, as defined by the interval between jaundice and encephalopathy,[6,13] serum bilirubin, and MELD scores, did not differ between groups. Although the proportion of children with stage 3-4 hepatic coma was lower than in adults, international normalized ratio of prothrombin was significantly higher in the pediatric population. Survival with medical therapy (18%), death without OLT (15%), and receipt of an OLT (67%) were similar in adults and children with FHF (Table 2). Among the 22 patients who survived with medical therapy, only 4 (2/11 adults and 2/11 children) were listed for OLT. The remaining 18 patients significantly improved or resolved hepatic encephalopathy within 48-72 hours of hospitalization and therefore were not listed. Of the 18 patients who died without OLT, 9 had contraindications for the procedure that were present on admission (5/11 adults and 4/7 children) and the other 9 died while awaiting an organ donor (Table 2). The diagnostic accuracy of King's College criteria and Clichy's criteria in patients who either survived or died without OLT was 73% and 71%, respectively, as shown in Table 3. Clichy's criteria had a higher positive predictive value (87% vs. 65%) than King's College criteria but a lower negative predictive value (67% vs. 83%). King's College criteria were more useful in adults (diagnostic accuracy of 78% vs. 67%) and Clichy's criteria in children (83%

TABLE 3. Positive Predictive Value, Negative Predictive Value, and Diagnostic Accuracy of King's College Criteria and Clichy's Criteria in Patients Who Survived or Died Without Liver Transplantation

Prognostic marker	PPV (%)	NPV (%)	DA (%)
King's College criteria			
Adults	80	77	78
Children	54	100	67
All patients	65	83	73
Clichy's criteria			
Adults	75	58	61
Children	100	79	83
All patients	87	67	71

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; DA, diagnostic accuracy.

vs. 61%). The diagnostic accuracy of the King's College criteria in adults with FHF of this study (78%) was similar to that of previously reported series (Table 4). MELD scores were significantly higher in patients who died compared to those who survived without OLT both in adults and children. Similar results were observed with PELD in the pediatric population (Table 5). Among the 22 patients who survived with medical therapy, MELD score was ≤30 in 20 (91%). Conversely, MELD was >30 in 17 of 18 (94%) patients who died without OLT (Fig. 1). PELD scores were >30 in the 7 children who died and <30 in 10 of 11 survivors (91%).

Using logistic regression analysis, all prognostic scores studied were significant predictors of death, with concordance statistic values ranging from 0.68 to 0.99. However, concordance statistics were much higher for MELD (0.95 in all patients) and PELD (0.99) when compared to Clichy's criteria (0.68) and King's College criteria (0.74), both in adults and children. (Table 6). Considering all patients, MELD score was significantly different from the King's College criteria ($P = 0.0037$) and Clichy's criteria ($P = 0.0001$). Comparison between subgroups is described in Table 6. When the data was analyzed in a Cox model including patients who survived or died without OLT and those who were transplanted censoring the time-interval from admission (n = 120), the concordance score for MELD (0.77) and PELD (0.79) remained higher than that of the Clichy's criteria (0.64). King's College criteria were not a significant predictor of death in this model (Table 7). Considering all patients, MELD score was significantly different from the King's College criteria ($P = 0.0001$) and marginally significantly different from the Clichy's criteria ($P = 0.064$). Comparison between subgroups is shown in Table 7.

Renal dysfunction, defined as serum creatinine concentrations >1.4 mg/dL, occurred in 5 of 11 (45%) adults who died without OLT and in 3 of 11 (27%) who survived with medical therapy. Mean serum creatinine was 2.8 ± 3.0 mg/dL and 1.4 ± 1.1 mg/dL, respectively. All children had serum creatinine levels <1 mg/dL.

MELD scores obtained on admission were significantly higher ($P = 0.03$) in adults with FHF who died after OLT (36 ± 9, n = 14) compared to those who survived (31 ± 7, n = 28). In contrast, no such difference was observed in children (36 ± 4 vs. 36 ± 5) who died (n = 7) or survived (n = 32) after liver transplantation.

DISCUSSION

A survey conducted in 2001 by the Argentina Society of Transplantation showed that among 212 adults with FHF referred for OLT there was not a single case of acetaminophen toxicity and that hepatitis A was the main cause of FHF in the pediatric group (127/219, 58%) (F. Villamil, personal communication). Therefore, etiology of FHF in this study is representative of our geographic region.

Over the last 2 decades, many static and dynamic variables have been proposed to assess prognosis in patients with FHF. This rather long list includes, among others: age,[6,18,19] etiology,[6,18,19] stage of encephalopathy,[6,18,19] biochemical tests, such as serum bilirubin,[5,18] serum phosphate,[20] alfa-fetoprotein,[21] arterial ketone body ratio,[22] and vitamin D-binding protein,[23] coagulation parameters, such as prothrombin time,[24] factor V,[25] and factor VIII,[26] and the extent of parenchymal necrosis on biopsies obtained by the transjugular route.[27] Although significant differences have been reported for some of these variables when comparing patients with FHF who survived or died, they are of little help to assess prognosis in an individual patient and, most importantly, to decide whether there is a need for OLT. Since their original description in the late 1980s, King's College and Clichy's criteria have been accepted and validated as the most useful tools to establish the risk of death and need for OLT among patients with FHF.[5,22,25,27-30] However, the major limitation of these criteria is their low negative predictive value. As shown in Table 4, a significant proportion of patients with negative criteria (23-70%) ultimately die or require OLT. In addition, up to 21% of adults with FHF who fulfill King's College criteria will survive without OLT (Table 4). These limitations mostly derive from the formula of both the King's College and Clichy criteria that allocate patients with FHF to only 2 categories, survival or death, which in clinical practice dictates the need for OLT. The efficacy of a categorical score such as the King's College criteria strongly relies on the accuracy of its components to distinguish between these 2 major outcomes. As an example, when comparing 2 given patients, 1 with bilirubin of 40 mg/dL and international normalized ratio of prothrombin of 6 and the other with 18 mg/dL and 3.6, respectively, no one will argue that the first case carries a higher risk of death. However, according to the King's College criteria, they both belong to the same prognostic category. In contrast, outcome of 2 patients with FHF of the same etiology and bilirubin/international normalized ratio of prothrombin of 16 mg/dL/3.4 and 18 mg/dL/3.6 should be similar, although according to the King's College crite-

TABLE 4. Positive Predictive Value, Negative Predictive Value, and Diagnostic Accuracy of King's College Criteria in Reported Series of Adults With Nonacetaminophen Fulminant Hepatic Failure

Authors	Year	Number	PPV (%)	NPV (%)	DA (%)
O'Grady et al.(5)	1989	42	97	75*	90
Pauwels et al. (28)	1993	81	96	50	80
Donaldson et al. (27)	1993	46	94	75*	89
Izumi et al. (25)	1996	17	93	67*	88
Annand et al. (29)	1997	25	79	50	68
Shakil et al. (30)	2000	144	91	42	74
Chung et al. (20)	2003	11	100	30	36*
This study	2006	64	80	77	78

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; DA, diagnostic accuracy.
*Calculated from data described in the publication.

TABLE 5. MELD and PELD Scores in 40 Patients With Fulminant Hepatic Failure Who Survived or Died With Medical Therapy and 80 Patients Who Underwent Liver Transplantation

Prognostic score	Survived	Died	Transplanted
MELD			
Adults	26 ± 7	38 ± 7*	33 ± 8†
Children	23 ± 6	39 ± 7‡	36 ± 5§
PELD			
Children	20 ± 9	48 ± 1‖	42 ± 8¶

*$P = 0.0003$ vs. survived and $P = 0.03$ vs. transplanted.
†$P = 0.008$ vs. survived.
‡$P = 0.0004$ vs. survived.
§$P \leq 0.00001$ vs. survived.
‖$P = 0.0002$ vs. survived.
¶$P < 0.0001$ vs. survived.

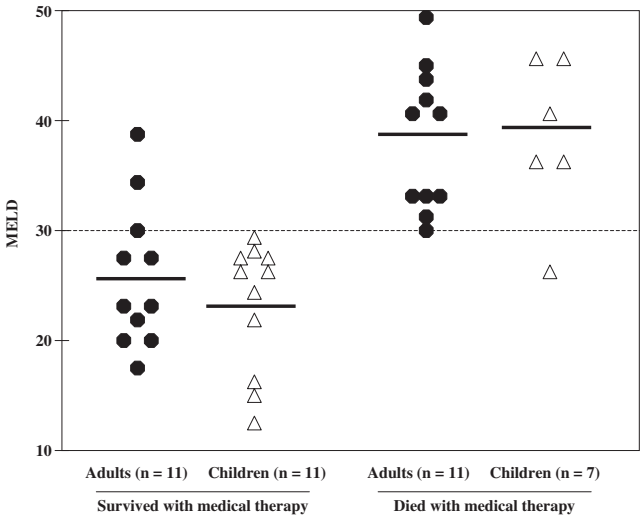

Figure 1. MELD scores of 22 patients who survived with medical therapy and 18 patients who died without liver transplantation. Horizontal bars represent mean values.

ria they are allocated to the good and poor prognostic categories, respectively.

MELD is a continuous score with no ceiling effect that includes only 3 simple, readily available, objective, reproducible, and quantitative variables. Validation studies performed in the United States have shown that MELD is superior to a categorical score such as the Child-Turcotte-Pugh to assess the risk of death in patients with chronic liver disease.[8,10] Our results suggest that this is true also in FHF. The concordance statistic for MELD score in adults and children and for PELD score in the pediatric population with FHF, as assessed by logistic regression, was >0.9 and significantly higher than that of both King's College and Clichy's criteria. When patients receiving transplants were included in the analysis using a Cox model, MELD and PELD remained as the most significant predictors of mortality within 30 days, with concordance statistics of 0.77 and 0.79, respectively (Table 7). Of note, Clichy's criteria were superior to King's College criteria, especially in children. In agreement with our results, Aydin et al.[31] recently showed that among 170 patients with FHF, MELD scores obtained on hospital admission were significantly higher among nonsurvivors (45 ± 12) compared to survivors (34 ± 13) and patients receiving transplants (39 ± 10).[31,32] In our study, MELD score was ≥30 in 94% of patients who died without OLT and <30 in 91% of those who survived with medical therapy. Rather than proposing a value of MELD as a prognostic dichotomous variable, our data suggest that MELD scores obtained upon admission may be of help to establish the optimal timing for pre-OLT evaluation and listing. However, the ideal cutoff value for MELD requires further validation in larger and independent series of patients with FHF. Renal dysfunction occurred in 45% of adults who died with supportive medical therapy. This represents an additional advantage of MELD over the King's College and Clichy's criteria, whose formula does not include serum creatinine as a prognostic variable

Worldwide, patients with FHF and those requiring emergency re-OLT are listed in a special category with priority for organ allocation designated as status 1 in the United States and emergency in other geographic

TABLE 6. Logistic Regression Analysis of King's College Criteria, Clichy's Criteria, MELD, and PELD in 41 Patients With Fulminant Hepatic Failure Who Survived or Died Without OLT Within 30 Days of Admission

Prognostic score	Odds ratio	95% CI	C-statistic	95% CI	*P*-value
King's College criteria					
Adults	13.33	2.1–130.8	0.78	0.60–0.96	0.0053
Children	>99.9	4.2-∞	0.73	0.57–0.88	0.0019
All patients	14.167	3.3–79.2	0.74	0.61–0.88	0.0002
Clichy's criteria					
Adults	4.125	0.44–92.3	0.59	0.43–0.75	0.2240
Children	>99.9	4.5-∞	0.79	0.59–0.98	0.0020
All patients	14.00	2.1–279.2	0.68	0.55–0.80	0.0042
MELD					
Adults	1.317	1.1–1.8	0.90*	0.78–1.00	0.0002
Children	1.826	1.2–9.3	0.96†	0.88–1.00	<0.0001
All patients	1.402	1.2–1.8	0.95‡	0.88–1.00	<0.0001
PELD					
Children	2.077	1.1–48.6	0.99§	0.95–1.0	<0.0001

Abbreviations: NS, nonsignificant; CI, confidence interval; ∞, infinity.
*P = 0.15 (NS) vs. King's College and 0.0026 vs. Clichy's.
†P = 0.004 vs. King's College and 0.067 (NS) vs. Clichy's.
‡P = 0.0037 vs. King's College and 0.0001 vs. Clichy's.
§P = 0.046 vs. King's College and 0.12 (NS) vs. Clichy's.

TABLE 7. Cox Analysis of King's College Criteria, Clichy's Criteria, MELD, and PELD in 120 Patients With Fulminant Hepatic Failure Who Survived or Died With Medical Therapy or Underwent Liver Transplantation

Prognostic score	Hazard ratio	95% CI	C-statistic	95% CI	*P*-value
King's College criteria					
Adults	2.185	0.6–10.1	0.52	0.35–0.69	0.230
Children	99.9	0.53-∞	0.57	0.53–0.62	0.136
All patients	2.369	0.8–10.3	0.54	0.42–0.65	0.142
Clichy's criteria					
Adults	2.481	0.5–8.8	0.57	0.42–0.71	0.221
Children	13.50	2.8–72.2	0.74	0.57–0.92	0.002
All patients	5.271	1.9–13.9	0.64	0.52–0.76	0.002
MELD					
Adults	1.119	1.04–1.20	0.78*	0.65–0.92	0.002
Children	1.139	1.02–1.30	0.75†	0.60–0.91	0.018
All patients	1.134	1.07–1.21	0.77‡	0.66–0.98	<0.0001
PELD					
Children	1.098	1.02–1.19	0.79§	0.64–0.94	0.008

Abbreviations: NS, non significant; CI, confidence interval; ∞, infinity.
*P = 0.001 vs. King's College and 0.013 vs. Clichy's.
†P = 0.055 (NS) vs. King's College and 0.09 (NS) vs. Clichy's.
‡P = 0.0001 vs. King's College and 0.064 (NS) vs. Clichy's.
§P = 0.02 vs. King's College and 0.69 (NS) vs. Clichy's.

areas such as Argentina. Within this category, organs are allocated according to waitlist time. Kremers et al.[11] recently showed that among patients listed as status 1 in the United States, the risk of death was significantly higher in FHF when compared to those requiring re-OLT for primary nonfunction or hepatic artery thrombosis.[11]

In conclusion, this study is the first to show that MELD and PELD are superior to the King's College and Clichy's criteria to assess prognosis in adults and children with FHF. We acknowledge that our study has a number of limitations. First, the number of patients who survived or died without OLT was rather small and the analysis included both adults and children, whose prognosis may differ. In addition, hepatitis A is an infrequent etiology of FHF in children from most geographies. Second, conclusions generated from single-center data may not be confirmed when assessed in larger studies or different patient populations. Last, the absence of acetaminophen toxicity limits the generaliz-

ability of our findings. Additional studies are therefore required to further assess the prognostic accuracy of MELD and PELD in FHF. However, if our results are confirmed in larger series, the benefits of stratifying patients with FHF within the status 1 category according to their MELD scores should be explored.

REFERENCES

1. Lee WM. Acute liver failure. N Engl J Med 1993;329:1862-1872.
2. Mas A, Rodes J. Fulminant hepatic failure. Lancet 1997; 349:1081-1085.
3. Castells A, Salmerón JM, Navasa M, Rimola A, Saló J, Andreu H, et al. Liver transplantation for acute liver failure: Analysis of applicability. Gastroenterology 1993;105: 532-538.
4. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SHB, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947-954.
5. O'Grady JG, Graeme JM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439-445.
6. Bernuau J, Benhamou JP. Fulminant and subfulminant liver failure. In: McIntyre N, Benhamou JP, Bircher J, Rizzeto M, Rodes J, editors. Oxford Textbook of Clinical Hepatology. Oxford: Oxford Medical Publications, 1991: 923-942.
7. Bernuau J, Goudeau A, Poynard T, Dubois F, Lesage F, Yvonnet B, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. Hepatology 1986;6:648-651.
8. Wiesner RH, Edwards EB, Freeman RB, Harper AM, Kim R, Kamath PS, et al. Model for end stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-96.
9. Kamath PS, Wiesner RH, Malinchoc M, Kremers WK, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end stage liver disease. Hepatology 2001; 33:464-470.
10. Wiesner RH, McDiarmid SV, Kamath PS, Edwars EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567-580.
11. Kremers WK, Van Ijperen M, Kim WR, Freeman RB, Harper AM, Kamath PS, Wiesner RH. MELD score as a predictor of pretransplant and posttransplant survival in OPTN/UNOS status 1 patients. Hepatology 2004;39:764-769.
12. Trey C, Lipworth L, Chalmers TC, Davidson CS, Gottlieb LS, Popper H, et al. Fulminant hepatic failure: presumable contribution to halothane. N Engl J Med 1968;279:798-801.
13. O'Grady JG, Schalm SW, Willliams R. Acute liver failure: redefining the syndromes. Lancet 1993;342:273-275.
14. United Network for Organ Sharing. Home Page. Available at http:/www.unos.org. Last accessed February 19, 2007.
15. Hanley JA, Mc Neil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
16. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-387.
17. Johnson RE, Quade D, Langstron RD. The MATPAR procedure. In: SUGI Supplemental Library User's Guide, version 5. Cary, NC: SAS Institute, Inc., 1986. pp. 295-306.
18. Hoofnagle JH, Carithers RL, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology 1995;21:240-252.
19. Dhiman RK, Seth AK, Jain S, Chawla YK, Dilawari JB. Prognostic evaluation of early indicators in fulminant hepatic failure by multivariate analysis. Dig Dis Sci 1998;43: 1311-1316.
20. Chung PY, Sitrin MD, Te HS. Serum phosphorus levels predict clinical outcome in fulminant hepatic failure. Liver Transpl 2003;9:248-253.
21. Murray-Lyon IM, Orr AH, Gazzard B, Kohn J, Williams R. Prognostic value of serum alpha-fetoprotein in fulminant hepatic failure including patients treated by charcoal haemoperfusion. Gut 1976;17:576-580.
22. Saibara T, Onishi S, Sone J, Yamamoto N, Shimahara Y, Mori K, et al. Arterial ketone body ratio as a possible indicator for liver transplantation in fulminant hepatic failure. Transplantation 1991;51:782-786.
23. Lee WM, Galbraith RM, Watt GH, Hughes RD, McIntire DD, Hoffman B, Williams R. Predicting survival in fulminant hepatic failure using serum Gc protein concentrations. Hepatology 1995;21:101-105.
24. Harrison PM, O'Grady JG, Keays RT, Alexander GJ, Williams R. Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure. Br Med J 1990;301:964-966.
25. Izumi S, Langley PG, Wendon J, Ellis AJ, Pernambuco RB, Hughes RD, Williams R. Coagulation factor V levels as a prognostic indicator in fulminant hepatic failure. Hepatology 1996;23:1507-1511.
26. Pereira LM, Langley PG, Hayllar KM, Tredger JM, Williams R. Coagulation factor V and VIII/V ratio as predictors of outcome in paracetamol induced fulminant hepatic failure: relation to other prognostic indicators. Gut 1992;33: 98-102.
27. Donaldson BW, Gopinath R, Wanless IR, Phillips MJ, Cameron R, Roberts EA, Greig PD. The role of transjugular liver biopsy in fulminant liver failure: relation to other prognostic indicators. Hepatology 1993;18: 1370-1374.
28. Pauwels A, Mostefa-Kara N, Florent C, Lèvy VG. Emergency liver transplantation for acute liver failure: evaluation of London and Clichy criteria. J Hepatol 1993;17:124-127.
29. Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. J Hepatol 1997;26:62-68.
30. Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. Liver Transpl 2000;6:163-169.
31. Aydin C, Berk BS, Fung JJ, Shakil AO. Applicability of MELD scoring system to predict prognosis in patients with acute liver failure [Abstract]. Hepatology 2003;38(Suppl 1):554A.
32. Sass DA, Shakil O. Fulminant hepatic failure. Liver Transpl 2005;11:594-605.