Cardiac surgery related cardio-renal syndrome assessed by conventional and novel biomarkers – under or overestimated diagnosis?

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Abstract

Introduction: Serum creatinine is a 'gold standard' criterion of recognizing and staging of acute kidney injury (AKI) despite it being a suboptimal, delayed indicator. The interpretation of increased values of biomarkers imposes great difficulty regarding cardiac surgery procedures performed with cardiopulmonary bypass and may lead to under- or overestimated diagnosis. The aim of this study was to evaluate the clinical utility of the sole serum creatinine or urine neutrophil gelatinase-associated lipocalin (NGAL) concentration used for identification of patients with AKI after cardiac surgery.
Material and methods: A prospective observational study was conducted on a group of 88 adult patients undergoing a coronary artery bypass grafting procedure. Serum creatinine was evaluated on the day of the operation, and 24 and 48 h post-operatively. Urinary NGAL concentration was measured: immediately after and one hour after cardiopulmonary bypass, and 24 h from the beginning of the operation. We assessed features of kidney injury and 30-day and 5-year mortality.
Results: Patients in the AKI group diagnosed with creatinine level and urine output criteria presented more advanced age (p = 0.01), higher body mass index (p = 0.01) and preoperative myocardial infarction (p = 0.02). Elevation of NGAL level was observed in 5 of 13 cases with AKI, based on creatinine criteria and 4 of 75 cases without AKI. Within 5 years after the surgical procedure the recurrence of renal failure was 36% in the AKI group (with perioperative NGAL elevation in 2 cases only).
Conclusions: In the cardiac surgery patients the diagnosis of AKI based on sole serum creatinine or urine NGAL concentration confirmed transient kidney injury. However, the clinical implications of these findings are insufficient for prediction of clinical outcome.

Key words: cardiac surgery associated acute kidney injury, neutrophil gelatinase-associated lipocalin, cardiorenal syndrome.

Introduction

Cardiac surgery associated acute kidney injury (CSA-AKI) is an independent entity posing an important clinical problem, with no direct ac-

tive therapy available at the time of writing. It is defined as type 3 cardio-renal syndrome, in which kidney injury occurs secondary to the cardiac surgery procedure [1–3]. The frequency of CSA-AKI is approximated to be between 2 and 30% depending on the type of surgical procedure: coronary artery bypass grafting (CABG) and/or vascular – valve procedures [1, 4]. However, the interpretation and clinical implications of many published papers impose great difficulty in everyday clinical practice, not only due to the unclear CSA-AKI definition, but also due to non-homogeneity of the reported case mix. It is common practice in CSA-AKI research to analyze the data from different types of cardiac operations altogether: CABG, CABG and valve repair, aortic aneurism repair, procedures performed in normothermia with those performed in hypothermia and elective combined with re-operations or emergency cases [5]. These "mixed" studies lead only to general conclusions from the field of cardiac surgery, without assessment of the real risk associated with each type of surgery or patient group. These data are not applicable to patients undergoing a simple CABG procedure with CPB.

Postoperative acute kidney injury and renal replacement therapy are associated with prolonged intensive care unit stay, and increased morbidity and mortality [6].

The main problem with a CSA-AKI definition lies with the fact that although the point of nephron injury is known, the surgery itself, including the cardio-pulmonary bypass, the pathomechanism is multifactorial [5]. It involves at least six major injury pathways: exogenous and endogenous toxins, metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation and oxidative stress [7].

At present, serum creatinine is the most commonly used biomarker of renal function. Together with hourly diuresis, the creatinine level is a way of recognizing and staging AKI [8]. The diagnosis of kidney failure in the early postoperative period may impose difficulties, due to the interplay of many factors, which include delayed increase of serum creatinine in response to nephron injury and a positive fluid balance influencing the volume of distribution of creatinine. A lack of predefined criteria for the use of early biomarkers of acute kidney injury stimulates the constant search for new biomarkers such as serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and kidney injury molecule 1 [9–12].

There are many models that estimate the risk of acute kidney injury after cardiac surgery [13]. The Thakar model is one of the most popular ones used worldwide [14]. It has been shown to offer the best discriminative value to calculate the risk of dialysis after cardiac surgery [15]. The factors incorporated into this model are gender, heart failure, low ejection fraction of the left ventricle, preoperative use of intra-aortic balloon pump, chronic obstructive pulmonary disease requiring medical therapy, diabetes requiring insulin, past cardiac surgery, serum creatinine level, emergency surgery and the type of surgery.

The frequency of CSA-AKI assessed by conventional or novel biomarkers without clinical observation may lead to under- or overestimated diagnosis in specific clinical situations [16]. The aim of this study was to evaluate the clinical utility of the sole serum creatinine or urine NGAL concentration used for identification of patients with AKI within the first 24 h after CABG including continuous renal replacement therapy (CRRT) requirement. We assessed features of kidney injury in the 30 days after the cardiac procedure and 30-day mortality. Finally, we analyzed 5-year mortality and history of kidney failure.

Material and methods

A prospective observational study was conducted in a group of adult Caucasian patients who presented with at least one of the risk factors for renal replacement therapy after cardiac surgery according to the Thakar model [15]. All patients included in this study signed an informed consent form, and the research was conducted according to the Declaration of Helsinki. All patients underwent a planned cardiac artery bypass grafting procedure using cardio-pulmonary bypass in the Department of Cardiac Surgery of the Pomeranian Medical University in Szczecin (Poland). Cardiac operations were performed by three consultant cardiac surgeons in a center that performs approximately 1100 procedures annually. The study protocol has been approved by the local Ethical Committee of the Pomeranian Medical University in Szczecin (Poland) (KB – 0012/146/10).

Study population

Inclusion criteria included a planned operation of coronary artery bypass grafting using cardio-pulmonary bypass and normal kidney function assessed by serum creatinine concentration. After analyzing the medical records of 250 consecutive patients, 162 patients were excluded from the study (due to the presence of exclusion criteria) and the remaining 88 patients were included in the study. Exclusion criteria regarding the preoperative period were: emergency operations, re-operations, procedures other than coronary artery bypass grafting, known pathology of the urinary tract, preexisting renal dysfunction and preoperative abnormal serum creatinine level. The

time-point of recruitment was 24 h before the operation, during premedication. However, if some complication existed (e.g. reoperation within the first 24 h), the patient was excluded from further participation.

Study definitions

Acute kidney injury (AKI) was defined according to AKI criteria by KIDGO [8]. The AKI is defined as any of the following: increase in serum creatinine by ≥ × 0.3 mg/dl within 48 h; or increase to ≥ × 1.5 times baseline, or urine volume ≤ 0.5 ml/kg/h for 6 h. The AKI is staged for severity.

Continuous replacement therapy (CRRT) was started when at least one of the following criteria was fulfilled:

1. urine output below 0.5 ml/kg/h within 12 h despite adequate treatment with fluid infusion, inotropes and/or vasoconstrictor infusions and furosemide,
2. significant organ edema (e.g. pulmonary) resistant to diuretic therapy,
3. serum creatinine concentration ≥ 3-fold increase compared to baseline or serum creatinine increase ≥ 4 mg/dl in the setting of an increase of ≥ 0.5 mg/dl within a 48-hour window (AKIN stage 3).

Fluid balance – the difference between fluid intake (intravenous fluids and medications, the volume of fluids used during the cardio-pulmonary bypass) and the fluid output (urine output, perspiration, postoperative drainage) were calculated within predefined time points: from the initiation until the end of CABG and 48 h after the initiation of the operation.

Study protocol

During the perioperative visit on the day before the cardiac surgery, a full physical examination was performed to verify the patient's clinical status and to qualify the patient for the study. In the operating room, standard patient monitoring was initiated and induction of general anaesthesia was performed using fentanyl, etomidate and pancuronium (doses calculated per body weight) and sevoflurane was used for maintenance of anaesthesia. The monitoring included electrocardiography, invasive blood pressure, central venous pressure, deep body temperature and mechanical ventilation parameters, which were performed continuously. The diuresis, fluid intake and fluid balance were evaluated on an hourly basis during the operation and for the first 48 h postoperatively. Serum creatinine level (normal range: 0.72–1.25 mg/dl) and other standard laboratory parameters were evaluated on the day of the operation, and 24 and 48 h post-operatively.

Additionally, we measured the NGAL level in the urine using a commercially available ELISA kit (Human Lipocalin -2/NGAL Quantikine ELISA Kit, R&D Systems, Minneapolis, MN, USA) with microplate reader ELx808 (BIO-TEK Instruments, Inc., USA), according to the manufacturer's instructions. The time points for NGAL measurement were: immediately after CPB (post-CPB sample), 1 h after the CPB (post-OP sample) and 24 h from the beginning of the operation (postoperative day 1, POD sample). Preoperative NGAL was not assessed, because of stable kidney function before the cardiac procedure.

After administration of 4 mg/kg of heparin the cardiopulmonary bypass was initiated using a non-pulsatile pump (Maquet, Hirrlingen, Germany) and a membrane oxygenator (Terumo, California, USA) primed with 1000 ml of Ringer's lactate solution, 500 ml of Gelafusine, 60 mEq of sodium bicarbonate and 250 ml of 20% mannitol according to the local protocol. An individual CPB flow was calculated to be at the level of 2.5 l/min/m^2 and the systemic mean arterial blood pressure was maintained between 50 and 70 mm Hg. If systemic perfusion pressure decreased, CPB flow was increased up to a maximum of 130% of the calculated flow. If systemic pressure decrease could not be compensated for by increasing CPB flow, norepinephrine infusion was used to keep the MAP above 50 mm Hg. The operation was performed in normothermia.

Outcomes and follow-up

We analyzed the following medical scenarios: the need for CRRT, clinical observation (general status of the patient, hemodynamic and respiratory stability), duration of post-operative mechanical ventilation, the length of the hospital stay, features of kidney injury in the 30 days after the cardiac procedure and 30-day mortality. Finally, we analyzed 5-year mortality and history of kidney failure. The data were collected from a questionnaire. Data were collected by phone or during the visit in the outpatient clinic.

Statistical analysis

The results were presented as median (lower quartile – upper quartile) or as number of cases and %. The Shapiro-Wilk test was used to check normality of sample data. To determine the differences between the AKI group vs. the non-AKI group the Mann-Whitney rank U test was used for quantitative variables, and Fisher's exact test was used for qualitative variables. The analysis was done using Statistica 10 software (StatSoft, Poland). Statistical significance was set at $p < 0.05$.

Results

The CSA-AKI was diagnosed using the serum creatinine criteria in 13/88 patients (14%) during the first 48 h post-operatively. In all of these cases the staging of AKI diuresis criteria were equivalent to the AKI creatinine criteria. The CRRT was initiated within 48 h after cardiac surgery in 7 of 13 patients (haemodiafiltration mode) due to oliguria. In one case we observed severe clinical symptoms of fluid overload despite AKI stage 1 regarding creatinine level.

The patient population characteristics regarding the acute kidney injury and CRRT requirement are shown in Tables I and II.

Among the study group some nephrotoxic medications were used chronically (furosemide, furosemide, angiotensin-converting-enzyme inhibitor (ACE inhibitor), nonsteroidal anti-inflammatory analgesics (NSAIAs)). None of the patients needed perioperative transfusions of blood products. The exposure to contrast medium was more than one month from the surgical procedure.

There was no difference between the AKI subgroups in the intra-operative period when comparing the minimal body temperature and the need for vasopressors or inotropes. None of the patients needed intra-aortic balloon pump support. Selected data from the intra-operative period and the first 48 h post-operatively are presented in Table III.

At day 30 postoperatively no patient had any biochemical or clinical features of kidney failure. In the long-term follow-up (5 years) 12 patients died and in 7 cases kidney failure were diagnosed and one was treated by chronic intermittent hemodialysis. The cause of kidney failure was not finally established.

There were no statistically significant differences in the biomarker levels during the pre-operative period (zero sample). A comparison of serum creatinine and NGAL excretion with urine in the pre-defined time-points is shown in Table IV for the study population and AKI subgroup.

Regarding AKI diagnosed by serum creatinine after 24 h there were 33% sensitivity and 50% specificity of urinary NGAL increase. After 48 h there were 55% sensitivity and 25% specificity of urinary NGAL increase.

Urine NGAL concentration at defined time points is depicted in Figure 1.

Regarding the staging we diagnosed AKI 1 in 6 cases, AKI 2 in 6 cases and AKI 3 in 1 case within the first 48 h after the operation. However, elevated NGAL level was observed in 5 of 13 patients and in 4 cases without AKI defined by conventional KIDGO criteria (Table V).

All cases of AKI resolved within the first few days after the operation. On day 30 there was no case of kidney failure. However, within 5 years during the

Table I. Demographic data and co-morbidities of the study population (part 1)

Characteristics	No AKI (n = 75)	AKI (n = 13)	P-value	No CRRT in AKI (n = 6)	CRRT in AKI (n = 7)	P-value
Age [years]	61 (57; 67)	70 (64; 77)	< 0.01	72.5 (64; 77)	68 (63; 78)	1.0
BMI	28.2 (25.2; 30.5)	30.7 (28.6; 34.3)	0.01	28.1 (26.8; 31.2)	31.6 (29.4; 34.6)	0.18
LV EF	55 (50; 60)	50 (40; 55)	0.08	47.5 (45; 50)	55 (30; 60)	0.83

BMI – body mass index, LV EF – left ventricle ejection fraction before procedure (%), n – number of patients. Data are given as median (lower quartile; upper quartile).

Table II. Demographic data and co-morbidities of the study population (part 2)

Characteristics	No AKI (n = 75)	AKI (n = 13)	P-value	No CRRT in AKI (n = 6)	CRRT in AKI (n = 7)	P-value
Gender (male)	61 (81%)	9 (53%)	0.32	5 (83%)	4 (57%)	0.34
NYHA ≥ II	48 (64%)	11 (84%)	0.53	6 (100%)	5 (71%)	0.23
Myocardial infarction	31 (41%)	10 (77%)	0.02	5 (83%)	5 (71%)	0.56
Arterial hypertension	64 (85%)	11 (84%)	0.46	5 (83%)	6 (85%)	0.73
Diabetes mellitus	23 (30%)	8 (61%)	0.07	5 (83%)	3 (42%)	0.18
Peripheral vascular disease	74 (98%)	13 (100%)	0.33	6 (100%)	7 (100%)	0.58
Atrial fibrillation	4 (5%)	1 (7%)	0.75	0	1 (14%)	0.54

n – number, NYHA – left ventricular dysfunction classified in New York Heart Association classification.

Table III. Interventions and clinical outcomes of the study population

Characteristics	No AKI (*n* = 75)	AKI (*n* = 13)	*P*-value	No CRRT in AKI (*n* = 6)	CRRT in AKI (*n* = 7)	*P*-value
Interventions:						
CPB time [min]	45 (40; 57)	45 (41; 52.5)	0.78	55 (46; 57)	43 (35; 48)	0.07
Clamping [min]	28 (23; 34)	28.5 (25.5; 33.5)	0.71	27 (27; 35)	30 (24; 32)	0.37
CABG [min]	170 (145; 185)	165 (150; 180)	0.82	173 (160; 180)	150 (150; 190)	0.87
Min. MAP [mm Hg]	52 (45; 60)	48 (45; 50)	0.24	47.5 (45; 50)	48 (46; 50)	0.23
UO CABG [ml]	500 (300; 1000)	500 (200; 500)	0.04	350 (200; 500)	500 (200; 700)	0.45
Fluid balance CABG [ml]	650 (300; 1050)	400 (–100; 1200)	0.33	350 (300; 1450)	450 (–300; 1200)	0.6
Urine output [ml]*	3080 (2650; 3800)	2600 (2300; 2900)	< 0.01	2605 (2550; 3150)	2300 (2000; 2900)	0.28
Fluid balance [ml]*	–696 (–1478; 200)	–700 (–1051; 14)	0.87	–541 (–1000; 14)	–762 (–1730; 370)	0.53
Clinical outcomes and follow-up:						
Mechanical ventilation [h]	14 (11; 19)	18 (10; 22)	0.13	19 (10; 25)	18 (10; 22)	0.94
Hospitalization [days]	6 (5; 7)	8 (7; 8)	0.01	7.5 (6; 8)	8 (7; 9)	0.78
30-day mortality	0	0	–	0	0	–
Kidney failure in 30 days	0	0	–	0	0	–
5-year mortality, *n* (%)	10 (13)	2 (15)	0.85	1 (16)	1 (14)	0.91
Kidney failure in 5 years, *n* (%)	3 (4)	4 (36)	< 0.01	2 (40)	2 (33)	0.66

*CPB – cardiopulmonary bypass, clamping – aorta cross-clamp time, CABG – surgical procedure time, min. MAP – minimal value of MAP (CPB), UO CABG – urine output during surgical procedure, hospitalization – length of stay in cardiac surgery department *from the beginning of the operation to 24 h later, MAP – mean arterial pressure. Data are given as median (lower quartile; upper quartile).*

Table IV. Peri-operative values of serum creatinine and urine NGAL in the study population regarding AKI and in the AKI subgroup regarding CRRT requirement

Characteristics/sample	No AKI (*n* = 75)	AKI (*n* = 13)	*P*-value	No CRRT in AKI (*n* = 6)	CRRT in AKI (*n* = 7)
Creatinine in serum [mg/dl]/zero	0.81 (0.75; 0.98)	0.82 (0.78; 1.09)	0.34	0.8 (0.78; 1.23)	0.91 (0.78; 1.09)
Creatinine in serum [mg/dl]/POD	0.8 (0.72; 0.95)	1.14 (1; 1.59)	< 0.01	1.26 (0.79; 1.61)	1.14 (1; 1.59)
Creatinine in serum [mg/dl]/48 h post-OP	0.79 (0.66; 0.93)	1.68 (1.14; 2)	< 0.01	1.12 (0.97; 1.52)	1.94 (1.68; 2.1)
NGAL [ng/ml]/post-CPB	1.83 (1.08; 3.46)	3.34 (1.94; 6.98)	0.02	2.64 (1.63; 4.12)	4.07 (2.15; 61.91)
NGAL [ng/dl]/post-OP	0.99 (0.65; 1.97)	1.6 (1.16; 7.91)	< 0.01	1.37 (1.15; 3.16)	3.92 (1.31; 27.75)
NGAL [ng/dl]/POD	7.77 (4.5; 15.21)	23.9 (17.4; 32.5)	< 0.01	15.9 (10.3; 19.5)	32.5 (28.4; 39.5)

AKI – acute kidney injury, POD – postoperative day, post-CPB – post cardiopulmonary bypass, post-OP – post-operation, n – number of patients, NGAL – neutrophil gelatinase-associated lipocalin, CRRT – continuous renal replacement therapy. Data are given as median (lower quartile – upper quartile).

follow-up period we noted 7 cases of renal failure recurrence (30%). The analysis of the long-term follow-up every year after the cardiac surgery procedure showed that the recurrence of AKI was observed only within the first year after the operation.

Discussion

The main result of this study showed that the diagnosis of CSA-AKI based on serum creatinine or urine NGAL concentration confirmed transient

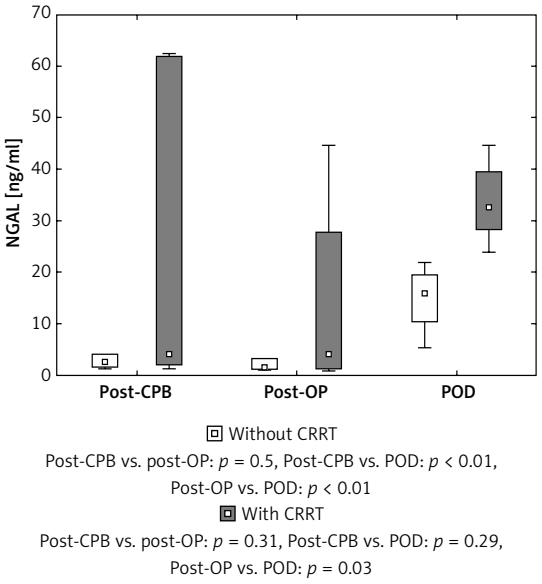

Figure 1. Urine NGAK concentration in the defined time points

POD – postoperative day, post-CPB – post-cardiopulmonary bypass, post-OP – post-operation, NGAL – neutrophil gelatinase-associated lipocalin, CRRT – continuous renal replacement therapy.

acute kidney injury, but is not sufficient to predict outcome.

CSA-AKI risk assessment

In our study the inclusion criteria were very restrictive, which led to a very homogeneous patient population undergoing planned CABG procedures with CPB. The expected risk for post-operative AKI in this type of surgical procedure is increased in our group. In our study, acute kidney injury as a postoperative complication occurred in 13 (14%) patients. We defined CSA-AKI according to the AKI criteria and staging published by KIDGO in 2012, because it is confirmed that even a seemingly negligible change of 0.3 mg/dl serum creatinine concentration may increase mortality [8]. AKI 1 was diagnosed using creatinine criteria in 7 cases and progression to AKI 2 was noted in 1 case only, whereas the remaining 6 AKI cases resolved. There are two groups of risk factors for CSA-AKI: patient- and procedure-related. Patient-related factors are usually known prior to surgery: older age, female sex, history of chronic kidney disease, heart failure with low ejection fraction, chronic obstructive

Table V. Biomarkers measured and CRRT requirement up to 48 hours after cardiac surgery procedures in the study population

Patient no.	AKI stage within 24 h post-op	AKI stage within 48 h post-op	NGAL within 24 h post-op	CRRT within 48 h post-op	AKI 30 days FU	AKI 5 years FU
1	0	1	+	+	–	+
2	1	2	+	+	–	+
3	0	2	+	+	–	–
4	2	2	+	+	–	–
5	0	2	–	–	–	+
6	0	1	–	–	–	–
7	1	0	–	–	–	–
8	1	0	–	–	–	–
9	0	3	–	+	–	–
10	2	2	+	+	–	–
11	0	1	–	–	–	–
12	1	1	–	–	–	+
13	2	2	–	+	–	–
14	0	0	+	–	–	–
15	0	0	+	–	–	–
16	0	0	+	–	–	–
17	0	0	+	–	–	–

AKI – acute kidney injury diagnosed by creatinine and urine output criteria, NGAL – urinary neutrophil gelatinase-associated lipocalin, n – number of the patients in the subgroups, "+" positive AKI diagnosis, "–" negative AKI diagnosis; AKI 30 days FU – AKI within 30 days after operation, AKI 5 years FU – AKI within 5 years after operation.

pulmonary disease, diabetes, emergent surgery, nephrotoxins – medications and contrast, and peripheral artery disease. Intra-operative risk factors are as follows: hemodynamic instability, mechanical blood trauma, regional hypoxia, embolic events, inflammation – cytokines, free radicals, hemodilution, perioperative blood transfusions, hypothermia, cross-clamp time and length of CPB. Typical risk factors of CSA-AKI assessed by available calculators were confirmed in our study group [15–17]. It was found that the patients with AKI were older and had a higher body mass index. Also, AKI occurred more frequently in patients with a past medical history of myocardial infarction. It may suggest the presence of the subclinical cardiorenal syndrome type 1 before the operation. It must be stressed that some of the AKI risk factors can be modified by the operating team, such as minimal and mean arterial pressure, hemodynamic stability and perioperative fluid balance. Long CPB time and low MAP (< 50 mm Hg) are well-known risk factors for CSA-AKI. However, in our population, mean arterial pressure and the length of CPB did not differ significantly. A comparison of intra-operative diuresis showed that in the group of patients who developed postoperative AKI the volume of urine output was significantly lower despite adequate fluid therapy. This finding may be explained as an early symptom of nephron insufficiency.

Biomarkers of CSA-AKI

Cardiac surgery with a cardiopulmonary bypass procedure in previously quite healthy patients is an easy clinical model to observe AKI scenario, because the time of insult is directly known. An ideal biomarker of kidney injury, especially in the acute setting, should be kidney specific objectively, easily, reliably, promptly, and noninvasively measurable, able to detect kidney injury early and inexpensive to measure. None of the novel biomarkers of AKI is ideal. Combinations of multiple biomarkers did not improve their diagnostic power [10, 12].

At present, serum creatinine is a widely studied, cheap and the most commonly used marker of renal function. Together with diuresis, creatinine is a 'gold standard' criterion of recognizing and staging of AKI [8]. That is why we diagnosed CSA-AKI using the serum creatinine criteria. However, serum creatinine is a suboptimal, delayed indicator of acute kidney injury, for many reasons. Serum creatinine level is influenced by multiple non-renal factors (age, gender, muscle mass and metabolism, hydration status, diet and medications) [9]. Because of renal reserve, it can take many hours to achieve a cut-off level for recognizing acute injury of the kidney. Delayed recognition means delayed intervention and treatment and worse outcome. The diagnosis of kidney failure based on the sole creatinine criterion in the early postoperative period may impose difficulties, due to the interplay of many factors: delayed increase of serum creatinine in response to nephron injury and positive fluid balance influencing the volume of distribution of creatinine. Given these limitations of serum creatinine, many urinary and serum molecules have been investigated [12, 17].

NGAL is a 25-kD protein of the lipocalin family. NGAL has been tested in many clinical studies of patients at risk for AKI. Elevation of NGAL levels has been documented in the plasma and urine of animal and human models of ischemic, septic, post-transplantation and nephrotoxic acute kidney injury [18]. NGAL measurements are clinically useful because a rise of this marker is earlier than creatinine. Prowle *et al.* support the thesis that examination of multiple biomarkers (including urinary NGAL) may inform us not only of the likely occurrence of AKI, but its nature, extent and pathogenesis [19]. Due to its origin from renal tubules, urinary NGAL may be of higher predictive value compared with plasma NGAL originating mostly from neutrophils, liver and renal epithelial cells. Thanakitcharu *et al.* showed the diagnostic value of urinary NGAL to predict AKI after cardiac surgery at 3 h after surgery, with a cut-off value for AKI prediction of > 11.3 ng/ml, sensitivity of 72% and specificity of 60%. This study was performed to assess a cut-off level for early detection of AKI in 130 Thai adult patients undergoing open cardiac surgery [20]. Our findings did not support this cut-off value. When considering the reliability of NGAL some authors found higher sensitivity and specificity of urinary NGAL increase [21]. This observation was supported in a pediatric cardiac surgery patient population [22]. Fadel *et al.* evaluated the efficiency of NGAL as an early AKI biomarker after CPB in pediatric cardiac surgery. They defined a cut-off level, very high specificity and sensitivity of plasma NGAL [23]. However, in the adult population these results are not so impressive. Haase *et al.* reported a meta-analysis of results of the potential of NGAL to identify patients with 'subclinical AKI' [24]. In this case there was no diagnostic rise in serum creatinine. The authors postulate redefining AKI criteria. However, to date NGAL is not a criterion of recognizing and staging of AKI.

In previous clinical studies urinary and plasma NGAL demonstrated improved risk stratification and identification of patients at higher risk for progression of AKI compared with the clinical model alone. Our study did not confirm these findings. Bennett *et al.* found that 2 h after CPB urine NGAL levels correlated with severity and duration

of AKI, length of stay, dialysis requirement, and death [25]. Sanjeevani *et al.* found that the 6-hour post-operative NGAL predicted severe AKI most reliably [26]. However, our observations in cardiac patients are different. There is abundant new evidence that the novel biomarkers need further large studies. The perioperative kinetics, the best timing to assess urinary NGAL concentration and the reference values are still a matter of discussion. Bignami *et al.* concluded that in high-risk AKI patients, urinary NGAL increased immediately after cardiac surgery and remained high for several hours. In our study perioperative kinetics of NGAL was different [27]. A systematic review and meta-analysis of the diagnostic performance of early urinary, plasma, and serum biomarkers of cardiac surgery-associated AKI was described by Ho *et al.* [28]. The authors found that current biomarkers (including NGAL) have poor discrimination for AKI when measured in the intraoperative period and within the first 24 h after cardiac surgery in adults. The conclusion is that urinary NGAL intraoperative diagnostic performance is limited [28]. Researchers in the TRIBE-AKI study concluded that the prognostic significance of the studied new biomarkers was less impressive than was previously reported [11, 29]. Haase-Fielitz *et al.* evaluated the current status of NGAL as a biomarker of AKI. They analyzed data from 7000 cardiac surgery patients reported in the available literature. They found some studies that strongly supported the use of urinary NGAL for the prediction of AKI. However, lack of applicable cut-off values and variability in the performance of commercially available NGAL assays are important limitations for implementation of NGAL to AKI definition [30].

Large multicenter studies are required for validation of the use of NGAL (defining cut-off values for diagnosis and outcomes of AKI) in the cardiac surgery adult patient population. In our study we established the diagnosis of AKI using the conventional laboratory biomarker (creatinine 24 h after the surgical procedure) in 13 cases. However, when we compared the NGAL level elevation group to the serum creatinine elevation group we found some differences. Urine NGAL concentration increased in 5 of 13 AKI cases only. This finding may show those cases of AKI that were underdiagnosed using NGAL. On the other hand, in 4 cases we observed elevation of urine NGAL concentration without any changes typical for KIDGO criteria. Therefore a question arises: do solely conventional or novel laboratory biomarkers lead to an under- or overestimation of CSA-AKI diagnosis? The result of our study showed that the diagnosis of CSA-AKI based on serum creatinine or urine NGAL concentration confirmed transient acute kidney injury only. We found very low sensitivity and specificity of urinary NGAL increase (regarding AKI diagnosed by serum creatinine after 24 and 48 h). Despite the importance of these findings, the clinical implications remain to be established, regarding the length of CRRT treatment or prediction of outcome scenario. Hence, in some cases the elevation of biomarkers (conventional or novel) without a clinical implication (e.g. decreased hourly diuresis, clinical features of fluid overload) may be recognized as subclinical. The laboratory results of biomarker elevation marks only the necessity of increased clinical vigilance. Only long-term observation may verify the clinical importance of these laboratory findings.

Outcome in CSA-AKI

An episode of AKI is associated with a number of adverse outcomes, including prolonged hospital stay, hemodialysis dependency, deterioration of quality of life, and increased morbidity and mortality. There are many clinical studies that have discussed the predictive value of conventional and novel biomarkers in AKI. Even small rises in serum creatinine were noted to have 3-fold to 18-fold higher mortality [31, 32]. The results of the study by Moledina *et al.* showed that pre-operative plasma NGAL levels were independently associated with 3-year mortality after cardiac surgery, while post-operative plasma NGAL was not. Higher AKI staging leads to higher mortality [33]. However, we did not confirm these findings in our study.

The course of CSA-AKI may show three scenarios: recovery, progression to chronic renal failure, or recurrence of kidney failure [34]. In our population, all cases of AKI resolved within the first few days after the operation, even though some of the patients needed renal replacement therapy. However, after an early recovery, some of the patients experienced renal failure recurrence within 5 years of the observation period (36% of CSA-AKI patients). The difference was significant and showed the important role of kidney monitoring after an episode of AKI.

According to recent literature, after an isolated CABG 1% of patients require dialysis [35, 36]. The requirement for renal replacement therapy after an episode of CSA-AKI increases morbidity and mortality [37]. Some patients require hemodialysis permanently. Diuretic resistant fluid overload may be a criterion for CRRT initiation despite the normal laboratory results. Usually, AKI 2 stage is an accepted trigger for CRRT initiation [8]. This is not an acceptable cut-off point of urine NGAL elevation used in CRRT requirement assessment. Early CRRT may improve kidney outcome and mortality. Our results confirmed this conclusion regarding recurrence of AKI within 5 years observation. Neither conventional nor novel biomarkers

were sufficient to predict the recurrence of AKI during long-term observation.

Adequate diagnosis and early treatment of CSA-AKI is a challenge because the pathogenesis is multifactorial. In conclusion, the present study showed imperfect aspects of biomarkers used for AKI assessment. The diagnosis of CSA-AKI based on conventional or novel biomarkers confirmed only transient kidney injury, but failed when considering a prognostic value of these biomarkers in adult cardiac surgery patients. The importance of kidney monitoring after an episode of AKI must be stressed, especially in the light of high risk of AKI recurrence.

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Conflict of interest

The authors declare no conflict of interest.

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