Prognostic Value of Model for End-Stage Liver Disease Incorporating with Serum Sodium Score for Development of Acute Kidney Injury after Liver Transplantation

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Background: Contribution of model for end-stage liver disease incorporating with serum sodium (MELD-Na) score in predicting acute kidney injury (AKI) after orthotopic liver transplantation (OLT) is yet to be identified. This study assessed the prognostic value of MELD-Na score for the development of AKI following OLT.

Methods: Preoperative and surgery-related variables of 321 adult end-stage liver disease patients who underwent OLT in Fuzhou General Hospital were collected. Postoperative AKI was defined and staged in accordance with the clinical practice guidelines developed by Kidney Disease: Improving Global Outcomes. Univariate and multivariate analysis was performed to determine the risk factors for AKI following OLT. The discriminating power of MELD/MELD-Na score on AKI outcome was evaluated by receiver operating characteristic (ROC) curve. Spearman’s correlation analysis was used for identifying the correlated relationship between MELD/MELD-Na score and the severity levels of AKI.

Results: The prevalence of AKI following OLT was in 206 out of 321 patients (64.2%). Three risk factors for AKI post-OLT were presented, preoperative calculated MELD score (odds ratio [OR] = 1.048, P = 0.021), intraoperative volume of red cell suspension transfusion (OR = 1.001, P = 0.002), and preoperative liver cirrhosis (OR = 2.015, P = 0.012). Two areas under ROC curve (AUCs) of MELD/MELD-Na score predicting AKI were 0.688 and 0.672, respectively; the difference between two AUCs was not significant (Z = 1.952, P = 0.051). The Spearman’s correlation coefficients between MELD/MELD-Na score and the severity levels of AKI were 0.406 and 0.385 (P = 0.001, 0.001), respectively.

Conclusions: We demonstrated that preoperative MELD score, intraoperative volume of red cell suspension transfusion and preoperative liver cirrhosis were risk factors for AKI following OLT. Furthermore, we preliminarily validated that MELD score seemed to have a stronger power discriminating AKI post-OLT than that of novel MELD-Na score.

Key words: Acute Kidney Injury; Liver Transplantation; Model for End-Stage Liver Disease Score

Introduction

In the context of orthotopic liver transplantation (OLT), acute kidney injury (AKI) is a major complication that is associated with increased morbidity, mortality, and the demand for postoperative renal replacement therapy.[¹] Therefore, it is a matter of utmost importance to develop reliable prognostic tools that may support in assessing risk of AKI and improving clinical strategies. Etiology of AKI is multifactorial including pre-, intra-, and post-OLT factors of renal and hepatic function.[²] The development of AKI is mainly influenced by more severe degrees of preoperative hepatic insufficiency, presence of ascites, prolonged intraoperative hypotension, liver graft dysfunction, and high model for end-stage liver disease (MELD) score.[³]

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There are more than 35 distinct definitions of acute renal failure (ARF) reported in the literature. Due to the absence of a reliable definition, the incidence of AKI following OLT has been reported to fluctuate between 17% and 95%.[8] In 2004, the Acute Dialysis Quality Initiative work-group published the so-called RIFLE criteria, which was a consensus and broad system for the definition and classification of AKI that moved beyond ARF.[9] However, RIFLE criteria had considerable defects in detecting AKI and failed to determine preventive reference recommendations.[7] In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) developed and implemented a formal clinical practice guidelines for the definition and staging of AKI [Table 1].[8] AKI is defined as any of following: increase in serum creatinine (SCr) by ≥0.3 mg/dl (≥26.5 µmol/L) within 48 h or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml·kg⁻¹·h⁻¹ for 6 h.

Initially, MELD score was entrenched to foresee the 3-month mortality of patients following transjugular intrahepatic portosystemic shunts, which was based on three objective biochemical parameters, including SCr concentration, serum total bilirubin concentration (TB), and the international normalized ratio of prothrombin time (PT-INR).[10] Over a decade, MELD score was extensively used as a benchmark for donor liver allocation and performed magnificently in predicting AKI following OLT.[3,10,11] Unfortunately, serum sodium concentration (Na), a readily available and objective parameter, was not included in MELD score. Besides, hyponatremia was recognized as an independent predictor for mortality among cirrhotic patients.[12,13] MELD incorporating with serum sodium (MELD-Na) score predicted the mortality among the waitlist for OLT more accurately compared to MELD score alone.[14,15] In 2016, the United Network for Organ Sharing in the United States formally determined that MELD-Na score replaced the historical MELD score for liver allocation.[16] Although the role of MELD-Na score in predicting AKI following OLT is yet to be identified.

The objectives of this study were to identify the independent risk factors and assess the prognostic value of MELD/MELD-Na score for the development of AKI in patients who had undergone OLT in our center.

**Methods**

**Ethical approval**

This retrospective study secured endorsement from the Ethics Committee of Fuzhou General Hospital. All analyses used anonymous data that were attained from each patient after they acknowledged a written agreement to undergo the treatment.

**Patients**

This retrospective study combined 367 patients out of which 321 patients were finally enrolled who underwent OLT using the approach of retrograde reperfusion (RETR) via vena cava from January 2005 to December 2015 in Fuzhou General Hospital. The remaining 46 patients were excluded due to various reasons as explained, 5 patients who were under the age of eighteen years, 9 patients who received dialysis treatment before OLT, 11 patients who died of primary graft liver nonfunction in the 1st week following OLT and 21 patients with insufficient preoperative clinical data.

**Clinical variables**

Donors’ hepatic steatosis was investigated by light microscopy. Demographic and clinical variables were extracted from the patients’ medical charts. The latest preoperative laboratory parameters were obtained, including SCr, TB, PT-INR, Na, blood urea nitrogen (BUN), and serum albumin (ALB). The immediate preoperative MELD score was calculated using the following equation:

$$\text{MELD} = (0.957 \times \ln \text{[SCr]} + 0.378 \times \ln \text{[TB]} + 1.120 \times \ln \text{[PT-INR]} + 0.643) \times 10;$$

MELD-Na score was calculated as follows:

$$\text{MELD-Na} = \text{MELD} + 1.32 \times (137-\text{Na}) - (0.033 \times \text{MELD} \times (137-\text{Na})) \text{ (the minimum limit of Na was set to be 125, whereas the maximum limit was set to be 137).}$$

Intraoperative period information was documented and included infusion quantity, volume of blood components transfusion, duration of inferior vena cava clamping and anesthesia. The etiology of OLT was on the basis of postoperative hepatic pathological examination and classified broadly into two types: hepatic cirrhosis and noncirrhosis. The etiologic factors of cirrhosis included hepatitis virus infection related-, alcoholic-, cholestatic-, and hepatolenticular degeneration caused cirrhosis, whereas indications of OLT for noncirrhotic patients included acute liver failure, hepatocellular and cholangiocellular carcinoma.

Urinary output, routine biochemical parameters and liver enzymes were analyzed constantly in the 1st week following surgery. Post-OLT AKI was defined and staged according to the clinical practice guidelines developed by KDIGO: Kidney Disease: Improving Global Outcomes; AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate.

### Table 1: KDIGO clinical practice guideline: Staging of AKI

| Stage | Serum creatinine | Urine output |
|-------|-----------------|--------------|
| 1     | 1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 µmol/L) increase | <0.5 ml·kg⁻¹·h⁻¹ for 6–12 h |
| 2     | 2.0–2.9 times baseline | <0.5 ml·kg⁻¹·h⁻¹ for ≥12 h |
| 3     | 3.0 times baseline or Increase to ≥4.0 mg/dl (≥353.6 µmol/L) or Initial of renal replacement therapy or, in patients <18 years, decrease in eGFR <35 ml·min⁻¹·1.73 m⁻² | <0.3 ml·kg⁻¹·h⁻¹ for ≥24 h or Anuria for ≥12 h |

KDIGO: Kidney Disease: Improving Global Outcomes; AKI: Acute kidney injury; eGFR: Estimated glomerular filtration rate.
Postoperative management and immunosuppressive regimen

Postoperative hemodynamic was monitored by central venous catheter and invasive arterial blood pressure control. During the first 2 postoperative days, patients received continuous intravenous pumping of terlipressin with dosage of 4 mg/24 h. Whenever possible, respiratory treatment was withdrawn immediately after surgery. On the second postoperative day, diabetic special enteral nutritional suspension (TPF-DM) was given through a jejunostomy feeding tube placed during surgery. Drainage tubes and suture lines were removed between 3 and 7 days following OLT. Patients received steroids and a tacrolimus (FK506)-based immunosuppression therapy. Patients with hepatitis B virus-related liver disease were treated with 4000 U of human hepatitis B immunoglobulin (pH 4) during the anhepatic time; 100 U of pH 4 and entecavir (0.5 mg) were given regularly after surgery until seroconversion was detectable.

Statistical analysis

Descriptive statistics were used to compile the baseline characteristics of total patients. Quantitative data were evaluated by the Kolmogorov-Smirnov test and distribution plot for the normality of distribution. Data that met the normal distribution were presented as mean ± standard error (SE); otherwise, data were presented as median (P25, P75 percentiles). Categorical variables were expressed by frequencies (percentages).

For univariate analysis, Student’s t-test or Mann-Whitney U-test were executed (depending on the conditions of normality of distribution) to compare the means of quantitative data. Pearson’s Chi-square test or Fisher’s exact test was tested for categorical variables. Factors which showed statistical significance on univariate analysis were subjected to a binary Logistic regression model with a forward stepwise (likelihood ratio) method to evaluate the effect of their independence.

Two receiver operating characteristic (ROC) curves were performed to examine the discriminating power of MELD/MELD-Na score for AKI outcome. The Youden Index was used to determine the optimal cutoff value, and the method of DeLong et al. (1988) was used for the comparison of areas under two ROC curves (AUCs). Spearman’s correlation analyses were used for identifying the correlated relationships between MELD/MELD-Na score and the severity levels of AKI.

Statistical analysis was performed with SPSS Software (Version 22.0; IBM Corp; New York, NY, USA). ROC curve was performed with MedCalc Software (Version 15.2.0; Ostend, Belgium). All tests performed were two-sided. A $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of patients

A total of 321 adults (age ≥18 years) patients were engaged in this study. Baseline characteristics of patients were presented in Table 2. Among 321 patients enrolled, most patients were male (83.2%), and the mean age was 48 ± 11 years. The calculated MELD/MELD-Na score were presented in 206 of 321 patients (64.2%) in the 1st week following OLT, including 111 patients (34.6%) who developed Stage 1 AKI, 52 patients (16.2%) who developed Stage 2 AKI, and 43 patients (13.4%) who developed Stage 3 AKI [Figure 1]. The univariate analysis of pre- and intra-operative variables was displayed in Table 3. Patients who developed post-OLT AKI shown significantly lower preoperative ALB ($t = 2.831, P = 0.005$) but higher preoperative BUN ($Z = −3.516, P = 0.001$), TB ($Z = −5.732, P = 0.001$), PT-INR ($Z = −5.193, P = 0.001$), the calculated MELD/MELD-Na score ($Z = −5.600, −5.113; P = 0.001, 0.001$, respectively), and intraoperative volume of fresh frozen plasma and red cell suspension transfusion ($Z = −2.507, −5.506; P = 0.012, 0.001$, respectively). Moreover, the incidence of preoperative hepatic cirrhosis in patients who developed post-OLT AKI was higher ($\chi^2 = 21.730, P = 0.001$). In the binary Logistic regression analysis, three independent risk factors related to post-OLT AKI were found; preoperative calculated MELD score (odds ratio [OR] = 1.048, $P = 0.021$), intraoperative volume of red cell suspension transfusion (OR = 1.001, $P = 0.002$), and preoperative liver cirrhosis (OR = 2.015, $P = 0.012$) [Table 4].

Two ROC curves of MELD/MELD-Na score predicting AKI post OLT were presented in Figure 2. As shown in Table 5, two AUCs were 0.688 and 0.672, respectively; the difference between two AUCs demonstrated no statistically significant ($Z = 1.952, P = 0.051$). Spearman’s correlation coefficients between MELD/MELD-Na score

![Figure 1: The development of AKI following OLT. AKI: Acute kidney injury; OLT: Orthotopic liver transplantation.](image-url)
Table 2: Baseline characteristics of study patients

| Characteristics                  | Values (n = 321) |
|----------------------------------|------------------|
| Age (years)                      | 48 ± 11\(^t\)    |
| Gender (male/female), n (%)      | 267/54 (83.2/16.8)* |
| Latest preoperative parameters   |                  |
| MAP (mmHg)                       | 80 ± 16\(^t\)    |
| BUN (mmol/L)                     | 4.8 (3.7, 6.1)   |
| ALB (g/L)                        | 35 ± 8\(^t\)     |
| SCr (µmol/L)                     | 66 (56, 79)      |
| TB (µmol/L)                      | 31.8 (16.9, 152.4) |
| PT-INR                           | 1.4 (1.2, 1.8)   |
| Na (mmol/L)                      | 138 ± 6\(^t\)    |
| MELD score                       | 12 (9, 20)       |
| MELD-Na score                    | 13 (9, 22)       |
| Etiology of liver transplantation|                  |
| Hepatic cirrhosis, n (%)         | 217 (67.6)*      |
| HBV-related cirrhosis with/without hepatocellular carcinoma | 195 (60.8) |
| HCV-related cirrhosis with/without hepatocellular carcinoma | 1 (0.3) |
| Alcoholic cirrhosis              | 3 (0.9)          |
| Cholestatic cirrhosis            | 12 (3.7)         |
| Hepatolenticular degeneration    | 6 (1.9)          |
| Noncirrhosis, n (%)              | 104 (32.4)*      |
| Acute liver failure              | 6 (2.2)          |
| Cholangiocellular carcinoma      | 6 (1.9)          |
| Hepatocellular carcinoma         | 91 (28.3)        |

Data was presented as *n (%), mean ± standard deviation, or median (P₂₅, P₇₅). MAP: Mean arterial pressure; BUN: Blood urea nitrogen; ALB: Serum albumin; SCr: Serum creatinine concentration; TB: Total serum bilirubin concentration; PT-INR: International normalized ratio of prothrombin time; Na: Serum sodium concentration; MELD: Model for end-stage liver disease; MELD-Na: Model for end-stage liver disease incorporating with serum sodium; OL T: Orthotopic liver transplantation; AKI: Acute kidney injury.

The prevalence of AKI varies with respect to the applied definition. During the 1st week, following OL T of our study 64.2% of patients were observed for AKI, as defined by clinical practice guidelines of KDIGO. Our retrospective study primarily focused on assessing the preoperative variables and the surgery-related events to observe better biomarkers for predicting AKI after OL T.

According to the computed comparison of MELD/MELD-Na score, whenever Na concentration exceeds 137 mmol/L, MELD-Na score, and MELD score are even. Prior studies revealed that dilutional hyponatremia was a frequent event in cirrhotic patients with ascites, so MELD-Na score could predict mortality among those patients more accurately than MELD score alone. In this ongoing study, we documented that preoperative MELD score was the independent risk factor for the occurrence of AKI post-OL T, instead of MELD-Na score. Besides, the discriminating power of MELD score on post-OL T AKI, as shown by ROC curve, seemed stronger than that power of MELD-Na score, but the difference demonstrated no statistical significance (Z = 1.952, P = 0.051). Furthermore, both positive correlation relationships were found between MELD/MELD-Na score and the severity levels of AKI, while correlation coefficient of MELD score was more than correlation coefficient of MELD-Na score. We found out that the prognostic value of the novel MELD-Na score for AKI following OL T was not enhanced. There was no significant difference in preoperative Na concentration between patients who developed postoperative AKI and who did not (t = 1.583, P = 0.114), which might be a major cause not to fully exploit the advantages of MELD-Na score.

The demonstration, as shown by our earlier studies, interestingly showed no significant difference between patients who developed post-OL T AKI and those who did not through preoperative SCr concentration which weighs heavily in MELD/MELD-Na score calculation. One cause might be that MELD score cannot distinguish SCr concentration within the range of 0–1 mg/dl (88.4 µmol/L). Moreover, SCr is not a dependable marker of renal function. Muscle mass, tubular secretion of creatinine, and medications can alter SCr without changing the glomerular filtration rate (GFR). In ongoing clinical practice, unfortunately, the GFR is widely overestimated when using creatinine-based equations.

With regard to the surgical procedure, duration of inferior vena cava clamping during the anhepatic phase is significantly related to AKI following OL T. In our institution, all patients underwent OL T using the approach of retrograde reperfusion through vena cava (RETR). Ischemia and reperfusion (I/R) injury in liver transplantation is a well-studied phenomenon, and the generation of reactive oxygen species (ROS) subsequent to reoxygenation inflicts tissue damage and initiates a cellular cascade leading to
In the present study, we found out the volume of red cell suspension transfusion was the independent risk factor for the development of AKI following OLT, which might be related to the subsequent hypovolemia induced by acute bleeding.[25]

A decrease in preoperative serum albumin is a prognostic factor in cirrhotic patients; moreover, various studies have shown that preoperative hypoalbuminemia is associated with a greater incidence of postoperative AKI in OLT.[21] In this series, our patients who encountered AKI post-OLT had a lower level of preoperative serum albumin and a higher incidence of liver cirrhosis. In addition to that, we found that patient with liver cirrhosis was an independent risk factor for the development of AKI following OLT.

Our study has a considerable amount of limitations that need to be taken account. First of all, this is a retrospective study that was conducted in a single center and in which data were collected from clinical records, rather than from a database that were specifically designed for this kind of study. This may lead to foreseeable heterogeneity of data. Second, preoperative laboratory parameters were collected at a single time, which may fluctuate and be affected by many circumstances. Last but not least, due to the involvement of many patients and during this study, many of them could not pursue the schedule; we were unable to analyze the prognostic value of MELD/MELD-Na score for long-term mortality.

In conclusion, we demonstrated that preoperative MELD score, intraoperative volume of red cell suspension transfusion and preoperative liver cirrhosis were three independent risk factors for the development of AKI following OLT.
independent risk factors for the development of AKI following OLT. Furthermore, we had preliminarily validated that MELD score seemed to be of a stronger discriminating power on post-OLT AKI than the novel MELD-Na score.

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**Conflicts of interest**

There are no conflicts of interest.

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摘要

背景：终末期肝病模型联合血钠（MELD-Na）评分对等待原位肝移植患者死亡率的预测较单独使用终末期肝病模型（MELD）评分更为准确。然而，尚未有研究评估MELD-Na评分对原位肝移植术后急性肾损伤的预测作用。因此，本研究对MELD和MELD-Na评分在原位肝移植术后发生急性肾损伤中的预测价值进行评估。

方法：收集2005年至2015年期间在本中心接受原位肝移植手术的321位成年（年龄≥18岁）终末期肝病患者的术前和手术相关指标。术后急性肾损伤的诊断和分期标准采用改善全球肾脏病预后组织（KDIGO）于2012年公布的临床实践指南。采用单因素和多因素分析检测原位肝移植术后发生急性肾损伤的独立危险因素。采用受试者操作特征（ROC）曲线评估MELD和MELD-Na评分对原位肝移植术后发生急性肾损伤的预测效能。采用Spearman相关分析检测MELD和MELD-Na评分与急性肾损伤严重等级之间的相关关系。

结果：在321位接受原位肝移植的患者中，共有206位患者术后发生急性肾损伤（64.2%）。术前MELD评分（似然比1.048, P=0.021），术中悬浮红细胞的输入量（似然比1.001, P=0.002）和术前存在肝硬化（似然比2.015, P=0.012）是术后发生急性肾损伤的危险因素。MELD和MELD-Na评分预测急性肾损伤的ROC曲线下面积分别为0.688和0.672，两条ROC曲线下的面积无显著性差异（Z=1.952, P=0.051）。MELD和MELD-Na评分与急性肾损伤严重等级之间的Spearman等级相关系数分别为0.406和0.385（P=0.001, 0.001）。

结论：基于本研究，术前MELD评分、术中悬浮红细胞的输入量和术前存在肝硬化是原位肝移植术后发生急性损伤的独立危险因素。而且，我们初步证实了MELD评分对原位肝移植术后急性肾损伤的预测效能强于较新的MELD-Na评分。