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

Xiao-Dong Zhou, Qin-Fen Chen, Dan-Qin Sun, Chen-Fei Zheng, Dong-Jie Liang, Jian Zhou, Song-Jie Wang, Wen-Yue Liu, Sven Van Poucke, Xiao-Dong Wang, Ke-Qing Shi, Wei-Jian Huang, and Ming-Hua Zheng

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
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.\(^8\) 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...
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. 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.

**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 ± 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 Cr\(_{48\text{hour}}/\text{Cr} \) 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.
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); Cr48hours/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 × \log_e(creatinine [mg/dL]) + 0.584 × \log_e(bilirubin [mg/dL]) + 0.179 × \log_e(INR); Del-Cr-MELD: R = 0.249 × \log_e(bilirubin [mg/dL]) + 0.595 × \log_e(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: Cr48hours/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 Cr48hours/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 × \log_e(Cr48hours/Cr) + 0.609 × \log_e(bilirubin [mg/dL]) + 0.562 × \log_e(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).
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/C21 ≤ 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 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 (56.3%)            |         |
| 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  |
| Cr48hr/Cr                              | 0.95 ± 0.48         | 1.08 ± 0.44            | <0.001  |
| INR                                   | 1.81 ± 0.70         | 2.33 ± 3.47            | 0.021   |
| Loge 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  |
| Cr48hr/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   |
| PaO2, mmHg                             | 160.02 ± 123.11     | 123.42 ± 96.68         | <0.001  |
| PCO2, mmHg                             | 37.20 ± 9.27        | 37.43 ± 11.67          | 0.795   |
| FiO2                                   | 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.

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

| Loge MELD components | 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 |
| Cr48hr/Cr            | 1.932  | (1.514-2.465)| <0.001|
| INR                  | 2.054  | (1.691-2.494)| <0.001|

**STRATIFIED ANALYSIS**

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

In our observation database, HRs of creatinine and Cr_{48hours}/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
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. Loef 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_{48h}/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_{48h}/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 6. Comparison of Relative Weights of MELD Components in MELD, Reweight-MELD, Del-Cr-MELD, and AKI-MELD Formulas

| MELD Component | Coefficient | SD | Coefficient × SD | Relative Weight* |
|----------------|-------------|----|------------------|------------------|
| 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_{48h}/Cr | 0.562  | 0.401 | 0.728            | 0.402           |
| Column sum       | –           | –    | 1.809            | 1               |

*Adjustment of coefficient × SD to a sum of 1.
†0.490/3.182 = 0.154.
REFERENCES

1) du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonne P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Med 2005;31:1693-1699.

2) Belcher JM, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology 2013;57:753-762.

3) Karvellas CJ, Durand F, Nadim MK. Acute kidney injury in cirrhosis. Critical care clinics. 2015;31:737-750.

4) Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48:2064-2077.

5) Boone MD, Celi LA, Ho BG, Pencina M, Curry MP, Lior Y, et al. Model for End-Stage Liver Disease score predicts mortality in critically ill cirrhotic patients. J Crit Care 2014;29:881.e887-813.

6) Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al.; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-96.

7) Francoz C, Prie D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, et al. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. Liver Transpl 2010;16:1169-1177.

8) Sharma P, Schaubel DE, Sima CS, Merton RM, Lok AS. Re-weighting the model for end-stage liver disease score components. Gastroenterology 2008;135:1575-1581.

9) Romano TG, Schmidtbauer I, Silva FM, Pompilio CE, D’Albuquerque LA, Macedo E. Role of MELD score and serum creatinine as prognostic tools for the development of acute kidney injury after liver transplantation. PloS One 2013;8:e64089.

10) Fagundes C, Barreto R, Guevara M, Garcia E, Sola E, Rodriguez E, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2013;59:474-481.

11) Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al.; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

12) Lim CC, Tan CS, Kaushik M, Tan HK. Initiating acute dialysis at earlier Acute Kidney Injury Network stage in critically ill patients without traditional indications does not improve outcome: a prospective cohort study. Nephrology (Carlton) 2015;20:148-154.

13) Pan HC, Chien YS, Jenq CC, Tsai MH, Fan PC, Chang CH, et al. Acute kidney injury classification for critically ill cirrhotic patients: a comparison of the KDIGO, AKIN, and RIFLE classifications. Sci Rep 2016;6:23022.

14) Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007;35:1837-1843.

15) Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006;34:1913-1917.

16) Gruber L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000;36:1542-1548.

17) Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-R212.

18) Praught ML, Shlipak MG. Are small changes in serum creatinine an important risk factor? Curr Opin Nephrol Hypertens 2005;14:265-270.

19) Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968-974.

20) Sun DQ, Zheng CF, Liu WY, Van Poucke S, Mao Z, Shi KQ, et al. AKI-CLIF-SOFA: a novel prognostic score for critically ill cirrhotic patients with acute kidney injury. Aging 2017;9:286-296.

21) Samuel D. MELD-Na as a prognostic score for cirrhotic patients: hyponatremia and ascites are back in the game. J Hepatol 2009;50:836-838.

22) Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. Hepatology 2003;37:233-243.

23) Moreau R, Lebrec D. Diagnosis and treatment of acute renal failure in patients with cirrhosis. Best Pract Res Clin Gastroenterol 2007;21:111-123.

24) Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. Lancet 2003;362:1819-1827.

25) Follo A, Llovet JM, Navasa M, Planas R, Forus X, Francitotta A, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20:1495-1501.

26) Cholongitas E, Senzolo M, Patch D, Shaw S, O’Beirne J, Burroughs AK. Cirrhotics admitted to intensive care unit: the impact of acute renal failure on mortality. Eur J Gastroenterol Hepatol 2009;21:744-750.

27) Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-871.

28) Loef BG, Epema AH, Smilde TD, Henning RH, Ebels T, Navis G, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. J Am Soc Nephrol 2005;16:195-200.

29) Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16:3365-3370.

30) Lee J, Baek SH, Ahn SY, Chin HJ, Na KY, Cha D, et al. Pre-stage acute kidney injury can predict mortality and medical costs in hospitalized patients. PloS One 2016;11:e0167038.

31) Caregaro L, Menon F, Angeli P, Amadio P, Mertel C, Bortoluzzi A, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. Arch Intern Med 1994;154:201-205.

32) Hoste EA, Damen J, Vanholder RC, Lameire NH, Delanghe JR, Van den Hauwe K, et al. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant 2005;20:747-753.

Author names in bold designate shared co-first authorship.