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Creatine kinase-MB and red cell distribution width as predictors of contrast-induced nephropathy after percutaneous coronary intervention in acute myocardial infarction

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Abstract: Introduction: Contrast-induced nephropathy (CIN) is acute kidney injury (AKI), caused by administration of iodinated contrast media. The reported risk factors of CIN are: pre-existing renal dysfunction, admission anemia, diabetic nephropathy, old age, dehydration, high volume and osmolarity of administered contrast media. Patients with acute myocardial infarction (AMI) have threefold higher risk of developing CIN.
The aim of the study was to identify risk factors of CIN among patients who underwent percutaneous coronary intervention (PCI) due to AMI.
Methods: This retrospective single-centre study included 257 patients (mean age, 69.19 ± 1.4 years; men 66.15%) undergoing PCI for AMI between January 2012 and January 2013. Demographic data, type and location of MI, co-morbidities and laboratory results were analysed.
Results: CIN was found in 50 out of 257 patients (19.5%). Patients who developed CIN were older ($p = 0.001$), more commonly had chronic kidney disease ($p = 0.01$) and lower LVEF ($p = 0.01$). Baseline Red Cell Distribution Width (RDW) was significantly higher in the CIN group (14.85 ± 4.6 vs. 13.62 ± 1.3, $p = 0.001$). CK-MB levels on admission were significantly higher in the CIN group compared to the non-CIN group (95.6 ± 129.9 vs. 47.03 ± 61.3, $p = 0.001$). Multivariate model including "classical" CIN risk

factors revealed that only baseline CK-MB level (p = 0.001), age >75 years (p = 0.001) and baseline RDW (p = 0.03) were independent predictors for the development of CIN.
C o n c l u s i o n: In conclusion, increased CK-MB on admission as a surrogate of time of ischemia, and increased RDW levels on admission as a marker of chronic inflammation are independently associated with higher risk of CIN among patients treated with primary PCI.

Key words: coronary angiography, contrast agents, primary PCI, acute renal disease.

Background

Contrast-induced nephropathy (CIN) is acute kidney injury (AKI), caused by administration of iodinated contrast media, that may lead to kidney insufficiency and end-stage renal disease [1]. The incidence of CIN reported in the literature can range between 1 and 50%, largely depending on the definition of CIN used and co-morbidities of the study population. The reported risk factors of CIN are: pre-existing renal dysfunction, diabetic nephropathy, old age, dehydration, high volume and osmolarity of administered contrast media. The most commonly used definition of CIN is an absolute increment of serum creatinine (SCr) exceeding 0.5 mg/dl or a relative increase of 25% over the baseline level within 72 hours of contrast administration [2]. Jin *et al.* reported that development of CIN after percutaneous coronary intervention (PCI) in the course of acute myocardial infarction (AMI) was associated with the increased mortality rate and end-stage renal disease (25.4% in CIN group vs. 6.3% in non-CIN group, p <0.001). In the CIN group 45.9% of patients developed chronic kidney disease and thus had higher incidence of death or dialysis. The risk was lower for patients in the CIN group who developed transient kidney insufficiency (defined as kidney function recovery after 1 month) and was the lowest in the non-CIN group (34.1%, 17.7% and 6.3%, respectively; p <0.001) [3]. Patients with chronic kidney disease (CKD) have the higher risk of the sudden cardiac death and this risk increases with the progression of renal dysfunction [4]. Since CKD is an important risk factor of CIN, it is crucial to avoid deterioration of kidney function in these patients. In the research of Santos *et al.* the risk factors of CIN in the univariate logistic regression analysis were: old age, LVEF ≤40% and Killip classification ≥2, whereas in the multivariate analysis no independent predictors of CIN were found [5]. Ivanes *et al.* found that only the glomerular filtration rate and cardiogenic shock at admission were independent variables predicting CIN [6]. We aimed to assess which routinely available clinical parameters may be helpful in the identification of patients at risk of CIN after PCI in the course of MI.

Materials and methods

Study population

Our retrospective single-centre study included all adult patients undergoing primary coronary intervention (PCI) for acute myocardial infarction (AMI). Both non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) patients hospitalized between January 2012 and January 2013 in the Department of Interventional Cardiology John Paul II Hospital in Krakow were included. AMI was diagnosed according to the Third Universal Definition of Myocardial Infarction announced in 2012 by ESC [7].

Exclusion criteria were end stage renal failure requiring dialysis and exposure to contrast media within 7 days before the index procedure.

Methods

The database included basic demographic data, type and location of MI, co-morbidities and laboratory results listed in Table 1. Particular emphasis was placed on the co-morbidites that are reported to be risk factors of CIN such as pre-existing chronic kidney disease (eGFR <60 ml/min/1.73 m^2), arterial hypertension, diabetes mellitus. In addition, we analyzed the presence of obesity defined as BMI ≥30 kg/m^2, hyperlipidemia, peripheral arterial disease, tobacco smoking and severe left ventricle systolic dysfunction (LVEF <30%). Factors related to procedure included culprit artery, contrast type and amount, as well as contrast volume per kilogram.

All baseline blood samples were obtained immediately after patient's admission to the Emergency Department, including: sCr, complete blood count (CBC) and cardiac necrosis markers: high-sensitivity troponin T (hsTnT), creatine kinase (CK) and creatine kinase-MB (CK-MB). Creatinine measurements were repeated at 24, 48 and 72 hours after index procedure. Estimation of the glomerular filtration rate was based on the modification of diet in renal disease (MDRD) equation. All the collected blood samples were processed in the central hospital laboratory.

Statistical analysis

Quantitative parameters were expressed as the mean value ± standard deviation. Qualitative parameters were coded using Arabic numerals. The data were analyzed using STATISTICA 10.0 software suite (StatSoft). The Shapiro-Wilk test and the Kolmogorov-Smirnov test with the Lilliefors correction were used to verify the normality of distribution of results. Depending on the result of the normality of distribution, the data were analyzed using parametric or non-parametric tests. For all variables, both qualitative and quantitative, a univariate regression analysis was

performed. The null hypothesis (H0) was rejected at the established level alpha lower than 0.05.

Results

Baseline characteristics

During 13 months of the study duration 455 patients were admitted to the department due to AMI. Of this group, 257 patients with complete data on renal function at baseline and during the 3-day follow-up period were included in the study. 198 patients were excluded due to insufficient data, mainly lack of second or third creatinine measurement in most of cases due to early discharge before day 3 after uncomplicated procedure. Mean age was 69.19 ± 1.4 years and 170 (66.15%) were males. CIN, defined as an absolute increment of more than 0.5 mg/dl or a relative increase by more than 25% over the baseline SCr level within 72 hours of contrast administration, was found in 50 out of 257 patients (19.5%). The study population was divided into "CIN Group" and "non-CIN Group". Overall, the mortality rate in our population was 2.3% and was significantly higher in the CIN Group (4 (8%) vs. 2 (1%); p = 0.003). Baseline clinical and procedural characteristics and laboratory examination results are shown in Table 1.

Table 1. Clinical characteristics of study population and subgroups with or without CIN.

		Total population (n = 257)	CIN (+) (n = 50)	CIN (–) (n = 207)	P value
Age	years (± SD)	69.15 (± 11.4)	74.7 (± 11.6)	67.8 (± 11.0)	0.001
Age >75	years (%)	88 (34%)	30 (60%)	58 (28%)	0.01
Women	n (%)	87 (34%)	23 (46%)	64 (31%)	0.43
Mortality rate	n (%)	6 (2.3%)	4 (8%)	2 (1%)	0.003
BMI	kg/m^2	27.4 (± 5.52)	27.16 (± 4.49)	27.5 (± 5.72)	0.38
LVEF	% (± SD)	43.54 (± 13.2)	38.75 (± 14.9)	44.43 (± 12.8)	0.01
LVEF <30	n (%)	29 (11%)	12 (24%)	17 (8.2%)	0.001
Risk factors					
Diabetes	n (%)	96 (37%)	26 (52%)	70 (34%)	0.38
Arterial hypertension	n (%)	222 (86%)	42 (84%)	180 (87%)	0.8
Dyslipidemia	n (%)	197 (77%)	37 (74%)	160 (77%)	0.78
Current smoker	n (%)	32 (12%)	2 (4%)	30 (14%)	0.47
Peripheral artery disease	n (%)	24 (9%)	7 (14%)	17 (8%)	0.18
Chronic kidney disease	n (%)	93 (36%)	25 (50%)	68 (33%)	0.01

Table 1. Cont.

		Total population (n = 257)	CIN (+) (n = 50)	CIN (–) (n = 207)	P value
Diagnosis					
STEMI	n (%)	118 (46%)	30 (60%)	88 (43%)	
NSTEMI	n (%)	139 (54%)	18 (36%)	121 (58%)	
Laboratory data					
Hct	n (%)	40.7 (± 5.2)	39.7 (± 6.1)	41.03 (± 4.9)	0.1
RDW	n (%)	13.87 (± 2.59)	14.85 (± 4.6)	13.62 (± 1.3)	0.001
hsTnT	ng/ml (± SD)	0.64 (± 3.08)	1.24 (± 2.9)	0.5 (± 1.2)	0.001
CK-MB	U/l (± SD)	56.48 (± 81.4)	95.6 (± 129.9)	47.03 (± 61.3)	0.001
CK-MB >55	n (%)	82 (25.3%)	20 (40%)	47 (22.7%)	0.01
CPK	U/l (± SD)	475.49 (± 764.42)	745.1 (± 1157.92)	410.05 (± 620.26)	0.02
SCr	µmol/l (± SD)	100.9 (± 48.8)	120.9 (± 87.6)	96.1 (± 31.8)	0.43
eGFR	ml/min/1.73 m^2 (± SD)	65.14 (± 18.9)	58.13 (± 24.0)	66.85 (± 17.1)	0.26
PCI data					
Contrast volume	ml (± SD)	244.15 (± 91.5)	233.3 (± 88.9)	246.75 (± 92.16)	0.22
Contrast vol. >100 ml	n (%)	233 (90%)	46 (92%)	187 (90%)	0.54
Contrast vol. >200 ml	n (%)	103 (40%)	17 (34%)	86 (42%)	0.33
Contrast vol. >300 ml	n (%)	77 (30%)	11 (22%)	66 (32%)	0.15
Contrast vol./kg ml/kg	(± SD)	3.41 (± 6.37)	3.01 (± 1.27)	3.68 (± 7.84)	0.95
Culprit artery					
Left main coronary artery	n (%)	4 (2%)	0	4 (2%)	ANOVA 0.083
LAD artery	n (%)	87 (34%)	23 (46%)	64 (31%)	
Circumflex artery	n (%)	67 (26%)	14 (28%)	53 (26%)	
Right coronary artery	n (%)	83 (32%)	10 (20%)	73 (35%)	

BMI — body mass index, CK-MB — creatine kinase-MB, CPK — creatine phosphokinase, eGFR — estinated glomerular filtration rate, Hct — hematocrit, hsTnT — high sensitivity troponin T, LAD — left anterior descending, LVEF — left ventricle ejection fraction, NSTEMI — non-ST-segment elevation myocardial infarction, PCI — percutaneous coronary intervention, RDW — red cell distribution width, SCr — serum creatinine, STEMI — ST-segment elevation myocardial infarction.

Patients who developed CIN were older (p = 0.001), had higher prevalence of chronic kidney disease (p = 0.01) and lower LVEF (p = 0.01) (Fig. 1). The incidence of diabetes mellitus and hypertension was not significantly different between the two groups. No significant differences in gender or BMI were identified between the groups. Baseline hematocrit levels were significantly lower in patients who developed CIN.

Baseline eGFR and serum creatinine levels were not significantly different between the groups. Baseline Red Cell Distribution Width (RDW) was substantially higher in the CIN group (14.8 ± 4.6 vs. 13.6 ± 1.3, p = 0.001). CK-MB levels at admission were significantly higher in the CIN group compared to the non-CIN group as well (95.6 ± 129.9 vs. 47.03 ± 61.3, p = 0.001) (Fig. 2). Baseline hsTnT and CK levels were also higher in the CIN group (1.2 ± 2.9 vs. 0.5 ± 1.2; p = 0.001 and 745.1 ± 1157.92 vs. 410.05 ± 620.26; p = 0.02, respectively). The most prevalent culprit vessel was the left anterior descending artery in the CIN group and right coronary artery in the non-CIN group, but the difference was not statistically significant. Average amount of injected contrast was 244.15 ± 91.5 ml. More than 200 ml of contrast was used in 103 patients and more than 300 ml was administered to 77 patients. Injected contrast type and volume did not differ significantly between the groups. Moreover, amount of administrated contrast per kilogram was not significantly different between the groups.

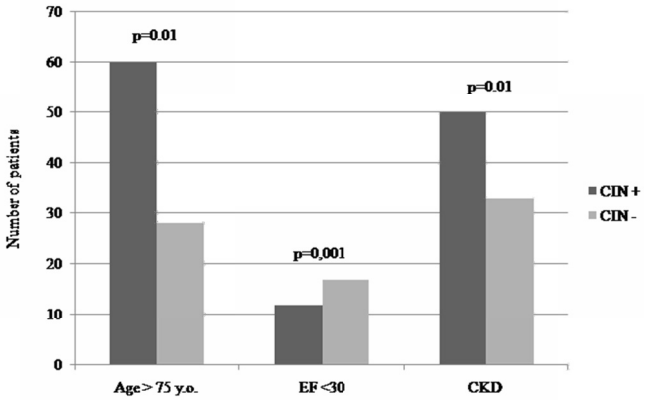

Fig. 1. Significantly different characteristics between the CIN and non-CIN groups. EF — ejection fraction, CKD — chronic kidney disease.

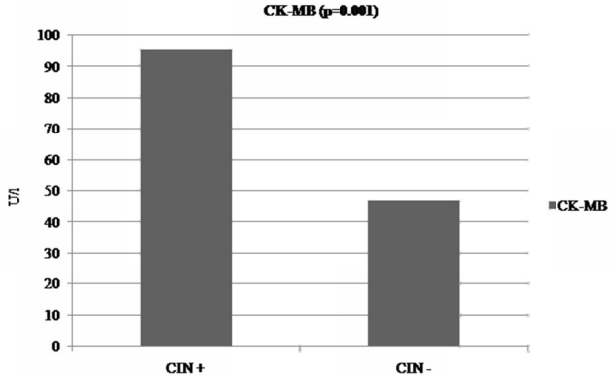

Fig. 2. CK-MB levels in the CIN and non-CIN groups. CK-MB — creatine kinase-MB.

Predictive factors of CIN

To assess independent predictors of CIN as a dependent variable, stepwise logistic regression was performed. Initially, we analyzed all the univariate associations and demonstrated in the univariate model a significant positive association between development of CIN and baseline CK-MB level, age above 75 years, smoking history, CKD, LVEF and STEMI presentation (Table 2). Baseline hsTnT and CPK level, as well as baseline sCr level and eGFR) also reached statistical significance. In order to include only one of the associated variables in our multivariate analysis, we investigated CK-MB and CKD further. Multivariate model revealed that only baseline CK-MB level (p = 0.002), age >75 years (p = 0.002) and baseline RDW (p = 0.02) were independent predictors of CIN development after urgent PCI in patients with AMI (Table 3) (Fig. 3). There was no significance in the Hosmer-Lemeshow test indicating that the model was properly matched (χ^2 = 3.36, p = 0.91).

Table 2. Predictive factors of CIN in AMI — univariate analysis.

	P value	OR [95% CI]
Age (years)	**0.001**	**1.06 [1.03–1.09]**
Age >75 years	0.001	**1.96 [1.42–2.71]**
Female gender	**0.046**	**1.38 [1.01–1.89]**
Obesity	0.540	1.11 [0.79–1.57]
LVEF	**0.009**	**0.97 [0.95–0.99]**
Risk factors		
Diabetes	0.089	1.32 [0.96–1.81]
Arterial hypertension	0.810	0.95 [0.65–1.49]
Dyslipidemia	0.790	0.95 [0.66–1.37]
Current smoker	**0.027**	**0.25 [0.06–1.09]**
Peripheral artery disease	0.210	1.36 [0.85–2.19]
Chronic kidney disease	**0.015**	**1.49 [1.08–2.04]**
Diagnosis		
STEMI	**0.026**	**1.42 [1.04–1.95]**
Laboratory data		
RBC	0.580	1.00 [1.0–1.0]
Hct	0.137	0.96 [0.9–1.01]
hsTnT	**0.018**	**1.20 [1.02–1.41]**
CK-MB	**0.001**	**1.01 [1.00–1.01]**

Table 2. Cont.

	P value	OR [95% CI]
CK-MB >55 U/l	**0.020**	**2.23 [1.16–4.28]**
RDW	**0.002**	**1.28 [1.07–1.54]**
CPK	**0.012**	**1.00 [1.00–1.00]**
SCr	**0.004**	**1.01 [1.00–1.02]**
eGFR	**0.004**	**0.98 [0.96–0.99]**
PCI data		
Contrast volume	0.360	0.998 [0.995–1.002]
Contrast volume >100 ml	0.530	1.60 [0.35–7.34]
Contrast volume >200 ml	0.330	0.85 [0.61–1.18]
Contrast volume/kilogram	0.690	0.96 [0.8–1.16]

CK-MB — creatine kinase-MB, CPK — ctreatine phosphokinase, eGFR — estinated glomerular filtration rate, Hct — hematocrit, hsTnT — high sensitivity troponin T, LVEF — left ventricle ejection fraction, PCI — percutaneous coronary intervention, RDW — red cell distribution width, SCr — serum creatinine, STEMI — ST-segment elevation myocardial infarction.

Table 3. Predictive factors of CIN in AMI — multivariate analysis.

	P value	OR [CI]
Age >75	**0.002**	**3.11 [1.50–6.40]**
Female gender	0.94	1.03 [0.46–2.32]
Obesity	0.64	1.22 [0.53–2.80]
LVEF	0.06	0.97 [0.95–1.00]
Diabetes	0.38	1.44 [0.64–3.26]
Arterial hypertension	0.64	0.76 [0.23–2.45]
Dyslipidemia	0.28	1.74 [0.63–4.75]
Current smoker	0.57	0.61 [0.11–3.28]
Chronic kidney disease	0.5	1.34 [0.58–3.08]
HCT	0.96	1.00 [0.93–1.07]
CK-MB	**0.002**	**1.01 [1.00–1.01]**
RDW	**0.02**	**1.30 [1.04–1.61]**
Contrast volume >200 ml	0.36	0.69 [0.31–1.53]

CK-MB — creatine kinase-MB, Hct — hematocrit, LVEF — left ventricle ejection fraction, RDW — red cell distribution width.

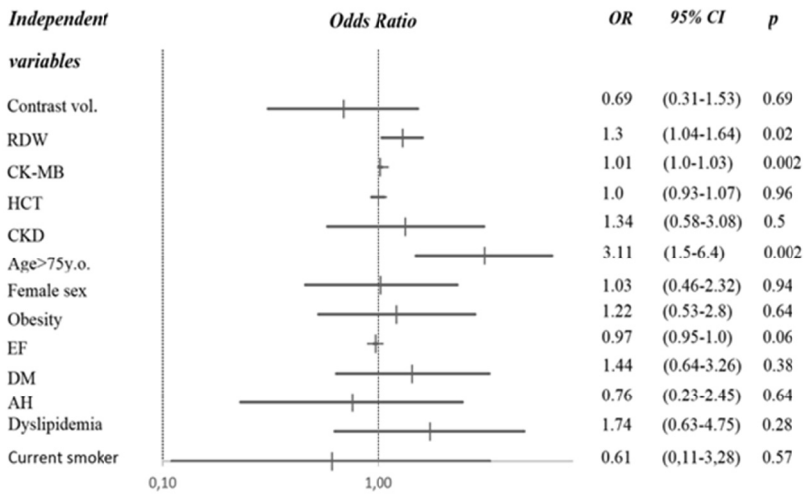

Fig. 3. Odds ratios (OR) and 95% confidence intervals (CI) of CIN risk factors in the multivariate logistic regression analysis. Vol. — volume, RDW — red cell distribution width, CK-MB — creatine kinase-MB, Hct — hematocrit, CKD — chronic kidney disease, EF — ejection fraction, DM — diabetes mellitus, AH — arterial hypertension.

Discussion

In our study we investigated predictors of contrast induced nephropathy among patients in acute settings of myocardial infarction. This group may be at a particular risk of CIN because many risk factors may be present in this population such as low hydration, decreased cardiac output causing renal hypoperfusion, drugs that compromise renal function and could not be discontinued prior to the procedure e.g. metformin. The main finding of our study was that risk factors for the development of CIN in the case of myocardial infarction (with exception to age), differ from classical predictors of AKI among patients undergoing elective procedures. Our data indicate that CK-MB as a surrogate for the objectively measured time of ischemia and elevated levels of RDW as a marker of inflammation and high oxidative stress were found to be independent predictors of CIN in patients treated with primary PCI. Prolonged hemodynamic deterioration as well as significant arrhythmias and conductance disturbances resulting from MI may lead to reduced renal blood flow due to vasoconstriction and impaired vasodilatation of cortical- and outer medullary vasculature, release of reactive oxygen species and direct tubular toxicity [1]. This hypoxic change depending on the duration of ischemia and its degree of severity may lead to reversible loss of renal function without structural damage but also in severe cases to irreversible loss or delayed restoration of renal function [8, 9]. Our findings were in line with previous reports suggesting a connection between

the longer time to reperfusion and the presence of CIN in patients undergoing primary PCI [10, 11].

High RDW as measurement of anisocytosis, which is related to impaired erythropoiesis and erythrocyte degradation and may reflect chronic inflammatory process and high level of oxidative stress [12, 13]. The higher level of RDW, interpreted as a marker of chronic inflammation in a group of 4159 patients, was a known risk factor for MI, increased in-hospital and long-term mortality among patients suffering from MI stroke, and symptomatic HF in patients with CAD [14]. Elevated RDW is also associated with increased levels of proinflammatory cytokines such as hsCRP, tumor necrosis factor TNF and interleukin 6 [15, 16]. In our group increased RDW levels on admission were associated with the development of CIN during the first three days of hospitalization. Similarly to our findings Kurtul *et al.* found that increased RDW levels at baseline were significantly associated with increased risk of CIN in patients who underwent urgent PCI due to ACS [17]. These observations were consistent with the report of Mizuno concerning the predictive value of RDW levels for the CIN development among 102 patients with STEMI treated with primary PCI [18]. Since RDW is a standard laboratory test available in every CBC result, it may also be easily used in CIN risk assessment in ACS patients treated with PCI.

As expected, old age was associated with the occurrence of CIN, both in univariate and multivariate regression analyses. It is known that the advanced age is associated with a decline in GFR and older patients tend to have more comorbidities. Increased risk of CIN probably results from the combination of a more severe coronary disease with a longer interventional procedure, an increased rate of heart failure associated with administration of intravenous diuretics and presence of a congestion being a contraindication to intravenous hydration. Higher proportion of diabetes and arterial hypertension in the elderly, leading to microvascular renal lesions, may also contribute to the higher risk of CIN [2].

The incidence of CIN in our study was 19.5%, which is a similar result to the studies that evaluated the occurrence of CIN among patients with ST-elevation MI. However such prevalence is substantially higher compared to the general population of patients undergoing radiological examinations with contrast media administration [19].

Our study group was admitted to the hospital in the acute setting, so the patients usually could not be properly hydrated and at that period no protocol of routine intravenous hydration was used. Such a procedure, recommended by the CIN Consensus Working Panel was introduced later [20]. The risk factors of CIN were common in our study group and they partially overlapped with risk factors of coronary artery disease. Although only 6 patients died in our population, CIN was strongly associated with the higher mortality rate. This confirms that the development of CIN is an important negative prognostic factor in patients after PCI due to AMI similar as in previous studies [21, 22].

Early identification of the subgroup of patients with particularly high risk of CIN could allow to plan strict follow-up of kidney function and receive best possible care. The study revealed that several variables reported to date as CIN risk factors were associated with CIN in the univariate analysis. They included: old age, female gender, low ejection fraction, cigarettes smoking, chronic kidney disease as well as its biochemical markers (creatinine level and eGFR), STEMI, RDW, biochemical tests for myonecrosis such as hsTnT, CK-MB and CPK. However, in the multivariate analysis only the advanced age, RDW and time of ischemia measured as CK-MB were found to be independent predictors of CIN in AMI patients treated with urgent primary PCI.

Although of borderline significance, CK-MB was another independent predictor of CIN. The underlying reason may be the fact that baseline CK-MB correlates with the time of myocardial ischemia in ACS. Long time of ongoing ischemia may affect cardiac output, causing hypoperfusion of numerous organs including kidneys. Concomitant administration of contrast media may increase the risk of CIN. According to our best knowledge, no studies have investigated the relationship between baseline CK-MB and CIN in patients with ACS. As CK-MB is a laboratory test performed in almost every patient with ACS it might be useful in CIN risk assessment in this clinical setting.

Several classical risk factors were not predictive of CIN in our population. Surprisingly, the volume of contrast medium was not significantly correlated with the occurrence of CIN. Advanced skills of the operators allowed to use minimal necessary contrast volumes. In most patients the volume injected was lower than 200 ml and did not exceed 400 ml of contrast in any of patient in this group. Modern contrast agent used in our patients may also explain this difference in comparison with older studies. Our population benefited from the use of low-osmolarity agents, which are considered to be less nephrotoxic. In our cohort, diabetes did not emerge as a predictor of CIN. Although it did not reach statistical significance, diabetes tended to be more prevalent among the patients with CIN.

Limitations

The study is retrospective but complete data was obtained in majority of cases. It was not possible for the patients whose clinical course was uncomplicated and therefore had creatinine level test ordered only once after procedure. It was because ordering laboratory tests repeatedly in patients with uneventful clinical course may have been regarded as excessive and unnecessary. Nevertheless, in these patients there was only a slight chance of CIN, since they had uneventful clinical course and few if any risk factors. However, they had to be excluded from the study and it is therefore possible that such a selection bias caused relatively high incidence of CIN in the presented analysis.

Conclusion

In conclusion our findings suggest that in the context of AMI, unlike the case of elective procedures, independent predictors of CIN are CK-MB levels on admission as an objective surrogate of ischemic time and RDW levels as a marker of increased oxidative stress and inflammation associated with myocardial necrosis.

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Conflict of interest

None declared.

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