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THE RELATIONSHIP OF POSTOPERATIVE CYSTATIN C LEVEL WITH EARLY ACUTE RENAL FAILURE IN ADULT PATIENTS UNDERGOING CARDIAC SURGERY

KARDİYAK CERRAHİ GEÇİREN ERİŞKİN HASTALARDA POSTOPERATİF SİSTATİN-C DÜZEYİNİN ERKEN DÖNEMDE AKUT BÖBREK YETMEZLİĞİ İLE İLİŞKİSİ

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ÖZET

Giriş: Kardiyovasküler hastalıklar halen dünyada mortalite ve morbiditenin en önemli nedenidir. Kalp cerrahisi hastanelerde en sık uygulanan büyük cerrahi girişimler olup, cerrahi sonrası gelişen akut böbrek hasarı (ABH) sıklıkla karşılaşılan ve mortaliteyi arttıran önemli bir durumdur. Operasyon sonrası gelişebilecek ABH erken tanısının belirlenmesi tedavi başarısını yükseltebilir. Biz de bu çalışmada kardiyak cerrahi geçiren hastalarda postoperative Cystatin C düzeyinin erken dönem akut böbrek yetmezliği ile ilişkisini değerlendirmeyi amaçladık.

Yöntemler: Çalışmamız 2016 - 2017 yılları arasında kardiyak operasyon geçiren, 18 yaşından büyük, başlangıç böbrek fonksiyonu normal (kreatinin <1,2 mg/dL) 40 erişkin hasta ile yapıldı. Hastaların bazal demografik özellikleri, biyokimya parametreleri kayıt edildi. Plazma Cystatin C seviyesi postop 6. saat ve 24. saat örnekleri alınarak postop ABH arasındaki ilişkisi araştırıldı.

Bulgular: Çalışmamızda 40 hastadan 12'sine Akut Kidney Injury Network (AKIN) ve 14'üne Risk-Injury-Failure-Loss-End stage (RIFLE) sınıflamasına göre ABH tanısı konuldu. ABH gelişmesi ile hastanede kalış süresinin anlamlı olarak arttığı, 24. saat Cystatin C seviyesinin ABH gelişmesi ile korele olduğu (p=0.048) ve ABH gelişen grupta anlamlı olarak yüksek olduğu belirlendi. Başlangıç diyabet varlığı ABH gelişen hastalarda anlamlı olarak yüksekti (p=0.045). Plazma Cystatin C 24. saat AUC_{ROC} değeri 0,78 (0,75-0,90 Güven aralığı, p:0.002) olarak hesaplandı. 6.saatte bakılan Cystatin C seviyesi ile ABH arasında korelasyon yoktu (p=0.358).

Sonuç: Kardiyak cerrahi sonrası ABH gelişmesi olumsuz klinik olay sıklığı ile ilişkilidir. 6.saat bakılan Cystatin C erken tanıda duyarlılığı düşük, 24.saat bakılan Cystatin C ise erken tanıda güçlü tanısal değere sahiptir. Postoperatif Cystatin C düzeyi ABH tanısında (özellikle 24.saatte) önemli katkı sağlayabilir.

Anahtar Kelimeler: Kardiyak Cerrahi, Akut Böbrek Yetmezliği, Cystatin C, Kreatinin.

ABSTRACT

Introduction: Cardiovascular diseases are still the most important cause of mortality and morbidity in the world. Cardiac surgery is the most frequently performed major surgical intervention in hospitals, and acute kidney injury (AKI) that develops after surgery is an important condition that is frequently encountered and increases mortality. The success of treatment may be increased by early detection of AKI that may appear following surgery. In this study, we sought to assess how early stage acute renal failure and postoperative Cystatin C levels related in patients underwent cardiac surgery.

Methods: 40 adult patients over the age of 18 who underwent cardiac surgery between 2016 and 2017 participated in our study. All of the participants had baseline renal function that was normal (creatinine 1.2 mg/dL). The patients' baseline biochemistry values and demographics were noted. The link between postoperative AKI and plasma cystatin C level was examined using samples collected at 6 hours and 24 hours.

Results: In our study, 12 out of 40 patients were diagnosed with AKI according to the Akut Kidney Injury Network (AKIN) classification and 14 according to the Risk-Injury-Failure-Loss-End stage (RIFLE) classification.It was determined that the duration of hospital stay increased significantly with the development of AKI, the 24th hour Cystatin C level was correlated with the development of AKI (p:0.048) and was significantly higher in the group developing AKI. Presence of baseline diabetes was significantly higher in patients who developed AKI (p:0.045). Plasma Cystatin C 24-hour AUC_{ROC} value was calculated as 0.78 (0.75-0.90 Confidence interval, p:0.002). There was no correlation between Cystatin C level measured at 6th hour and AKI (p:0.358).

Conclusion: The development of AKI after cardiac surgery is associated with the frequency of adverse clinical events. Cystatin C tested at 6 hours has low sensitivity in early diagnosis, while Cystatin C at 24 hours has a strong diagnostic value in early diagnosis. Postoperative Cystatin C level can make a significant contribution to the diagnosis of AKI (especially at the 24th hour).

Keywords: Cardiac Surgery, Acute Renal Failure, Cystatin C, Creatinine.

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INTRODUCTION

Cardiovascular diseases (CVD) are still the group of diseases that are the most important cause of mortality and morbidity worldwide (1). According to a 2016 research, although the age-standardized death rate from CVD has fallen by 27.3%, it is estimated that CVD causes around one-third of all fatalities worldwide. In recent years, the number of deaths has climbed by 42.4% from 1990 to 2015. According to reports, this growth is ongoing, particularly in developing countries. (2). Coronary artery disease (CAD) is the leading cause of death in this group, causing approximately 610,000 deaths (an estimated 1 in 4 deaths) per year in the United States, the third leading cause of death worldwide, and the disease associated with 17.8 million deaths per year (3). Cardiopulmonary bypass (CPB) still has an important place in the treatment of CAD, and this method is applied in more than 80% of patients undergoing cardiac surgery (4). Acute kidney injury (AKI) is a very common complication following cardiac surgery. The early and late results of surgery are significantly impacted by this condition. Postoperative AKI is known to cause a lengthy hospital stay, significant mortality, and an increase in healthcare expenses (5). Nevertheless has been demonstrated that the systemic inflammatory response seen in patients undergoing cardiopulmonary bypass, which is mediated by a variety of pathways, results in significant clinical disorders affecting all organs and raises the risk of AKI (6).

The diagnosis of AKI is generally based on elevation in serum creatinine (SCr), decrease in glomerular filtration rate (GFR), and oliguria. SCr varies depending on many different factors such as muscle mass and tubular functions. For an early diagnosis of AKI following surgery in the intensive care unit, the currently available parameters are insufficient (7). In patients undergoing cardiac surgery, early detection of AKI can lower mortality, morbidity, and treatment expenses. Finding molecular indicators that can predict the onset of AKI quickly, reliably, conveniently, simply, and affordably has recently been the subject of numerous investigations. Some recently discovered biomarkers have been promising in the diagnosis of AKI. Some of those; plasma Cystatin C, plasma neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin-18 (IL-18) stand out. Cystatin C is a cysteine protease inhibitor that all nucleated cells produce at the same rate and release into the systemic circulation. It is completely filtered by glomeruli filtration and completely absorbed by the proximal renal tubule. The blood level is not affected by age, gender, race or muscle mass (8). According to studies, it is a more accurate method than SCr for determining GFR and shows glomerular function in individuals with chronic renal disease more clearly. Cystatin C excretion in the urine can predict AKI patients' requirement for renal replacement therapy one day in advance. There is a 1-2 day advantage over SCr when evaluating a 50% serum Cystatin C rise in the ICU for the identification of AKI (9).

We intended to examine the use and validity of Cystatin C levels as a biomarker in the early diagnosis of postoperative AKI in a group of adult patients who underwent cardiac surgery in this prospective clinical trial.

METHODS

This study was conducted with 40 patients who were planned for elective open-heart surgery as of January 1, 2016, in Afyon Kocatepe University Medical Faculty Hospital Cardiovascular Surgery Clinic and with the support of Internal Medicine Department. The study was designed as a single-center, prospective observational study. A follow-up form was created to determine the characteristics of the patients, preoperatively; demographic data, body mass index, urea, SCr, GFR values were also recorded. The procedure's nature, clinical data such as renal and hemodynamic parameters, medications and doses, aortic cross clamp time, and CPB duration were all noted intraoperatively. BUN, SCr, hemoglobin, haematocrit (Hct), GFR, regular urine output, regular drainage quantity, diuretic dose administered, time spent on a mechanical ventilator, length of stay in the intensive care unit (ICU), and length of hospital stay at the six and twenty-four hours following the patient's admission to the intensive care unit are all measured postoperatively. Mortality and morbidity data was maintained record of.

Cystatin C levels were evaluated with 8 mL samples taken from the venous route at 6 and 24 hours. Blood samples were separated into two separate purple capped EDTA, vacuumed 5 ml glass tubes of 3-4 mL. Within approximately one hour after the samples were taken, they were centrifuged at 2500 rpm for 10 minutes and separated into their plasma. The separated plasmas were kept in the biochemistry laboratory at -50 ^{0}C until they were studied. Results were obtained using SunRed brand Human Cystatin C Elisa kits (Jufengyuan Road, Baoshan District, Shanghai, China). With the results of the blood samples taken at the planned hours in the study, the patients were classified according to the (risk, injury, failure, loss, end-stage kidney disease (RIFLE) criteria and the acute kidney injury network (AKIN) classifications used as the gold standard in the diagnosis of AKI (10). The values obtained were compared with each other in terms of the definition of AKI and with preoperative, intraoperative and postoperative risk factors. RIFLE and AKIN classifications used in the diagnosis of AKI are summarized in Table 1.

All participants completed an informed consent form, the study was conducted out in accordance with the Declaration of Helsinki, and it was authorized by the institutional local ethics committee (Number: 2015/04-103). The study excluded patients who were younger than 18 years old, having emergency surgery (patients operated within 4 hours of ICU admission), having end-stage renal

replacement therapy and having pre-operative SCr values above 1.2 mg/dL, being pregnant, having a serious infection, or having poor initial hemodynamics.

Statistical analysis

Statistical analyses were conducted using SPSS software version 20.0 (SPSS Inc. Chicago, Illinois, ABD) determine the normal distribution of variables. Non-parametric variables were expressed as median and interquartile, while normally distributed variables were expressed as mean and standard deviation. Nonparametric data and parametric data were compared using the Mann-Whitney U test and the T-test, respectively. Ordinal and categorical variables were compared using the chi-square test. The patients were evaluated by pairwise comparisons as groups with and without postoperative AKI according to GFR and SCr parameters. Statistical significance was defined as a P-value < 0.05.

The ability of the markers focused on in the study (6th hour SCr, Cystatin C,GFR and 24th hour SCr, Cystatin C, GFR) to differentiate the disease were performed by ROC analysis. Evaluated with AUC_{ROC} and 95% confidence intervals. AUC_{ROC} values were 0.90-1.0 excellent, 0.75-0.89 good, 0.75-0.50 poor, and <0.50 no diagnostic value. Finally, correlation analysis was performed in accordance with the distribution among the variables and significant results were reported.

RESULTS

A total of 40 patients were included in the study. The mean age of the patient was 61.37 ± 10.42 (42-78 years). 29 (72.5%) of the patients were male and 11 (27.5%) were female. The baseline demographic characteristics of the patients are presented in Table 2.

According to the AKIN criteria, AKI was found at the 24th hour in 12 (30%) of the 40 patients who were included in the study. Eight of these patients had stage-1 disease, whereas the remaining four had stage-2 disease. According to RIFLE criteria, AKI was detected in 14 patients (35%) at 24 hours. Eight of the patients were evaluated as class 1 (class 1=AKIN stage 1). The other 6 (class 2 = AKIN stage 2) were considered class 2. In both classifications, clinical acute renal failure was observed in 4 of the patients who developed AKI after 72 hours. In the other 8 patients, the entry and exit of AKI took 72 hours. Preoperative DM in patients with AKI was significantly higher in the group with AKI (p=0.045) (Table 3).

In the study, the intraoperative characteristics of the patients were compared between the patient groups with and without AKI. No statistically significant difference was found in terms of type of surgery and aortic cross clamp time (p>0.05). It was determined that the use of diuretics (p=0.001) and blood products (p=0.002) and total perfusion time (TPZ) (p=0.003) during surgery were significantly prolonged in the patients in the AKI group. A comparison of the intraoperative characteristics of the patients is presented in Table 4.

According to the postoperative AKIN classification, among the groups with and without AKI; There were significant differences between the groups in terms of length of stay in ICU, length of hospital stay, extubation time, postoperative diuretic use, blood product use, 24-hour thorax tube drainage, development of delirium, and 24-hour Cystatin C levels (p=0.002) (Table 5). Similarly, statistically significant differences were found in many parameters such as extubation time, 24-hour Cystatin C level (p=0.001), 24-hour drainage, diuretic use, and blood product use according to RIFLE classification.

There was no statistically significant difference between the mean of preoperative (p=0.942) and postoperative 6th hour (p=0.358) Cystatin C measurements between the groups with and without AKI. There was a statistically significant difference between the mean values of Cystatin C measurements at 24 hours postoperatively (p=0.002) (Table 6).

In the study, AUC^{ROC} values were calculated for 6th hour BUN, SCr, GFR and Cystatin C according to the AKIN classification. SCr (0.77) and GFR (0.75) values were significant, while BUN (0.70) and Cystatin C (0.50) values were not statistically significant. According to the AKIN classification, the parameters were evaluated again with AUC^{ROC} analysis for the 24th hour (Figure 1). As a result of the analysis, the values for BUN, SCr, GFR, and Cystatin C were determined as (0.85, 0.99, 0.76 and 0.78), respectively, and all variables showed AKI significantly. The threshold value calculated for these values was determined as BUN: 24.45 mg/dL, SCr: 1.55 mg/dL, GFR: 73 (mL/min/1.73 m²), Cystatin C: 31.6 ng/mL. It was determined that the 24th hour Cystatin C level was correlated with the development of acute renal failure (p=0.048).

DISCUSSION

A significant issue that needs to be carefully considered is the treatment of CAD, whose prevalence is rising globally on a daily basis. With more than one million operations conducted each year, cardiac surgery with CPB is the most common major surgical procedure in hospitals around the world. After CPB, AKI is a frequent and sometimes fatal consequence that affects 30% to 40% of adults and kids (11). Patients with AKI that occurred after heart surgery were carefully assessed in our study. Numerous patient variables, including those from the pre-, intra-, and post-operative periods, were used to obtain significant findings. The existence of AKI damage was highly correlated with the occurrence of hyperglycaemia in the patients during the preoperative period. As is well known, in our patient population, we noticed that diabetes increased the incidence of events in all cardiovascular treatments.

In a study evaluating 374 pediatric patients undergoing CPB, 119 (32%) patients developed AKI using the SCr criteria. In AKI patients, serum Cystatin C concentrations increased significantly at 12 hours after CPB and remained elevated at 24 hours. Again in the same study,

Table 1. Acute kidney injury classification according to RIFLE and AKIN classifications.

RIFLE classification	Scr Criteria	Urine Output Criteria
Risk	1.5-fold increase in SCr / >25% decrease in GFR from baseline	<0,5ml/kg/h for >6h
Injury	2-fold increase in SCr / > 50% decrease in GFR from baseline	<0.5 ml/kg/h for >12h
Failure	3-fold increase in SCr / decrease in GFR > 75% from baseline / an acute increase in SCr	<0.3 ml/kg/h for >24h or anuria for 12h
Loss	complete loss of kidney function >4 weeks (AKI)	anuria
End stage Kidney Disease	End-stage renal disease: Complete loss lasting >3 months	anuria
AKIN SClassificaiton	**Scr Criteria**	**Urine Output Criteria**
1	≥26.5 µmol/L (≥0.3 mg/dL) increase in SCr / 1.5–2-fold increase from baseline	<0,5 mL/kg/h for 6h
2	>2-3 fold increase in SCr compared to baseline	<0,5 mL/kg/h for 12h
3	>3.0-fold increase in SCr compared to baseline	<0,3mL/kg/h for 24h / anuria for 12h

Table 2. Baseline demographics of patients.

Variables	Mean	Standart Deviation	Minimum	Maximum
Age (year)	61,37	10,42	42	79
BMİ (kg/m²)	27,40	3,90	19,5	36,5
SCr (mg/dL)	0,86	0,18	0,50	1,20
BUN (mg/dL)	17,34	5,33	10,80	35,10
GFR (mL/dk/1.73m²)	80,37	4,91	70,00	90,00

it was reported that Cystatin C measured at the 12th hour was strongly correlated with the severity and duration of AKI and the length of hospital stay. In multivariate analysis, 12 h Cystatin C was reported as a strong independent predictor of AKI (12). In our study, when the Cystatin C results of the patients in the preoperative and postoperative periods are examined, it is seen that there is a serious upward curve in the postoperative period. A significant increase in serum Cystatin C level was detected in all patients undergoing CPB, especially at 24 hours. However, pre-op and postoperative 6 hours of patients who develop AKI. We did not find a significant relationship with the Cystatin C levels measured. The difference in the evaluated patient population may explain this situation.

SCr, which is used as a standard in the diagnosis of AKI, is reported to be an insufficient marker for AKI because there is usually a delay before it rises. Improved sensitivity and speed of measurement of biomarkers may enable early patient management and enhance patient outcomes, particularly in intensive care units and patients when rapid action is essential (13). In our study, we determined that the presence of AKI negatively affects many characteristics of the patients (length of stay in the intensive care unit, length of hospital stay, extubation time, postoperative diuretic use, blood product use, 24-hour thorax tube drainage, delirium development) similar to the literature. Studies have found that CPB-related AKI is associated with a more than 2-fold increase in early mortality compared to unrelated AKI (14).

It is crucial to thoroughly assess individuals who will have cardiac surgery and to identify any AKI conditions that can worsen more quickly. Serum cystatin C has been validated as a good marker for predicting GFR in many patient populations, including kidney transplant and critically ill patients, and has more recently been reported to show promise as a good biomarker for the early diagnosis of AKI after adult cardiac surgery (15). Although the 6th hour Cystatin C level is not significantly sensitive in the diagnosis of AKI in our study, we have shown that it can be a usable biomarker at the 24th hour.

Table 3. Comparison of preoperative characteristics of patients according to AKIN and RIFLE classification.

	24. hour AKIN			24. hour RIFLE		
Variables	**ABH – (n=28)**	**ABH + (n=12)**	**P Value**	**ABH – (n=26)**	**ABH + (n=14)**	**P Value**
Age	59,85±9,68	64,91±11,86	0,122	59,53±9,28	64,78±12,05	0,110
Female	7 (%25)	4 (%33)	0,694	8 (%30)	5 (%35)	0,944
BMI(kg/m2)	27,28±3,54	27,68±4,87	0,610	27,20±3,48	27,76±4,76	0,547
Preop. SCr(mg/dL)	0,80±0,16	1,01±0,13	0,110	0,78±0,15	1,01±0,15	0,080
Preop. GFR (ml/dk/1.73 m²)	80,57±5,43	79,66±3,60	0,610	80,9±5,46	79,57±3,85	0,392
Reoperation	0 (%0)	2 (%17)	0,422	0 (%0)	2 (%14,2)	0,474
HT	10 (%35)	8 (%67)	0,130	8(%30,7)	10 (%71,4)	0,347
AF	3 (%10)	3 (%25)	0,493	3 (%11,5)	3 (%21,4)	0,624
Carotid stenosis	2 (0,71)	3 (%25)	0,389	2 (%7,6)	3 (%21,4)	0,492
COPD	1 (%3,5)	5 (%42)	0,060	1 (%3,8)	5 (%35,7)	0,104
DM	8 (%28,5)	8 (%66,7)	0,050	7 (%26,9)	9 (%64,2)	0,045

Table 4. Comparison of intraoperative characteristics of patients according to AKIN and RIFLE classification

	24. hour AKIN			24. hour RIFLE		
Variables	**ABH – (n=28)**	**ABH + (n=12)**	**P Value**	**ABH – (n=26)**	**ABH + (n=14)**	**P Value**
AKZ (min)	35,53±9,36	40,41±6,55	0,090	35,00±9,48	40,71±6,15	0,039
TPZ (min)	55,67±9,94	65,83±11,04	0,003	57,19±8,17	67,14±11,38	0,001
CABG	23 (%82,1)	8 (%66,7)	0,210	22 (%84,7)	10 (%71,4)	0,156
Lid surgery	3 (%25)	3 (%25)		3 (%11,5)	3 (%21,4)	
Others	2 (%7,1)	1 (%8,3)		1 (%3,8)	1 (%7,1)	
Use of Blood Product	7,25±1,67	10,59±2,15	0,001	7,26±1,71	7,26±1,71	0,001
Diuretic use	6 (%21,4)	10 (%83,4)	0,002	8 (%30,7)	10 (%71,4)	0,012

Table 5: Comparison of post-operative characteristics of patients according to AKIN and RIFLE classification

	24. hour AKIN			24. hour RIFLE		
Variables	**ABH – (n=28)**	**ABH + (n=12)**	**P Value**	**ABH – (n=26)**	**ABH + (n=14)**	**P Value**
extubation time	8,9±6,2	13,0±11,4	0,085	8,8±6,3	12,6±10,2	0,040
ICU stay (hour)	54,4±23,6	63,5±35,0	0,402	54,3±22,53	62,0±35,7	0,896
Discharge (day)	6,8±2,34	8,3±3,15	0,119	6,85±2,3	8,1±2,9	0,147
6.h Drainage	257,2±170,3	263,1±162,5	0,500	256,3±166,2	265±279,6	0,654
6.h Cys (ng/ml)	23,37±18,79	24,25±14,08	0,358	22,75±18,1	27,2±15,8	0,092
24.h Drainage (cc)	542,85±205,35	787,50±253,27	0,002	542,3±211,5	753,5±251,5	0,005
24.hour Cys (ng/ml)	25,37±16,23	44,75±18,37	0,002	0,86±0,12	1,75±0,41	0,001
Postoperative Use of inotropes	2 (%7,1)	3 (%25)	0,115	2 (%7,6)	5 (%35,7)	0,115
Postoperative Blood Product	7,25±1,67	10,59±2,15	0,001	7,26±1,71	7,26±1,71	0,001
Diuretic	6 (%21,4)	10 (%83,4)	0,002	8 (%30,7)	10 (%71,4)	0,012
Revision	0 (%0)	2 (%17)	0,422	0 (%0)	2 (%14,2)	0,474
SVD	2 (%7,1)	1 (%8,3)	0,965	2 (%7,6)	1 (%7,1)	0,989
Delirium	0 (%0,0)	3 (%3,25)	0,039	0 (%0,0)	4 (%28,5)	0,067
Arrhythmia	8 (%28,5)	3 (%25)	0,050	2 (%7,6)	5 (%35,7)	0,104

Table 6. Evaluation of Cystatin C Levels in Patient Groups

	AKI (-) (n=28)	**AKI (+) (n=12)**	**P Value**
Preoperative Cys C	15,35±14,9	11,63±4,2	**0,942**
Postoperative 6.h Cys C	23,37±18,79	24,25±14,08	**0,358**
Postoperative 24.h Cys C	25,37±16,23	44,75±18,37	**0,002**

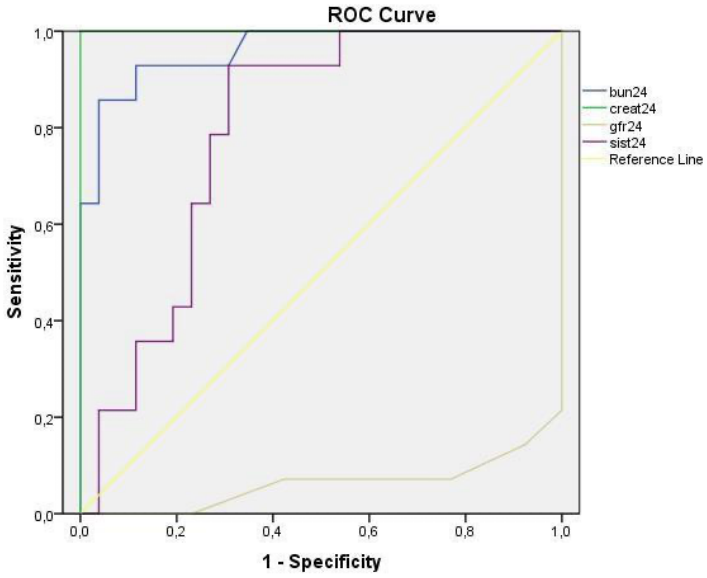

Figure 1. 24-hour ROC analysis result according to AKIN classification

CONCLUSION

The diagnosis of AKI developing in patients undergoing cardiac surgery is made according to results such as increased creatinine, urine output and decreased GFR. However, other research indicate that the diagnosis of creatinine is delayed. Patients with postoperative AKI face serious issues with treatment costs and patient prognosis. Use of early diagnostic biomarkers with high sensitivity and specificity is crucial for this reason. In our study, the role of BUN, SCr, GFR and Cystatin C in the early diagnosis of AKI after CPB was evaluated. In patients who developed AKI, serum BUN, SCr and GFR measured at the 6th postoperative hour were found to be important in early diagnosis. We determined that Cystatin C, which was checked at the postoperative 24th hour, could be used in the diagnosis of AKI.

Ethics Committee Approval: Afyon Health Sciences University Local Ethics Committee approved this study (Number: 2015/04-103).

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

Authorship Contributions: Concept and design of article: ET, SAY, MA; Data Collecting: ET, SAY; Writing: ET, SAY, MA; Drafting and critical revision of the article: SAY, MA.

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