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

Dejan Pilčević*, Nemanja Rančić†‡, Zoran Jović‡§, Violeta Rabrenović*‡,
Svetlana Antić*, Marijana Petrović*‡, Dejan Petrović‖¶, Djoko Maksić*‡

Military Medical Academy, *Clinic for Nephrology, †Centre for Clinical Pharmacology,
§Clinic for Cardiology, Belgrade, Serbia; University of Defence, ‡Faculty of Medicine of
the Military Medical Academy, Belgrade, Serbia; Clinical Centre of Kragujevac, ‖Clinic
for Urology, Nephrology and Dialysis, Kragujevac, Serbia; University of Kragujevac,
Faculty of Medical Sciences, ¶Department of Internal Medicine, Kragujevac, Serbia

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.

Correspondence to: Dejan Pilčević, Military Medical Academy, Clinic for Nephrology, Crnotravska 17, 11 000 Belgrade, Serbia.
E-mail: dejan.pilcevic@gmail.com

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 m²), n (%)	10 (38.5)	5 (26.3)	
eGFR (60 to 89.9 mL/min/1.73 m²), n (%)	9 (34.6)	6 (31.6)	0.529[2]
eGFR (30 to 59.9 mL/min/1.73 m²), 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 m²), mean ± SD	78.25 ± 15.90	70.65 ± 17.00	0.131[1]
eGFR 24 hours post CM exposure (mL/min/1.73 m²), 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).

R E F E R E N C E S

1. *Aubry P, Brillet G, Catella L, Schmidt A, Bénard S.* Outcomes, risk factors and health burden of contrast-induced acute kidney injury: an observational study of one million hospitalizations with image-guided cardiovascular procedures. BMC Nephrol 2016; 17: 167.

2. *Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME,* et al. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. JACC Cardiovasc Interv 2014; 7(1): 1–9.

3. *Nash K, Hafeez A, Hou S.* Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39(5): 930–6.

4. *Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK,* et al. Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR) Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol 2011; 21(12): 2527–41.

5. *Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS.* Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol 2014; 9(1): 12–20.

6. *Kellum JA, Lameire, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL,* et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kindey Int Suppl 2012; 2(1): 1–138.

7. *Solomon R, Natarajan MK, Doucet S, Sharma SK, Staniloae CS, Katholi RE,* et al. The CARE (Cardiac Angiography in Renally Impaired Patients) Study: A randomized, double-blind trial of contrast-induced nephropathy in high risk patients. Circulation 2007; 115(25): 3189–96.

8. *Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ,* et al. Nephrotoxic effects in highrisk patients undergoing angiography. N Engl J Med 2003; 348(6): 491–9.

9. *Morcos SK, Thomsen HS.* European Society of Urogenital Radiology. European Society of Urogenital Radiology guidelines on administering contrast media. Abdom Imaging 2003; 28(2): 187–90.

10. *McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW.* Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103(5): 368–75.

11. *Rudnick MR, Goldfarb S, Wexler L, Ludbrook PA, Murphy MJ, Halpern EF,* et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial: the Iohexol Cooperative Study. Kidney Int 1995; 47(1): 254–61.

12. *Bellomo R, Kellum JA, Ronco C.* Defining acute renal failure: Physiological principles. Intensive Care Med 2004; 30(1): 33–7.

13. *American Society of Nephrology.* American Society of Nephrology Renal Research Report. J Am Soc Nephrol 2005; 16(7): 1886–903.

14. *Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P.* Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004 Aug; 8(4): R204-12.

15. *Wasung ME, Chawla LS, Madero M.* Biomarkers of renal function, which and when? Clin Chim Acta 2015; 438: 350–7.

16. *Kyhse-Andersen J, Schmidt C, Nordin G, Andersson B, Nilsson-Ehle P, Lindström V,* et al. Serum cystatin C, determined by a rapid, automated particle-enhanced turbidimetric method, is a better marker than serum creatinine for glomerular filtration rate. Clin Chem 1994; 40: 1921–6.

17. *Onopiuk A, Tokarzewicz A, Gorodkiewicz E.* Cystatin C: a kidney function biomarker. Adv Clin Chem 2015; 68: 57–69.

18. *Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R,* et al. Cystatin C and contrast-induced acute kidney injury. Circulation 2010; 121(19): 2117–22.

19. *Rickli H, Benou K, Ammann P, Fehr T, Brunner-La Rocca HP, Petridis H,* et al. Time course of serial cystatin C levels in comparison with serum creatinine after application of radiocontrast media. Clin Nephrol 2004; 61(2): 98–102.

20. *Ribichini F, Gambaro G, Graziani MS, Pighi M, Pesarini G, Pasoli P,* et al. Comparison of serum creatinine and cystatin C for early diagnosis of contrast-induced nephropathy after coronary angiography and interventions. Clin Chem 2012; 58(2): 458–64.

21. *Xu Q, Wang N, Duan S, Liu N, Lei R, Cheng W, Zhou SK.* Serum cystatin c is not superior to serum creatinine for early diagnosis of contrast-induced nephropathy in patients who underwent angiography. J Clin Lab Anal 2017; 31(5): doi: 10.1002/jcla.22096.

22. *National Kidney Foundation.* K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002; 39(2 Suppl 1): S1–266.

23. *Kim GS, Ko YG, Shin DH, Kim JS, Kim BK, Choi D,* et al. Elevated serum cystatin C level is an independent predictor of contrast-induced nephropathy and adverse outcomes in patients with peripheral artery disease undergoing endovascular therapy. J Vasc Surg 2015; 61(5): 1223–30.

24. *Dalton RN.* Serum creatinine and glomerular filtration rate: Perception and reality. Clin Chem 2010; 56(5): 687–9.

25. *Filler G, Bökenkamp A, Hofmann W, Le Bricon T, Martínez-Brú C, Grubb A.* Cystatin C as a marker of GFR – history, indication and future research. Clin Biochem 2005; 38: 1–8.

26. *Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN,* et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology 2006; 105(3): 485–91.

27. *Rickli H, Benou K, Ammann P, Fehr T, Brunner-La Rocca HP, Petridis H,* et al. Time course of serial cystatin C levels in comparison with serum creatinine after application of radiocontrast media. Clin Nephrol 2004; 61(2): 98–102.

28. *Bellomo R.* Decade in review – acute kidney injury: acute kidney injury - a decade of progress. Nat Rev Nephrol 2015; 11(11): 636–7.

29. *Kim BJ, Sung KC, Kim BS, Kang JH, Lee KB, Kim H,* et al. Effect of N-acetylcysteine on cystatin C-based renal function after elective coronary angiography (ENABLE Study): a prospective, randomized trial. Int J Cardiol 2010; 138(3): 239–45.

30. *Feng Y, Zhang Y, Li G, Wang L.* Relationship of cystatin-C change and the prevalence of death or dialysis need after acute kidney injury: a meta-analysis. Nephrology (Carlton) 2014; 19(11): 679–84.

31. *Yin L, Li G, Liu T, Yuan R, Zheng X, Xu G, Xu Y et al.* Probucol for the prevention of cystatin C-based contrast-induced acute kidney injury following primary or urgent angioplasty: a randomized, controlled trial. Int J Cardiol 2013; 167(2): 426–9.

32. *Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R,* et al. Cystatin C and contrast-induced acute kidney injury. Circulation 2010; 121(19): 2117–22.

33. *Zhang WF, Zhang T, Ding D, Sun SQ, Wang XL, Chu SC,* et al. Use of Both Serum Cystatin C and Creatinine as Diagnostic Criteria for Contrast-Induced Acute Kidney Injury and Its Clinical Implications. J Am Heart Assoc 2017; 6(1): pii: e004747.

34. *Liu XL, Wang ZJ, Yang Q, Yu M, Shen H, Nie B,* et al. Plasma neutrophil-gelatinase-associated lipocalin and cystatin C could early diagnose contrast-induced acute kidney injury in patients with renal insufficiency undergoing an elective percutaneous coronary intervention. Chin Med J (Engl) 2012; 125(6): 1051–6.

35. *Ribichini F, Gambaro G, Graziani MS, Pighi M, Peasrini G, Pasoli P,* et al. Comparison of serum creatinine and cystatin C for early diagnosis of contrast-induced nephropathy after coronary angiography and interventions. Clin Chem 2012; 58(2): 458–64.

36. *Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ,* et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105(19): 2259–64.

37. *Iakovou I, Dangas G, Mehran R, Lansky AJ, Ashby DT, Fahy M,* et al. Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. J Invasive Cardiol 2003; 15(1): 18–22.

38. *Davidson CJ, Hlatky M, Morris KG, Pieper K, Skelton TN, Schwab SJ,* et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization: a prospective trial. Ann Intern Med 1989; 110(2): 119–24.

39. *Hall KA, Wong RW, Hunter GC, Camazine BM, Rappaport WA, Smyth SH,* et al. Contrast-induced nephrotoxicity: the effects of vasodilator therapy. J Surg Res 1992; 53(4): 317–20.

40. *Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM,* et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000; 36(5): 1542–8.

41. *Gami AS, Garovic VD.* Contrast nephropathy after coronary angiography. Mayo Clin Proc 2004; 79(2): 211–9.

42. *Zhang T, Shen LH, Hu LH, He B.* Statins for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Am J Nephrol 2011; 33(4): 344–51.

43. *Gupta R, Moza A, Cooper CJ.* Intravenous hydration and contrast-induced acute kidney injury: too much of a good thing? J Am Heart Assoc 2016; 5(6). pii: e003777.