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Article

Can Inflammation Indices Preoperatively Predict Acute Kidney Injury after Cardiac Surgery?

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Abstract

Background: Coronary artery disease is a condition characterized by atherosclerosis and inflammation in the vessel wall. In patient undergoing surgery, a systemic inflammatory-like condition occurs in the postoperative period through mediators that develop due to acute stress. **Methods**: 581 patients enrolled from the hospital records from 2019 and 2022 retrospectively. Systemic immune inflammation index (SII), systemic inflammation response index (SIRI) and aggregated index of systemic inflammation (AISI) values were calculated from peripheral blood samples taken at hospital admission using the formula SII = platelet (P) $\times$ neutrophil (N) / lymphocyte (L), SIRI = N $\times$ monocyte (M) / L, AISI = (N $\times$ M $\times$ P) / L. **Results**: The mean age of the 581 patients included in the study was 63.97 $\pm$ 8.77 years. 45% of the patients were women. Mean cardio-pulmonary bypass time (CPBT) was 100.31 $\pm$ 31.94 and mean cross-clamp time (CCT) was 59.79 $\pm$ 24.07. When the correlation of acute kidney injury (AKI) development was analyzed with the variables (P/L ratio, N/L ratio, SII, SIRI, AISI, CCT and CPBT), all variables we tested and age were found to be significantly correlated ($p < 0.01$). **Conclusion**: We think that the calculations we tested in our study, together with the understanding of the complexity of the inflammatory system, will constitute an important step in the detection of AKI.

Keywords

cardiac surgery; inflammation; acute kidney injury

Introduction

Coronary artery disease is a condition characterized by atherosclerosis and inflammation in the vessel wall. In patient undergoing surgery, a systemic inflammatory-like condition occurs in the postoperative period through mediators that develop due to acute stress. The main cells in the subsequent inflammation are neutrophils, platelets, and lymphocytes [1,2]. The incidence of cardiac, pulmonary, and renal complications is high in patients after cardiac surgery. With the effect of inflammation, the risk of morbidity and mortality increases in these patients. Surgical revascularization is still the most effective treatment for coronary artery disease. Cardiac surgical methods such as off-pump surgery have been developed to minimize postoperative systemic inflammation and thus neurological events and renal failure. Healthcare professionals have thus aimed to reduce the length of hospital stay and mortality [3]. European Cardiac Operative Risk System Assessment II (EuroSCORE II) is the most widely used in practice today as a preoperative risk scoring method. However, the inflammatory process of the patients is not evaluated in this test [4].

Laboratory parameters such as white blood cell counting (WBC), C reactive protein (CRP), procalcitonin can be used in the preoperative evaluation to show the burden of inflammation in patients. Since preoperative and postoperative comparison does not have a linear relationship and is more costly, alternative methods are being emphasized. The systemic immune inflammation index (SII), the systemic inflammation response index (SIRI), and the aggregated index of systemic inflammation (AISI), calculated according to the number of cells involved in inflammation, reflect the balance between inflammation and the immune system in many studies. Platelet, neutrophil, monocyte, and lymphocyte ratios used in the index calculation are preferred in many studies to predict inflammation because they are easily accessible and reflect cumulative variability [5,6].

Acute kidney injury (AKI) after cardiac surgery is a sudden deterioration in glomerular filtration. Studies have found that it is seen between 1% and 30% [7]. Studies have shown that an increase of 0.3–0.5 mg/dL in serum creatinine level in the postoperative period causes an approximately 3-fold increase in 30-day mortality, while an increase of >0.5 mg/dL causes an 18-fold increase in 30-day mortality [8].

Cardiac surgery with cardiopulmonary bypass (CPB) is the second most common cause of acute renal failure after sepsis in intensive care unit patients [9]. The development of acute renal failure in these patients is associated with a significant increase in infectious complications [10]. Preoperative risk factors include advanced age, cardiac disease and impaired renal function measured in the preoperative period. Intraoperative risk factors also affect the postoperative period. These factors that are effective during cardiac surgery can be listed as cardiopulmonary bypass duration and type of surgery. Since systemic inflammation is one of the factors leading to the development of acute renal failure, predicting the intensity of inflammation in these patients in the preoperative period will be meaningful in terms of mortality [11].

In this study, SIRI, SII and AISI measurements were used to predict the development of AKI, which is an important problem in the postoperative period, in patients who underwent open heart surgery with CPB values have been investigated.

Table 1. Descriptive statistics of n = 581 patients.

	Minimum	Maximum	Mean	Std. Deviation
AGE	36	90	63.97	8.77
CCT (min)	26	201	59.79	24.07
CPBT (min)	43	256	100.31	31.94
SII	111.23	5554.44	750.18	463.98
SIRI	0.10	19	1.9	1.55
AISI	27.91	5221.18	484.60	431.56

CCT, cross-clamp time; CPBT, cardio-pulmonary bypass time; SII, systemic inflammation index; SIRI, systemic inflammation response index; AISI aggregated index of systemic inflammation; Std, standard.

Material- Methods

In our study, the clinical data of patients who underwent heart-lung machine-assisted open cardiac surgery in our clinic between January 2019 and August 2022 were retrospectively reviewed in order to examine the predictive effect of pre-operative AISI, SII and SIRI value in the development of postoperative AKI. 615 patients were included in the study. All data were obtained from the patient archives, and patients with missing data and results (n = 34) in the archive were excluded. Only patients with complete archival documents were included in the study (n = 581). This study was approved by the local ethics committee with decision number 15468. Patients' age, gender, comorbidities, other demographic characteristics, and the type of surgery performed were noted, and the patients were grouped according to the development of post-operative AKI.

The patients were randomly divided into two groups. The pre-operative, and post-operative laboratory results of the patients in these two groups, the length of stay in the intensive care unit (ICU), the duration of the operation and the duration of the cross clamp were noted. SII, SIRI and AISI values were calculated from peripheral blood samples taken at hospital admission using the formula SII = platelet (P) × neutrophil (N) / lymphocyte (L), SIRI = N × monocyte (M) / L, AISI = (N × M × P) / L. Postoperative AKI development was determined based on urea-creatinine values on the 1st and 2nd postoperative days and according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. The KDIGO Criteria were used as follows, $\geq$0.3 mg/dL increase or $\geq$50% increase in serum creatinine level within 48 hours; known or estimated to occur in the last seven days; an increase in serum creatinine $\geq$1.5 times the baseline value, or urine output $<$0.5 mL/kg/hr for six hours.

Cases older than 18 years of age, patients with complete archival documents, patients who had heart-lung machine assisted open cardiac surgery, and patients who developed post-operative AKI were included in the study. Cases younger than 18 years of age, patients with oncological malignancy, patients with endocarditis, pregnant and lactating patients, and patients with pre-operative acute kidney injury of chronic kidney disease (AKI-CKD) were excluded from the study.

Statistical Analysis

The difference between the groups was evaluated by statistical comparison. Percentage distributions were calculated in the analysis of the descriptive findings to be made with the median, the largest and the smallest values in the analysis of continuous variables. Those with a statistical significance level of $p < 0.05$ were considered significant. Cut-off value was calculated by receiver operating characteristic (ROC) analysis. The data were analyzed with the SPSS 20.0 package program (IBM Corp., Armonk, NY, USA).

Results

The mean age of the 581 patients included in the study was 63.97 ± 8.77 years. 45% of the patients were women. The demographic results of our study are summarized in Table 1.

In 112 of 581 patients, AKI developed in the early postoperative period, and 11 of them had to undergo dialysis. Seven of the patients who developed acute renal failure died in the intensive care unit. When the patients who developed AKI among the patients followed in the intensive care unit were examined, a significant increase was found in the preoperative SII and SIRI results compared to those who did not.

Mean cardio-pulmonary bypass time (CPBT) was 100.31 ± 31.94 and mean cross-clamp time (CCT) was 59.79 ± 24.07.

When we analyzed the correlation of AKI development with variables, all variables we tested and age were found to be significantly correlated ($p < 0.01$) (Table 2).

When we analyzed the development of AKI depending on the variables, the values we found were found to be statistically significant as shown in Table 3.

Table 2. Correlation of the variables.

N = 581		AGE	AKI	P/L ratio	N/L ratio	SII	SIRI	AISI	CCT (Min)	CPBT (Min)
AGE	Pearson Correlation	1	0.183	0.215	0.008	0.104	0.076	0.052	0.109	0.098
	Sig. (2-tailed)		<0.001	<0.001	0.851	0.012	0.069	0.206	0.010	0.019
AKI	Pearson Correlation	0.183	1	0.162	0.038	0.195	0.218	0.203	0.190	0.158
	Sig. (2-tailed)	<0.001		<0.001	0.383	<0.001	<0.001	<0.001	<0.001	<0.001
P/L ratio	Pearson Correlation	0.215	0.162	1	–0.146	0.728	0.420	0.513	0.150	0.107
	Sig. (2-tailed)	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	0.010
N/L ratio	Pearson Correlation	0.008	0.038	–0.146	1	0.101	0.213	0.102	0.018	0.014
	Sig. (2-tailed)	0.851	0.383	0.001		0.019	<0.001	0.018	0.683	0.744
SII	Pearson Correlation	0.104	0.195	0.728	0.101	1	0.804	0.866	0.128	0.110
	Sig. (2-tailed)	0.012	<0.001	<0.001	0.019		<0.001	<0.001	0.002	0.009
SIRI	Pearson Correlation	0.076	0.218	0.420	0.213	0.804	1	0.929	0.139	0.137
	Sig. (2-tailed)	0.069	<0.001	<0.001	<0.001	<0.001		<0.001	0.001	0.001
AISI	Pearson Correlation	0.052	0.203	0.513	0.102	0.866	0.929	1	0.134	0.135
	Sig. (2-tailed)	0.206	<0.001	<0.001	0.018	<0.001	<0.001		0.001	0.001
CCT (Min)	Pearson Correlation	0.109	0.190	0.150	0.018	0.128	0.139	0.134	1	0.909
	Sig. (2-tailed)	0.010	<0.001	<0.001	0.683	0.002	0.001	0.001		0.000
CPBT (Min)	Pearson Correlation	0.098	0.158	0.107	0.014	0.110	0.137	0.135	0.909	1
	Sig. (2-tailed)	0.019	<0.001	0.010	0.744	0.009	0.001	0.001	0.000	
	N	581	581	581	581	581	581	581	581	581

AKI, Acute kidney injury; P/L Ratio, platelet to lymphocyte ratio; N/L Ratio, neutrophil to lymphocyte ratio; CCT, cross-clamp time; CPBT, cardio-pulmonary bypass time; SII, systemic inflammation index; SIRI, systemic inflammation response index; AISI, aggregated index of systemic inflammation.

Table 3. Impact of variables on the development of AKI.

	AGE	SII	SIRI	AISI	CCT (Min)	CPBT (Min)
Mann-Whitney U	19,143.500	21,224.000	20,505.000	20,520.000	20,071.000	21,527.000
Wilcoxon W	129,358.500	131,439.000	130,720.000	130,735.000	123,811.000	126,180.000
Z	–4.464	–3.158	–3.608	–3.599	–3.355	–2.607
Asymp. Sig. (2-tailed)	<0.001	0.002	<0.001	<0.001	<0.001	0.009
Grouping Variable: AKI						

AKI, Acute kidney injury; CCT, cross-clamp time; CPBT, cardio-pulmonary bypass time; SII, systemic inflammation index; SIRI, systemic inflammation response index; AISI, aggregated index of systemic inflammation.

When we determined the cut-off for SII, SIRI and AISI values and performed ROC analysis, we found that the sensitivity of the SII value was 72%, while the values of the other two measurements were 59% for SIRI and 61% for AISI (Table 4, Fig. 1).

When logistic regression analysis was performed to determine whether the variables that were significantly correlated with each other in our study were independent risk factors for AKI, only age was significant (Table 5).

Discussion

AKI is one of the major complications frequently seen after open heart surgery. It is clinically important because it develops in the postoperative period and affects mortality in patients. Even a small decrease in renal functions prolongs the length of stay in the intensive care unit and causes an increase in costs [12].

When we look at the literature, it has been seen that there are more than 30 classifications when diagnosing acute kidney injury. The most commonly used classifications are RIFLE (Risk, Injury, Failure, Renal dysfunction and end-stage renal disease), AKIN (Acute Kidney Injury Network), KDIGO (Kidney Disease Improving Global Outcomes) [13,14].

Although many new biomarkers are working for acute kidney injury, the most commonly used markers are still creatine and urea. Creatinine is a product of skeletal muscle metabolism that occurs after the breakdown of creatine phosphate. While it is secreted steadily through glomerular filtration, it gives reliable results because it is not reabsorbed. Its disadvantage is that the amount may vary depending on muscle mass, muscle breakdown and drug use. Urea is a product of nitrogen metabolism consisting of amino acids. Urea carries nitrogen to water, creating an osmotic gradient for water reabsorption. In case of weight loss and dehydration, the amount can be misleading [15]. Dif-

Table 4. ROC curve.

	AUC	Sensitivity	Specificity	95% CI		*p* value
				Lower Bound	Upper Bound	
SII	0.645	0.720	0.460	0.568	0.721	$<$0.001
SIRI	0.628	0.590	0.410	0.552	0.705	0.002
AISI	0.631	0.610	0.390	0.554	0.708	0.001

SII, systemic inflammation index; SIRI, systemic inflammation response index; AISI, aggregated index of systemic inflammation.

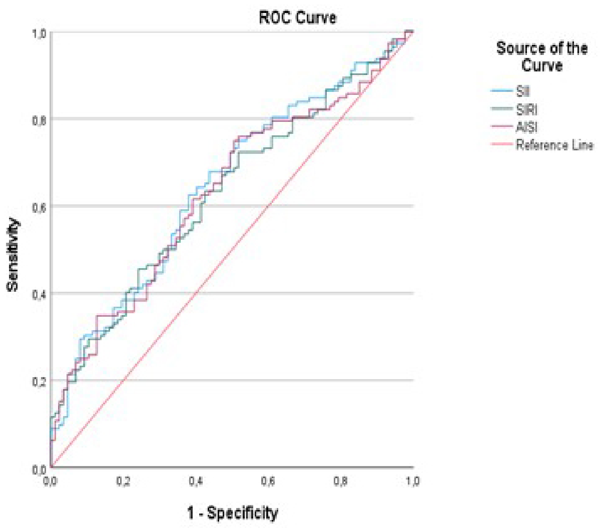

Fig. 1. Receiver operating characteristic (ROC) curve.

Table 5. Logistic regression of the values.

	Sig.	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
SII	0.507	1.000	0.999	1.002
SIRI	0.122	1.359	0.921	2.006
AISI	0.465	0.999	0.998	1.001
AGE	0.001	1.049	1.019	1.079
P/L	0.595	1.002	0.995	1.009
CCT (min)	0.055	1.022	1.000	1.046
CPBT (min)	0.479	0.994	0.977	1.011

SII, systemic inflammation index; SIRI, systemic inflammation response index; AISI, aggregated index of systemic inflammation; P/L, platelet to lymphocyte ratio; CCT, cross-clamp time; CPBT, cardio-pulmonary bypass time; Sig, Significance.

ferent mechanisms are effective in the formation of acute kidney injury. These are decreased renal perfusion, inflammation, use of nephrotoxic drugs [16,17].

Despite new biomarkers such as cystatin-c, NGAL neutrophil gelatinase-associated lipocalin have been used in the detection of acute kidney injury, there is no clinical test or biomarker that can detect the possibility of AKI development in the preoperative period. New biomarkers such as cystatin-c, neutrophil gelatinase-associated lipocalin (NGAL) have been used in the detection of acute kidney injury, there is no clinical test or biomarker that can detect the possibility of AKI development in the preoperative period.

During cardiac surgery, low flow, rapid circulation and rapid temperature changes predispose to renal hypoperfusion. Again, a decrease in renal perfusion may develop due to excessive bleeding during surgery. A decrease of 20% or more in cardiac output during open heart surgery causes pathology in the kidneys. The areas where the proximal tubules are most abundant are the metabolically active areas and are the area's most susceptible to anoxic. As a result, a picture of renal failure due to acute tubular necrosis develops [18].

Inflammatory substance accumulation due to tissue trauma and blood transfusion during surgery is one of the factors that cause renal failure by causing inflammation in renal cells [19]. Kidney function is also affected by various medications that are commonly used before, during, and after surgery. Antibiotics, nonsteroidal anti-inflammatory drugs, antihypertensive drugs are the most commonly used and affecting drugs in this process. Again, contrast agents used in imaging methods applied for diagnosis before surgery may pose a risk in the development of renal failure [20].

Preoperative risk factors include female gender, preexisting chronic kidney disease, diabetes, chronic obstructive pulmonary disease, previous cardiac surgery, arterial hypertension, congestive heart failure, left ventricular ejection fraction $<$35% and obesity. Considering the intraoperative factors, it was determined that CPBT is one of the most important risks factors [21,22].

As far as our research shows, these calculations have not been used for the early detection of AKI in the literature. None of the markers currently used for detecting AKI are suitable for preoperative use as they only detect AKI and acute tubular necrosis after they have already occurred. The calculations implemented in our study were specifically developed and tested for preoperative detection. Detecting AKI during the preoperative period will not only ensure important precautions can be taken while treating the patient but will also significantly reduce hospital stay, financial burden, and ultimately mortality.

Conclusion

All improvements in AKI detection will help to reduce the mortality of cardiac surgery. Being able to detect AKI before it develops and being in a position to avoid it is a happiness that every cardiac surgeon would like to have. We think that the calculations we tested in our study, together with the understanding of the complexity of the inflammatory system, will constitute an important step in the detection of AKI.

Abbreviations

WBC, white blood cell counting; CRP, C reactive protein; EuroSCORE II, European Cardiac Operative Risk System Assessment II; SII, Systemic immune inflammation index; SIRI, Systemic inflammation response index; AISI, Aggregated index of systemic inflammation; AKI, Acute kidney injury; CPB, Cardiac surgery with cardiopulmonary bypass; CPBT, cardio-pulmonary bypass time; CCT, cross-clamp time.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

SY: Designing, data collecting, analyzing, and writing the manuscript. All procedures completed by the author.

Ethics Approval and Consent to Participate

This study was approved by the Necmettin Erbakan University School of Medicine ethics comitee with decision number 15468. This is a retrospective study, so we do not signed informed consent form to the patients.

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Conflict of Interest

The authors declare no conflict of interest.

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