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Syndecan-1 as a marker to predict acute kidney injury after isolated coronary artery bypass graft operations

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SUMMARY

OBJECTIVE: Postoperative acute kidney injury is an important problem that can occur after coronary artery bypass graft operations, and it is important to identify risky patient groups preoperatively. This study aimed to investigate the importance of preoperative syndecan-1 levels in predicting acute kidney injury after elective coronary artery bypass graft operations accompanied by cardiopulmonary bypass.

METHODS: Patients who underwent coronary artery bypass graft operation in our clinic between March 1 and May 10, 2022, were included in this prospective study. Patients who did not develop acute kidney injury in the postoperative period were recorded as group 1 and patients who developed it were recorded as group 2.

RESULTS: A total of 79 patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass were included in the study. There were 55 patients in group 1 and 24 patients in group 2. There was no difference between the groups in terms of age, gender, diabetes mellitus, body mass index, smoking, and hyperlipidemia rates. In multivariate logistic regression analysis, increased blood product use (odds ratio 1.634; 95%CI 1.036–2.579; p=0.035), preoperative high creatinine (odds ratio 59.387; 95%CI 3.034–1162.496; p=0.007), and high syndecan-1 (odds ratio 1.015; 95%CI 1.002–1.028; p=0.025) were independent predictors of acute kidney injury.

CONCLUSION: This study revealed that elevated preoperative syndecan-1 is associated with acute kidney injury after isolated coronary artery bypass graft accompanied by cardiopulmonary bypass and has prognostic utility independent of other recognized risk factors.

KEYWORDS: Cardiopulmonary bypass. Inflammation. Acute kidney injury. Coronary artery bypass.

INTRODUCTION

Coronary artery bypass graft (CABG) operations are one of the most significant treatment modalities in the treatment of atherosclerotic heart disease. These operations are frequently performed with cardiopulmonary bypass (CPB)[1]. In the early period after these operations, undesirable problems such as heart failure, rhythm problems, cerebrovascular events, and acute kidney injury (AKI) may occur. AKI occurs in up to 25–40% of cases after CABG operations, and the use of CPB systems can raise these rates[2]. It is important to identify risky patient groups preoperatively for taking necessary precautions.

Some parameters obtained from preoperative routine blood tests have been investigated to predict the risk of AKI after cardiac surgery. Neutrophil lymphocyte ratio (NLR) is one of the most commonly used parameters. In a recent study, it was shown that a preoperative high NLR value could predict the risk of AKI after CABG operations accompanied by CPB[3]. Syndecan-1 (SDC-1) is an important indicator of endothelial glycocalyx damage, which plays an important role in the pathophysiology of AKI[4]. In a study, it was shown that it may be a predictor of AKI developing after pediatric cardiac surgery[5].

This study aimed to investigate the importance of preoperative SDC-1 levels in predicting AKI after elective CABG operations accompanied by CPB.

METHODS

Patients who underwent CABG operation with CPB in our clinic between March 1 and May 10, 2022, were included in this prospective study. The study was started after the approval of the local ethics committee. The study was carried out in accordance with the Helsinki Declaration criteria. Demographic data of the patients (age, gender, etc.), preoperative blood values (hemoglobin, white blood cell, neutrophil, lymphocyte, albumin, C-reactive protein, SDC-1, etc.), operation data (CPB and aortic cross-clamp [ACC] duration), and postoperative

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characteristics (AKI status, blood product usage status, etc.) were recorded.

Patients with concomitant cardiac surgery disease, serum creatinine values above 1.5 mg/dL in the preoperative period, liver failure, active infection or malignancy, preoperative hemoglobin values of 10 g/dL and below, and patients with congestive heart failure were excluded from the study. In all, 82 consecutive patients were included in the study. Due to bleeding diathesis in 1 patient in the early postoperative period, development of early cardiopulmonary failure in 1 patient, and operative mortality in 1 patient, they could not be included in the postoperative AKI evaluation and were excluded from the study. After applying the exclusion criteria, a total of 79 patients were included in the study.

Blood samples were taken from antecubital veins before the operation. Hemogram parameters were measured by using an automated hematological analyzer (Coulter LH 780 Analyzer, CA, USA). The complete blood cell parameters were measured through Coulter Erythrolyse II Reagent Kit (Beckman Coulter, Ireland). EDTA tubes were used to collect blood samples that were immediately centrifuged for 20 min at 2,000–3,000 rpm and frozen at -80°C for later measurement of SDC-1. SDC-1 was measured as a biomarker of endothelial glycocalyx injury (Abcam, Cambridge, MA, USA). The detection range for SDC-1 is 8–256 ng/mL and the intra-assay coefficient of variation is 6.2%[6].

Diagnosis of postoperative AKI was determined according to the Kidney Disease Improving Global Outcomes (KDIGO) classification[7]. According to the results of this evaluation, patients who did not develop AKI in the postoperative period were recorded as group 1 (n=55), and patients who developed any of the KDIGO stages were recorded as the renal failure group (group 2, n=24).

Surgical technique

General anesthesia and median sternotomy technique were used in all patients. Aortic-venous two-stage cannulation was performed in all CABG operations, and standard CPB systems were used in mild hypothermia (32°C). In all patients, cardiac arrest was achieved with an initial blood cardioplegia of approximately 1,000 mL (10–15 mL/kg). Continuation of cardiac arrest was maintained with approximately 300 mL of blood cardioplegia at 15–20-min intervals. CPB was provided by roller pumps and membrane oxygenator (Maquet, Getinge Group, Rastatt, Germany) at a flow rate of 2–2.4 L/min/m^2, and arterial filters were used in all patients. Distal and proximal anastomoses were performed under ACC. Hot-shot blood cardioplegia without hot potassium was given to all patients before the ACC was removed. After the operation was completed, all patients were transferred to the intensive care unit with vital monitoring.

Statistical analysis

Statistical analysis was utilized using SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc., version 21.0, Chicago, IL, USA). Normality distribution of data was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests. The Student's t-test was used for normally distributed data (mean and standard deviation), and the Mann-Whitney U test was used for non-normally distributed data (median and minimum-maximum). Nominal variables were expressed in frequency and percentage, and the chi-square test was used for analysis. Postoperative AKI predictors were analyzed using binary logistic regression analysis. The predictive value of SDC-1 was determined using receiver operating characteristic (ROC) curve analysis and calculation of area under curve. A $p<0.05$ was considered significant.

RESULTS

A total of 79 patients undergoing CABG surgery with CPB were included in the study. There were 55 patients in group 1 (without kidney injury) and 24 patients in group 2 (with kidney injury). There was no difference between the groups in terms of age, gender, DM, BMI, smoking, and hyperlipidemia rates. In addition, preoperative ejection fraction and use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and acetylsalicylic acid were similar in both groups (Table 1).

Preoperative blood parameters and operative and postoperative features of all patients are presented in Table 1. There was no difference between the groups in terms of white blood cells, hemoglobin, platelet counts, neutrophil, lymphocyte, blood urea nitrogen, and C-reactive protein value. While cross-clamp times and the number of distal anastomoses were similar between the two groups, total perfusion times and the use of packed blood products were significantly higher in group 2 ($p=0.038$ and $p<0.001$, respectively). Creatinine, SDC-1, and NLR values were significantly higher in group 2 ($p<0.001$, $p<0.001$, and $p=0.037$, respectively).

To analyze the factors affecting the development of AKI in the postoperative period, binary logistic regression analysis was utilized (Table 2). In univariate analysis, total perfusion time (OR [odds ratio] 1.021; 95%CI [confidence interval] 1.001–1.043; $p=0.045$), need of inotropic support (OR 4.523; 95%CI 1.627–12.575; $p=0.004$), increased blood product use (OR 1.971; 95%CI 1.358–2.861; $p<0.001$), preoperative high creatinine (OR 125.742; 95%CI 10.773–1467.616; $p<0.001$), NLR (OR 0.826; 95%CI 0.678–0.982; $p=0.039$), and high SDC-1 (OR 1.016; 95%CI 1.004–1.027; $p=0.008$) were correlated with the development of AKI. In multivariate logistic regression analysis, increased blood product use (OR 1.634; 95%CI 1.036–2.579;

Table 1. Demographic data, preoperative laboratory variables, and perioperative features of the patients.

Variables	Group 1 (n=55)	Group 2 (n=24)	p-value
Age (years)	60.8±8.7	62.2±10.3	0.237
Male gender, n (%)	44 (80%)	21 (87.5%)	0.422
Diabetes mellitus, n (%)	16 (29.1%)	9 (37.5%)	0.460
Hypertension, n (%)	30 (54.5%)	17 (70.8%)	0.175
BMI, kg/m^2	27.9±3.4	28.3±3.3	0.934
Smoking, n (%)	31 (56.4%)	16 (66.7%)	0.391
Hyperlipidemia, n (%)	33 (60%)	19 (79.2%)	0.163
Ejection fraction (%)	55 (30–67)	55 (35–65)	0.338
ASA use, n (%)	30 (54.5%)	16 (66.6%)	0.315
ACEI/ARB use, n (%)	33 (67.3%)	16 (66.6%)	0.574
White blood cell (10^3/μL)	8.5 (4.4–14.8)	8.8 (4.8–16.6)	0.498
Hemoglobin (mg/dL)	13.5±1.9	13.7±1.4	0.143
Platelet (10^3/μL)	259.9±62.6	261±72.7	0.216
Neutrophil (10^3/μL)	4.1 (1.3–15.1)	4.8 (1.3–18.8)	0.085
Lymphocyte (10^3/μL)	1.5±0.5	1.3±0.8	0.122
NLR	2.5 (0.9–9.3)	4.2 (1.4–10.9)	0.037
BUN	16 (9–37)	18 (11–35)	0.217
Creatinine (mg/dL)	0.92±0.2	1.18±0.24	<0.001
CRP (mg/dL)	14.4±3.9	16.7±4.5	0.290
Syndecan-1	63.7 (7.4–253.5)	91.1 (42.8–620.6)	0.001
Total perfusion time	96.7±20.9	109±29	0.038
Cross-clamp time	72.1±20.5	70.6±23.2	0.287
Number of distal anastomoses	3 (16)	3 (2–6)	0.935
Packed blood products (units)	7 (4–9)	9 (4–13)	<0.001
Inotropic support, n (%)	13 (23.6%)	14 (58.3%)	0.003

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ASA: acetylsalicylic acid; BMI: body mass index; CRP: C-reactive protein; BUN: blood urea nitrogen; NLR: neutrophil to lymphocyte ratio.

Table 2. Logistic regression analysis to identify factors affecting postoperative acute kidney injury.

Variables	Univariate analysis			Multivariate analysis		
	p-value	Exp(B) odds ratio	95%CI Lower-upper	p-value	Exp(B) odds ratio	95%CI Lower-upper
Age	0.527	1.017	0.9656–1.073	–	–	–
Hypertension	0.179	2.024	0.724–5.657	–	–	–
Total perfusion time	0.045	1.021	1.001–1.043	–	–	–
Inotropic support	0.004	4.523	1.627–12.575	0.453	1.707	0.422–6.903
Blood product use	<0.001	1.971	1.358–2.861	0.035	1.634	1.036–2.579
Pre-creatinine	<0.001	125.742	10.773–1467.616	0.007	59.387	3.034–1162.496
NLR	0.039	0.826	0.678–0.982	–	–	–
Syndecan-1	0.008	1.016	1.004–1.027	0.025	1.015	1.002–1.028

NLR: neutrophil to lymphocyte ratio.

p=0.035), preoperative high creatinine (OR 59.387; 95%CI 3.034–1162.496; p=0.007), and high SDC-1 (OR 1.015; 95%CI 1.002–1.028; p=0.025) were independent predictors of AKI.

ROC analysis was performed to evaluate SDC-1 in predicting AKI after CABG operations performed with CPB. The cutoff value was 79.4 (area under the curve: 0.739; 95%CI 0.621–0.857; p=0.001, with 58.3% sensitivity and 46.8% specificity) (Figure 1).

DISCUSSION

CABG operation is an effective and important treatment modality in coronary artery disease; AKI is an important complication that can occur after these operations and can lead to increased mortality and morbidity. Therefore, it is very important to reveal the risk factors for AKI. For the first time in the literature, in this prospective study, we demonstrated that preoperative high SDC-1 serum levels were an independent predictor of postoperative AKI risk in patients undergoing isolated CABG operation accompanied by CPB.

Endothelial surface proteins act as a barrier between the blood and the endothelium, preventing the extravasation of electrolytes, water, and proteins. These proteins are also known as endothelial glycocalyx structures[8]. SDC-1 is a family of protein groups. It has been shown that high serum SDC-1 levels were associated with impaired endothelial glycocalyx structures and elevated serum catecholamine levels in cases with acute myocardial infarction[9]. In a study conducted on patients with acute decompensated heart failure, a significant relationship was revealed between high serum SDC-1 levels (at the time of admission) with AKI and 6-month mortality[10].

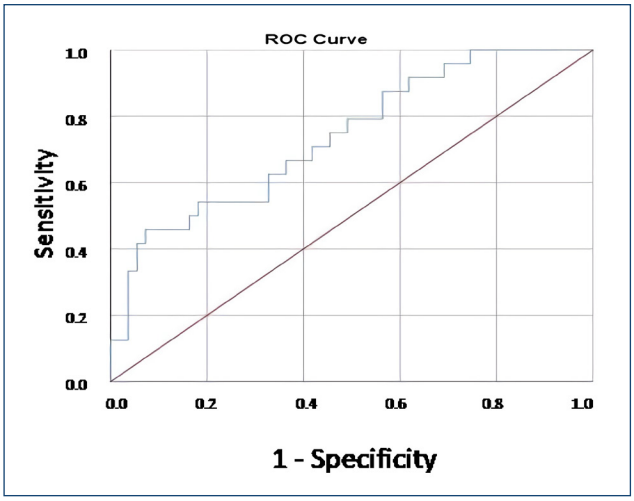

Figure 1. Data figure of the area under the curve, confidence interval, and cutoff value in receiver operating characteristic curve analysis for syndecan-1 to predict acute kidney injury (cutoff: 79.4; AUC: 0.739; 95%CI 0.621–0.857, p=0.001, with 58.3% sensitivity and 46.8% specificity).

In another study conducted in the following years, the importance of SDC-1 was investigated in patients with heart failure. A prospective study by Liu et al. included 96 patients with non-ischemic dilated heart failure. In this study, high SDC-1 levels were shown as an independent predictor of major adverse events[11]. Schellings et al. investigated the relationship between SDC-1 and hypertension in their experimental study. They demonstrated that SDC-1 expression increased significantly in experimental mice with angiotensin II-induced hypertension[12].

In the study conducted by Wernly et al., the prognostic importance of plasma SDC-1 levels in patients with acute reperfused ST-segment elevation myocardial infarction was investigated. A total of 206 patients were followed up for 6 months. SDC-1 levels were evaluated from blood samples taken after coronary intervention. No significant correlation was found in correlation analyses between various biochemical prognostic markers and SDC-1. However, a significant correlation was found between high SDC-1 levels and mortality[13].

Two studies were identified in the literature investigating the relationship between AKI and SDC-1 in cardiac surgery. Patients under the age of 18 years, who underwent cardiac surgery, were included in the prospective study conducted by Cavalcante et al. In this study, SDC-1 levels were measured in the early postoperative period. At the end of the study, high SDC-1 levels were found to be an independent predictor of the presence of severe AKI[5]. Different from this study, we included adult patients who underwent isolated CABG and evaluated their SDC-1 levels preoperatively. Xu et al.[14] used SDC-1 to predict the risk of AKI after cardiac surgery in adult patients. This study was carried out on patients who had undergone various cardiac surgeries (valvular, coronary, etc.), and blood samples of the patients were collected at the time of AKI diagnosis (in the first 48 h after the operation) for the SDC-1 measurements. In the multivariate analysis performed in the study, high plasma SDC-1 levels were shown as an independent predictor of AKI progression[14]. Unlike this study, we included only isolated CABG patients. In addition, SDC-1 levels were evaluated only preoperatively. In our study, preoperative high SDC-1 levels were shown as an independent predictor of the development of AKI after isolated CABG operations.

Our study is a prospective, single-center study and has some limitations. First, the number of patients was limited. SDC-1 value was evaluated only preoperatively; measurements could not be made during CPB or in the postoperative period. In addition, other AKI-related inflammatory parameters such as cystatin C, neutrophil gelatinase-associated lipocalin, and kidney injury molecule could not be evaluated. Therefore, new studies are needed.

CONCLUSION

Although CABG operations are performed with high success rates today, some morbid and mortal complications may occur in the postoperative period. Renal failure is one of the most common complications of this operation. For the first time in the literature, this study revealed that elevated preoperative SDC-1 is associated with AKI after isolated CABG accompanied by CPB and has prognostic utility independent of other recognized risk factors.

ETHICS APPROVAL

The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Protocol number: 2011-KAEK-25 2022/02-17).

AUTHORS' CONTRIBUTIONS

DA: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SAS:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ME:** Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **FA:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RFK:** Validation, Visualization, Writing – original draft, Writing – review & editing. YU: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SY:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AFO:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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