


Remodeling the Model for End-Stage Liver Disease for Predicting Mortality Risk in Critically Ill Patients With Cirrhosis and Acute Kidney Injury

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Serum creatinine measurement demonstrates a poor specificity and sensitivity for the early diagnosis of acute kidney injury (AKI) in patients with cirrhosis. The existing model for end-stage liver disease (MELD) score reveals multiple pitfalls in critically ill patients with cirrhosis and acute kidney injury (CAKI). The aim of this study was to re-evaluate the role of creatinine values in the existing MELD score and to develop a novel score for CAKI, named the “acute kidney injury–model for end-stage liver disease score” (AKI-MELD score). We extracted 651 CAKI from the Multiparameter Intelligent Monitoring in Intensive Care database. A time-dependent Cox regression analysis was performed for developing remodeled MELD scores (Reweight-MELD score, Del-Cr-MELD score, and AKI-MELD score). The area under the receiver operating characteristic curve provided the discriminative power of scoring models related to outcome. The hazard ratio of creatinine was 1.104 [95% confidence interval [CI], 0.945–1.290; $P = 0.211$]. Reweight-MELD score and Del-Cr-MELD score (decreasing the weight of creatinine) were superior to the original MELD score (all $P < 0.001$). The new AKI-MELD score consists of bilirubin, the international normalized ratio, and the ratio of creatinine in 48 hours to creatinine at admission. It had competitive discriminative ability for predicting mortality (area under the receiver operating characteristic curve, 0.720 [95% CI, 0.653–0.762] at 30 days, 0.688 [95% CI, 0.630–0.742] at 90 days, and 0.671 [95% CI, 0.612–0.725] at 1 year). Further, AKI-MELD score had significantly higher predictive ability in comparison with MELD score, MELD-Na score, and Updated MELD score (all $P < 0.001$). **Conclusion:** The predictive value of creatinine for CAKI should be re-evaluated. AKI-MELD score is a potentially reliable tool to determine the prognosis for mortality of CAKI. (*Hepatology Communications* 2017;1:748–756)

Introduction

Acute kidney injury (AKI) is one of the most common complications in critically ill patients with cirrhosis and is linked to increased morbidity and mortality.^(1–3) The progression of AKI is often

associated with the onset of progressive multiorgan dysfunctions or failure, which occurs in up to approximately 20% of critically ill patients with cirrhosis.^(2,4)

The model for end-stage liver disease (MELD) score, a well-known and useful tool for patients with cirrhosis, is calculated based on serum creatinine, the

Abbreviations: AKI, acute kidney injury; AKI-MELD, acute kidney injury–model for end-stage liver disease; AUROC, area under the receiver operating characteristic curve; CAKI, critically ill patients with cirrhosis and acute kidney injury; CI, confidence interval; Cr_{48hour}/Cr , ratio of creatinine in 48 hours to creatinine at admission; Del-Cr-MELD, deleted-creatinine–model for end-stage liver disease; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease.

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international normalized ratio (INR), and serum bilirubin.⁽⁵⁾ Although the MELD score has resulted in successfully predicting prognosis, creatinine as a suboptimal marker for renal function has poor specificity and sensitivity for the early diagnosis of critically ill patients with cirrhosis and acute kidney injury (CAKI).⁽⁶⁻⁸⁾

Further studies have enhanced the debate on the actual role of creatinine in the existing MELD score.^(8,9) Romano et al.⁽⁹⁾ suggested that serum creatinine had no impact in predicting AKI after orthotopic liver transplantation despite its importance in the MELD score calculation. Sharma⁽⁸⁾ analyzed data from 38,899 liver transplantation candidates from the Scientific Registry of Transplant Recipients and updated the MELD score formula with a lower relative weight for serum creatinine and a higher relative weight for bilirubin. Moreover, serum creatinine concentration remains questionable as an indicator for the severity of renal dysfunction of CAKI. The stable high creatinine values of patients with chronic renal insufficiency may be considered to have an equal mortality risk for CAKI with normal renal function. Our first aim in this study was to determine whether creatinine has a substantial discriminating potential for predicting mortality in CAKI.

We hypothesized that a modified MELD score incorporating new AKI-related variables can provide an improvement on its prognostic accuracy. Although the diagnosis of AKI has been a source of significant controversy in nephrology, the Acute Kidney Injury Network criteria are based on an absolute serum creatinine change in a 48-hour period and possess adequate prognostic accuracy for both established and early detection of AKI in hospitalized patients.⁽¹⁰⁻¹³⁾ The

risk, injury, failure, loss, and end-stage kidney disease classification provides three grades of severity for AKI and is also based on serum changes in creatinine in the short-term from the baseline condition.^(14,15) Recent studies have demonstrated that even minor changes in serum creatinine are an indication of an acute deterioration of renal function.⁽¹⁶⁻¹⁸⁾ For this reason, changes in serum creatinine may be a more suitable predictor for mortality in CAKI. Therefore, our second aim was to develop a new model incorporating the ratio of creatinine in 48 hours to creatinine at admission ($Cr_{48\text{hours}}/Cr$) rather than creatinine for CAKI to predict mortality.

Patients and Methods

SUBJECTS

A longitudinal study was performed using the Multiparameter Intelligent Monitoring in Intensive Care database, version 3.0. This a freely accessible, large-scale, critical care database and a collection of around 50,000 medical records from patients admitted to the Intensive Care Unit (ICU) at Beth Israel Deaconess Medical Center (Boston, MA) from June 2001 to October 2012.

A total of 651 CAKI in the ICU were recruited. Inclusion criteria included individuals with a primary diagnosis of cirrhosis and who presented with symptoms of AKI (increased creatinine and/or oliguria). Excluded from our study were individuals with pregnancy, toxicity conditions, autoimmune diseases, past or current hepatocellular carcinoma, other causes that

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might lead to AKI, or other identifiable causes of serious diseases in other organ systems.

DEFINITION

The diagnosis of cirrhosis was made either by histology if liver biopsy showed evidence or by compatible imaging findings and clinical manifestations (e.g., ascites, esophageal varices, sepsis, gastrointestinal hemorrhage, progressive jaundice, hepatic encephalopathy, or spontaneous bacterial peritonitis).

AKI is defined as any of the following: increase in serum creatinine equal to or greater than 0.3 mg/dL within 48 hours; increase in serum creatinine to 1.5 times baseline; urine output less than 0.5 mL/kg/hour for 6 hours.⁽¹³⁾ For patients without an available creatinine value before admission, we followed the recommendations of the International Club of Ascites and used the first creatinine value measured during hospitalization as the baseline creatinine.^(19,20)

DATA COLLECTION

For all study patients, data contained clinical and laboratory parameters within the first 24 hours after admission to the ICU. Clinical parameters included heart rate, respiration, temperature, and systolic and diastolic blood pressure, while laboratory parameters included glucose, white blood cell count, platelet count, sodium, potassium, blood urea nitrogen, partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide, fraction of inspired oxygen, bicarbonate, creatinine, lactate, INR, and bilirubin. The following relevant variables were included: age, sex, height, weight, ethnicity, vasopressin used, and the diagnosis of cirrhosis.

OUTCOME

All patients were followed up for at least 1 year. The primary endpoints were defined at 30-day, 90-day, and 1-year all-cause mortality. Our permission to access the database was approved after completion of the National Institutes of Health web-based training course "Protecting Human Research Participants" (our certification number, 1605699).

MELD SCORING SYSTEMS

MELD score, MELD-Na score, and Updated MELD score (described in more detail under Statistical Analysis) were computed using the aforementioned indicators as follows:

1. MELD: $R = 9.57 \times \log_e(\text{creatinine [mg/dL]}) + 3.78 \times \log_e(\text{bilirubin [mg/dL]}) + 11.2 \times \log_e(\text{INR}) + 6.43$.⁽⁵⁾
2. MELD-Na: $R = \text{MELD} + 1.59 \times (135 - \text{Na [mmol/L]})$.⁽²¹⁾
3. Updated MELD: $R = 1.27 \times \log_e(1 + \text{creatinine [mg/dL]}) + 0.94 \times \log_e(1 + \text{bilirubin [mg/dL]}) + 1.66 \times \log_e(1 + \text{INR})$.⁽⁸⁾

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY) and MedCalc version 12.7 (MedCalc Software, Ostend, Belgium). Continuous and categorical data were presented at baseline using mean \pm SD and frequencies (percentage), respectively. The Student *t* test was performed for comparisons of continuous baseline characteristics, and the chi-square test was performed for categorical values. Cox's proportional hazards regression was used to calculate hazard ratios (HRs) for relative risk of mortality.

To evaluate the effect of creatinine in the MELD formula, a time-dependent Cox regression model was performed to develop novel remodeled MELD scores. One scoring tool, the Reweight MELD score, assigned a lower weight to creatinine, which is similar to the Updated MELD score. Another score (Del-Cr-MELD score) removed the creatinine component from the existing MELD score and reweighted the coefficient components of the other two variables (INR and bilirubin). We then developed the AKI-MELD score as it related to its $\text{Cr}_{48\text{hours}}/\text{Cr}$ ratio to better associate it with CAKI. All scoring tools were compared using the area under the receiver operating characteristic curve (AUROC). The area under the curve provided the discriminative power of MELD score for the outcome of CAKI. A *P* value less than 0.05 was considered statistically significant.

Results

BASELINE CHARACTERISTICS OF THE STUDY POPULATION

The study population comprised 651 CAKI admitted to the ICU (median age, 57.46 ± 11.71 years; male patients, 418 [67.3%]) (Table 1). There were 75 (11.5%) patients who died in the 3-month follow-up. The most common ethnicity was Caucasian (442 [71.2%]). Detailed information is shown in Table 2.

TABLE 1. CHARACTERISTICS OF 651 CRITICALLY ILL PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY

Variable	Mean \pm SD or N (%)
Age, year	57.46 \pm 11.71
Sex,	
Male patients, number (%)	418 (67.3%)
Female patients, number (%)	203 (32.7%)
Ethnicity	
Caucasians, number (%)	442 (71.2%)
African Americans, number (%)	46 (7.4%)
Other (%)	133 (21.4%)
Cirrhosis	
Alcoholic cirrhosis, number (%)	348 (56.0%)
Biliary cirrhosis, number (%)	12 (1.9%)
Nonalcoholic cirrhosis, number (%)	261 (42.0%)
MELD	24.24 \pm 10.33
Reweight-MELD	0.60 \pm 0.37
Del-Cr-MELD	0.57 \pm 0.37
AKI-MELD	0.58 \pm 0.51
MELD components	
Bilirubin, mg/dL	8.31 \pm 10.48
Creatinine, mg/dL	2.25 \pm 1.74
48-hour creatinine, mg/dL	2.14 \pm 1.66
Cr _{48hours} /Cr	1.03 \pm 0.45
INR	2.12 \pm 2.74
Log _e MELD components	
Bilirubin, mg/dL	1.35 \pm 1.30
Creatinine, mg/dL	0.58 \pm 0.66
48-hour creatinine, mg/dL	0.53 \pm 0.66
Cr _{48hours} /Cr	-0.05 \pm 0.40
INR	0.64 \pm 0.39

IS CREATININE RELATED TO A PERFECT PREDICTIVE PERFORMANCE IN CAKI?

Univariate analysis was performed for bilirubin (HR, 1.293; 95% confidence interval [CI], 1.194-1.401; $P < 0.001$); Cr_{48hours}/Cr (HR, 1.932; 95% CI, 1.514-2.465; $P < 0.001$); INR (HR, 2.054; 95% CI, 1.691-2.494; $P < 0.001$), and creatinine (HR, 1.104; 95% CI, 0.945-1.290; P , 0.211) (Table 3).

Creatinine at admission to the ICU was not associated with the mortality of CAKI in our study despite its high impact on the existing MELD formula. We therefore evaluated the role of creatinine in the MELD formula. We hypothesized that the remodeled MELD scores without creatinine or with a relatively lower weight of creatinine might have a better predictive performance. The Cox regression model was performed, and the final models were represented as follows: Reweight-MELD: $R = 0.250 \times \log_e(\text{creatinine [mg/dL]}) + 0.584 \times \log_e(\text{bilirubin [mg/dL]}) + 0.179 \times \log_e(\text{INR})$; Del-Cr-MELD: $R = 0.249 \times$

$\log_e(\text{bilirubin [mg/dL]}) + 0.595 \times \log_e(\text{INR})$ (Table 4).

The performances of Reweight-MELD score and Del-Cr-MELD score for predicting mortality were competitive with an AUROC of 0.675 and 0.678 at 30 days, 0.669 and 0.671 at 90 days, and 0.637 and 0.636 at 1 year, respectively. The MELD score had an AUROC of 0.639 at 30 days, 0.637 at 90 days, and 0.614 at 1 year (all $P < 0.05$) (Table 5). With advanced critical illness, patients with increasing MELD score were found to have increased area under the curve gap of MELD score and other remodeling scoring (Reweight-MELD score and Del-Cr-MELD score). Therefore, we considered that creatinine was too heavily weighted in the existing MELD formula for CAKI.

AKI-MELD: Cr_{48hours}/Cr MAY BE A BETTER PREDICTOR THAN CREATININE WHEN MELD IS USED IN CAKI

The AKI-MELD formula derived from the time-dependent model was based on all the serial Cr_{48hours}/Cr, bilirubin, and INR values in the Multiparameter Intelligent Monitoring in Intensive Care 3.0 database for the study cohort. The final model was represented as follows: $R = 0.225 \times \log_e(\text{Cr}_{48\text{hours}}/\text{Cr}) + 0.609 \times \log_e(\text{bilirubin [mg/dL]}) + 0.562 \times \log_e(\text{INR})$ (Table 4).

THE PERFORMANCE OF AKI-MELD COMPARED WITH OTHER MELD SCORES

Kaplan-Meier curves were generated for time to event. All individuals were categorized into four groups by the AKI-MELD level: Q₁ (≤ 0.220), Q₂ (0.220-0.564), Q₃ (0.564-0.952), and Q₄ (≥ 0.952). Increasing AKI-MELD was progressively associated with an increased MELD of CAKI (Fig. 1).

Performance of AKI-MELD score in predicting short-term mortality in the internal cohort was competitive, with an AUROC of 0.720 (95% CI, 0.653-0.762) at 30 days, 0.688 (95% CI, 0.630-0.742) at 90 days, and 0.671 (95% CI, 0.612-0.725) at 1 year. Compared to MELD score, MELD-Na score, and Updated MELD score, AKI-MELD score indicated a 6% to 15% improvement in discriminative capability (all $P < 0.001$).

TABLE 2. CHARACTERISTICS OF 651 CRITICALLY ILL PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY, STRATIFIED BY SURVIVAL

Variable	Survivors (n = 277)	Nonsurvivors (n = 374)	P Value
Age, year	55.96 ± 10.63	58.45 ± 12.28	0.009
Sex			0.930
Male patients, number (%)	167 (67.6%)	251 (67.1%)	
Female patients, number (%)	80 (32.4%)	123 (32.9%)	
Ethnicity			0.050
Caucasians, number (%)	183 (74.1%)	259 (69.3%)	
African Americans, number (%)	25 (10.1%)	21 (5.6%)	
Other (%)	39 (15.8%)	94 (25.1%)	
Cirrhosis			0.843
Alcoholic cirrhosis, number (%)	141 (57.1%)	207 (55.3%)	
Biliary cirrhosis, number (%)	4 (1.6%)	8 (2.1%)	
Nonalcoholic cirrhosis, number (%)	102 (41.3%)	159 (42.5%)	
MELD	21.74 ± 9.07	25.9 ± 10.77	<0.001
Reweight-MELD	0.49 ± 0.32	0.67 ± 0.38	<0.001
Del-Cr-MELD	0.47 ± 0.32	0.64 ± 0.38	<0.001
AKI-MELD	0.4 ± 0.49	0.69 ± 0.48	<0.001
MELD components			
Bilirubin, mg/dL	6.03 ± 8.97	9.81 ± 11.12	<0.001
Creatinine, mg/dL	2.17 ± 1.67	2.31 ± 1.78	0.316
48-hour creatinine, mg/dL	1.83 ± 1.34	2.35 ± 1.81	<0.001
Cr _{48hours} /Cr	0.95 ± 0.46	1.08 ± 0.44	<0.001
INR	1.81 ± 0.70	2.33 ± 3.47	0.021
Log _e MELD components			
Bilirubin, mg/dL	1.03 ± 1.21	1.56 ± 1.31	<0.001
Creatinine, mg/dL	0.56 ± 0.64	0.60 ± 0.68	0.413
48-hour creatinine, mg/dL	0.41 ± 0.61	0.62 ± 0.68	<0.001
Cr _{48hours} /Cr	-0.15 ± 0.44	0.01 ± 0.36	<0.001
INR	0.54 ± 0.31	0.70 ± 0.42	<0.001
Laboratory parameters			
Glucose, mg/dL	142.81 ± 85.51	127.76 ± 58.19	0.009
Sodium, mEq/L	134.13 ± 6.92	133.90 ± 7.33	0.696
Potassium, mEq/L	4.21 ± 0.91	4.42 ± 1.03	0.013
PaO ₂ , mmHg	160.02 ± 123.11	123.42 ± 96.68	<0.001
PCO ₂ , mmHg	37.20 ± 9.27	37.43 ± 11.67	0.795
FI _{O2}	55.60 ± 34.17	66.16 ± 32.32	<0.001
Lactate, mg/dL	2.86 ± 2.14	3.72 ± 3.14	<0.001
Urine output, mL	1,934.91 ± 2,414.36	994.5 ± 1,415.54	<0.001

Abbreviations: FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PCO₂, partial pressure of arterial carbon dioxide.

STRATIFIED ANALYSIS

TABLE 3. UNIVARIATE AND MULTIVARIATE ANALYSIS OF ASSOCIATION BETWEEN LOG_E MELD COMPONENTS AND 1-YEAR MORTALITY IN CRITICALLY ILL PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY

Log _e MELD components	Univariate Analysis		
	HR	95% CI	P
Bilirubin, mg/dL	1.293	(1.194-1.401)	<0.001
Creatinine, mg/dL	1.104	(0.945-1.290)	0.211
Cr _{48hours} /Cr	1.932	(1.514-2.465)	<0.001
INR	2.054	(1.691-2.494)	<0.001

In the stratified analysis, AKI-MELD score for more critically ill candidates (with higher MELD scores) had a significantly higher predictive ability. As MELD score was considered to be a predictive tool for CAKI with MELD ≥ 25, the MELD score performance was undesirable, having an AUROC of 0.591 at 30 days, 0.581 at 90 days, and 0.562 at 1 year (Table 5; Fig. 2). These patients with high MELD scores may be overestimated, especially when they had a higher serum creatinine level along with lower bilirubin and/or INR.

TABLE 4. COMPARISON OF COEFFICIENTS OF MELD COMPONENTS IN MELD, REWEIGHT-MELD, DEL-CR-MELD, AND AKI-MELD FORMULAS

	MELD	Reweight-MELD		Del-Cr-MELD		AKI-MELD	
	Coefficient	Coefficient	HR	Coefficient	HR	Coefficient	HR
Log _e bilirubin	0.378	0.250	1.285 (1.142-1.445)	0.249	1.283 (1.140-1.445)	0.225	1.252 (1.110-1.412)
Log _e INR	1.120	0.584	1.792 (1.380-2.328)	0.595	1.813 (1.401-2.345)	0.609	1.839 (1.416-2.388)
Log _e creatinine	0.957	0.179	1.196 (0.973-1.471)	–	–	–	–
Log _e Cr _{48hours} /Cr	–	–	–	–	–	0.562	1.754 (1.265-2.432)

PERFORMANCE OF AKI-MELD IN PREDICTING MORTALITY: COMPARISON OF MELD, MELD-Na, AND UPDATED MELD

A comparison between AKI-MELD score and other MELD scoring systems (MELD-Na score and Updated MELD score) was also completed to assess the discriminative power of this new scoring model. AKI-MELD score was considered to be a reliable model in predicting all mortality (Fig. 3) (AUROC, 0.715 [95% CI, 0.678-0.750] at 30 days, 0.704 [95% CI, 0.666-0.739] at 90 days, and 0.667 [95% CI, 0.629-0.704] at 1 year) compared with MELD-Na (0.589 [0.549-0.628] at 30 days, 0.603 [95% CI, 0.563-0.641] at 90 days, and 0.573 [95% CI, 0.533-0.612] at 1 year) and Updated MELD (0.666 [95% CI, 0.628-0.703] at 30 days, 0.661 [95% CI, 0.623-0.699] at 90 days, and 0.633 [95% CI, 0.594-0.671] at 1 year) (Fig. 2; Table 6). The Updated MELD score with relatively lower creatinine weight was

slightly superior to the other existing MELDs (MELD score and MELD-Na score).

Discussion

AKI is a severe complication in critically ill patients with cirrhosis that occurs in a substantial proportion of the patients admitted with cirrhosis.^(22,23) Severe hypoperfusion causes acute kidney failure/injury and impairment in the systemic arterial circulation, which can lead to marked splanchnic arterial vasodilatation and arterial hypotension.^(3,24,25) Subsequent studies have confirmed several other causes leading to acute impairment of kidney function, including bacterial infections, volume depletion, chronic kidney diseases, and administration of nephrotoxic agents.⁽²⁶⁾ It has been unequivocally demonstrated that serum creatinine is associated with short- and long-term mortality in patients with cirrhosis.⁽²⁷⁾ MELD score was calculated based on the creatinine level at the time of ICU admission, while the definitions of AKI depended on changes in serum creatinine within 48 hours. We

TABLE 5. COMPARISON OF INDEX OF CONCORDANCE FOR MELD, REWEIGHT-MELD, DEL-CR-MELD, AND AKI-MELD

	MELD	Reweight-MELD	Del-Cr-MELD	AKI-MELD
30-day mortality				
All	0.639	0.675	0.678	0.715
MELD ≥10	0.648	0.688	0.689	0.723
MELD ≥15	0.642	0.685	0.684	0.717
MELD ≥20	0.617	0.678	0.677	0.709
MELD ≥25	0.591	0.663	0.665	0.710
90-day mortality				
All	0.637	0.669	0.671	0.704
MELD ≥10	0.642	0.677	0.676	0.708
MELD ≥15	0.631	0.672	0.671	0.701
MELD ≥20	0.591	0.653	0.655	0.685
MELD ≥25	0.581	0.650	0.652	0.688
1-year mortality				
All	0.614	0.637	0.636	0.667
MELD ≥10	0.621	0.646	0.643	0.672
MELD ≥15	0.600	0.636	0.635	0.667
MELD ≥20	0.573	0.629	0.630	0.662
MELD ≥25	0.562	0.626	0.629	0.671

All P values < 0.05 (versus AKI-MELD).

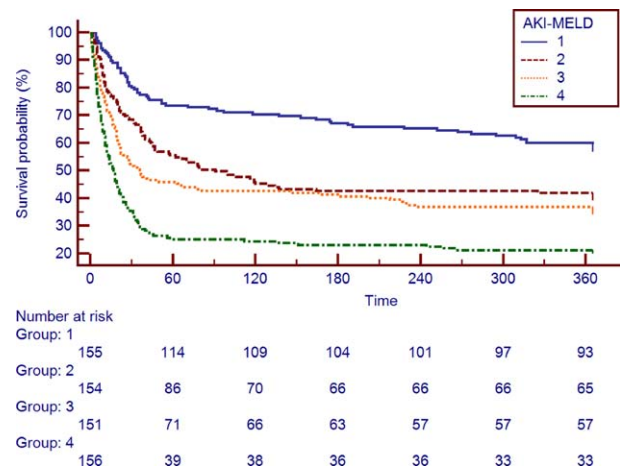


FIG. 1. Kaplan-Meier curves stratified by different risk levels of AKI-MELD (P < 0.05).

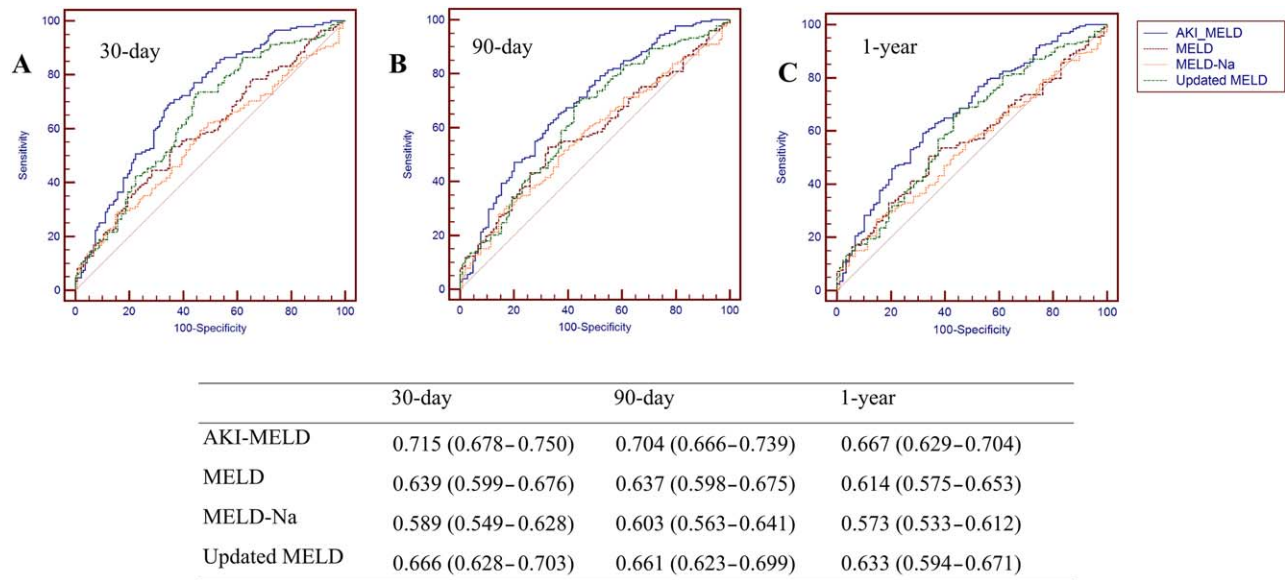


FIG. 2. AUROC analysis of the prognostic efficiency of AKI-MELD and other existing MELD models (MELD, MELD-Na, and Updated MELD) to predict (A) 30-day, (B) 90-day, and (C) 1-year mortality of CAKI (all $P < 0.05$).

questioned which value and change of creatinine was more accurate for prognosis mortality.

In our observation database, HRs of creatinine and $Cr_{48\text{hours}}/Cr$ were 1.104 (95% CI, 0.945–1.290; $P = 0.211$) and 1.932 (95% CI, 1.514–2.465; $P < 0.001$),

respectively. While the relative weight of creatinine in the MELD formula was 0.390, the relative weights of Reweight-MELD score and Del-Cr-MELD score were 0.177 and 0, respectively (Table 7). Reweight-MELD score and Del-Cr-MELD score showed a

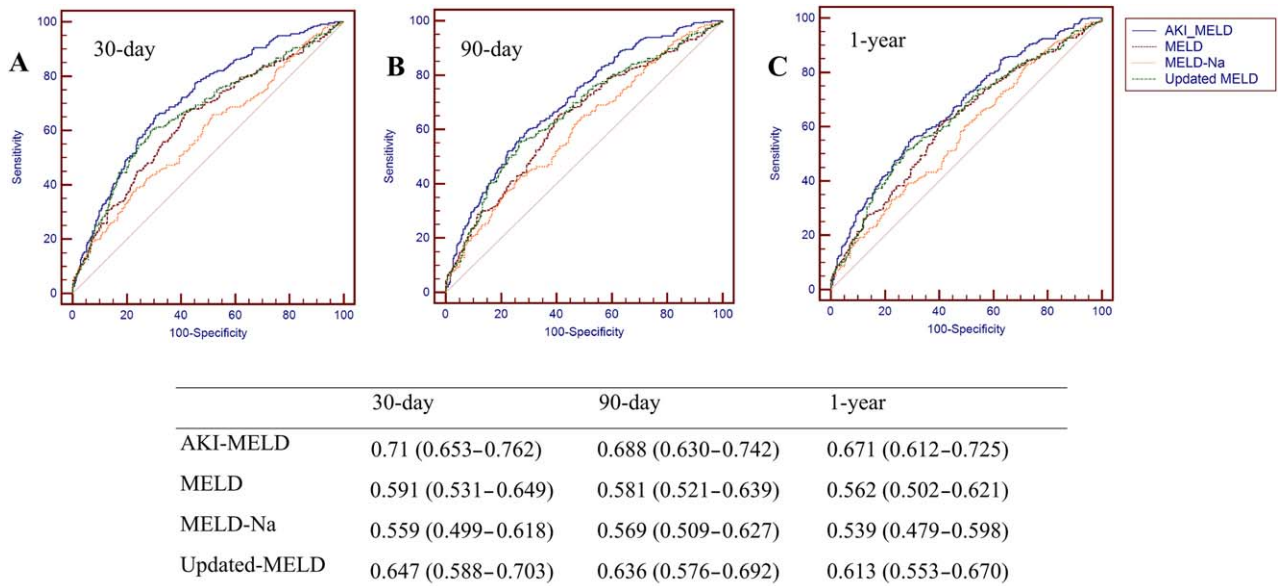


FIG. 3. AUROC analysis of the prognostic efficiency of AKI-MELD and other existing MELD models (MELD, MELD-Na, and Updated MELD) to predict (A) 30-day, (B) 90-day, and (C) 1-year mortality of CAKI with MELD ≥ 25 (all $P < 0.05$).

TABLE 6. DIAGNOSTIC ACCURACY OF DIFFERENT PROGNOSTIC MODELS IN PREDICTING 1-YEAR MORTALITY USING THE OPTIMAL CUT-OFF POINT

Prognostic models	Cutoff	AUROC	95% CI	Sensitivity	Specificity	Youden Index	Goodness-of-Fit (χ^2)	df	P
AKI-MELD	0.75	0.667	(0.629-0.704)	0.547	0.770	0.317	4.167	8	0.842
MELD	23.01	0.614	(0.575-0.653)	0.666	0.601	0.267	12.379	8	0.135
MELD-Na	32.70	0.573	(0.533-0.612)	0.436	0.735	0.171	7.593	8	0.474
Updated-MELD	4.95	0.633	(0.594-0.671)	0.578	0.723	0.300	8.329	8	0.402

limited improvement in discriminative capability, indicating that the predictive value of creatinine for CAKI should be re-evaluated. Although the definition of AKI is debatable, the risk, injury, failure, loss, and end-stage kidney disease classification and the Acute Kidney Injury Network criteria are based on the changes of creatinine. Loeffel et al.⁽²⁸⁾ also revealed that changes in serum creatinine during the first postoperative week are related to short- and long-term mortality. In a similar population, the patients with AKI had significantly increased mortality under a broad spectrum of conditions.^(29,30) Furthermore, the severity of AKI is linked directly to mortality risk.^(29,30)

In the majority of patients, a transient rise in creatinine is the single manifestation of renal function impairment. Therefore, the change in creatinine within 48 hours was considered as a perfect variable for AKI. In accordance with other studies, we found that a substantial proportion of patients with cirrhosis with

serum creatinine within the normal range had impaired renal function.^(31,32) A remodeled model with the substitution of creatinine by $Cr_{48\text{hours}}/Cr$ may result in an improvement in its prognostic accuracy.

In our study, the novel specific prognostic score AKI-MELD score was developed and consisted of bilirubin, INR, and $Cr_{48\text{hours}}/Cr$. Compared to MELD score, the AUROC performance of AKI-MELD score showed an improvement in discriminating survivors at each period. In the stratified analysis, the AUROC performance of MELD was undesirable (less than 0.60) for critically ill patients ($MELD \geq 25$). CAKI with $MELD \geq 25$ had transient increases in Cr (lower bilirubin and/or INR) and may have less severe liver synthetic dysfunction, but the mortality risk was overestimated based on MELD score.

This research is the first and largest study to generate a specific clinical risk prognostic model (AKI-MELD score) for discriminating survivors from CAKI. However, the study has potential limitations. First, because this was a retrospective study from a single center, potential selection bias might exist. Second, although AKI-MELD score showed a preferable discriminative performance for predicting mortality in this large-scale database, the estimate of predictive ability of the AKI-MELD equation was based on the same data from which it was derived. This could potentially lead to overfitting, and further multicenter studies are needed to verify its applicability in a broad spectrum database. Third, the classification of histology may have contributed to a stratified analysis; however, a liver biopsy was not completed for each candidate and detailed histology data were absent in our research. Fourth, ignoring technological advances and changes in medical practice may have produced a certain bias on the database over an 11-year period.

In conclusion, the predictive value of creatinine for CAKI should be re-evaluated. AKI-MELD score provided an improvement over the existing MELD score and may provide an optimal scoring system for CAKI. Further research is needed to clarify the validity of the AKI-MELD score.

TABLE 7. COMPARISON OF RELATIVE WEIGHTS OF MELD COMPONENTS IN MELD, REWEIGHT-MELD, DEL-CR-MELD, AND AKI-MELD FORMULAS

MELD Component	Coefficient	SD	Coefficient \times SD	Relative Weight*
MELD				
Log _e bilirubin	0.378	1.296	0.490	0.154 [†]
Log _e INR	1.120	0.386	1.452	0.456
Log _e creatinine	0.957	0.662	1.24	0.390
Column sum	–	–	3.182	1
Reweight-MELD				
Log _e bilirubin	0.250	1.296	0.324	0.247
Log _e INR	0.584	0.386	0.757	0.577
Log _e creatinine	0.179	0.662	0.232	0.177
Column sum	–	–	1.313	1
Del-Cr-MELD				
Log _e bilirubin	0.249	1.296	0.323	0.295
Log _e INR	0.595	0.386	0.771	0.705
Column sum	–	–	1.094	1
AKI-MELD				
Log _e bilirubin	0.225	1.296	0.292	0.161
Log _e INR	0.609	0.386	0.789	0.436
Log _e $Cr_{48\text{hours}}/Cr$	0.562	0.401	0.728	0.402
Column sum	–	–	1.809	1

*Adjustment of coefficient \times SD to a sum of 1.

[†]0.490/3.182 = 0.154.

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