Using Postoperative Coagulation Parameters Within 24 h After Liver Transplantation to Predict Incidence of Stage 3 Acute Kidney Injury (AKI)

Chen Chen*  
Xiaolan Chen*  
Xianyuan Zhao  
Junqi Feng  
Yuan Gao  
Yuxiao Deng  
Zhe Li

* Chen Chen and Xiaolan Chen contributed equally to this work

Corresponding Authors: 
Zhe Li, e-mail: slamy1987@126.com, Yuxiao Deng, e-mail: dengyuxiao@renji.com

Financial support: 
None declared

Conflict of interest: 
None declared

Background: 
This study aimed to investigate the relationship between coagulation function and the incidence of acute kidney injury (AKI) stage 3 within 24 h after liver transplantation (LT) and explore the predictive value of coagulation parameters for post-LT stage 3 AKI.

Material/Methods: 
A retrospective study was conducted on 241 patients who underwent LT at the Renji Hospital affiliated with Shanghai Jiao Tong University School of Medicine between February 2021 and February 2022. The coagulation parameters within 24 h after LT and the incidence of post-LT AKI within 7 days were recorded. The correlation between post-LT coagulation function and post-LT stage 3 AKI was determined using binary logistic regression analysis.

Results: 
Post-LT AKI occurred in 99 cases (41.1%), 28 (28.3%) of which developed AKI stage 3. In univariate logistic regression analysis, multiple coagulation indexes of the AKI stage 3 group were worse than in the AKI stage 0-2 group. In multivariate logistic regression analysis, lower post-LT ADP-induced PLT aggregation rate (cut-off: 15.75%), higher D-dimer level (cut-off: 3.52 ug/ml), and prolonged R-value (cut-off: 7.5 min) within 24 h were independent risk factors for post-LT AKI stage 3. The AUROC value for predicting the incidence of post-LT AKI stage 3 combining the 3 indices was 0.835 (sensitivity: 83.3%, specificity: 76.9%). The decision curve showed that combining D-dimer, R-value, and ADP-induced PLT aggregation rate yielded the highest net benefit for predicting the incidence of stage 3 AKI.

Conclusions: 
Post-LT coagulation function within 24 h correlated with the incidence of post-LT AKI stage 3. Lower ADP-induced PLT aggregation rate, higher D-dimer level, and prolonged R-value from the TEG were independent risk factors for the incidence of post-LT AKI stage 3.

Keywords: 
Acute Kidney Injury • Blood Coagulation • Liver Transplantation

Full-text PDF: 
https://www.annalsoftransplantation.com/abstract/index/idArt/937535
Background

Acute kidney injury (AKI) is one of the most common post-LT complications. The incidence of post-LT AKI is 12.3-56.6% [1]. Compared to patients with AKI stage 1-2, post-LT stage 3 AKI has a greater impact on mortality and hospital stay [2,3]. However, studies on the prediction of post-LT stage 3 AKI are limited.

Previous studies have explored the risk factors for post-LT AKI incidence. These factors include the preoperative model for end-stage liver disease (MELD) score [4], intraoperative blood loss, infusion of blood products [5], and vasoactive drug use [6]. Furthermore, some clinical and mechanistic studies have suggested that extended-criteria donor grafts could lead to AKI through hepatic ischemia-reperfusion injury (HIRI). Nevertheless, most data were from single-center studies with limited patient samples, thus impeding the clinical application of these parameters. HIRI has been reported as an independent risk factor for post-LT AKI, and its severity is related to the severity of the AKI [7]. Pathophysiological changes induced by HIRI damage endothelial cells, ultimately impairing the coagulation function [8,9]. Furthermore, post-LT coagulation disorder is influenced by several parameters related to post-LT AKI and its severity, including preoperative MELD score, intraoperative bleeding, infusion of coagulation substances, and postoperative HIRI [10-13]. However, the relationship between post-LT coagulation function and the incidence of post-LT AKI and its severity has not been explored thus far. Hence, we hypothesized that post-LT coagulation function might be associated with post-LT AKI and could influence its severity. We conducted a retrospective study to evaluate the impact of miscellaneous coagulation parameters on the development of post-LT stage 3 AKI and to identify the parameters with high predictive value for post-LT stage 3 AKI.

Material and Methods

Study Population and Ethical Approval

Patients who underwent LT in the Department of Critical Care Medicine at the Renji Hospital between 2021.02 and 2022.02 were enrolled in this retrospective study. This study was approved by the Ethics Committee of the Renji Hospital, School of Medicine, Shanghai Jiao Tong University (KY2021-019).

The data of adult patients (>18 years) admitted to the intensive care unit (ICU) due to LT operation were screened. Patients with preoperative AKI, history of chronic kidney disease with a glomerular filtration rate less than 60 ml/min, combined liver and kidney transplantation, reoperation within 72 h, sudden cardiac arrest, and death within 72 h after the operation were excluded from the study. Additionally, the NYHA of all the patients finally included in this study was ≤2, and none of them had recently used anticoagulant and antiplatelet drugs. ADP or AA-induced platelet aggregation rate were measured using an ag800 automatic platelet aggregator. The reagent was AA and ADP activator provided by Shandong Tailixin Medical Co., Ltd. The quality of the reagent was qualified through sampling inspection at the factory and at the station. It is used within the valid time period. The reagent storage conditions meet the requirements.

Diagnostic Criteria

AKI is a syndrome that was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines [14]: (1) an increase in serum creatinine (Scr) by 26.5 mmol/L within 48 h; (2) an increase in Scr to 1.5 times baseline within the first 7 postoperative days; (3) the urine volume (UV) <0.5 ml/kg/h lasted more than 6 h after LT. Moreover, AKI was classified into 3 stages: stage 1, creatinine increased to 26.5 mmol/L or increased to 1.5-1.9 fold from baseline, or the UV <0.5 ml/(kg/h) lasting for 6-12 h; stage 2, increase by 2-2.9 fold or UV <0.5 ml/(kg/h) lasted >12 h; stage 3, increased ≥3-fold or increased in Scr to 354 umol/L or initiation of continuous renal replacement therapy (CRRT). Baseline Scr was defined as the lowest creatinine level within 1 month before transplantation. Patients were divided into the grade 0-2 AKI group and the grade 3 AKI group based on their AKI stage.

Data Collection

The demographic data included pre-transplant data, sex, age, causes of LT, ascites volume, MELD score, laboratory data such as alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TB), and coagulation parameters namely international normalized ratio (INR), D-dimer, and fibrinogen degradation products (FDP). The whole blood cell analysis parameters included hemoglobin (HB) and platelet (PLT), while the intraoperative data included intraoperative blood loss and blood transfusion volume. Furthermore, the parameters measured within 24 h of admission to the ICU included liver function (ALT, AST, TB), platelet count, functional parameters (ADP or AA-induced platelet aggregation rate), various coagulation factors percentages (FII, FV, FVII, FVIII, FIX, FX, FXI, FXII, Protein S, Protein C, Antithrombin III, INR), and multiple parameters of TEG (R-value, k-value, α-angle, maximum amplitude (MA) value, Ly 30, coagulation time, and clot strength). Additionally, this study recorded creatinine and urine volume permutations within 7 days of surgery to diagnose AKI.

Statistical analysis

The continuous data are expressed as mean±standard deviation for normally distributed data and as median with interquartile
range (IQR) for non-normally distributed data. The chi-square test or Fisher’s exact test was employed to compare the categorical variables. Continuous variables that did not have normal distribution were compared using the Mann-Whitney U test. Decision curve analysis was used to assess the net benefit. The AUROC expressed the predictive accuracy of the R-value, D-dimer level, and ADP-induced PLT aggregation rate. Moreover, the optimal cut-off values were obtained using Youden’s parameters. Statistical significance was set at P<0.05. MICE (multivariate imputation by chained equations) was employed to assess the missing data in SPSS. Statistical analysis was performed using SPSS (version 26.0; SPSS, Inc., Chicago, IL, USA).

Results

In this study, 267 patients who consented to LT were admitted to the ICU; 26 patients were excluded because of preoperative AKI (n=3), prior history of chronic kidney disease and glomerular filtration rate of less than 60 ml/min (n=5), combined liver and kidney transplantation (n=3), reoperation within 72 h (n=5), death within 72 h after the operation (n=6), and sudden cardiac arrest (n=4) (Figure 1).

Demographic Characteristics of Patients Undergoing LT

The study population (n=241) comprised 175 men (72.6%) and 66 women (27.4%). The average age was 50.9±10.9 years. Demographic data are presented in Table 1. Among the 241 patients who underwent LT, the proportion of post-LT AKI was 41.1% (99/241). Out of the patients who developed AKI, the incidence of stage 1 AKI was 57.6% (57/99), stage 2 was 6.5% (14/99), and stage 3 was 28.3% (28/99). In this cohort, the post-LT mortality rate was 7.9% (19/241). The stage 3 mortality rate was 42.9% (12/28) among the patients with AKI, which was significantly higher than in the stage 0-2 patients (3.3%). Furthermore, patients with severe hepatic failure had a higher incidence of post-LT AKI stage 3 (43.9 vs 18.3, P=0.003). CRRT treatment was only performed in patients with stage 3 AKI, accounting for 21.4% (6/28) of patients, with a mortality rate of 66.7% (4/6).

Comparing Pre- and Intra-Operative Clinical Data Between the Post-LT stage 0-2 AKI and Stage 3 AKI Groups

The pre- and intraoperative clinical data are presented in Table 1. The preoperative MELD scores of patients with AKI stage 3 were higher than those in the stage 0-2 AKI group (17 vs 13, P=0.006). There was no significant difference in preoperative liver function (AST, ALT, ALB, and Scr) between the 2 groups. In contrast, the preoperative D-dimer and FDP levels were higher in patients with stage 3 AKI than in patients with stage 0-2 AKI (1.86 vs 0.85, P=0.002 and 12.4 vs 5.2, P=0.001, respectively). Regarding intraoperative markers, intraoperative bleeding in the stage 3 AKI group was greater than that in the stage 0-2 AKI group (800 vs 500, P=0.023). Moreover, patients with stage 3 AKI were infused with more red blood cell (RBC) suspension (8 vs 4,0.004) and plasma (850 vs 400, P=0.01).

Comparisons of Coagulation Function Parameters Within 24 h after LT Between the Stage 0-2 AKI and Stage 3 Groups

Table 2 shows the comparisons of coagulation parameters and other laboratory test within 24 h between the 2 groups. Compared with stage 0-2 AKI patients, patients in the stage 3 group had higher ALT level (815 vs 500, P<0.001) and AST level (2496 vs 962, P<0.001). Patients in the stage 3 group had higher Scr than those in the stage 0-2 group. When univariate were included in logistic regression (Table 3), patients in the stage 3 group had lower platelet counts (30.5 vs 52.0, P<0.001, OR=0.993), ADP (11.2 vs 38.2, OR=0.953, P<0.001), and AA (5.6 vs 34.4, OR=0.969, P=0.003)-induced platelet aggregation rates than in the stage 0-2 group. In addition, FV (16.0 vs 34.7, OR=0.950, P<0.001), FVII (96.1 vs 142.7, OR=0.989, P=0.005), and FIX (43.6 vs 51.8, OR=0.975, P=0.022) levels were markedly lower in the stage 3 group. The stage 3 AKI group had a higher INR (1.9 vs 1.5, OR=2.654, P<0.001) than the stage 0-2 group. Compared with stage 0-2, the stage 3 group had higher D-dimer levels (2.1 vs 4.9, OR=1.004, P<0.001) and significantly higher levels of FDP (13.3 vs 24.9, OR=1.007, P<0.001). However, the stage 3 group had lower FIB levels than the stage 0-2 group (0.9 vs 1.7, OR=0.231, P<0.001).

The stage 3 AKI group had a more heterogeneous TEG appearance; the R and K values were extended by 2.2 (6.8 vs 9.0, OR=1.204, P<0.001) and 2.7 (4.0 vs 6.7, OR=1.041, P=0.186), respectively. The α-angle was narrowed in the stage 3 group (60.2 vs 54.0, OR=0.955, P=0.006). Furthermore, the MA value was lower in the stage 3 group (33.4 vs 41.4, OR=0.947, P=0.005) and its setting time was longer than in the stage 0-2 group (32.5 vs 28.8, OR=1.104, P=0.001).

Multivariate Logistic Regression Analysis of the Incidence of AKI Stage 3 After LT

This study combined meaningful parameters from univariate and multivariate regression analyses, and the results determined that D-dimer, R-value, and ADP-induced platelet aggregation rates were independent risk factors for AKI stage 3 after LT. Table 3 shows the results from multivariate logistic regression analysis. Figure 2 displays how the incidence of stage 3 AKI increased with the number of independent risk factors. Indeed, when patients did not carry these 3 independent risk factors, the incidence rate of stage 3 AKI was 0%. Conversely, when patients had all 3 independent risk factors,
Liver transplantation admission to ICU n=267
Patients finally included n=241
AKI diagnosis criteria by KDIGO 2012 guidelines

Excluded:
- Preoperative AKI, n=3
- History of chronic kidney disease (CKD), n=5
- Combined liver and kidney transplantation, n=3
- Reoperating within 72 hours, n=5
- Sudden cardiac arrest, n=4
- Died within 72 hours after operation, n=6

AKI stage 0-2 n=213
AKI stage 3 n=28

Figure 1. Flowchart of the study process.

Table 1. Demographic and pre-and intraoperative clinical data of the studied population (n=241).

| Group          | AKI stage 0-2 | AKI stage 3 | P value |
|----------------|---------------|-------------|---------|
| Male (n, %)    | 155 (72.8)    | 20 (71.4)   | 0.881   |
| Age [mean±SD, y] | 50.7±10.9     | 52.5±11.8   | 0.508   |
| AKI stage 3 requiring CRRT (n, %) | 0 (0)         | 6 (21.4)    | <0.001  |
| Etiology of liver transplantation |              |             |         |
| cirrhosis      |               |             |         |
| Hepatitis B (n , %) | 40 (18.8)    | 4 (14.3)    | 0.556   |
| PBC (n, %)     | 13 (6.1)      | 1 (3.6)     | 0.590   |
| Alcoholic (n, %) | 11 (5.2)      | 0 (0)       | 0.218   |
| AIH (n, %)     | 13 (6.1)      | 3 (10.7)    | 0.357   |
| Other (n, %)   | 12 (5.6)      | 3 (10.7)    | 0.296   |
| Liver cancer (n, %) | 96 (45.1)    | 10 (35.7)   | 0.097   |
| Hepatic failure (n, %) | 39 (18.3)    | 12 (43.9)   | 0.003   |
| Other (n, %)   | 4 (1.8)       | 0 (0)       | 0.419   |
| Ascites [M (P25, P75), mL] | 200 (0, 1500) | 200 (0, 2000) | 0.893 |
| MELD score [M (P25, P75)] | 13 (9, 21)      | 17 (11, 32) | 0.006  |
| Bleeding [M (P25, P75), mL] | 500 (400, 800) | 800 (500, 1000) | 0.023 |
| RBC suspension infusion [M (P25, P75), u] | 4 (0, 8)       | 8 (4, 10)   | 0.004  |
| Plasma infusion [M (P25, P75), mL] | 400 (0, 1000) | 850 (400, 1300) | 0.010 |
| Hospital mortality (n, %) | 7 (3.3)       | 12 (42.9)   | <0.001  |

AKI – acute kidney injury; CRRT – continuous renal replacement therapy; PBC – primary biliary cirrhosis; AIH – autoimmune hepatitis; MELD – model for end stage liver disease; ALT – alanine transaminase; AST – aspartate transaminase; TB – total bilirubin; INR – international normalized ratio; FDP – fibrinogen degradation products; HB – hemoglobin; PLT – platelet; Scr – creatinine.

The incidence rate of AKI stage 3 was 60%. Hence, the higher the number of risk factors, the greater the incidence of stage 3 AKI ($R^2=0.9213$, $P=0.04$).

The AUROC Analysis of D-dimer, R-value, and ADP-Induced PLT Aggregation as Parameters for Incidence of Stage 3 AKI

Table 4 shows the result from AUROC analysis. The AUROC value of D-dimer was 0.723 (95% CI: 0.621-0.825), with a cut-off value of 3.52 ug/ml, a sensitivity of 60.7% and specificity of 74.5%, while that of the R-value was 0.815 (95% CI: 0.739-0.890), with a cut-off value of 7.5 min, a sensitivity of 92%, and specificity of 64.6%. The AUROC value of ADP-induced PLT aggregation was 0.758 (95% CI: 0.654-0.862), with a cut-off value of 15.75%, a sensitivity of 82.7% and a specificity of
Table 2. Comparison of liver function and coagulation parameters between the 2 groups within 24 h of LT.

| Group n | AKI stage 0-2 | AKI stage 3 | P value |
|---------|--------------|-------------|---------|
|         | 213          | 28          |         |
| ALT [M (P<sub>25</sub>, P<sub>75</sub>), u/l] | 500 (274, 860) | 815 (269, 2085) | <0.001 |
| AST [M (P<sub>25</sub>, P<sub>75</sub>), u/l] | 962 (455, 2006) | 2496 (575, 6979) | <0.001 |
| Scr [M (P<sub>25</sub>, P<sub>75</sub>), umol/L] | 79 (64, 102) | 205 (177, 269) | <0.001 |
| PLT count [M (P<sub>25</sub>, P<sub>75</sub>), ×10<sup>9</sup>/L] | 52.0 (32.0, 85.0) | 30.5 (19.0, 53.5) | 0.003 |
| ADP-induced PLT aggregation [M (P<sub>25</sub>, P<sub>75</sub>)] | 38.2 (21.2, 59.3) | 11.2 (7.0, 31.5) | <0.001 |
| AA-induced PLT aggregation [M (P<sub>25</sub>, P<sub>75</sub>)] | 34.4 (13.1, 63.9) | 5.6 (4.5, 40.6) | 0.003 |
| FII [M (P<sub>25</sub>, P<sub>75</sub>), %] | 37.1 (28.9, 52.1) | 40.1 (30.3, 52.1) | 0.885 |
| FV [M (P<sub>25</sub>, P<sub>75</sub>), %] | 34.7 (22.9, 51.4) | 16.0 (7.0, 30.5) | <0.001 |
| FVII [M (P<sub>25</sub>, P<sub>75</sub>), %] | 47.8 (33.5, 63.8) | 35.0 (26.7, 51.5) | 0.065 |
| FVIII [M (P<sub>25</sub>, P<sub>75</sub>), %] | 142.7 (102.3, 193.2) | 96.1 (56.6, 170.6) | 0.005 |
| FIX [M (P<sub>25</sub>, P<sub>75</sub>), %] | 51.8 (40.4, 71.1) | 43.6 (31.1, 57.2) | 0.022 |
| FX [M (P<sub>25</sub>, P<sub>75</sub>), %] | 43.2 (30.9, 57.2) | 40.3 (28.4, 55.6) | 0.512 |
| FXI [M (P<sub>25</sub>, P<sub>75</sub>), %] | 33.4 (24.7, 50.2) | 26.3 (17.5, 45.4) | 0.073 |
| FXII [M (P<sub>25</sub>, P<sub>75</sub>), %] | 22.9 (18.6, 29.5) | 19.6 (15.5, 29.9) | 0.088 |
| Protein S [M (P<sub>25</sub>, P<sub>75</sub>), %] | 31.0 (17.2, 44.1) | 25.00 (13.60, 32.7) | 0.028 |
| Protein C [M (P<sub>25</sub>, P<sub>75</sub>), %] | 41.9 (34.2, 59.6) | 41.5 (29.6, 52.4) | 0.410 |
| Antithrombin III [M (P<sub>25</sub>, P<sub>75</sub>), %] | 38.8 (29.8, 49.7) | 27.8 (21.9, 43.8) | 0.002 |
| INR [M (P<sub>25</sub>, P<sub>75</sub>)] | 1.5 (1.3, 1.8) | 1.9 (1.5, 2.5) | <0.001 |
| D-dimer [M (P<sub>25</sub>, P<sub>75</sub>), ug/ml] | 2.1 (1.0, 3.6) | 4.9 (2.0, 37.4) | <0.001 |
| FDP [M (P<sub>25</sub>, P<sub>75</sub>), ug/ml] | 13.9 (8.3, 23.7) | 24.3 (12.1, 125.6) | <0.001 |
| FIB [M (P<sub>25</sub>, P<sub>75</sub>), g/l] | 1.7 (1.2, 2.2) | 0.9 (0.6, 1.5) | <0.001 |
| R-value [M (P<sub>25</sub>, P<sub>75</sub>), min] | 6.8 (5.8, 8.2) | 9.0 (7.8, 14.9) | <0.001 |
| K value [M (P<sub>25</sub>, P<sub>75</sub>), min] | 4.0 (2.5, 6.5) | 6.7 (4.8, 8.9) | 0.186 |
| α-angle [M (P<sub>25</sub>, P<sub>75</sub>), deg] | 60.2 (52.5, 67.4) | 54.0 (46.1, 59.9) | 0.006 |
| MA [M (P<sub>25</sub>, P<sub>75</sub>), mm] | 41.4 (34.5, 51.7) | 33.4 (28.5, 38.6) | 0.005 |
| Ly30 [M (P<sub>25</sub>, P<sub>75</sub>), %] | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 0.753 |
| Setting time [M (P<sub>25</sub>, P<sub>75</sub>), min] | 28.8 (26.6, 31.3) | 32.5 (28.9, 38.1) | 0.001 |
| Clot strength [M (P<sub>25</sub>, P<sub>75</sub>), d/sc] | 3525.4 (2568.2, 5294.3) | 2312.8 (1931.2, 2952.6) | 0.042 |

AKI – acute kidney injury; ALT – alanine aminotrans; AST – aspartate transaminase; INR – international normalized ratio; FDP – fibrinogen degradation products; FIB – fibrinogen; PLT – platelet; α-angle – rate of clot formation; K value – coagulation value to 20-mm clot; Ly 30 – % of clot lysis at 30min; MA – maximum amplitude (maximum strength of clot); R value – reaction value (value to fibrin formation 2mm clot).
65.4%. Notably, using these 3 parameters in combination to predict the incidence of AKI stage 3 could boost the AUROC score to 0.835, sensitivity to 83.3% and specificity to 76.9%. Figure 3 shows the sensitivity and specificity of each parameter and Figure 4 shows the ROC curve of combining D-dimer, R-value, and ADP-induced PLT aggregation rate for predicting the incidence of stage 3 AKI. The decision curve shows that combining D-dimer, R-value, and ADP-induced PLT aggregation rate yielded highest net benefit for predicting the incidence of stage 3 AKI (Figure 5).

| Variable                         | Crude OR (95% CI)   | P value | Adjusted OR (95% CI) | P value |
|----------------------------------|---------------------|---------|----------------------|---------|
| PLT count                        | 0.993 (0.983-1.003) | <0.001  |                      |         |
| ADP-induced PLT aggregation      | 0.953 (0.929-0.978) | <0.001  | 0.965 (0.936-0.994)  | 0.020   |
| AA-induced PLT aggregation       | 0.969 (0.949-0.989) | 0.003   |                      |         |
| FII                              | 1.002 (0.980-1.023) | 0.885   |                      |         |
| FV                               | 0.950 (0.924-0.977) | <0.001  |                      |         |
| FVII                             | 0.982 (0.964-1.001) | 0.065   |                      |         |
| FVIII                            | 0.989 (0.982-0.997) | 0.005   |                      |         |
| FIX                              | 0.975 (0.954-0.996) | 0.022   |                      |         |
| FX                               | 0.994 (0.976-1.012) | 0.512   |                      |         |
| INR                              | 2.654 (1.562-4.507) | <0.001  |                      |         |
| D-dimer                          | 1.004 (1.020-1.060) | <0.001  | 1.032 (1.010-1.054)  | 0.004   |
| FDP                              | 1.007 (1.003-1.11)  | <0.001  |                      |         |
| FIB                              | 0.231 (0.106-0.504) | <0.001  |                      |         |
| R-value                          | 1.204 (1.017-1.309) | <0.001  | 1.168 (1.044-1.307)  | 0.007   |
| K value                          | 1.041 (0.981-1.104) | 0.186   |                      |         |
| α-angle                          | 0.955 (0.924-0.987) | 0.006   |                      |         |
| MA                               | 0.947 (0.912-0.984) | 0.005   |                      |         |
| Setting time                     | 1.104 (1.040-1.171) | 0.001   |                      |         |
| Clot strength                    | 1.000 (0.999-1.000) | 0.042   |                      |         |
| Protein S                        | 0.971 (0.945-0.997) | 0.028   |                      |         |
| Protein C                        | 0.990 (0.968-1.013) | 0.410   |                      |         |
| ATIII                            | 0.948 (0.916-0.980) | 0.002   |                      |         |

OR = odds ratio; CI = confidence interval; INR = international normalized ratio; FDP = fibrinogen degradation products; FIB = fibrinogen; PLT = platelet; ATIII = antithrombin III; α-angle = rate of clot formation; K value = coagulation value to 20-mm clot; LY 30 – % of clot lysis at 30min; MA = maximum amplitude (maximum strength of clot); R value = reaction value (value to fibrin formation 2-mm clot).

Since the baseline data of the 2 groups were different, we performed subgroup analysis on hepatic failure, bleeding volume, MELD score, RBC suspension, and plasma infusion volume. We found that for different subgroups, the combination of the 3 indexes has good ability to predict the incidence of stage 3 AKI after LT. There was no significant statistical difference in AUROC among different subgroups (Table 5).
Discussion

The incidence of post-LT AKI is closely related to the length of hospital stay, hospital mortality rate, and chronic kidney disease [15,16]. In our study, the incidence of post-LT AKI was 41%. In patients who developed AKI, the incidence of stage 3 AKI was 28%. AKI stage 3 patients had higher mortality and CRRT rates than those in the stage 0-2 AKI group.

To the best of our knowledge, our study is the first to investigate the relationship between 24-h post-LT coagulation function and the incidence of post-LT stage 3 AKI. It was determined that D-dimer, ADP-induced platelet aggregation levels, and R-values of TEG were independent risk factors for post-LT stage 3 AKI.

The coagulation function within 24 h after LT revealed that patients with stage 3 AKI had platelet dysfunction with lower platelet counts, lower aggregation rates, and lower levels of coagulation factors V, VIII, and IX, but they had higher serum D-dimer and FDP levels than the control group. Platelets, coagulation factors, and fibrinolytic activation represent the different stages of coagulation reaction in vivo. Our results suggest that coagulation disorders occurred in patients with stage 3 AKI within 24 h after LT. Early post-LT coagulation dysfunction might be due to intraoperative state and organ dysfunction.

Table 4. Predictive values of D-dimer, R-value, and ADP-induced PLT aggregation for the incidence of stage 3 AKI after LT.

|                          | Cutoff | AUROC | 95% CI        | Sensitivity (%) | Specificity (%) |
|--------------------------|--------|-------|---------------|-----------------|-----------------|
| D-dimer                  | 3.52   | 0.723 | 0.621-0.825   | 60.7            | 74.5            |
| TEG R value              | 7.5    | 0.815 | 0.739-0.890   | 92.0            | 64.6            |
| ADP-induced PLT aggregation | 15.75 | 0.758 | 0.654-0.862   | 82.7            | 65.4            |
| Combined                 | /      | 0.835 | 0.733-0.937   | 83.3            | 76.9            |

AUROC = area under the receiver operating characteristic curves; CI = confidence interval; R value – reaction value (value to fibrin formation 2-mm clot).

Figure 2. Relationship between the number of independent risk factors and the incidence of AKI stage 3.

Figure 3. Sensitivity and specificity of different parameters in predicting the incidence of AKI stage 3.

Figure 4. ROC curve of combining D-dimer, R-value and ADP-induced PLT aggregation rate for predicting the incidence of AKI stage 3.
Table 5. Subgroup analysis of the combined 3 indexes for predicting the incidence of stage 3 AKI after LT.

|                          | AUROC  | 95% CI          | P value |
|--------------------------|--------|-----------------|---------|
| **Hepatic failure**      |        |                 |         |
| Yes                      | 0.716  | 0.560-0.842     | 0.137   |
| No                       | 0.896  | 0.842-0.937     |         |
| **Bleeding >600ml**      |        |                 |         |
| Yes                      | 0.879  | 0.797-0.936     | 0.251   |
| No                       | 0.736  | 0.648-0.936     |         |
| **Meld score >15**       |        |                 |         |
| Yes                      | 0.784  | 0.681-0.866     | 0.282   |
| No                       | 0.890  | 0.824-0.937     |         |
| **RBC suspension infusion >6u** |     |                 |         |
| Yes                      | 0.858  | 0.756-0.929     | 0.506   |
| No                       | 0.786  | 0.711-0.850     |         |
| **Plasma infusion >800 ml** |     |                 |         |
| Yes                      | 0.760  | 0.627-0.864     | 0.417   |
| No                       | 0.860  | 0.797-0.909     |         |

AUROC – area under the receiver operating characteristic curves; CI – confidence interval.
preservation-related HIRI and secondary release of circulating cytokines, which were reported to participate in kidney injury and post-LT AKI [17]. However, the relevant mechanism may be partly LT-induced inflammatory response and endothelial injury. During the hyperacute phase of HIRI, necrotic hepatocytes release damage-associated molecular patterns (DAMPs) that activate liver Kupffer cells to stimulate the release of circulating cytokines, directly damaging the vascular endothelium and inducing coagulation dysfunction. DAMPs bind to Toll-like receptors in the kidney, recruit and activate immune cells, impair renal tubule capillary endothelium function, and lead to micro-thrombosis and AKI [18]. Furthermore, endothelial cells play an essential role in maintaining coagulation homeostasis. HIRI-induced endothelial injury contributes to neutrophil trapping, platelet aggregation, and modulation of the inflammatory response [19]. This observation is consistent with Agarwal’s finding that the endothelial injury biomarker VWF is elevated in acute liver failure patients with stage 3 AKI [20].

Our results further demonstrated that D-dimer levels were an independent risk factor for the incidence of post-LT stage 3 AKI. D-dimer has been reported to effectively predict the incidence of AKI induced by infection, contrast agents, and hematopoietic stem cell transplantation [21-23]. Although current research focuses on the inherent relationship between D-dimer and AKI, our results further showed that serum D-dimer and FDP levels were higher in the post-LT stage 3 AKI group than in the stage 0-2 AKI group. As a marker of a hypercoagulable state, D-dimer may indicate the degree of renal microvascular thrombosis and hypoperfusion [24]. A recent study reported that higher D-dimer levels were correlated with more severe liver dysfunction [25-27], suggesting that D-dimer can predict the severity of organ injury after LT. In addition, the D-dimer value not only represents the imbalance of hypocoagulability and hypercoagulation during LT [28], but is also involved in the vicious circle of the ischemia-induced inflammatory response [29-30]. Hence, we posited that D-dimer reflects the excessive activation of coagulation, fibrinolysis, and inflammatory cytokines in the early phase after LT and effectively predicts the incidence of post-LT stage 3 AKI.

The ADP-induced platelet aggregation rate was another independent risk factor for post-LT stage 3 AKI incidence. As mentioned above, an interactive relationship develops between inflammatory cytokines, coagulation disorders, and endothelial injury in the early phase after LT. This promotes persistent and over-activation of platelets, resulting in a decrease in the platelet aggregation rate, which has been reported to contribute to AKI [31]. The activation of platelets damages the endothelial vascular wall, promotes intravascular thrombus, and activates chemokines such as chemokine ligand 5 and platelet factor 4, leading to AKI [32,33]. Another study reported an increase in AKI in patients with severe thrombocytopenia after living-donor LT [34]. There are few published studies on the platelet aggregation rate and severity of post-LT AKI, and our result may provide direction for follow-up research.

Patients with post-LT stage 3 AKI had a lower coagulable state on TEG within 24 h. This result may be because TEG is an ex vivo test dependent on the procoagulant factors and platelets counts [35], both of which were noticeably lower in post-LT stage 3 AKI patients than in stage 0-2 AKI. In addition, the R-value, which represents the activity of coagulation factors and reflects the common pathway of internal and external coagulation on TEG, was an independent risk factor for post-LT stage 3 AKI.

In addition to the above 3 independent risk factors, other coagulation indexes were also significantly different between the 2 groups. The coagulation process can be roughly divided into 3 basic processes: platelet activation, activation of coagulation system, and activation of fibrinolytic system. In univariate logistic analysis, the count and function of platelet were all different between the 2 groups. After multivariate logistic regression, the ADP-induced platelet aggregation was screened as an independent risk factor for grade 3 AKI. In univariate logistic analysis, factor V, factor VIII, and antithrombin III are all produced by the liver, so the stage 3 AKI group was lower than the stage 0-2 AKI group. It is well known that INR is an important indicator used to evaluate liver synthetic function. Higher AKI stage was associated with worse liver function. Some patients with stage 3 AKI have a coagulation cascade that activates the fibrinolytic system, which may be why FDP in the stage 3 AKI group was much higher and FIB was much lower than in the stage 0-2 AKI group.

Finally, our patients in the post-LT stage 3 AKI group had higher baseline MELD scores, greater blood loss, and more RBC and plasma infusions required during the operation, which would impact the post-LT coagulation function. However, we can see that even if patients in the grade 3 AKI group receive more plasma, the coagulation indexes within 24 h after the operation were still worse than those in grade 0-2 AKI patients, which can also indicate that the HIRI in this group is stronger than that in the control group, and the severity of AKI is higher. In subgroup analysis, the predictive ability did not differ between groups. Despite these differences and whether they were combined with HIRI during LT, our results demonstrate that post-LT coagulation function after 24 h is a suitable parameter for detecting post-LT stage 3 AKI in all patients who underwent LT.

Limitations

Firstly, this was a single-center, small-sample, retrospective study. Larger prospective studies are warranted to explore
the association between coagulation function and post-LT stage 3 AKI. Secondly, the coagulation function within 24 h after LT was selected for earlier prediction of AKI incidence. In the future, several additional time points should be included in a specifically designed clinical study to predict the value of those coagulation parameters. Thirdly, VWF is an indicator of endothelial injury that was missing in our study. HIRI was a crucial mechanism related to post-LT coagulation functions and stage 3 AKI in our study. However, there is a lack of clinical indicators to diagnose HIRI. Hence, further laboratory and clinical research is required to elucidate this process. Finally, we lacked some key surgical data (eg, caval anastomosis technique), warm and cold ischemia times, and immunosuppression regimens, which have been related to postoperative renal injury.

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Conclusions

The postoperative coagulation function within 24 h correlated with the incidence of post-LT AKI stage 3. Specifically, lower ADP-induced PLT aggregation rate, higher D-dimer level, and prolonged R-value from the TEG were independent risk factors for the incidence of post-LT stage 3 AKI.

Declaration of Figures’ Authenticity

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