ORIGINAL ARTICLE

Association between elevated urinary levels of kidney injury molecule type 1 and adverse cardiovascular events at 12 months in patients with coronary artery disease

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KEY WORDS

interleukin 18, kidney injury molecule type 1, liver fatty acid-binding protein, prognosis, renalase

ABSTRACT

INTRODUCTION Contrast-induced nephropathy is associated with worse prognosis in patients with coronary artery disease (CAD); however, the prognostic role of urinary biomarkers of renal injury has not been fully established.

OBJECTIVES We evaluated the clinical utility of urinary biomarkers for the prediction of major adverse cardiac and cerebrovascular events (MACCEs) in patients undergoing coronary angiography.

PATIENTS AND METHODS This prospective study included 95 consecutive patients with stable and unstable CAD (men, 69.5%; median age, 65 years), referred for coronary angiography and monitored for MACCEs during 12-month follow-up. MACCEs were defined as cardiovascular death, myocardial infarction, myocardial revascularization, or stroke. Urine samples were collected 24 hours before and 6 hours after coronary angiography and assayed for kidney injury molecule type 1 (KIM-1), interleukin 18, liver fatty acid-binding protein, and renalase, using an enzyme-linked immunosorbent assay. The results were adjusted for urinary creatinine concentration.

RESULTS MACCEs occurred in 10 patients (10.5%). These patients had a higher rate of postprocedural contrast-induced acute kidney injury than patients without MACCEs (30.0% vs 7.1%, $P = 0.02$), higher median SYNTAX score (25.5 points vs 11.5 points, $P = 0.04$), higher postprocedural KIM-1 concentrations (0.45 ng/mg vs 0.21 ng/mg, $P = 0.03$), and a larger absolute increase of urinary KIM-1 levels (ΔKIM-1; 0.41 ng/mg vs 0.10 ng/mg, $P = 0.01$). Preprocedural values of KIM-1 and other biomarkers were comparable between groups. Patients with ΔKIM-1 levels above the 75th percentile had worse 12-month prognosis ($P = 0.0004$). ΔKIM-1 levels were an independent predictor of 12-month MACCEs ($P = 0.001$). MACCEs were accurately predicted by ΔKIM-1 levels exceeding 0.093 ng/mg (area under the curve, 0.752; $P = 0.0001$).

CONCLUSIONS Excessive increase of urinary KIM-1 levels after coronary angiography may help identify CAD patients with poor 12-month prognosis.

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INTRODUCTION Prognosis of patients with coronary artery disease (CAD) can be improved not only by advances in pharmacology and stent design, but also by the detection and management of periprocedural complications.[1-2] Contrast-induced acute kidney injury (CI-AKI) represents one of the major detrimental sequelae of contrast agent administration.[3] Depending on the criteria applied and population, CI-AKI was associated with short- and long-term prognosis, both in patients with stable angina[3] and those with acute coronary syndromes (ACSs).[4-5] Patients with CAD and chronic kidney disease (CKD) were characterized by an even higher risk associated with

postprocedural worsening of kidney function, reflected by higher in-hospital and long-term mortality.[6,7]

Although the prognostic role of CI-AKI itself remains undisputed, its diagnosis is precluded by delayed accumulation of routinely utilized serum creatinine concentrations.[8] For this purpose, numerous serum and urinary biomarkers were proposed for an early and effective identification of patients with CI-AKI.[9] Accordingly, circulating serum levels of biomarkers such as interleukin 18 (IL-18)[10-12] and cystatin C[13] accurately stratified the risk of adverse cardiovascular events in patients with CAD. However, it is unclear whether also urinary levels of biomarkers could serve as reliable predictors of poor cardiovascular outcome in patients with CAD. Urinary proteome and certain biomarkers were associated with the risk of adverse cardiovascular events in long-term follow-up.[14-15] Of note, in a large cohort of patients with CKD, urinary levels of kidney injury molecule type 1 (KIM-1) were independently associated with adverse cardiovascular events, heart failure, and death.[16]

Based on the above findings, we decided to continue our previous research in which we evaluated the urinary concentrations of KIM-1, IL-18, liver fatty acid-binding protein (L-FABP),[17] and renalase[18] as possible diagnostic markers of CI-AKI. The aim of the current study was to establish the clinical utility of these urinary biomarkers for the prediction of major adverse cardiac and cerebrovascular events (MACCEs) in patients with CAD undergoing coronary angiography.

PATIENTS AND METHODS

In this study, we focused on the survival analysis of patients enrolled in our previous study of different urinary biomarkers used for diagnosis of CI-AKI.[17,18] The detailed characteristics of the study population can be found in the previous report concerning different preprocedural and ultrasound markers of CI-AKI.[19] The research was conducted in adherence with the Declaration of Helsinki. The study protocol was approved by the local ethics committee, and all patients gave written informed consent to participate in the study.

In the present study, 95 patients with the suspicion of (CAD) were referred for elective or urgent coronary angiography or percutaneous coronary intervention (PCI). Data concerning clinical and demographic parameters were collected on admission. Apart from routine laboratory tests, urine samples were obtained 24 hours before and 6 hours after coronary angiography and assayed for KIM-1, IL-18, L-FABP, and renalase. Directly after the procedure, the rate of CI-AKI was established based on the definition of Acute Kidney Injury Network criteria, namely, ≥50% relative or ≥0.3 mg/dl absolute increase of serum creatinine (SCr) concentration at 48 hours after the procedure.[20]

Patients were then followed for 12 months to establish the rate of MACCEs. The composite primary endpoint of MACCE consisted of cardiovascular death, myocardial infarction, urgent coronary revascularization, or ischemic stroke. Urgent revascularization was defined as hospitalization due to unstable angina leading to urgent PCI.

Inclusion and exclusion criteria

The inclusion criteria were stable angina with high pretest probability confirmed using a noninvasive stress test, or non–ST-segment elevation ACS (NSTE-ACS) in line with the 2011 European Society of Cardiology guidelines.[21] On admission, patients were assessed for the possible exclusion criteria including acute or chronic respiratory failure, severe valvular heart disease, active thyroid disease, pregnancy, allergy to iodine-based contrast agents, CKD with an estimated glomerular filtration rate (eGFR) of less than 50 ml/min/1.73 m^2 or proteinuria higher than 500 mg/l, active urinary tract infection, or renal artery stenosis.

Laboratory tests

Venous blood samples were obtained prior to coronary angiography, as well as 24 and 48 hours after the procedure. Blood samples collected at baseline were tested for a set of basic laboratory data and SCr levels, whereas 24-hour and 48-hour specimens were assayed only for SCr levels.

Midstream urine samples were acquired within 24 hours preceding the procedure and 6 hours after the procedure. The samples were centrifuged for 15 minutes at 1000 × *g* at a temperature of 2°C to 8°C within 15 minutes after acquisition and deposited at a temperature of –80°C with no freeze–thaw incidents. The urinary concentrations of KIM-1 and L-FABP (both using an enzyme-linked immunosorbent assay [ELISA] kit by EKF Diagnostics, Cardiff, United Kingdom), IL-18 (eBioscience, San Diego, California, United States), and renalase (Cloud-Clone Corp, Houston, Texas, United States) were evaluated within 3 months after the collection of specimens. All the ELISA-based measurements were performed according to the manufacturers' instructions. Furthermore, the creatinine concentration was measured in all urine samples, using a colorimetric assay (Oxford Biomedical Research, Oxford, Michigan, United States). The levels of urinary biomarkers were then expressed as a biomarker-to-creatinine ratio. The concentrations of all urinary biomarkers were thus expressed as a biomarker-to-creatinine ratio.

Follow-up

At 12 months after the procedure, we collected data concerning the onset of MACCEs. The follow-up was conducted using a structured telephone interview and verified on the basis of data derived from recurrent hospitalizations in the same hospital and information provided by the national health care provider. The follow-up was completed by all patients.

Management of patients

Both pharmacotherapy and procedural management of all the study

TABLE 1 Clinical and demographic parameters depending on the presence of major adverse cardiac and cerebrovascular events during 12-month follow-up

Parameter	No MACCE (n = 85)	MACCE (n = 10)	*P* value
Age, y	65 (60–70)	68.5 (57–74)	0.55[a]
BMI, kg/m^2	28.4 (26.1–32.8)	27.5 (24.8–30.1)	0.28[a]
Male sex	58 (68.2)	8 (80.0)	0.36[c]
Current smoking	51 (60.0)	7 (70.0)	0.40[c]
Arterial hypertension	81 (95.3)	10 (100.0)	0.64[c]
Type 2 diabetes / IFG / IGT	32 (37.7)	5 (50.0)	0.33[c]
Previous MI	36 (42.4)	5 (50.0)	0.45[c]
Peripheral artery disease	13 (15.3)	3 (30.0)	0.22[c]
Atrial fibrillation	20 (23.5)	1 (10.0)	0.30[c]
Former TIA or stroke	7 (8.2)	0 (0.0)	0.45[c]
CI-AKI onset	6 (7.1)	3 (30)	0.02[c]
Baseline eGFR by MDRD, ml/min/1.73 m^2	81.0 (20.50)	77.6 (24.58)	0.62[b]
Baseline SCr, mg/dl	0.93 (0.79–1.11)	1.025 (0.84–1.25)	0.31[a]
SCr at 48 hours, mg/dl	1.00 (0.80–1.17)	1.30 (0.86–1.50)	0.05[a]
ΔSCr, mg/dl	0.03 (–0.02 to 0.09)	0.075 (0.01–0.46)	0.08[a]
Hemoglobin, g/dl	14.0 (1.21)	13.3 (1.32)	0.12[b]
Platelet count, 1000/mm^3	197 (175–233)	201.0 (186–265)	0.31[a]
Hs-TnT, ng/ml	0.02 (0.01–0.03)	0.02 (0.01–0.15)	0.52[a]
IMT, mm	0.09 (0.03)	0.10 (0.03)	0.28[b]
EMT, mm	0.06 (0.05–0.08)	0.08 (0.06–0.09)	0.04[a]
LVEF, %	55 (50–60)	50 (48–55)	0.25[a]
E/e' ≥12	21 (25.0)	1 (10.0)	0.27[c]
Mitral valve insufficiency (mild-moderate)	57 (67.1)	4 (40.0)	0.09[c]
NSTE-ACS	46 (54.1)	8 (80.0)	0.11[c]
NSTEMI	24 (28.2)	4 (40)	0.44[c]
Left main disease	5 (5.9)	5 (50.0)	0.001[c]
SYNTAX score, points	11.5 (4–24)	25.5 (8–36)	0.08[a]
Ad hoc PCI	38 (44.7)	4 (40.0)	0.53[c]
Referral for CABG	11 (12.9)	3 (30.0)	0.16[c]

Data are presented as number (percentage) of patients or median (interquartile range).

a Mann–Whitney test; **b** *t* test; **c** Fisher exact test or Pearson χ^2 test

SI conversion factors: to convert SCr to μmol/l, multiply by 88.42.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; EMT, extra-medial thickness; hs-TnT, high-sensitivity troponin T; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intima–media thickness; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiovascular and cerebral event; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SCr, serum creatinine; TIA, transient ischemic attack

participants was based on the European Society of Cardiology Non-ST-elevation-Acute Coronary Syndromes (NSTE-ACS) guidelines.[21] The prevention of CI-AKI entailed the use of low-osmolar or iso-osmolar contrast media at the lowest possible dose. Patients with mild impairment of renal function (eGFR, 50–60 ml/min/1.73 m^2) were pretreated with an intravenous infusion of 0.9% saline at a rate of 1 ml/kg/h, starting from 12 hours before to 24 hours after coronary angiography, while patients with an eGFR exceeding 60 ml/min/1.73 m^2 received 500 ml of 0.9% saline prior to the procedure. The use of biguanides was discontinued 1 day before the procedure and restarted 48 hours after the procedure, once the SCr level was considered stable based on laboratory test results.

Statistical analysis Statistical analysis was performed using the MedCalc v.14.8.1 software (MedCalc, Ostend, Belgium). Quantitative variables were reported as mean and SD or median and interquartile range (IQR), whereas qualitative variables were presented as number and percentage. Distribution of variables was verified using the Shapiro–Wilk test. The *t* test for unpaired samples was applied for normally distributed variables, and the Mann–Whitney test was used for nonnormally distributed variables. The univariate Cox analysis of different predictors of MACCE occurrence was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). All the variables with a *P* value of less than 0.1 in the univariate model were included in the Cox proportional hazards model. The receiver operating characteristic (ROC) curve analysis was performed for all 4 biomarkers. The diagnostic threshold of different variables was established using the Youden's J statistic. The Kaplan–Meier survival curves and log-rank tests were established for all the dichotomous variables with a *P* value of less than 0.1 in the univariate analysis. A *P* value of less than 0.05 was considered significant.

RESULTS

General characteristics of the study population The study population consisted of 95 patients with CAD, who were admitted to the department of cardiology with the diagnosis of either NSTE-ACS (56.8% of patients) or stable angina (43.2% of patients). Most participants were men (69.5%) at a median age of 65 years (IQR, 59–71). The primary aim of this study was to establish reliable risk factors of CI-AKI; detailed characteristics of the study group were reported previously.[19] The relationship between periprocedural variables and urinary biomarkers and CI-AKI was also described previously.[17]

Primary endpoint At 12 months, MACCEs were reported in 10 patients (10.5%). None of the study participants died. Myocardial infarction was reported in 3 patients, 6 patients required urgent myocardial revascularization, and 1 patient had ischemic stroke.

The differences in clinical parameters between MACCE and non–MACCE groups are shown in TABLE 1. The MACCE group was characterized by a higher rate of postprocedural CI-AKI and left main disease, as well as greater extra-medial thickness. A trend towards a higher SYNTAX score was reported in the MACCE group. The groups did not differ in terms of age, sex, or cause of intervention (stable angina vs NSTE-ACS).

TABLE 2 Preprocedural and postprocedural urinary biomarker concentrations depending on the presence of major adverse cardiac and cerebrovascular events during 12-month follow-up

Variable	No MACCE (n = 85)	MACCE (n = 10)	*P* value
Baseline L-FABP, ng/mg	0.30 (0.15–0.75)	0.30 (0.15–0.452)	0.64[a]
L-FABP at 6 hours[a], ng/mg	0.30 (0.15–0.90)	0.45 (0.15–0.45)	0.96[a]
ΔL-FABP, ng/mg	0.00 (–0.30 to 0.45)	0.08 (–0.53 to 0.34)	0.76[a]
Relative ΔL-FABP, %	0.00 (–66.6 to 113.8)	58.4 (–67.8 to 200.3)	0.93[a]
Baseline IL-18, pg/mg	50.5 (32.6–73.4)	55.1 (38.7–59.1)	0.80[a]
IL-18 at 6 hours[a], pg/mg	81.9 (61.5–105.6)	94.5 (75.6–94.5)	0.96[a]
ΔIL-18, pg/mg	24.9 (11.7–58.2)	35.4 (14.5–56.8)	0.76[a]
Relative ΔIL-18, %	62.8 (15.9–197.2)	65.6 (34.2–128.9)	0.93[a]
Baseline renalase, ng/mg	3.73 (3.24–4.44)	3.43 (3.13–4.55)	0.49[a]
Renalase at 6 hours[a], pg/mg	2.1 (1.93–2.34)	2.3 (1.93–2.34)	0.56[a]
ΔRenalase, pg/mg	–1.5 (–2.24 to –1.04)	–1.1 (–2.44 to –0.85)	0.27[a]
Relative Δ renalase, %	–43.5 (–51.4 to –33.7)	–37.1 (–53.6 to –26.1)	0.35[a]
Baseline KIM-1, ng/mg	0.07 (0.04–0.19)	0.05 (0.04–0.124)	0.49[a]
KIM-1 at 6 hours[a], ng/mg	0.21 (0.12–0.51)	0.45 (0.32–0.94)	0.03[a]
ΔKIM-1, ng/mg	0.10 (0.04–0.34)	0.41 (0.20–0.89)	0.01[a]
Relative ΔKIM-1, %	187.5 (28.1–540.0)	659.5 (209.5–1772.0)	0.04[a]

Data are presented as median (interquartile range).

a After coronary angiography

Abbreviations: IL-18, interleukin 18; KIM-1, kidney injury molecule type 1; L-FABP, liver fatty acid-binding protein; others, see TABLE 1

TABLE 3 Univariate Cox proportional hazards analysis of different predictors of major adverse cardiac and cerebrovascular events during 12-month follow-up

Variable	HR	95% CI	*P* value
Age, per 1 year	1.025	0.953–1.103	0.51
BMI, per 1 kg/m^2	0.933	0.819–1.063	0.30
Male sex	1.856	0.397–8.674	0.43
Hemoglobin, per 1 g/dl	0.686	0.419–1.122	0.14
ΔSCr, per 1 mg/dl	5.750	0.99–33.32	0.05
CI-AKI onset	4.399	1.142–16.947	0.03
NSTE-ACS	3.209	0.687–14.992	0.14
NSTEMI	1.639	0.466–5.772	0.44
Left main disease	9.952	2.886–34.323	0.0003
SYNTAX score, per 1 point	1.041	1.001–1.081	0.045
Ad hoc PCI	0.832	0.236–2.928	0.78
Referral for CABG	2.636	0.686–10.130	0.16
KIM-1 at 6 hours[a], per 1 ng/mg	1.698	0.656–4.396	0.28
ΔKIM-1, per 1 ng/mg	2.068	0.756–5.659	0.16
ΔKIM-1 >75 percentile	10.754	2.247–51.474	0.003

a After coronary angiography

Abbreviations: HR, hazard ratio; others, see TABLES 1 and 2

The subanalysis revealed that the rate of primary endpoint did not differ between patients with ACS and those with stabile angina (14.8% vs 4.9%, *P* = 0.12). The rate of MACCEs was also comparable between patients with non–ST-segment elevation myocardial infarction (NSTEMI) and those with negative troponin levels (14.3% vs 9.0%; *P* = 0.44), and between patients undergoing PCI and those managed conservatively (9.5% vs 11.3%, *P* = 0.78).

Data on urinary biomarkers are presented in TABLE 2. Patients with confirmed primary endpoint were characterized by higher postprocedural KIM-1 concentrations (0.45 ng/mg vs 0.21 ng/mg, *P* = 0.03) and both absolute and relative increase of KIM-1 concentrations (0.41 ng/mg vs 0.10 ng/mg, *P* = 0.01 and 659.5% vs 187.5%, *P* = 0.04, respectively) in comparison with the non–MACCE group. Preprocedural KIM-1 concentrations were similar between groups. The remaining urinary biomarkers, including IL-18, renalase, and L-FABP, were comparable between groups both at baseline and after the procedure (TABLE 2).

Univariate Cox proportional hazards model

The results of the univariate analysis of different predictors of MACCE occurrence during the follow-up are shown in TABLE 3. In the univariate Cox analysis, MACCE was accurately predicted by the onset of postprocedural CI-AKI (HR, 4.399; *P* = 0.03), left main disease (HR, 9.9; *P* = 0.0003), higher SYNTAX score (unit HR, 1.041 per 1 point; *P* = 0.045), and the highest quartile of an absolute increase of urinary KIM-1 concentrations (ΔKIM-1 >75 percentile; HR, 10.7; *P* = 0.003). The presence of NSTE-ACS (HR, 3.209; *P* = 0.14), NSTEMI (HR, 1.639; *P* = 0.44), PCI during index hospitalization (HR, 0.832; *P* = 0.78), or referral for coronary artery bypass grafting (CABG; HR, 2.636; *P* = 0.16) were not associated with the 12-month MACCE (TABLE 3).

The multivariable Cox proportional hazards model indicated that left main disease (HR, 25.8; 95% CI, 3.71–179.0; *P* = 0.001), onset of CI-AKI after the procedure (HR, 2.94; 95% CI, 1.45–8.42; *P* = 0.04), and the highest quartile of ΔKIM-1 concentrations (HR, 18.74; 95% CI, 2.67–131.7; *P* = 0.003) were independent predictors of MACCE (overall model fit *P* = 0.0001).

Receiver operating characteristic curve analysis

The results of the ROC curve analysis are presented in TABLE 4. Renalase, L-FABP, and IL-18 were not predictors of MACCE in the 12-month follow-up. Conversely, although baseline KIM-1 levels failed to predict the onset of cardiovascular events, both postprocedural KIM-1 concentrations exceeding 0.184 ng/mg (area under the curve [AUC], 0.725; *P* = 0.001) and ΔKIM-1 concentrations exceeding 0.093 ng/mg (AUC, 0.752; *P* = 0.0001; FIGURE 1) predicted the occurrence of MACCE. SCr levels at 48 hours postprocedure (AUC, 0.688; *P* = 0.07) and ΔSCr levels (AUC, 0.672; *P* = 0.07) showed a trend towards prediction of the primary endpoint.

Kaplan–Meier survival analysis Patients who experienced an increase in KIM-1 levels in the fourth quartile (ΔKIM-1 >0.412 ng/mg) after coronary

TABLE 4 Receiver operating characteristic curve analysis of different laboratory predictors of major adverse cardiac and cerebrovascular event occurrence at 12 months

Variable		Criterion	Sensitivity	Specificity	AUC	*P* value
SCr, mg/dl	Baseline	>1.12	50.0	77.6	0.601	0.30
	At 48 hours[a]	>1.26	60.0	87.1	0.688	0.07
	Δ	>0.05	70.0	64.7	0.672	0.07
Renalase, pg/mg	Baseline	≤3.43	55.6	63.2	0.573	0.51
	At 6 hours[a]	>2.29	55.6	70.2	0.561	0.60
	Δ	>-1.17	66.7	68.7	0.615	0.36
L-FABP, ng/mg	Baseline	≤1.506	100.0	17.4	0.549	0.4
	At 6 hours[a]	≤0.753	88.9	25.7	0.520	0.86
	Δ	>0.151	50.0	68.1	0.513	0.91
IL-18, pg/mg	Baseline	≤67.29	100.0	28.4	0.527	0.74
	At 6 hours[a]	>92.97	55.6	64.9	0.506	0.95
	Δ	>29.85	66.7	56.2	0.533	0.74
KIM-1, ng/mg	Baseline	≤0.063	66.7	55.3	0.572	0.46
	At 6 hours[a]	>0.184	100.0	44.1	0.725	0.001
	Δ	>0.093	100.0	50.0	0.752	0.0001

a After coronary angiography

Abbreviations: AUC, area under the curve; others, see **TABLES 1** and **2**

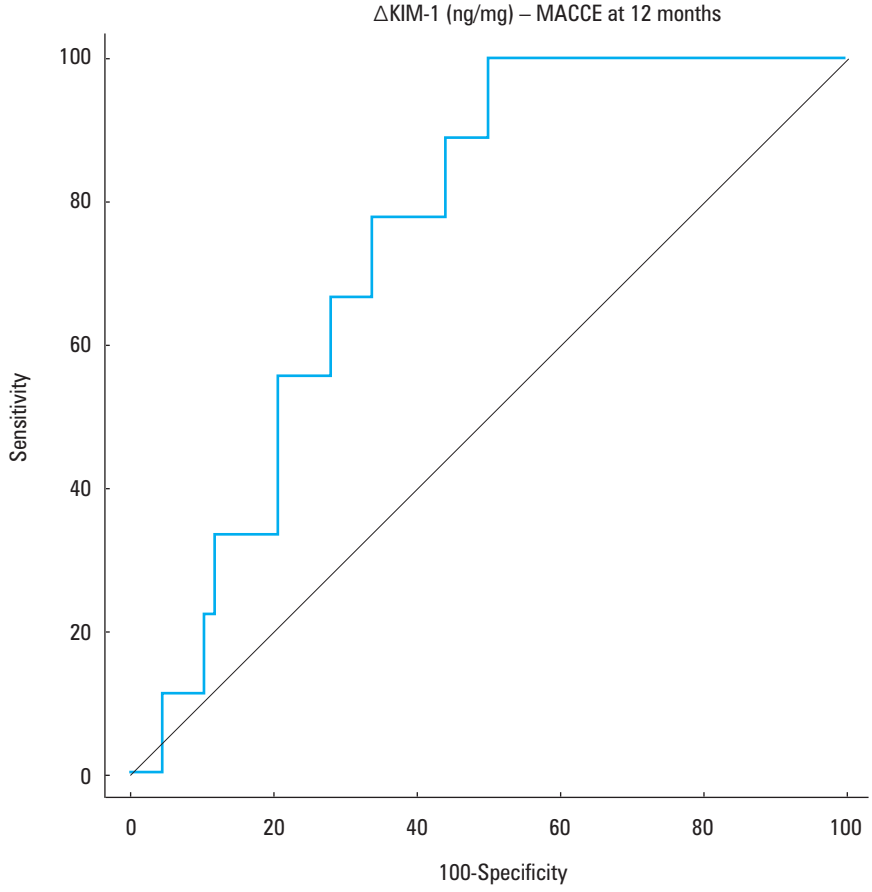

FIGURE 1 Receiver operating characteristic curve: prediction of major adverse cardiac and cerebrovascular events (MACCEs) at 12 months by an absolute increase of kidney injury molecule type 1 (ΔKIM-1)

angiography were characterized by worse prognosis reflected by a higher rate of MACCE (31.8% vs 4.1%; log-rank $P = 0.0004$; **FIGURE 2**). Patients with ΔKIM-1 above the Youden threshold of 0.093 ng/mg and those with postprocedural KIM-1 levels exceeding 0.184 ng/mg also showed a higher rate of MACCE (20.9% vs 1.9%, log-rank $P = 0.005$ and 19.2% vs 3.2%, log-rank $P = 0.01$, respectively).

The onset of postprocedural CI-AKI and ΔSCr levels exceeding 0.05 mg/dl were also associated with a higher risk of MACCE in 12-month follow-up (CI-AKI vs non–CI-AKI, 33.3% vs 8.14%, log-rank $P = 0.02$, **FIGURE 3**, and ΔSCr >0.05 mg/dl vs ≤0.05 mg/dl, 18.9% vs 5.2%; log-rank $P = 0.04$; **FIGURE 4**). Finally, the risk of MACCE was higher

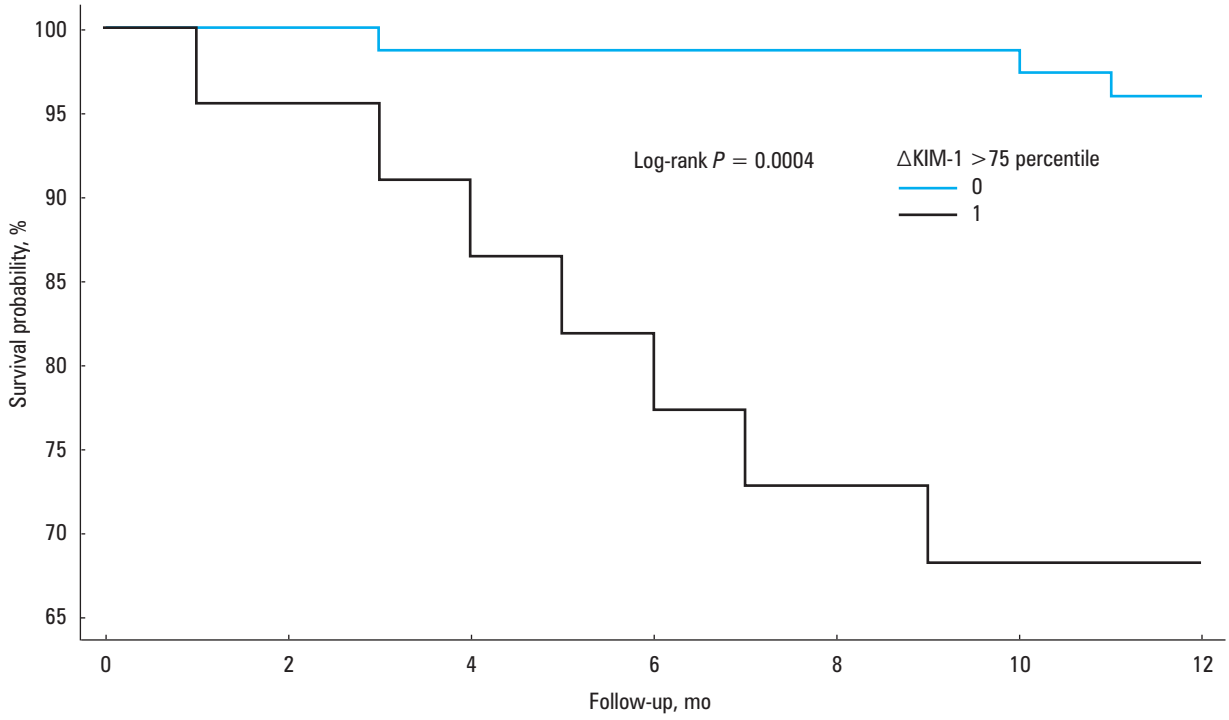

FIGURE 2 Kaplan–Meier survival curve of major adverse cardiac and cerebrovascular event (MACCE) occurrence at 12 months depending on the increase of postprocedural urinary kidney injury molecule type 1 events (KIM-1) concentration: ≥75 and <75 percentile

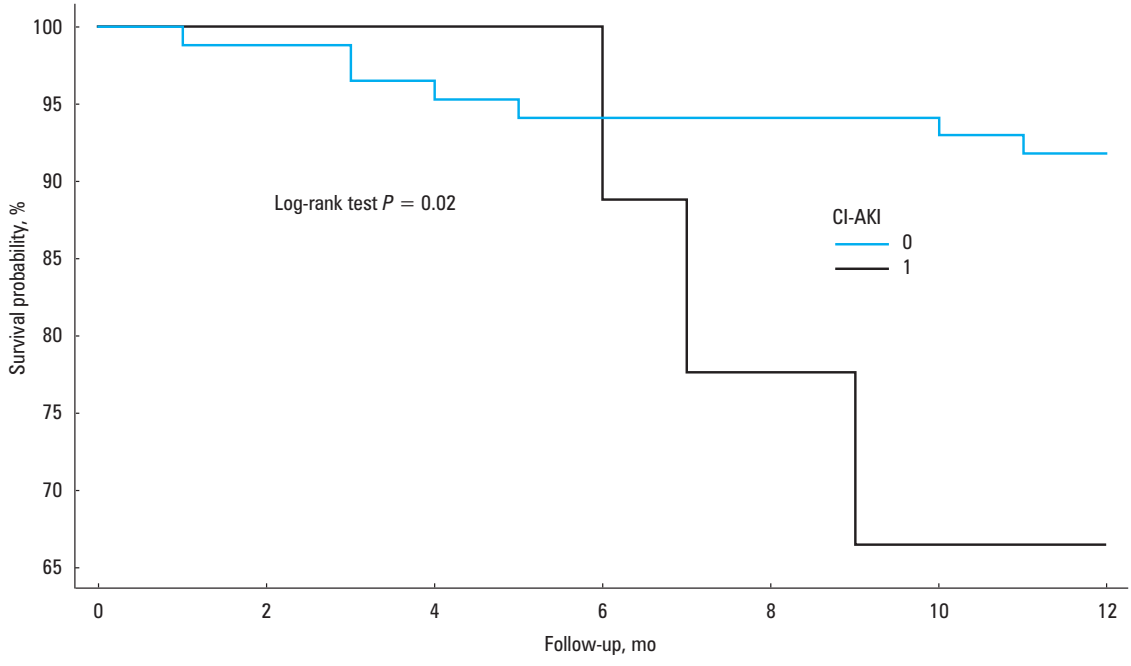

FIGURE 3 Kaplan–Meier survival curve of major adverse cardiac and cerebrovascular event (MACCE) occurrence at 12 months depending on the presence of postprocedural contrast-induced acute kidney injury (CI-AKI; defined according to Acute Kidney Injury Network criteria[20])

in patients with left main disease compared with those without (50% vs 5.9%; log-rank $P = 0.0001$).

The risk of MACCE was not associated with referral for CABG ($P = 0.14$), referral for PCI ($P = 0.78$), presence of NSTE-ACS ($P = 0.12$), or presence of NSTEMI at baseline ($P = 0.44$).

DISCUSSION In the analyzed cohort of patients with stable angina or NSTE-ACS undergoing coronary angiography, the onset of MACCEs in the 12-month follow-up was linked to higher postprocedural urinary KIM-1 concentrations at 6 hours after the procedure and a greater absolute and relative increase of KIM-1 concentrations. To our knowledge, our study is the first to evaluate the urinary biomarkers KIM-1, IL-18, L-FABP, and renalase as predictors of composite endpoint in a broad population of patients

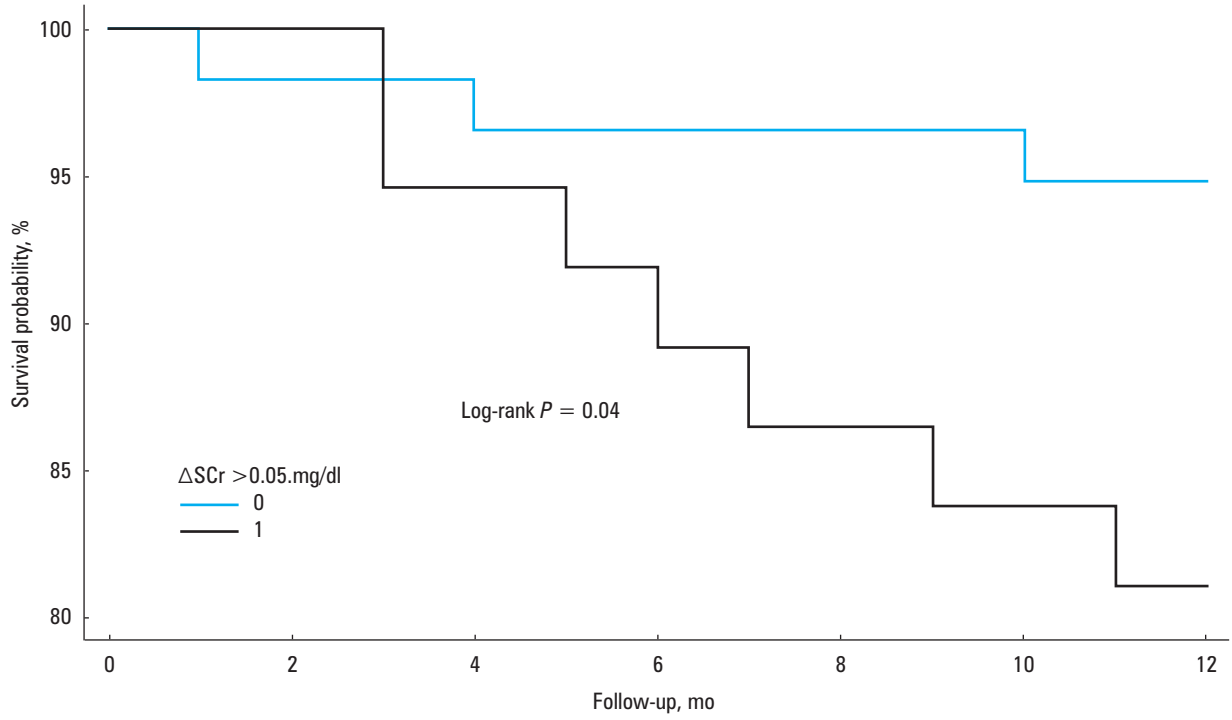

FIGURE 4 Kaplan–Meier survival curve of major adverse cardiac and cerebrovascular event (MACCE) occurrence at 12 months depending on the absolute increase of serum creatinine (SCr) concentration (>0.05 mg/dl)

with CAD. It provided evidence for the prognostic significance of urinary KIM-1 levels. Since no studies so far have assessed urinary KIM-1 in CAD patients, our results cannot be directly compared with other reports. However, in a previous high-volume research based on the Chronic Renal Insufficiency Cohort study (CRIC), Park et al[16] revealed that the highest quintile of urinary KIM-1 levels was independently associated with the development of heart failure (HR, 1.73) and death (HR, 1.56), as well as the composite endpoint of myocardial infarction, ischemic stroke, and peripheral artery disease (unit HR, 1.18 per log SD) among 2466 patients with the diagnosis of CKD, followed for a median time of 6.5 years.[16] Unlike participants in our study, those patients had CKD, had no CAD, and were not administered a contrast agent. Unlike the CRIC cohort, in our study only postprocedural and an absolute increase of urinary KIM-1 levels was predictive of MACCE, while baseline KIM-1 concentrations prior to contrast agent use were not linked to prognosis.

In another study, urinary KIM-1 concentrations were demonstrated to correlate with carotid-femoral pulse wave velocity in patients with CAD, but not among healthy controls.[22] This report provided evidence for the relationship between KIM-1 concentrations and arterial stiffness on applanation tonometry, a well-established marker of subclinical organ damage.[22]

KIM-1 belongs to adhesion glycoproteins expressed in proximal tubular cells, primarily in response to cellular injury.[23] Its biological function consists in restoration of integrity of proximal tubular cells in the aftermath of injury.[24,25] Since KIM-1 is expressed in the luminal part of proximal tubular cells, it can be detected exclusively in urine. KIM-1 was found to be a reliable diagnostic marker of acute kidney injury, given its urinary surge occurring as early as 12 hours following contrast agent administration.[26] In a previous paper reporting results from the same cohort of patients, we demonstrated that the increase of urinary KIM-1 levels 6 hours after the procedure also identified patients with contrast-induced nephropathy.[17] Of note, in the present study the highest postprocedural increase of KIM-1 levels and the onset of CI-AKI were independently associated with MACCE onset in 12-month follow-up, as revealed by the Cox proportional hazards model. Therefore, it may be speculated that the value of KIM-1 for predicting the onset of MACCE is only partially related with its association with CI-AKI.

The mechanism underlying the observed relationship between KIM-1 and adverse cardiovascular events remains unknown. In a rat model of cardiorenal syndrome, tubular KIM-1 expression was upregulated after myocardial infarction and corresponded with gradual impairment of renal function mediated via the Smad2-signaling pathway,[27] suggesting a more profound interplay between the kidney and heart in cardiorenal syndrome. In our previous study, we confirmed a higher postoperative increase of KIM-1 and ΔKIM-1 levels among patients with NSTE-ACS in comparison with patients with stable angina.[17] Yet, NSTE-ACS was not associated with the onset of MACCE in the current study.

The prognostic value of CI-AKI for the prediction of MACCE in the present analysis is not

a novel finding and confirms the results of previous studies.[3-7] Of note, the significance of left main disease for risk stratification has been long established.[21]

In the present study, none of the remaining urinary biomarkers proved useful for assessing the cardiovascular risk in patients with CAD. The plasma concentration of proinflammatory IL-18 was previously associated with the occurrence of adverse events at 30 days[28] and 60 days[29] in patients with myocardial infarction. Despite being an accurate predictor of postprocedural CI-AKI in the previous study,[17] urinary IL-18 concentrations failed to differentiate patients in terms of the future development of MACCE. Also, neither L-FABP[16,30] nor renalase[31] identified patients at risk of long-term adverse events.

Of note, other urinary biomarkers have previously been linked to cardiovascular outcome. A set of 75 different urinary biomarkers included in urinary proteome was shown to identify initially asymptomatic patients who later experienced ACS during a 5-year follow-up.[14] Also, Pedersen et al[15] reported a predictive role of urinary concentrations of inflammation-associated kynurenine, which was associated with major adverse cardiovascular events in patients with suspected stable CAD.

The main limitation of the current study is the relatively low number of study participants. On the other hand, no deaths occurred during follow-up, and the composite endpoint consisted mainly of urgent revascularization. In addition, the analyzed population was relatively heterogeneous (patients with stable angina and those with NSTE-ACS). However, in our analysis of the primary endpoint, we did not observe significant differences in terms of prognosis between patients with NSTE-ACS vs stable angina, as well as those treated with PCI vs CABG. Another limitation is the lack of serial measurements of biomarker levels because there may have been circadian fluctuations in urinary excretion. However, participants were admitted during the day and night, which might have compensated for the possible temporal variations. Finally, the study did not include simultaneous evaluation of plasma IL-18, L-FABP and renalase levels, which could also prove useful as the CI-AKI biomarker.

Our study group combined patients with stable and unstable coronary syndromes, which may represent another shortcoming of the study. In the previous publication, we proved that patients with NSTE-ACS are characterized by higher levels of urinary renalase in comparison with stable individuals.[17] Nonetheless, the cause of admission (NSTE-ACS vs stable angina), elevated troponin levels (NSTEMI vs non–NSTEMI), or the type of revascularization (PCI or CABG) did not differentiate patients in terms of the 12-month prognosis. The Cox proportional hazards model failed to include these variables in the predictive model. Importantly, ACS has been repeatedly linked to worse prognosis, and our study indicated only a trend towards a higher rate of MACCE in the acute setting, which was probably caused by a small sample size. Yet, the highest quartile of the ΔKIM-1 concentration predicted MACCE irrespective of admission type.

Our findings show that urinary KIM-1 may be used as a combined biomarker of renal function worsening and long-term cardiovascular morbidity and mortality in patients referred for coronary angiography. Patients with the postprocedural increase of urinary KIM-1 could be followed more carefully after the initial procedure to exclude possible disease progression. Still, larger studies are needed to fully validate the application of this kidney biomarker in patients with CAD.

In conclusion, an excessive increase of urinary KIM-1 concentrations after coronary angiography may help identify patients with worse 12-month prognosis. Patients with postprocedural CI-AKI are characterized by a considerably higher risk of MACCE.

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CONTRIBUTION STATEMENT MTW conceived the concept of the study. MTW, JC, and KM-S drafted the final version of the manuscript. MTW was involved in data collection. JC dealt with laboratory analysis. MTW was involved in statistical analysis. MTW and KM-S raised funds for the study. All authors edited and approved the final version of the manuscript.

REFERENCES

1 Narula A, Mehran R, Weisz G, et al. Contrast-induced acute kidney injury after primary percutaneous coronary intervention: results from the HORIZONS-AMI substudy. Eur Heart J. 2014; 35: 1533-1540.

2 Gąsior M, Pres D, Wojakowski W, et al. Causes of hospitalization and prognosis in patients with cardiovascular diseases. Secular trends in the years 2006-2014 according to the SILesian CARDiovascular (SILCARD) database. Pol Arch Med Wewn. 2016; 126: 754-762.

3 Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2002; 105: 2259-2264.

4 Valle JA, McCoy LA, Maddox TM, et al. longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. Circ Cardiovasc Interv. 2017; 10: e004439.

5 Uzunhasan I, Yildiz A, Arslan S, et al. Contrast-induced acute kidney injury is associated with long-term adverse events in patients with acute coronary syndrome. Angiology. 2017; 68: 621-626.

6 Kim JH, Yang JH, Choi SH, et al. Predictors of outcomes of contrast--induced acute kidney injury after percutaneous coronary intervention in patients with chronic kidney disease. Am J Cardiol. 2014; 114: 1830-1835.

7 Watabe H, Sato A, Hoshi T, et al. Association of contrast-induced acute kidney injury with long-term cardiovascular events in acute coronary syndrome patients with chronic kidney disease undergoing emergent percutaneous coronary intervention. Int J Cardiol. 2014; 174: 57-63.

8 Newhouse JH, Kho D, Rao QA, et al. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. AJR Am J Roentgenol. 2008; 191: 376-382.

9 Vanmassenhove J, Vanholder R, Nagler E, et al. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 2013; 28: 254-273.

10 Youssef AA, Chang LT, Hang CL, et al. Level and value of interleukin-18 in patients with acute myocardial infarction undergoing primary coronary angioplasty. Circ J. 2007; 71: 703-708.

11 Opstad TB, Arnesen H, Pettersen AÅ, et al. Combined Elevated Levels of the Proinflammatory Cytokines IL-18 and IL-12 Are Associated with Clinical Events in Patients with Coronary Artery Disease: An Observational Study. Metab Syndr Relat Disord. 2016; 14: 242-248.

12 Gao Y, Tong GX, Zhang XW, et al. Interleukin-18 levels on admission are associated with mid-term adverse clinical events in patients with ST--segment elevation acute myocardial infarction undergoing percutaneous coronary intervention. Int Heart J. 2010; 51: 75-81.

13 Sai E, Shimada K, Miyauchi K, et al. Increased cystatin C levels as a risk factor of cardiovascular events in patients with preserved estimated glomerular filtration rate after elective percutaneous coronary intervention with drug-eluting stents. Heart Vessels. 2016; 31: 694-701.

14 Htun NM, Magliano DJ, Zhang ZY, et al. Prediction of acute coronary syndromes by urinary proteome analysis. PLoS One. 2017; 12: e0172036.

15 Pedersen ER, Svingen GF, Schartum-Hansen H, et al. Urinary excretion of kynurenine and tryptophan, cardiovascular events, and mortality after elective coronary angiography. Eur Heart J. 2013; 34: 2689-2696.

16 Park M, Hsu CY, Go AS, et al. Chronic Renal Insufficiency Cohort (CRIC) Study Investigators; CKD Biomarkers Consortium. Urine kidney injury biomarkers and risks of cardiovascular disease events and all-cause death: The CRIC Study. Clin J Am Soc Nephrol. 2017; 12: 761-771.

17 Wybraniec MT, Chudek J, Bożentowicz-Wikarek M, et al. Prediction of contrast-induced acute kidney injury by early post-procedural analysis of urinary biomarkers and intra-renal Doppler flow indices in patients undergoing coronary angiography. J Interv Cardiol. 2017; 30: 465-472.

18 Wybraniec MT, Bożentowicz-Wikarek M, Chudek J, et al. Urinary renalase concentration in patients with preserved kidney function undergoing coronary angiography. Nephrology (Carlton). 2018; 23: 133-138.

19 Wybraniec MT, Bożentowicz-Wikarek M, Chudek J, et al. Pre--procedural renal resistive index accurately predicts contrast-induced acute kidney injury in patients with preserved renal function submitted to coronary angiography. Int J Cardiovasc Imaging. 2017; 33: 595-604.

20 Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007; 11: R31.

21 Hamm CW, Bassand JP, Agewall S, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011; 32: 2999-3054.

22 Paapstel K, Zilmer M, Eha J, et al. Early biomarkers of renal damage in relation to arterial stiffness and inflammation in male coronary artery disease patients. Kidney Blood Press Res. 2016; 41: 488-497.

23 Ichimura T, Bonventre JV, Bailly V, et al. Kidney injury molecule-1 (KIM--1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem. 1998; 273: 4135-4142.

24 Rosner MH, Ronco C, Okusa MD. The role of inflammation in the cardio-renal syndrome: a focus on cytokines and inflammatory mediators. Semin Nephrol. 2012; 32: 70-78.

25 Serwin NM, Wiśniewska M, Jesionowska A, et al. Serum levels of 12 renal function and injury markers in patients with glomerulonephritis. Pol Arch Med Wewn. 2016; 126: 483-493.

26 Torregrosa I, Montoliu C, Urios A, et al. Urinary KIM-1, NGAL and L-FABP for the diagnosis of AKI in patients with acute coronary syndrome or heart failure undergoing coronary angiography. Heart Vessels. 2015; 30: 703-711.

27 Lekawanvijit S, Kompa AR, Zhang Y, et al. Myocardial infarction impairs renal function, induces renal interstitial fibrosis, and increases renal KIM--1 expression: implications for cardiorenal syndrome. Am J Physiol Heart Circ Physiol. 2012; 302: H1884-1893.

28 Youssef AA, Chang LT, Hang CL, et al. Level and value of interleukin-18 in patients with acute myocardial infarction undergoing primary coronary angioplasty. Circ J. 2007; 71: 703-708.

29 Gao Y, Tong GX, Zhang XW, et al. Interleukin-18 levels on admission are associated with mid-term adverse clinical events in patients with ST--segment elevation acute myocardial infarction undergoing percutaneous coronary intervention. Int Heart J. 2010; 51: 75-81.

30 Manabe K, Kamihata H, Motohiro M, et al. Urinary liver-type fatty acid--binding protein level as a predictive biomarker of contrast-induced acute kidney injury. Eur J Clin Invest. 2012; 42: 557-563.

31 Xu J, Li G, Wang P, et al. Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. J Clin Invest. 2005; 115: 1275-1280.