Analysis of Risk Factors Related to Acute Kidney Injury After Liver Transplantation in Children

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Research Article

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Abstract

Objective: To identify risk factors related to the development of acute kidney injury (AKI) in children who underwent liver transplantation.

Methods: We retrospectively analyzed data of pediatric patients who underwent liver transplantation at the pediatric surgery department of the First Affiliated Hospital of Guangxi Medical University from July 2017 to November 2018. Subjects were grouped into the non-AKI group (group A) and AKI group (group B). General information, preoperative, intraoperative, and postoperative clinical data were statistically analyzed in the two groups.

Results: Among the 31 patients identified, there were 17 cases in group A (six male, 11 female) and 14 cases in group B (seven male and seven female). The baseline data of the patients included age, BMI index; BSA index; PELD score, TBiL count, ALB count, INR index, Scr count, DBiL, and other liver function indexes. There was no difference observed in the demographic and preoperative factors, including infection rates ($P > 0.05$) between the two groups. There was no difference between the two groups in terms of intraoperative indicators including vena cava occlusion time, cold ischemia time, warm ischemia time, blood loss, donor liver graft-to-recipient body weight, graft volume/standard liver volume, or use of vasopressor drugs ($P > 0.05$). There was no significant difference in postoperative factors (FK506 blood concentration, ICU length of stay, and length of hospital stay) ($P > 0.05$). Operation of group A (653±205 min) was significantly shorter than that of group B (852±299 min) ($P = 0.03$). The duration of anhepatic phase was shorter in group A (57 ± 15 min) than in group B (73 ± 20 min) ($P = 0.02$).

Conclusion: The incidence of AKI in children after liver transplantation was 45.2%. The operation time and duration of the anhepatic phase were closely related to the occurrence of AKI after liver transplantation in children. Improving the surgical technique and the optimization of surgical procedures can shorten the operation time and the anhepatic phase, therefore reducing the incidence of AKI.

Introduction

Liver transplantation has made significant progress since its introduction in 1963. It is an effective treatment for end-stage liver disease. However, fatal complications after liver transplantation restrict further advancement in the field. Acute kidney injury (AKI) is one of the main causes of death secondary to liver transplantation. Studies of liver transplantation in adults have shown that the incidence of AKI is 17%–95%, and it can develop into chronic kidney disease and graft failure. There are limited studies about AKI in children. The incidence and related risk factors of AKI after liver transplantation remain unclear. The primary causes of liver transplantation in children are benign end-stage liver disease, biliary atresia, and congenital metabolic liver disease. It is significantly different from adult liver transplantation in terms of surgical tolerance, intraoperative hemodynamic changes, and renal reserve capacity. The risk factors for AKI in children are likewise different from those of adults.
This study retrospectively analyzed the clinical data of children undergoing liver transplantation at a single center and explored the incidence and related risk factors of AKI after liver transplantation. The results of our study will provide a reference for clinical prevention and treatment of AKI after liver transplantation.

**Methods**

1. Patients

1.1 Data

We collected the clinical data of pediatric patients who underwent liver transplantation at the Organ Transplantation Center of the First Affiliated Hospital of Guangxi Medical University, China from July 2017 to November 2018, which included their general information, preoperative, intraoperative, and postoperative data. Informed consent was obtained from the parents/guardians of the patients included in our study. The form was approved by the Ethics Committee of our hospital, passed the ethical review of the Guangxi District Health and Family Planning Commission, and was in line with the regulations of medical ethics.

1.2 Study design

We conducted a retrospective analysis of the data of patients undergoing liver transplantation. Diagnosis of AKI was based on the regulations of the international 2012 guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO) group:\(^\text{16}\) (1) Serum creatinine (Scr) increased by ≥26.5 µmol/L within 48 hours; (2) Scr increased to ≥1.5 times from baseline value within 7 days; (3) a urine output of <0.5 ml/kg/h for 6 consecutive hours. End-stage renal disease was defined as an estimated glomerular filtration rate <35 ml/min/1.73 m\(^2\) according to the Schwartz equation. The grading criteria for acute kidney injury are shown in Table 1. Patients were divided into the postoperative non-AKI group (group A) and the AKI group (group B).

2. Perioperative treatment

2.1 (1) All patients included in the study perioperatively completed the following laboratory (routine complete blood count, liver and kidney function test, coagulation profile, pre-transfusion test, blood gas analysis, etc.) and imaging (CT, B-ultrasound) examinations. (2) Infectious and metabolic conditions were corrected, including treatment of identified infections, anemia, hypoproteinemia, coagulation function disorders, and hydration and electrolyte disorders.

2.2 Intraoperative treatment: (1) Surgical method: Under general anesthesia, an arc-shaped incision under the costal margin was performed. Piggyback orthotopic liver transplantation was done. (2) Vascular reconstruction: Hepatic vein reconstruction consisted of an improved triangular anastomosis method. The portal vein reconstruction method adopted was end-to-end anastomosis of the donor and recipient
portal veins (when the diameters of the two were similar) or the anastomosis of the bifurcation of the left and right branches of the recipient portal vein with the donor portal vein (when the diameter of the recipient portal vein and that of the donor hepatic portal vein were dissimilar), and the growth factor was retained by 1.5 cm. (3) Bile duct reconstruction: Roux-en-Y bile duct jejunum anastomosis was used.

2.3 Postoperative management: After surgery, the patients were monitored and treated in the pediatric intensive care unit (PICU). The patient was then transferred to the general ward once stable to continue treatment. (1) Anticoagulation regimen: Heparin sodium was used alone for anticoagulation until 7 days after surgery. APTT was maintained at 60–80 s, which was gradually transitioned to anticoagulation therapy with warfarin. The international normalized ratio (INR) was maintained at 1.5–2.0. Secondly, alprostadil 0.5 ng/kg/min was continuously pumped intravenously until 7 days after surgery. (2) Immune suppression regimen: Tacrolimus combined with methylprednisolone, or tacrolimus + methylprednisolone + mycophenolate mofetil was used. The initial dose of tacrolimus was 0.10–0.15 mg/kg/d. The concentration was maintained at 8–12 ng/ml in the first month after surgery and at 7–10 ng/ml for the second to sixth months, then to 5 ng/ml thereafter. The initial dose of methylprednisolone was 4 mg/kg/d, which was gradually reduced to 1 mg/kg/d and tapered further, then discontinued after 3 months or half a year after surgery. If mycophenolate mofetil was added, the dose was 10–15 mg/kg/d. (3) Symptomatic and supportive treatments such as liver protective agents, antacids, antimicrobials, antifungals, and antiviral medications were given. (4) Routine re-examinations included determination of routine blood count, liver and kidney function studies, coagulation tests, FK506 blood concentration, Epstein-Barr virus, cytomegalovirus, B-mode ultrasound monitoring of liver blood flow, CT, and MRI.

2.4 Postoperative treatment for the AKI group: (1) Nephrotoxic drugs were administered until indications for discontinuation were noted. (2) Blood volume and perfusion pressure were maintained with normal levels. (3) FK506 blood concentration, renal function, and urine output were monitored, and the dose of tacrolimus was adjusted accordingly. (4) Renal replacement therapy (RRT) was administered.

3. Data collection

3.1 General information: Data on age, sex, height, weight, body mass index (BMI), and body surface area (BSA) at the time of surgery were collected.

3.2 Preoperative clinical data: The following clinical and laboratory information were collected including liver disease classification, preoperative infection status, pediatric end-stage liver disease (PELD) model score, liver function (total bilirubin (TBiL), direct bilirubin (DBiL), albumin (ALB), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)), routine complete blood count (hemoglobin (HB), platelets (PLT)), coagulation function (activated partial thromboplastin time (APTT), INR, prothrombin time (PT)), renal function, creatinine (CREA), uric acid (UA), endogenous creatinine clearance (Ccr), and cystatin C (CysC)).

3.3 Intraoperative clinical data: Operation time, vena cava occlusion time, anhepatic phase, warm ischemia time, cold ischemia time, blood loss, and vasopressor drug administration were noted.
3.4 Postoperative clinical data: Postoperative data such as renal function, FK506 blood drug concentration, PICU length of stay, total length of hospital stay, and survival rate were determined.

4. Statistical analysis

SPSS 13.0 statistical software (SPSS, Chicago, IL, USA) was used to analyze the data collected. For measurement variables, the normal distribution test was first performed. Data with normal distribution were expressed as mean ± standard deviation and compared using the t-test. Data with non-normal distribution were expressed as M (minimum value-maximum value) and compared using the Mann–Whitney U test. The categorical variables were expressed in percentage (%), and the χ² test was used for comparison. All statistical tests were two-sided, and a $P < .05$ was considered statistically significant.

**Results**

1. Comparison of general information

We obtained data from 31 pediatric patients who underwent liver transplantation surgery. There were 17 patients in group A (six male and 11 female) and 14 patients in group B (seven male and seven female). Age, height, weight, BMI, and BSA were not statistically significant between the two groups. Further details are shown in Table 2.

2. Primary study endpoints

For the preoperative data, the primary diseases in group A consisted of 14 cases of biliary atresia, and three cases of others (one case of ornithine transcarbamylase deficiency, one case of portal spongiform transformation, and one case of cholestatic liver disease). The primary diseases in group B consisted of 12 cases of biliary atresia, and two cases of others (one case of congenital bile acid synthesis disorder type I and one case of cholestatic liver disease). There was no statistically significant difference in composition ratio between the two groups ($P = 1.00$). There was no significant difference between the two groups in terms of PELD score, TBiL, ALB, INR, Scr, DBiL, ALT, AST, HB, PLT, PT, INR, APTT, FIB, UREA, UA, Ccr, or Cys ($P > .05$) (Table 3).

Intraoperative data in this study revealed that the operation time of group A (653 ± 205 min) was significantly shorter than that of group B (852 ± 299 min), and the result was statistically significant ($P < 0.05$). The duration of the anhepatic phase was shorter in group A (57 ± 15 min) than in group B (73 ± 20 min), and the difference was statistically significant ($P < .05$) (Table 4).

In the comparison of postoperative data, there was no significant difference between group A and group B in terms of FK506 blood concentration, ICU length of stay, or total length of hospital stay ($P > .05$). Table 5 shows the results of preoperative data in the two groups.

3. Secondary study endpoints
There were no patients with end-stage renal disease identified preoperatively. The short-term survival rate after the operation was compared between the two groups. Among the 17 patients in group A, one died after the operation. The survival rate of group A was 94%. In group B, there were eight cases of grade 1 AKI, four cases of grade 2 AKI, and two cases of grade 3 AKI. The renal function of the grade 1 and grade 2 AKI patients improved after active treatment. The two grade 3 AKI patients both died postoperatively. The survival rate of group B was 85%. There was no statistically significant difference in the postoperative survival rate between the two groups ($P = .58$). The survival functions of the two groups are shown in Figure 1.

**Discussion**

In this retrospective study, we aimed to identify risk factors associated with the development of AKI in children who underwent liver transplantation surgery. Our results showed that risk factors to the development of AKI in post-transplantation pediatric patients include intraoperative factors such as operation time and the duration of the anhepatic phase.

A meta-analysis analyzed 38 cohort studies comprised of 13,422 patients who underwent liver transplantation that revealed that the rates of postoperative AKI and need for RRT treatment were 40.8% and 7%, respectively\(^\text{12}\). The incidence of AKI after liver transplantation in children was 46.2%\(^\text{14}\). The incidence of AKI was 45.2%. Strict monitoring of renal function and urine output after surgery is essential for the diagnosis and treatment of AKI.

This study found that height, weight, age, and developmental status were not closely related to renal function. A study\(^\text{17}\) pointed out that the preoperative Scr value of patients with AKI after transplantation was significantly higher than that of patients without AKI and that it was an independent risk factor for AKI after liver transplantation. Another study\(^\text{10,14}\) noted that a preoperative increase in TBiL might reflect the severity of the underlying liver disease. This study found that there was no statistically significant difference between the two groups with regards to liver and kidney functions or PELD score\(^\text{18}\). For children, the PELD score is mainly calculated using serum TBiL, ALB, INR, and other indicators, but it does not include Scr\(^\text{19}\), which is an indicator of renal function. For this group of patients, although liver function decompensation had occurred before surgery, HRS did not occur. Even if Scr increased preoperatively, the liver and kidney functions were corrected post-transplant allowing a subsequent improvement in Scr values\(^\text{20}\).

Our study found that intraoperative factors demonstrated an association to the development of AKI. Operation time, vena cava occlusion time, anhepatic phase, warm ischemia time, cold ischemia time, blood loss, vasoactive drug administration, operation time, and duration of anhepatic phase were related to the occurrence of AKI in children after liver transplantation. Intraoperative hypotension and renal ischemia-reperfusion injury might also be related to AKI\(^\text{21}\). Prolonged operation time can induce the occurrence of postoperative AKI, which may be secondary to the ischemic damage to renal function and
inflammation. Therefore, the operation time and anhepatic phase should be shortened optimally during an operation to reduce the impact of these two factors on renal function.

In our study, vena cava occlusion time did not cause postoperative AKI. The possible reasons are as follows: (1) Compared to adults, children have less blood volume rendering the hemodynamic impact weaker. This is evidenced by the lack of obvious changes in blood pressure after vena cava occlusion intraoperatively. (2) Cases with profound preoperative liver cirrhosis had collateral circulations formed allowing the return of blood from the digestive tract to the heart through the collaterals; thus, reducing the hemodynamic changes caused by the vena cava blockade. Insufficient blood volume, reduced preload, and a corresponding reduction in renal perfusion resulted in renal insufficiency. This study found that the intraoperative blood loss in the non-AKI group was significantly less than that in the AKI group, but there was no statistically significant difference between the two groups. Timely blood transfusion during the operation and the use of vasoactive drugs to maintain renal perfusion may account for these results.

Warm ischemia and cold ischemia-reperfusion injury of the donor’s liver during operation jointly induced ischemia-reperfusion injury\textsuperscript{17,22,23}. This can activate the complement system to promote the occurrence of an inflammatory response and the production of large amounts of reactive oxygen species\textsuperscript{23}. By avoiding interruption of liver perfusion which could lead to tissue damage and dysfunction, renal injury during the warm ischemia time can be reduced.

The anti-rejection regimen used in our study was tacrolimus + low-dose corticosteroids or both combined with mycophenolate mofetil. The results of our study found that there was no significant difference in FK506 plasma concentration between the two groups. Possible reasons include: (1) The nephrotoxicity of acute CNI anti-rejection drugs is partially reversible\textsuperscript{24}. (2) Prostaglandin E1 was routinely used until 7 days after surgery to inhibit platelet aggregation and inhibit intravascular thrombosis after transplantation. Therefore, the advantages and disadvantages of administering anti-rejection regimens to patients with AKI post-liver transplantation should be considered judiciously. Drug-related nephrotoxicity should be avoided as far as possible while avoiding rejection. The anti-rejection regimen using mycophenolate mofetil + low-dose CNI or delayed/reduced CNI is worth recommending.

A higher AKI grade was associated with a worse prognosis and higher postoperative mortality\textsuperscript{25}. In this group of AKI patients, eight cases had grade 1 AKI, four cases had grade 2 AKI, and two cases had grade 3 AKI. The kidney function of grade 1 and 2 AKI patients improved after the maintenance of blood volume and renal perfusion, adjustment of the dose of tacrolimus, and discontinuation of other nephrotoxic drugs. Among the two patients with grade 3 AKI, one patient had no improvement in renal function after RRT treatment and died after 10 days postoperatively. The other patient failed to receive RRT treatment and died on the 8th day after the operation. Therefore, grade 3 AKI may be an independent risk factor affecting the survival rate of patients after surgery.

There are several limitations to our study. This is a single-center retrospective study with a small sample size and short follow-up period. The results of our analysis may be subject to selection bias. Future
studies should confirm our findings by employing large-sample prospective clinical studies.

In conclusion, the incidence of AKI after liver transplantation in children is high, which is 45.2%. After transplantation, kidney function and urine output should be closely monitored to administer timely diagnosis and treatment. The operation time and the duration of the anhepatic phase are closely related to the occurrence of AKI after liver transplantation in children. Improvement in surgical techniques and the optimization of surgical procedures can shorten the operation time and anhepatic phase, and thus can help prevent the occurrence of AKI.

Declarations

Author contributions: The manuscript was critically revised by all of the authors. KD and CD contributed to the study conception and design. KD, JL, CZ, JC, CD enrolled patients and collected clinical data. KD analyzed clinical data and drafted the manuscript. CD had contributions to the revision of the manuscript in discussion, data re-evaluation and presentation, and manuscript edition. All authors approved the final version of the manuscript, including the authorship list.

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Availability of data: We declared that data described in the manuscript would be freely available to any scientist wishing to use them for noncommercial purposes.

Conflict of interest: All authors declare no conflicts of interest about this work.

Ethical approval: The present study was approved by Ethical Review Committee of First Affiliated Hospital of Guangxi Medical University.

Consent for publication: All authors read and approved the manuscript.

References


**Tables**
**Table 1: The grading criteria for acute kidney injury**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for 6–12 h</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥0.3 mg/dl (≥26.5 mol/l) increase</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for ≥12 h</td>
</tr>
<tr>
<td>3</td>
<td>3 times baseline</td>
<td>&lt;0.3 ml/kg/h for ≥24 h</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥4.0 mg/dl (≥353.6 mol/l) increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>initiation of RRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in patients &lt;18 years a decrease in eGFR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;35 ml/min/1.73 m²</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; BSA, body surface area

**Table 2: Comparison of general information between group A and group B**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group A</th>
<th>Group B</th>
<th>z/χ² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: (Female)</td>
<td>11 (64.7%)</td>
<td>7 (50%)</td>
<td>0.682</td>
<td>0.481</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>65 (62-138)</td>
<td>66 (60-122)</td>
<td>-0.359</td>
<td>0.720</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>7 (5.4-28.5)</td>
<td>7.2 (5.5-23)</td>
<td>-0.06</td>
<td>0.952</td>
</tr>
<tr>
<td>Age at transplantation (m)</td>
<td>7 (5-106)</td>
<td>9 (5-75)</td>
<td>-0.419</td>
<td>0.632</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.6 (13.18-18.93)</td>
<td>16.4 (14.78-18.81)</td>
<td>-0.953</td>
<td>0.341</td>
</tr>
<tr>
<td>BSA (l)</td>
<td>0.345 (0.29-1.10)</td>
<td>0.352 (0.29-0.91)</td>
<td>-0.06</td>
<td>0.952</td>
</tr>
</tbody>
</table>

BMI, body mass index; BSA, body surface area

**Table 3: Comparison of preoperative data between group A and group B**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group A</th>
<th>Group B</th>
<th>t/χ² value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PELD score</td>
<td>7.76 ± 10.75</td>
<td>7.29 ± 9.38</td>
<td>0.131</td>
</tr>
<tr>
<td>Preoperative TBiL (umol/L)</td>
<td>199.87 ± 196.1</td>
<td>112.97 ± 83.17</td>
<td>1.443</td>
</tr>
</tbody>
</table>

Preoperative TBiL (umol/L)
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group A</th>
<th>Group B</th>
<th>t/χ² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min)</td>
<td>653 ± 205</td>
<td>852 ± 299</td>
<td>-2.192</td>
<td>0.037</td>
</tr>
<tr>
<td>Vena cava occlusion time (min)</td>
<td>30 ± 16</td>
<td>42 ± 18</td>
<td>-1.956</td>
<td>0.06</td>
</tr>
<tr>
<td>Anhepatic phase (min)</td>
<td>57 ± 15</td>
<td>73 ± 20</td>
<td>-2.439</td>
<td>0.021</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>621 ± 435</td>
<td>982 ± 1168</td>
<td>-1.184</td>
<td>0.246</td>
</tr>
<tr>
<td>Warm ischemia time (min)</td>
<td>10 ± 8</td>
<td>11 ± 7</td>
<td>-0.122</td>
<td>0.903</td>
</tr>
<tr>
<td>Cold ischemia time (min)</td>
<td>135 ± 66</td>
<td>169 ± 82</td>
<td>-1.288</td>
<td>0.208</td>
</tr>
<tr>
<td>GRBW</td>
<td>3.73 ± 1.33</td>
<td>3.28 ± 0.93</td>
<td>1.065</td>
<td>0.296</td>
</tr>
<tr>
<td>GV/SLV</td>
<td>1.105 ± 0.36</td>
<td>0.931 ± 0.30</td>
<td>1.428</td>
<td>0.164</td>
</tr>
</tbody>
</table>

Table 4: Comparison of intraoperative data between group A and group B
Note: GRBW: donor liver graft-to-recipient body weight; GV/SLV: graft volume/standard liver volume

Table 5: Comparison of postoperative data between group A and group B

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group A</th>
<th>Group B</th>
<th>t/χ² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FK506 greater than 15</td>
<td>6 (35.3%)</td>
<td>9 (64.3%)</td>
<td>2.584</td>
<td>0.156</td>
</tr>
<tr>
<td>ICU length of stay (d)</td>
<td>7.87 ± 4.96</td>
<td>9.17 ± 4.90</td>
<td>-0.685</td>
<td>0.499</td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>37.1 ± 14.8</td>
<td>37.5 ± 10.4</td>
<td>-0.075</td>
<td>0.941</td>
</tr>
</tbody>
</table>

Figures

Figure 1

Survival functions for group A and group B