Journal of Critical Care 50 (2019) 275–279

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Prevalence of acute kidney injury after liver transplantation in children: Comparison of the pRIFLE, AKIN, and KDIGO criteria using corrected serum creatinine

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ARTICLE INFO

Keywords:
Liver transplantation
Acute kidney injury
Children
KDIGO
pRIFLE
AKIN

ABSTRACT

Purpose: To compare the application of three standardized definitions of acute kidney injury (AKI), using corrected serum creatinine values, in children immediately after liver transplantation.
Methods: Retrospective search of a tertiary pediatric hospital database yielded 77 patients (age < 18 years) who underwent liver transplantation in 2007–2017. Serum creatinine levels during the 24 h before and after surgery were corrected to daily fluid balance, and the prevalence of AKI was calculated using the Pediatric RIFLE (pRIFLE), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) criteria.
Results: AKI occurred in 44 children (57%) according to the pRIFLE criteria (stage I, 34%; stage II, 10%, stage III, 13%) and 33 children (43%) according to the AKIN and KDIGO criteria (stage I, 20%; stage II, 10%; stage III, 13%). There was a good correlation (kappa = 0.78) among the three criteria. AKI was associated with longer duration of mechanical ventilation (5.5 ± 6.2 vs 3.6 ± 4.0 days, $p < .05$) and longer ICU stay (15.2 ± 8.8 vs 12.1 ± 7.5 days, $p < .05$). Serum creatinine normalized in all patients (mean, 0.43 ± 0.17 mg/dl) by one year.
Conclusions: There is a good correlation among the three criteria defining AKI in pediatric liver transplant recipients. AKI is highly prevalent in this patient group and confers a worse ICU course.

1. Introduction

Acute kidney injury (AKI) in critically ill children poses an increased risk of longer intensive care unit (ICU) stay, more days on mechanical ventilation, and increased mortality [1-3]. Liver transplantation in children is often complicated by acute kidney injury [4-6] because of the high incidence of infections before surgery; prolonged operative time and high risk of bleeding and bowel insult secondary to inferior vena cava clamping during surgery; and intravascular volume depletion, increased abdominal pressure, and nephrotoxic drug administration postoperatively. Its early recognition in the immediate postoperative period is crucial, and the prevention of further renal deterioration should be taken into consideration in all postoperative management decisions in the ICU (fluid balance, type of inotropic support, blood pressure target, type and dose of medication etc.).

There are currently three standardized definitions for AKI. The Pediatric RIFLE (pRIFLE) criteria [7] are based on changes in estimated glomerular filtration rate (eGFR) or relative changes in baseline serum creatinine level or urine output. The AKI Network (AKIN) criteria [8] exclude eGFR changes, add an absolute change in serum creatinine level to the relative serum creatinine changes, and use a different time scale to determine oliguria. The most recent Kidney Disease Improving Global Outcomes (KDIGO) criteria [9] combines (with a few changes) the two previous criteria with the addition of a recommended staging method. All three are still in use [10-14]. The only pediatric study to date comparing the three criteria [1] had a retrospective chart review design, and therefore baseline GFR was assumed in many cases and daily serum creatinine was missing in all patients, and the authors failed to correct serum creatinine levels for fluid balance.

We hypothesized that in children after liver transplantation, the application of different definitions of AKI when data are incomplete or serum creatinine levels are not corrected could lead to differences in prevalence calculations and staging. The aim of the present study was to determine the prevalence of AKI in pediatric liver transplant

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https://doi.org/10.1016/j.jcrc.2019.01.010
0883-9441/

recipients according to the three AKI staging criteria using highly informative patient charts with correction of daily serum creatinine levels for cumulative fluid balance. The findings were compared among the three classification criteria, and the prevalence of AKI was evaluated in relation to patient outcome.

2. Materials and methods

A retrospective cohort design was used. The study was conducted in the 16-bed ICU of a major tertiary pediatric medical center. The study was approved by the Institutional Review Board which waived the need for informed consent.

The database of the medical center was searched for all children who underwent liver transplantation in 2007–2017. Exclusion criteria were age over 18 years and treatment with peritoneal or hemodialysis due to end-stage renal failure prior to transplantation. Data were collected from the electronic files of the ICU (Metavison software, iMDsoft, Wakefield, MA, USA) as follows: patient demographics, indication for transplantation, type of transplant, baseline serum creatinine level (24 h postoperatively), postoperative course: inotropic support, daily serum creatinine level, hourly urine output, nephrotoxic medications (tacrolimus- normal range < 15 ng/ml, aminoglycoside, gentamycin, trough concentration < 2 μg/mL, amikacin trough concentration < 8 mg/dl), use of diuretics, complications (bleeding, bile leak, infection), days on mechanical ventilation, and length of ICU stay. In addition, we searched the electronic files of the nephrology department outpatient clinic (Ofek software, dbMotion, Ra'anana, Israel) for serum creatinine levels at 1–5 years after transplantation.

Postoperative serum creatinine was corrected according to the fluid balance using the formula [15]: corrected creatinine = Measured creatinine level × [1 + accumulated net fluid balance/total body water], where total body water = 0.6 × body weight. AKI was classified according to the pRIFLE [7], AKIN [8] and KDIGO [9] criteria using the changes in corrected serum creatinine relative to baseline serum creatinine or urine output. We calculated eGFR according to the revised Schwartz formula [16], and the vasoactive inotropic score (VIS) with the formula [17]: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min).

2.1. Statistical analysis

Data were analyzed using BMDP statistical software (Statistics Solutions, Clearwater, FL, USA). Discrete variables are expressed as number and percent and continuous variables and mean and standard deviation. Pearson's chi-square test or Fisher's exact test was used, as appropriate, to analyze between-group differences in discrete variables; the Kappa measurement of reliability was derived from the chi-square test. Spearman's rank correlation was used to measure linear correlation between two variables. Analysis of variance (ANOVA) was used for continuous variables. The Mann-Whitney non-parametric test was applied for analysis of parameters with a non-Gaussian distribution.

3. Results

During the 10-year study period, 87 children underwent 88 liver transplantations. Ten of them were excluded from the study: 8 had previous renal failure (hyperoxaluria); one was transferred to an adult ICU directly from the operating room; and one had acute primary graft nonfunction and died 36 h postoperatively.

The detailed demographic and background data of the 77 eligible patients are presented in Table 1. The cohort included 45 male and 32 female children of mean age 5.8 ± 4.9 years (median 4.3 years) and mean weight, 21.1 ± 15.8 kg (median 16.5 kg). Reasons for liver transplantation were biliary atresia in 30 patients, acute fulminant liver failure in 14, and progressive familial intrahepatic cholestasis in 9. Living-related or split liver transplantation was performed in 48 children, and whole- liver transplantation in 29. All children in the cohort survived to discharge from the ICU. Serum creatinine level measured within 24 h before transplantation indicated normal kidney function in all patients. Maximal serum creatinine level was measured at a mean of 3.7 ± 2.1 days after transplantation.

Table 1
Demographic data and ICU course of children undergoing liver transplantation.

Characteristics	Values
Total patients	77
Sex, n(%)	
Male	45 (80%)
Female	32(42%)
Age (yr), mean ± SD (range)	5.8 ± 4.9 (0.4–17)
Weight (kg), mean ± SD (range)	21.1 ± 15.8 (4.1–86.7)
Indication for transplantation, n (%)	
Biliary atresia	30 (38.9%)
Fulminant liver failure	14 (18.2%)
PFIC	9 (11.8%)
Tyrosinemia	4 (5.2%)
Cystic fibrosis	3 (3.9%)
Other	17 (22.1%)
Type of transplant, n(%)	
Whole liver	29 (37.7%)
Living related/split	48 (62.3%)
Ventilation time (days), mean ± SD (range)	4.4 ± 5.1 (0.5–23)
ICU stay (days), mean ± SD (range)	13.4 ± 8.2 (5–47)
VIS, mean ± SD (range)	4.7 ± 13

ICU, intensive care unit, PFIC, progressive familial intrahepatic cholestasis; VIS, vasoactive inotropic score.

According to the pRIFLE criteria, 44 children (57%) had postoperative AKI and 33 (43%) did not. Division by AKI stage yielded 26 children (34%) with stage I, 8 (10%) with stage II, and 10 (13%) with stage III. There was a good correlation (kappa = 0.69) between the rate of AKI according to the pRIFLE serum creatinine criteria and the rate of AKI by the pRIFLE eGFR criteria (Fig. 1). Nevertheless, 11 patients who met the eGFR criteria for stage I AKI were missed using the serum creatinine criteria, and 5 patients diagnosed with AKI stage II by the serum creatinine criteria were found to have stage III by the eGFR criteria.

According to the AKIN criteria, 33 children (43%) had postoperative AKI and 44 (57%) did not. Division by AKI stage yielded 15 children (20%) with stage I, 8 (10%) with stage II, and 10 (13%) with stage III. Identical results, overall and by AKI stage, were found using the KDIGO criteria (Fig. 2). Overall, there was a good correlation among the three criteria (kappa = 0.78).

Diuretics were administered to 43 children (56%). When urine output was used to determine AKI, 9 children (12%) were found to have stage I according to all 3 criteria. None had AKI stage II or stage III. None of the children required renal replacement therapy.

Statistically significant correlations were found between the presence of AKI (by the KDIGO/AKIN criteria) and the rate of tacrolimus toxicity (>15 ng/ml; p = .001), administration of diuretics (p = .01), and partial liver transplantation (split or living-related; p = .05) (Fig. 3). The association of AKI with indication for liver transplantation, surgical complications, and VIS achieved trend-level significance.

Children with AKI had required mechanical ventilation for a significantly longer time than children without AKI (5.5 ± 6.2 vs 3.6 ± 4.0 days, p < .05) and had a significantly longer stay in the ICU(15.2 ± 8.8 vs 12.1 ± 7.5 days, p < .05) (Table 2). There was a weak Spearman rank correlation between stage of AKI and number of days on mechanical ventilation (r = 0.21) and length of ICU stay (r = 0.25).

The long-term follow-up ranged from 1 to 5 years (median 4 years). At one year, all children showed normal kidney function, with normal age-adjusted serum creatinine levels, ranging from 0.14 to 0.97 mg/dl (mean 0.43 ± 0.17 mg/dl). None of the children had abnormally high serum creatinine levels at any time during the follow-up period.

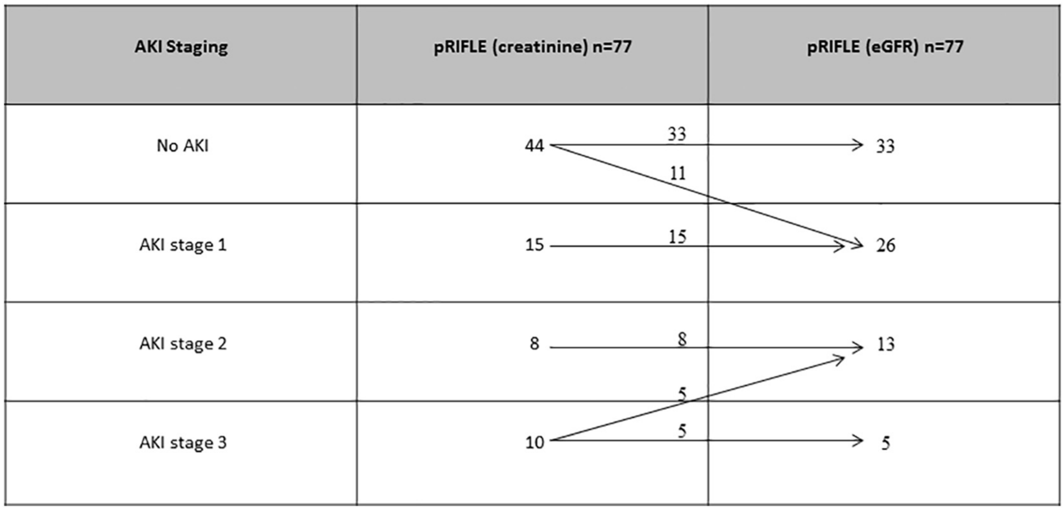

Fig. 1. AKI classification by pRIFLE serum creatinine or eGFR criteria. Numbers above arrows represent the number of patients in whom AKI stage was changed when the serum creatinine or eGFR criteria were used.

4. Discussion

The present study shows that AKI is common in pediatric liver transplant recipients, with rates ranging from 43% to 57% depending on the classification criteria used. The pRIFLE criteria were more sensitive for detecting AKI stage I than the AKIN and KDIGO criteria. The presence of postoperative AKI was associated with tacrolimus toxicity, use of diuretics, and longer ICU course with more days on mechanical ventilation.

Our study has several advantages over previous studies comparing the three criteria defining AKI to evaluate prevalence. First, we corrected serum creatinine, a crucial parameter in AKI, to the accumulated fluid balance. Fluid overload, especially in young children, can skew the true level of serum creatinine. For example, in an infant weighing 10 kg with a cumulative fluid overload of 1.5 l, the corrected serum creatinine will be 25% higher than the measured serum creatinine. Second, in all our patients, serum creatinine was measured 24 h prior to liver transplantation and daily thereafter, which allowed us to achieve a very high accuracy of AKI detection.

Application of the KDIGO or AKIN criteria in the children after liver transplantation yielded a 43% rate of AKI, whereas the rate according to the pRIFLE criteria was 57%. Thus, 11 children identified by the pRIFLE as having AKI (all stage I) were missed by the AKIN and KDIGO criteria. The other patients with AKI were identified by all three criteria. Earlier studies comparing these criteria reported contradictory results. Erdost et al. [18], in a study on 440 adults undergoing liver transplantation, found that the RIFLE criteria were less sensitive for the detection of AKI than the AKIN and KDIGO criteria. In a much larger study of 16,784 adults hospitalized in 303 ICUs, Joannidis et al. [19] found that the RIFLE criteria missed cases of AKI stage II or III that were identified by the AKIN criteria. However, the results of pediatric studies were similar to ours. Volpon et al. [20] evaluated the rate of AKI in 214 consecutive children admitted to the pediatric ICU and found a slightly higher sensitivity of the pRIFLE criteria (49.4%) than the KDIGO criteria (46.2%). Specifically, using the pRIFLE criteria, a larger proportion of the children were classified with AKI stage I and a lower proportion with AKI stage III. Zappiteli et al. [21] found that the pRIFLE criteria were more sensitive than the AKIN criteria in detecting AKI stage I. It is possible that the pRIFLE criteria have a higher relative sensitivity in children because the AKIN and KDIGO 0.3 mg/dl increase in serum creatinine parameter, is a relatively large change in this age group in whom muscle mass is low, and the pRIFLE eGFR parameter corrects this imbalance.

Only one study of pediatric patients, by Sutherland et al. [1], compared all three criteria for AKI detection They showed that according to the pRIFLE criteria, 26.9% of hospitalized children had AKI stage I, but the rates according to the AKIN and KDIGO criteria were 19.4% and 18.2%, respectively. The pRIFLE criteria were more sensitive than the AKIN criteria in detecting AKI stage III. However, Sutherland et al. [1] did not correct serum creatinine for fluid balance, and premorbid serum creatinine and daily serum creatinine levels were missing in an unknown number of patients. Hamada et al. [22], in the only study conducted on pediatric liver transplant recipients, reported that according to the KDIGO criteria, the rate of AKI was 46.2% (stage I, 21.8%; stage II, 20.5%; stage III, 3.8%). In our study, the identical rates of AKI achieved when applying the AKIN or KDIGO criteria can be explained by the

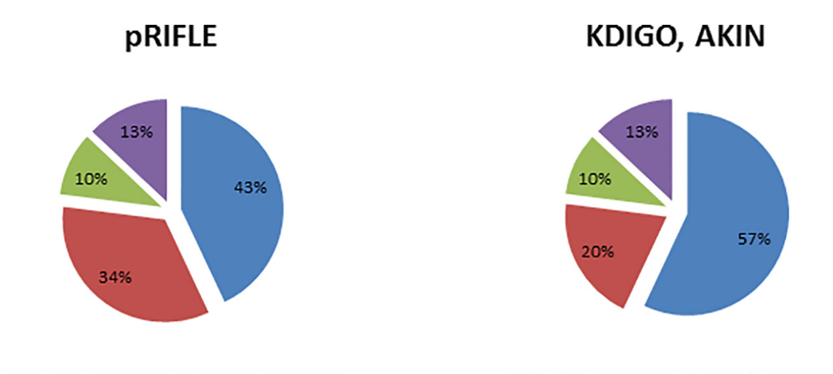

Fig. 2. AKI incidence according to KDIGO, pRIFLE and AKIN criteria.

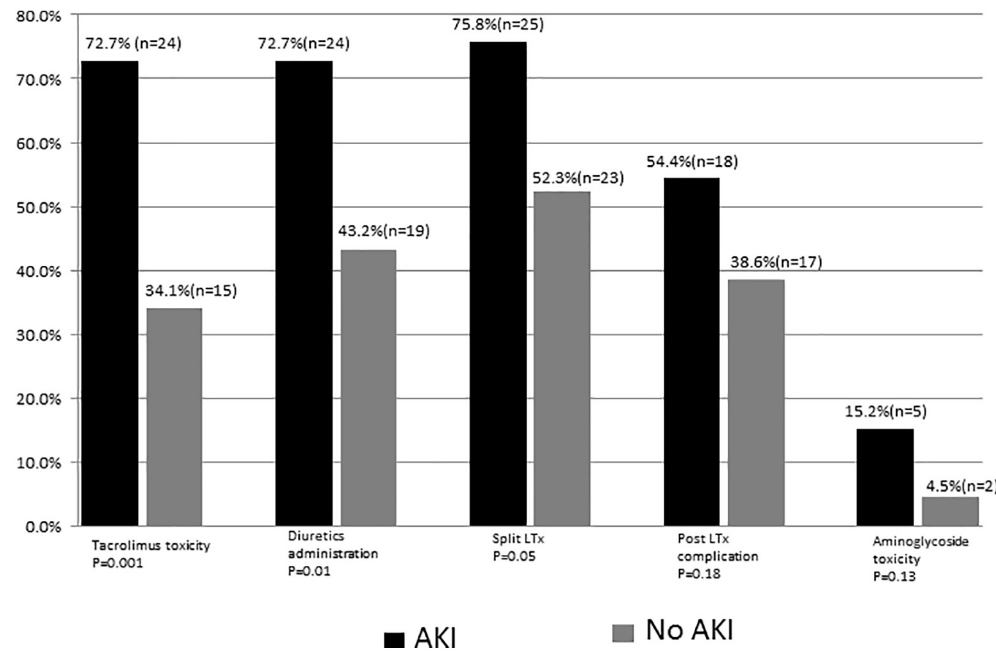

Fig. 3. Risk factors for AKI according to KDIGO/AKIN criteria.

relatively minor differences between their parameters and the relatively small cohort (77 patients) which may not have had sufficient power to achieve statistical significance compared to the much larger study (14,795 children) of Sutherland et al. [1].

We found hourly urine output to be a poor parameter for detecting AKI according to all three criteria. This finding was not surprising as the oligouric state in patients with AKI is masked by the frequent use of diuretics in the pediatric ICU, especially in continuous drips, in order to avoid fluid overload and maintain hemodynamic stability.

Tacrolimus toxicity was associated with an increased risk of AKI in our cohort. Tacrolimus is a known nephrotoxic drug, and its effects are usually reversible. Another risk factor for AKI was partial liver transplantation (split or living-related) relative to whole-liver transplantation. We speculate that partial liver transplantation may cause increased fluid loss from the raw surface of the transplanted liver, resulting in a greater fluid imbalance between chambers and consequent renal hypoperfusion.

Similar to previous studies in adults [23,24] and children [1,7,20,21], we found that AKI was associated with increased morbidity. Kavaz et al. [25], in a study of 189 children, reported significantly more days on mechanical ventilation and longer ICU stay in those with AKI, and Akcan-Arikan et al. [7]. reported longer hospital and ICU stays in 150 critically ill children with AKI.

A major limitation of the present study is the relatively small sample size and single-center setting, especially compared to adult studies, which may have decreased the study's power to delineate differences among the three criteria, identify risk factors, and find correlations among the parameters. The main strength of the study is its high accuracy owing to the availability of both preoperative and postoperative serum creatinine levels and hourly urine measurements in all patients, in addition to our correction of serum creatinine levels to daily fluid balance.

Table 2
Duration of mechanical ventilation and ICU stay by AKI staging.

AKI stage	Ventilation time (days)	ICU LOS (days)
AKI 0	3.6 ± 4.0	12.1 ± 7.5
AKI 1	4.8 ± 3.1	12.8 ± 4.7
AKI 2	5.1 ± 6.2	16.6 ± 9.8
AKI 3	6.9 ± 9.3	17.8 ± 2.2
Total AKI	5.5 ± 6.2	15.2 ± 8.8
Spearman r	0.21	0.25

Values are mean ± SD.
AKI, acute kidney injury; ICU, intenstive care unit; LOS, Length of stay.

In conclusion, AKI was appears to be common in pediatric liver transplant recipients, with agreement between the three diagnostic criteria. It may adversely affect the short-term outcome in terms of more days on mechanical ventilation, and longer pediatric ICU stay. Kidney serum creatinine levels normalized in all patients by one year. Given the widespread use of electronic files, we suggest that in pediatric patients after liver transplantation, AKI be evaluated daily accordiJCRCng to the corrected serum creatinine and documented. This will provide the treating ICU physician with continuous information on the state of the kidneys so that necessary and timely steps can be taken to prevent further injury by close follow-up and adjustment of medications.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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