Int Surg 2016;**101:**390–398
DOI: 10.9738/INTSURG-D-16-00075.1

Cystatin C and NGAL as Biomarkers for Early Detection of Acute Kidney Injury in Geriatrics

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Acute kidney injury (AKI) is associated with cardiovascular mortality and morbidity especially in high-risk patients undergoing cardiac surgery. It ranges from 7.7% to 28.1% in different studies. The aim of this study was to compare cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) with Creatinine as an early marker for acute kidney injury in geriatrics. From 2013 through 2015, 307 consecutive high-risk elderly patients older than 70 years undergoing emergency coronary artery bypass grafting using extracorporeal circulation were studied. All patients underwent diagnostic coronary angiography and the surgical procedure within 1 week in single hospital stay and were randomized according to timing of interval between coronary angiographyand cardiac procedure as follows: group I, less than 2 days; group II, between 2 and 4 days; and group III, higher than 4 days. Renal function was analyzed by serum cystatin C, NGAL, and creatinine. Blood samples were obtained from each patient at five time points: basal value before operation, in the four hours after operation, and on the first, third, and fifth postoperative days. Glomerular filtration rate (GFR) was calculated by Cockcroft-Gault (CG). A total of 56 patients developed postoperative acute kidney failure according to the risk, injury, and failure; and loss; and end-stage kidney disease classification. Perioperative fluid requirements, urine output, and vasopressor need during and after cardiopulmonary bypass were similar. 30-day mortality in groups was higher in group I

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than group II and group III ($P = 0.025$). AKI was least prominent in group III compared to group I and group II ($P = 0.001$) and expectedly, postoperative dialysis requirement was least common in group III (15, 16.66%). Patients in group III had the most favorable clinical outcome with regards to the length of ICU and hospital stay. Overall serum creatinine, cystatin C, and urine NGAL levels changed significantly throughout the entire length of following-up period in group I and group II, but not in group III. Changes in serum levels of cystatin, creatinine, and creatinine clearance were prominent in later than 24 hours. Urinary NGAL was the first variable to rise in the immediate postoperative period. Cystatin GFR was a more rapid marker than serum creatinine GFR to show acute kidney injury in three groups was a significant marker.

Key words: Acute renal injury – Elderly patients – Renal biomarker – Coronary bypass

Acute kidney injury (AKI) is a serious complication that is most common after cardiac surgery in 5% to 40% of patients and is associated with lengthened intensive care unit (ICU) stay, increased costs, a deteriorating quality of life, and significant morbidity and mortality rates.[1,2] Cardiopulmonary bypass (CPB) is an important risk factor for AKI in elderly patients undergoing coronary bypass, mostly due to nonpulsatile flow of an extracorporeal circulation, hemodilution, possible renal hypoperfusion, and atheroembolization.[3,4] Renal dysfunction is one of the most important responsible factors to increase perioperative mortality and morbidity in elderly patients undergoing coronary bypass.[5,6] A great number of studies having cardiovascular disease or diabetes mellitus show that low glomerular filtration rate (GFR) is the independent risk factor in new onset cardiovascular events and overall mortality.[7] In clinical practice, GFR is estimated from serum creatinine levels that may be of limited value for the early detection of renal impairment, because creatinine is not only filtered by the glomeruli, but also secreted by the tubules.[8] Moreover, serum creatinine may not adequately assess acute changes in GFR.[9] Serum creatinine is influenced not only by renal function, but also by lean body mass (*i.e.*, muscle mass), sex, age, and ethnicity.[10]

Serum cystatin C (CysC) is a newly identified marker of renal function. Cystatin C is a low-molecular-weight protein (13,359 Da) that is produced by all nucleated cells at a constant rate, released into the bloodstream, freely filtered by the renal glomeruli, and catabolized in the proximal tubules.[10,11] Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25-kDa glycoprotein secreted by activated neutrophils. In normal conditions, kidney tubule cells produce and excrete NGAL at low levels (37–106 ng/mL); nevertheless, in inflammatory, infective, ischemic, or nephrotoxic conditions, its plasma and urine levels rise significantly. This elevation occurs as early as 2 hours after injury.[12] The predictive value of increased urinary NGAL concentration in developing AKI has been previously confirmed.

We have evaluated cystatin-C and NGAL as renal biomarkers of acute kidney injury and cardiac adverse events in high-risk elderly patients undergoing pump coronary artery bypass for emergency myocardial revascularization.

Patients and Methods

Patient selection

A total of 307 patients aged older than 70 years undergoing coronary artery bypass graft (CABG) using extracorporeal circulation between 2013 and 2015 were prospectively included in the study. All patients underwent diagnostic coronary angiography and the surgical procedure within 1 week in single hospital stay and were randomized according to timing of interval between coronary angiography and cardiac procedure as follows: group I, less than 2 days; group II, between 2 and 4 days; and group III, higher than 4 days. Subjects were blind to operators and researchers. Inclusion criteria included all patients aged older than 70 years and candidates for sole CABG surgery with normal preoperative renal function based on criteria from the American College of Cardiology and American Heart Association. Exclusion criteria included patients with additional valvular disease; carotid artery stenosis or peripheral artery disease; any concomitant operation; congenital heart disorder; raised basal creatinine level (up to 1.5 mg/dL); preexisting renal insufficiency or GFR smaller than

50 mL/minute); unstable hemodynamic or pulmonary situation; chronic obstructive pulmonary disease or abnormal pulmonary function test (respiratory distress, partial carbon dioxide pressure greater than 45 mmHg and partial oxygen pressure of 60 mm); recent cerebral vascular accident; neurologic complications, consciousness disorder, or significant neurologic defect; uncontrolled diabetes mellitus; preoperative infection; blood transfusion before surgery; serum sodium concentrations higher than 150 meq/dL; head trauma and body mass index greater than 40 kg/m^2, as well as those who used nephrotoxic drugs before the operation; blood hemoglobin (Hb) levels less than 11 mg/dL of unknown cause.

Acute kidney injury was defined as an increase in serum creatinine from the preoperative values by either more than 50% or more than 0.3 mg/dL within the first 48 hours after surgery (AKI classification stage 1). European system for cardiac operative risk evaluation (EuroSCORE), as a well-validated risk adjustment model, was used to avoid overfitting or underfitting. Local institutional ethics committee approval and informed consent from the patients were obtained in compliance with the tenets of the Declaration of Helsinki.

Surgical technique

All the procedures were performed via a standard median sternotomy and a standard cardiopulmonary bypass. Hyperkalemic cardiac arrest was induced using cold-blood intermittent anterograde cardioplegia.

Collection of blood samples and measurements of biomarkers

Serum cystatin C and NGAL concentrations were analyzed prior to the induction of anesthesia, immediately after CPB, and 2 hours after CPB, and serum creatinine levels were assessed the day before the operation and on postoperative days (POD) 1, 2, and 3. The serum creatinine (SCr), serum cystatin C and the estimated glomerular filtration rate (eGFR) were obtained as basal values before surgery, then 4 hours after surgery and on POD 1, 3, and 6 to assess renal function. The postoperative AKI was diagnosed if there was $\geq$50% or $\geq$0.3 mg/dL increase in the serum creatinine level within 48 hours, compared with the preoperative baseline value.[12] Biovendor CysC is an enzyme-linked immunosorbent assay (ELISA) for the quantitative determination of CysC levels in human plasma or serum. NGAL was measured from urine samples using ELISA kits (Human NGAL ELISA, Hycult Biotechnology B.V., Plymouth Meeting, Pennsylvania). The urine samples were diluted at 1:20 in a dilution buffer provided by manufacturing laboratory, and 0.1 mL aliquots were taken for analysis. The minimum detection level for this test is 0.4 ng/mL. The detection limit for this test was 9 pg/mL. Cystatin C levels were measured with a standardized immunonephelometry analysis using a BNII nephelometer (Siemens Healthcare Diagnostics, Erlangen, Germany). The GFR was estimated through the following formulas largely used in literature[16–19]: Cockcroft-Gault (CG) = ([(140 – age) $\times$ weight (kg)]/plasmatic creatinine $\times$ 72) $\times$ (0.85 in case of the female patients); the formula of Larsson (Cys GFR) = 77.24 $\times$ (cystatin C$^{-1.2623}$).

Statistical analysis

All continuous data were presented as the median and the interquartile range (25–75 percentile), or the total range. Discrete data were given as counts and percentages. All continuous variables were initially tested for normality using the Kolmogorov-Smirnov test. We used the Student's *t*-test or Mann-Whitney *U* test whenever data showed normal distributions. The categorical variables were compared using the χ^2 or the Fisher's exact test, as required. The repeated measure analysis of variance was employed to evaluate intergroup differences and intragroup changes. Differences between variables to estimate GFR were tested post hoc using the Bonferroni test. For the statistical analyses, we used statistical software (SPSS version 20.0 for Windows, SPSS, Inc, Chicago, Illinois). A value of $P < 0.05$ was considered statistically significant. The graphs were constructed using commercial software (Statistica, version 20.0, StatSoft, Tulsa, Oklahoma).

Results

Preoperative demographics and variables were similar in 3 groups (Table 1). A total of 56 patients developed postoperative acute kidney failure according to the risk, injury, and failure; and loss; and end-stage kidney disease (RIFLE) classification. Perioperative fluid requirements, urine output, and vasopressor need during and after CPB were similar (Table 2). Perioperatively, the mean number of red blood cells or fresh frozen plasma transfusions were

Table 1 Preoperative patient characteristics

	Group I (<2 d), n (%)	Group II (2–4 d), n (%)	Group III (>4 d), n (%)	*P*
Age	73.23 ± 8.37	73.65 ± 8.23	74.12 ± 9.21	0.152
Sex				
Male, n (%)	43	50	65	0.922
Female, n (%)	47	45	57	0.871
DM	52 (58)	48 (51)	55 (45)	0.091
Hypertension	67 (74)	62 (65)	91 (75)	0.085
Hyperlipidemia	50 (56)	52 (55)	71 (58)	0.631
Smoking	70 (78)	68 (72)	85 (70)	0.065
BMI	28.69 ± 5.02	29.01 ± 4.87	27.97 ± 3.75	0.876
NYHA				
Grade I–II	72 (80)	80 (84)	95 (76)	0.518
Grade III–IV	18 (20)	15 (16)	27 (22)	0.563
Non ST MI or intractable angina				
Yes	68 (76)	75 (79)	94 (77)	0.728
No	22 (24)	20 (21)	28 (23)	0.813
Left ventricle function	52.94 ± 9.60	51.90 ± 10.87	54.67 ± 10.16	0.342
Number of CIN risk factors	3	2	3	0.721
Preoperative Htc	38 ± 5	36 ± 3	40 ± 2	0.462
EuroSCORE II	3.45 ± 2.14	3.59 ± 1.82	3.66 ± 2.16	0.072
Syntax score	28.79 ± 13.66	35.18 ± 6.15	32.87 ± 8.91	0.418

4 ± 2, 3 ± 3, and 4 ± 1 packs in groups I, II, and III, respectively ($P = 0.347$); 30-day mortality was 10%, 4.21%, 2.67%, respectively ($P = 0.025$).

AKI was least prominent in group III (n = 12, 9.08%) compared with groups I and II, (n = 24, 26.66% and n = 20, 21.05%, respectively; $P = 0.001$) and expectedly, postoperative dialysis requirement was least common in group III (n = 15, 16.66%). Patients in group III had the most favorable clinical outcome with respect to the length of ICU and hospital stay (Table 3).

Table 4 shows the respective changes of renal variables in 3 groups from basal levels to 4 predetermined time points. Preoperative serum creatinine, cystatin C, urine NGAL, creatinine clearance levels, eGFR, and CysGFR were similar among the 3 groups (Table 4). Overall serum creatinine, cystatin C, and urine NGAL levels changed significantly throughout the entire length of following up period in group I and group II, but not in group III. Changes in serum levels of cystatin, creatinine, and creatinine clearance were prominent in later than 24 hours (Fig. 1). However, urinary NGAL was the first variable to rise in the immediate postoperative period (Fig. 2); it was similar in all groups after 3 days. Cystatin GFR was a more rapid marker than serum creatinine GFR to show acute kidney injury in 3 groups (Fig. 3) was a significant marker until day 6.

Discussion

Acute kidney injury following CABG surgery is a relatively common, yet serious complication. Serial measurements of cystatin C levels enable clinicians to identify renal failure in early stages in the postoperative period.[13] Thus, preoperative determination of possible predictors is of the utmost importance in identification of such patients preoperatively.[12–18]

Prolonged duration in ICU or in hospital due to AKI is also associated with the increase in utilization of resources,[13] mostly in elderly patients who undergo CABG under CPB and are at a particularly

Table 2 Intraoperative need for transfusions, vasopressor drug and fluid administration

	Group I (<2 d), n (%)	Group II (2–4 d), n (%)	Group III (>4 d), n (%)	*P*
Crystalloid amount, mL	2850	2640	2760	0.355
Colloid amount, mL	1250	1280	1320	0.412
Total fluid balance for 24 h	1370 ± 950	1050 ± 1180	1160 ± 850	0.761
Total urine output on by pass, mL	440 ± 150	360 ± 180	415 ± 135	0.420
Transfusion, U	4 ± 2	3 ± 3	4 ± 1	0.347
Vasopressor usage	14 (15.55)	15 (15.78)	18 (14.75)	0.225

Table 3 Perioperative outcome

	Group I (<2 d), n (%)	Group II (2–4 d), n (%)	Group III (>4 d), n (%)	*P*
Cross-clamp time, min	56 ± 25.12	52 ± 18.67	59 ± 16.34	0.786
Total bypass time, min	85 ± 22.84	92 ± 18.35	90 ± 16.41	0.562
Number of grafts	3 (2–4)	3 (2–5)	3 (1–4)	0.778
Intubation duration, h	12.45 ± 3.16	12.65 ± 2.85	13.14 ± 3.76	0.951
ICU stay, d	3.55 ± 6.37	1.46 ± 1.35	1.38 ± 2.25	0.038
Hospital stay, d	12.78 ± 8.49	8.35 ± 2.18	7.16 ± 2.15	0.027
Re-exploration for bleeding	5 (5.56)	2 (2.10)	2 (1.63)	0.045
Acute renal injury	25 (27.77)	20 (21.05)	12 (9.08)	0.001
Dialysis requirement	15 (16.66)	13 (13.68)	8 (6.55)	0.001
30-day mortality	9 (10)	4 (4.21)	3 (2.67)	0.025

high risk of developing AKI. Because of high prevalence of AKI and association with increased morbidity and mortality, renoprotective strategies and early diagnosis is important. Renal damage can occur as a result of many factors, such as oxidative stress that can occur due to reperfusion in CPB.[14] Renal dysfunction following cardiac surgery is frequently observed, particularly in high-risk patients, even though there are common ways to control these risk factors.

Therefore, early detection of developed AKI is very important for effective prevention and treatment during postoperative period. Effective treatment of AKI depends on changes that occur in early biomarkers. Serum creatinine level is currently used for the diagnosis of renal failure. However, it is not a reliable indicator during acute changes in renal function[15] because the level can be within the normal range even in patients with >50% kidney damage.[16] Therefore, there is an urgent need for

Table 4 Implications of renal function in 3 groups

	Basal	4 h	POD 1	POD 3	POD 6	*P*
Serum cystatin C(mg/L)						
Group I (<2 d)	0.78 ± 0.30	0.84 ± 0.32	1.27 ± 0.51	1.54 ± 0.09	0.93 ± 0.2	0.001
Group II (2–4 d)	0.72 ± 0.27	0.89 ± 0.25	0.92 ± 0.26	0.95 ± 0.18	0.91 ± 0.5	0.732
Group III(>4 d)	0.75 ± 0.22	0.92 ± 0.31	0.94 ± 0.45	0.86 ± 0.16	0.78 ± 0.1	0.425
P	0.25	0.035	0.028	0.012	0.06	
Urine NGAL (mg/L)						
Group I (<2 d)	54.25 ± 126.2	89.32 ± 118.6	130.46 ± 58.83	62.16 ± 34.56	56.34 ± 18.2	0.003
Group II (2–4 d)	55.4 ± 16.1	62.16 ± 28.24	84.25 ± 16.82	69.52 ± 22.91	55.71 ± 25.3	0.015
Group III (>4 d)	52.1 ± 34.4	58.16 ± 18.91	62.18 ± 14.28	66.75 ± 13.15	57.18 ± 24.2	0.247
P	0.38	0.001	0.001	0.38	0.78	
Serum creatinine (mg/dL)						
Group I (<2 d)	1.08 ± 1.15	1.15 ± 0.32	1.25 ± 0.21	1.75 ± 0.67	1.65 ± 0.7	0.006
Group II(2–4 d)	0.95 ± 0.11	0.98 ± 0.21	1.12 ± 1.48	1.45 ± 1.68	1.12 ± 1.9	0.037
Group III (>4 d)	0.98 ± 0.26	0.92 ± 0.32	0.94 ± 0.45	0.95 ± 0.25	0.83 ± 0.4	0.223
P	0.32	0.51	0.058	0.002	0.027	
Cr clearance						
Group I (<2 d)	66.31 ± 12.42	62.64 ± 24.84	58.11 ± 8.68	37.22 ± 14.92	39.48 ± 12.2	0.003
Group II(2–4 d)	68.57 ± 35.86	66.47 ± 34.65	58.16 ± 12.32	44.92 ± 6.75	52.16 ± 12.1	0.025
Group III (>4 d)	72.63 ± 12.78	70.8 ± 27.17	69.3 ± 31	68.57 ± 32.17	78.48 ± 22.4	0.321
P	0.85	0.87	0.058	0.001	0.031	
eGFR (mL/min/1.75 m^2)						
Group I(<2 d)	74.15 ± 25.6	72.16 ± 28.77	65.25 ± 18.95	51.5 ± 32.98	56.7 ± 36.1	0.001
Group II (2–4 d)	82.16 ± 18.8	88.26 ± 32.18	76.18 ± 22.95	72.34 ± 42.25	70.18 ± 42.1	0.002
Group III (>4 d)	75.8 ± 23.4	82.16 ± 16.42	84.12 ± 12.25	80.14 ± 16.91	78.6 ± 18.5	0.768
P	0.78	0.41	0.062	0.001	0.027	
CysGFR (mL/min/1.75 m^2)						
Group I (<2 d)	89 ± 18.12	73.14 ± 12.46	55.83 ± 16.25	39.18 ± 28.26	58.14 ± 35	0.001
Group II (2–4 d)	94.65 ± 26.24	82.32 ± 32	74.35 ± 25	62.18 ± 18	75.83 ± 24	0.012
Group III (>4 d)	97.4 ± 37.6	84.16 ± 39	81.28 ± 29	86.25 ± 32.2	96 ± 28.6	0.78
P	0.66	0.031	0.01	0.041	0.52	

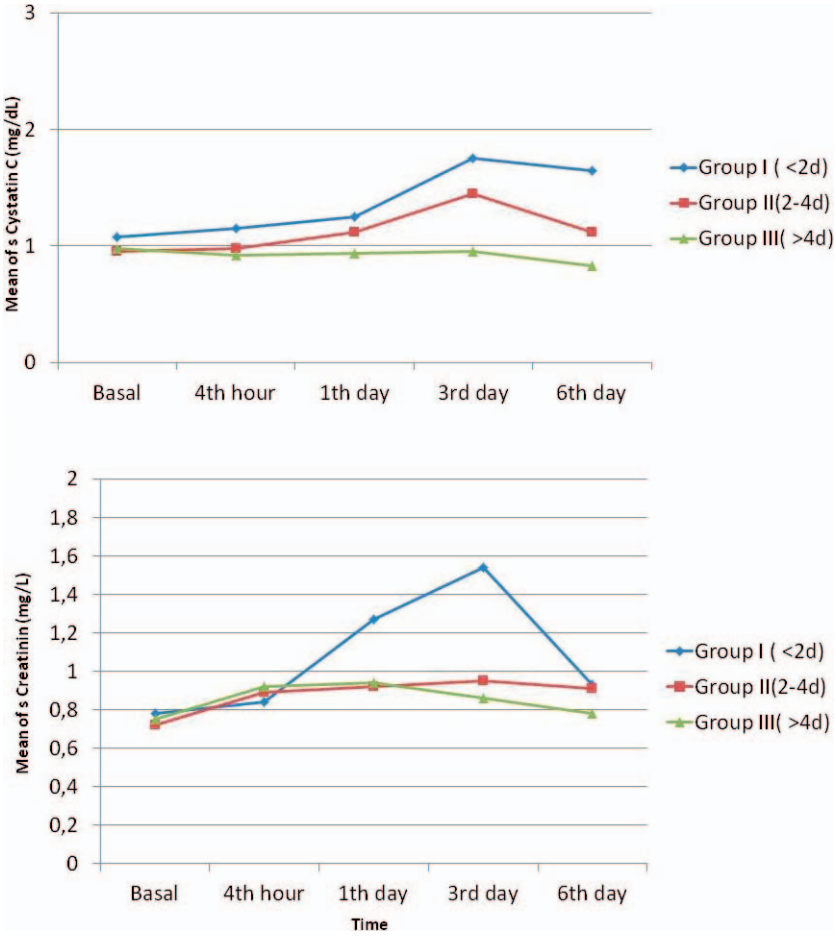

Fig. 1 Serum cystatin (top) and creatinine (bottom) in 3 groups over predetermined time points.

additional early biomarkers to detect CABG-related AKI.Cystatin C has been reported to be a poor biomarker preoperatively, but rather good in the immediate postoperative period. With respect to CABG surgery, a preoperative coronary angiography is almost always essential; but the ideal interval between the former and surgery is not well-established as it relates to renal failure in particular risk groups. Serum creatinine has been shown to rise within 24 hours of angiography and

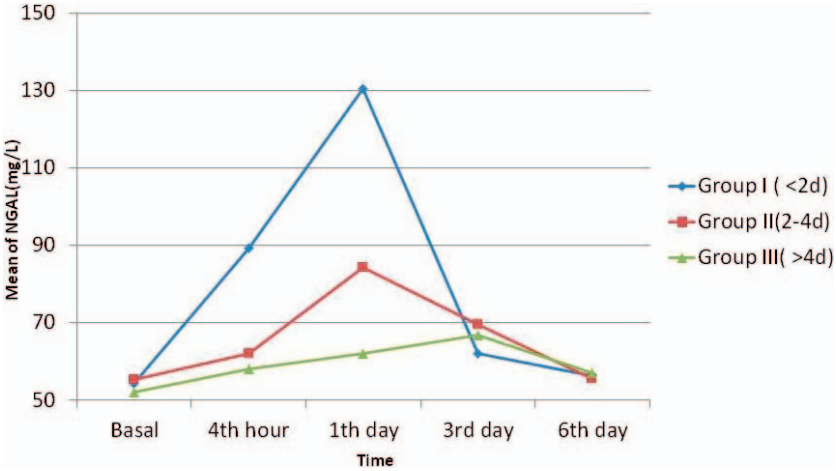

Fig. 2 Urinary NGAL levels over time in 3 groups.

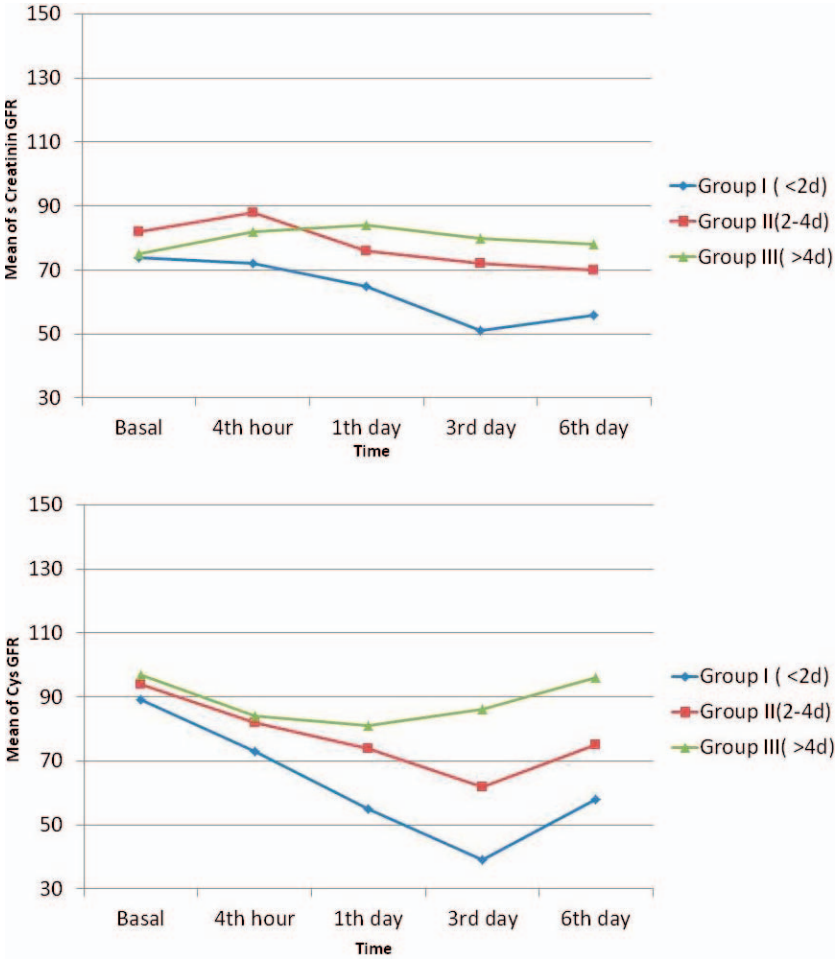

Fig. 3 Changes in serum creatinine GFR (top) and CysGFR (bottom) over time for all 3 groups.

peaks from POD 3 to 5.[14,15] Cystatin C and NGAL, when compared with creatinine, may be considered as a reliable diagnostic biomarker for the early detection of kidney injury.[19] CABG surgery using extracorporeal circulation techniques may enhance such effects in various ways. The impact of cardiopulmonary bypass in such patients has been investigated in quite a number of studies.[18–30] However, preoperative predictors or early markers have not been identified. Serum creatinine was the obvious marker for acute kidney failure in most of these studies; same-day-surgery following coronary angiography or CABG within 5 days has all been reported.[26–29]

The subsequent exposure to CPB after the use of a contrast agent can have a synergistically adverse effect on the postoperative renal function. Therefore, the impact of the timing of angiography might be different between cardiac surgery using CPB to those performed off-cardiopulmonary bypass. The differences in the patient selection can also contribute to the differences in the results.

We have identified significantly higher values of cystatin C and NGAL as well as higher renal failure rates in groups I and II in our cohort. Group III patients had significantly shorter ICU and hospital stays compared with patients in groups II and III. Acute kidney injury was recognized in these patients using early peaks of cystatin and NGAL, rather than serum creatinine and creatinine clearance. Hobson *et al*[3] reported that 45% of patients requiring dialysis following cardiac surgery remained dialysis-dependent and only a small fraction recovered fully at the time of discharge. Thus earlier recognition of kidney injury before creatinine rise, which is a major indication for dialysis may enable earlier treatment in this particular subset of patients possibly leading to a reduction of morbidity and even mortality. Retrospective analysis of 2973 patients showed a significant reduction of mortality (11% versus 5%) in patients without acute kidney

failure compared to those with it. Interestingly, not only immediate and early survival benefit favorably from avoidance from acute kidney failure, but also long-term survival is better in those patients.[33,34] Thus earlier recognition of kidney injury and appropriate therapy in earlier stages of renal disease in CABG patients may yield to improved long-term survival in these patients.

Conclusion

The preliminary findings of this study are considered preliminary: NGAL and cystatin C are early renal biomarkers for impaired renal function. These biomarkers provide more information than the established estimates of GFR derived from cystatin C, thereby improving the identification of high-risk elderly patients before cardiac surgery.

Acknowledgments

Declaration of conflicting interests: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article. Funding: The authors received no financial support for the research and/or authorship of this article.

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