Kidney Diseases

Prognostic Significance of Serum NGAL and Troponin I against Acute Kidney Injury in Egyptian ICU Patients after Open Heart Surgery: A Pilot Study

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Abstract

Background: Acute kidney injury (AKI) is a common complication following cardiac surgery and percutaneous coronary interventions, with an estimated incidence rate around 30%, depicted by long-term intensive care unit stay and culminating renal dysfunction over time, triggering either perpetual renal damage evolving to chronic kidney disease/end-stage renal disease transitions or high vulnerability for sudden death after surgery. The classical diagnosis of AKI is based on a sharp rise in serum creatinine that takes at least 48 h to be visible and is associated with multiple nonrenal factors. ***Objective:*** We aimed to evaluate the predictive performance of both neutrophil gelatinase-associated lipocalin (NGAL) and Klotho for AKI in patients who underwent cardiothoracic surgery using cardiopulmonary bypass (CPB). ***Results:*** Out of the 182 patients included in the study, 65 had AKI and 117 had non-AKI according to the Kidney Disease: Improving Global Outcomes criteria relying on serum creatinine levels. Baseline serum NGAL was 103.5 ± 41.69 µg/L in the AKI group compared to 79.12 ± 48.02 µg/L in the non-AKI group ($p <$ 0.01) and then manifested a peak-fall-rise pattern until 48 h of CPB, with a more remarkable change in the AKI than in the non-AKI group. ROC curve analysis for all measured biomarkers after 2 h of CPB showed that serum NGAL (0.819, >75% cutoff, 83.5% accuracy) came after serum creatinine (0.864, >140% cutoff, 85% accuracy), and troponin I was poorer than both (0.606, >5.5% cutoff, 60% accuracy). Furthermore, multivariate analysis showed that preoperative serum NGAL, preoperative eGFR ≤60 mL/min/1.73 m^2, and arterial hypertension were possible risk factors for AKI with adverse outcomes. ***Conclusions:*** Our study suggests the role of preoperative serum NGAL as a prognostic tool for renal consequences after cardiac surgery. Besides, postoperative serum NGAL is a sensitive marker for AKI, but is less specific than serum creatinine. Troponin I is considered to be a risk confirmatory tool and may help in the prediction of AKI. However, its diagnostic utility is restricted due to age-dependent cutoff values and poor standardization and harmonization because of interassay variations.

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Introduction

Acute kidney injury (AKI) is a critical time-based problem with a pathophysiological impact on renal function ranging from slight temporary to severer permanent insult. Moreover, open heart surgery is a potential reason for prerenal AKI with a proportion of 40%, which badly affects 10% of hospital inpatients, leading to delayed discharge and a highly rate of short- or long-term deaths in the intensive care unit (ICU) [1–3]. In a related context, AKI was shown to be a firm transition state between normal kidney function and the worse chronic kidney disease/end-stage renal disease stage that absolutely raises the burden of research for alternatives to the poor prognosis routine renal troponins. Many papers have specified the type of AKI that comes after cardiac surgery, such as cardiovascular surgery-associated AKI (CSA-AKI), and have confirmed it to be the second reason for renal function impairment postoperatively due to related surgical procedures [4] that leads to systemic inflammation, ischemic reperfusion, oxidative stress, neurohormonal activation, intermittent hemodilution, as well as renal and tubular insult [5, 6].

The best way to screen for AKI is in the earlier period, in order to have a sufficient time for therapeutic intervention relying on novel biomarkers besides serum creatinine that exhibited slow changes despite AKI progression [7]. Revelation and testing of these biomarkers is not an easy process and should be less influenced by nonrenal factors, high sensitivity and/or specificity, changes synchronically regarding AKI staging and severity, and high discriminative power, depicted with a convergent kinetic behavior in both animals and humans [8].

A standard definition of AKI is still a challenge and is based on recommended international criteria from professionals and expert societies and is generally described as abrupt retrogradation of kidney function resulting in retention of uremic waste products and extracellular fluid volume disturbances [9]. However, the Kidney Disease: Improving Global Outcomes (KDIGO) criteria surpassed the clinical misapproach of baseline creatinine and kinetics associated with interindividual variations via independent case-by-case assessment rather than the whole assessment [10–13]. Thus, the KDIGO criteria were selected to classify our patients in the study. Besides, serum levels of neutrophil gelatinase-associated lipocalin (NGAL) and Klotho were evaluated in the preoperative (2 h and 1 day) and the postoperative (2 days) period of cardiac surgery using cardiopulmonary bypass (CPB).

NGAL is a secretory glycoprotein that belongs to the lipocalin superfamily, with effective bacteriostatic properties in the innate immunity-related neutrophils, besides iron metabolism regulator functions in other epithelial cells [14]. In response to ischemic renal tubular injury, NGAL is filtered by the glomerulus, reabsorbed via megalin-dependent endocytosis in proximal tubules, and concomitantly rises in urine as well as blood [15]. Previous reports postulated that serum and urine NGAL levels exhibited better sensitivity and/or specificity as an early marker of AKI after cardiac surgery [16, 17]. However, the possible diagnostic utility of NGAL towards acute kidney stress, the pre-injury stage, is still under investigation and is required for understanding the evolution of AKI.

Cardiac troponins isoforms (cTnT, cTnI) are considered to be diagnostic markers for myocardial injury with higher sensitivity and specificity than creatine kinase-MB (CK-MB) [18, 19]. However, the present link between cardiac troponins and the probabilities for chronic kidney disease and end-stage renal disease in cardiovascular disease patients as well as their roles in AKI are still scarce and not well elucidated [20]. A recent study by Omar et al. [21] showed a significant rise in cTnT and overcoming CK-MB levels in AKI patients after cardiac surgery, thus postulating their ability to discriminate high risks for AKI among patients with myocardial injury, ischemia, or even myocardial infarction.

Materials and Methods

Study Population
Our pilot study encompassed 182 age- and sex-matched patients who underwent invasive cardiothoracic surgery using CPB and were transferred to the ICU for postsurgical observation and follow-up. Patients were then classified according to the KDIGO criteria into an AKI and a non-AKI group. The inclusion criteria were age ≤80 years, controlled diabetic patients, and cardiovascular disease patients. The exclusion criteria were patients with diabetic nephropathy, cardiorenal syndrome, hepatorenal syndrome, history of renal disease (either hemodialysis or renal transplants), malignancy, endocrine disorders, autoimmune diseases, and pregnancy.

Methods
Blood samples were collected from all patients five times: before CPB, at the time of CPB (0 h), and 2, 12, and 24 h after CPB. Thereafter, serum aliquots were separated immediately and stored at –20°C to be analyzed as a single serial batch on the Roche Hitachi 912 Chemistry Analyzer for serum creatinine using the BioAssay QuantiChrom™ Assay Kit and the Beckman Coulter UniCel DxI 800 Immunoassay Analyzer for serum NGAL, Troponin I Ultra, CK, and C-reactive protein (CRP) using specialized ELISA kits from Elabscience Ltd., Wuhan, China.

Table 1. Demographic and baseline clinical data of the studied groups

Parameter	Non-AKI group ($n = 117$)	AKI group ($n = 65$)	p value
Age, years	64.15±7.44	64.02±7.49	0.910
Sex			
Male	61 (52.1%)	36 (55.4%)	0.674
Female	56 (47.9%)	29 (44.6%)	
eGFR ≤60 mL/min/1.73 m^2	0 (0.0%)	42 (64.6%)	0.0001*
Arterial hypertension	8 (6.8%)	46 (70.8%)	0.001*
Diabetes mellitus	38 (32.5%)	19 (29.2%)	0.731
Inotropes	80 (68.4%)	48 (73.8%)	0.373
Mechanical ventilation	23 (19.7%)	71 (51%)	0.014*
Left ventricular ejection fraction, %	60.9±9.73	58.8±8.94	0.224
Body mass index	29.63±4.02	29.44±4.22	0.765
Transfusion			
Red blood cells	2.17±2.90	2.46±3.25	0.536
Plasma	1.48±2.43	1.92±3.13	0.289
Thrombocytes	0.15±0.42	0.15±0.40	0.894
Euroscore	2.6±2.55	2.42±2.43	0.649
Preoperative NYHA score			
I	15 (12.8%)	15 (23.1%)	0.189
II	60 (51.3%)	31 (47.7%)	
III	42 (35.9%)	19 (29.2%)	
Surgery type			
CABG	14 (12.0%)	10 (15.4%)	0.206
CABG+AVR	26 (22.2%)	20 (30.8%)	
AVR	63 (53.8%)	26 (40.0%)	
Bentall	3 (2.6%)	4 (6.2%)	
MVR	7 (6.0%)	1 (1.5%	
PMV	4 (3.4%)	4 (6.2%)	
Surgical approach			
Median sternotomy	96 (82.1%)	54 (83.1%)	0.558
Mini-sternotomy	15 (12.8%)	5 (7.7%)	
Mini-thoracotomy	4 (3.4%)	4 (6.2%)	
Endoscopic	2 (1.7%)	2 (3.1%)	
Number of cardiopulmonary bypasses	0.52±0.95	0.71±1.01	0.105
Cardiopulmonary bypass time, min	99.71±33.3	100.3±35.17	0.911
Aortic cross-clamping time	74.86±26.98	80.62±30.03	0.190
Intensive care unit stay, days	7.53±9.70	7.71±9.07	0.904

Figures are presented as mean ± standard deviation or n (%). AKI, acute kidney injury; AVR, aortic valve replacement; CABG, coronary artery bypass graft; MVR, mitral valve replacement; NYHA, New York Heart Association; PMV, percutaneous mitral valvuloplasty. * Significant at $p \leq 0.05$.

Statistics

Data were fed to the computer and analyzed using IBM SPSS software package version 22. Quantitative data were described using range, mean, and standard deviation. The significance of the obtained results was judged at the 5% level. The Student t test was used to compare normally quantitative variables between the two groups. ANOVA was used for comparison between more than two groups. Pearson correlation was used to find the association between each two parameters. ROC curve was used to determine the sensitivity, specificity, and cutoff value of each marker to predict the disease. Multivariate analysis was done to determine the most significant risk factors that affect the outcomes.

Results

All 182 patients studied were distributed according to the KDIGO classification criteria into an AKI group (65 patients) and a non-AKI group (117 patients) according to serum creatinine levels (Fig. 1). The demographic and baseline clinical data of the two studied groups are presented in Table 1. The basic demographic data (age and sex) were matched in the AKI and non-AKI group ($p > 0.05$).
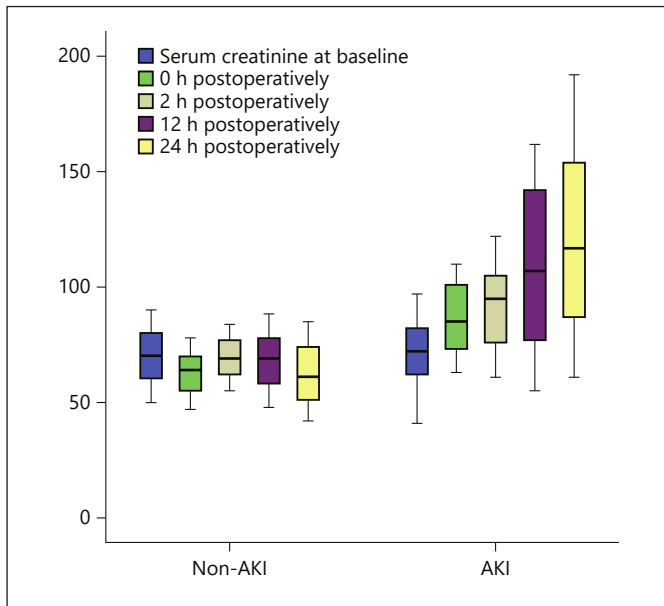
Fig. 1. Serum creatinine in the AKI and the non-AKI group at different follow-up times. AKI, acute kidney injury.

Regarding eGFR ≤60 mL/min/1.73 m², no patients were observed in the non-AKI group, whereas only 42 patients (64.6%) in the AKI group were observed, with an apparent significant difference ($p < 0.01$). Also, there was a significant increase in the number of patients with arterial hypertension in the AKI group compared to the non-AKI group ($p < 0.01$). The other clinical data listed in Table 1 showed no significant difference between the studied groups.

The preoperative baseline serum NGAL levels were superior in the AKI (104.22 ± 23.2 μg/L) compared to the non-AKI group (82.22 ± 30.5 μg/L) ($p < 0.01$) and persisted in the same manner until the end of time fractions. Subsequently, an increase was observed in the preoperative period for the AKI group (213.52 ± 53.6 μg/L) versus the non-AKI group (156.25 ± 45.9 μg/L) ($p < 0.01$). A stepwise superfast in the postoperative periods started from 2 h until it reached a maximum peak after 24 h of CPB (154.14 ± 63.5 μg/L in the AKI group and 69.96 ± 28.5 μg/L in the non-AKI group, $p < 0.05$). Impressively, using the Kruskal-Wallis test to show the extent of divergence between periods revealed a strong significance in the AKI group ($p < 0.001$) and the non-AKI group ($p < 0.01$). Table 2 and Figure 2 presented a compendium of serum NGAL concentrations during the studied periods.

Table 2. Pre- and postoperative values of measured traditional and novel parameters in the AKI and the non-AKI group

Measured biomarker	Studied groups/measurement times											p values at definite times				
	non-AKI group (n = 117)					AKI group (n = 65)										
	pre	post				pre	post					pre	post			
		0 h	2 h	12 h	24 h		0 h	2 h	12 h	24 h			0 h	2 h	12 h	24 h
SCr, μmol/L	69.93±11.6	63.02±9.2	69.39±8.5	68.37±11.7	62.56±12.5	70.88±13.8	86.32±14.3	92.98±17.6	109.15±33.3	122.29±38.4		0.622	0.001*	0.001*	0.001*	0.001*
SNGAL, μg/L	82.22±30.5	156.25±45.9	156.32±30.3	75.21±28.9	69.96±28.5	104.22±23.2	213.52±53.6	215.32±62.3	143.58±50.1	154.14±63.5		0.001*	0.001*	0.001*	0.001*	0.001*
SCK, U/L	5.81±1.7	29.82±9.6	50.77±14.8	85.92±28.5	110.61±46.7	3.42±1.2	6.60±2.4	10.34±5.2	1.53±0.3	8.29±3.7		0.524	0.547	0.001*	0.001*	0.001*
ScTnI, ng/L	5.29±2.5	5.22±2.6	5.16±2.6	3.47±1.3	2.69±1.1	5.38±2.3	6.80±3.1	6.08±2.1	3.97±1.4	2.98±0.9		0.809	0.001*	0.014*	0.012*	0.060
SCRP, μg/L	5.81±1.71	29.82±9.61	50.77±14.82	85.92±28.5	110.61±46.7	5.93±1.88	29.57±9.17	50.10±13.92	85.71±28.24	102.90±49.4		0.668	0.865	0.764	0.963	0.297
eGFR, mL/min/1.73 m²	93.95±15.4	98.37±16.90	85.36±14.05	84.53±14.0	84.55±13.6	91.44±16.91	77.52±14.61	75.08±14.91	61.85±18.22	55.56±14.64		0.311	0.001*	0.001*	0.001*	0.001*

AKI, acute kidney injury; SCK, serum creatine kinase; SCr, serum creatinine; SCRP, serum C-reactive protein; ScTnI, serum cTnI; SNGAL, serum neutrophil gelatinase-associated lipocalin. * p values were calculated to compare between non-AKI and AKI at the same time and considered to be significant at $p \leq 0.05$ using the Student t test.
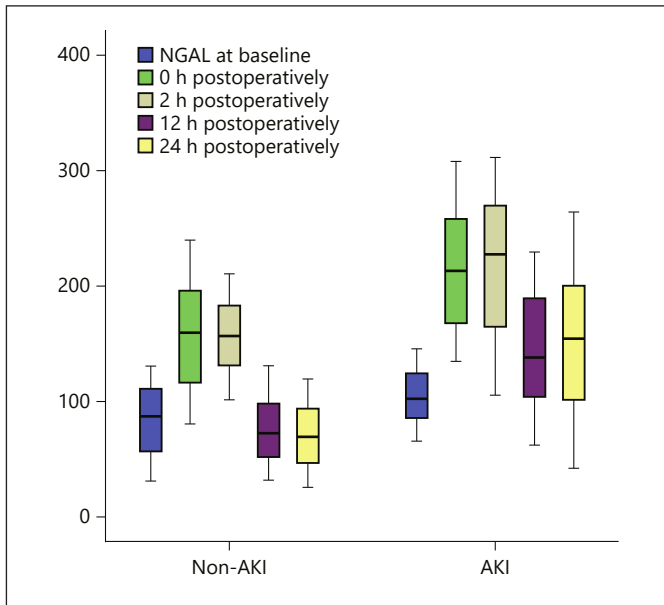
Fig. 2. Serum NGAL in the AKI and the non-AKI group at different follow-up times. AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin.
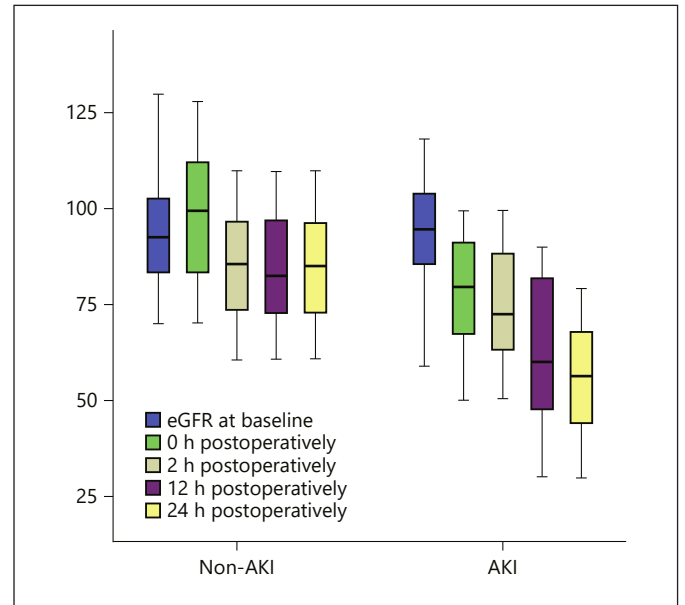

Fig. 3. eGFR in the AKI and the non-AKI group at different follow-up times. AKI, acute kidney injury.
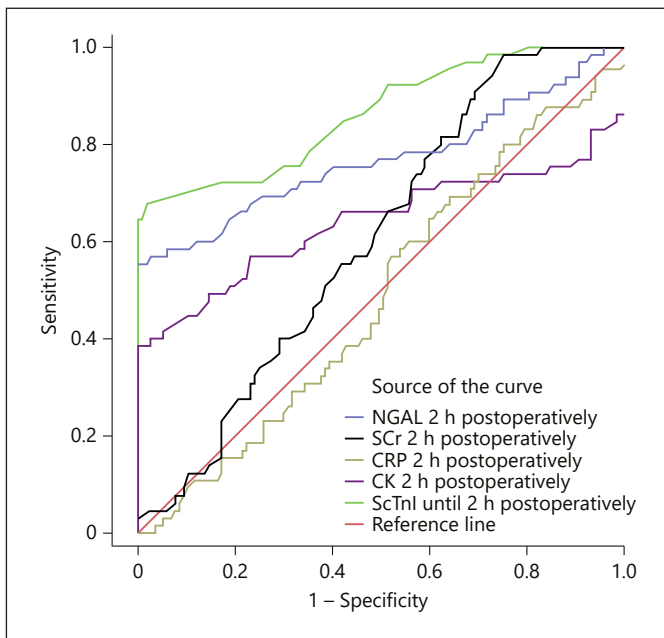

Fig. 4. ROC curve to determine the cutoffs, sensitivity, specificity, and cutoff values of each marker. CK, creatine kinase; CRP, C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine; ScTnI, serum cTnI.

Table 2 also shows the serum creatinine level, eGFR, and serum cTnI in the two groups at different follow-up periods. Preoperative serum creatinine, eGFR, and serum cTnI were matched in the two groups without significant differences. Serum creatinine and serum cTnI increased significantly in the AKI group immediately after operation, and this increase was noticed over the whole follow-up period. On the other hand, eGFR decreased significantly after operation, and the decrease was observed over the whole follow-up period (Fig. 3). Serum CRP showed no significant difference between the two groups over the follow-up period, while serum CK exhibited only a significant difference ($p = 0.001$) 2–24 h postoperatively in the postoperative periods from preoperative as well as immediately after operation between the AKI and the non-AKI group.

Evidently, significant positive correlations were found between serum levels of NGAL and creatinine in the postoperative periods (2, 24, and 48 h) only. However, a direct significant relationship was observed postoperatively between 2-h serum CRP and 2-day serum creatinine ($r = 0.290$ and $p \leq 0.05$). Additionally, serum NGAL at 0 h showed positive correlations with preoperative troponin and 2-day postoperative troponin ($r = 0.306$, $p \leq 0.05$ and $r = 0.282$, $p \leq 0.05$, respectively).

The predictive performance analysis using ROC curve for the measured biomarkers 2 h after CPB is plotted in

Table 3. The area under the ROC curve data with sensitivity, specificity, and cutoff values of each marker

Test variable	AUC	Cutoff value	Sensitivity	Specificity	Accuracy
Cr	0.864	>140.0	88.0	82.0	85.0
NGAL	0.819	>75.0	85.0	82.0	83.5
CK	0.640	>50.0	68.0	62.0	64.6
cTnI	0.606	>5.5	56.0	62.0	60.0
CRP	0.487	>25.0	45.0	50.0	48.0

CK, creatine kinase; Cr, creatinine; CRP, C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin.

Table 4. Logistic multivariate regression analysis of different risk factors with short-term outcomes

Model		Unstandardized coefficients		Standardized coefficients	t	p value
		B	SE	beta		
1	(Constant)	−0.138	0.125		−1.106	0.270
	Baseline NGAL	0.003	0.001	0.175	4.352	0.0001*
	Baseline serum creatinine	0.000	0.002	−0.010	−0.258	0.796
	Arterial hypertension	0.453	0.045	0.432	10.050	0.0001*
	eGFR ≤60 mL/min/1.73 m^2	0.588	0.050	0.517	11.830	0.0001*

Dependent variable: acute kidney injury. NGAL, neutrophil gelatinase-associated lipocalin; SE, standard error. * Significant at $p \leq 0.05$.

Figure 4 regarding AUCs, showing the superiority of the classical serum creatinine compared to the remaining biomarkers (0.864; NGAL, CK, troponin I, and CRP: 0.819, 0.640, 0.606, and 0.487, respectively) (Table 3). Further, multivariate analysis of different risk factors showed that the probable risk factors with adverse outcomes were preoperative serum NGAL and preoperative eGFR ≤60 mL/min/1.73 m^2 and arterial hypertension (Table 4).

Discussion

In our study, KDIGO serum creatinine concentrations showed significant disparity among the studied time intervals. Starting with elevated baseline in the AKI compared to the non-AKI group, lasted longer by the same way in both preoperative as well as postoperative timings too. The rise in serum creatinine levels in cardiac patients prior to surgery might explain persistent hypertension and subclinical inflammation derived from atherosclerotic endothelial dysfunction accompanied by cardiovascular diseases that initially upsets renal function [22]. While the deleterious influences of some anesthetics [23],

catheterization used in critically ill patients [24], and the circulatory pump machine probably result in fluid overload [25], low blood viscosity [26], hemodilution anemia [27], microembolism [28], tissue hypoperfusion [29], hypothermia [30], and hypotension due to the low cardiac output lead to exaggerated elevations of intra- and postoperative levels [31]. In a related context, CRP levels increased massively after surgery in the AKI versus the non-AKI group, indicating the presence of localized inflammation as one of the heart-lung machine adverse effects [32]. However, the other conventional eGFR parameters decreased markedly compared with serum creatinine and CRP in the AKI compared to the non-AKI group, predicting delayed postoperative renal complications.

Despite being indicative of renal function, classical biomarkers, such as serum creatinine, are badly affected by factors such as age, sex, race, medications, diet, muscle mass, hemodilution, and extracorporeal circulation, which presents an inevitable pitfall to the diagnostic propensity of the test over time [33]. As eGFR calculation is always subsidiary to serum creatinine measurement, it is firmly biased too. To prognosticate AKI at earlier stages, new markers of sufficient sensitivity and specificity than

traditional troponins are needed to predict clinical outcomes and potentiate therapeutic interventions.

Assessment of NGAL at serum levels is justified as almost all previous reports on urine and plasma NGAL proved that it could be a surrogate marker for AKI [34, 35]. In addition, studies on serum NGAL are scarce, and its diagnostic utility has not been shown well regarding the CSA-AKI situation. The current study showed that preoperative serum NGAL levels in the non-AKI group were overridden significantly by those in the AKI group, which might be due to the endothelial cell injury accompanying the preexisting coronary artery disease mediated by activated neutrophil recruitment or myocardial contribution beyond congestive heart failure [36, 37].

By the same pattern, serum NGAL concentrations substantially increased during surgery in the AKI compared to the non-AKI group, thus pointing out the impact of the heart-lung machine that upsets cardiac output due to the lack of normalized steady pulsatile flow, lower hematocrit, trigger hypoxemia, launch cell-mediated and humoral immune cascade involving complement activation, and release of inflammatory mediators leading to ischemic renal tubular injury [38, 39]. This observation was consistent with the assumptions of Shemin and Dworkin [40] and Legrand et al. [41] of NGAL being a convenient alert against cumulative structural changes of renal tubular epithelia in patients suffering from consolidated nephrotoxic consequences emanating from CPB or radiocontrast agents. In the postoperative period, a continual increment of serum NGAL levels from 2 to 24 h eventually manifested with a plateau within 48 h compared with a higher starting baseline in the AKI group (228.58 μg/L) than in the other group (178.08 μg/L). Compatibly, Kadry et al. [42] disclosed a profound increase in serum NGAL in the AKI group after 48 h (202 ng/mL). Furthermore, ROC curve analyses elucidated that serum NGAL failed to overcome the superiority of serum creatinine even 2 h earlier in the postoperative period, which supports the findings of Nickolas et al. [43], but contradicts the findings of Mishra et al. [44] The cutoff value of serum NGAL after 2 h was 78 μg/L, with 76.9% sensitivity, 54% specificity, and an AUC of 0.761. In contrast, different cutoff values obtained by Krawczeski et al. [45] in young children and by El-Farghali et al. [46] in neonates were 100 and 117.5 ng/mL, with 82% sensitivity, 89% specificity, and an AUC of 0.95, respectively. These salient interstudy variations suggest the presence of comorbidities affecting the performance of serum NGAL over time, including age, sepsis, diabetes, population size, sex, body fat, and liver function [47, 48]. Impressively, high preoperative concentrations of serum NGAL may predict ongoing renal tubular insult after cardiothoracic surgery, predominantly encompassing the uppermost value by the end of the time course.

Preoperative serum levels of troponin I in both groups were matched without any significant difference. At the perioperative (0 h) and postoperative (2 and 12 h) periods, troponin I levels showed significant increases in the AKI group compared to the non-AKI group that might have been influenced by cardiac surgical consequences, including trauma, sepsis, acute pericarditis, and acute heart failure [49, 50].

Inferior levels 1 day after surgery ($p < 0.06$), near the statistical significance shown by Croal et al. [51], might predict ongoing peri-/postoperative problems. In a related context, ROC analysis showed low sensitivity, specificity, and accuracy for troponin I. This is in agreement with Omar et al. [21], who suggested the possibility of troponin I being an inaccurate marker of perioperative myocardial infarction in patients who develop AKI after cardiac surgery.

Conclusion

We conclude that preoperative serum NGAL may act as a prognostic predictor for renal tubular injury after cardiothoracic surgery, and that its sensitivity and specificity may be increased by designing a smart combination of preoperative eGFR and serum NGAL. However, postoperative NGAL was found to be a more sensitive marker for AKI than creatinine, but creatinine was found to be more specific than NGAL. Furthermore, we suggest the presence of multiple factors with direct or indirect impact on the diagnostic performance for AKI that will be worth investigating on a large scale. Troponin I was a promising prognostic biomarker for CSA-AKI due to early increase at the immediate (0 h) period with NGAL. However, age-dependent cutoffs, lack of standardization and harmonization because of the interassay variations, and influences of surgical events remains obstacles to the diagnostic utility of troponin I.

Statement of Ethics

Inclusion of the study population after obtaining written consent was in accordance with the declaration of Helsinki code of ethics and the National Egyptian Committee of Biomedical Ethics.

Disclosure Statement

All authors declare that they have no conflicts of interest.

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