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ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION: INCIDENCE, RISK FACTORS, AND OUTCOMES

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Abstract

Aim: Although numerous risk factors for acute kidney injury (AKI) have been identified, their cumulative impact remains unclear. This study aimed to identify perioperative risk factors for early post-transplant AKI on patients and outcomes and to predict AKI using clinical variables.

Methods: A single-center, retrospective cohort study involving 34 pediatric patients and 31 adults who underwent LT between 2015 and 2017.

Results: AKI occurred in 16 (47%) pediatric patients during the first-week post-LT with stage 1, stage 2, and stage 3 AKI frequencies of 43.8, 50, and 6.3%, respectively. Renal replacement therapy (RRT) was initiated in 18.8% of pediatric LT patients. Preoperative liver enzymes and the etiology of liver failure are the most critical factors affecting AKI in pediatric LT patients. AKI occurred in 15 (48%) adult patients during the first-week post-LT with stage 1, stage 2, and stage 3 AKI frequencies of 43%, 21%, and 21%, respectively. The requirement for RRT was seen in 43% of adult LT patients. There were also statistical differences between the two groups regarding the number of patients with preoperative kidney dysfunction (20-80%, p=.047) and mortality rates (6-31 %, p=.047). In adult patients who developed post-LT AKI compared with those who did not develop post-LT AKI, they had significantly higher levels of serum creatinine (sCr) (1.9±1.9 mg/dL vs. 0.7±0.1 mg/dL, p=.013), were given lower amounts of crystalloids (73±32 mL/kg vs. 106±33 mL/kg, p=.018) and had lower urine output (UO) intraoperatively (11±9 mL/kg vs. 20±9 mL/kg, p=.047). There was a higher mortality rate in adult patients with post-LT AKI (89 vs. 11%, p=.003).

Conclusions: The results of our study contribute to raising awareness of the potential risk factors associated with preoperative evaluation, intraoperative and postoperative close follow-up, careful anesthesia management, and early onset of post-LT AKI.

Keywords: *Liver transplantation, acute kidney injury, perioperative management, risk factors, outcomes*

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Introduction

AKI is one of the most common postoperative complications of LT. In the adult population, the incidence of AKI in the postoperative period has ranged from 4-94%. Several studies have demonstrated that post-AKI is a significant risk factor for poor prognosis post-LT outcomes[1,2]. As a result of severe AKI, 40.8 and 7.0% of LT adult patients require RRT. In pediatrics, the incidence of AKI ranges from 34-67%[3]. The development of post-LT AKI appears to be multifactorial, with multiple perioperative factors involved[4]. Risk factors associated with preop-LT include aging, malnutrition, dehydration, exposure to high levels of toxic free radicals, use of nephrotoxic medications, obesity, diabetes mellitus (DM), a history of viral hepatitis (especially hepatitis C) or nonalcoholic steatohepatitis, a high MELD/MELD-Na^{++} score, end-stage liver disease (ESLD), hypoalbuminemia, hepatorenal syndrome, and lower baseline glomerular filtration rate (GFR)[3,5-7].

Intraop-LT factors include management of hemodynamics, choice of fluid balance targets, bleeding and transfusion volume, anesthetic and operative time, hepatic ischemia-reperfusion injury, perioperative events, and renal ischemia[5-7]. In addition, sepsis post-LT, a high Acute Physiology, and Chronic Health Evaluation II score (APACHE II), thrombotic microangiopathy, the toxicity of immunosuppressive therapy and antibiotic prophylaxis, nephrotoxicity of calcineurin inhibitors, increased use of high-risk or marginal grafts, and LT in sicker patients with higher MELD-Na^{++} score or with more comorbidities may contribute to AKI[3,8-11].

In the few studies focused on pediatry, the incidence has ranged from 34 to 67%[8,9,12]. Contrary to the etiological factors in adult patients, LT indications in pediatric patients include extrahepatic and intrahepatic cholestasis, metabolic disorders, acute liver failure, and primary liver malignancy[13].

Even mild or transient AKI in patients who underwent LT can have severe consequences due to prolonged intensive care unit (ICU) and hospital stay, as well as increased mortality and morbidity[14]. For instance, mortality after LT is reported to be 2-6% in patients not developing AKI, compared to a 47–55% mortality in patients who develop post-LT AKI[15].

AKI's significant effect on hospital resources and short- and long-term outcomes and the numerous risk factors for AKI highlights the need for a standardized prediction model for AKI after LT surgery. Therefore, this study aimed to identify perioperative risk factors for early post-LT AKI on patients and outcomes and to predict AKI using clinical variables.

Materials and Methods

Approval to conduct the study was obtained from the Institutional Review Board and Ethics Committee (KA22/228) with a waiver of informed consent.

We conducted a retrospective cohort study of 34 pediatric and 31 adult patients with ESLD. All consecutive patients who underwent primary recipients of grafts from live donors in the hospital of medical faculty between January 2015 and May 2017 were included, and their medical records were retrospectively assessed. Demographics data retrieved included patient age, sex, height, weight, indication for LT, and perioperative data, which are effective as risk factors in the development of AKI were collected. Exclusion criteria were transplantation, super-urgent transplantation, patients with fulminant hepatic failure and hepatorenal syndrome, prior solid-organ transplants, candidates for simultaneous liver-kidney transplants, chronic kidney disease (CKD), RRT before LT, machine perfusion of the graft, and patients with missing data. This study aimed to identify perioperative risk factors for early post-LT AKI on patients and outcomes and to predict AKI using clinical variables.

The primary outcome was to identify risk factors post-LT AKI. The secondary outcome was to determine the effects of the

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identified risk factors on developing post-LT AKI. Post-LT AKI is defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria; an increase in sCr by ≥ 26.5 μmol/L or 0.29 mg/dL within 48 h or an increase in sCr to ≥ 1.5 times baseline within the first seven post-LT days. AKI is classified into three stages: stage 1, sCr increase to ≥ 26.5 μmol/L or increase to 1.5-1.9-fold from baseline; stage 2, increase to 2–2.9-fold; stage 3, increase> 3-fold or increase in sCr to ≥ 354 μmol/L or 4.0044 mg/dL or the initiation of RRT. Preoperative and intraoperative parameters were used to predict post-LT AKI, including age, gender, primary diagnosis, comorbidities before LT, drugs, MELD-Na++, and PELD scores. The last laboratory values for bilirubin, Na^{++}, and sCr levels, international normalized ratio (INR) obtained before LT, perioperative hemodynamic parameters, UO, intraoperative bleeding amount, and hospital mortality. In addition, intraoperative parameters of red blood cells (RBCs) transfusion (homologous or autologous), fresh frozen plasma (FFP), and total fluids were analyzed. Postoperative data; RRT, length of ICU and hospital stay, mortality, and morbidity used to define the end-point and outcome analysis within 30 days post-LT.

Due to adult and pediatric patients, the etiology of liver disease, coexisting conditions, and reserve capacity of the kidney, epidemiological features of pediatric post-LT AKI may differ from adult post-LT AKI. So, we analyzed it as two different groups.

Anesthesia induction was performed in all patients using the same procedure and standard anesthetic monitoring (ECG, NIBP, $EtCO_2$, HR, SpO_2, T^o). Anesthesia was induced via the intravenous (IV) injection of 2-3 mg/kg propofol, 1 μg/kg fentanyl, and 0.6 mg/kg rocuronium to facilitate endotracheal intubation. Anesthesia was maintained via the continuous infusion of 0.05-0.3 μg/kg/min remifentanil, 0.3 mg/kg/h rocuronium, and sevoflurane inhaled at a concentration of 2-2.2%. After induction of anesthesia, under ultrasound guidance, an intravenous catheter (IVC) was inserted into the left or right jugular vein, and an arterial catheter known as transpulmonary thermodilution (PiCCO) was inserted into the femoral artery (3-Fr PV2013L07 at<20 kg and 4-Fr PV2014L08 at>20 kg). The PiCCO system measures hemodynamic volumetric parameters were; mean arterial pressure (MAP), central venous pressure (CVP) and cardiac index (CI), global end-diastolic volume (GEDV), intrathoracic blood volume index (ITBVI), extravascular lung water index (EVLWI), systemic vascular resistance index (SVRI) and stroke volume variability (SVV). All these additional variables can be helpful in decision-making regarding hemodynamic stability.

Vasoactive and inotropic medications are started in case of hypotension after anesthesia induction. In our institution, we used norepinephrine (NE) IV infusion (0.01 to 0.2 μg/kg/min) in cases of hypotension (MAP<65 mmHg), low CO, and low SVR during the intraoperative period, postreperfusion syndrome and post-LT.

All patients underwent first-time LT with whole grafts from live donors using the piggyback technique without venovenous bypass. If autologous RBCs transfusion was used, the cell salvage technique was employed. Both adult and pediatric antimicrobial prophylaxis and triple-therapy immunosuppression post-LT were provided per standard hospital protocol. Our hospital regimen consists of Tacrolimus, azathioprine or MMF, and prednisolone, all introduced at day 0. Prednisolone therapy is generally discontinued after three months. A renal-sparing protocol is considered in recipients with impaired renal function. It consists of either low-dose Tacrolimus introduction combined with MMF or delayed introduction of Tacrolimus (on days 3-5) with MMF and Basiliximab on days 0 and 4.

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Statistical analysis

Statistical analyses were performed using the SPSS software package (SPSS: Version 25.0. Armonk, NY: IBM Corporation, Armonk, NY, USA). Differences between the groups tested using chi-square and Fischer's exact test (categorical variables) or Student's t-test and/or Mann-Whitney U tests (continuous variables). The association between AKI and potential risk factors was analyzed using univariate and multiple logistic regression. The level of statistical significance was set at $\alpha = 0.05$.

Results

The population's median age was 25±24 years and 12 (38%) of them were female. There were 34 pediatric patients younger than 18 years. This group had a median age of 64±72 months, and 14 (41%) were female (Table 1). AKI occurred in 16 (47%) pediatric patients during the first-week post-LT with stage 1, stage 2, and stage 3 AKI frequencies of 43.8%, 50 %, and 6.3%, respectively (Table 2).

Table 1. Pediatric Patients

Characteristics		AKI (+)(*n* = 17)	AKI (-)(*n* = 14)	*P* value
Age, yr		5.8±5.6	3.4±6.1	0.126 #
Male/female, *n* (%)		6 (%42.9)	8 (%57.1)	0.420 *
Weight (kg)		18.9±12.4	17.2±20.2	0.142 #
Etiology of liver disease	Viral diseases, *n* (%)	0 (%0)	1(%100)	0.012
	Bilier, *n* (%)	2 (%20)	8 (%80)	
	Idiopathic, *n* (%)	4 (%100)	0 (%0)	
	Others, *n* (%)	10 (%55.6)	8 (%44.4)	
Laboratory values	PELD	13.2±7.4	13.5±7.2	0.935
	MELD	11±3.5	19.3±1.1	0.069
	Assit	7 (%58.3)	5 (%41.7)	0.311
	Encephalopathy	4 (%66.7)	2 (%33.3)	0.298
Preoperative parameters	Hb (mg/dL)	9.3±1.9	9.8±1	0.272
	BUN (6-26 mg/dL)	11.7±7.6	8.9±4.5	0.159
	Creatinine (0.7-1.3 mg/dL)	0.6±0.4	0.4±0.1	0.193
	Sodium (135-146 mmol/L)	125.2±34.9	133.9±2.4	0.292 #
	Potassium (3.5-5.2 mmol/L)	3.9±0.9	4±0.9	0.205
	SGOT (5-34 U/L)	105.3±165.8	233.8±227.4	0.016 #
	SGPT (0-55 U/L)	61.9±71.8	127.5±98.8	0.049 #
	INR	1.5±0.3	1.5±0.5	0.770
	Albumin (3.4-4.8 g/dL)	3.4±0.7	3.1±0.7	0.134
	Total bilirubin (0.2-1.2 g/dL)	9.6±10.8	13.6±10.7	0.105 #
	Direct bilirubin (0-0.5 mg/dL)	5.4±7.0	8.7±7.4	0.108 #
Intraoperative parameters	pH (7.35-7.45)	7.3± 0.7	7.3±0.1	0.683
	PaO_2 (32-48 mmHg)	167.1±43.2	196.6±29.5	0.999
	$PaCO_2$ (32-48mmHg)	35.3±3	32.9±10.5	0.190
	Lactate (0.5-1.6 mmol/L)	8.01±4.2	5.8±3.8	0.129
	Bicarbonate (22-24 mmol/L)	24.8±30.7	16.2±5.3	0.666 #
	Urine output (mL/kg))	21±19.4	17.9±14.7	0.955 #
	RBCs (mL/kg)	22.5±16.8	321.7±40.1	0.936
	FFP (mL/kg)	7.7±7.7	9.3±13.7	0.854 #
	Crystalloids (mL/kg)	100.9±33.3	108.2±27.2	0.674
	Colloids (mL/kg)	80.7±36.7	79.7±42.8	0.431
Intraoperative and postoperative parameters	Anesthesia time (hr)	9.3±1.4	9.6±1.2	0.483
	Clemp time (min)	73.4±14.7	68.1±10.3	0.705
	ICU time (day)	7.81±6.41	6.18±7.44	0.183 #
	Mortality	5 (%83.3)	1 (%16.7)	0.047

** p-value for chi-square test and all others from Fisher's exact test, # p-value for Mann-Whitney U test and all others from Student's t-test*

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When compared with those who developed AKI, the median age, body weight, MELD scores, PELD scores and graft recipient ratio were similar between the pediatric patients who did not develop AKI. There were also statistical differences between the two groups in terms of the number of patients who had preoperative kidney dysfunction (80-20%, p=.047) and mortality rates (31- 6%, p=.047) (Table 1). RRT was initiated in 18.8% of pediatric LT patients (Table 2).

Table 2. Pediatric Patients

AKI incidence (KDIGO)	n (%)
Stage 1	7 (43.8)
Stage 2	8 (50)
Stage 3	1 (6.3)
Postop RRT	3 (18.8)

The percentage of patients older than 18 was 48% (n=31). This group had a median age of 46±17 years, and 7 (23%) were female. When compared with those who developed AKI, the median age, body weight, and MELD scores were similar among the pediatric patients who did not develop AKI. AKI occurred in 15 (48%) adult patients during the first-week post-LT with stage 1, stage 2, and stage 3 AKI frequencies of 43%, 21%, and 21%, respectively. The requirement for RRT was seen in 43% of adult LT patients. In adult patients who developed post-LT AKI compared with those who did not develop post-LT AKI, they had significantly higher levels of SCr (1.9±1.9 mg/dL vs. 0.7±0.1 mg/dL, p=.013) (Figure 1), were given lower amounts of crystalloids (73±32 mL/kg vs. 106±33 mL/kg, p=.018) (Figure 2) and had lower UO intraoperatively (11±9 mL/kg vs. 20±9 mL/kg, p=.047) (Table 3) (Figure 3). There was a higher mortality rate in adult patients post-LT AKI (89 vs. 11%, p=.003) (Table 4).

Discussion

AKI occurred in 16 (47%) pediatric patients during the first-week post-LT with stage 1, stage 2, and stage 3 AKI frequencies of 43.8%, 50 %, and 6.3%, respectively. AKI occurred in 15 (48%) adult patients during the first-week post-LT with stage 1, stage 2, and stage 3 AKI frequencies of 43%, 21%, and 21%, respectively. We found the following parameters significant for the development of AKI: preoperative period: renal dysfunction, high sCr levels; intraoperative period: UO, insufficient volume replacement; postoperative period: increased mortality rate. In addition, the following parameters were significantly associated with pediatric post-LT patients developing AKI: etiologies, preoperative SGOT (due to etiologies), and postoperative period: increased mortality rate. In our study, more than half of the adult and about half of the pediatric patients developed post-LT AKI. AKI-related mortality was also significantly higher in both the pediatric and adult groups.

AKI is a common and significant complication in LT patients. For LT, a multidisciplinary evaluation of all systems should be performed on these patients. Anesthetic management includes controlling rapidly fluctuating hemodynamic, physiologic, metabolic, and coagulation status. The formation of specialized and experienced teams in LT plays an essential role in patient outcomes.

We aimed to compare the risk factors that affect the development of AKI in patients who underwent LT using the KDIGO criteria. In addition, we would like to highlight possible strategies for prevention and point to future opportunities to prevent the development of post-LT AKI.

Even mild or transient AKI in patients who underwent LT can have severe consequences due to prolonged intensive care unit (ICU) and hospital stay, as well as increased mortality and morbidity[14].

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Table 3. Adult Patients

Characteristics	AKI (+) (*n* = 17)	AKI (-) (*n* = 14)	*P* value
Age, yr	42.8 ± 18.5	48.8 ± 18.5	0.608
Male/female, *n* (%)	2 (%40)	3 (%60)	0.462
Weight (kg)	72.2 ± 17.2	70.7 ± 16.8	0.948
Etiology of liver disease			
Viral diseases, *n* (%)	4 (%36.4)	7(%63.6)	0.594
Bilier, *n* (%)	1 (%100)	0 (%0)	
Idiopathic, *n* (%)	1 (%100)	0 (%0)	
Others, *n* (%)	7 (%50)	7 (%50)	
Comorbidities, *n* (%)			
Coronary arterial disease (CAD)	2 (%50)	2 (%50)	0.672
Encephalopathy	5 (%71.4)	2 (%28.6)	0.155
Hypertension	2 (%66.7)	1 (%33.3)	0.469
Diabetes Mellitus (DM)	3 (%50)	3 (%50)	0.637
Oesophageal Varices	4 (%44.)	5 (55.6)	0.560
Preoperative kidney dysfunction	4 (%80)	1 (%20)	0.047
Cigarette	5 (%45.5)	6 (%54.5)	0.665
Laboratory values			
MELD-Na^{++}	18.3 ± 9.4	14.3 ± 5.8	0.229
Preoperative			
Hemoglobin (mg/dL)	10.3 ± 1.8	11.4 ± 2.4	0.121
BUN (6-26 mg/dL)	33.0 ± 22.2	14.8 ± 8.8	0.073 #
Creatinine (0.7-1.3 mg/dL)	1.9 ± 1.9	0.7 ± 0.1	0.013 #
Sodium (135-146 mmol/L)	133.8 ± 4.9	127.9 ± 25.7	0.532
Potasium (3.5-5.2 mmol/L)	4.1 ± 0.6	4.1 ± 0.7	0.505
SGOT (5-34 U/L)	59.1 ± 42	48.3 ± 38.8	0.519 #
SGPT (0-55 U/L)	44.5 ± 35.8	41.1 ± 35.8	0.117 #
INR	2.35 ± 1.43	1.41 ± 0.25	0.282
Albumine (3.4-4.8 g/dL)	3.2 ± 0.6	3.2 ± 0.7	0.943
Total bilirubin (0.2-1.2 g/dL)	8.3 ± 8.8	3.15 ± 3.4	0.166 #
Intraoperative parameters			
pH (7.35-7.45)	7.31±0.06	7.32±0.06	0.875
PaO_2 (32-48 mmHg)	152.7±69.1	149.3±46.5	0.972
$PaCO_2$ (32-48 mmHg)	36.0±4.16	35.8±3.9	0.396
Lactate (0.5-1.6 mmol/L)	5.8±4.4	3.9±2.6	0.379
Bicarbonate (22-24 mmol/L)	18.8±6.4	20.0±1.19	1.000
Urine output (mL/kg))	10.6±9.4	20.3±8.9	0.047 #
RBCs (mL/kg)	16.7±16.4	12±8.1	0.233 #
FFP (mL/kg)	16.6±15.9	6.2±5.5	0.080 #
Crystalloids (mL/kg)	73.0±31.6	105.7±33.4	0.018
Colloids (mL/kg)	66±35	44.7±18.5	0.177
Intraoperative and postoperative parameters			
Anesthesia time (hr)	9.6 ± 1.7	10.5 ± 2	0.255
Clemp time (min)	77.6 ± 26.5	74.7 ± 16.6	0.809
ICU time (day)	5.07±5.25	5.07±6.17	0.199#
Mortality	8 (%88.9)	1 (%11.1)	0.003

For all categorical comparisons, Fisher's exact test p values were given, # p-value for Mann-Whitney U test and all others from Student's t-test

Table 4. Adult Patients

AKI incidence (KDIGO)	n (%)
Stage 1	6 (43)
Stage 2	3 (21)
Stage 3	3 (21)
Postop RRT	6 (43)

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For example, mortality post-LT is reported to be 2-6% in patients not developing AKI, compared to a 47–55% mortality in patients who develop post-LT AKI[15]. Furthermore, post-LT AKI increased healthcare resource utilization and hospital care costs[3,8].

Hamada et al.[12] reported that 46.2% of pediatric LT patients developed AKI postoperatively. Silver et al.[9] stated in their report that AKI is a significant postoperative complication in pediatrics LT, with the incidence ranging from 53.6-69.2% and severe AKI (stages 2 and 3) occurring in 27.5-38.5%. In our setting, the incidence of stage 1, stage 2, and stage 3 AKI frequencies of 43.8%, 50 %, and 6.3%, respectively. Barri et al.[16] observed that in adult patients, the incidence of post-LT AKI varies from 17% to 95%. Arani et al.[17] AKI episodes in stage 1, stage 2, and stage 3 were observed in 49.2%, 29.7%, and 21.2%, respectively. In our setting, the incidence of stage 1, stage 2, and stage 3 AKI episodes was 43%, 21%, and 46%, respectively.

In the study by Mrzljak et al.[18], differences in MELD scores, etiology of liver disease, comorbidities, cold and warm ischemia times, age, and gender between patients with and without AKI did not reach statistical significance. Previous studies have shown that patients with a high MELD score at the time of LT have a higher risk of developing post-LT AKI[16,19,20]. Indeed, the severity of the liver disease is related to post-LT AKI[21], as patients with decompensated livers are more susceptible to renal ischemia due to the activation of endogenous vasoactive substances released during the procedure[7]. Hilmi et al.[8] showed a high incidence of post-LT AKI during the first 72 hours after surgery. In addition, it documented the adverse effects of AKI on long-term morbidity in the adult population. Female gender, weight, DM, and Child-Pugh score were risk factors for post-LT AKI in their model, but there was no difference between children and adults in terms of scoring and demographics in our results. As in the results of Mrzljak et al.[18], comorbidities in adult patients, in addition to age and gender, did not reach statistical significance between adult and pediatric patients with and without AKI, contrary to some previous reports. When the etiologic factors of our pediatric patients were examined, this was a significant risk factor for post-LT AKI.

Because of the exclusion of patients with renal failure before LT with high MELD scores and sCr in the study by Hilmi et al.[8], neither the MELD score nor baseline sCr was a risk factor for post-LT AKI. This result contrasts with the study by Karapanagiotou et al.[10], in which these variables were significant risk factors. Zongyi et al.[7] showed that MELD score, Child-Pugh grade, preoperative hypoalbuminemia, cirrhosis, liver failure, and duration of surgery were not risk factors for post-LT AKI similar to the results of our study.

Thongprayoon et al.[3] stated that post-LT AKI and severe AKI requiring RRT is high at 40.8% and 7.0% overall. Additionally, post-LT AKI is significantly associated with increased mortality rate and liver graft failure[3]. In our study, the rate of AKI in children and adults within seven days of LT was 47% and 48%, respectively, the need for RRT was 18.3 and 43%, and the mortality rate post-LT AKI was 83.3% and 88.9%. There was no difference between the two groups regarding RRT for pediatric and adult patients post-LT ($p > 0.05$).

Mizota et al.[21] found that degree of hypotension during LT was independently associated with an increased risk of post-LT severe AKI. Even short-term severe intraoperative hypotension was significantly associated with severe AKI[21]. An analysis of intraoperative factors showed that MAP has a strong association with the development of AKI during surgery, similar to what has been shown previously[22]. Larsson et al.[15] have shown that restoring MAP from 60 to 75 mmHg by increasing the dose of NE improves renal oxygenation, GFR, and renal oxygenation in postoperative patients with NE-dependent systemic vasodilation and AKI[23]. Our study found no statistical correlation between pediatric and adult patients with intraoperative hypotension and post-

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LT AKI. We also used NE to prevent hypotension in both adult and pediatric patients. Mrzljak et al.[18] have shown that RBCs transfusion is an independent predictor of AKI in the early period post-LT. However, in both our pediatric and adult groups, there is no significant association between transfusion of RBCs and post-LT AKI.

We found no association between more extended hospital stays and post-LT AKI in our pediatric cohort. However, we did find an association between high preoperative SGPT level and post-LT AKI. No study has been published on the association between high preoperative SGOT and SGPT levels and post-LT AKI. In contrast to our study, Hamada et al.[12] showed that increased preoperative total bilirubin and increased blood loss during surgery were both associated with post-LT AKI.

Silver et al.[9] showed that in patients with noncongenital metabolic disorders, the risk of post-LT AKI increased with increasing preoperative INR after controlling for covariates such as preoperative sCr. However, no association was found between the post-LT AKI and preoperative INR and sCr values in our pediatric recipients. The lack of hourly UO data in the study by Silver et al.[9] was mentioned as a limitation. Although we performed intraoperative measurements of hourly UO in the pediatric recipients in our study, no statistically significant differences were found between them and post-LT AKI[9].

Arani et al.[17] pointed out that the level of sCr plays the most critical role in the occurrence of mild/moderate and severe AKI, which is consistent with the existing literature[11,24,25]. Haan et al.[11] noted that impairment of preoperative renal function, either as CKD or AKI, could be a risk factor for post-LT AKI (26). Feldcamp et al.[27] found that patients with pre-LT renal dysfunction assessed by sCr were significantly more likely to develop AKI requiring RRT. However, there was no correlation with milder forms of AKI. Also, this is consistent with the study by O'Riordan et al.[6], who found that sCr was associated with severe AKI requiring RRT but not with milder forms of AKI. Bilbao et al.[5] reported that elevated sCr (> 1.5mg/dL) was highly associated with severe AKI (sCr> 3 mg/dL requiring RRT). Interestingly, the sCr value before LT predicted only more severe forms of AKI and not AKI in general and is probably related to the fact that sCr, as a marker of AKI, does not distinguish between a functional and structural decline in renal function. Functional decline in renal function occurs independently of underlying renal damage before LT. In contrast, structural damage in AKI, as evidenced by AKI requiring RRT, is related to underlying renal damage before LT[27]. Renal dysfunction assessed by sCr before LT was also a significant risk factor post-LT AKI and showed statistically significant results in the adult group in our study.

Saner et al.[28] showed that factors that may contribute to postoperative AKI include prolonged cava cross-clamp time and massive perioperative transfusions. However, no meaningful association was found between these parameters in our adult cohort. We also examined cross-clamp time and found no significant association with post-LT AKI. Mrzljak et al.[18] emphasized that intraoperative volume shifts are one of the main factors, as they found that FFP and colloids have a significant association with post-LT AKI. We observed that intraoperative replacement of crystalloids in kg/hour was significantly associated with post-LT AKI in adults. In addition, we demonstrated a significant relationship between intraoperative UO and post-LT AKI in our adult cohort. Crystalloid exchange and hourly UO monitoring are as crucial for post-AKI progression as PiCCO monitoring in adult and pediatric LT patients.

Kalisvaart et al.[29] identified five predictors in their study: Donor BMI, DCD graft, recipient BMI, FFP count, and WIT. In contrast to Kalisvaart's study, our study emphasizes that in pediatric patients, etiologic factors, preoperative high SGPT values, and in adult patients, preoperative sCr-induced renal dysfunction, intraoperative UO, and ap-

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plied crystalloid volume can be evaluated, and these predictors can be assessed in the development of post-LT AKI. The significance of these values in our study suggests that this relationship should be further investigated.

Necessary measures should be performed to reduce the severity and incidence of AKI. These include avoiding unnecessary nephrotoxic medications, considering alternatives to radiocontrast, maintaining tight control of hemodynamic parameters, and avoiding hyperglycemia. In addition strategies to prevent or attenuate AKI in the perioperative LT patient or to facilitate recovery are urgently needed[1,2,4].

There are some limitations of our study: 1) It was a retrospective study. 2) Our study has a small sample population. 3) The duration of intraoperative hypotension, the amount of drained acid in adult patients), the time of cold-warm ischemia, and total blood gas values (only records belonging to the neophepatic phase) were not documented in our study.

Conclusion

According to our study, the following parameters are significant for the development of AKI: preoperative period: renal dysfunction and high creatinine; intraoperative period: UO, inadequate volume replacement; postoperative period: an increased mortality rate. Moreover, the following parameters were significantly associated with pediatric patients developing AKI after LT: etiologies, preoperative SGOT, and postoperative period: increased mortality rate. In our study, more than half of the adult and about half of the pediatric patients developed post-LT AKI. AKI-related mortality was also significantly higher in both the pediatric and adult groups. The results of our study contribute to raising awareness of the potential risk factors associated with preoperative evaluation, intraoperative and postoperative close follow-up, careful anesthesia management, and early onset of post-LT AKI. Further studies are needed to determine risk profiles, incidence, and outcomes of post-LT AKI.

Abbreviations

AKI: Acute kidney injury; APACHE II: Acute physiology and chronic health evaluation II; BT: Body temperature; CI: Cardiac index; CKD: Chronic kidney disease; CVP: Cardiac venous pressure; DM: Diabetes mellitus; ECG: Electrocardiography; EVLWI: Extravascular lung water index; ESLD: End-stage liver disease; FFP: Fresh frozen plasma; GEDV: Global end- diastolic volume; GFR: Glomerular filtration rate; HR: Heart rate; ICU: Intensive care unit; INR: International normalized ratio; ITBVI: Intrathoracic blood volume index; IV: Intravenous, IVC: Intravenous catheter; KDIGO: Kidney disease: Improving global outcomes; LT: Liver transplantation; MAP: Mean arterial pressure; NIBP: Noninvasive blood pressure; NE: Norepinephrine; PiCCO: Pulse contour cardiac output; RBCs: Red blood cells; RRT: Renal replacement therapy; sCr: Serum creatinine, SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; SpO2: Peripheral capillary oxygen saturation; SVRI: Systemic vascular resistance index; SVV: Stroke volume variation; UO: Urine output.

Author contributions

ZE, NÇ: concepts, design, data acquisition, statistical analysis, manuscript editing and manuscript review.
NÇ: definition of intellectual content, literature search, data analysis, manuscript preparation and manuscript review.
ZAÖ, AT, PZ, MH: clinical studies, data acquisition, manuscript review.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

This study was approved by the Başkent University Institutional Review Board and Ethics Committee (KA22/228) with a waiver of informed consent.

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