Acute Kidney Injury and Renal Regional Oxygen Saturation During Pediatric Liver Transplantation

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Data Collection B
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Background: Kidney injury is a complication among children undergoing liver transplantation (pLTx). Cystatin C serum concentration seems to be superior to creatinine-based determination of kidney injury in adults and children. Near-infrared spectroscopy (NIRS) technology provides non-invasive and real-time measurement of renal tissue oxygenation. Here, we compared renal tissue oximetry ($rSrO_2$) with conventional diagnostic criteria cystatin C and creatinine concentration in children undergoing pLTx.

Material/Methods: $rSrO_2$ was measured intraoperatively in children undergoing pLTx over the left kidney, and was statistically compared with pre- and postoperative serum creatinine and cystatin C concentrations.

Results: $rSrO_2$ was affected by hemoglobin concentration, bilirubin concentration, and FiO_2. Statistical analysis demonstrated that $rSrO_2$ was significantly reduced in children with preoperative pathologic increased cystatin C concentrations compared to children without (63.7±4.3 vs. 53.4±4.9, p<0.05). We did not detect a significant difference in $rSrO_2$ between children who developed postoperative renal impairment, either determined by increased postoperative cystatin C concentration, creatinine concentration, or the pRIFLE criteria. Intraoperative increase or decrease in $rSrO_2$ did not predict the development of postoperative kidney injury.

Conclusions: In children with liver failure undergoing pLTx, a preoperative decrease in $rSrO_2$ indicates compromised renal function. However, intraoperative $rSrO_2$ is not predictive of postoperative kidney injury.

MeSH Keywords: Acute Kidney Injury • Liver Transplantation • Pediatrics • Spectroscopy, Near-Infrared

Abbreviations: AKI – acute kidney injury; AKIN – Acute Kidney Injury Network; ALV – acute liver failure; Cl⁻ – chloride; CO_2 – carbon dioxide; $cSrO_2$ – cerebral regional oxygen saturation; FiO_2 – fraction of inspired oxygen; Hb – hemoglobin; ICU – Intensive Care Unit; K⁺ – potassium; KDIGO – Kidney Disease for Improving Global Outcomes; LTx – liver transplantation; MAP – mean arterial pressure; Na⁺ – sodium; NIRS – near-infrared spectroscopy; OR – odds ratio; paO_2 – partial pressure of carbon oxygen; $paCO_2$ – partial pressure of carbon dioxide; PELD – model of pediatric end-stage liver disease; pLTx – pediatric liver transplantation; pRIFLE – Pediatric Risk, Injury, Failure, Loss of function and End-stage renal disease; SaO_2 – peripheral arterial oxygen saturation; SE – standard error; $rSrO_2$ – renal regional oxygen saturation; SSC – secondary sclerosis cholangitis

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/919717

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Background

Acute or chronic liver failure in children affects various organs, among which, acute kidney injury (AKI) is a potentially serious complication. Pediatric liver transplantation (pLTx) is associated with hemodynamic and procedural alterations and thus can aggravate AKI in children undergoing pLTx. Although there have been few studies focussed on these patients, some studies showed that the incidence of AKI is about 5.2% and increases postoperatively to up to 46% [1].

Near-infrared spectroscopy (NIRS) technology uses an infrared light source to measure regional oxyhemoglobin (SrO_2) saturation non-invasively, continuously, and in real-time [2].Several studies have been published on infants and children who underwent cardiac surgery with cardiopulmonary bypass, showing that changes in renal SrO_2 ($rSrO_2$) are significantly correlated with development of postoperative AKI [3–7].

We hypothesized that intraoperative NIRS is a helpful tool to detect preoperative renal failure and that the intraoperative decrease in $rSrO_2$ is associated with postoperative kidney injury. Therefore, we retrospectively analyzed intraoperative $rSrO_2$ in children undergoing pLTx and compared the $rSrO_2$ with the incidence of pre- and postoperative AKI.

Material and Methods

Patients

This study was conducted in agreement with the regulations of the Ethics Committee of the University of Regensburg (approval no. 16-101-0005) and according to the ethics guidelines of the 1975 Declaration of Helsinki. Infants and children who underwent liver transplantation for acute or chronic liver failure at our clinic between March 2011 and March 2016 were included. Patients received no oral premedication and were fasted according to the local protocol. The initial monitoring included electrocardiogram, non-invasive blood pressure, and pulsoxymetric saturation (SpO_2). Anesthesia was induced with sufentanil (0.2 µg/kg per BW), propofol (2–4 mg/kg per BW), and rocuronium (0.5 mg/kg per BW). After intubation, desflurane 0.6–0.9 MAC (in 30–50% O_2/air mixed to keep the paO_2 >100 mmHg) was used for maintaining anesthesia. Gas monitoring for desflurane was performed and end-tidal CO_2, inspiratory and expiratory oxygen concentration, as well as spirometry (gas flows, volumes, and pressures), were measured. Body temperature was measured in the oesophagus and in the bladder via a urinary catheter. In all children, invasive arterial blood pressure, continuous central venous pressure, and urinary output were monitored. Blood for arterial blood gases were taken after the induction of anesthesia,

prior to reperfusion, approximately 5 min after reperfusion of the new graft and whenever indicated by the anesthesiologist. The concentrations of hemoglobin, electrolyte, lactate, and glucose and arterial blood gases were measured and recorded. Blood samples to determine laboratory values (for creatinine, cystatin C, and bilirubin) were taken prior to transplantation, on arrival in the ICU, and on the following 7 days in the morning. For volume replacement, the children received crystalloid (5–15 mg/kg/h) and colloidal solutions. Blood transfusion for maintaining the hemoglobin concentration above 7 mg/dl and fresh frozen plasma were transfused when thromboplastin time was below 50% and pooled thrombocyte concentrate in the case of a thrombocyte count below 60 000/µl.

Creatinine and cystatin C concentration

Creatinine values were taken from the laboratory results of the patients. Creatinine concentration threshold was determined according to the method described by Lechner and Liebau [8]. According to the local protocol, serum creatinine concentrations were determined preoperatively and once every postoperative day. For analysis, preoperative and highest concentrations during the first postoperative creatinine values of the first 7 postoperative days were used.

Normal values for cystatin C concentration were determined according to the method described by Ziegelasch et al., and the 50th percentile was used as the threshold value [9]. According to the institutional standards, serum cystatin C concentrations were determined preoperatively and on postoperative day 7.

Urea nitrogen concentrations were determined preoperatively and every day following pLTx; according to the references our laboratory, threshold values were set at 48 mg/dl.

Pediatric RIFLE criteria

KI was defined using the pediatric RIFLE (pRIFLE) criteria for acute kidney injury. This creatinine-based definition is determined by glomerular filtration rates or reduction in urine output. The GFR was calculated using the Schwartz formula. AKI is categorized into stage I (risk), stage II (injury), and stage III (failure). These stages correspond with a decrease in the GFR of 25%, 50% or 75%, respectively, or a decrease in urine output [10].

Chronic renal failure

Chronic renal failure was defined when children had increased cystatin C or creatinine concentrations in the 3 months prior to LTx.

Table 1. Demographic data of the 41 children undergoing pLTx and probable risk factors for postoperative kidney injury.

	Total	Children without postoperative AKI	Children with postoperative AKI	Level of significance between children with and without AKI
Age (months)	26.5±39.0	34.9±12.5	22.2±6.6	0.332
Sex	19 girls, 22 boys	10 girls, 12 boys	9 girls, 9 boys	0.512
Height (cm)	81.7±25.2	79.7±4.8	82.3±28.5	0.750
Weight (kg)	11.5±8.2	10.8±1.6	11.7±9.0	0.736
Mean PELD	30.5±3.5	14.2±1.8	17.7±2.5	0.251
Bilirubin concentration (mg/dl)	11.4±1.4	10.6±1.7	13.0±2.5	0.433
Creatinine concentration (mg/dl)	0.27±0.1	0.25±0.02	0.30±0.03	0.145
Hb concentration (mg/dl)	9.6±0.3	9.5±0.5	9.4±0.4	0.853
Preop. AKI	14	12	6	0.000*
Preop. diuretics	19	9	10	0.273
FiO_2	0.43±0.03	0.37±0.02	0.48±0.05	0.037*
MAP (mmHg)	55.8±1.6	55.8±1.2	54.2±2.7	0.602
Mean duration of pLTx (min)	324.3±74.3	316.1±13.0	339.4±20.5	0.326
Mean duration of the anhepatic period (min)	85.8±35.2	95.8±7.7	75.9±7.3	0.072
$rSrO_2$	60.2±3.3	59.86±4.8	58.72±4.5	0.866

AKI – acute kidney injury; PELD – pediatric endstage liver disease; FiO_2 – fracture of inspired oxygen; MAP – mean arterial pressure; NIRS – near infrared spectroscopy. This Table shows the demographic data of the 41 children included in the retrospective analysis. There was no significant difference between preoperative PELD score or laboratory values between children who had postoperative kidney injury *vs*. those without. However, children with preoperative kidney injury had significantly increased rates of postoperative renal failure. In addition, and as a probable indicator of severity of the liver disease, children with preexisting renal failure needed more FiO_2 intraoperatively (* $p<0.05$ was regarded as statistically significant).

Near-infrared spectroscopy measurement

Following induction of anesthesia, the left kidney was identified using ultrasound, and a pediatric (<40 kg BW) or adult (>40 kg) SrO_2 electrode (pediatric or adult INVOS™ system oximetry sensor, Covidien, Minneapolis, MN, USA) was placed on the back over the left kidney. $rSrO_2$ was continuously measured using the INVOS 5100B oximeter sensor system (Covidien, Minneapolis, MN, USA). Measurements were recorded throughout the pLTX until the patient was transferred to the ICU. The 5100B cerebral oximeter generates low-intensity near-infrared light and directs the light onto the patient's skin at wavelengths of 730 and 810 nm. The light penetrates the skin and passes through the tissue. The sensor of the oximeter consists of a light-emitting diode and 2 detectors located at a distance of 3 and 4 cm from the diode.

Data collection

All demographic patient data and laboratory values were taken from the patients' records. Information on drugs and laboratory values were recorded prior to and during the first 7 postoperative days. The hemodynamic parameters were taken from the anesthesia charts. Data were recorded 45 min after the induction of anesthesia, 45 min after the start of the anhepatic phase, and 45 min after reperfusion. Laboratory values were taken from the patients' electronic records.

$rSrO_2$ data were collected automatically every 5 to 6 s and stored in 2.5-min intervals on a computer hard drive for later analysis. For statistical analysis, the mean of $rSrO_2$ was used. A decrease in $rSrO_2$ was defined as a reduction of the $rSrO_2$ for more than 20% for more than 10 min compared to the preparation period. Hemodynamic data and blood gas analysis were taken from the anesthesia protocol. Hemodynamic data and SrO_2 were analyzed every 5 min.

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Table 2. Preoperative patient characteristics and renal function.

diagnosis	Number	Age (months)	No. of children with aszites	Mean PELD	Preop. total bilirubin [mg/dl]	Cystatin C [mg/dl] (min–max)	Creatinine [mg/dl] (min–max)
Biliary atresia	27	7.3±4.7	12	28.6±2.3	13.6±8.1	1.0±0.4	0.23±0.83
SSC	3	71.3±43.8	0	38.0±2.6	5.3±3.2	1.4±0.3	0.34±0.06
Liver failure of unknown origin	2 one child with preop. dialysis	1 & 113	1	30.5±3.5 2×HU	12.4 &1.0	1.55 & 0.66	0.35±0.17
CF	1	175	0	22	0.8	0.77	0.37
Chronic liver failure	1	98	1	28	36.9	1.25	0.29
Connatal CMV infection	1	20	0	35	15.8	0.72	0.21
Budd Chiari	1	64	1	35	1.0	0.74	0.49
Chronic rejection	1	72	0	40	16.7	0.81	0.41
Hepatoblastoma	1	14	0	40.HU	1.0	1.08	0.21
Abernethy malformation type 1b	1	56	0	33	1.5	0.62	0.17
alpha-1 AT deficency	1	37	0	33	3.4	0.79	0.32
Congenital liver fibrosis	1	50	0	30	9.3	0.8	0.47

This Table shows patient characteristics, PELD scores, preoperative bilirubin, and markers for renal failure in the children of our study group subdivided by diagnosis. The concentrations of bilirubin, cystatin C, and creatinine concentrations, as well as the number of children on diuretics, were taken from the patients' charts. The threshold values for cystatin C and creatinine serum concentration were defined according to methods described by Ziegelasch and Lechner and Liebau, respectively [8,9]. Children with increased cystatin C or creatinine concentration 3 months prior to pLTx were regarded as having chronic renal failure.

Statistical analysis

Statistical analysis was performed with SPSS software version 24 (SPSS, Inc., Chicago, IL, USA). The relationship between SrO_2, $rSrO_2$, MAP, creatinine, cystatin C, bilirubin, and other laboratory variables was assessed using Pearson's correlation coefficient. Data were tested for normal distribution using the Kolmogorov-Smirnoff test. Comparisons of the means of the 2 groups were conducted after the Levène test by using paired or unpaired t tests where necessary. Kruskal-Wallis test with Bonferroni correction or χ^2 test were performed to assess significant differences between groups. Stepwise logistic regression was conducted to evaluate the influence of bilirubin on NIRS measurement and renal failure. A p value <0.05 was regarded as statistically significant.

Results

We retrospectively analyzed data on 47 children undergoing pLTx between Jan 2014 and Jan 2017. The group included 26 boys and 21 girls. In 6 children (4 girls and 2 boys), renal NIRS could not be detected due to disruption of the NIRS signal by the electrocautery, as the neutral electrode was also placed on the back of the child.

Demographic data of the remaining 41 children (19 girls and 22 boys) undergoing liver transplantation are listed in Table 1. One child died on day 7 and postoperative laboratory values for this day are missing. Table 2 contains diagnosis and preoperative indications for pLTx as well as renal parameters prior and following pLTx. Most children were transplanted due to extrahepatic biliary atresia. Mean age at transplantation was 26.5±39.0 months. The mean PELD score was 30.2±4.1. One child received the fourth pLTX, 2 infants received the third, and 1 child a second liver transplantation. Three patients were on high urgency status. One child needed hemodialysis prior to pLTx. As there were fewer than 5 deaths, we did not evaluate mortality as an outcome. Two children died within 30 days following pLTx. The 1 child who received preoperative renal replacement therapy died on postoperative day 2.

Table 3. Influence of laboratory values on the $rSrO_2$ (n=41).

		Hemoglobin	Total bilirubin	Na+	K+	Cl–	paO_2	SpO_2	FiO_2	$paCO_2$
$rSrO_2$	Correlation	0.371	−0.487	0.297	−0.147	0.267	0.333	−0.073	0.258	0.021
	p-value	**0.01**	**0.001**	**0.01**	**0.01**	**0.01**	**0.01**	**n.s.**	**0.01**	**n.s.**

Table 4. Differences in perioperative parameters in children with pre- and postoperative normal and pathologic increased values for serum cystatin C concentration.

	Preop, normal values (n=27)	Preop, elevated cystatin C concentration (n=14)	Level of significance	Postop, normal values (n=22)	Postop, elevated cystatin C concentration (n=18)	Level of significance
PELD	13.5±9.3	19.3±9.3	0.068	14.2±8.5	17.7±10.6	0.251
Duration of the transplantation (min)	321.1±74.4	330.4±76.5	0.7	325.81±76.0	310.0±64.2	0.7
Duration of the anhepatic period (min)	89.1±37.6	78.0±29.8	0.314	95.8±36.1	75.9±31.1	0.072
Duration of ICU stay (days)	20.38±20.0	21.4±14.2	0.864	16.3±11.6	26.2±22.2	0.103
Duration of ventilation (days)	5.21±7.7	5.3±7.9	0.977	3.6±4.3	6.9±10.1	0.212
Intraop, transfused erythrocyte concentrate (ml/kg)	33.0±31.7	58.3±45.2	0.046*	37.2±36.5	50.3±40.3	0.298
Intrapo, FFP (ml(kg)	64.3±52.3	69.0±38.1	0.77	70.1±57.6	62.5±31.8	0.603
Intraop, transfusion of thrombocytes (ml/kg)	1.5±4.6	4.8±11.0	0.306	0.9±4.3	5.1±10.1	0.124

Children with preoperative pathologic increase in cystatin C concentration needed significantly more FFP than children with normal preoperative values. * p<0.05 was regarded as statistically significant.

Factors influencing $rSrO_2$ measurement

The rSO_2 measurements were affected by several factors (Table 3).

PELD score

The PELD score inversely correlated with $rSrO_2$ (r=−0.378, p=0.05), indicating that sicker children presented with lower $rSrO_2$.

Laboratory values

Several laboratory values affect the NIRS technology. Correlations are summarized in Table 3. Hemoglobin levels significantly affect NIRS measurements (r=0.371, p<0.001). Lower hemoglobin levels were associated with decreased $rSrO_2$ measurements. Blood gas parameters, which are associated

with renal perfusion and oxygen supply, revealed that $rSrO_2$ was significantly dependent on paO_2.

When comparing children with increased pre- or postoperative cystatin C levels, there was no significant increase in duration of transplantation, anhepatic period, days on ventilation, or ICU stay between groups (Table 4). However, when defining kidney injury by increased serum creatinine concentration, we detected a significant difference in the duration of ICU stay in children with and without kidney injury (Table 5).

Bilirubin

Bilirubin interferes with NIRS measurement. In our study population, the total bilirubin levels dropped significantly from 11.4±9.2 to 4.5±4.1 (r=0.994, p<0.001) during liver transplantation. The level of bilirubin significantly affected the $rSrO_2$ measurement (Table 3).

Table 5. Differences in perioperative parameters in children with pre- and postoperative normal and pathologic increased values for serum creatinine.

	Preop, normal values (n=37)	Preop, elevated creatinine concentration (n=4)	Level of significance	Postop, normal values (n=23)	Postop, elevated creatinine concentration (n=17)	Level of significance
PELD	16.4±9.5	6.8±6.1	0.054	16.1±7.9	14.7±11.6	0.238
Duration of the transplantation (min)	325.8±76.0	310.0±64.0	0.7	310.0±69.3	349.1±75.6	0.097
Duration of the anhepatic period (min)	85.8±36.9	85.3±10.5	0.975	91.5±34.9	80.5±35.1	0.33
Duration of ICU stay (days)	20±17.7	27.5±20.9	0.434	13.9±10.2	29.7±21.5	0.01*
Duration of ventilation (days)	5.1±8.0	1.25±0.5	0.277	4.1±6.7	6.5±8.9	0.361
Intraop, transfused erythrocyte concentrate (ml/kg)	42.8±39.9	33.4±22.9	0.648	49.0±42.7	34.2±29.9	0.241
Intrapo, FFP (ml(kg)	68.6±49.2	42.3±12.7	0.021*	69.2±48.6	63.4±47.7	0.715
Intraop, ransfusion of thrombocytes (ml/kg)	3.0±7.9	0	0.461	2.4±8.2	3.3±6.9	0.729

Children with postoperative pathologic increase in creatinine concentration had significantly longer ICU stays than children with normal values. * p<0.05 was regarded as statistically significant.

Time course of rSrO$_2$ during pLTx and mean arterial pressure

Figure 1 indicates the cumulative results of the temporal course in all 41 children undergoing pLTx (Figure 1). The rSrO$_2$ did not significantly differ between the preparation period (61.1±21.8) and the anhepatic phase (62.4±18.9, p=0.253) but significantly increased in the reperfusion period (65.2±20.7, anhepatic period *vs.* reperfusion: p<0.001) compared to the preparation period.

Mean arterial pressure

Mean arterial pressure was significantly correlated with the renal NIRS measurement (r>0.5, p<0.01) except for the first 10 min following reperfusion (r=027, p=0.165) (Figure 1). MAP increased significantly but without correlation with the rSrO$_2$ measurement.

Preoperative serum cystatin C and creatinine concentration and rSrO$_2$

Fourteen out of 41 children presented with increased preoperative cystatin C levels. Children with increased cystatin C concentrations had significantly lower rSrO$_2$ during pLTx than children without (63.7±4.3 *vs.* 53.4±4.9, p<0.05) (Figure 2A). Stepwise logistic regression revealed that the significant difference in rSrO$_2$ was not due to increased serum bilirubin,

hemoglobin concentration, or FiO$_2$ in these children (cystatin C: regression coefficient −9.979 SE: 5.9, OR: −21.8–1.9 p=0.096, total bilirubin: regression coefficient: −0.557, SE: 0.322, OR: −1.21–0.096, p=0.092. Hb: regression coefficient: 6.599 SE: 0.94, OR: 4.673–8.525, p=0.01, FiO$_2$: regression coefficient: 0.239, SE: 0.07 OR: 0.095–0.382 p=0.106). Before pLTx, serum creatinine concentration was pathologically increased in 4 out of 41 children. There was no statistically significant difference in rSrO$_2$ in children with normal *vs.* increased serum creatinine concentrations (Figure 2B).

Postoperative serum cystatin C and creatinine concentrations and intraoperative rSrO$_2$

Serum cystatin C concentration did not change significantly between preoperative and postoperative values on day 7 (preoperative cystatin C serum concentration was 1.01±0.4 mg/dl and postoperative concentration was 1.03±0.3 mg/dl). We could not detect any significant difference between children with (n=22) preoperative or postoperative elevated (n=18) cystatin C concentrations and the rSrO$_2$ (Figure 3A).

In the study group, 17 out of the 41 children developed kidney failure according to the increase in serum creatinine concentration during the first week after pLTx. There was a tendency to increased rSrO$_2$ in children with postoperative AKI, but this did not reach statistical significance (Figure 3B).
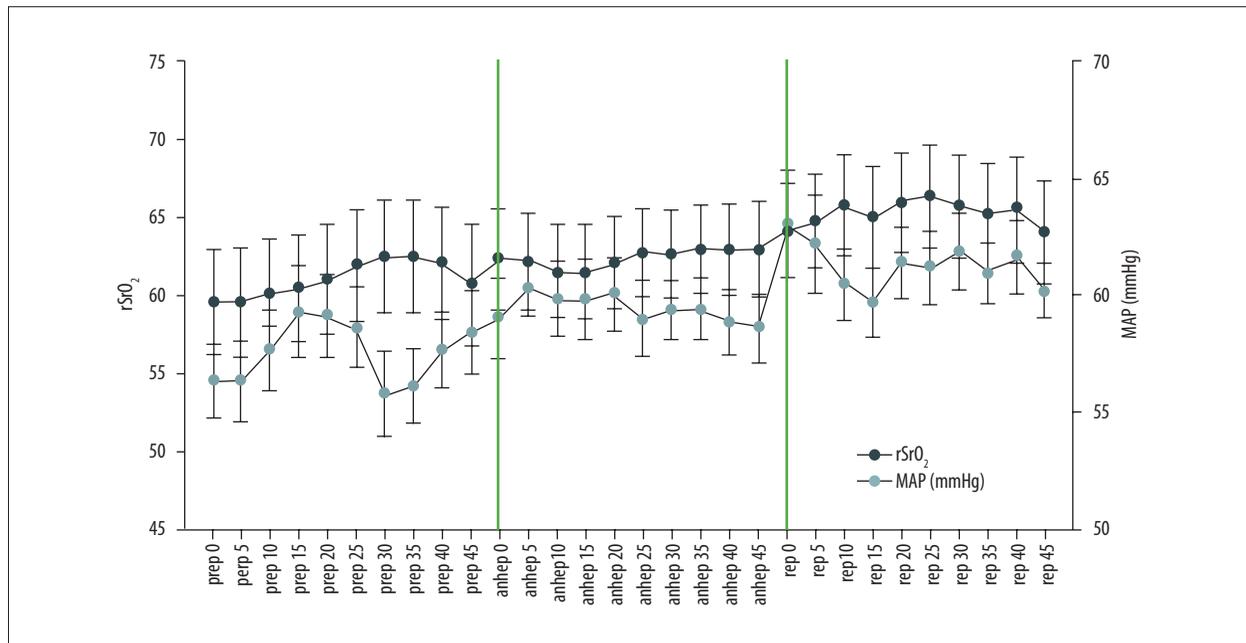
Figure 1. Temporal time course of $rSrO_2$ (●) and mean arterial pressure (MAP) (●). The blots show the time course during the first 45 min following induction of anesthesia, the first 45 min after removal of the liver and the third phase demonstrates the first 45 min following reperfusion. The bars demonstrate the beginning of the anhepatic and the reperfusion period. The $rSrO_2$ (●) increases during LTx. This increase was significant between the preparation and the reperfusion period. The overall mean blood pressure in the preparation period was 57.5±10.2 mmHg, 60.2±10.0 mmHg during the anhepatic phase, and 60.2±9.7 mmHg following reperfusion. We detected a statistically significant difference between the preparation phase and the anhepatic phase of the pLTx (n=41, paired t test, p<0.001). The $rSrO_2$ and the MAP (●) were moderately correlated during pediatric liver transplantation, with the $rSrO_2$ being more stable than the MAP. However, in the period during and following reperfusion, the correlation between $rSrO_2$ and MAP dropped to insignificant levels. The data represent the values during the first 45 min of the preparation period, the anhepatic phase, and the reperfusion period, respectively (n=41, bivariate correlation analysis with Pearson's correlation coefficient, * p<0.05).

Perioperative pRIFLE and intraoperative $rSrO_2$

Children developed renal failure during the first 7 days following transplantation, with a peak on postoperative day 7. During the postoperative period, 11 children developed stage I renal failure according to the pRIFLE criteria, 1 child developed stage II, and 6 children stage III, and 23 children no renal failure. There was a significant difference between the 4 RIFLE stages on postoperative days 2–5 (p<0.05). However, there was no significant difference in intraoperative $rSrO_2$ in children who developed renal failure and those without. A significant correlation between the length of ICU stay (p=0.038) and the development of pRIFLE stage I to III was detected. However, no significant correlation could be shown between PELD score, the duration of the transplantation or mortality, and the development of kidney failure (Figure 4).

Increase or drop in $rSrO_2$ and postoperative kidney injury

Significant alterations in $rSrO_2$ might be associated with postoperative compromised renal function. We examined whether the increase or the drop in $rSrO_2$ for 25% or more for more than 10 min was associated with the worsening of kidney function, defined by an increase in serum cystatin C, creatinine concentration, or pRIFLE criteria. There was no significant increase or decrease in worsening of renal function in children who experienced a drop or increase in $rSrO_2$ of 25% or more (cystatin C, n=10, p=0.421, creatinine concentration, n=6, p=0.477).

Discussion

Renal failure is common in children undergoing pLTx. Due to delayed response in kidney injury, currently available biomarkers provide only delayed information about kidney function. Here, we show that $rSrO_2$ was correlated with renal failure defined by increased preoperative serum cystatin C concentration but not serum creatinine concentration. In addition, the intraoperative increase or decrease in $rSrO_2$ was not associated with the development of postoperative kidney injury defined either by the postoperative increase in serum creatinine concentration, cystatin C concentration, or the pRIFLE criteria. Renal NIRS might provide additional information on renal function during pLTx.
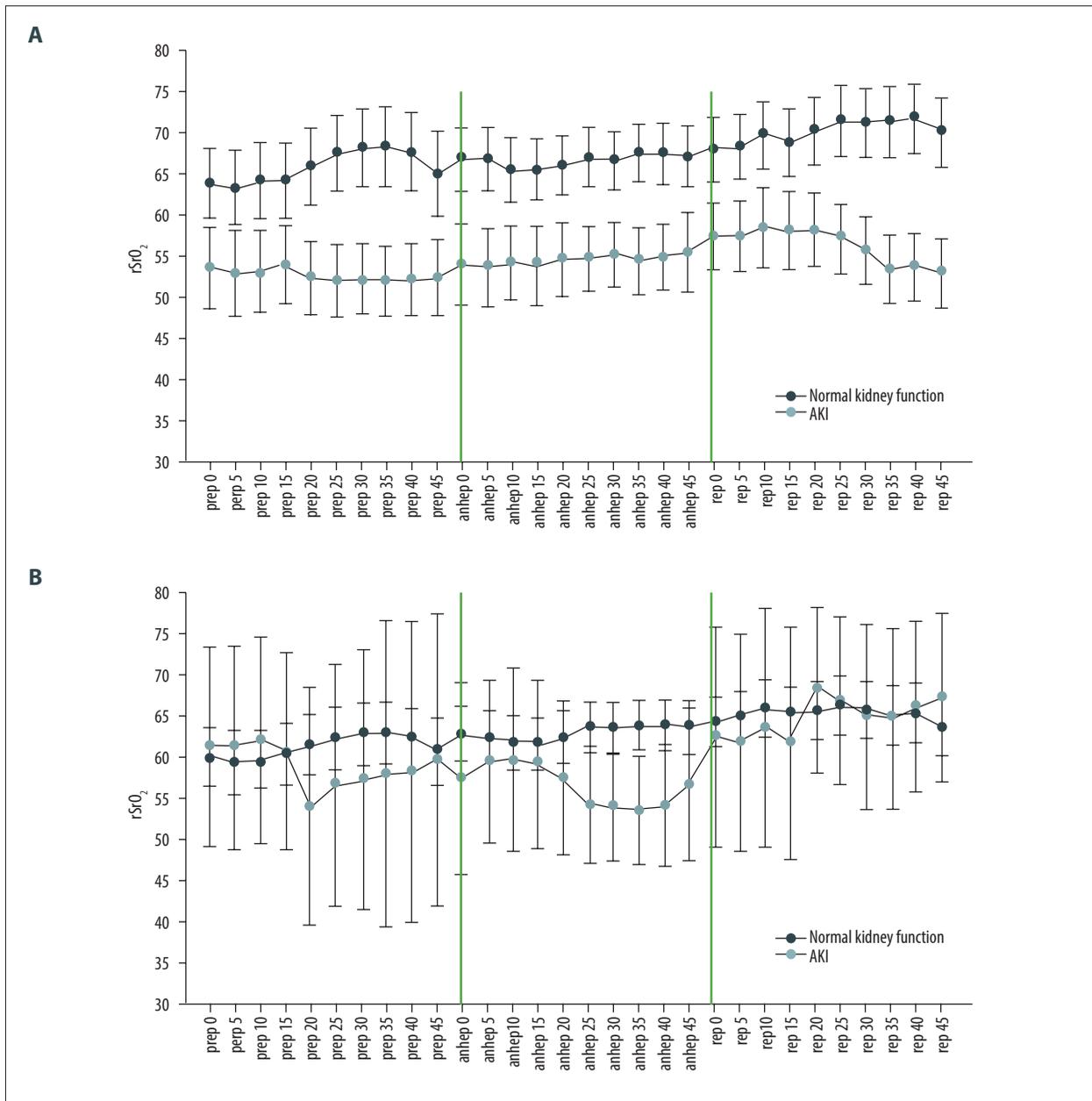
Figure 2. rSrO$_2$ and preoperative serum cystatin C and creatinine concentration. (**A**) rSrO$_2$ in children with preoperative increased cystatin C concentration. Children with increased cystatin C (n=14, ●) had significantly lower rSrO$_2$ than children with normal renal function (n=27, ●). (**B**) rSrO$_2$ in children with preoperative increased cystatin C concentration. There was no significant difference in rSrO$_2$ in children with increased (n=4, ●) and with normal (n=37, ●) creatinine concentration. The green bars indicate the start of the anhepatic and the reperfusion phase (unpaired *t* test, * p<0.05 was regarded as significant).

Renal failure is a common complication in patients with acute or chronic liver disease. In contrast to conditions with multiorgan involvement, like the Alagille Syndrome or metabolic disorders, most children with end-stage liver disease develop AKI secondary to the chronic liver disease they originated during infancy [11,12].

The incidence in children with liver disease is reported to be about 20% [13].

There are several definitions of renal failure in children, including pediatric RIFLE criteria (Pediatric Risk, Injury, Failure, Loss of function and End-stage renal disease), AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease for Improving Global Outcomes) [10]. All clinically relevant definitions of AKI are based on serum creatinine and urine output. However, both parameters are underestimated in children with liver failure [14]. In addition, the definitions for AKI were not developed
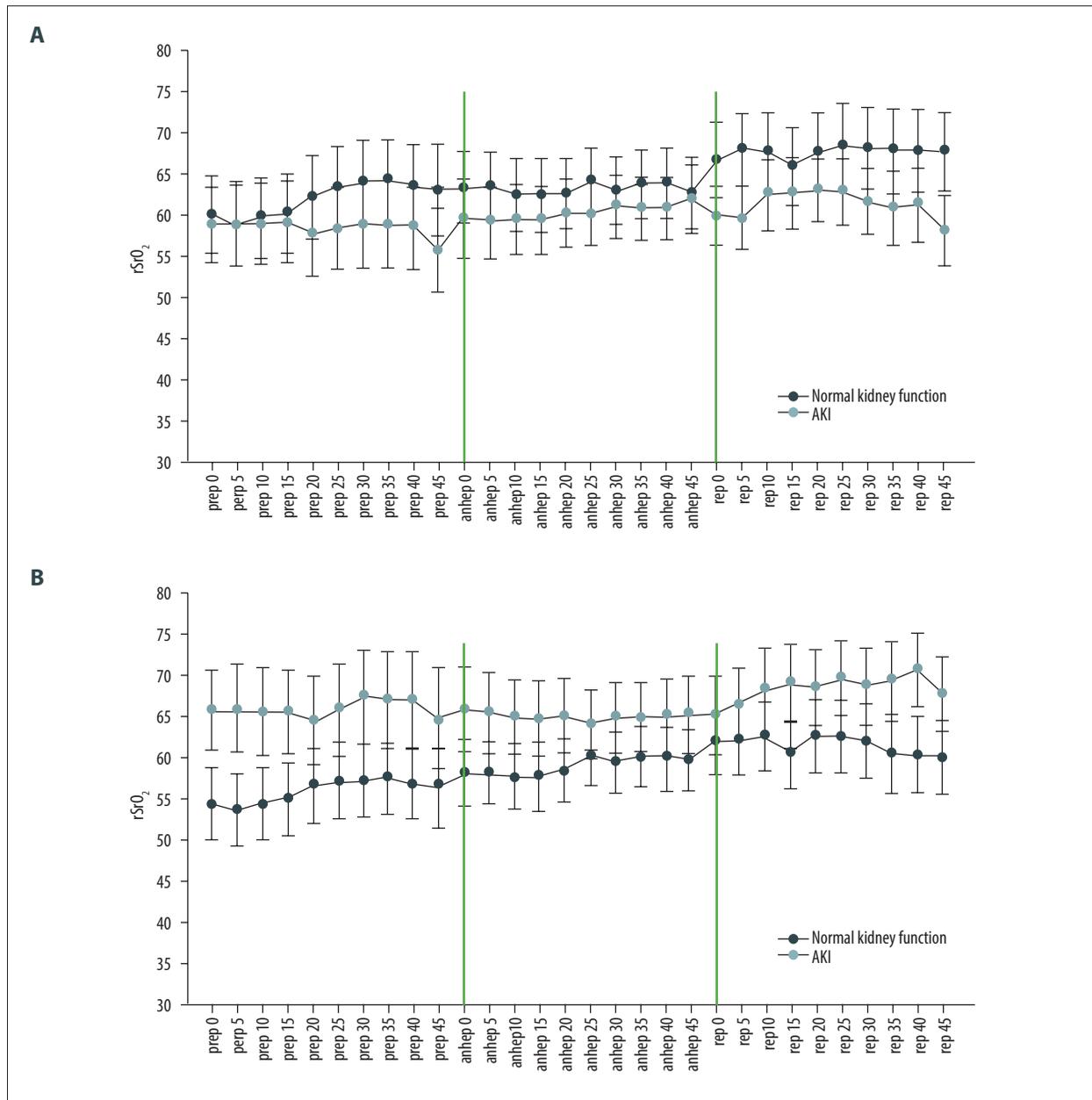
Figure 3. rSrO$_2$ and postoperative serum cystatin C and creatinine concentration. (**A**) Figure **A** demonstrates the rSrO$_2$ in children with postoperative normal (n=22, ●) and kidney injury (n=18, ●) indicated by increased serum cystatin C concentrations. (**B**) rSrO$_2$ in children following LTx with postoperative normal (n=23, ●) and increased (n=17, ●) creatinine concentration. The green bars indicate the start of the anhepatic and the reperfusion phase (unpaired *t* test, * p<0.05 was regarded as significant).

for patients with liver failure and lack standardization and sensitivity [15]. More than 50% of the glomerular function is thought to be lost before the diagnosis of AKI is considered, and this affects prognosis because possible therapy is usually delayed [16]. Cystatin C is a newer biomarker for kidney injury. The concentration is independent of muscle mass and it was shown that it is a reliable marker for assessment of renal dysfunction in children with liver disease and after LTx [17]. In a meta-analysis, cystatin C was reported to have acceptable

prognostic value for the prediction of AKI in children [18]. Due to metabolism and reabsorption, urea nitrogen is a weak parameter for renal failure.

NIRS technology enables non-invasive and real-time measurement of tissue oxygenation. In pediatric cardiac anesthesia, NIRS allows continuous monitoring of non-invasive organ-specific perfusion. Particularly, regional cerebral oxygen saturation (cSrO$_2$) in infants and neonates is now widely accepted as a standard
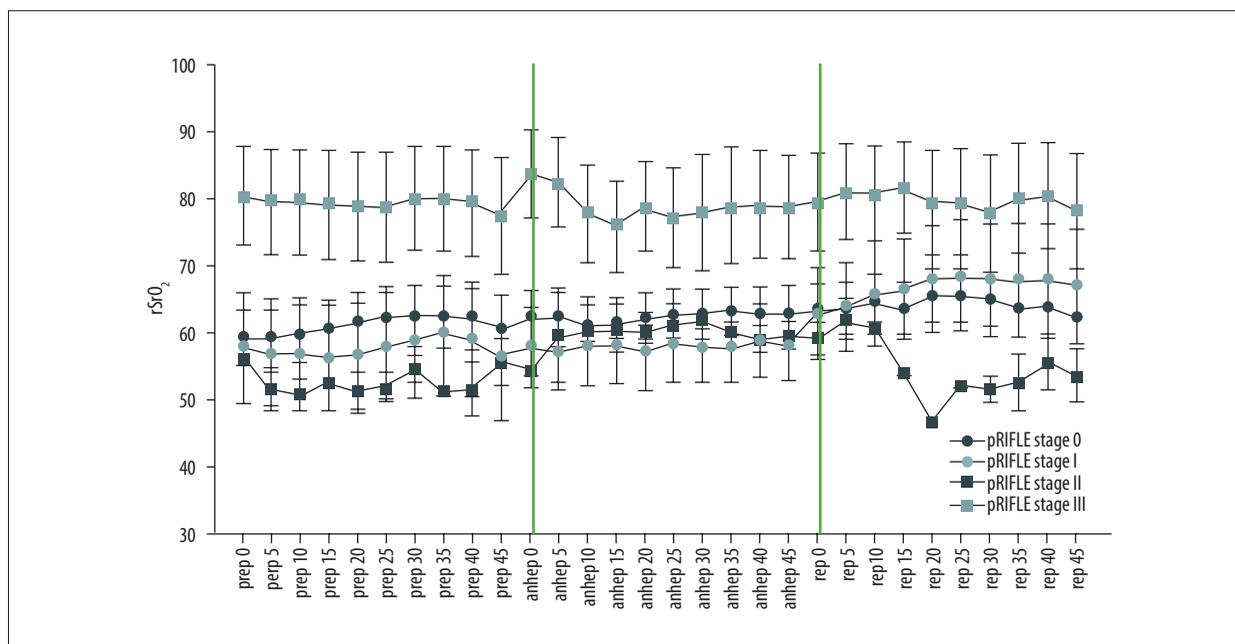
Figure 4. rSrO$_2$ and postoperative AKI according to the pRIFLE criteria. This figure demonstrates the rSrO$_2$ in the children with respect to the pRIFLE criteria. There was no statistically significant difference in rSrO$_2$ in children with the 4 pRIFLE stage 0 (n=27), stage I (n=2), and stage III (n=3). However, children with pRIFLE stage III had a tendency to elevated rSrO$_2$ compared to the other 2 stages (p<0.05 was regarded as statistically significant). The green bars indicate the start of the anhepatic and the reperfusion phase.

monitoring tool to detect oxygenation. Perfusion mismatch and low cSrO$_2$ values were associated with poorer patient outcome or longer hospitalization [19]. NIRS technology is affected by various laboratory parameters. As shown previously for cSrO$_2$, total and unconjugated bilirubin significantly influence rSrO$_2$ during LTx [20,21]. rSrO$_2$ is significantly correlated with the hemoglobin concentration. In addition, we detected a significant positive correlation between serum Na$^+$ and Cl$^-$ concentrations and a negative correlation for K$^+$ and cSrO$_2$. These electrolytes may represent indirect parameters for the severity of liver disease resulting in skin edema formation or renal dysfunction [22,23]. We detected a significant correlation between rSrO$_2$ and the PELD scores in our study population. The PELD score reflects waiting time and severity of liver disease in children up to 12 years of age. The calculating factors include age, international normalized ratio, bilirubin and albumin concentrations, a history of growth failure, and time on the waiting list.

In our study, we could not find a correlation between markers of renal failure and rSrO$_2$. In contrast to other studies, we did not detect an association between the intraoperative increase or decrease of 25% or more in rSrO$_2$ compared to baseline and postoperative renal failure according to the pRIFLE criteria, the serum creatinine, or the cystatin C concentration [24].

Several studies in pediatric cardiac surgery in which the correlation of rSrO$_2$ with postoperative AKI revealed only inconsistent results, which might be explained by the different definitions for AKI used in the studies [3–6]. When using the pRFILE criteria to define AKI, 2 studies demonstrated a significant correlation between intra- or postoperative AKI and a decrease in rSrO$_2$ compared to children with normal kidney function [3,4,6]. Hazle et al. found a significant correlation of AKI defined by various urinary biomarkers and the cumulative time of NIRS < 50% [4]. However, in children following aortic arch repair, no significant correlation between the development of AKI and rSrO$_2$ was found [5]; For the estimation of creatinine concentration, they also used the Schwartz formula and determined the threshold according to the pRIFLE criteria. In a recently published trial, serum creatinine concentrations were used to define AKI according to the pRIFLE criteria in children undergoing cardiac surgery with cardiopulmonary bypass. As in our study, when comparing rSrO$_2$ with the development of renal failure, they also detected an increased rSrO$_2$ in the children who presented with postoperative renal failure [7]. In children undergoing kidney transplantation, postoperative renal rSrO$_2$ assessed by NIRS strongly correlates with common markers of kidney graft function and perfusion, allowing continuous real-time monitoring of blood flow in renal grafts by NIRS [25].

There are several definitions of AKI in children [10], and the incidence of AKI depends on the definition of AKI [10]. Serum cystatin C concentration seems to be a more reliable indicator, especially in children with liver failure, than serum

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creatinine-derived values [16,17,26]. Additional, there are several other reasons for the development of renal failure in children undergoing pLTx, including immunosuppression (e.g., with ciclosporin which has profound effects on renal function) [27].

The present study has several limitations. Due to its retrospective design, postoperative cystatin C values were only available on the 7th day after liver transplantation. We did not determine edema and could not determine the impact of skin perfusion or the impact of invasive ventilation on NIRS measurement.

Conclusions

In this retrospective study, we show that decreased rSrO$_2$ during pLTx indicates compromised renal function as represented by increased serum cystatin C concentration. rSrO$_2$ did not correlate with preoperative serum creatinine concentration. In addition, intraoperative renal NIRS did not predict postoperative renal failure, indicated by increased postoperative serum cystatin C, serum creatinine concentration, or pRILFE. Renal NIRS indicated compromised renal function and can be included in pLTx. The role in therapeutic interventions needs to be evaluated in prospective studies.

Conflict of interest

None.

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