ORIGINAL ARTICLE

UDC: 616.132.2-079-06:616.61-07
https://doi.org/10.2298/VSP190418075P

Diagnostic importance of cystatin C and creatinine for contrast-induced acute kidney injury

Značaj cistatina C i kreatinina u dijagnostici akutnog oštećenja bubrega izazvanog kontrastom

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Abstract

Background/Aim. Contrast-induced acute kidney injury (CI-AKI) is a common complication after the percutaneous coronary intervention, associated with a prolonged hospital stay, increased medical costs, and risk of adverse clinical outcomes. The aim of this study was to compare changes in levels of serum creatinine (sCr) and cystatin C (sCyC) 24 h after coronary angiography as an early indicator of CI-AKI. **Methods.** The study included 45 patients with chronic renal failure grade I–III scheduled for coronary angiography. Levels of sCr and sCyC were measured a day before and 24 h after coronary angiography. CI-AKI was defined as a 25% and 10% increase of sCr and sCyC levels from baseline within 24 h from contrast media exposure, in the absence of alternative causes. **Results.** Mean sCr and sCyC concentrations were 86.4 ± 22.6 μmol/L and 1.18 ± 0.52 mg/dL, respectively before contrast administration, and 90.6 ± 24.1 μmol/L and 1.24 ± 0.65 mg/dL, respectively 24 h after contrast media exposure. sCr-based CI-AKI occurred in 4 patients (8.89%) and sCyC-based CI-AKI was detected in 19 patients (42.22%) after the contrast procedure ($p < 0.001$). **Conclusion.** sCyC level measured 24 h after contrast media exposure is a more sensitive indicator of CI-AKI than sCR level.

Key words:
kidney failure, acute; kidney failure, chronic; coronary angiography; creatinine; cystatin c.

Apstrakt

Uvod/Cilj. Kontrastom izazvano akutno oštećenje bubrega (KI-AOB) uobičajena je komplikacija nakon perkutane koronarne intervencije i dovodi do produžene hospitalizacije, povećanih medicinskih troškova i rizika od neželjenih kliničkih ishoda. Cilj rada bio je da se uporede promene u nivou serumskog kreatinina (sKr) i cistatina C (sCiC) 24 sata nakon učinjene koronarne angiografije kao ranih indikatora KI-ABO. **Metode.** Studija je obuhvatila 45 bolesnika sa hroničnom bubrežnom insuficijencijom 1–3. stadijuma kojima je planirana koronarna angiografija. Nivoi sKr i sCiC su mereni dan pre, kao i 24 sata posle koronarne angiografije. KI-ABO je bilo definisano kao povećanje nivoa sKr i sCiC od 25%, odnosno 10% u odnosu na bazalni nivo u roku od 24 sata nakon izlaganja kontrastnom sredstvu, a u odsustvu drugih alternativnih uzroka. **Rezultati.** Srednje vrednosti nivoa sKr i sCiC iznosile su 86,4 ± 22,6 μmoL/L i 1,18 ± 0,52 mg/dL, redom, pre primene kontrasta, odnosno 90,6 ± 24,1 μmoL/L i 1,24 ± 0,65 mg/dL, 24 sata nakon izlaganja kontrastnom sredstvu. S obzirom na nivo sKr, KI-ABO evidentirano je kod 4 bolesnika (8,89%), a s obzirom na nivo sCiC kod 19 bolesnika (42,22%) ($p < 0,001$). **Zaključak.** Nivo sCiC je osetljiviji indikator KI-ABO od sKr 24 sata nakon izlaganja kontrastnim sredstvima.

Ključne reči:
bubreg, akutna insuficijencija; bubreg, hronična insuficijencija; angiografija koronarnih arterija; kreatinin; cistatin c.

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Introduction

Contrast-induced acute kidney injury (CI-AKI) is a common complication after the percutaneous coronary intervention (PCI), associated with a prolonged hospital stay, increased medical costs, and risk of adverse clinical outcomes [1, 2]. This complication has become the third cause of hospital-acquired acute kidney injuries (11.3%) [3]. Since effective treatment measures for preventing CI-AKI have not been completely established, early diagnosis in previously identified high-risk patients for the development of this complication is necessary [4]. CI-AKI is usually defined as an absolute increase ≥ 0.3 mg/dL, or a relative increase > 25% of serum creatinine (sCr) from baseline level within the period of 24–48 h after contrast exposure in the absence of an alternative cause [5–11]. However, sCr concentration is affected by gender, age, muscle mass, and diet. Moreover, its increase could be delayed, which can discredit it as a certain indicator of acute renal failure [12–15]. Cystatin C (CyC), a cationic low molecular weight cysteine protease produced by all nucleated cells at a constant rate but not metabolized in the serum, is freely filtered by the glomeruli [16]. Compared with sCr, cystatin C is less affected by the previously mentioned factors. Its half-life is 3 times shorter, and maximum levels are reached within 24 h after contrast exposure, which recommend it as the marker of early changes in glomerular filtration rate (GFR) [17–19]. However, some studies reported its low predictive value for CI-AKI compared with sCr [20, 21]. According to the fact that the majority of our patients are discharged from the hospital 24 hours after the coronary angiography, in the present study, we compare changes in sCr and sCyC levels in that period with the aim to establish a reliable early diagnostic tool for predicting CI-AKI.

Methods

Design and participants

During 2018, 45 consecutive patients over 18 years of age, with chronic renal failure (CRF) stages I–III, scheduled to undergo coronary angiography at the Military Medical Academy (MMA) in Belgrade, Serbia, were prospectively recruited. The exclusion criteria were pregnancy, lactation, malignancy, GFR > 100 mL/min, GFR < 30 mL/min, age < 18 years, recent exposure to contrast medium (CM) (within the period of 3 months before the procedure), and the use of more than 300 mL of CM.

As CM, we used non-ionic, low-osmolality iodinated CM, either iohexol (Omnipaque®, 350 mg I/mL) or iopromid (Ultravist®, 370 mg I/mL) for all patients. For the purpose of CI-AKI prophylaxis, all patients received a continuous intravenous infusion of 1,000 mL isotonic saline at least 1–6 h after the procedure [with or without N-acetyl-cysteine (NAC) – 2 × 600 mg *per os* – the day before and on the day of procedure]. The study protocol was approved by the Ethics Committee of MMA. Informed consent was obtained from all participants.

Data collection, biomarker measurement, and follow-up

Demographic and clinical data were recorded for each participant. All biochemical indicators – sCr, sCyC, hemoglobin (Hgb), albumins, lipids, C-reactive protein (CRP), brain natriuretic peptide (BNP), urinary beta-2 microglobulin (beta-2 MCG), urinary albumin/creatinine ratio (alb/cr) – were collected in the morning prior to the procedure and 24 h after the coronary angiography. They were measured in the Central Biochemistry Laboratory of MMA. sCyC was quantified with particle-enhanced nephelometric immunoassay (PENIA) method (BN II Dade Behring, Germany).

The Chronic Kidney Disease Epidemiology (CKD EPI) formula was used to calculate the estimated GFR (eGFR) [22]. For the purpose of this study, sCr-based AKI was defined as a relative increase > 25% from baseline level within the 24 h after contrast exposure, and sCyC-based AKI was defined as an increase in the sCyC concentration greater than 10% within the 24 h of contrast media exposure in the absence of an alternative cause [23].

Statistical analyses

The continuous variables were presented as the mean ± standard deviation (SD) or median [with interquartile range (IQR): 25th and 75th percentiles] and categorical variables as percentages. For continuous variables, comparisons between groups were made using the independent samples *t*-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. Categorical data were compared using the chi-squared (χ^2) test. The value of $p < 0.05$ was considered significant throughout the analyses. All analyses were performed using SPSS 19.0 software.

Results

The demographic and biochemical characteristics of our patients are shown in Table 1. The majority of them were male (66.67%), mean age 66.9 ± 8.2 years, mean body mass index (BMI) 26.87 ± 3.94 kg/m². Thirty-four patients (75.6%) had high blood pressure, 16 patients (35.6%) were diabetics, the same number of patients was detected in the population of former or active smokers, and 4 patients (8.9%) had asymptomatic heart failure. Baseline levels of sCr and sCyC were 86.4 ± 22.6 μmol/L and 1.18 ± 0.52 mg/dL, respectively. Mean eGFR calculated by CKD EPI formula was 75.04 ± 16.62 mL/min *per* 1.73 m². Mean values of CRP, BNP, Hgb, albumins, lipids, alb/cr ratio in urine were in the normal range. Seven patients (15.56%) had abnormal baseline values of urinary beta-2 MCG. Twenty-five patients (55.6%) were treated with the prophylactic regime with

Table 1

Demographic and biochemical characteristics of the patients

Variables	Values
Sociodemographic characteristics	
age (years), mean ± SD	66.89 ± 8.22
male, n (%)	30 (66.7)
female, n (%)	15 (33.3)
BMI (kg/m²), mean ± SD	26.87 ± 3.94
Comorbidities	
current or prior smoking; n (%)	16 (35.6)
hypertension, n (%)	34 (75.6)
prior MI or stroke, n (%)	6 (13.3)
diabetes mellitus, n (%)	16 (35.6)
NYHA Grade III–IV, n (%)	4 (8.9)
Renal function	
eGFR (mL/min/1.73 m^2), mean ± SD	75.04 ± 16.62
eGFR (90 to 99.9 mL/min/1.73 m^2), n (%)	15 (33.3)
eGFR (60 to 89.9 mL/min/1.73 m^2), n (%)	15 (33.3)
eGFR (30 to 59.9 mL/min/1.73 m^2), n (%)	15 (33.3)
sCr baseline (μmol/L), mean ± SD	86.44 ± 22.64
sCyC baseline (mg/L), median (IQR)	1.06 (0.87–1.25)
Biochemical characteristics	
CRP baseline (mg/L), median (IQR)	2.95 (0.72–7.25)
BNP baseline (pg/mL), median (IQR)	78.10 (31.40–134.56)
Hgb baseline (g/L), mean ± SD	138.51 ± 11.27
Alb baseline (g/L), mean ± SD	43.49 ± 3.22
Chol baseline (mmol/L), mean ± SD	4.64 ± 1.25
Tg baseline (mmol/L), median (IQR)	1.56 (1.14–2.64)
Alb/Cr urine, median (IQR)	0.016 (0.011–0.035)
Beta-2 MCG > 0,200 mg/L, n(%)	7 (15.56)
Contrast protocol	
volume of CM (mL), median (IQR)	100 (100–100)
prophylaxis without NAC, n (%)	25 (55.6)
prophylaxis with NAC, n (%)	20 (44.4)

CI-AKI – contrast-induced acute kidney injury; CM – contrast media; eGFR – estimated glomerular filtration rate; MI – myocardial infarction; NYHA – New York Heart Associations; BMI – body mass index; sCr – serum creatinine; sCyC – serum cystatin C; Chol – cholesterol; Tg – triglycerides; CRP – C-reactive protein; BNP – brain natriuretic peptide; Hgb – hemoglobin; Alb – albumin; Alb/Cr – albumin/creatinine ratio; MCG –microglobulin; NAC – N-acetyl-cysteine; IQR – interquartile range; SD – standard deviation.

isotonic saline alone and another 20 patients (44.4%) with additional NAC (2 × 600 mg *per os*).

In our study, after contrast media exposure, mean sCr and sCyC concentrations were 90.6 ± 24.1 μmol/L and 1.24 ± 0.65 mg/dL, respectively. sCyC based CI-AKI occurred in 19 patients (19/45, 42.22%) including 4 patients (4/45, 8,89%) with sCr based CI-AKI (χ^2 test; $p < 0.001$).

After this finding, we decided to form 2 groups based on CI-AKI development. In the group with CI-AKI, sCyC levels significantly increased 24 h after coronary angiography ($p < 0.03$), and eGFR values were found to be significantly decreased ($p < 0.012$) (Table 2). We also found significant differences in the percentage of changing sCr and sCyC concentrations ($p < 0.001$). Among the demographic parameters, only age and diabetes mellitus were found to be associated with CI-AKI development ($p < 0.015$ and $p < 0.04$, respectively). However, the medication therapy, CM volume, and other demographic characteristics and biochemical parameters

Table 2

Characteristics of patients after contrast applications according to contrast-induced nephropathy

Variables	No CI-AKI (n = 26)	CI-AKI (n = 19)	*p*-value
Age (years), mean ± SD	64.38 ± 8.08	70.32 ± 7.29	0.015[1]
Gender (male/female), n (%)	19 (73.1)/7 (26.9)	11 (57.9)/8 (42.1)	0.455[2]
BMI (kg/m²), mean ± SD	27.38 ± 4.48	26.18 ± 3.04	0.320[1]
Current or prior smoking, n (%)	9 (56.3)	7 (43.8)	1.000[2]
Hypertension, n (%)	7 (26.9)	4 (21.1)	0.919[2]
Prior MI or stroke, n (%)	4 (15.4)	2 (10.5)	0.976[2]
Diabetes mellitus, n (%)	13 (50.0)	16 (84.2)	0.040[2]
NYHA Grade III–IV, n (%)	2 (7.0)	2 (10.5)	0.741[2]
eGFR (90 to 99.9 mL/min/1.73 m^2), n (%)	10 (38.5)	5 (26.3)	
eGFR (60 to 89.9 mL/min/1.73 m^2), n (%)	9 (34.6)	6 (31.6)	0.529[2]
eGFR (30 to 59.9 mL/min/1.73 m^2), n (%)	7 (26.9)	8 (42.1)	
sCr baseline (μmol/L), mean ± SD	87.12 ± 20.28	85.53 ± 26.07	0.819[1]
sCr 24 hours post CM exposure (μmol/L), mean ± SD	86.69 ± 20.42	96.00 ± 27.97	0.203[1]
sCy baseline (mg/L), median (IQR)	1.10 (0.89–1.24)	0.97 (0.82–1.49)	0.654[3]
sCyC 24 hours post CM exposure (mg/L), median (IQR)	1.02 (0.86–1.24)	1.23 (0.95–1.81)	0.030[3]
eGFR baseline (mL/min/1.73 m^2), mean ± SD	78.25 ± 15.90	70.65 ± 17.00	0.131[1]
eGFR 24 hours post CM exposure (mL/min/1.73 m^2), mean ± SD	77.82 ± 14.54	65.09 ± 17.95	0.012[1]
CRP baseline (mg/L), median (IQR)	2.99 (0.86–7.30)	2.95 (0.65–7.69)	0.597[3]
CRP 24 hours post CM (mg/L), median (IQR)	3.42 (1.26–11.17)	5.58 (2.21–12.09)	0.312[3]
BNP baseline (pg/mL), median (IQR)	70.93 (25.17–122–90)	92.31 (49.53–142.83)	0.290[3]
BNP 24 hours post CM(pg/mL), median (IQR)	52.72 (32.37–116.36)	86.40 (51.64–160.81)	0.198[3]
Hgb baseline (g/L), mean ± SD	140.62 ± 11.32	135.63 ± 10.83	0.145[1]
Hgb 24 hours post CM (g/L), mean ± SD	138.19 ± 11.94	138.63 ± 14.66	0.912[1]
Alb baseline (g/L), mean ± SD	43.65 ± 3.11	43.26 ± 3.43	0.692[1]
Alb 24 hours post CM (g/L), mean ± SD	43.35 ± 3.27	44.05 ± 3.20	0.475[1]
Chol baseline (mmol/L), mean ± SD	4.82 ± 1.33	4.40 ± 1.11	0.268[1]
Chol 24 hours post CM (mmol/L), mean ± SD	4.83 ± 1.41	4.35 ± 1.06	0.223[1]
Percentage of changing sCr, median (IQR)	-0.43 (–6.19–7.16)	10.67 (4.61–21.31)	< 0.001[3]
Percentage of changing sCyC; median (IQR)	-3.22 (–10.86–5.45)	18.56 (14.15–29.24)	< 0.001[3]
Tg baseline (mmol/L), median (IQR)	1.75 (1.18–2.86)	1.50 (1.08–2.11)	0.265[3]
Tg 24 hours post CM (mmol/L), median (IQR)	1.73 (1.19–2.42)	1.36 (1.05–1.84)	0.103[3]
Beta-2 MCG > 0.200 mg/L, baseline, n (%)	2 (7.7)	2 (10.5)	1.000[2]
Beta-2 MCG > 0.200 mg/L, 24 hours post CM, n (%)	4 (15.4)	3 (15.8)	1.000[2]
Alb/Cr urine baseline, median (IQR)	0.018 (0.011–0.044)	0.014 (0.010–0.029)	0.638[3]
Alb/Cr urine 24 hours post CM exposure, median (IQR)	0.021 (0.009–0.045)	0.012 (0.010–0.042)	0.296[3]
Volume of CM (mL), median (IQR)	100 (100-105)	100 (100-100)	0.681[3]
Prophylaxis without NAC, n (%)	17 (65.4)	8 (42.1)	0.212[2]
Prophylaxis with NAC, n (%)	9 (34.6)	11 (57.9)	

For abbreviations see under Table 1.

[1]Independent samples *t*-test; [2]Chi-squared test; [3]Mann-Whitney test.

were similar between the two groups (Table 2). The results of our study showed that sCyC can significantly improve the early prediction of CI-AKI.

Discussion

Although sCr is not a reliable biomarker of glomerular filtration rate (according to the well-known variations related to gender, age, muscle mass, and nutrition), CI-AKI has been traditionally diagnosed based on the dynamic changes in sCr level after contrast exposure [24]. CyC, a cysteine protease freely filtered by the glomeruli (without previous metabolization in the serum), has a shorter half-life, a more rapid rise, and an earlier achievement of a new steady-state compared with sCr which recommends it as the alternative to sCr for evaluating GFR [25, 26]. The reliability of sCyC as a biomarker in detecting acute changes in kidney function has been proven in several previous studies, including CI-AKI patients [27–29]. However, like other available biomarkers, it is not ideal – the level of sCyC could be impacted with atherosclerosis and cardiac structural abnormalities processes. Moreover, a very serious problem demonstrated in the previously reported studies was the lack of consensus for the cut-off value for CyC elevation [30]. Yin et al. [31], in a study including a total of 204 patients undergoing primary angioplasty, found that CyC relative increase ≥ 10% within 72 h had a good predictive value for CI-AKI. Briguori et al. [32], in one of the most apostrophized studies related to CyC, which included patients with chronic kidney disease followed for one consecutive year, concluded that CyC increase ≥ 10%, 24 h after contrast media exposure, was the best increment cut-off value for the early diagnosis of CI-AKI. Zhang et al. [33] confirmed this claim in their study. Contrary to these studies, Liu et al. [34], in another study that encompassed 311 patients with CRF, did not find the superiority of CyC for detecting CI-AKI. Moreover, Ribichini et al. [35], in a study that included 166 patients with the risk of developing CI-AKI, found that variations of the

baseline serum creatinine are more reliable for detecting CI-AKI at an earlier stage than similar variations in CyC.

In our study, 19 CI-AKI cases were detected by sCyC and 4 of them fulfilled criterion for sCr based CI-AKI, too. We did not find any case where sCr was superior to sCyC as a biomarker of CI-AKI. The overall incidence of CI-AKI in our analysis (19 cases or 42.22%) was higher than in most previous reports, but the fact that it was conducted on patients with pre-existing CRF stages I–III provides a reasonable explanation for this and corresponds to the previous results in similar patient populations [36–42].

Furthermore, during these procedures, some patients, who underwent coronary angiography with stent implantation, received a significantly higher dose of CM than usually (more than 100 mL). On the other hand, the incidence of sCr-based CI-AKI (8.89%) was less than in other studies, which can be explained by the fact that we have measured sCr 24 hours after contrast media exposure. We believe this percentage is underestimated due to a short follow-up period.

According to these results, we concluded that an increase of 10% in sCyC can be reliable for early diagnosis of CI-AKI. On the other hand, we consider that 25% of the increase in sCr is a too strict criterion for this early period, and perhaps we should define a new cut-off for this marker at that time interval. This claim is further supported by the fact that we found statistically significant results in the percentage of creatinine and eGFR change.

This study had several limitations. Firstly, this was a single-center study with a small number of patients hence the results of our study should be confirmed by further larger multicenter studies. Secondly, the majority of patients were discharged 24 h after coronary angiography, which may have led to an underestimation of the true incidence of CI-AKI. Thirdly, our study is not designed to evaluate long-term outcomes. Additionally, other prevention measures, such as statin, diuretic, or angiotensin converting enzyme (ACE) inhibitors use, were not standardized in our study, which may have influenced the development of this complication [43, 44]. Our upcoming study will include a larger number of patients with the use of other early biomarkers and prophylactic regimes, which can additionally confirm and improve the results of this study.

Conclusion

Patients with a high risk of developing contrast-induced acute kidney injury (especially with chronic renal failure) should be monitored with serum cystatin C for 24 hours after exposure to contrast media or more than 48 hours if serum creatinine is used. On the other hand, when considering the economic cost-effectiveness of using serum cystatin C apart from the difference in the price of these two markers, the costs of prolonged hospitalization due to acute kidney injury treatment should be considered as well. It is certain that the untimely diagnosis of contrast-induced acute kidney injury represents the worst possible scenario for our patients, both financially and in terms of the quality of their treatment, and the same must be avoided. Therefore, the use of contrast-induced acute kidney injury markers should be considered rationally, but with an individual approach (especially in patients with a higher risk of developing contrast-induced acute kidney injury).

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Received on April 18, 2019.
Accepted June 19, 2019.
Online First June, 2019.