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Original Paper

Risk Factors for Acute Kidney Injury after Coronary Artery Bypass Surgery and Its Detection Using Neutrophil Gelatinase-Associated Lipocalin

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Key Words
Acute kidney injury · Neutrophil gelatinase-associated lipocalin · Inflammation · Atherosclerosis · Cardiac surgery

Abstract
Introduction: Acute kidney injury (AKI) is an important complication of cardiac surgery due to its high mortality. The aim of the present study was to detect the factors leading to AKI in patients who underwent coronary artery bypass surgery (CABS) and also to determine the optimal timing for detecting AKI using the biomarker neutrophil gelatinase-associated lipocalin (NGAL). ***Materials and Methods:*** The records of 375 patients who underwent CABS were reviewed in this case-control study. Ejection fraction (EF), common carotid artery intima-media thickness (CCA-IMT) and cross-clamp (C-C) time of the patients were recorded. Blood samples were taken from all patients on preoperative day 1 as well as 6, 12, 24, 36, 48 h and 7 days after operation. Biochemical parameters were studied in patients with and without AKI. ***Results:*** According to the Risk Injury Failure Loss End Stage criteria, 24 patients had renal risk, 17 had injury and 4 had failure. Postoperative 24-hour serum creatinine levels indicated the risk of renal dysfunction for only 4 patients in the AKI group. CCA-IMT, C-C time, haematocrit (HCT) and preoperative interleukin-6 levels were significantly higher in the AKI group than in the non-AKI group. Postoperative 6- and 12-hour NGAL levels in the AKI group correlated with postoperative 36-hour serum creatinine levels. The optimal cut-off values for postoperative 6- and 12-hour NGAL test were 310 and 283 ng/ml, respectively. The area under the curve was higher in the 12-hour NGAL test ($p < 0.0086$). ***Conclusion:*** The number of stenotic coronary arteries, EF, CCA-IMT and HCT are all important risk factors. Early postoperative NGAL results were highly specific for the early recognition of AKI.

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Introduction

Acute kidney injury (AKI) is considered an independent risk factor for morbidity and mortality in hospitalised patients, especially in those who have undergone major surgery [1, 2]. The severity and progression of AKI have significant deleterious effects on patient outcomes after cardiovascular surgery [3, 4]. Recent research has shown that AKI is related to inflammation and atherosclerosis, especially after cardiac surgery. In this regard, inflammatory cytokines such as C-reactive protein, interleukin-6 (IL-6) and tumour necrosis factor-alpha were used to detect preoperative inflammation [5]. A negative correlation was also found between common carotid artery intima-media thickness (CCA-IMT), an important finding in atherosclerosis, and renal function [6], which may indicate a relationship between inflammation and AKI after coronary artery bypass surgery (CABS). As a result of chronic inflammatory processes, atherosclerosis might affect both coronary and renal arteries. In this context, coronary artery disease was found to be closely associated with AKI [7].

Recently, the definition of AKI was standardised by the Acute Kidney Injury Network [8] and the Risk Injury Failure Loss End Stage (RIFLE) criteria [9]. Serum creatinine (SCr) levels are routinely used for detecting postoperative AKI. However, urine and SCr levels are insufficient for the early detection of postoperative short-term acute renal pathologies, and SCr levels are affected by haemodilution protocols during CABS [10]. Recent studies have shown that neutrophil gelatinase-associated lipocalin (NGAL) can be a useful biomarker for the early prediction of acute renal injury after CABS [4]. In a multicentre study aimed at demonstrating the importance of NGAL, Haase et al. [11] clearly showed that this novel marker could detect subclinical AKI even in the absence of diagnostic increases in SCr. Additionally, NGAL has been reported to be predictive 48 h prior to the actual time of injury; therefore, renal replacement therapy can be planned earlier [12]. Wagener et al. [13] reported that after cardiac surgery, an increase in postoperative 3-hour urinary NGAL levels poses a high risk in adults. However, the optimal time at which to use NGAL for detecting AKI due to renal parenchyma damage is still unknown and needs further research. Also, the relationship between NGAL and those factors causing renal parenchymal damage during the preoperative and postoperative periods is very important while planning prophylactic treatment for possible acute renal failure [7].

This study was designed based on previous knowledge to detect factors leading to AKI in patients who underwent CABS and to determine the optimal time for detecting AKI using the biomarkers NGAL and SCr.

Materials and Methods

The records of 375 patients (210 male, 165 female) who underwent CABS at Mengücek Education and Research Hospital between January 2013 and June 2015 were reviewed for eligibility. The blood samples of all patients were centrifuged at 3,500 rpm for 10 min, and serum and plasma (EDTA) samples were stored at –80°C. The same surgical team operated on all patients included in the study using the same technique for CABS. Propofol (5–6 mg/kg/h) + fentanyl (3–5 μg/kg/h) or propofol (2–3 mg/kg/h) + fentanyl (3–5 μg/kg/h) + 5% desflurane infusion was used for the anaesthetic preconditioning protocol. Bispectral index monitoring was performed to assess the depth of anaesthesia. The bispectral index was maintained between 40 and 50 for all patients. During CABS, the heart was separated from the circulatory system using an aortic cross-clamp (C-C), and heart and lung functions were carried out using an extracorporeal circulation (ECC) machine. For adequate oxygen concentration and optimum perfusion, the ECC flow rate was 1.8–2.4 litres/min/m^2 and the mean perfusion pressure was 50–70 mm Hg [14]. Forty-five patients who developed different degrees of acute renal failure after surgery according to the RIFLE criteria were included in the AKI group [9]. In these patients, SCr and creatinine clearance (CrCl) values were used to assess the severity of damage, risk of renal dysfunction, injury to the kidney and failure of kidney function. There were no patients with persistent or end-stage renal injury. Forty-five patients were chosen randomly from the reviewed patients

who underwent CABS and did not develop acute renal failure; they formed the non-AKI group. The following exclusion criteria were applied: patients with congenital heart disease, tumours and inflammatory diseases (rheumatoid arthritis, Behçet disease, sarcoidosis, systemic lupus erythematosus, scleroderma, polyarteritis nodosa, Sjögren syndrome); patients who might have elevated levels of IL-6 due to excessive exercise (until 1 month before surgery); patients who had renal failure before cardiac surgery with a high SCr or patients with chronic renal diseases (lupus nephritis, glomerulonephritis, obstruction, dysplasia, polycystic renal disease, IgA nephropathy); and patients who died after surgery, because postoperative analyses could not be performed. Demographic characteristics of the patients, such as gender, age, weight, height, waist circumference, chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus, hypertension, hyperlipidaemia, smoking and alcohol consumption (at least 1 year), were recorded.

The same cardiologist evaluated the coronary X-ray angiographies of all patients included in the study with regard to the severity of coronary artery stenosis and the number of stenotic arteries. Coronary artery stenosis was accepted as 50% and higher, and the number of stenotic coronary arteries (NSCA) per patient was recorded. Also, the same cardiologist measured the CCA-IMT values of all patients by ultrasonography. Mean CCA-IMT was calculated using bilateral artery values. Ejection fraction (EF) was calculated for all patients using the ratio of total left ventricular stroke volume to end-diastolic volume, which was measured by echocardiography. Anaesthetic preconditioning protocol, C-C time and intensive care time for all patients were recorded.

Study Design and Laboratory Parameters

For both the AKI and the control group, IL-6, NGAL and SCr levels were analysed from the blood samples taken from all patients on preoperative day 1 as well as 6, 12, 24, 36, 48 h and 7 days after operation. High-sensitivity C-reactive protein, creatine kinase-myocardial band, troponin-I, glucose, urea, SCr, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, low-density lipoprotein, high-density lipoprotein, triglyceride, total protein, albumin, iron, sodium, potassium, calcium and haematocrit (HCT) were studied in the preoperative blood samples. For the easy and quick approximation of glomerular filtration rate, the Cockcroft-Gault formula was used. This method was also preferred for the calculation of CrCl [15].

Glucose, urea, SCr, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase-myocardial band, low-density lipoprotein, high-density lipoprotein, triglyceride, total protein, albumin, iron, sodium, potassium and calcium levels were measured using a Olympus AU2700TM Chemistry-Immuno Analyzer (Olympus, Tokyo, Japan). The HCT ratio was measured using a BT PRO 2401 5-part-Diff Auto Hematology Analyzer (URIT, Guilin, People's Republic of China). Also, high-sensitivity C-reactive protein levels were measured using the latex-enhanced method in a Siemens Dade Behring BN II Nephelometer (Siemens, Deerfield, Ill., USA). Troponin-I levels were measured using a Siemens Advia Centaur XP immunoassay machine. A human IL-6 ELISA Kit (MyBioSource, San Diego, Calif., USA) with an analytical sensitivity of 1 pg/ml was used for IL-6 levels, which were assessed using an Epoch Microplate ELISA Reader (BioTec, Winooski, Vt., USA). NGAL levels were measured using the Triage NGAL Test kit (Biosite Inc., San Diego, Calif., USA) in an Alere Triage MeterPro machine.

Statistical Analysis

The SPSS 15.0 statistical software and the InStat3 GraphPad software were used for all statistical analyses. The PS Power and Sample Size Calculation Program was used for validation of the difference between the NGAL levels of independent groups and power analysis of two or more independent groups. Data are expressed as mean ± standard deviation. Dichotomous variables were compared using the χ^2 test. Statistical differences between parametric data of two groups were analysed using Student's t test. The Mann-Whitney U test was used to determine differences between non-parametric data. One-way analysis of variance (ANOVA) was used to test the differences between parametric data, and the Kruskal-Wallis test was used for non-parametric data. In two or more dependent groups, repeated measures ANOVA was used to test the differences between parametric data, and the Friedman test was used for non-parametric data. Pearson correlation analysis was used for parametric data, and Spearman correlation analysis was used for non-parametric data. EF, C-C time, CCA-IMT and HCT were chosen for the receiver operating characteristic (ROC) analyses, and a comparison of ROC analyses was performed to evaluate the diagnostic power of the NGAL test in the early postoperative period (two independent samples at postoperative hours 6 and 12). Also, Fisher's exact test was used for relative risk analysis to test the risk of AKI development posed by inflammation, which can be explained by IL-6 levels.

Table 1. Patient characteristics and analysis results according to the occurrence of AKI

	All patients	Non-AKI	AKI	p value[a]
Number	90	45	45	–
Male	52 (58%)	26 (58%)	26 (58%)	–
Female	38 (42%)	19 (42%)	19 (42%)	–
Age, years	66±10	65±11	66±9	0.7212[b]
Body mass index	28.1±3.1	28.6±3.1	27.1±3.1	0.0810[b]
Waist circumference, cm	94±12	95±11	92±13	0.2943[b]
Cigarette use	47 (52%)	22 (49%)	25 (56%)	0.5320[c]
Alcohol use	19 (21%)	9 (20%)	10 (22%)	0.8543[c]
COPD	13 (14%)	7 (16%)	6 (13%)	0.8529[c]
Primary hypertension	39 (43%)	17 (38%)	22 (49%)	0.3577[c]
Diabetes mellitus	26 (29%)	12 (27%)	14 (31%)	0.7126[c]
Hyperlipidaemia	29 (32%)	13 (29%)	16 (36%)	0.5802[c]
Glucose, mg/dl	116±26	112±21	119±30	0.1679[b]
HCT, %	42.7±6.3	44.3±5.7	41.1±6.5	0.0151[b]
Aspartate aminotransferase, IU/l	37±18	36±16	38±20	0.6068[b]
Alanine aminotransferase, IU/l	48±33	44±29	53±37	0.0564[c]
Lactate dehydrogenase, IU/l	302±83	289±55	315±103	0.1262[b]
Triglyceride, mg/dl	178±99	161±106	194±91	0.1112[b]
Low-density lipoprotein, mg/dl	137±26	135±26	140±26	0.3810[b]
High-density lipoprotein, mg/dl	39±10	41±11	38±10	0.1670[b]
Urea, mg/dl	37±9	38±8	36±9	0.5046[b]
T-protein, g/dl	7.5±0.5	7.5±0.5	7.4±0.5	0.3835[b]
Albumin, g/dl	4.3±0.4	4.2±0.4	4.3±0.4	0.7284[b]
Iron, mg/dl	88±31	89±33	87±29	0.7663[b]
Sodium, mEq/l	141±3.5	141±3.7	140±3.2	0.0655[b]
Potassium, mEq/l	4.2±0.4	4.2±0.4	4.3±0.4	0.0670[b]
Calcium, mEq/l	9.4±0.7	9.3±0.6	9.5±0.7	0.3925[b]
High-sensitivity C-reactive protein	3.8±2.2	3.5±2.0	4.0±2.4	0.2743[b]
Creatine kinase-myocardial band, IU/l	15.0±5.3	14.0±4.4	16.0±5.3	0.0706[b]
Troponin-I, ng/ml	0.48±0.41	0.50±0.43	0.45±0.39	0.5645[b]
Preconditioning type I/II	50/40	29/16	21/24	0.1408[c]
EF, %	53.0±10.5	56.0±9.9	51.0±10.5	0.0251[b]
Pump time, min	103±28	102±33	105±22	0.5478[b]
C-C time, min	56±24	51±26	61±21	0.0482[b]
Intensive care time, days	7.0±5.2	7.0±5.3	6.0±5.1	0.5313[c]
NSCA	4±2	4±2	4±2	0.7310[c]
CCA-IMT, mm	0.86±0.29	0.76±0.27	0.95±0.27	0.0011[b]

Preconditioning type I/II: propofol + fentanyl/propofol + fentanyl + desflurane.
[a] Comparison between non-AKI and AKI. [b] Unpaired t test. [c] Mann-Whitney test.

Results

Sample Size and Power Analysis

The smallest sample sizes required for 6- and 12-hour NGAL were found to be 19 and 11, respectively, by priority power analysis ($n2/n1 = 1$, $\beta = 0.20$ vs. $\alpha = 0.05$). Power was detected as 0.992 and 1.000, respectively, when the sample size was 45.

Subject Characteristics

The incidence of AKI after CABS was found to be 12%. The mean age of the patients was 66 ± 10 (50–84) years [male 64 ± 11 (50–84) and female 67 ± 9 (51–83)]. The mean body

Table 2. Classification of patients with varying degrees of AKI according to the RIFLE criteria

	At the 24th hour	At the 36th hour	At the 48th hour
Risk	4	20	24
Injury			17
Failure			4
Total	4	20	45

The classification system includes separate criteria for SCr and glomerular filtration rate. Glomerular filtration rate was calculated with Cockcroft-Gault CrCl. Risk: Increase in SCr × 1.5 or CrCl decrease >25%. Injury: SCr × 2 or CrCl decrease >50%. Failure: SCr × 3 or CrCl decrease >75% or SCr ≥4 mg/dl.

mass index was 28.1 ± 3.1 and the mean waist circumference 94 ± 12 cm. Table 1 shows no statistical difference between the AKI and the non-AKI groups in the distribution of age, obesity indicators (body mass index and waist circumference), smoking, alcohol consumption, COPD, primary hypertension, type 2 diabetes mellitus, hyperlipidaemia, preconditioning type I/II, pump time, intensive care time, NSCA and biochemical parameters, excluding HCT ($p > 0.05$).

The AKI group was evaluated using the RIFLE criteria; 24 patients had renal risk, 17 kidney injury and 4 kidney failure. The 24-hour postoperative CrCl or SCr levels indicated the risk of renal dysfunction for only 4 patients in the AKI group (table 2). In all patients, it later evolved into renal damage 48 h postoperatively. In the majority of patients in the AKI group, 48-hour postoperative CrCl or SCr levels indicated kidney injury.

CCA-IMT and C-C time were significantly higher and EF and HCT values were significantly lower ($p < 0.05$) in the AKI group than in the non-AKI group (table 1).

There was no significant difference between SCr and CrCl levels ($p > 0.05$) in the groups for preoperative levels and levels 6, 12, 24 h and 7 days after operation. 36- and 48-hour postoperative SCr levels were higher in the AKI group, and CrCl levels were higher in the non-AKI group ($p < 0.0001$) (table 3). Preoperative IL-6 levels were higher in the AKI group ($p < 0.001$). No significant difference was observed between the postoperative IL-6 levels of both groups ($p > 0.05$). On the contrary, no significant difference was observed between the preoperative NGAL levels of both groups ($p > 0.05$), but postoperative NGAL levels were significantly higher in the AKI group ($p < 0.0001$). In intergroup comparisons, CrCl and SCr levels were significantly different preoperatively and 6, 12, 24 h and 7 days after operation compared with 36- and 48-hour postoperative levels ($p < 0.001$). For both groups, there was a significant difference between IL-6 and NGAL levels for seven different time points ($p < 0.001$).

Correlation Analysis of Parameters

Preoperative IL-6 levels showed a low positive correlation with NSCA, a high positive correlation with CCA-IMT and a low negative correlation with EF (fig. 1). In correlation studies regarding the preoperative period (fig. 2), there was no correlation between NGAL and SCr levels, but a moderate negative correlation with CrCl ($p < 0.001$). IL-6 levels were not correlated with SCr or CrCl during the preoperative period ($p > 0.05$).

When changes in IL-6 and NGAL levels in the AKI group were evaluated (fig. 3), contrary to IL-6 levels, 6- and 12-hour postoperative NGAL levels were highly correlated with 36- and

Table 3. Comparison of biomarkers and CrCl according to the occurrence of AKI

	All patients	Non-AKI	AKI	p values[a]
SCr, mg/dl				
Preoperatively	1.27±0.21	1.29±0.19	1.25±0.22	0.3815[b]
At the 6th hour	1.25±0.20	1.27±0.20	1.24±0.21	0.4464[b]
At the 12th hour	1.29±0.20	1.31±0.19	1.26±0.20	0.2581[b]
At the 24th hour	1.60±0.22	1.31±0.20	1.40±0.23	0.0545[b]
At the 36th hour	1.48±0.32	1.32±0.24	1.64±0.31	<0.0001[b]
At the 48th hour	1.95±0.74	1.38±0.29	2.51±0.62	<0.0001[b]
On the 7th day	1.30±0.18	1.27±0.17	1.33±0.18	0.1258[b]
CrCl, ml/min				
Preoperatively	63±17.6	63±16	63±19	0.9008[b]
At the 6th hour	64±17.6	64±16	64±19	0.9197[b]
At the 12th hour	62±16.0	61±14	62±18	0.8444[b]
At the 24th hour	59±15.7	61±14	56±17	0.1181[b]
At the 36th hour	55±16.6	62±16	48±15	<0.0001[b]
At the 48th hour	45±18.6	59±15	32±9	<0.0001[b]
On the 7th day	61±15.1	63±13	59±17	0.2123[b]
IL-6, pg/ml				
Preoperatively	9.6±6.9	7.1±4.2	12.1±8.2	0.0004[b]
At the 6th hour	368±211	362±201	374±222	0.7878[b]
At the 12th hour	282±147	274±130	289±164	0.6342[b]
At the 24th hour	202±96	198±83	205±108	0.7555[b]
At the 36th hour	136±63	126±44	146±77	0.1248[b]
At the 48th hour	84±43	76±26	92±55	0.3349[c]
On the 7th day	22.6±11.0	21±8	23.8±13.4	0.3055[b]
NGAL, ng/ml				
Preoperatively	111±47	102±44	119±48	0.0905[b]
At the 6th hour	318±133	256±86	381±143	<0.0001[b]
At the 12th hour	307±132	222±77	392±121	<0.0001[b]
At the 24th hour	272±124	189±64	355±115	<0.0001[b]
At the 36th hour	206±74	168±49	243±77	<0.0001[b]
At the 48th hour	157±55	137±45	177±57	0.0004[b]
On the 7th day	113±41	96±37	130±39	<0.0001[b]

[a] Comparison between non-AKI and AKI. [b] Unpaired t test. [c] Mann-Whitney test.

48-hour postoperative SCr and CrCl levels ($p < 0.05$). NGAL values 6 and 12 h postoperatively showed a low positive correlation with 36- and 48-hour postoperative SCr levels and a moderately negative correlation with 36- and 48-hour CrCl levels ($p < 0.01$) (fig. 4). Similarly, the 6- and 12-hour postoperative levels of all patients had a higher negative correlation with CrCl levels than with SCr levels ($p < 0.001$) (fig. 5).

NSCA-, CCA-IMT-, EF- and HCT-independent variables were thought to be responsible for the development and severity of AKI. To explain the cause-effect relationship, multiple regression analysis was performed, which showed that 24% of the development of AKI is influenced by these variables (fig. 6).

IL-6 levels were used to indicate inflammation. Relative risk analysis was conducted to test the risk of inflammation in AKI development; the relative risk was found to be 1.917 (95% CI 1.092–3.364, $p = 0.0299$) in patients with IL-6 levels >9.0 ng/ml.

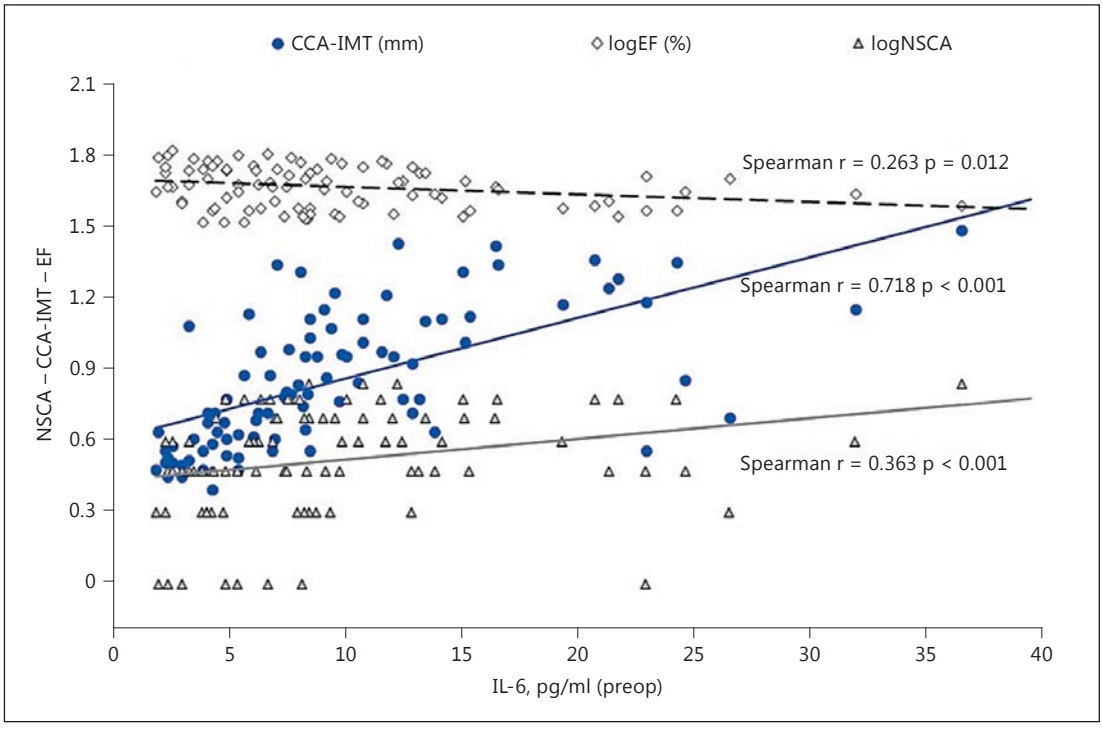

Fig. 1. Correlation between IL-6 levels and NSCA, CCA-IMT and EF.

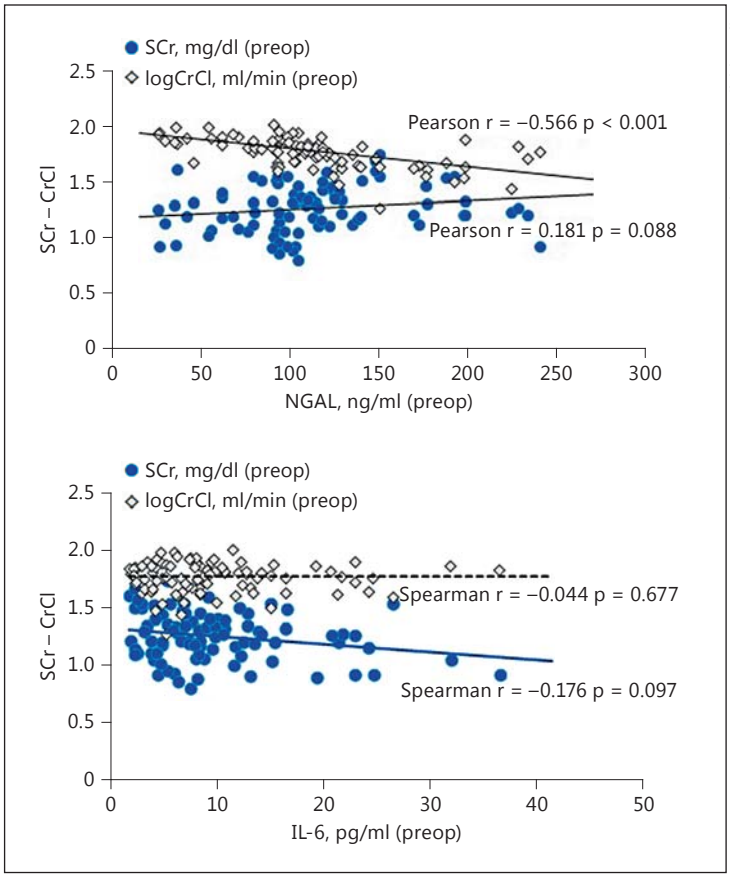

Fig. 2. Pearson correlation graph between preoperative NGAL levels and SCr/CrCl. There was no correlation between NGAL and SCr, but there was a moderate correlation between NGAL and CrCl, which was calculated using the Cockcroft-Gault formula. There was no correlation between preoperative IL-6 levels and SCr/CrCl.

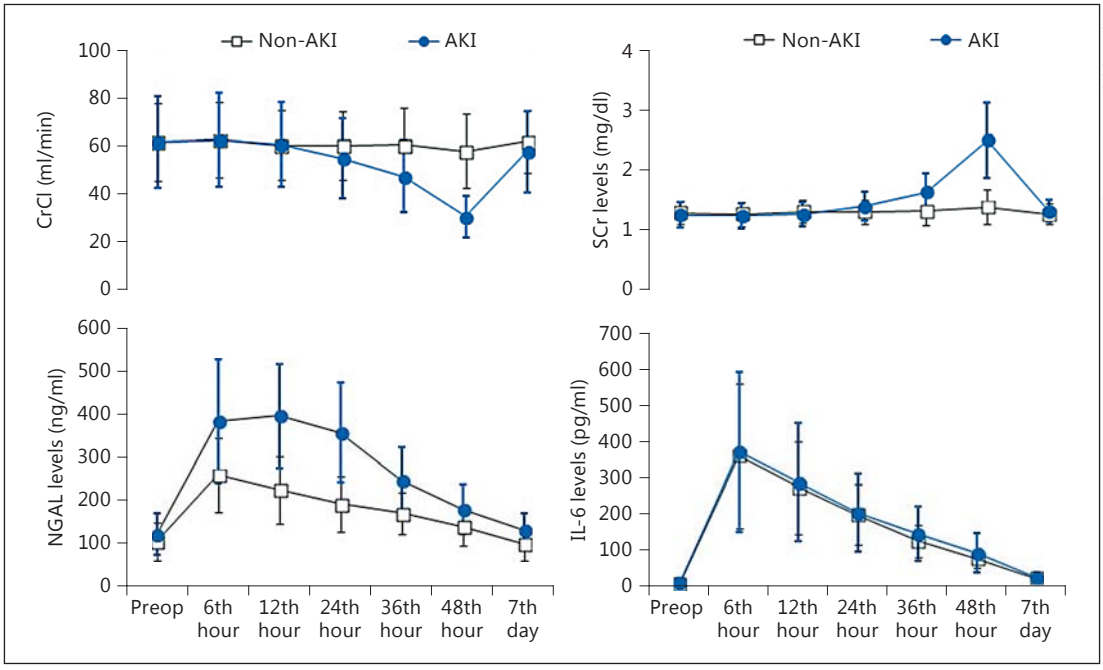

Fig. 3. NGAL, IL-6, CrCl and SCr levels for different times (preoperative and 6, 12, 24, 36, 48 h and 7 days after operation) in the AKI group. Contrary to the IL-6 levels, 6- and 12-hour postoperative NGAL levels were significantly correlated with postoperative 36- and 48-hour SCr and CrCl levels ($p < 0.001$).

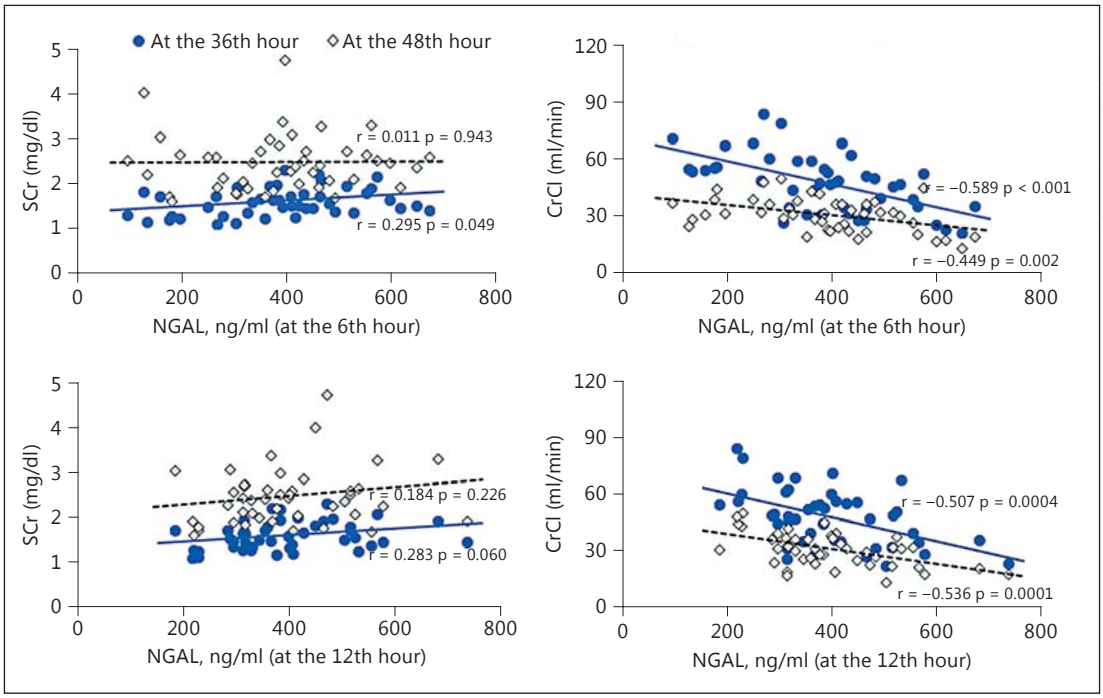

Fig. 4. In the AKI group, postoperative 6- and 12-hour NGAL levels showed a higher correlation with CrCl levels at the 36th and 48th hours than with SCr levels at the 36th and 48th hours.

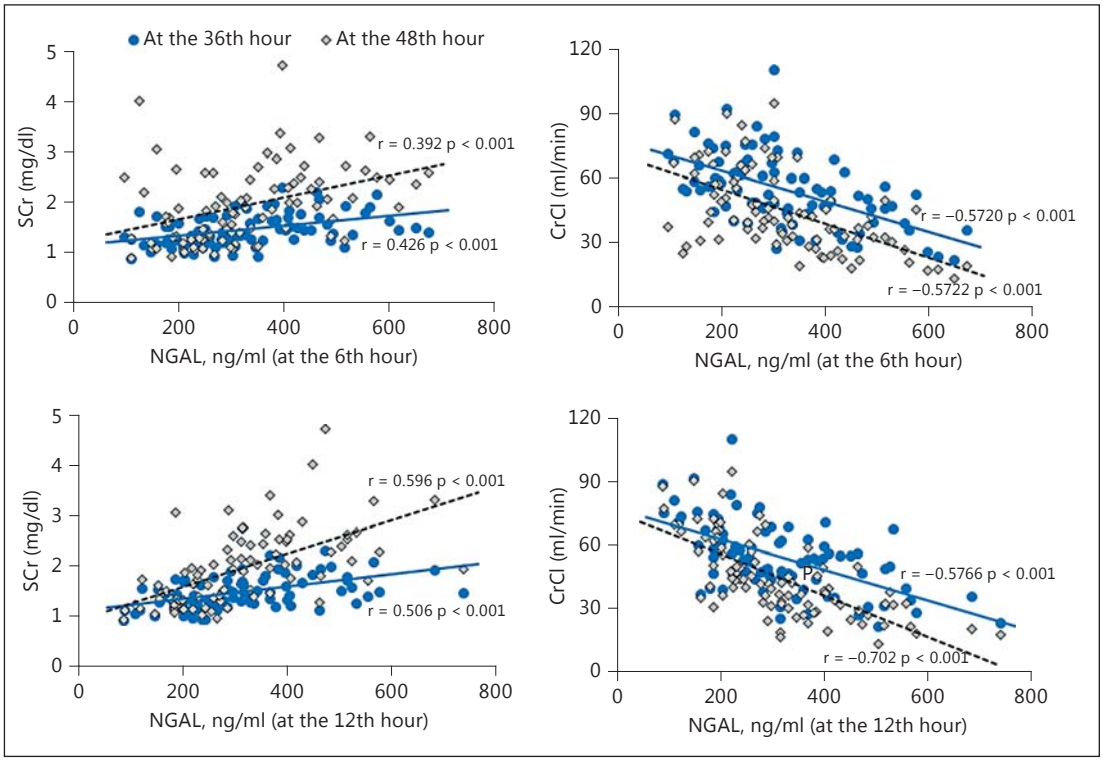

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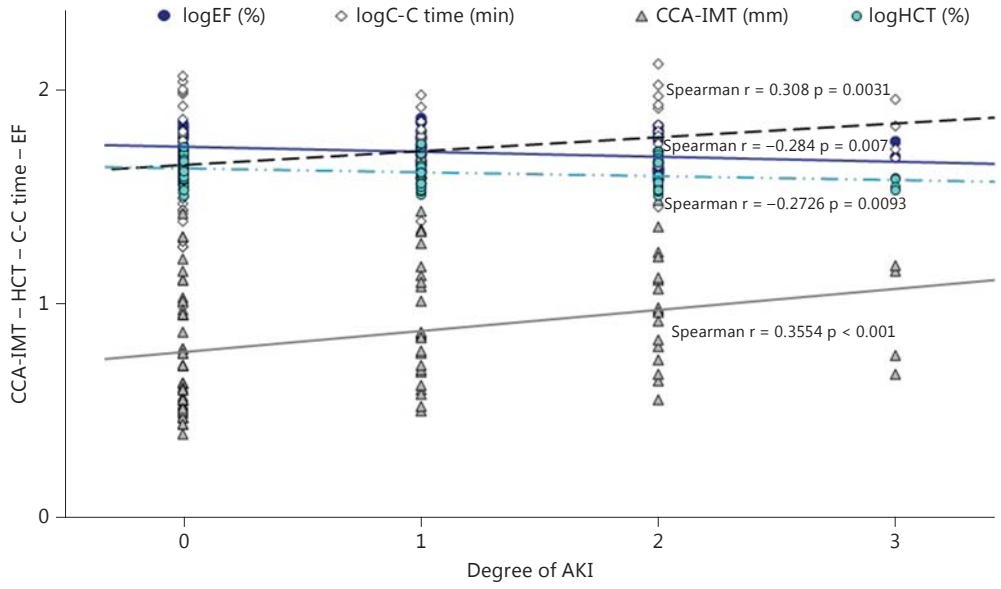
Fig. 5. When the results of all patients were taken into consideration, NGAL levels at the 6th and 12th hours showed a higher correlation with CrCl levels at the 36th and 48th hours than with SCr levels at the 36th and 48th hours.

ROC Curve Analysis

ROC curve analysis was performed to test the diagnostic power of 6- and 12-hour postoperative NGAL for the early detection of AKI. The sensitivity and specificity of 12-hour postoperative NGAL was higher than that of 6-hour postoperative NGAL (fig. 7). The optimal cut-off values for 6- and 12-hour postoperative NGAL levels were 310 and 283 ng/ml, respectively. The area under the curve (AUC) for ROC was higher for 12-hour postoperative NGAL levels when compared to 6-hour postoperative NGAL levels (the AUC for 6- and 12-hour postoperative NGAL was 0.77 and 0.90, respectively, $p < 0.001$ for both; difference between areas: 0.128, $p < 0.0086$).

Discussion

There were five main findings of the present study. (1) The incidence of AKI after CABS was found to be 12%. This rate was compatible with the current data. (2) In the AKI group 24 patients had renal risk, 17 kidney injury and 4 kidney failure. (3) CCA-IMT, C-C time and preoperative IL-6 levels were significantly higher and EF and HCT values were significantly lower in patients with AKI. (4) 6- and 12-hour postoperative NGAL levels showed a positive correlation with 36-hour postoperative SCr levels in the AKI group. (5) Optimal cut-off values for 6- and 12-hour postoperative NGAL tests were 310 and 283 ng/ml, respectively, and the AUC was higher in the 12-hour postoperative NGAL test.



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[Degree of AKI] = 2.092 − 0.02041 × [EF (%)] + 0.007541 × [C-C time (min)] + 0.7664 × [CCA-IMT (mm)] − 0.03041 × [HCT]

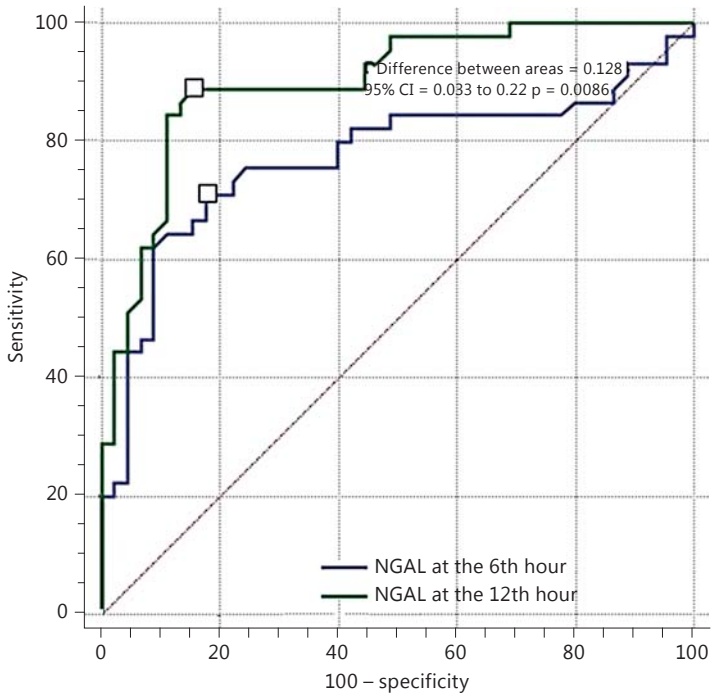
R^2 = 0.2444, adjusted R^2 = 0.2089, multiple R = 0.4944, F = 6.8751, p < 0.0001

Variable	Coefficient	SE	95% CI	t ratio	p value
(constant)	2.092	0.8698	0.3599 to 3.825	2.405	0.0183
EF	−0.0204	0.0084	−0.0371 to −0.0038	2.442	0.0167
C-C	0.0075	0.0036	0.00029 to 0.0148	2.072	0.0413
CCA-IMT	0.7664	0.3060	0.1570 to 1.376	2.072	0.0142
HCT	−0.0304	0.01387	−0.058 to −0.0028	2.192	0.0311

Fig. 6. Multiple regression analysis of the effect of independent variables (HCT, EF, C-C time and CCA-IMT) on AKI severity. All four variables had a significant influence on AKI development ($p < 0.05$).

AKI is a common disease that can be observed under various conditions, including dehydration, sepsis, glomerular disease and nephrotoxic drug use, and following cardiovascular surgery. AKI after CABS is characterised by the disruption of acid-base, electrolyte and fluid balance due to preoperative, operative and postoperative procedures. It can be seen in 30% of CABS patients, and approximately 1% require dialysis. Mortality rates can increase to 60–70% in patients requiring renal replacement therapy. More interestingly, higher mortality rates were reported for even small increases in SCr levels [16]. This is possibly related to SCr levels being a bad indicator of AKI and/or only a delayed increase can be seen after 25–50% of renal function is lost [10]. The most important risk factors for AKI after cardiac surgery are type of surgery, decreased left ventricle function, diabetes, COPD, peripheral vascular diseases, cardiopulmonary bypass time, C-C time, recurrent surgical interventions, blood transfusions, thrombocytopenia and leucocytosis after surgery, advanced age, female gender, use of drugs that disrupt the autoregulation of renal blood flow (non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, etc.) as well as high preoperative SCr and uric acid levels [17, 18].

Several biomarkers have been defined to diagnose and predict AKI in recent years [19]. NGAL is one of them. It is a small protein of the lipocalin superfamily and is expressed by renal tubular cells [20]. Both urine and serum NGAL levels were shown to be early predictors of



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Variable	AUC	SE	95% CI	Sig. p (area = 0.5)
At the 6th hour	0.772	0.050	0.671 to 0.854	0.0001
At the 12th hour	0.900	0.34	0.818 to 0.953	0.0001

Variable	Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	–LR
At the 6th hour	>310	71.11	55.7–83.6	82.22	67.9–92.0	4.00	0.35
At the 12th hour	>283	86.67	73.2–94.9	86.67	73.2–94.9	6.50	0.15

Fig. 7. Comparison of ROC curves for NGAL levels 6 and 12 h postoperatively. According to the sensitivity and specificity results, the diagnostic value of 12-hour NGAL was higher compared with that of 6-hour NGAL.

AKI in critically ill patients [12, 21]. In a meta-analysis, Hjortrup et al. [22] reported that there were no differences in terms of predictive values of urinary and plasma NGAL for AKI in adult intensive care patients. We therefore preferred to use plasma NGAL levels in the present study.

In recent years, a multicentre prospective randomised study named the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) assembled a cohort of 1,219 adults undergoing cardiac surgery [23]. According to the results of this study, plasma NGAL levels peaked within 6 h after surgery and the AUC for plasma NGAL was 0.7. In this context, plasma NGAL significantly improved the risk prediction of AKI and poor outcomes among adults undergoing cardiac surgery. Our results are in accordance with those of the TRIBE-AKI trial.

In the present study, the 12-hour postoperative NGAL test was found to be the most effective, but the 6-hour postoperative NGAL test also showed good correlation with SCr levels. Since this study and other previous studies [23, 24] showed that NGAL can predict AKI 24–72 h before SCr increase, one might consider repetitious NGAL levels during the first 24 h to provide a projection to the clinician regarding AKI development in the first 3–4 post-operative days.

Previous studies have shown that inflammatory mediators activated by inflammation during the preoperative period play an important role in physiopathological processes causing AKI. Also, it has been proposed that cardiac surgery itself can trigger a systemic inflammatory response and the secretion of inflammatory mediators, adhesion molecules and proinflammatory transcription factors [4, 23]. It has been presumed that these effects can cause renal vascular and cellular damage. In a subanalysis of the TRIBE-AKI trial, preoperative concentrations of IL-6 were not significantly associated with AKI and mortality in patients who had undergone cardiac surgery [25]. However, an elevated postoperative IL-6 concentration was found to be significantly associated with a higher risk of AKI. In accordance with previous findings, a significant increase in IL-6 levels was observed following surgery in this study. Nonetheless, there was no increase related to the increase in SCr levels or the decrease in CrCl levels, and we could not find a significant correlation between AKI severity and IL-6. This could be related to the small sample size of the present study. In this study, the relationship between NSCA, CCA-IMT, EF and HCT levels and AKI severity was not independent of chronic inflammation because the preoperative IL-6 levels were significantly higher in the AKI group than in the non-AKI group. This is evidence of the hypothesis claiming that inflammation is an important risk factor in the development and severity of AKI. Also, the relative AKI risk was 1.9 times higher in patients with preoperative IL-6 levels >9.0 ng/ml, which suggests that chronic inflammation increases NSCA and CCA-IMT, thereby affecting EF and increasing the frequency of AKI after CABS.

Atherosclerosis developing as a result of chronic inflammatory processes can affect both coronary and renal arteries at the same time. Because of this, coronary pathologies can be accompanied by renal pathologies or may trigger renal pathologies causing AKI [26]. This may also induce a decrease in HCT ratio due to the effect of atherosclerosis on middle- and small-sized arteries causing haemolysis and haemorrhages. It was found that CCA-IMT, HCT and EF contribute to AKI severity, which completely overlaps with the finding of this study. In this context, Karkouti et al. [27] suggested that therapies aimed at mitigating preoperative anaemia, perioperative red blood cell transfusions and surgical re-exploration may offer protection against this complication.

ECC and aortic cross-clamping during CABS can cause ischaemia and cellular damage. Adverse effects related to this can be seen in all tissues. Also, during ECC, contact of the blood with foreign objects and surgical trauma initiate the systemic inflammatory response and cause an increase in free oxygen radicals [28]. Cremer et al. [29] reported that systemic inflammatory response after open heart surgery can cause hyperdynamic circulatory instability. Also, the levels of tumour necrosis factor-alpha, IL-8, IL-6 and soluble intercellular adhesion molecule were higher in patients with postoperative hyperdynamic circulatory instability. All of these findings might explain the significant correlation found between AKI severity and ECC.

It has been observed in the present study that the problems during both operative (C-C time, etc.) and postoperative periods can contribute to the development of AKI. These preoperative problems can be listed as haematological, inflammatory, vascular and atherosclerotic, as well as problems with the cardiac pump. Based on these findings, it can be stated that the preoperative and operative periods are important for AKI development, but the use of classical markers such as SCr levels to diagnose AKI can cause a delay in the diagnosis. To prevent CABG-related AKI, three predictive risk scores based on preoperative variables have been developed: the Cleveland Clinic Score, the Mehta Score and the Simplified Renal Index Score [7]. However, there has been no consensus among authors with regard to recommending the use of a specific score to predict AKI before CABG. In addition, Parolari et al. [30] underlined that the predictive models mentioned above can be improved by the addition of perioperative management variables. Therefore, the cardiac surgeon should pay attention to the possible

preoperative and operative risk factors that may lead to complications. Volume depletion and heart failure should be treated before surgery, and nephrotoxic drugs such as non-steroidal anti-inflammatory drugs should be ceased during the preoperative period. Disruption in the perfusion flow due to vasoconstrictors, hypotension and microemboli should be prevented during the operation. Perioperative hydration would increase cardiac output and renal perfusion. Continuous haemodynamic monitoring, the timely administration of inotropic agents for cardiac output optimisation, proper pharmacological treatment (fenoldopam, atrial natriuretic peptide, mannitol, pentoxifylline, clonidine, etc.) and also timely interventions to address acute tubular necrosis, which is due to the precipitation of haemoglobin after haemolysis, by postoperative diuresis should be used to minimise the AKI risk.

Our study has several limitations. First, it had a single-centre design and the sample size was relatively small. Second, all of the patients enrolled in the study were Turkish. One should consider that our results cannot therefore be applied to all patients because of the differences between nationalities. Finally, therapeutic interventions and medical treatments were not evaluated in the present study.

In conclusion, HCT ratio, CCA-IMT and inflammation that can be detected using the IL-6 biomarker, C-C time and EF of the heart are important risk factors for AKI after CABS. Also, with repetitions of the NGAL test during the early postoperative period (first 24 h), the development of AKI during the first 3–4 postoperative days can be detected.

Statement of Ethics

This study was approved by the local ethics committee of Erzincan University.

Disclosure Statement

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