

# Can Preoperative Parameters of Inflammation be Used to Predict Acute Kidney Injury in Pediatric Liver Transplant Recipients? A Single-Center Retrospective Study

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## ABSTRACT

**Introduction:** Inflammation is one of the factors involved in the occurrence and progression of acute kidney injury (AKI). We evaluated the relationship between preoperative systemic inflammatory markers and early postoperative AKI development in pediatric liver transplantation (LT) patients.

**Methods:** Data from 190 pediatric patients were retrospectively analyzed. The preoperative neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and pan-immune-inflammation value (PIV) levels were calculated. AKI was classified according to the Kidney Disease: Improving Global Outcomes staging. Patients who did not develop AKI in the early postoperative period were classified as group 0, patients with stage 1 AKI were classified as group 1, and patients with stage 2-3 AKI were classified as group 2. The relationship between the inflammatory parameters and AKI was evaluated.

**Results:** AKI developed in 20% of patients, and 16.31% of these patients had severe AKI. The NLR, SII, and PIV values were significantly higher in patients with severe AKI ( $p < 0.001$ ). Preoperative high PIV values were found to be an independent predictor of AKI development.

**Conclusion:** High preoperative PIV values may be used as a predictive factor for the development of early AKI in patients undergoing pediatric LT.

**Keywords:** Acute kidney injury, pediatric transplantation, systemic immune inflammation index, pan-immune-inflammation value

## Introduction

Acute kidney injury (AKI) is a complication after liver transplantation (LT) that is associated with morbidity and mortality (1,2). It is clear that around 20-47% of paediatric LT patients experience AKI (3). The etiology of AKI is complex and multifactorial. Although the primary cause of AKI is ischemia, mounting evidence suggests that AKI may occur without signs of hypoperfusion and may be linked to immune and inflammatory responses. The pathogenesis of AKI in the early post-LT period is not fully understood. The cause of AKI in pediatric patients is likely to be multifactorial, with patient characteristics, pre-transplant organ function, donor components, intraoperative factors, and postoperative course potentially contributing to AKI (4,5).

Inflammation is a complex biological response required to eliminate microbial pathogens and repair tissue after injury. AKI is associated

with intrarenal and systemic inflammation. The Systemic Immune-Inflammation Index (SII) has been linked to diseases accompanied by renal dysfunction (6,7). The neutrophil-to-lymphocyte ratio (NLR), SII, and pan-immune-inflammation value (PIV) are reliable markers of potential inflammation. These values are based on peripheral lymphocyte, neutrophil, and platelet counts. These parameters can be easily calculated from the hemogram without additional cost (8).

Our literature review revealed that no studies have evaluated the relationship between AKI and inflammatory parameters in pediatric patients undergoing LT. Our study aimed to determine whether an early post-LT AKI is associated with preoperative inflammatory parameters in pediatric patients.



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## Methods

### Study Population

This retrospective cohort study was conducted at the Liver Transplant Institute in İnönü University. The files of 216 patients aged 18 years who underwent elective LT between January 2018 and June 2022 were evaluated. Six patients with end-stage kidney disease, hepatorenal syndrome clinic and diagnosis and creatinine values elevation, 4 patients with retransplantation, 12 patients with massive blood transfusion, and 4 patients with missing information in the electronic data system were excluded. A total of 190 patients were included in our study.

### Data Collection

Age, gender, weight, reason for LT, and duration of operation were recorded from the electronic data system of the hospital. Haemogram and biochemical parameters are routinely studied from blood samples taken from patients for preoperative preparation 1 day before the operation. Neutrophil (N) ( $10^9/L$ ), lymphocyte (L) ( $10^9/L$ ), platelet (P) ( $10^9/L$ ), monocyte (M) ( $10^9/L$ ), and creatinine values were recorded from the data system.

Preoperative inflammation parameters were calculated and recorded using the following formulae (8).

NLR: N/L,

SII: NxP/L,

PIV: Nx Px M/L,

The relationship among NLR, SII, PIV, and AKI development was evaluated.

Intraoperative data: The cold ischemia time (CIT) is the time that elapses between the clamping of the donor vessels and the graft being implanted into the abdominal cavity of the recipient. The warm ischemia time (WIT), on the other hand, is the time that elapses between the graft being removed from the ice and the anastomoses being opened for implantation. At our clinic, the operation time, WIT, and CIT operation time are routinely recorded on anesthesia forms. The relationship between operation time, CIT, WIT, and AKI development was evaluated.

Definition of acute kidney injury: AKI was evaluated in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Table 1) (9). Postoperative laboratory data were collected, including creatinine values on postoperative days 1, 2, and 7 and urine output data recorded in the intensive care unit (ICU) in the first week.

**Table 1. Acute kidney injury Kidney Disease: Improving Global Outcomes staging**

Stage	Serum creatinine level	Amount of urine
1	1.5-1.9 times the basal value or >0.3 mg/dL increase	<0.5 mL/kg/h for 6 h
2	2.0-2.9 times increase from baseline	Across two 6-h blocks <0.5 mL/kg/h
3	A 3-fold increase from baseline or serum creatinine >4.0 mg/ initiation of dl or renal replacement therapy	<0.3 mL/kg/day for more than 24 h clock or anuria for ≥12 hours

### Patient Grouping

Group 0: Patients not diagnosed with AKI,

Group 1: Patients diagnosed with stage 1 AKI,

Group 2: Patients diagnosed with grade 2 and 3-AKI (Table 1) (9).

In addition, the duration of postoperative ICU and hospital stays were also recorded. Mortality from transplantation to hospital discharge was recorded and considered as in-hospital mortality. The relationship between the development of AKI and in-hospital mortality and length of hospital stay was evaluated.

Anesthesia modality: Anaesthetic drugs used in LT management were standardized in our hospital. After the depth of anesthesia is achieved with pentothal (3-8 mg/kg) and fentanyl (1-2 µg/kg) as opioid agents during induction, rocuronium bromide is administered at a dose of 0.9-1.2 mg/kg. Anesthesia is maintained with an oxygen/air mixture and sevoflurane (1-1.5%).

Although the decision to use vasopressors is made by the anesthetist, norepinephrine is the first choice during surgery. During the postoperative period, patients are transferred to the ICU without extubation. When the general condition and vital signs of the patient stabilize, extubation is performed and the patient is transferred to the ward.

Surgical method: An L-shaped incision is made from above the umbilicus to the groin. After abdominal exploration, the liver is evaluated. Following the transplantation decision, the falciform ligament is released and dissection is performed up to the suprahepatic vena cava. The hepatic veins are isolated and the hepatic artery, portal vein, and common bile duct were prepared. All connections are cut, and the liver is removed. Implantation is completed by placing the graft into the abdomen, followed by vascular and biliary anastomoses. Bleeding is controlled, a drain is placed, and the abdomen is closed.

### Compliance with Ethical Standards

Our study was conducted after approval by the Scientific Review Board and Ethics Committee of the İnönü University and in accordance with the principles of the Declaration of Helsinki (approval number: 2022/3909, date: 04.10.2022). Considering the retrospective nature of the study, patient consent was waived.

### Statistical Analysis

The SPSS package program (version 23.0, IBM, USA) was used for statistical analysis. Continuous variables are reported as the mean ± standard deviation, whereas categorical variables are presented as numbers and percentages. Whether the data conformed to the normal distribution was evaluated using the Shapiro-Wilk test. One-Way ANOVA or Kruskal-Wallis test was used in the analysis of continuous variables. The Bonferroni test was used for post-hoc correction. The chi-square test was the appropriate statistical tool for analyzing the categorical variables. Pearson's or Spearman's tests were used according to the data type in the correlation analysis of the variables between the groups. We used multiple logistic regression analysis to identify the independent variables that predicted the occurrence of AKI and mortality. For the

univariate analysis, we conducted regression analysis on the variables with p-values <0.10, and we considered the results statistically significant if the p-values were <0.05.

## Results

Retrospective analysis was performed on two hundred and sixteen LT patients. Twenty-six patients were excluded from the study because they did not meet the inclusion criteria, resulting in the inclusion of 190 patients. The mean age of our patients was  $3.73\pm 3.5$  years, with the oldest being 14 years old. Among the patients, 76 were female and 114 were male. The average weight of the patients was  $15.3\pm 8.5$  kg, with the lowest weight recorded at 3 kg and the highest at 48 kg. Demographic data were similar across all groups (Table 2). When evaluating etiological factors, biliary atresia was the most common (65.2%), followed by primary sclerosing cholangitis. A similar etiology was observed in all groups ( $p=0.658$ ).

AKI was observed in 38 patients (20%), with severe AKI noted in 31 patients (16.31%) (Table 2). When evaluating the inflammation parameters of patients in the preoperative period, upon assessing NLR a clear and significant difference was observed between the groups ( $p<0.001$ ; for all). When the patients were evaluated between the groups, similarities were observed between group 0 and group 1, whereas a statistically significant difference was observed between group 1 and group 2 and between group 0 and group 2 ( $p<0.001$ ) (Table 3).

When the SII and PIV values of the patients were compared, a significant

difference was observed for both parameters between the patients who developed AKI in the early period and those who did not develop AKI ( $p<0.001$ ; for all). In the intergroup evaluation, PIV and SII values were significantly higher in the group of patients with severe AKI than in the group without AKI ( $p<0.001$ ) (Table 3).

When intraoperative variables were evaluated, the length of the operation time and similarly, the duration of hot ischemia and cold ischemia were statistically significant between the groups. In the group of pediatric patients who developed severe AKI, it was observed that patients who did not develop AKI were significantly longer than those who did not develop AKI ( $p<0.001$ ) (Table 4).

The mean length of stay in the ICU in the postoperative period was  $25.2\pm 29.9$  days, and all groups were similar in this regard ( $p=0.153$ ). When the mean length of hospital stay is evaluated was  $48.7\pm 41.1$  days, there was a significant difference between the groups ( $p=0.154$ ). It was observed that this period was significantly longer in group 0 compared to group 2 (Table 3). Mortality was observed in 13.68% of the patients. Mortality was observed in 50% of patients who developed severe AKI. There is a clear statistical difference between the groups ( $p<0.001$ ) (Table 4).

The analysis of predictors of AKI revealed significant correlations between cold and WIT, operation time, and PIV. These findings were further validated by logistic regression analysis, which demonstrated a clear association between cold and WIT. and PIV were found to be independent predictors of AKI (Table 5).

**Table 2. Demographic data of the groups and AKI**

	Group 0, (n=152)	Group 1, (n=7)	Group 2, (n=31)	p-value
Age (years)	$3.86\pm 3.54$	$6.14\pm 3.76$	$2.54\pm 2.2$	0.020
Weight (kg)	$15.75\pm 8.59$	$18.57\pm 7.39$	$12.5\pm 11.35$	0.055
Gender (female, %)	64 (84.2)	2 (2.6)	10 (13.2)	0.657
Etiology Biliary atresia (n, %)	102/53.68	4/57.1	18/58.06	0.658

AKI: Acute kidney injury

**Table 3. Evaluation of the relationship between preoperative data of the groups and AKI**

	Group 0, (n=152)	Group 1, (n=7)	Group 2, (n=31)	p-value
NLR	$2.03\pm 2.22$	$6.77\pm 7.34$	$4.73\pm 8.73$	$<0.001^{\beta,\phi}$
SII	$324.09\pm 359.16$	$650.57\pm 423.94$	$1293.68\pm 2522.17$	$<0.001^{\beta}$
PIV	$259.93\pm 325.40$	$576.31\pm 452.72$	$848.47\pm 1222.15$	$<0.001^{\beta}$

$^{\alpha}$ :  $p<0.05$  in group 0 vs. group 1,  $^{\beta}$ :  $p<0.05$  in group 0 vs. group 2,  $^{\phi}$ :  $p<0.05$  in group 1 vs. group 2, AKI: Acute kidney injury, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value

**Table 4. Evaluation of the relationship between intraoperative variables and postoperative AKI data in the groups**

	Group 0, (n=152)	Group 1, (n=7)	Group 2, (n=31)	p-value
Operation time (minute)	$371.03\pm 67.46$	$445.71\pm 102.77$	$495.45\pm 104.72$	$<0.001^{\beta}$
CIT (minute)	$60.34\pm 20.52$	$78.42\pm 19.99$	$94.63\pm 34.75$	$<0.001^{\beta}$
WIT (minute)	$53.61\pm 13.8$	$51\pm 15.74$	$73.27\pm 15.42$	$<0.001^{\beta}$
ICU stay (days)	$27.57\pm 31.54$	$23.14\pm 8.97$	$14.55\pm 12.4$	0.153
Hospital stay (days)	$53.66\pm 40.76$	$38\pm 20.76$	$42.27\pm 38.23$	0.066
Mortality, (n, %)	12 (7.89)	0 (0)	14 (45.16)	$<0.001^{\beta,\phi}$

$^{\alpha}$ :  $p<0.05$  in group 0 vs. group 1,  $^{\beta}$ :  $p<0.05$  in group 0 vs. group 2,  $^{\phi}$ :  $p<0.05$  in group 1 vs. group 2, AKI: Acute kidney injury, CIT: Cold ischemia time, WIT: Warm ischemia time, ICU: Intensive care unit

**Table 5. Predictors of AKI and mortality**

Predictors of AKI						Predictors of mortality				
Parameters	Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
	r	p-value	OR	95% CI	p-value	r	p-value	OR	95% CI	p-value
CIT	0.384	<0.001	1.045	1.007-1.086	0.028	0.109	0.136			
WIT	0.430	<0.001	1.038	1.014-1.063	0.002	0.149	0.040	1.027	1.003-1.0381	0.023
Operation time	0.480	<0.001	1.017	1.007-1.027		0.155	0.032			
PIV	0.160	0.027	1.002	1.001-1.003	<0.001	0.183	0.012	1.001	1.000–1.002	0.002

AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval, CIT: Cold ischemia time, WIT: Warm ischemia time, PIV: Pan-immune-inflammation value

When analyzed for predictors of mortality, a significant correlation was observed between AKI and CIT, operation time, and PIV. In the logistic regression analysis, it was determined that CIT and PIV value were independent predictors of mortality (Table 5).

## Discussion

This is the first study to investigate the relationship between inflammatory parameters and the risk of AKI development in the early postoperative period in pediatric patients undergoing LT. The study revealed a strong link between high NLR, SII, and PIV values before surgery and the risk of developing AKI. Elevated PIV levels before surgery also indicate a higher chance of AKI and in-hospital mortality.

AKI is a common and serious complication of LT, its incidence varies between 5% and 94%, and 11% to 17% of these are severe AKI (10). A study conducted in a paediatric patient group highlighted that AKI was seen in 46.2% of the patients, 20.5% had stage 2 AKI and 3.8% had stage 3 AKI (2). The wide range in these rates is due to the breadth of the parameters used in n to diagnose AKI. In our study, we used KDIGO staging to define early-stage AKI in the pediatric patient group (10). In our study, 20% of the patients developed AKI, with 16.31% experiencing severe AKI. We observed a lower rate of AKI development compared with other studies, whereas the rate of severe AKI development was similar to that reported in the literature. We believe that this difference is attributable to the exclusion of patients with preoperative renal dysfunction in our study.

To date, numerous studies have been conducted on the risk factors for early AKI after LT. These studies have emphasized that various factors, such as hypotension during the preoperative and intraoperative periods, cold and WIT, and immunosuppressive therapy, may contribute to AKI. However, there is still uncertainty regarding the factors that cause AKI, and early recognition and AKI remain difficult to treat. It is crucial to identify the risk factors for AKI (11-13).

There is an opinion that excessive activation of inflammatory mediators is an important mechanism in the development of AKI (14). It has been argued that the disruption of tissue oxygenation initiates the release of proinflammatory cytokines from damaged kidney cells, leading to subsequent renal dysfunction (15). Recently, NLR, SII, and PIV parameters have been used as inflammatory markers (16). Studies have reported that SII can predict postoperative AKI in patients with hepatocellular carcinoma after hepatectomy (17,18). Lu et al. (18) and Biyik et al. (19) emphasized that SII and AKI can be similarly predicted in their studies involving patients with acute pancreatitis (20).

Lai et al. (21) emphasized that a high pre-procedural SII level is a significant and independent risk factor for post-procedure AKI in patients undergoing coronary angiography. Similarly, in our study, a significant relationship was observed between preoperative NLR, SII, PIV values, and AKI. It was also observed that high PIV values were independent predictors of AKI development.

It is emphasized that AKI causes death in the early period after LT (22,23). Similarly, in our study, it was observed that deaths due to AKI increased. A development in the ICU revealed an association between SII and mortality (24). Vasculitis-related deaths are similarly associated with SII (25). In our study, unlike the literature, high PIV values were determined to be a predictive factor for mortality in patients undergoing LT.

We believe that incorporating inflammatory hematological markers, in addition to the known risk factors, can be effective in predicting AKI and preventing its occurrence. This approach may contribute to early diagnosis and treatment, thereby helping to prevent or limit AKI and mitigate the potential short-term and long-term consequences, such as chronic kidney disease or end-stage kidney disease, associated with AKI.

## Study Limitations

It should be acknowledged that the current study has certain limitations. First, I would like to make clear that this study is single-center and retrospective. It also did not evaluate other potential causes of AKI. Additionally, the effect of postoperative treatments and other intraoperative causes of AKI were excluded from the study because of lack of data. To reinforce these results, more comprehensive, multicenter prospective studies are required.

## Conclusion

The PIV value, which can be calculated inexpensively and easily in the preoperative period, is associated with early AKI development in patients undergoing pediatric LT. We believe that PIV values in the preoperative evaluation may serve as a parameter for predicting AKI and in-hospital mortality. Multicenter prospective studies are required to further explore this association.

**Ethics Committee Approval:** Our study was conducted after approval by the Scientific Review Board and Ethics Committee of the İnönü University and in accordance with the principles of the Declaration of Helsinki (approval number: 2022/3909, date: 04.10.2022).

**Informed Consent:** Retrospective study.

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