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CLINICAL STUDY

Serum NGAL, cystatin C and urinary NAG measurements for early diagnosis of contrast-induced nephropathy in children

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Abstract

Aim: The study investigated a number of biomarkers for the early diagnosis of contrast-induced nephropathy (CIN), which is an important cause of acute kidney injury (AKI). *Material and methods*: The study included 91 children scheduled for elective cardiac angiography and 50 healthy controls. Biomarkers including serum (s) and urinary (u) sodium, serum and u-creatinine, s-cystatin-C, serum neutrophil gelatinase-associated lipocalin (NGAL) and urinary *N*-acetyl beta glucosaminidase (u-NAG)/creatinine ratio were measured 4 times sequentially in the patients and once in the controls. *Results*: The patient group comprised 40 males (44%) and 51 females (56%) while the control group comprised 16 males (32%) and 34 females (68%). Age, gender, s-creatinine, estimated-glomerular filtration rate (eGFR), s-cystatin-C and fractional-excretion of sodium did not differ significantly between the groups. Serum sodium and s-NGAL were found to be lower in the patients than those of in the controls, while their u-NAG/creatinine ratio was found to be higher. Sequential data analysis revealed that s-NGAL and u-NAG/creatinine ratio increased in the first 6 h after radiocontrast media (RCM) administration and decreased at 12 and 24 h. Serum BUN and s-cystatin-C levels also showed a significant difference during the 24-h follow-up. eGFR, s-sodium and s-creatinine levels did not change in the following period. Serum cystatin-C levels revealed a significant negative correlation with eGFR. Administered RCM doses showed a positive correlation only with u-NAG/creatinine ratios. *Conclusion*: In the first 24 h, s-cystatin-C, s-NGAL and especially u-NAG/creatinine ratio showed promise as biomarkers, but eGFR is not adequate for early diagnosis of CIN. Sequential measurement of biomarkers may contribute to more accurate diagnosis of AKI.

Keywords

Acute kidney injury, contrast-induced nephropathy, cystatin C, N-acetyl beta glucosaminidase, neutrophil gelatinase-associated lipocalin

History

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Introduction

Contrast-induced nephropathy (CIN) is defined as an increase in serum creatinine (sCr) of >0.5 mg/dL (which may be an increase of 25% in sCr from baseline) or a decrease in estimated-glomerular filtration rate (eGFR) of >25% within 48 h following the administration of radiocontrast media (RCM);[1] this effect should not be attributable to any other identifiable cause of renal failure. This may apply for up to 72 h, and may still occur up to 7 days after administration of RCM. In children, the percentage reduction in eGFR is a more appropriate indicator than serum creatinine increase.[2] It is important to note that in cases of nephrotoxic acute kidney injury (AKI) caused by RCM, it may be possible to reduce kidney damage by early diagnosis. Because CIN is a leading cause of hospital-acquired acute renal failure associated with a significantly higher risk of in-hospital and 1-year mortality (even in patients who do not need dialysis), early diagnosis is crucial. Wider use of radiologic imaging methods has increased the importance of CIN.

The biomarkers of AKI may be direct or indirect indicators of renal injury. Creatinine, creatinine-based eGFR and cystatin C indicate AKI through decreased GFR. When GFR decreases, creatinine and cystatin C cannot be adequately excreted to urine, and for this reason, blood creatinine and cystatin C levels increase. In contrast, neutrophil gelatinase-associated lipocalin (NGAL) and *N*-acetyl beta-glucosaminidase (NAG) are secreted directly as a result of kidney injury, which need not be accompanied by a decrease in GFR.[3] Ideal biomarkers for the early diagnosis of AKI are required for several reasons: to distinguish between subtypes of AKI, to assess etiology, to distinguish AKI from other kidney diseases, to enable predictions of prognosis and severity and for evaluation of the efficacy of treatment. Further, these indicators should be analyzable by standard, low-cost laboratory testing, from samples obtained by noninvasive methods.

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Although there are some biomarkers with one or more of these features, none of those currently available meets all the requirements. For this reason, studies have been conducted to develop an AKI panel that can make use of several biomarkers together.

In this study, the aim was to investigate the early diagnosis of CIN by simultaneous measurement of several biomarkers.

Material and methods

The study looked at 91 patients (aged 3–19 years) who were scheduled for elective angiography between 17 May 2010 and 10 March 2011 at the Pediatric Angiography Unit of the Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Research and Training Hospital. They had no renal abnormalities or acquired renal disorders. Fifty healthy age-and sex-matched children were selected as the control group.

The study was approved by the Scientific Council of the Ministry of Health at the Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Research and Training Hospital (0B.10.4.İSM.4.34.8720/32032) and by the Research Assessment Commission of Marmara University Medical Faculty (B.30.2.MAR.0.01.02/AEK/697). The *Informed Consent Form* was read by the parents, who gave their written consent.

Age, gender, body weight and height were recorded. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2), and the BMI standard deviation *z*-score (SDS *Z*) was determined. Diagnoses of disease, presence of any medications and fasting period were also recorded.

Initial blood and urine samples were taken from all the patients during placement of the vascular access line for angiography. Following the angiography procedure, the doses of contrast media were recorded. Blood and urine samples were also taken from the patients at 6, 12 and 24 h after RCM administration; these samples were taken once from the control group. The samples were immediately processed, aliquoted and stored at below −20 °C prior to analysis.

NGAL was studied manually from the serum samples (human lipocalin-2/NGAL Elisa, BioVendor, Brno, Czech Republic), using the sandwich enzyme immunoassay method. Lower levels of detection were 0.02 ng/mL, the intra-assay coefficients of variation for low and high levels were 8.38% and 7.03%, respectively, and the inter-assay coefficients of variation for low and high lipocalin-2 levels were 9.73% and 9.77%, respectively. NAG was studied from the urine samples by means of an automatized technique (Modular P, Roche Diagnostics, Mannheim, Germany; Diazyme, Poway, CA). The serum and urinary creatinine levels were studied by means of an automatized process using the kinetic colorimetric method based on the Jaffé mode (Cobas 8000 Modular Analytics, Roche Diagnostics, Mannheim, Germany). Serum cystatin C levels were also studied by automatized means, using the immunoturbidimetric method (Cobas 8000 Modular Analytics, Roche Diagnostics, Mannheim, Germany). Serum sodium levels were studied in automatized fashion, using the ion selective electrode method (Cobas 8000 Modular Analytics, Roche Diagnostics, Mannheim, Germany). Urinary NAG/creatinine ratios were computed. For calculation of eGFR, the Schwartz formula was used.[4]

AKI development and staging were assessed by use of the pediatric RIFLE criteria.[2] Based on the initial values of eGFR, decreases of 25%, 50% and 75% were defined as Risk, Injury and Failure, respectively, and were accepted as AKI.

Statistical evaluation

SPSS 15 was used for the statistical analysis. Age, gender and the mean values of anthropometric measurements of patients and controls were compared. The initial blood and urine analyzes of the patient group were compared with those of the control group. All continuous data were assessed by use of the Kolmogorov–Smirnov test to determine the distribution pattern, and these are reported as mean ± SD or median and quartiles. Student's *t*-tests or Mann–Whitney–*U* tests were used for the comparisons. Categorical data were compared by means of the chi-squared test. The Student–Newman–Keuls multi-comparison test was performed for analysis of the sequential variables of patients from whom four consecutive blood and urine samples could be taken. Correlations between the data were evaluated by linear regression. A p value of <0.05 (two-tailed testing) was considered to be significant. Data analysis was conducted in three stages: (1) comparison of patient and control groups, (2) assessment of the patients group's sequential data and (3) correlations of patients' data.

Results

The study evaluated 91 patients and 50 healthy controls. According to pediatric RIFLE criteria, AKI was found to have developed in 18 patients. Thirteen of these patients were at the *Risk* stage (R:14.3%), two were at the *Injury* stage (I:2.2%), and three were at the *Failure* stage (F:3.3%). Multiple comparison tests were carried out on 85 patients from whom four consecutive blood and urine samples could be taken. According to the diagnosis, 54 of total 91 patients had acyanotic congenital heart disease (CHD), 28 of them had cyanotic CHD and 9 of them had aortic coarctation or stenosis.

Patient and control groups

The mean ages of patients and controls were 8.37 ± 4.29 and 9.49 ± 3.85 years, respectively. The patient group comprised 40 males (44%) and 51 females (56%),while the control group comprised 16 males (32%) and 34 females (68%). Data and p values for both groups are shown in Table 1. There were no significant differences between the patient and control groups for mean age, gender, mean or median BMI SDS *z*-score, serum creatinine, eGFR, serum cystatin C and fractional-excretion of sodium (FENa). However, BMI, serum sodium and serum NGAL were found to be lower in the patient, and urinary NAG/creatinine ratio was found to be higher in that group (Table 1).

Initial eGFR values were not significantly different between the patient and control groups (Table 1).

Table 1. Demographics and initial laboratory findings of patients and controls.

	Patients (n=91)	Controls (n=50)	p
Age (years) Mean ± SD (range)	8.37 ± 4.29 (3–19 years)	9.49 ± 3.85 (3–18 years)	0.13
Male (%)/Female (%)	40 (44%)/51 (56%)	16 (32%)/34 (68%)	0.23
BMI (kg/m^2) Median (quartiles)	16.04 (15–19.2)	17.15 (16.24–19.91)	0.012*
BMI SDS z score Mean ± SD	−0.205 ± 1.41	0.156 ± 1.08	0.119
Serum sodium (mEq/L) Median (quartiles)	138 (134–140)	142 (140–143.2)	<0.0001*
FENa (%) Median (quartiles)	0.59 (0.3–1.01)	0.51 (0.3–0.82)	0.27
Serum creatinine (mg/dL) Mean ± SD	0.45 ± 0.12	0.46 ± 011	0.41
Cystatin C (mg/L) Mean ± SD	0.81 ± 0.15	0.83 ± 0.11	0.47
Serum NGAL (ng/mL) Median (quartiles)	18.06 (9.18–32.1)	78.45 (59.02–96.67)	<0.0001*
Urinary NAG/creatinine (IU/g) Median (quartiles)	2.02 (0.88–3.76)	1.62 (0.71–2.29)	0.036*
e-GFR mL/min/1.73m^2 Mean ± SD	166.46 ± 38.3	167.51 ± 26.14	0.45
Urinary NAG IU/L Median (quartiles)	1.5 (0.5–2.8)	1.5 (0.5–2.5)	0.69
Urinary creatinine (mg/dL) Median (quartiles)	64.64 (44.35–109.25)	92.57 (46.66–120.77)	0.081

Notes: SD: standard deviation.
*Significant p values.

Table 2. Sequential data of the patients.

	Basement mean ± SD median**		6th hour mean ± SD median**		12th hour mean ± SD median**		24th hour mean ± SD median**	p
Serum creatinine (mg/dL) (n = 85)	0.45 ± 0.12	→	0.42 ± 0.12	→	0.45 ± 0.31	→	0.42 ± 0.14	0.3636
Cystatin C (mg/L) (n = 84)	0.81 ± 0.15	→	0.73 ± 0.16	→	0.74 ± 0.16	→	0.79 ± 0.15	<0.0001*
Serum NGAL (ng/mL) (n = 78)	23.26 ± 20.73		30.12 ± 26.45		20.11 ± 15.35		21.68 ± 17.04	0.0037
	17.5	→	24.16	→	17.85	→	18.79	
Serum sodium (mEq/L) (n = 85)	136.33 ± 6.22	→	134.49 ± 6.26	→	134.89 ± 7	→	135.4 ± 7.28	0.1068
Urinary NAG/creatinine (IU/g) (n = 82)	3.01 ± 4.04		7.09 ± 8.25		4.78 ± 5.67		4.3 ± 4.15	<0.0001*
	1.96	→	4.39	→	2.67	→	2.98	
e-GFR (Schwartz) (mL/min/1.73 m^2) (n = 85)	165.05 ± 38	→	169.49 ± 39.8	→	177.18 ± 54.02	→	172.92 ± 38.18	0.1506

Notes: *Significant p values.
**For the data without normal distribution.
SD, standard deviation.

Urinary NAG medians were similar for patients and controls. Mean urinary creatinine was found to be lower for the patients than for the controls, but the difference was not significant (Table 1).

Serum creatinine and cystatin C values did not differ between the two groups (Table 1).

Based on their diagnosis the study group consisted of 54 patients with acyanotic CHD, 28 patients with cyanotic CHD and 9 patients with aortic coarctation or stenosis. Among these three groups, serum creatinine, cystatin C, NGAL and urinary NAG/creatinine ratio were not significantly different. Whereas urinary creatinine was significantly lower ($p = 0.009$) and urinary NAG/creatinine ratio was significantly higher ($p = 0.005$) in the cyanotic CHD patients than the control group. Body mass index was also significantly lower in the cyanotic patient group than the controls ($p = 0.001$).

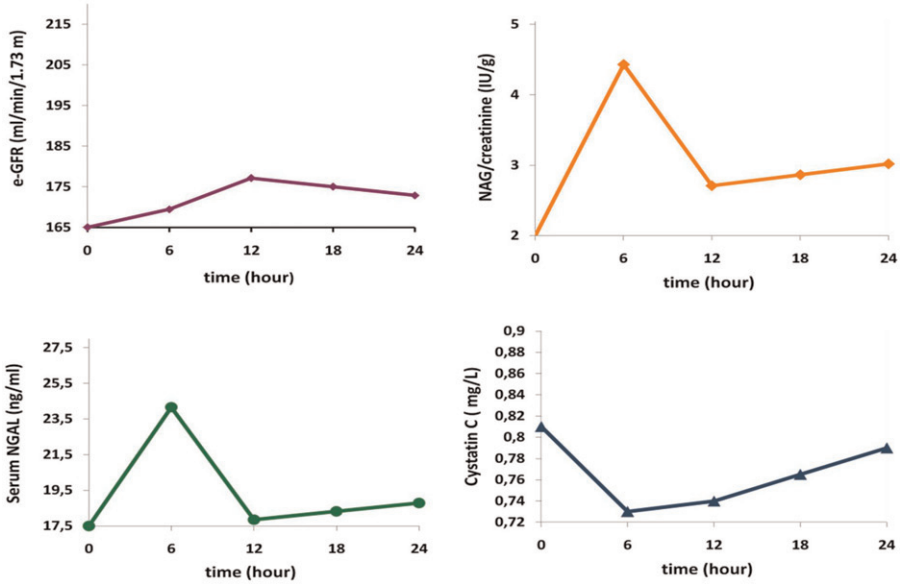
Sequential data of the patient group

The sequential data of 85 patients were evaluated. The mean of serum cystatin C decreased in the first 6 h, remained unchanged between hours 6 and 12, and increased significantly after 12 h (Table 2).

An elevation was observed in serum NGAL levels in the first 6 h, and after that a decrease occurred at hours 12 and 24. Differences in NGAL values between the baseline and hour 12, and between the baseline and hour 24, were not significant (Table 2).

The median values for urinary NAG/creatinine ratios in the follow-up period were similar to those for NGAL. In the first 6 h, there was an increase in the NAG/creatinine ratio, followed later by a significant decrease. However, unlike the NGAL level, a significant difference persisted between the baseline and hour 12 and the baseline and hour 24 measurements of the NAG/creatinine ratio (Table 2).

Figure 1. Sequential data of biomarkers during the follow-up.



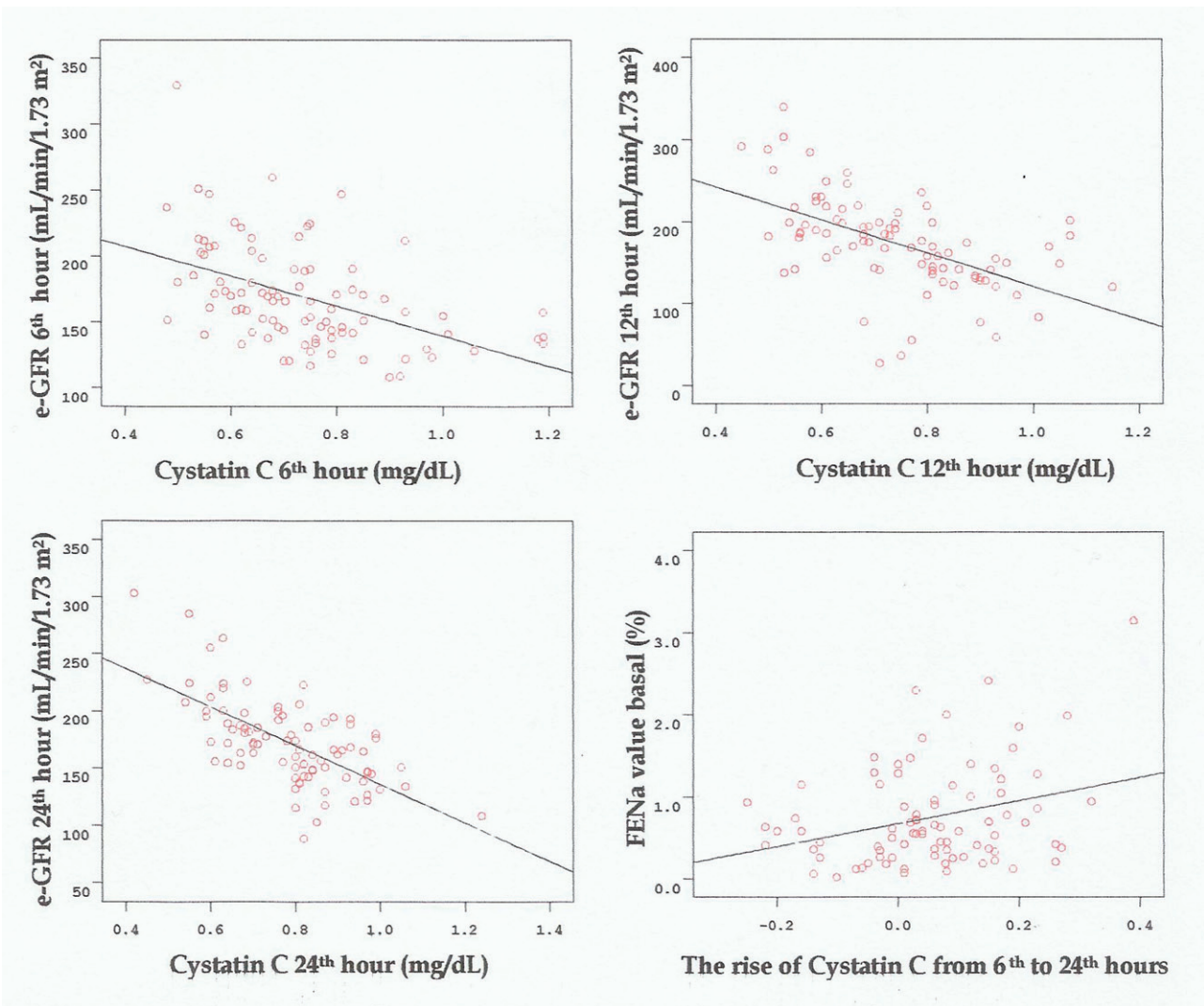


Figure 2. Correlations of serum cystatin C with e-GFR at 6th, 12th, 24th hours and correlation of basal FENa with cystatin C rise between 6th and 12th hours.

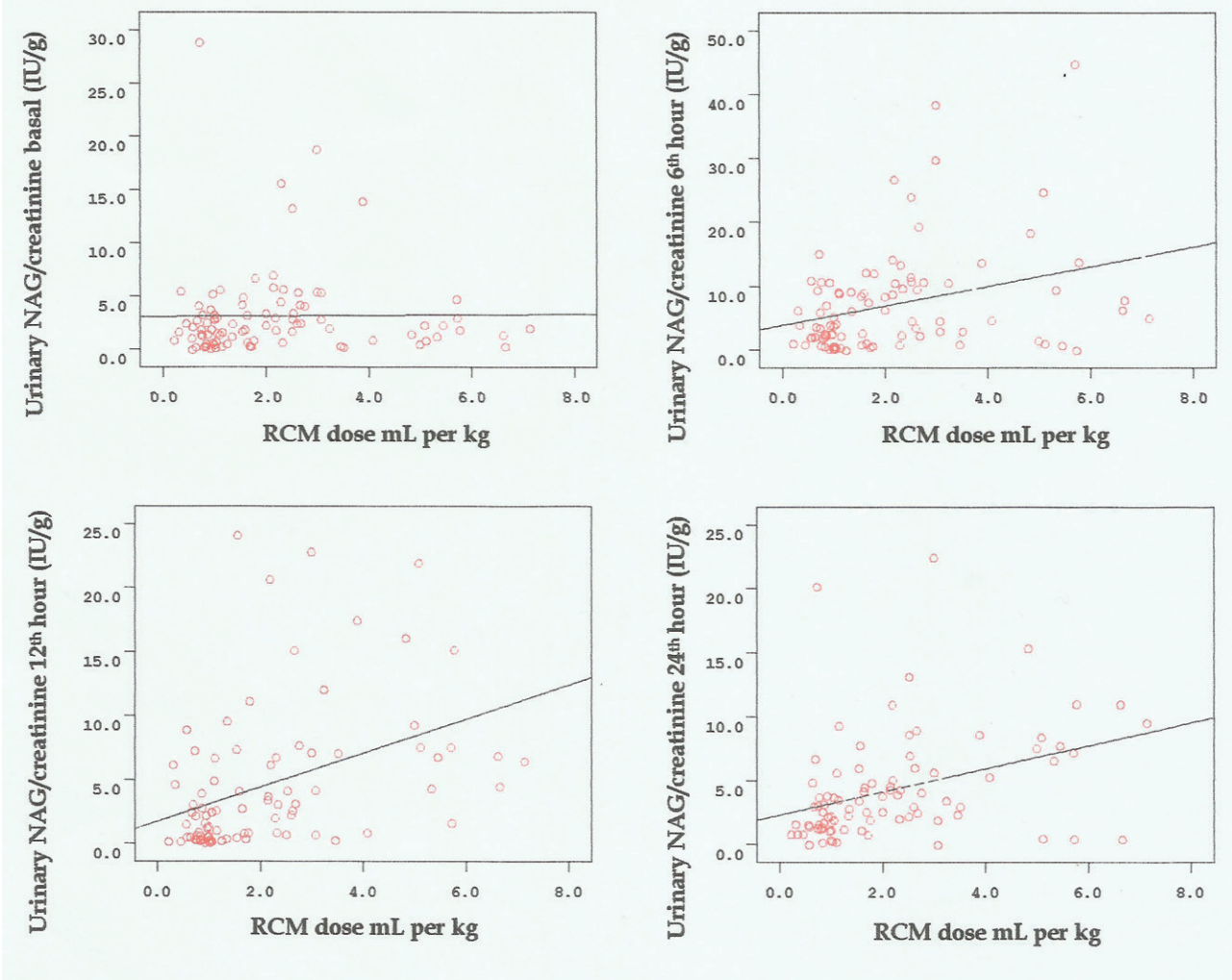


Figure 3. Correlations of urinary NAG/creatinine ratio with RCM doses (per kilograms) initially and at 6th, 12th and 24th hours.

Table 3. Correlations between e-GFR and serum cystatin C.

	e-GFR-1	e-GFR-2	e-GFR-3	e-GFR-4
Cystatin C-1				
r	−0.282*	−0.373*	−0.391*	−0.293*
p	0.001	<0.001	<0.001	0.006
Cystatin C-2				
r	0.13	−0.472*	−0.367*	−0.319*
p	0.22	<0.001	<0.001	0.002
Cystatin C-3				
r	0.036	−0.330	−0.549*	−0.404*
p	0.743	0.002	0.001	<0.001
Cystatin C-4				
r	−0.005	−0.413*	−0.410*	−0.652*
p	0.961	<0.001	<0.001	<0.001

Notes: *Significantly correlated according to Pearson correlation.
1, basal; 2, 6th hour; 3, 12th hour; 4, 24th hour.

Serum creatinine, serum sodium and eGFR values showed no significant change. Changes in biomarkers in the follow-up are shown in Table 2 and Figure 1.

Correlations of the sequential data

To evaluate correlations between the data, a linear regression analysis was performed. Serum cystatin C levels (initial, 6 h, 12 h and 24 h) revealed a significant negative correlation with eGFR values but showed no correlation with serum NGAL, urinary NAG/creatinine ratio and 6, 12 and 24 h FENa values (Figure 2). A significant correlation was observed between the increase in serum cystatin C from hour 6 to hour 24 and initial FENa values (Figure 2). Administered RCM doses per kilogram showed a positive correlation with urinary NAG/creatinine ratios only, measured at hours 6, 12 and 24 (Figure 3). Correlation coefficients are shown in Tables 3 and 4.

Discussion

Acute kidney injury is an important topic because it has a considerable impact on the morbidity, mortality and hospital stay of the patients. Early detection of AKI requires new and more convenient biomarker testing. CIN is one of the major causes of AKI; it has been reported that almost half of these cases occur following diagnostic and interventional cardiovascular procedures.[5]

Practical use of new biomarker and biomarker combinations to early detection of AKI is not widespread at present. Because changes in these biomarkers may occur at different time intervals following AKI, simultaneous measurement of

Table 4. Correlation between RCM doses, FENa and the biomarkers.

	RCM dose (per kg)[a]	FENa-1 (%)[b]
NAG/creat-1		
r	0.010	−0.171
p	0.922	0.048
NAG/creat-2		
r	0.311*	0.045
p	0.003	0.679
NAG/creat-3		
r	0.407*	−0.027
p	<0.001	0.808
NAG/creat-4		
r	0.366*	−0.117
p	<0.001	0.288
NGAL-1		
r	0.008	−0.152
p	0.945	0.083
NGAL-2		
r	0.038	−0.104
p	0.725	0.341
NGAL-3		
r	0.046	−0.03
p	0.68	0.79
NGAL-4		
r	−0.102	−0.104
p	0.353	0.35
Cystatin C-1		
r	−0.062	0.199
p	0.559	0.021
Cystatin C-2		
r	0.053	−0.075
p	0.621	0.488
Cystatin C-3		
r	0.019	0.104
p	0.862	0.347
Cystatin C-4		
r	−0.056	0.179
p	0.605	0.101
Cystatin C 4-2		
r	−0.144	0.304*
p	0.180	0.005

Notes: *Significantly correlated according to [a]Pearson correlation and [b]Spearman correlation.
1, basal; 2, 6th hour; 3, 12th hour; 4, 24th hour.

several biomarkers may be helpful in determining the development of AKI at an early stage.[6,7]

The present study aimed to investigate multiple biomarkers for the early detection of CIN. All the blood samples can be taken sequentially and were obtained from 85 patients. The study evaluated data from 91 patients and 50 controls for the comparison tests and from 85 patients for the sequential analyzes.

Patients' serum NGAL and serum sodium were lower and their urinary NAG/creatinine ratios were higher than those of the controls at baseline. It has been reported that measurement of serum NGAL can be affected by many conditions. For instance, NGAL level in the blood and urine is elevated during infections, inflammations and neoplastic processes relating to the tissues that normally produce NGAL (kidney, liver, ducts, lungs, trachea, intestine, bone marrow, thymus, prostate, macrophages, pancreas, peripheral blood leukocytes, endometrium and epidermis).[8] Normal serum NGAL values in healthy people are also reported to vary considerably,[9–11] but there is little information in the literature about the conditions leading to a decrease in serum NGAL. In a study carried out on 56 chronic hemodialysis patients, it was reported that lower levels of serum NGAL were detected in patients with a transferrin saturation of <20%.[12] Bolignano et al.[9] noted that serum and urinary NGAL levels were lower in 15 adult patients who had been treated by intravenous immunoglobulin (IVIG) for idiopathic membranous nephropathy.

Probable iron deficiency in the patient group may have contributed to their low NGAL values; the lack of any assessment of iron deficiency in patients and controls limits any comment on this point.

Urinary NAG/creatinine ratio in the patient group was found to be lower than that of the control group. The presence of either a high NAG or a low creatinine in urine would affect this ratio, and for this reason, urinary NAG and urinary creatinine levels were evaluated in both the patient and control groups. While the respective urinary NAG medians were found to be equal, the mean urinary creatinine in the patient group was a little low. Median BMI was significantly lower in the patient group than in the control group; lower BMI and urinary creatinine levels in the patient group may reflect their lack of muscle tissue. These data indicate that the NAG/creatinine ratio may also be affected by reduced individual muscle mass, leading to a decrease in the excretion of the urinary creatinine,[13] as well as by an increase in urinary NAG excretion.

Several studies showed that congenital heart diseases effect renal tubular functions. In a study by Agras et al.[14] reported that median FeNa and urinary NAG/creatinine were significantly higher in cyanotic patient group but there were no significantly differences among the groups in respect of urinary β_2-microglobulin/creatinine or GFR. Amornchaicharoensuk et al.[15] reported that 15 patients with cyanotic CHD had more prevalence and higher abnormal biomarkers for renal dysfunction than those of 31 acyanotic CHD patients. In our study no difference was observed between the renal biomarkers of cyanotic and acyanotic CHD patients. However urinary creatinine was significantly lower and urinary NAG/creatinine ratio was significantly higher in the cyanotic CHD patients than the control group. This may mean that a lower urinary creatinine level may result to increased urinary NAG/creatinine ratio.

The significantly low sodium levels in the patient group may reflect the low sodium intake of patients managed in cardiology clinics.

Measurements of sequential serum creatinine were found to be in line with expectations, as a loss of >50% of kidney function would be required for a creatinine increase in the serum, and because the meaningful increases occurred after 24 h.[5]

The decrease in the level of cystatin C in the first 6 h reflects the rise in body fluid following intravenous fluid administration to patients during and after the procedure. Both creatinine and cystatin C are biomarkers for the estimation of GFR. In this study, levels of cystatin C were significantly negatively correlated with eGFR, but the analyses of sequential data show that, in contrast to serum creatinine, serum cystatin C showed a significant increase between hours 12 and 24. However, the means of cystatin C levels were within normal limits. These changes in

serum cystatin C levels suggest that measures of the increase in cystatin C were more sensitive than absolute values, and that cystatin C could reflect the change in eGFR better than creatinine. The presence of a positive correlation between initial FENa values and the rise of serum cystatin C from hour 6 to hour 24, may indicate that the patients with more urinary sodium loss are more prone to develop CIN. This result is inconsistent with the findings reported as the urinary sodium had little predictive or diagnostic value in critically ill patients at risk of or with septic AKI.[16] Because the pathophysiology of septic AKI and toxic AKI are different, the value of urinary sodium loss may be variable in various cases.

The half-life of cystatin C is one-third of creatinine's, and so it is much more affected by acute changes in renal function. However, cystatin C resides only in extracellular spaces while creatinine can spread into all the body fluids, and it follows that cystatin C can better reflect chronic changes in eGFR. Cystatin C is not affected by age, sex, muscle mass or nutritional conditions, but its serum levels decrease in hypothyroidism and increase in hyperthyroidism.[17]

The study highlights urinary NAG/creatinine ratio as a promising biomarker; as in the case of serum NGAL levels, an increase was observed between the basal and hour 6 measurements. Later, although a decrease was observed by comparison with hour 6, the hour 12 and hour 24 measurements remained significantly higher than the initial levels. Increase in the urine NAG/creatinine ratio continued for a longer time than for serum NGAL, which may provide the opportunity for a longer follow-up. Measurements at hour 6 showing an increase in the NAG/creatinine ratio also suggested that this marker does not depend on hydration. Values for urinary NAG/creatinine at hour 6 and subsequently were significantly correlated with administered dosage of RCM; this relation could not be shown between RCM dosage and serum NGAL. These results suggest that NAG/creatinine ratio is a more valuable biomarker for diagnosis of RCM-induced AKI. Ren et al.[18] investigated urinary NAG/creatinine at the first, second and sixth days after contrast agent exposure in 590 patients who underwent diagnostic coronary intervention; they proposed that urinary NAG may be a useful early biomarker for CIN. Katagiri et al. reported that in 77 patients who had undergone cardiac surgery, AKI developed at a rate of 36.4%. They noted that, in these patients, urine NAG values increased in the 4th postoperative hour and decreased in the 12th hour, but that the latter measurement was still higher than the baseline.[19] The first studies of the relation between kidney injury and NAG commenced in 1969,[20,21] and diagnosis of AKI by testing for urinary NAG elevation remains valid today.[19,22] Skalova et al. studied urinary NAG/creatinine ratios in 262 healthy children aged between 0 and 18 years (141 boys and 121 girls). Mean values were found to be 53.44 ± 35.7 (IU/g) between 0 and 1 months of age and 20.28 ± 13.1 (IU/g) between 1 and 12 months; averages later decreased to 6.19 ± 3.7 (IU/g) between 1 and 3 years of age and to 4.98 ± 3.3 (IU/g) between 3 and 6 years.[23] Because the age distribution of our patients was 3–19 years, the higher NAG/creatinine ratio in normal children in the first 3 years of age had no impact on our study. Liangos et al.[24] reported that for the detection of AKI following cardiopulmonary operations, the NAG/creatinine ratio was among the three best urinary biomarkers (along with KIM-1 and IL-18), showing significant increases as early as the second hour following the operation. In another study, carried out in Japan, of 98 children who had undergone cardiac catheterization at between 5 days and 18 years, serum creatinine levels and urinary NAG/creatinine ratios were measured 24 h prior to the procedure and at 12 h and 2 weeks after the procedure. No significant increase was reported in the serum creatinine levels of the patients while conversely, urinary NAG/creatinine levels increased at hour 12.[25]

The present study identified serum NGAL as a promising biomarker. Mishra et al.[26] reported that in patients who developed AKI following cardiac surgery, serum and urinary NGAL levels increased after the second hour and despite decreasing afterward, remained at higher levels when compared with the initial values. In another study by Liangos et al.[24], it was observed that urinary NGAL levels increased in the second hour following cardiopulmonary bypass, but decreased in hour 24. Reporting on 91 children (0–18 years of age) who had undergone elective angiography, Hirsch et al.[27] found that NGAL in both blood and urine increased significantly in hours 2 and 6; however, no further findings were reported as the measurements were discontinued. Parikh et al.[28] reported that urinary NGAL levels reached a maximum in hour 4 and began to decrease following hour 6. NGAL may be affected by a range of physiological and pathological conditions.[8] Because normal values can vary so much, measurement of serum NGAL in the diagnosis and follow-up of AKI is useful only with sequential measurements. In the present study, the increase at hour 6 was followed by a significant decrease, and levels at hour 12 were found not to differ from the baseline levels. The increase in the first 6 h may show that levels were not affected by hydration status and increased independently of eGFR decrease.

Contrast nephropathy is defined as a decrease of 25% in GFR or an increase of 50% in creatinine levels within 48 h after the RCM administration.[1] However, in clinical practice, it is difficult to assess the patient for AKI development after 48 h. For adult angiographic procedures, patients are discharged after a 6–8 h follow-up. In pediatric patients, the follow-up period is <24 h for patients without any complications. Therefore, in the patients for the presence of any contrast nephropathy, sequential measurements of biomarkers rising before hour 24 are important, along with creatinine.

In a 24-h follow-up period, AKI development was detected in 18 patients (19.8%) according to the p-RIFLE criteria,[2] although a complete record was not obtained because 48 h is the standard period for CIN, and this period could not be completed because the patients were discharged. In the study conducted by Hirsch et al.[27], between the years 2004–2006, contrast nephropathy development in 91 patients—defined as a 50% increase in creatinine level after a 24-h follow-up—was found to be 12%.

The following are some limitations of the present study.

We could not assess the period after hour 48 of RCM exposure, and so the actual incidence of CIN could not be obtained.

Patients who developed CIN during the 24-h period constituted a small group for statistical analysis. Comparisons between the AKI and non-AKI groups could not be performed.

We used the Schwartz formula based on serum creatinine to calculate e-GFR and this made limit the accuracy of the diagnosis of AKI.

In conclusion, as is known, for diagnosis of AKI in the first 24 h, creatinine and the creatinine-derived eGFR formulas are insufficient. In this study, the increase in serum cystatin C levels in the first 24-h follow-up before reduction of GFR suggests that serum cystatin C is more useful than serum creatinine for early diagnosis of AKI. Because they increased in the first 6 h, urinary NAG/creatinine ratio and serum NGAL were considered to be promising markers for early diagnosis of AKI; however, these markers should be measured sequentially. For diagnosis of CIN, NAG/creatinine ratio seems more sensitive than serum NGAL. It would be possible to reach further information with long-term studies to be conducted >48 h.

Declaration of interest

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