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RĪGAS STRADIŅA UNIVERSITĀTE

Jēkabs Krastiņš

PERIOPERATIVE DYNAMICS OF RENAL FUNCTIONAL AND STRUCTURAL DAMAGE MARKERS IN CHILDREN, UNDERGOING OPEN HEART SURGERY

Summary of the Doctoral Thesis
for obtaining the degree of a Doctor of Medicine
Specialty – Anaesthesiology and Intensive Care

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The Doctoral Thesis was carried out at Rīga Stradiņš University, Children`s Clinical University Hospital, Clinics for Anesthesiology and Intensive Care, Clinic for Pediatric Cardiology and Cardiac Surgery

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Dr. med., Associate Professor **Iveta Dzīvīte-Krišāne**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACS	Abdominal compartment syndrome
ADQI	Acute dialysis quality initiative
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ARF	Acute renal failure
ATN	Acute tubular necrosis
AUC	Area under the curve
CHD	Congenital heart disease
CI	Confidence interval
ClCr	Creatinine clearance
CPB	Cardiopulmonary bypass
CRRT	Continous renal replacement therapy
CSA-AKI	Cardiac surgery associated AKI
CVP	Central venous pressure
Cys C	Cystatin C
eClCr	Estimated ClCr
FABP	Fatty-acid-binding protein
FB	Fluid balance
FeNa	The Fractional Excretion of Sodium
FeUrea	The Fractional Excretion of Urea
FST	Furosemide stress test
GFR	Glomerular filtration rate
GST-π	Placental glutathione S–transferase
HD	Hemodyalisis
IAH	Intraabdominal hypertension
IAP	Intraabdominal pressure
IGFPB-7	Insulin-like growth factor-binding protein 7
IHD	Intermittent hemodialysis
IL-18	Interleukin-18
IL-6	Interleukin-6
IQR	Interquartile range

KDIGO	Kidney diseases improving global outcome
KIM-1	Kidney injury molecules-1
LCOS	Low cardiac output syndrome
LD	Loop diuretic
LOS	Lengths of stay
MAP	Mean arterial pressure
MODS	Multiple organ dysfunction syndrome
MV	Mechanical ventilation
NGAL	Neutrophil gelatinase–associated lipocalin
OR	Odds ratio
PD	Peritoneal dialysis
POD	Postoperative day
RACHS-1	Risk assessement for congenital heart surgery-1
RBF	Renal blood flow
RIFLE	Risk, injury, failure, loss of functions, end–stage renal disease
ROC	Receiver–operator curve
RRT	Renal replacement therapy
RVO_2	Renal oxygen consumtion
SCr	Serum creatinine
SCys C	Serums Cystatin C
SD	Standard deviation
TBW	Total body water
TIMP-2	Tissue metallopeptidase inhibitor 2
uCys C	Urinary Cystatin C
UF	Ultrafiltration
UMS	Urine microscopy score
uNGAL	Urinary NGAL
UO	Urine output
VIS	Vasoactive inotrope score

INTRODUCTION

Kidneys participate in all vital processes of the body to maintain overall homeostasis. These organs receive 20% of cardiac output and are central to numerous homeostatic control mechanisms, including water balance, electrolyte handling, erythropoiesis, vascular tone, acid-base status, regulation of normal glucose metabolism and assist with detoxification and excretion of metabolites and drugs. Kidneys also moderate communication with other organs, such as heart, lung, brain, intestines and liver, and compensate the internal environment when these organs go into states of dysfunction [1]. Thus, during surgical interventions, when kidneys are injured, metabolic and hemodynamic control is disrupted. Advances in surgical techniques, medical devices, and anesthetic procedures have allowed clinicians to perform organ transplants, insert artificial devices, and conduct complex surgeries that not too long ago would have been considered high risk to perform. Now, over 200 million surgical procedures are performed worldwide. However, the number of hospitalizations that include AKI have risen to epidemic proportions, with an over eightfold increase in last decade [2]. With the central role of kidneys in precisely maintaining the internal milieu, it follows that surgeries complicated by kidney injury and dysfunction are associated with greater perioperative mortality, length of hospital stay and cost.

Pediatric patients comprise an ideal and informative population for the study of AKI biomarkers as they do not exhibit common adult confounding factors that complicate similar studies in adults, such as diabetes, hypertension, atherosclerosis, and nephrotoxin use [3].

Aim of the study

The aim of study was to investigate perioperative dynamics of kidney injury markers and to identify early and sensitive marker of kidney injury, suitable for application in children, undergoing open heart surgery for correction of congenital heart lesions.

Objectives

1. To establish prevalence and severity of AKI in children after open heart surgery, using KDIGO criteria.
2. To investigate the accuracy and diagnostic performance of structural and functional kidney injury markers.
3. To investigate postoperative fluid balance and it's association with renal dysfunction.
4. To evaluate the role of intraoperative hypotension in the development of postoperative AKI:
    - Urinary NGAL
    - Serum Cystatin C
5. To evaluate early clinical outcomes of AKI in children after open heart surgery.
6. To create an algorithm of diagnosis and management of AKI after pediatric open-heart surgery, based on postoperative fluid balance.

Hypothesis

1. Body fluid balance can be used as a marker of postoperative renal dysfunction.
2. Systemic arterial pressure is a determinant of renal oxygen supply and intraoperative hypotension is associated with postoperative AKI.

Importance of the problem

Despite more than half a century of investigation, acute kidney injury (AKI) remains a major healthcare issue in medicine today. Furthermore, the incidence of AKI is increasing. Based on a large administrative database study of hospital admissions from 1992 to 2001, Xue et al. estimated an 11% increase per year in the incidence of AKI [4]. Sanchez-Pinto et al. [5] have utilized a regional clinical database to investigate the link between AKI progression and death in over 8000 critically ill children over almost a decade. **AKI incidence was almost 10%, with 10-fold increased mortality in patients with AKI compared with those patients with intact renal function.** As expected, patients with worse AKI had greater mortality. Patients with persistent AKI throughout the PICU stay **had four-fold higher mortality than patients who had resolved AKI**. In fact**, patients who had resolved AKI still had almost five-fold higher mortality than patients who never have had AKI**. Today, postoperative renal dysfunction is becoming the next major target for investigation. Kidneys have long been thought of as a resilient organ able to endure significant stress and injury during other systemic illnesses. However, more recently we have learnt of the independent negative influence AKI has on patient outcomes [6]. In the largest cohort to date, Aydin et al. [7] demonstrated a 51% incidence of AKI, and when limiting the analysis to neonates, 60% were

affected. Importantly, AKI was found to be independently associated with a prolonged ICU and hospital length of stay and prolonged duration of mechanical ventilation. Similar findings were reported by Li et al. [8] in a prospective mulitcenter study, with a 41% incidence of AKI in children undergoing CPB, which was associated with the same morbidities. Insults related to the provision of CPB are largely responsible for kidney injury, where the duration of bypass directly correlates with the degree of renal injury. Furthermore, despite considerable advances in diagnosis and management of severe AKI, including renal replacement therapy (RRT), mortality for this subgroup is 40–83% [9]. These wide ranges can be explained by lack of comparability of case mix, use of different criteria for diagnosis and classification of AKI and need for RRT [10].

Scientific novelty

1. One of the first clinical studies on epidemiology and early outcome of AKI after pediatric cardiac surgery.
2. The first study, evaluating accuracy and predictive ability of renal structural and functional injury markers and investigating the impact of postoperative fluid balance on the development of AKI in children after surgical correction of congenital heart lesions.

1 MATERIAL AND METHODS

1.1 Setting

The study was conducted in the Clinics of Anesthesiology and Intensive Care and Cardiology and Cardiac Surgery at the University Children's Clinical Hospital.

RACHS-1 consensus-based scoring system to categorize the complexity of surgery [11] was applied. This method of risk stratification has emerged as a widely accepted tool for the evaluation of differences in outcomes of surgery for congenital heart disease.

1.2 Inclusion and exclusion criteria

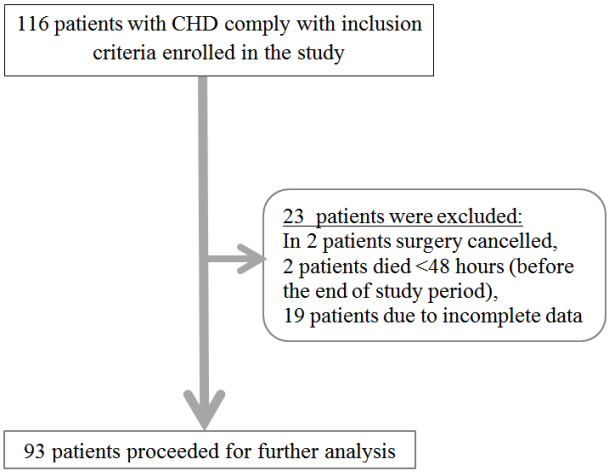


Fig. 1.1 **Patient flow diagram**

Children undergoing elective CPB for surgical correction or palliation of congenital heart lesions between January 2011 and June 2015 were prospectively enrolled (Fig. 1.1). Exclusion criteria included preexisting renal dysfunction. Renal insufficiency was defined as a SCr level that was greater than the 90th percentile for the child's age and gender. Patients with a history of potential nephrotoxin use during the preoperative day were excluded because of potential confounding effects on urinary NGAL measurements.

1.3 Ethical statement

This prospective nonrandomized observational study, without any specific intervention, was reviewed and approved by University Children's Hospital Ethics board and all data were anonymously processed.

1.4 Study design

This was a prospective, non-randomized observational cohort study. All kidney injury markers were taken at baseline, then 12, 24 and 48 hours after completion of surgical repair (Fig. 1.2).

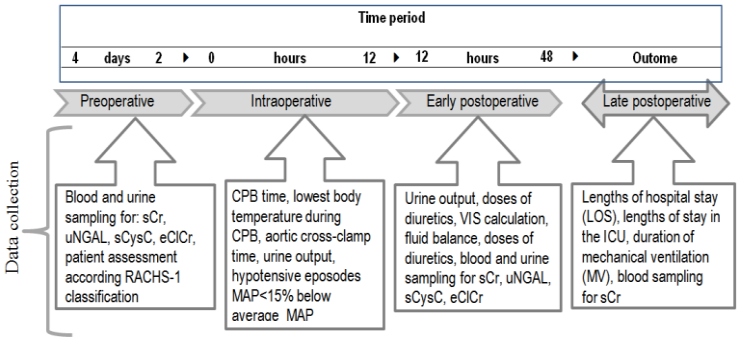


Fig. 1.2 **Study design**

Other variables (CPB time, lowest body temperature, aortic cross-clamp time, urine output, duration of intraoperative hypotension, doses of diuretics, VIS calculation, fluid balance, lengths of hospital stay (LOS), lengths of stay in the ICU, duration of mechanical ventilation were retrieved from the Clinical Information system *Intelly View Clinical Information Portfolio®,* (Philps).

1.5 Sample collection and processing

Creatinine concentrations were measured in the hospital's clinical chemical laboratory Jaffes method on a Cobas 8000 analyzer. SCys C was analized using particle-enhanced turbidimetric immunoassay (PETIA) for the quantitative determination, using COBAS C 501 analyzer.

Serial urine samples from 93 children undergoing CPB were assayed for uNGAL using the latest uNGAL chemiluminescent microparticle immunoassay developed for a standardized clinical platform (ARCHITECT analyzer, Abbott Diagnostics Division, Abbott Laboratories, Abbott Park, IL, USA) in the Laboratory of Renal Transplants Centre, Stradin's Clinical University Hospital. Urine samples were collected using a bladder catheter.

All samples were obtained at at the following time points: (1) preoperative; (2) 12 hours after the surgical repair, (3) 24 hours after the second probe (4) 24 hours after the third probe. Urine samples were left refrigerated for sedimentation for 2 to 3 hours, aliquoted and stored within twelve hours after collection at −80ºC until the assay.

The primary outcome variable was the development of AKI. AKI was defined according the KDIGO classification and staging system based on urine output and SCr level: Stage I was SCr 1.5–1.9 times baseline ≥26.5 μmol/L increase or UO < 0.5 mL/kg/h for 6–12 hours, stage II was SCr 2–2.9 times baseline and UO < 0.5 mL/kg/h for ≥12 hours , stage III was SCr 3 times baseline

or ≥354 μmol/L and/or UO < 0.3 mL/kg/h for ≥24 hours OR anuria for ≥12 hours [12].

Recorded variables included age, gender, CPB time, lowest temperature during CPB and urine output, doses of diuretics, inotropes and vasopressors, postoperative fluid balance. Outcome variables included percent change in serum creatinine, days in AKI, dialysis requirement, duration of MV, lengths of stay in ICU and hospital LOS.

1.6 Anesthesia management

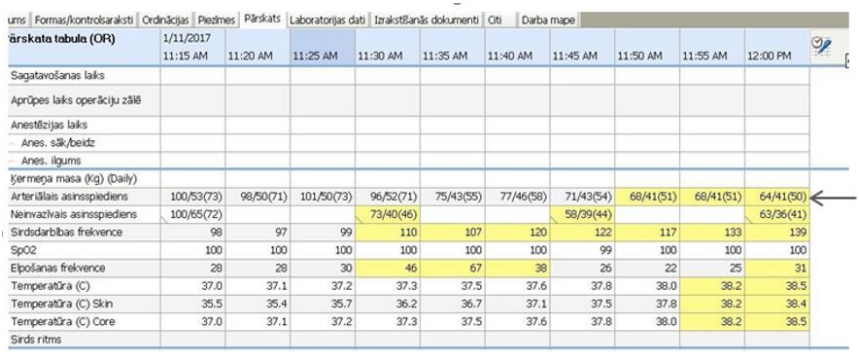
Induction to anesthesia was provided using inhalation of Sevoflurane by face mask or intravenously by Propofol or Midazolam in combination with Ketamine. Anesthesia was maintained at (0.8–1.0 minimal alveolar concentration) of sevoflurane and fentanyl (3–5 μg kg/h) using Primus anesthesia machine (Drãger Medical, Lübeck, Germany). Muscle relaxation was achieved with pipecuronium (0.6 mg/kg). During CPB, isoflurane was applied via the CPB circuit. All patients were ventilated in a volume-controlled mode; with a tidal volume of 6 mL/kg and respiratory rate adjusted to achieve normocapnia. The heart-lung machine SORIN S 5 (LivaNova, United Kingdom) with a membrane oxygenator Affinity Pixie® Oxygenatior (Medrtronics, USA) for neonates, infants and small children requiring cardiopulmonary bypass at flow rates up to 2.0 L/min. was used. For older patients Terumo, Medtronic C oxygenator with CPB circuit was used. Surgical procedures were performed with CPB in moderate hypothermia. Cardioplegic arrest was achieved by cold blood cardioplegia and repeated every 20 minutes. Nonpulsatile perfusion was performed during CPB. Pump flow, oxygen flow, and MAP were adjusted to maintain $ScvO_2$ levels within the preoperative range and at least higher than 50% absolute. In patients monitored with pulmonary artery catheter (PAC),

hemodynamic therapy was titrated to achieve cardiac index > 2.2 L/min/m^2 and mixed venous oxygen saturation (Sv O_2) greater than 65%.

Fluid therapy was performed with balanced crystalloid (Lactated Ringers solution, Sterofundin VG, BBraun; Melsungen, Germany). Pump prime consisted of various amounts of Ringer lactate and whole blood, depending on estimated blood volume, hematocrit, and total priming volume used. Hypothermic myocardial protection was provided by core cooling at flow rates of 150 to 200 mL/kg/ min. (2.0 to 3.0 kg) or 100 to 150 mL/kg/min. (3.0 to 5.0 kg) to rectal and esophageal temperatures of ≤ 30°C, followed by aortic cross clamping. Once optimal hypothermic temperatures were reached, continuous low-flow cardiopulmonary bypass was instituted during completion of intracardiac stage. Core rewarming was instituted during completion of the intracardial stage. Mean perfusion pressures were maintained between 30 mm Hg and 70 mm Hg during rewarming. All patients were weaned from cardiopulmonary bypass after the rectal temperature reached 35°C. Lactated Ringers, fresh whole blood, blood products, and increased inotropic support were given as necessary to maintain normal filling pressures and a systolic perfusion pressure of at least 60 mm Hg.

1.7 Evaluation of intraoperative hypotension

Blood pressure in all patients was measured by means of an intra-arterial (radial or femoral) line (systolic, diastolic and mean) with Philips Vital signs monitor and stored automatically every 5 minutes (300 sec. or 12 times during one hour) in the patient data management system (Philips IntelliView Clinical Information Portfolio, ICIP).



ums | Formas/kontrolsaraksti | Ordinācijas | Piezīmes | Pārskats | Laboratorijas dati | Izrakstīšanās dokumenti | Citi | Darba mape

ārskata tabula (OR)	1/11/2017 11:15 AM	11:20 AM	11:25 AM	11:30 AM	11:35 AM	11:40 AM	11:45 AM	11:50 AM	11:55 AM	12:00 PM
Sagatavošanas laiks										
Aprūpes laiks operāciju zālē										
Anestēzijas laiks										
Anes. sāk/beidz										
Anes. ilgums										
Ķermeņa masa (Kg) (Daily)										
Arteriālais asinsspiediens	100/53(73)	98/50(71)	101/50(73)	96/52(71)	75/43(55)	77/46(58)	71/43(54)	68/41(51)	68/41(51)	64/41(50)
Neinvazīvais asinsspiediens	100/65(72)			73/40(46)			58/39(44)			63/36(41)
Sirdsdarbības frekvence	98	97	99	110	107	120	122	117	133	139
SpO2	100	100	100	100	100	100	99	100	100	100
Elpošanas frekvence	28	28	30	46	67	38	26	22	25	31
Temperatūra (C)	37.0	37.1	37.2	37.3	37.5	37.6	37.8	38.0	38.2	38.5
Temperatūra (C) Skin	35.5	35.4	35.7	36.2	36.7	37.1	37.5	37.8	38.2	38.4
Temperatūra (C) Core	37.0	37.1	37.2	37.3	37.5	37.6	37.8	38.0	38.2	38.5
Sirds ritms										

Fig. 1.3 **Screenshot from anesthesia flowchart, generated by IntelliView Clinical Information Portfolio® (Philips)**
Systolic, diastolic and mean arterial pressure recordings during anesthesia (Indicated by arrow)

MAP data were extracted from anesthesia charts and transfered to MS Excell spredsheets for further processing. Then an average of all validated MAP recordings was calculated for each patient. Hypotension was defined as a MAP < 15% less than averagee MAP value. Then all MAP recordings were compared to average (except MAP recordings during CPB, when pulsatile blood flow was absent). Ratio of hypotensive MAP recordings (MAP < 15% less than averagee MAP value) to total MAP recordings was calculated and expressed as %. Artefacts (arterial cannulae flushing, sensor calibration etc. were marked by operator).

1.8 Fluid balance calculations

Intraoperative fluid intake was assessed by totaling the intravenous fluids, cardioplegia volume, and pump volume (total volume added during cardiopulmonary bypass plus reservoir volume at the start of cardiopulmonary bypass minus reservoir volume at the termination of cardio-pulmonary bypass).

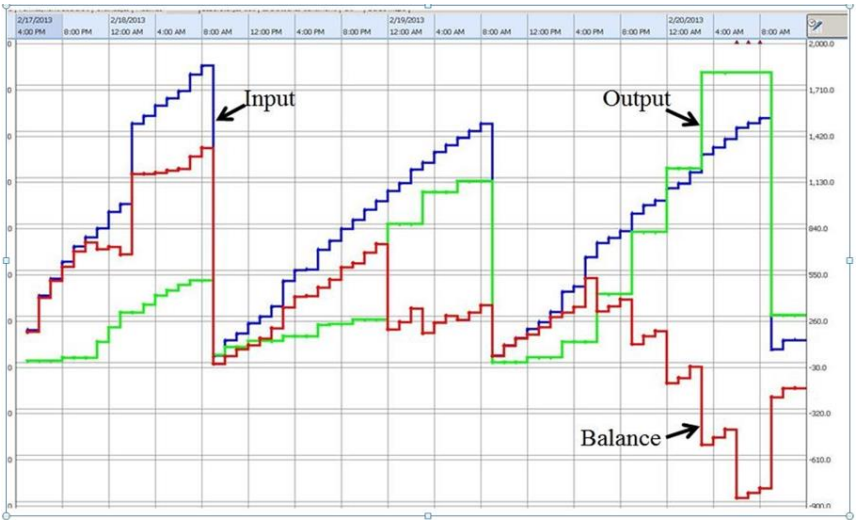


Fig. 1.4 **Postoperative fluid balance**
Screenshot from IntelliView Clinical Information Portfolio® (Philips)

Fluid balance calculations Intraoperative fluid output was the total of urine produced on cardiopulmonary bypass, chest tube drainage before the patient left the operating room, and estimated blood loss. Intraoperative net fluid balance was the difference between fluid intake and output. Data for further processing were retrieved from anesthesia and intensive care data management system flowsheets (Fig. 1.4). Similarly, fluid balance was calculated after the completion of surgical repair. Patient data were collected from day of admission to Intensive care (denoted as POD-1).

1.9. Postoperative management

Analgesia and sedation were provided by a continuous fentanyl or morphine infusion, typically 2–4 $\mu g \times kg^{-1} \times h^{-1}$ and Midazolam or Dexmedetomidine. Routine continuous postoperative monitoring included the surface ECG, transcutaneous pulse oximetry, pulmonary arterial and right and left atrial

pressures (through transthoracic catheters), and systemic arterial pressure. Inotropic, chronotropic, and afterload reducing agents were used as clinically indicated. Vasoactive medications are typically started in the operating room at the discretion of the attending cardiac surgeon and anesthesiologist based on individual patient characteristics, including, residual lesions, transesophageal echocardiographic findings, and physiological status. On arrival to the ICU, medications are adjusted by the bedside nurse under the direction of the ICU team. Patients with hypotension typically receive norepinephrine and epinephrine initially, Volume infusions (Plasma or 5% albumin) were given to maintain adequate filling pressures with systolic perfusion pressures of at least 50 mm Hg. Diuretics (usually furosemide 1 to 2 mg/kg per dose, two to four times daily) were prescribed at the attending physician's discretion if a targeted fluid balance or urine output of > 0.5 mL/kg/hour could not be achieved. Some patients received continuous infusion of Furosemide and Aminophilline.During the study continuous fentanyl or morphine infusions were discontinued on the first postoperative morning in the hemodynamically stable patient or continued for longer periods as dictated by the clinical status of the patient. Mechanic ventilation was provided with Viasys Avea ventilator (Cardinal Health, USA). At the mode suitable for specific cardiac lesion. The rate of weaning of mechanical ventilation was determined by the patient's fluid balance and gas exchange as indicated by arterial blood sampling, pattern of breathing, and daily radiographic findings.VIS score was calculated according the formula [13]:

VIS = 1 dopamine (μg/kg per minute) + 1 dobutamine (μg/kg per minute) + 10 milrinone (μg/kg per minute) + 100 epinephrine (μg/kg per minute) + 100 norepinephrine (μg/kg per minute) + 1000 vasopressin (expressed as U/kg per minute).

The initial mode of ventilation was pressure-regulated volume control in all patients. Once the patient was breathing spontaneously and ready for weaning,

the ventilator mode was switched to pressure-controlled, synchronized, intermittent, mandatory ventilation.

The criteria for extubation was protocolized, as follows: stable hemodynamic profile, normal cardiac rhythm, adequate oxygenation on fraction of inspired oxygen < 0.4, maintenance of a pH > 7.35, and $PacCO_2$ < 45 mm Hg on continuous positive airway pressure < 6 cm H_2O with pressure support < 8 cm H_2O for at least 1 h, the level of consciousness consistent with adequate airway protective reflexes, absence of accessory respiratory muscle recruitment, and approval by the attending intensivists. Corticosteroids were routinely administrated 4 to 6 h before extubation. All patients were monitored with invasive arterial and central blood pressure monitoring. In patients undergoing complex cardiac surgery left atrial or pulmonary artery catheter was inserted during surgical repair. Transesophageal echocardiography was performed in all valve surgery cases. Cerebral oxygen saturation (ScO_2) was determined in all patients with an INVOS 5100 monitor (Somanetics, Troy, USA). All patients received routine standard of care during the study period which included the use of dextrose-containing crystalloid solutions (Sterofundin HEG, Sterofundin BG, Sterofundin VG (BBraun, Melsungen, 50–80 mL/kg/day) during the first 24–48 hours postoperatively, followed by the initiation of enteral tube feeding.

1.10 Staistical methods

Unless indicated otherwise, continuous data are expressed as median values with interquartile range (IQR) and discrete data as numbers with percentages (%). Patients were grouped according to whether they lacked AKI or had AKI within 48 hours following CPB. Clinical characteristics and biomarker levels were compared between AKI- and non-AKI patients using Student’s t test for normally distributed continuous variables, Mann-Whitney

U test was performed for non-normally distributed continuous variables and Pearson's χ^2 or Fisher's exact test, (as appropriate) was performed on all categorical variables. Statistical significance was defined as a probability value less than 0.05.

Univariate logistic analysis was performed to examine the relationship between multiple clinical variables as well as the presence of AKI and clinical outcomes (ICU length of stay, hospital length of stay, duration of mechanical ventilation, and in-hospital mortality). Variables with a probability value less than 0.1 were then cast into a multivariate logistic regression analysis. Odds ratio, CI, and probability values were calculated. All univariate and multivariate logistic regression analyses were conducted for the entire cohort. Receiver operating characteristics (ROC) curves were generated for the occurrence of AKI within 48 hours following cardiopulmaonary bypass using biomarker levels at four different time points (baseline, 12 hours, 24 hours and 48 hours). The areas under the curve (AUC), with 95% confidence intervals (95% CI), were calculated. Also, for each time point the optimal cut-of value was calculated with corresponding sensitivity and specificity. Using those cut-of values, sensitivity and specificity of both biomarkers for predicting AKI were calculated for patients who developed AKI. Two-sided $p = 0.05$ was considered the limit of significance in all analyses. Data were analyzed using IBM SPSS statistics version 21 (Statistical Package for the Social Sciences, Chicago, IL).

2 RESULTS

2.1 Cochort characteristics

Majority from 93 included patients 54 (58%) were less than 12 months old, 6 patients (6.45%) were less than 1 months old, 20 (21.51%) patients were between 1 and 6 months of age; patients at age of 7 to 12 months were 28 (30.11%). Age group of 1 to 3 years represents 23 (24.73%) children.

Table 2.1

Age structure

Age group	No of pts	(%)
Less than 1 month	6	6.45
1 < 6 months	20	21.51
7 < 12 months	28	30.11
1 < 3 years	23	24.73
3 < 7 years	6	6.45
7 years and older	10	10.75
Total:	93	100.00

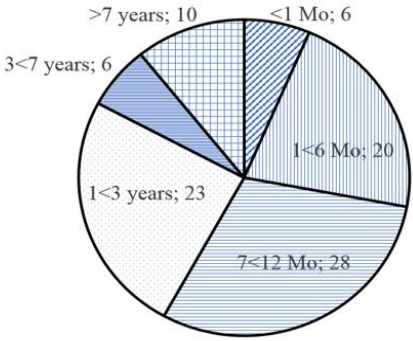


Fig. 2.1 **Age distribution of patients**

Table 2.2

Demographic data

Variable	Median	IQR (Q1-Q3)	Range
Age, months	10.0	6.0–17	0.2–180.0
Body weight (kg)	7.6	5.6–10	2.6–60.0
M/F ratio:	35/58	–	–

Types of congenital heart lesions undergoing surgical repair are summarized in Table 2.3:

Table 2.3

Types of surgical intervention

Surgical intervention	No of pts	%
AVSD (atrioventricular septal defect) repair	20	21.51
Double outlet right ventricle (DORV)	3	3.23
Pulmonary stenosis repair	5	5.38
Tricuspid regurgitation repair	2	2.15
Unifocalization procedure	2	2.15
Aortic stenosis repair	3	3.23
VSD (ventricular septal defect) repair	37	39.78
Mitral valve plastics	2	2.15
TAPVD (total anomalous pulmonary vein drainage)	4	4.30
TGA (transposition of great arteries)	6	6.45
TOF (tetralogy of Fallot)	9	9.68
Total:	93	100.00

Postoperative AKI occurred in 42 (45.16%) from 93 children. 37 of them reached severity stage I according the KDIGO classification and stating system, 3 reached stage II and two reached stage III, based on SCr and (or) urine output criteria (Fig. 2.2).

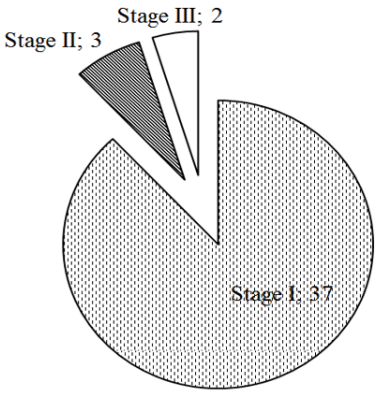


Fig. 2.2 **Severity of AKI**

Fig. 2.3 shows changes in % from the baseline SCr concentration to maximum during 48 hours. It represents number of patients for each AKI severity stage.

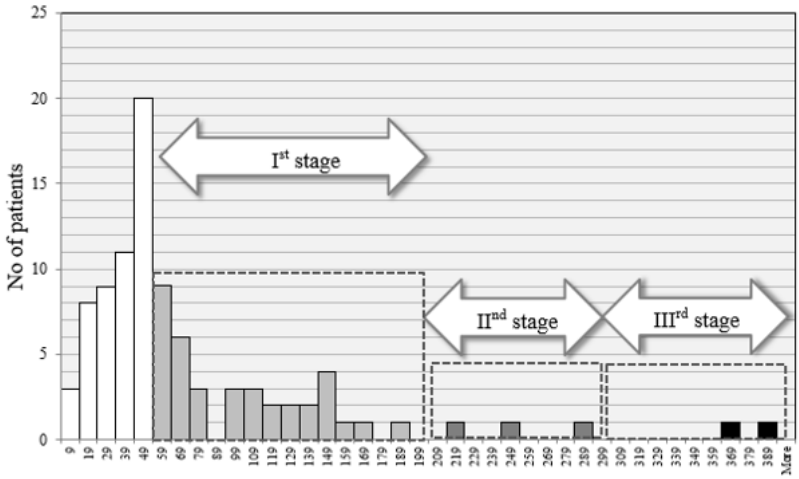


Fig. 2.3 **Histogram of ΔSCr**

Table 2.4 shows the characteristics in patients with and without postoperative AKI, as asseded by univariated analysis. Those with AKI were younger (12.5 months in non-AKI group versus 8.0 months in AKI group, p = 0.014) and having less body weight (7.0 kg versus 8.0 kg in AKI group, p = 0.026). Male gender dominates in the AKI group 69.04% versus 56.86%, but the difference was not statistically significant (p = 0.39). There was no difference in aortic cross-clamp time, body temperature during cooling, urine output, and the proportion of patients having cyanotic lesions. CPB time, diuretic doses, GFR, VIS and RACHS-1 scores differs significantly in AKI and non-AKI groups (Table 2.4).

Postoperative reduction of GFR differs in AKI and non-AKI group: eClCr in non-AKI group was 106.48 (IQR 86.26–127.09) mL/min/1.73 m^2 versus 61.57 (IQR 44.91–89.85) mL/min/1.73 m^2 in AKI group, p = 0.0001 (Table 2.4).

Median doses of furosemide used for patients in AKI group was higher (2.68 mg/kg/h) versus 1.63 mg/kg/h in non-AKI group, p = 0.024 (Table 2.4). Number of patients having cyanotic lesions was 9 from 51 (17.64%) in non-AKI group versus 14 from 42 (33.33%) in AKI group, but the difference was not statistically significant (Table 2.4).

Table 2.4

Characteristics of study cochort by AKI status

Variable (Median, IQR)	All	Non-AKI	AKI	p value
Gender male	58/93 (62.36%)	29/51 (56.86)	29/42 (69.04%)	0.39[#]
Age, months	10.00 (6.00–17.00)	12.50 (7.00–25.75)	8.0 (3.00–13.00)	0.0014[*]
Age < 12 months	52/93 (55.91%)	26/51 (50.98%)	30/42 (71.42%)	0.056[#]
Body weight, kg	7.60 (5.60–10.00)	8.00 (6.73–11.63)	7.00 (4.28–8.33)	0.026[*]
Body weight < 8 kg	52/93 (55.91%)	23/51 (45.09%)	29/42 (69.04%)	0.023[#]

Table 2.4 continued

Variable (Median, IQR)	All	Non-AKI	AKI	p value
CPB time (min.)	156.00 (58.00–560.00)	86.00 (30.00–116.00)	166.00 (146.60–231.50)	0.0024*
Aortic cross-clamping time (min.)	99.00 (64.75–126.50)	90.00 (60.00–120.00)	107.00 (81.75–128.75)	0.44*
Lowest body temperature (C°)	30.00 (28.00–31.92)	30.45 (26.18–32.00)	30.00 (27.63–31.50)	0.303*
Urine output (mL/kg/h)	2.28 (1.28–2.82)	2.26 (1.57–2.92)	1.90 (0.98–2.47)	0.083*
RACHS-1 category	3 (2–3)	2 (2–3)	3 (2–3)	0.0098*
RACHS-1 category ≥3	44/93 (25.80%)	18/51 (35.29%)	26/42 (61.90%)	0.0129#
VIS score	6 (5–7)	5 (5–6)	7 (6–10)	0.0098*
Cyanotic lesions (%)	23/93 (24.73%)	9/51 (17.64%)	14/42 (33.33%)	0.15#
Dose of furosemide (mg/kg/day)	2.04 (1.02–3.11)	1.63 (1.02–3.11)	2.68 (1.84–4.85)	0.024*
Postoperative eClCr mL/min/1.73 m^2	82.48 (50.37–106.48)	106.48 (86.26–127.09)	61.57 (44.91–89.85)	0.0001*

#Fisher's exact test * Mann-Whitney U Test

2.2 Biomarker expression

Concentration of SCys C rise at 12 hours from surgery from 0.86 mg/L (0.73–0.92) to 1.06 mg/L (0.83–1.37) in AKI group. In the non-AKI group SCys C incteases to 0.82 mg/L. (0.68–0.98). Maximum expression of SCys C was observed at 24 hours after the surgery.

In the AKI group SCys C level was 1.31 mg/L (1.06–1.48) versus 0.77 mg/L (0.63–1.06) in non–AKI group. The rise from the baseline value was statistically significant (p = 0.003). Then, after 48 hours biomarker level returns to baseline (Fig. 2.4, Table 2.5). Concentration of uNGAL has the maximum expression at 12 hours after surgery. It rises from 7.05 ng/mL (2.7–12.13) to 132.85 ng/mL (60.78–257.23), reching a peak level of 1680 ng/mL in AKI group.

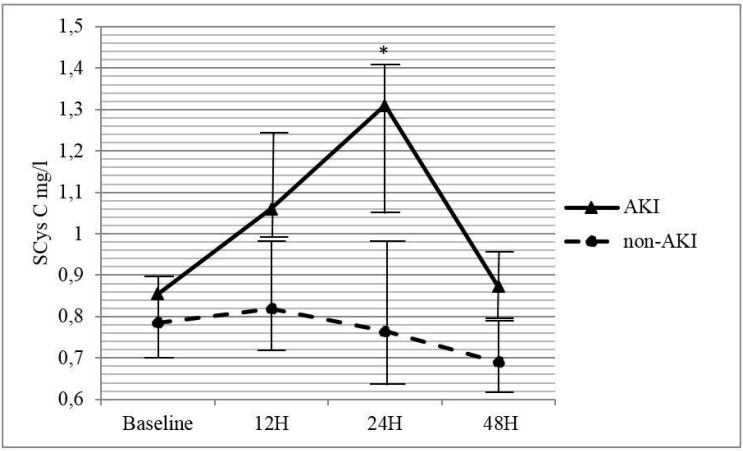


Figure 2.4 **Postoperative dynamics of SCys C**
Serum Cystatin C (sCysC) concentrations measured at intervals at baseline and at 12, 24, and 48 hr after CPB in patients with (continuous line) or without (dashed line) acute kidney injury (AKI). Median and interquartile range (IQR) are presented.

In the probe taken at 24 hours expression of uNGAL gradually decreases to 36.60 ng/mL in AKI group and 13.40 ng/mL in non-AKI group. At 48 hours uNGAL level returns to baseline: 7.40 ng/mL (4.00–23.20) in AKI group and 4.80 ng/mL (2.20–15.00) in non-AKI group (Fig. 2.5, Table 2.5).

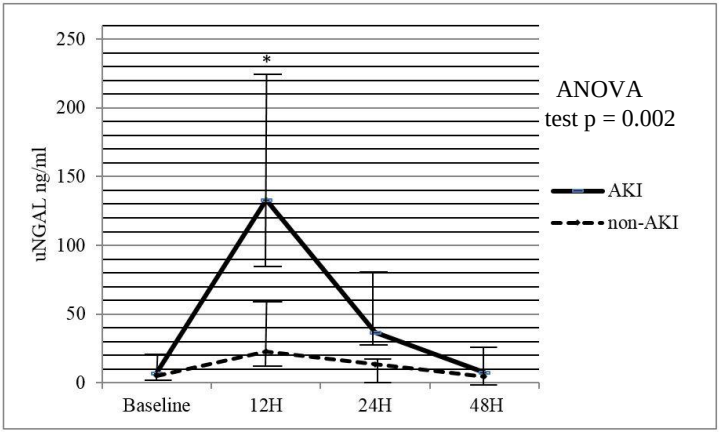


Figure 2.5 **Postoperative dynamics of uNGAL**
Urine neutrophil gelatinase–associated lipocalin (uNGAL) concentrations measured at intervals at baseline and at 12, 24, and 48 hr after CPB in patients with (continuous line) or without (dashed line) acute kidney injury (AKI). Median and interquartile range (IQR) are presented.

Table 2.5

Dinamics of perioperative expression of SCys C and uNGAL

Categ.	Biomarker	Baseline	12H	24H	48H
AKI	SCys C (mg/L) Median (Q1-Q3) [Range]	0.86 (0.73–0.92) [0.57–1.20]	1.06 (0.83–1.37) [0.60–2.44]	1.31 (1.06–1.48) [0.69–2.95]	0.87 (0.78–1.10) [0.59–1.92]
Non-AKI	SCys C (mg/L) Median (Q1-Q3) [Range]	0.79 (0.72–0.89) [0.55–0.99]	0.82 (0.68–0.98) [0.48–1.98]	0.77 (0.63–1.06) [0.45–1.65]	0.69 (0.66–0.82) [0.47–1.61]
AKI	uNGAL ng/mL Median (Q1-Q3) [Range]	7.05 (2.7–12.13) [0.6–49.26]	132.85 (60.78–257.23) [8.70–1680]	36.60 (7.3–74.68) [1.30–980.001]	7.40 (4.00–23.20) [0.4–863.00]
Non-ANB	uNGAL ng/mL Median (Q1-Q3) [Range]	5.35 (2.25–7.75) [0.40–62.25]	22.90 (12.3–75.65) [1.20–451.00]	13.40 (6.73–19.6) [1.20–203.90]	4.80 (2.20–15.00) [0–124.50]

2.3 Sensitivity and specificity of various biomarkers

ROC analysis of uNGAL showed the best discriminative ability at 12 hours: AUC of 0.911, sensitivity of 88%, specificity of 92%, CI 95% 0.852–0.971 and cut-off value of 70, $p < 0.001$. (Table 2.6, Fig. 2.6) ROC analysis of

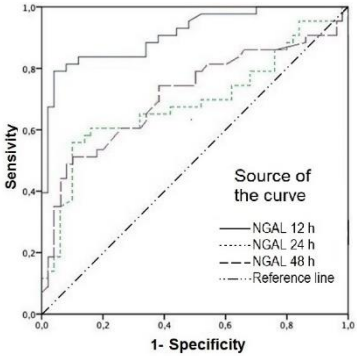


Fig. 2.6 **ROC curve of uNGAL at different time points**

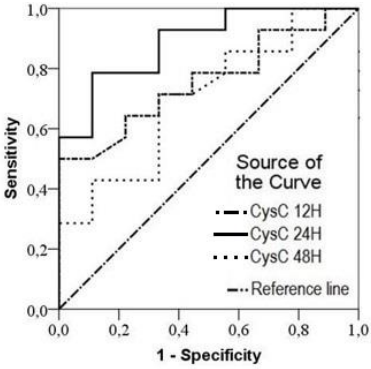


Fig. 2.7 **ROC curve of SCys C at different time points**

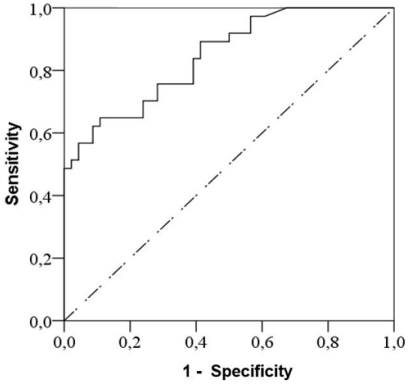


Fig. 2.8 **ROC curve of FB POD–1 in AKI and non-AKI patients`1**

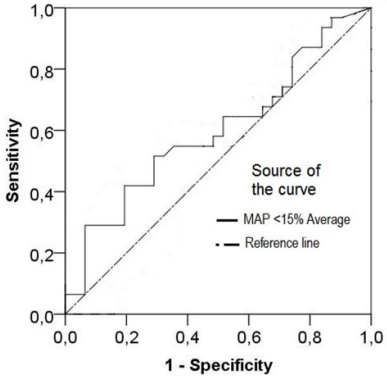


Fig. 2.9 **ROC curve of MAP<15% from average MAP in AKI and non-AKI patients**

AUC of 0.843, sensitivity of 81%, specitify of 72%, CI 95% 0.843–0.926, p < 0.001 (Table 2.6, Fig. 2.7). ROC analysis of postoperative fluid balance on postoperative day 1 (FB POD-1) showed AUC of 0.842 CI 95% CI 0.838–0.926, cut-off value of 25, p < 0.001 (Table 2.6, Fig. 2.8). ROC analysis of intraoperative hypotension (MAP < 15% average MAP) showed low sensitivity and specificity: AUC of 0.591, sensitivity 53%, specificity 65%, CI 95% 0.452–0.741, p = 0.12 (Table 2.6, Fig. 2.9).

Table 2.6

Sensivity and specificity of various biomarkers at different time points

Bio-marker	Area under the curve (AUC)	Sensi-vity (%)	Specifi-city (%)	Cut-of value	95% CI	Positive predic-tive value (PPV)	Negative predic-tive value (NPV)	p value
SCys C 12 H	0.703	62	70	0.96	0.589–0.817	0.830	0.437	0.004
SCys C 24 H	0.843	81	72	0.99	0.843–0.926	0.939	0.413	< 0.001
SCys C 48 H	0.741	67	75	0.79	0.627–0.854	0.884	0.443	0.04
uNGAL 12 H	0.911	88	92	70	0.852–0.971	0.991	0.431	< 0.001
uNGAL 24 H	0.715	66	74	64	0.606–0.824	0.864	0.464	0.002
uNGAL 48 H	0.688	59	70	62	0.574–0.802	0.812	0.436	0.011
FB POD-1	0.842	80	71	25	0.838–0.926	0.936	0.399	< 0.001
MAP < 15%	0.591	53	65	56	0.452–0.741	0.686	0.489	0.12

Postoperative fluid balance (FB POD-1) was 13.58 mL/kg (Median) in non-AKI group versus 27.20 mL/kg in AKI group, p = 0.025 (Fig. 2.10) In addition, FB was calculated separately according the severity stage of AKI. Fluid balance in patients reaching 1st stage of AKI severity increased from 13.58 mL/kg (Median) to 26.27 mL/kg, 2nd stage to 36.29 mL/kg and 3rd stage to

90.09 mL/kg, ANOVA test p = 0.002 (Table 2.7, Fig. 2.11). To evaluate postoperative fluid balance as a marker for AKI, ROC analysis was performed (Fig. 2.8, Table 2.6). AUC was 0.842 (CI 95% 0.838–0.926), sensitivity of 80%, specificity of 71% and cut-off value of 25 mL/kg.

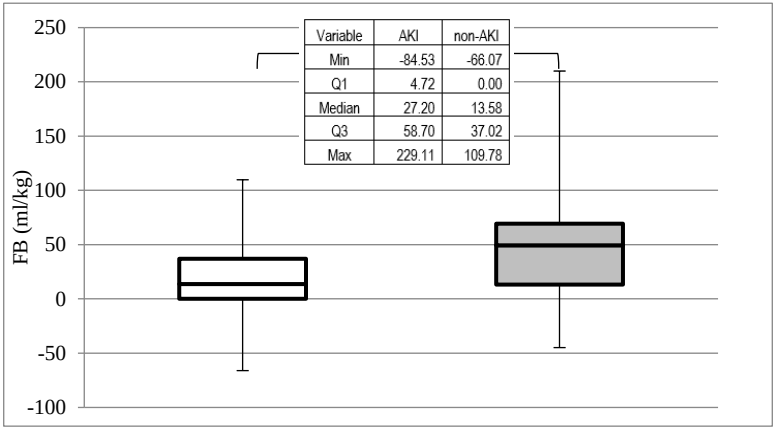


Fig. 2.11 **FB at POD-1 in AKI and non-AKI patients**
Box and whisker plot showing FB (ml/kg) in AKI (filled box) and non-AKI (emtv box) patients

Table 2.7

Postoperative fluid balance (mL/kg) at POD-1 and severity of AKI

Variable/Severity	Non-AKI	AKI Ist stage	AKI IInd stage	AKI IIIrd stage
Median	13.58	26.27	36.29	90.19
Interquartile range (Q1-Q3)	0–37.02	0–39.63	5.60–58.56	70.97–130.61
Range (Min.-Max.)	−66.07–109.78	−63.10–210.00	−44.85–171.01	55.25–229.11

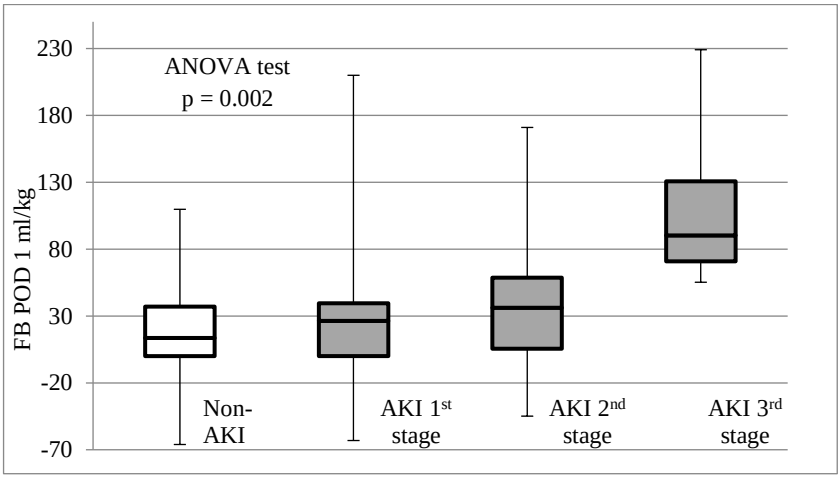


Fig. 2.11 **Postoperative FB and severity of AKI**
Box and whisker plot showing FB POD-1 in non-AKI patients (emty box) and patients having Ist, 2nd and 3rd stage of AKI (filled boxes)

Table 2.8

Intraoperative hypotension in AKI and non-AKI patients

Variable/Category	All	AKI	Non-AKI	p value*
No of MAP measurements (per patient) Median (IQR), [Range]	42.41 (33.00–50.00) [22.00–80.00]	45.32 (35.00–56.00) [24.00–80.00]	39.59 (32.25–43.75) [22.00–74.00]	0.080
Hypotensive episodes (% from all MAP) Median (IQR)	12.29 (9.11–19.92) [0–33.33]	19.66 (12.91–25.80) [5.56–33.33]	11.03 (8.28–14.05) [0–26.98]	0.075

* Mann-Whitney test

To determine the role of hypotension in the development of postoperative AKI, blood pressure measurements were collected from the Anesthesia Clinical Information system (Intelly View, Philips) and analyzed after transition to MS Excell workbook. In total there were about 4.000 validated MAP reacordings processed. There was no statistically signicicant difference in the number of

MAP measurements between two groups, 45.32 in AKI group, 35.59 in non-AKI group, p = 0.08. There was no difference in the proportion of hypotensive episodes in both groups: 11.03 versus 19.66 in AKI group, p = 0.075. Ratio of hypotensive episodes with MAP less than 15% from average MAP was 19.66 in AKI group versus 11.03 in non-AKI group, p = 0.075 (Table 2.8, Fig. 2.12).

ROC analysis of MAP < 15% shoved low sensitivity and specificity of intraoperative hypotension. AUC was 0.591 with sensitivity of 53% and specificity of 65%, CI 95% 0.452–0.741 (Fig. 2.12, Table 2.6).

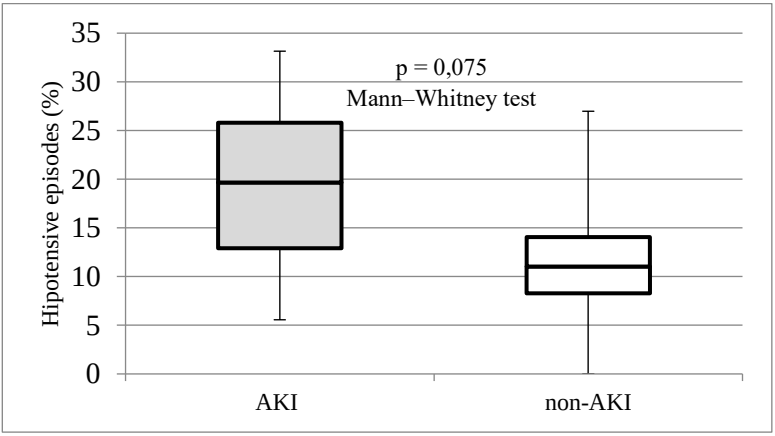


Fig. 2.12 **Intraoperative hypotension in AKI and non-AKI patients**

Box and whisker plot showing ratio of hypotensive (MAP < 15% less than averagee MAP value) MAP recordings to all MAP recordings (in %) in AKI (filled box) and non-AKI patients (emty box).

2.4. Outcome of AKI

Duration of mechanical ventilation (MV) was 22 hours in non-AKI group versus 92 hours in AKI group, p = 0.0001. Proportion of patients ventilated ≥48 hours in AKI group was 65.10% versus 26.50% in non-AKI group, p = 0.0001.

Length of treatment in the hospital, longer than 21 days had 38.09% of patients in AKI group versus 17.64% in non-AKI group, p = 0.035. Length of treatment in ICU ≥5 days had 21.56% patients in non-AKI group versus 54.76% in AKI group, p = 0.012. Fluid balance exceeding 50 ml/kg was observed in 59.52% patients of AKI group versus 35.29% of patients from non-AKI group, p = 0.046. Three patients in AKI group undergo RRT, none in non-AKI group. There was no death in non-AKI group versus two in AKI group, p = 0.21 (Table 2.9).

Table 2.9

Clinical outcome characteristics by AKI status

Variable/category	Non-AKI	AKI	p value
Mechanical ventilation (hours), median (IQR)	22.00 (14.00–61.00)	92.00 (36.00–216.00)	0.0001*
Mechanical ventilation ≥ 48 hrs, n (%)	13.00 (26.50%)	28.00 (65.10%)	0.0001#
FB POD-1 > 50ml/kg, median (IQR)	13.58 (0.00–37.02)	27.20 (4.72–58.70)	0.025*
FB POD-1 ≥50 ml/kg, n (%)	18/51 (35.29%)	25/42 (59.52%)	0.046#
ICU LOS, days, median (IQR)	4 (4.0–5.5)	7 (4.0–12.0)	0.0027*
ICU LOS, days ≥5 n (%)	11/51 (21.56%)	23/42 (54.76%)	0.012#
Hospital LOS, days, median (IQR)	13 (10.0–21.5)	19 (13.0–38.0)	0.0003*
LOS ≥21 day, n (%)	9/51 (17.64%)	16/42 (38.09%)	0.035#
RRT	0/51 (0.00%)	3/42 (7.14%)	0.088#
Case fatality rate	0/51	2/42	0.21#

#Fisher's exact test, *Mann-Whitney U test

Table 2.10

Duration of mechanical ventilation, lenghts of stay in the ICU, lenghts of stay in the hospital in AKI and non-AKI patients

Variable, category	AKI	Non-AKI	p value
Mechanical ventilation hours, Median (IQR) [Range]	92.00 (36.00–216.00) [4.00–408.00]	22.00 (14.00–61.00) [6.00–179.00]	0.0001*
Lenghts of stay in the ICU days, Median (IQR) [Range]	7.0 (4.0–12.0) [3.00–20.00]	4.0 (4.0–5.5) [3.00–18.00]	0.0001*
Lenghts of stay in the hospital days, Median (IQR) [Range]	19 (13.0–38.0) [7.00–116.00]	13 (10.0–21.5) [3.00–43.00]	0.0027*

* Mann-Whitney U test

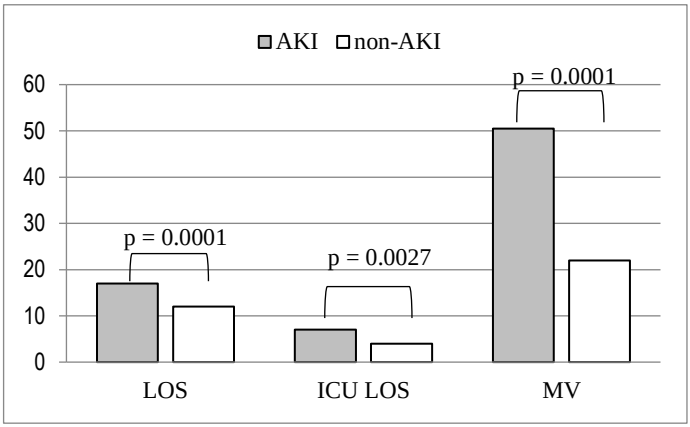


Fig. 2.13 **Median values of LOS, ICU LOS (days) and duration of MV (hours) in AKI and non-AKI patients**
Abbreviations: LOS – Lengths of stay in the hospital, ICU LOS – Lengths of stay in the ICU, MV – Mechanical ventilation

OR were calculated to assess factors, associated with postoperative renal dysfunction. One of the variables was CPB time. Unajusted OR for CPB time ≥ 180 min. was 2.47 (CI 95% 0.99–6.13, p = 0.048, Table 2.9). OR for mechanical ventilation > 2 days was 5.17 (CI 95% 2.12–12.61, p = 0.027). OR for ICU LOS ≥ 5 days was 4.4 (CI 95% 1.78–10.85, p = 0.0012, Table 2.9).

After performing multivariate logistic regression analysis OR were adjusted to age and summarized in Table 2.11.

After the adjustment for age, OR for ICU LOS > 5 days decreased from 4.40 (CI 95% 1.78–10.85) to 1.21 (CI 95% 1.07–1.40), p = 0.003. OR for LOS ≥ 21 day decreased from 2.87 (CI 95% 1.11–7.44) to 1.046, (CI 95% 1.009–1.085), p = 0.035. OR for CPB time ≥180 min. from 2.47 (CI 95% 0.99–6.13), decreased to 2.32 (CI 95% 1.07–1.40), p = 0.003. OR for MV ≥48 hours after the adjustment for age from 5.17 (CI 95% 2.12–12.61), decreased to 1.008 (CI 95% 1.003–1.014), p = 0.004. OR for VIS ≥7 from 12.26 (CI 95% 4.05–37.11),

decreased to 5.85 (CI 95% 5.85–56.66), p < 0.001. OR for FB POD–1 ≥ 50 mL/kg from 2.69 (CI 95% 1.16–6.26) dereased to 2.58 (CI 95% 0.94–7.07), p = 0.06. OR for RACHS–1 ≥3 from 2.98 (CI 95% 1.28–6.95) decreased to 2.86 (CI 95% 1.15–7.15), p = 0.02.

Table 2.11

Odds ratio in AKI and non-AKI patients

Variable	OR (CI 95%)	p value
AKI versus non-AKI, CPB time ≥180 min.	2.47 (0.99–6.13)	0.048#
AKI versus non-AKI, body weight < 8 kg	1.82 (0.77–4.31)	0.201#
AKI versus non-AKI, mechanical ventilation >2 days, OR (CI 95%)	5.17 (2.12–12.61)	0.027#
AKI versus non-AKI, ICU LOS ≥5 days OR (CI 95%)	4.40 (1.78–10.85)	0.0012#
AKI versus non-AKI, LOS ≥21 day OR (CI 95%)	2.87 (1.11–7.44)	0.035#
AKI versus non-AKI FB POD-1 ≥50 mL/kg	2.69 (1.16–6.26)	0.026#
AKI versus non-AKI VIS ≥7	12.26 (4.05–37.11)	< 0.0001#
AKI versus non-AKI RACHS-1 score ≥3	2.98 (1.28–6.95)	0.01#

#Fisher's exact test

Table 2.12

Age adjusted Odds ratio

Variable	Odds ratio	CI (95%)	p value
ICU LOS ≥5 days AKI vs. non-AKI	1.21	1.07–1.40	0.003
CPB ≥180 min. AKI vs. non-AKI	2.32	0.91–5.91	0.07
RACHS-1 >3 AKI vs. non-AKI	2.86	1.15–7,15	0.02
VIS ≥7 AKI vs. non-AKI	5.85	5.85–56.66	0.001
MV ≥48 hours AKI vs. non-AKI	1.008	1.003–1.014	0.004
LOS ≥21 days AKI vs. non-AKI	1.046	1.009–1.085	0.01
FB ≥50 mL/kg AKI vs. non-AKI	2.58	0.94–7.07	0.06

Values are reported as adjusted odds ratios (95% confidence intervals) by multivariate logistic regression analysis. Odds ratio analyses for all patients are per unit increase.

3 DISCUSSION

Despite many years of research, AKI remains an important and life-threatening complication in patients undergoing cardiac surgery, and with respect to high prevalence of this interference in this specific population has even got a sub-designation: CSA-AKI [14].

Postoperative AKI occurred in 42 (45.16%) from 93 children. 37 (88.02%) reached severity stage I according the KDIGO classification, 3 (7.14%) reached stage II and two (4.76%) reached stage III. (Fig. 2.2, 2.3). Prior to 2005 there were no studies of cardiac surgery associated AKI using the currently accepted definition. These studies used definitions ranging from doubling of serum creatinine to requirement of dialysis. Pederson et al. [15] performed one of the larger single center prospective studies enrolling children from 1993 to 2002 and used dialysis as their AKI definition. They found that 11.5% of their patients developed AKI. However, the use of dialysis as the definition of AKI is concerning since most clinicians agree that AKI develops before the need for dialysis. In a large study of by Zappitelli et al. 35.9% of all children having cardiac surgery developed AKI [16].

Analysis of preoperative risk factors demonstrated that children who were in the youngest age group were at higher risk for developing AKI compared to the older age groups (Table 2.4) The reason for this is not completely clear. Though full-term infants are usually born with their full complement of nephrons, maximal GFR is not achieved until about 2 years of age [17]. Thus, children less than 2 years old may be more susceptible to the ischemic and inflammatory insults that may be occurring in patients undergoing heart surgery. Examples of these surgeries include simple ASD closures and repair of partially anomalous pulmonary veins. This is not surprising since these surgeries are less complex and relatively rapid with low CPB times [18].

The finding that higher RACHS-1 scores were associated with higher prevalence of postoperative AKI. [7, 19]. RACHS-1 score ≥ 3 had 18/51 patients (35.29%) in non-AKI group versus 26/42 patients (61.90%) in AKI group, p = 0.0129 (Table 2.4). In the multivariate regression analysis OR for RACHS-1 >3 AKI vs. non-AKI was 2.86 CI 95% 1.15–7.15, p = 0.02 (Table 2.12) Garcia et al. evaluated the Vasoactive Inotropic Score (VIS) as a prognostic marker in adolescents following surgery for congenital heart disease. They found that maximal VIS at 24 and 48 h following surgery was significantly higher in subjects who suffered an adverse outcome [20]. Subjects with adverse outcome had longer bypass and cross-clamp times, durations of stay in the hospital, and a higher rate of acute kidney injury. In current study VIS score in non-AKI group was 5 (IQR 5–6) versus 7 (IQR 6–10) in AKI group, p = 0.0098 (Table 2.4). In multivariate regression analysis OR for VIS ≥7 was 5.85 (CI 95% 5.85–56.66), p < 0.001, Table 2.12.

Not surprisingly, the duration of CPB has been the single most consistently identified risk factor for pediatric CS-AKI. Age-adjusted OR for CPB time ≥ 180 min. AKI versus non-AKI patients was 2.32 (CI 95% 1.07–1.40), p = 0.003 (Table 2.12). This finding of increased risk of AKI is consistent with numerous past studies. The mechanism for this is probably due to a combination of ischemia, loss of pulsatile flow and progressive inflammation which adds to kidney injury [21]. Further research into issues such as temperature, pressure and the amount and type of bypass circuit flows will be needed to explore this relationship. Strategies to limit bypass time may help decrease the rate of cardiac surgery-associated AKI. It is possible that in children who have surgery requiring bypass the duration may also be a marker for case complexity and severity of the congenital anomaly. Adults undergoing cardiac surgery typically have several pre-operative cardiovascular risk factors such as diabetes, peripheral vascular disease, and chronic kidney disease.

These same risk factors often emerge as pre-operative cardiovascular risk factors for developing AKI in adults [22]. In children with congenital heart disease these factors are not usually present. In fact, most children do not have any other comorbidities. Risk factors for AKI in children are usually limited to the age of the child and the severity of insult (e.g. CPB time).

The use of Cystatin C as a diagnostic tool for AKI has recently been explored. Two meta-analyses have revealed that serum cystatin C outperforms SCr as a predictor of AKI and a marker of AKI severity [23, 24]. A multicenter prospective study of children undergoing cardiac surgery showed that early measurements of cystatin C (within 6 h of initiating CPB) strongly and independently predicted the development of SCr-based AKI with an adjusted odds ratio of 17.2 and adjusted area under the receiver operating characteristic curve (AUC) of 0.89 [25].

Serum Cystatin C concentrations were similar in the AKI and non-AKI patients before surgery but began to increase in the AKI patients at 12 hours after CPB and became significantly higher at 24 hours after CPB. (Fig. 2.7, Table 2.5) SCys C levels rise from the baseline to 1.06 mg (IQR 0.83–1.37) after 12 hours and reached their maximum at 24 hours after surgery: 1.31 mg/L (IQR 1.06–1.48) in AKI group versus 0.77 mg/L (IQR 0.63–1.06) in non-AKI group, $p = 0.0002$ (Fig. 2.7, Table 2.5). In the ROC analysis, predictor performance for SCys C peaked 24 hours after the first probe was taken and reached AUC of 0.843, (CI 95% 0.843–0.926), with sensitivity of 81%, specificity of 72% and cut-off of 0.99 mg/L, $p < 0.001$ (Table 2.7, Fig. 2.7).

The most extensively studied biomarker in pediatric CS-AKI is NGAL. It was measured in more than 7000 patients after cardiac surgery can predict the subsequent development of AKI (AUC 0.82–0.83). Most recently, the multicenter TRIBE (Translational Research Involving Biomarkers and Endpoints) study [26], prospectively assessed the value of NGAL in 1219 adults and 311 children undergoing cardiac surgery. In both populations, NGAL

concentrations measured in urine or plasma peaked within 6 h after surgery and significantly improved risk prediction over the clinical models alone [27]. In pediatrics, uNGAL levels demonstrated sharp increases to > 5000 ng/mg within 2–4 hours in patients who would eventually require RRT [28]. Urinary NGAL (uNGAL) levels of ≥ 50 μg/L were 100% sensitive and 98% predictive in the 20 from 71 children post CPB who developed AKI [17]. Serum NGAL levels within 2 hours of CPB of ≥ 150 mg/L were 84% sensitive and 94% predictive in children who developed AKI within 3 days [116]. However, Parikh et al. [27] demonstrated lower values for the prediction of AKI in children, defined as doubling in creatinine or the need for acute RRT (AUC approximately 0.7) and lower cut-off values. The reasons for this discrepancy may include the different patient populations (exclusion of neonatal patients), differences in assay platforms and prolonged sample storage times compared to earlier single-centre studies. Indeed, recent study has shown that the performance of NGAL in older adults is inferior to that in children, likely related to the comorbidities (such as chronic kidney disease, chronic heart failure, atherosclerosis, diabetes, medications) that can hinder NGAL's predictive ability [28–30]. Second, there are no uniformly accepted cut-offs, although the literature would suggest that an NGAL cut-off value of < 100 ng/ml (measured on a standardized clinical platform) would rule out AKI in those with normal baseline function, and a cut-off > 150 ng/ml can be diagnostic for AKI, Cut-offs may be dependent on age, gender, underlying clinical setting, and the specific assay employed.

Concentration of uNGAL has the maximum expression at 12 hours after surgery. It rises from 7.05 ng/mL (2.7–12.13) to 132.85 ng/mL (60.78–257.23), reaching a peak level of 1680 ng/mL in AKI group. In the probe taken at 24 hours expression of uNGAL gradually decreases to 36.60 ng/mL in AKI group and 13.40 ng/mL in non-AKI group. At 48 hours uNGAL level returns to baseline: 7.40 ng/mL (4.00–23.20) in AKI group and 4.80 ng/mL (2.20–15.00) in non-AKI group (Fig. 2.5, Table 2.5). In the ROC analysis, predictor performance

for uNGAL at 12 hours was AUC 0.911, CI 95% 0.852–0.971, cut-off value 70 ng/mL (Table 2.6, Fig. 2.5).

Studies of adult critically ill patients have shown that positive FB above 10% is associated with a higher long-term mortality and a higher occurrence of AKI, thus indicating this threshold as a potential indicator of adverse outcomes [31, 32]. Studies of pediatric patients requiring RRT showed a correlation of the degree of positive FB with poor outcomes and mortality, hinting at a dynamic positive FB value for predicting adverse outcomes, with the 10% cut-off value proving to be clinically significant [33]. Recent study by Hazle et al. [34] demonstrates that increasing positive FB, as measured by daily fluid balance, is associated with worse outcomes following congenital heart surgery in infants. In the recent study of Lex et al. authors analyze postoperative FB in 1520 pediatric patients after open heart surgery [208]. They find positive FB between 5% and 10% in 120 patients (7.8%), in 33 patients (2.1%) FB was above 10%. After multivariable analysis, higher fluid overload on the day of the surgery was independently associated with mortality (adjusted odds ratio, 1.14; 95% CI, 1.008–1.303; p = 0.041) and low cardiac output syndrome (adjusted odds ratio, 1.21; 95% CI, 1.12–1.30; p = 0.001). Higher maximum SCys C levels (adjusted odds ratio, 1.01; 95% CI, 1.003–1.021; p =.009), maximum vasoactive-inotropic scores (adjusted odds ratio, 1.01; 95% CI, 1.005–1.029; p = 0.042), and higher blood loss on the day of the surgery (adjusted odds ratio, 1.01; 95% CI, 1.004–1.025; p = 0.015) were associated with a higher risk of fluid overload that was greater than 5%.

The etiology of positive FB in this patient population is multifactorial. Cardiopulmonary bypass results in both hemodilution and increased capillary permeability, both of which promote extravasation of fluid into the extracellular fluid compartment [35]. Fluid resuscitation and blood product administration in the immediate postoperative period further contributes to third spacing. As body wall edema increases, intra-abdominal pressure rise and renal perfusion pressure

is decreased [36]. When combined with postoperative myocardial dysfunction, there is also a stimulus to retain fluid via the renin-angiotensin-aldosterone system [37]. Given the acute nature of CPB mediated kidney injury and the observation that most infants have normal renal function prior to surgery, these patients may be ideal candidates for aggressive postoperative goal-directed protocols aimed at minimization of positive FB. Peritoneal dialysis has been shown to be a safe and effective method of fluid removal in postcardiotomy infants [38], and early initiation of this therapy can improve hemodynamics and ICU outcomes [39].

By examining fluid balance early after cardiac surgery, current study adds to the growing body of evidence that positive fluid balance is independently associated with kidney dysfunction. FB POD-1 ≥50 mL/kg, in AKI group was 35.29% versus 59.52% in AKI group, p = 0.046 (Table 2.9). Median postoperative fluid balance in non-AKI group was 13.58 mL/kg versus 27.20 mL/kg in AKI group, p = 0.025 (Fig. 2.10), OR of FB ≥50 mL/kg in AKI vs. non-AKI was 2.58 (CI 95% 0.94–7.07), p = 0.06. After performing ROC analysis, AUC of FB POD-1 was 0.842 with sensitivity of 80%, specificity of 71% (CI 95% 0.838–0.926) and cut-off value of 25 ml/kg, p = 0.001. Similar results are published in the study of Hassinger et al. [40]. They found postoperative positive fluid balance > 50 ml/kg in 31% of patients which is less than in this study (59.52%). Reported AUC was 0.963; 95% CI, 0.916–1.000; p = 0.002.

The kidneys account for less than 5% of total body weight and yet receive about 25% of our cardiac output, to maintain glomerular filtration and waste excretion, they only consume 5% of the body's oxygen. It is of no surprise, therefore, that targeting adequate renal perfusion is considered as a potential factor for modifying the risk of AKI. It is commonly purported that poor perioperative hemodynamic control during cardiac surgery leads to postoperative CS-AKI.

Study of Lehman et al. [41] evaluated hypotension severity and duration as risk factors for AKI development using a large ICU database. Results from multivariate logistic regression indicate that the severity and duration of hypotension are both significant risk factors in AKI development in ICU patients. Odds of AKI increased by 3% per 1 mmHg decrease in MAP below 80 mmHg. Further, as the degree of hypotension worsened, the increased risk for AKI from each additional hour of continuous hypotension more than doubled for each 10 mm Hg drop in MAP below 80 mmHg. These results indicate that raising MAP targets during CPB might reduce the frequency of postoperative AKI. Kanji et al. [42] in their study on 157 high-risk cardiac patients establish a relationship between intraoperative hypotension and postoperative CS-AKI.

Delta MAP was defined as baseline MAP (acquired from three independent pre-operative blood pressure readings) minus the average MAP on CPB (calculated as the average of MAP readings at 15 minutes intervals during CPB). They found that a large delta MAP and lower CPB flow during cardiac surgery are independently associated with early post-operative CSA-AKI in high-risk patients. In children, however, it is difficult to obtain correct baseline MAP measurements before tracheal intubation and surgical intervention. In pediatric anesthesia induction and tracheal intubation usually precedes vascular cannulation and invasive pressure monitoring, therefore average MAP during anesthesia was used as a reference and hypotension was defined as a MAP < 15% less than average MAP value. Blood pressure measurements during CPB were also excluded since nonpulsatile CPB perfusion pressure variation is dissimilar to blood pressure variation unrelated to CPB. In total, more than 4.000 validated MAP recordings collected in 5-minute intervals were transferred from the Intelly View Clinical Information Portfolio (Philips) anesthesia flowsheets to MS Excell workbook for analysis. Then all MAP recordings were compared to average (except MAP recordings during CPB, when pulsatile blood flow was absent). Ratio of hypotensive MAP recordings (MAP < 15% less than average

MAP value) to total MAP recordings was calculated and expressed as %. There were 12.29% (IQR 9.11–19.92) hypotensive MAP recordings in all patients, 19.66% (IQR 12.91–25.80) in AKI group versus 11.03% (8.28–14.05) in non-AKI group, (Table 2.8, Fig. 2.12). ROC analysis showed an AUC of 0.591 with sensitivity of 53% and specificity of 65%, CI 95% 0.452–0.741 (p = 0.12), Table 2.6, Fig. 2.9.

Duration of mechanical ventilation in patients with or without AKI is displayed in Table 2.9. Twenty-eight patients (65.10%) of those with some degree of AKI were mechanically ventilated ≥ 48 hours compared with 13 patients (26.50%) of those with no evidence of AKI (p = 0.0001).

Median duration of mechanical ventilation (MV) was 22 hours in non-AKI group versus 50.50 hours in AKI group, p = 0.0001 (Table 2.9). Multivariate logistic regression analysis demonstrated that patients with AKI were more likely to have longer ICU and hospital lengths of stay: OR for ICU LOS ≥ 5 days was 1.21 (CI 95% 1.07–1.40), p = 0.003. OR for LOS ≥21 was 1.046, (CI 95% 1.009–1.085), p = 0.035 (Table 2.12). Previous studies [9, 15, 43] have showed younger age to be associated with longer ICU and hospital lengths of stay but have not explored the impact of AKI specifically or defined AKI simply as the need for renal replacement therapy [43]. The longer lengths of stay may be related to fluid retention and concomitant effects on respiratory mechanics causing longer durations of mechanical ventilation, the heterogeneous nature of CHD, institutional and practice guidelines (e.g., no protocol for early extubations), use of diuretics, and limited practice variation. The impact of longer lengths of stay, including increased risks of nosocomial infections medical errors, and greater utilization of resources, with associated escalation of health care costs, are well known [44].

No degree of AKI was associated with in-hospital mortality, irrespective of the age group examined. This is likely related to the relatively low rate of occurrence of in-hospital mortality.

CONCLUSIONS

1. The rate of AKI in the current approach of pediatric cardiac surgery in Latvia is high and is associated with important patient outcomes. From 93 patients included in the study, 42 (45.2%) met at least KDIGO Stage I (UO or SCr) criteria for AKI.
2. This study shows that both uNGAL and Cys C levels after pediatric open-heart surgery increase following ICU admission and peak, respectively, 12 to 24 thereafter: uNGAL reliably discriminated between infants who met AKI criteria within 48 hours following admission and those who did not. uNGAL was able to predict AKI development correctly in 91% children, before any rise in SCr became apparent. These findings support the emerging role of uNGAL in identifying AKI at an early stage, which, in the future, may help us to establish timely renoprotective interventions to reduce AKI in those most vulnerable patients in hospital.

   SCys C, a GFR marker of renal dysfunction predicted AKI in 84% of children undergoing open heart surgery in 24 hours after the event preceding concomitant changes in SCr.
3. Fluid balance too, is a suitable marker for the prediction of postoperative AKI. FB POD–1 ≥50 mL/kg, in non-AKI group had 35.29% patients versus 59.52% in AKI group, $p = 0.046$. Median postoperative fluid balance in non-AKI group was 13.58 mL/kg versus 27.20 mL/kg in AKI group, $p = 0.025$, OR of FB ≥50 mL/kg in AKI versus non-AKI was 2.58 (CI 95% 0.94–7.07), $p = 0.06$. After performing ROC analysis, AUC of FB POD–1 was 0.842 with sensitivity of 80%, specificity of 71% (CI 95% 0.838–0.926) and cut-off value of 25 ml/kg, $p = 0.001$. Role of fluid balance in the postoperative management is underestimated and daily FB monitoring now becomes essential.

4. The hypothesis of the association of intraoperative hypotension and postoperative AKI was not confirmed using methodology, applied in this study.
5. CS-AKI had severe clinical outcomes: MV in AKI group was 50.50 hours (IQR 36.50–201.00) versus 22.00 hours (IQR 14.50–50.00) in non-AKI group, p = 0.0001. Lengths of ICU stay increased from 4.00 days (IQR 4.00–5.00) in non-AKI group to 7.00 days (IQR 4.50–11.50) in AKI group, p = 0.0001. LOS increased from 12.00 days (IQR 10.00–20.00) in non-AKI group to 17.00 days (IQR 10.00–20.00), p = 0.023. In multivariate regression analysis OR for ICU LOS >5 days was 1.21 (CI 95% 1.07–1.40), p = 0.003. OR for LOS ≥21 was 1.046, (CI 95% 1.009–1.085), p = 0.035. OR for MV ≥ 48 hours after the adjustment for age was 1.008 (CI 95% 1.003–1.014), p = 0.004.

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2. RSU 2011. gada zinātniskā konference (Rīgā, 2011. gada 14.–15. aprīlī).
3. 6th International Baltic Congress of Anaesthesiology and Intensive Care, 18–20 October 2012. Vilnius, Lithuania.
4. RSU 2012. gada zinātniskā konference (Rīgā, 2012. gada 29.–30. martā).
5. RSU 2013. gada zinātniskā konference (Rīgā, 2013. gada 14.–15. aprīlī).
6. 2nd Baltic Paediatric Congress Pärnu, Estonia (30 May–1 June 2013).
7. 24th Annual ESPNIC congress Rotterdam, Netherlands (12–15 June 2013).
8. RSU 2014. gada zinātniskā konference (Rīgā, 2014. gada 10.–11. aprīlī).
9. 7th International Baltic Congress of Anesthesiology (Riga, 4–6 December 2014).
10. 7th World Congress on Pediatric Intensive and Critical Care, Istambul (4–7 May 2014).
11. 47th Annual Scientific Meeting of the European Society for Pediatric Nephrology, Porto (18–20 September 2014).
12. RSU 2015. gada zinātniskā konference (Rīgā, 2015. gada 26.–27. martā).
13. 26th Annual ESPNIC Congress Vilnius Lithuania (10–13 June 2015).
14. 3rd Baltic Paediatric Congress in Riga, Latvia (19–21 August 2015).
15. RSU 2016. gada zinātniskā konference (Rīgā, 2016. gada 16.–17. martā).
16. 8th International Baltic Congress of Anesthesiology and Intensive Care, Tallinn, Estonia (1–3 December 2016).
17. 28th Annual ESPNIC Congress Lisbon Portugal (6–9 June 2017).
18. LARA 6. Nacionālais kongress (Ventspilī, 2017. gada 8.–9. decembrī).

Summary

Activity	Qty.
Oral presentation in International Congress	5
Oral presentation in National Congress	2
Oral presentation in local conference	5
Article published in journal, listed in LCS	4
Article published in peer–reviewed journal	2
Abstract published in peer rewieved journal	6
Abstract published in the Proceedings	4
Published Monograph	1

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