BIOMEDICAL
Journal of Scientific & Technical Research

Predictive Value of Baseline Cystatin C for Acute Kidney Injury After Cardiac Surgery

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Abstract

Introduction: This study aimed to investigate the predictive value of preoperative serum cystatin C (S-cystatin C), in identifying patients whom at higher risk of acute kidney injury after cardiac surgery (AKI).

Methods: To predict the early mortality, we used the European system for cardiac operative risk evaluation (Euro score). Serum creatinine levels on admission were used to evaluate the glomerular filtration rate (GFR) by using the Modification of Diet in Renal Disease (MDRD) equation. S-cystatin C, NT proBNP and procalcitonin were measured before cardiac surgery (H0), 4 hours after the end (H4) and every day during the first two days (H24, H48). All patients were followed during a whole year.

Results: Positive associations were observed between baseline s-cystatin C value and Euro score and with Rifle classification. Different positive correlations were observed between baseline s-cystatin C, cardiac markers and procalcitonin. A preoperative s-cystatin C cutoff 1.025 mg/L demonstrated higher sensitivity than preoperative s-creat cutoff, in discriminatory accuracy of one-year mortality. Estimated GFR, procalcitonin and NT pro BNP showed a decreased AUC values compared to s-cystatin After multivariate analysis, S-cystatin C and NT pro BNP were independently associated with cardiovascular events accuracy and re-hospitalization risk after cardiac surgery.

Conclusion: Our results demonstrated that pre-operative s-cystatin C could be an early biomarker of surgery-related AKI and can predict mortality and severe outcomes after cardiac surgery.

Keywords: Cardiac Surgery; Cystatin C; Mortality; Biomarker; Acute Kidney Injury

Introduction

Cardiac surgery is an invasive procedure and often associated with a high morbidity and mortality risk [1]. Acute kidney injury (AKI) is a common and serious complication in hospitalized intensive care unit patients with incidence of 11% to 67%, and mortality of 13% to 36%, depending on the definition of AKI [2]. Preoperative renal insufficiency has been shown to be independently associated with acute kidney injury (AKI) and increased mortality after cardiac surgery (CS) [3]. Factors such as surgical trauma, myocardial ischemia reperfusion, body temperature and cytokines cascade have been shown to induce systemic inflammatory response syndrome (SIRS) after cardiac surgery with or without cardiopulmonary bypass (CPB) [3]. Previous studies of patients undergoing coronary artery bypass grafting (CABG) or valvular replacement (VR) have generally relied on plasma creatinine to determine preoperative renal function [4].

However, subclinical increases in serum creatinine do not meet current Acute Kidney Injury Network or RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria for acute renal injury. Recent research has focused on novel biomarkers of injury, which have the potential to diagnose AKI much earlier [5]. Serum s-cystatin C (s-cystatin C), which is an alternative estimated glomerular filtration rate marker s a low molecular weight protein that is freely filtered through the glomerular membrane and metabolized in the proximal tubules [6]. We aimed in this study to investigate the predictive value of preoperative s-cystatin C, in identifying those at higher risk of AKI after cardiac surgery in a Tunisian cohort of patients undergoing cardiac surgery (CABG or VR).

Materials and Methods

Patient Selection

After approval from the local ethics committee and written informed consent, 42 consecutive eligible patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) were enrolled prospectively. All patients were free from active preoperative

infection or inflammatory disease (leukocyte count <12,000/L, C-reactive protein [CRP] <5 mg/L, body temperature <38°C). Their preoperative medication did not include any antibiotic or corticosteroid. Inclusion criteria were: age >18 years and programmed or semi-urgent heart surgery under CPB. Patients with recent myocardial infarction (MI) <7days, hepatic failure and infective endocarditis or documented infection within the last 7 days before surgery were excluded. SIRS was defined according to the classification of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [7]. SIRS classification was performed on all patients on the first postoperative day and every day during the first 4 postoperative days. To predict the early mortality in cardiac surgical patients, we used the European system for cardiac operative risk evaluation (EuroSCORE) [8].

To evaluate Acute Kidney Injury (AKI) after cardiac surgery, we used the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification, proposed by the Acute Dialysis Quality Initiative (ADQI) [9]. AKI was defined as ≥ 50% increase in serum creatinine concentration, absolute increase ≥ 26 µmol/L, or new requirement for dialysis [10]. Serum creatinine (s-Creat) concentration on admission which was measured by the modified Jaffe's techniques, was used to calculate the estimated glomerular filtration rate (e GFR) by using the Modification of Diet in Renal Disease (MDRD) equation [9]. According to the RIFLE criteria, the decrease in percentage of the calculated GFR must be >25, >50 or >75 % as compared to the standard (ADQI).

Anesthesia and Surgery

Patients were premedicated with oral hydroxyzin (Atarax®)1 mg/kg, the night and 2 hours before surgery. Detailed surgical techniques and anesthetic preconditioning were described previously by Kallel S et al. [11].

Blood Samples

We performed seven blood samplings for each patient: the first one immediately after the induction of anesthesia and before CPB. The following samples were taken at the end of CBP (H0), 4 hours later (H4) and every day during the first four days (H24, H48, H72 and H96). Serum Creatinine and S-cystatin C were measured in each sample. Blood samples were collected from the radial artery and immediately centrifuged for 10 min. Plasma samples frozen at -20°C were stable for assays for >20 days after sampling, and all samples were analyzed within 2 weeks.

S-Cystatin C, Troponin, Nt Probnp and Procalcitonin Measurements

S-cystatin C value was measured with particle-enhanced turbidimetric immunoassay (PETIA) using a Cobas® e 411 analyzers (REF. 04975723 190, Roche Diagnostics, Mannheim, Germany). N terminal -pro-brain natriuretic peptide (Nt-pro-BNP) concentrations were measured with an enzyme-linked fluorescence assay (ELFA, miniVidas®, Biomérieux, France), using polyclonal antibodies that recognize epitopes located in the N-terminal part (1–76) of pro-BNP (1–108). NT-proBNP was dichotomized with a cutoff value 4125 pg/ mL as recommended for preoperative

screening in moderate- to high-risk patients [12]. Troponin Ic and Procalcitonin (PCT) concentrations in serum were measured by electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

Statistical analysis was performed with the software Statistical Package for Social Sciences (SPSS) for Windows (version 20.0, SPSS Inc., Chicago, IL). Quantitative variables were expressed as mean ± SD or median [minimum-maximum], depending on the nature of the distribution. Qualitative variables were expressed as frequencies.

For the comparison of means, we used Student's t-test or the Mann-Whitney U test whenever the normality of the distributions was not observed (non-Gaussian distribution) or the size of one of the groups was small (<10). Categorical variables were analyzed by the c2 test or Fisher's exact test whenever a population was <5. Differences between results were considered significant at a value of p<0.05. For multiple comparisons we used the Bonferroni correction. In order to see the power of the different biomarkers in the prediction of ICU stay, we used linear regression to calculate predicted length of stay by each marker and we compared the predicted stays with the observed one. To determine the different threshold values, we used the ROC (receiver operating characteristic). The best threshold value is the value having the best sensitivity and specificity.

Results

Baseline and Outcomes Values

42 patients were enrolled in this study, 2 patients died, leaving 40 (17 women, 23 men). Mean age was 56,1±14,9 years [18,17]. Follow-up was 100% complete. The general characteristics of the study cohort were summarized in Table 1. Mean durations of cardiac surgery and extracorporeal circulation were 268 ± 54,6 min and 97 ± 30,6 min respectively.

Post-Operative Complications

Post-operative complications were summarized in Table1. SIRS developed in 35 patients (87.5 %). The 30-day mortality was 2.5 %. Overall survival was 87.5 % at 1 year. 4 patients had a high Euroscore (>6). At H 24, the proportion of patients under the RIFLE classes was 20 % in R, 17.5 % in I, and 62.5 % as non AKI. At H48, 30 % of patients were classified in R and 25 % in I and 45% as non AKI (data not shown). S-cystatin C levels decreased significantly between H0 and H4, then increased gradually (Figure 1A). S-cystatin C levels increased significantly in patients with high Euro SCORE (>6) (Table 2). Also, positive associations were observed between baseline s-cystatin C value and EuroSCORE (r =0.372, p=0.02, Figure 1B) and with RIFLE classification (p=0.02 at H24, Figure 1C, p=0.01 at H48, Figure 1D). Different positive correlations were observed between baseline s-cystatin C and cardiac and inflammatory markers as it is shown in Table 2. A preoperative s-cystatin C cutoff value 1.025 mg/L demonstrated higher sensitivity than preoperative s-creat cutoff 106.5µmol/L in discriminatory accuracy of one-year mortality (85.7 % vs 71.4 %) but both showed good specificity (80% and 83.3% respectively).
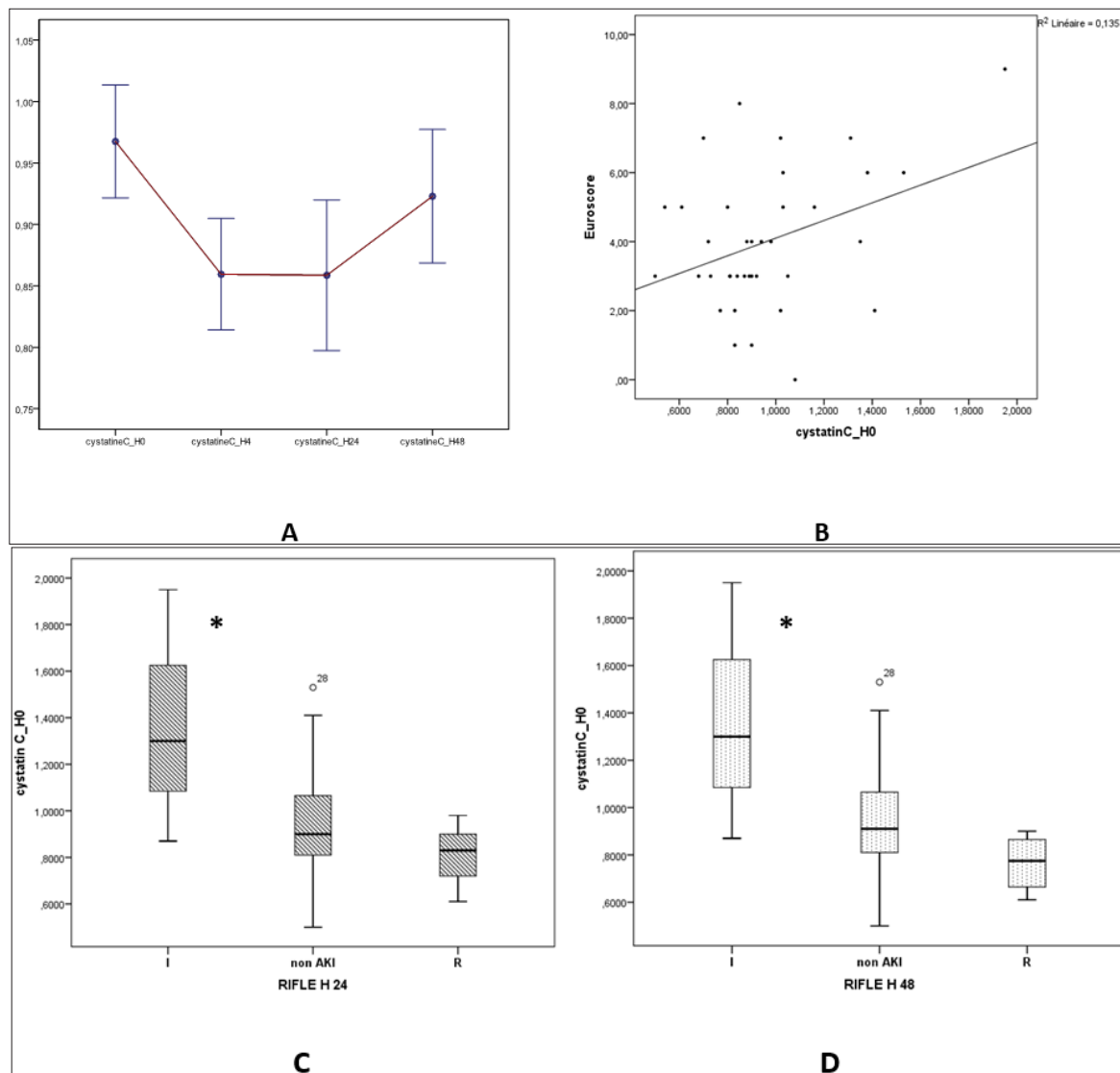
Figure 1: The kinetics of Cystatin C after cardiac surgery (A), Association between baseline cystatin C levels and EuroSCORE (B). Variation of baseline Cystatin C levels according to RIFLE classification at one (C) and 2 days after cardiac surgery (D). *: $p < 0.05$; ANOVA test.

Table 1: Clinical characteristics of the studied cohort.

Preoperative characteristics (n=40)	mean ± SD	Postoperative Outcomes	n (%)
Short Term Outcomes			
Age (years)	56.1 ± 14.9	AMI CS-AKI	1 (2,5)
BMI (Kg/m^2)	24.3 ± 4.4	Postop AF	7 (17,5)
Euroscore (points)	4.07 ± 2.04	Cardiogenic pulmonary edema	2 (5)
Male	23 (57.5)	Hemorrhagic shock	1 (2,5)
Female	17 (42.5)	RBC massive transfusion	4 (10)
Hypertension	15 (37.5)	Hypoxia	10 (25)
Diabetes	12 (30)	Mechanical ventilation >24H	0 (0)
COPD	3(7.5)	Reintubation	5 (12,5)
LVEF < 50	4 (10)	Pulmonary atelectasis	9 (22,5)
Dyslipidemia	7 (17)		

Long Term Outcomes			
Preop AF	2 (5)	1-year Rehospitalisation	12 (30)
MI < 3 months	11(27)	1-year CV events accuracy	13 (32.5)
Valvular Replacement	23 (57.5)	1-year Mortality	5 (12.5)
CABG	17 (42.5)		

CABG: coronary artery bypass grafting, VR: valvular replacement BMI: body mass index; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Preop AF: preoperative atrial fibrillation. AMI: acute myocardial infarction, AKI: Acute kidney injury, Postop AF: postoperative atrial fibrillation. CS: cardiac surgery, CV: cardio vascular.

Table 2: Different associations between cystatin C and cardiac / inflammatory markers after cardiac surgery.

Cystatin C (mg/L)		NT-proBNP H4	NT-proBNP H24	NT-proBNP H48	CRP H4	CRP H24	CRP H48	PCT H48
Cystatin C H0	r	0,458	0,505	0,230	0,028	0,162	0,310	0.33
	p	0,003	0,001	0,159	0,867	0,324	0,055	0.04
Cystatin C H4	r	0,318	0,407	0,095	0,230	0,307	0,279	0.223
	p	0,049	0,011	0,565	0,159	0,057	0,085	0.172
Cystatin C H24	r	0,277	0,372	0,048	0,204	0,341	0,352	0.347
	p	0,088	0,021	0,771	0,213	0,034	0,028	0.03
Cystatin C H48	r	0,484	0,477	0,140	0,055	0,185	0,278	0.402
	p	0,002	0,003	0,410	0,747	0,272	0,095	0.014

NT-proBNP: N terminal pro-brain natriuretic peptide (pg/mL); CRP: Creactive protein (mg/L); PCT: procalcitonin (ng/mL); *p* significant if < 0.05.
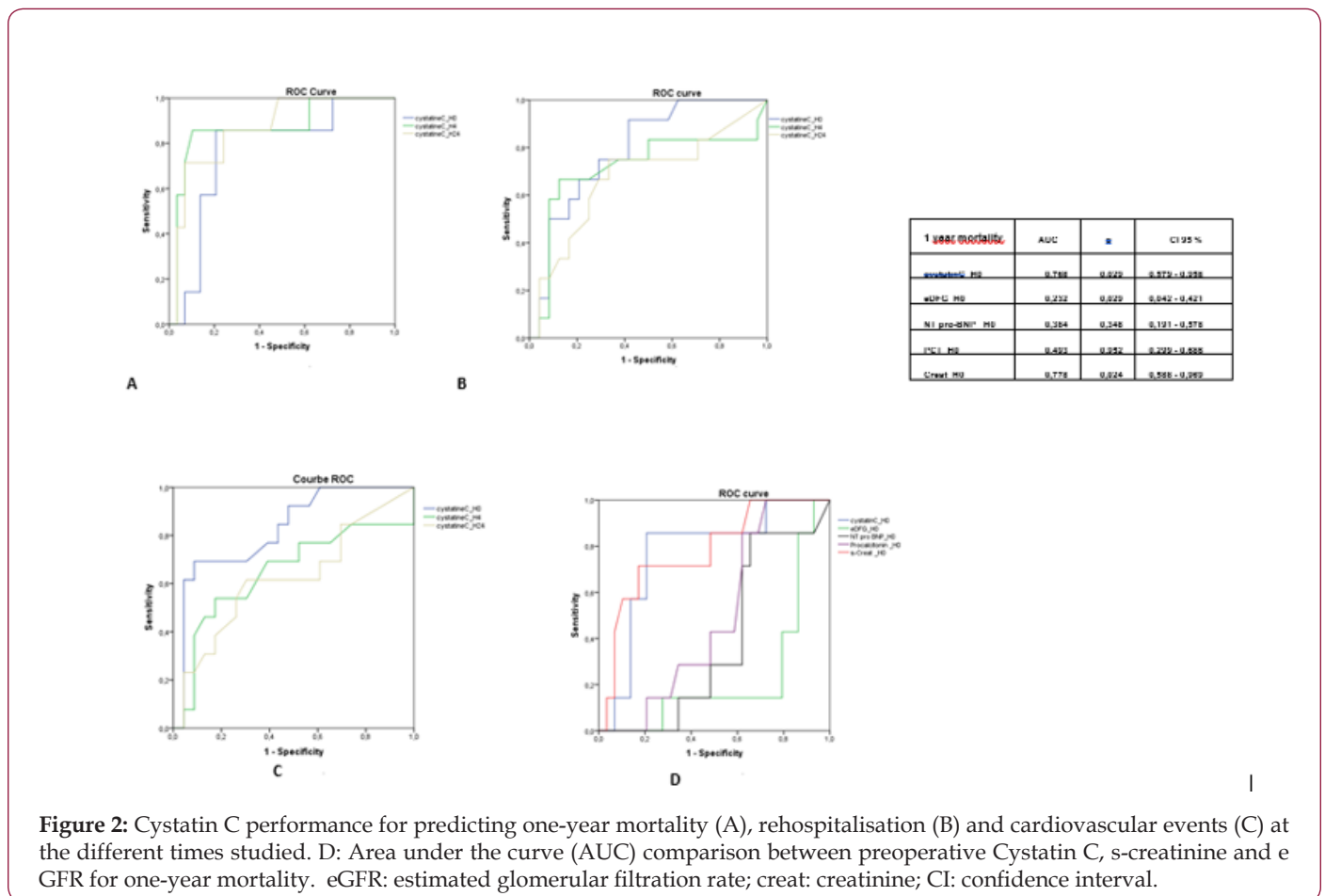

Figure 2: Cystatin C performance for predicting one-year mortality (A), rehospitalisation (B) and cardiovascular events (C) at the different times studied. D: Area under the curve (AUC) comparison between preoperative Cystatin C, s-creatinine and e GFR for one-year mortality. eGFR: estimated glomerular filtration rate; creat: creatinine; CI: confidence interval.

Estimated GFR, PCT and proBNP showed a decreased AUC values compared to s-cystatin C (Figure 2). After multivariate analysis, independent variables tested in different models of binary logistic regression, were cardiovascular (CV) events accuracy and rehospitalisation, dependent variables were age, s-cystatin C, s-creat, troponin and NT proBNP baseline levels. S-cystatin C and NT proBNP were independly associated with CV events accuracy and rehospitalisation risk after cardiac surgery (Table 3).

Table 3: multivariate analysis showing associations between S-cystatin C, NT proBNP, CV accuracy and rehospitalisation risk after cardiac surgery.

Rehospitalisation	A	p	Exp(B)	CI 95%	
Cystatin C_H0	5,692	,017	296,537	2,807 - 31322,5	
Age	,003	,924	1,003	0,938 - 1,073	
CREAT_J0	-,011	,598	,989	0,951 - 1,029	
NT pro BNP	-,003	,066	,997	0,994 - 1,000	
Troponin Ic_H0	,246	,697	1,279	0,370 - 4,418	
Cardiovacular events accuracy	A	p	Exp(B)	CI 95%	
CystatineC_H0	6,662	,023	782,431	2,481	-246760,783
Age	,089	,088	1,093	0,987	1,210
CREAT_J0	-,001	,955	,999	0,956	1,044
NT proBNP	-,004	,024	,996	0,993	0,999
Troponin Ic_H0	-,830	,495	,436	0,040	4,747

Creat : serum creatinine, H0 : baseline

Discussion

In this study, we aimed to investigate the value of baseline s-cystatin C in identifying patients at greater risk for AKI after cardiac surgery. The identification of pre-operative risk factors for AKI after cardiac surgery is important to determine which resources and interventions will ensure an optimal outcome. Serum s-cystatin C is a newly identified marker of renal function [13]. S-cystatin C, is a 13-kDa secreted cysteine protease inhibitor ubiquitously expressed in all nucleated cells and presented in all body fluids, freely filtered by the renal glomeruli, and catabolized in the proximal tubules [13]. S-cystatin C plays various roles in many pathological processes, including tumor metastasis, atherosclerosis, inflammatory responses and immunomodulation [14]. Several studies have shown that serum s-cystatin C is a better indicator of GFR and a more reliable marker of mild renal dysfunction, compared with serum creatinine [10]. S-cystatin C has been suggested as a more sensitive marker for determining impaired eGFR, because its levels are not significantly affected by sex, race, muscle mass, infection, liver disease, or inflammatory disease, and it is not secreted by the renal tubules [15].

Ledoux et al. demonstrated that preoperative eGFR based on s-cystatin C level may provide a better risk assessement of AKI after cardiac surgery than e GFR based on s-creat. The authors suggested that this could be related to the inability of s-creat to detect subclinical renal impairment [16]. The pathogenesis of AKI is multifactorial, mainly related to a complex interaction among baseline predisposition, hemodynamic disturbances, nephrotoxic insults and inflammatory responses. Inadequate renal perfusion traditionally has been considered the most important event in the course of AKI after cardiac surgery [17]. In fact, Rosner and Moran et al. explained the changes in S-cystatin C levels in AKI as a consequence of renal tubular damage which affected upstream glomerular filtration due to congestion [18]. Zheng et al. noticed that post-operative serum concentrations of S-cystatin C in AKI group initially declined for 6 h, then subsequently rose again in 12 h, and got stabilized between 24 and 48 h after CPB [19]. This is in accordance with our findings about kinetic variations of cystatin C levels during CS.

This may be attributed to hemodilution associated with CPB. This effect could be more prominent in infants and young children because of their lower body weight and blood volume [19]. Recently, we have demonstrated that eGFR based on both serum creat-cystatin is more accurate to obtain eGFR than can be obtained from eGFR creat alone [20]. In view of crescent evidences in its favors, several authors suggested that cystatin-C should be added to creat in the calculation of the CDK-EPI cystatin equation for better estimation of GFR [20].Furthermore, recent studies confirmed that estimated GFR combining both creat and cystatin C provided significant incremental information regarding the risk of AKI beyond traditional, clinical risk factors [10]. Improved prediction was especially seen in patients with intermediate AKI risk, where a net of 27% of AKI cases and 29% of control patients were correctly reclassified [10]. AKI is a common postoperative complication that greatly increases morbidity and mortality. Our study showed that patients with a baseline Cystatin C >1.025 mg/L demonstrated a high risk of 1year rehospitalization, CV events accuracy and mortality.

After multivariate analysis, S-cystatin C and NT proBNP were independently associated with 1- year cardiovascular events accuracy and 1-year re-hospitalization risk after cardiac surgery. NTproBNP is biomarker of heart failure which is released into the circulation in situations with volume expansion or pressure overload [21]. Vale NC et al. demonstrated that baseline NT-proBNP did not predict one-year mortality. However, only hsTnT and cystatin C were significant predictors of survival under multivariable Weibull and Cox regression [22]. Recently, it has

been recommended the use of baseline multimarker strategy to improve preoperative risk stratification of CS-AKI, to optimize supportive treatment and to avoid secondary renal injury [23]. Findings from this study underlined the importance of baseline S-cystatin C assay to improve preoperative prediction of CS-AKI and mortality. Additional large scale studies are needed to explore whether other useful biomarkers exist or not such as urinary biomarkers (neutrophil gelatinase-associated lipocalin, midkine, proteinuria…). Nevertheless, the cost-effectiveness remains to be demonstrated.

Fundings

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