

The ratio of contrast volume to glomerular filtration rate predicts in-hospital and six-month mortality in patients undergoing primary angioplasty for ST-elevation myocardial infarction

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Abstract

Background: *The aim of this study is to determine the impact of ratio of contrast volume to glomerular filtration rate (V/GFR) on development of contrast-induced nephropathy (CIN) and long-term mortality in patients with ST-segment elevation acute myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).*

Methods: *A total of 645 patients with STEMI undergoing primary PCI was prospectively enrolled. CIN was defined as an absolute increase in serum creatinine > 0.5 mg/dL or a relative increase > 25% within 48 h after PCI. The study population was divided into tertiles based on V/GFR. A high V/GFR was defined as a value in the third tertile (> 3.7).*

Results: *Patients in tertile 3 were older, had higher rate of smoking, diabetes mellitus and CIN, lower left ventricular ejection fraction, hemoglobin, and systolic and diastolic blood pressure compared to tertiles 1 and 2 ($p < 0.05$). V/GFR was found an independent predictor of in-hospital and 6-month mortality. We found 2 separate values of V/GFR for 2 different end points. While the ratio of 3.6 predicted in-hospital mortality with 78% sensitivity and 82% specificity, the ratio of 3.3 predicted 6-month mortality with 71% sensitivity and 76% specificity. Survival rate decreases as V/GFR increases both for in-hospital and during 6-month follow-up. Diabetes mellitus and multivessel disease were other predictors of in-hospital mortality.*

Conclusions: *High V/GFR level is associated with increased in-hospital and long-term mortality in patients with STEMI undergoing primary PCI. (Cardiol J 2015; 22, 1: 101–107)*

Key words: contrast-induced nephropathy, contrast volume to glomerular filtration rate ratio, ST-segment elevation myocardial infarction

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Introduction

Decreased glomerular filtration rate (GFR) is an important predictor of adverse cardiovascular events in acute coronary syndromes [1–5]. Patients with normal renal functions who undergo percutaneous coronary interventions (PCI) are also at risk of adverse events due to contrast-induced nephropathy (CIN) [6, 7].

Contrast volume is a modifiable major risk factor for CIN and closely related with in-hospital mortality [8–10]. Recently, the ratio of contrast volume to GFR (V/GFR) was found a predictor of increase in creatinine values and CIN following PCI [11–13]. However, the impact of V/GFR on short- and long-term prognosis after primary PCI has not been evaluated so far. Therefore, we aimed to investigate the impact of V/GFR for predicting adverse cardiac events after primary PCI for ST-segment elevation acute myocardial infarction (STEMI) [14].

Methods

Study population

We prospectively enrolled 645 consecutive patients with STEMI who were admitted to the Emergency Department and underwent urgent cardiac catheterization procedures between December 2009 and July 2011. The patients were assigned into tertiles according to their V/GFR. The patients were enrolled into the study if they fulfilled the following criteria: (i) the onset of symptoms presenting within 12 h (typical chest pain lasting for > 30 min); (ii) ≥ 1 mm ST-segment elevation in at least 2 contiguous electrocardiogram (ECG) leads except V_2 – V_3 which required 1.5 mm for female and 2 mm for male patients or new onset left bundle-branch block; (iii) treatment with primary PCI (angioplasty and/or stent deployment). All primary PCI procedures were performed in a single high-volume tertiary center (> 3,000 PCI/year) by expert operators performing more than 75 PCIs per year (15 of them are primary PCI). The study protocol was approved by the Institutional Ethics Committee.

Analysis of patient data

The cardiovascular history, demographic information, and risk factors (diabetes mellitus, smoking, hypertension and hypercholesterolemia) of the patients were obtained from their medical records. Reperfusion time and door-to-balloon time were also recorded. On admission, blood values

were obtained from all patients. Serum creatinine was also measured before the angiography procedure and within 48 h afterwards. A 12-lead ECG was recorded in each patient just after hospital admission, and the myocardial infarction type was also obtained from the ECGs. Twenty four to 72 h after revascularization, a transthoracic echocardiography was performed by using system V (Vingmed, GE, Horten, Norway) with a 2.5-MHz phased-array transducer, and the left ventricular ejection fraction (LVEF) was calculated using a modified Simpson's method [15].

Coronary angiography and PCI

All patients were given a chewable 300 mg aspirin and 600 mg loading dose of clopidogrel before coronary angiography. After the procedure, all patients were prescribed 100 mg of aspirin and 75 mg of clopidogrel daily. Angiographic data of the patients were assessed from the catheter laboratory records. All procedures were performed via femoral route. A nonionic, low osmolar contrast agent (Iopromide, 370 mg/mL Bayer HealthCare Pharmaceuticals Inc., Germany) was utilized in all patients. The artery that was anticipated to be unhindered was injected first. Heparin (100 IU/kg) was administered when the coronary anatomy was first described. After visualizing the left and right coronary arteries, 200 μ g of nitroglycerine was selectively injected into the infarct related artery (IRA) to exclude a possible coronary spasm. Angiographic evaluation was made by visual assessment. Primary angioplasty (including balloon angioplasty and/or stent implantation) was performed just for IRA according to lesion type. For each procedure, interventional success at the acute phase was defined as reducing to < 30% of obstruction and stenosis of the IRA with Thrombolysis in Myocardial Infarction 3 flow just after primary angioplasty. The use of tirofiban was left to the discretion of the operator.

Definitions

The time from symptom onset to the coronary reperfusion was defined as time to reperfusion with balloon inflation. Door-to-balloon time was defined as the time between Emergency Department and balloon inflation. Patients were assessed according to Killip clinical examination classification [16]. Advanced heart failure was defined as New York Heart Association (NYHA) class 3 and 4. Non-diabetic patients were defined as the patients without documented diabetes using neither oral hypoglycemic agents nor insulin treatment at

admission. Hypercholesterolemia was defined as total cholesterol of at least 200 mg/dL or use of cholesterol-lowering drugs. A family history of coronary artery disease (CAD) was defined as a documented case of CAD in a parent or sibling before 60 years of age. Anemia was defined as hemoglobin concentration lower than 13 mg/dL in men and 12 mg/dL in women. We defined repeat target vessel revascularization as a necessity for PCI or coronary surgery due to restenosis or reocclusion of the IRA. Reinfarction was defined as an elevation of serum creatinine kinase myocardial band level more than 2 times from the upper limit of normal and ST-segment re-elevation.

The estimated GFR (eGFR) was calculated by using the modified Modification of Diet in Renal Disease (MDRD) equation [17]: $eGFR \text{ (mL/min/1.73 m}^2\text{)} : 186 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} (\times 0.742 \text{ if women})$, where SCr defines serum creatinine concentration in milligrams per deciliter as measured immediately before PCI, and age is given in years. The V/GFR ratio was calculated by dividing the volume of contrast medium used during the PCI by the patient's eGFR. CIN was defined as an increase in SCr by either $> 0.5 \text{ mg/dL}$ or by $> 25\%$ from baseline within the first 2–3 days after contrast medium administration, when another explanations for renal insufficiency have been excluded [18].

Statistical analysis

Analyses were performed using SPSS Statistics, version 17.0 (SPSS Inc, Chicago, IL). To test the distribution pattern, the Kolmogorov-Smirnov method was used. Data were summarized as a mean standard deviation, median and interquartile range, or proportions. The Student's t-test was used to compare data with normal distribution and the Mann-Whitney U test was applied to compare the data without normal distribution. Categorical variables were compared with the χ^2 test. The effects of different variables on clinical outcomes were calculated by univariate analysis for each. The variables for which the unadjusted p value was < 0.10 in Cox regression analysis were identified as potential risk markers and included in the multivariable Cox regression model. An exploratory evaluation for additional cut points of different variables was performed using the receiver operating characteristic (ROC) curve analysis. The survival curve during hospitalization for V/GFR was analyzed using the Kaplan-Meier method, and statistical assessment was performed using the log-rank test. A p value < 0.05 was considered statistically significant for all analyses.

Results

Baseline characteristics of the study population are shown in Table 1. Patients in tertile 3 were older, had higher rate of smoking, diabetes mellitus and CIN, lower LVEF, hemoglobin, and systolic and diastolic blood pressure compared to tertiles 1 and 2 ($p < 0.05$).

Nineteen patients died during hospital stay and 34 patients died within the first 6 months of the follow-up period. Univariable and multivariable Cox regression analyses revealed CIN (HR 2.99, confidence interval [CI] 1.96–4.02, $p < 0.001$) and V/GFR (HR 1.07, CI 1.04–1.12, $p < 0.001$) as the predictors of in-hospital mortality (Table 2). Diabetes mellitus and multi-vessel disease were the other predictors of in-hospital mortality. CIN (HR 2.17, CI 1.47–2.84, $p < 0.001$) and V/GFR (HR 1.08, CI 1.02–1.15, $p < 0.003$) also predicted 6-month mortality (Table 3). Apart from these findings, presence of diabetes mellitus, multi-vessel disease, and admission Killip class more than 1 independently predicted 6-month mortality.

A ROC curve analysis revealed V/GFR ratio of 3.6 for prediction of in-hospital mortality with 78% sensitivity and 82% specificity (C statistics = 0.850, $p < 0.001$). The V/GFR ratio of 3.3 predicted 6-month mortality with 71% sensitivity and 76% specificity (C statistics = 0.790, $p < 0.001$). Figure 1 shows Kaplan-Meier curves among tertiles for both in-hospital and 6-month mortality which represent worse outcome as the V/GFR increases.

Discussion

Our study results showed that V/GFR ratio independently predicted both in-hospital and 6-month mortality in patients undergoing primary PCI. To our knowledge, our study is an original one in terms of evaluating the impact of V/GFR ratio on long-term mortality in STEMI patients undergoing primary PCI.

Patients who present with acute myocardial infarction and decreased GFR have higher mortality rate even after optimal treatment [19]. Presence of calcified atherosclerosis, large vessel remodeling, left ventricular hypertrophy, chronic volume overload, and pressure overload in renal failure was thought to play a role in this situation. Additionally, comorbidities accompanying impaired GFR could explain this higher mortality after acute myocardial infarction [20–22]. Furthermore, cardiovascular medications and invasive therapeutic strategies are underused in patients with poor

Table 1. Clinical and hematologic characteristics of ratio of contrast volume to glomerular filtration rate (V/GFR) tertiles.

Variables	V/GFR			P
	Tertile 1 (n = 215) 1.34 (1.1–1.6)	Tertile 2 (n = 215) 2.1 (1.9–2.4)	Tertile 3 (n = 215) 3.7 (3.2–4.8)	
Age [years]	50.0 ± 10.1	56.6 ± 11.4	62.8 ± 11.8	< 0.001
Male	200 (93%)	183 (85%)	167 (77%)	< 0.001
Female	15 (7%)	32 (15%)	48 (22%)	
Diabetes mellitus	32 (15%)	39 (18%)	55 (26%)	0.016
Hypertension	79 (37%)	90 (42%)	96 (45%)	0.240
Peripheral arterial disease	6 (3%)	4 (2%)	7 (3%)	0.655
Post TIMI 1	4 (2%)	3 (1%)	10 (5%)	
Post TIMI 2	9 (4%)	11 (5%)	10 (5%)	0.097
Post TIMI 3	202 (94%)	201 (94%)	195 (91%)	
Contrast-induced nephropathy	17 (8%)	23 (11%)	48 (22%)	< 0.001
Ejection fraction [%]	45 (40–50)	45 (40–50)	45 (40–50)	0.004
Glucose [mg/dL]	131 (112/169)	137 (113/166)	147 (119/196)	0.007
HDL [mg/dL]	37 (31–43)	38 (31–43)	38 (32–48)	0.147
LDL [mg/dL]	124.8 ± 36.6	122.7 ± 36.4	111.8 ± 37.6	< 0.001
Triglycerides [mg/dL]	148 (100/199)	142 (95/205)	126 (90/176)	0.022
Hemoglobin [g/L]	14.6 (13.6/15.5)	14.1 (13.1/15.1)	13.5 (12.5/14.9)	< 0.001
Total WBC [$\times 10^9/L$]	12.3 (10.3/14.6)	12 (10.1/14)	11.9 (10/14.6)	0.561
Peak CK-MB [U/L]	141 (75–216)	123 (69–211)	149 (81–271)	0.098
Early creatinine [mg/dL]	0.8 (0.7–0.9)	0.9 (0.8–1)	1 (0.85–1.2)	< 0.001
Creatinine clearance [mL/min]	136 (122–166)	106 (89–129)	76 (61–100)	< 0.001
Contrast volume [mL]	200 (100–200)	200 (200–300)	300 (200–400)	< 0.001
Killip class > 1	5 (2.3%)	7 (3.3%)	29 (13.5%)	< 0.001
Heart rate [bpm]	80 (72–84)	80 (70–85)	80 (70–85)	0.835
In-hospital mortality	0 (0%)	4 (2%)	15 (7%)	< 0.001
Six-month mortality	2 (1%)	8 (4%)	24 (11%)	< 0.001

TIMI — Thrombolysis in Myocardial Infarction; HDL — high density lipoprotein; LDL — low density lipoprotein; WBC — white blood cell; CK-MB — creatinine kinase myocardial band

Table 2. Significant predictors of in-hospital mortality in univariable and multivariable Cox regression analyses.

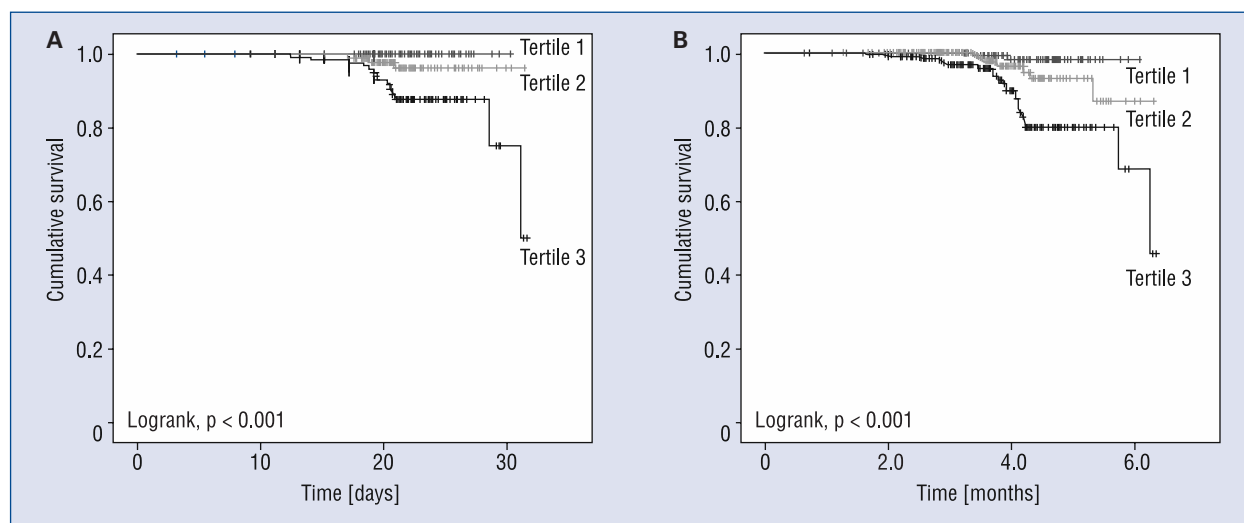
Variables	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.05 (1.02–1.07)	< 0.001	1.03 (0.95–1.13)	0.245
Male/female	1.02 (0.80–1.19)	0.189	–	–
Diabetes mellitus	2.92 (1.97–5.89)	< 0.001	2.01 (1.39–2.64)	< 0.001
Smoking	1.18 (1.11–1.25)	0.001	0.88 (0.75–1.00)	0.122
Killip class > 1	15.2 (6.65–21.7)	< 0.001	7.71 (3.78–23.9)	< 0.001
Ejection fraction	1.51 (0.40–4.66)	< 0.001	2.91 (1.26–6.72)	0.012
Contrast induced nephropathy	4.05 (2.02–6.27)	< 0.001	2.99(1.96–4.02)	< 0.001
V/GFR	1.08 (1.03–1.13)	< 0.001	1.07 (1.04–1.12)	0.001
Low density lipoprotein	1.14 (0.88–1.41)	0.622	–	–
Multi vessel disease	2.51 (1.53–3.04)	< 0.001	2.55 (1.74–3.34)	< 0.001
Hemoglobin	1.22 (1.10–1.35)	0.003	1.17 (1.08–1.26)	0.007

HR — hazard ratio; CI — confidence interval; V/GFR — contrast volume-glomerular filtration rate ratio

Table 3. Significant predictors of mortality at 6-month follow-up in univariable and multivariable Cox regression analyses.

Variables	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.09 (1.02–1.16)	0.002	1.00 (0.94–1.07)	0.344
Male/female	0.88 (0.77–1.02)	0.207	–	–
Diabetes mellitus	3.01 (1.88–4.17)	< 0.001	2.61 (1.89–3.23)	< 0.001
Smoking	1.04 (0.94–1.15)	0.411	–	–
Killip class > 1	10.4 (5.71–16.4)	< 0.001	4.64 (3.27–5.18)	< 0.001
Ejection fraction	1.04 (1.02–1.06)	< 0.001	1.02 (1.01–1.03)	0.009
Contrast induced nephropathy	3.84 (2.47–5.22)	< 0.001	2.17 (1.47–2.84)	< 0.001
V/GFR	1.06 (1.01–1.12)	< 0.001	1.08 (1.02–1.15)	0.003
Low density lipoprotein	1.04 (0.84–1.26)	0.577	–	–
Multi vessel disease	2.88 (1.85–3.92)	< 0.001	2.61 (1.92–3.53)	< 0.001
Hemoglobin	1.27 (1.13–1.43)	0.001	1.22 (1.10–1.36)	0.024

HR — hazard ratio; CI — confidence interval; V/GFR — contrast volume-glomerular filtration rate ratio

**Figure 1.** Kaplan-Meier curves of ratio of contrast volume to glomerular filtration rate (V/GFR) tertiles for in-hospital mortality [A] and 6-month mortality [B].

renal function [4, 22–24]. However, presence of normal renal function may not guarantee favorable outcomes in terms of CIN and renal deterioration following coronary angiography is still possible. The kidneys are vulnerable to contrast-induced toxicity during primary PCI, but the mechanism and role of contrast agents in the pathogenesis of acute renal damage remain controversial and are not completely understood. Direct contrast-related toxicity and renal ischemia may play an important role due to circulatory impairment. An increase in serum creatinine during the acute phase of STEMI

may be an indicator for more severe and extensive atherosclerosis and circulatory instability. Impaired renal function and radiographic contrast volume are important risk factors for development of CIN. Above all, the risk of CIN augments as the GFR values decrease [25]. As a major clinical determinant, the development of CIN is strongly associated with increased morbidity and mortality [26]. In 1 study, in-hospital mortality was found at a level of 22% among patients who developed CIN after PCI [25]. In another one, McCullough et al. [27] found an in-hospital mortality of 7% in patients who developed

CIN after PCI and did not need hemodialysis, and 36% among those who needed hemodialysis after PCI. The contrast volume is a modifiable factor for the development of CIN. In patients presented with STEMI who underwent primary PCI, in-hospital mortality and CIN are closely associated with the contrast volume [6].

The ratio of contrast volume to GFR was proposed as a predictor of early increase in serum creatinine undergoing PCI. The ratio of 3.7 for V/GFR was found the cut-off value for predicting this increase [13]. Mager et al. [14] studied the association between V/GFR, post-procedural CIN and 1-month mortality in patients with STEMI. In line with Laskey et al. [13], the ratio of > 3.7 was found to be associated with CIN and 1-month mortality.

In our study, V/GFR ratio was found an independent predictor of both in-hospital and 6-month mortality. We found 2 separate values of V/GFR for 2 different end points. The ratio of 3.6 predicted in-hospital mortality with 78% sensitivity and 82% specificity. On the other hand, the ratio of 3.3 predicted 6-month mortality with 71% sensitivity and 76% specificity. Our values are different from those of the previous studies regarding the cut off V/GFR ratios. As in line with previous studies, V/GFR was associated with worse outcomes. Among tertiles, tertile 3 had a worse survival rate. Survival rates decrease as V/GFR increases both for in-hospital and during 6-month follow-up periods.

Conclusions

V/GFR is an important parameter for predicting adverse events in STEMI patients undergoing primary PCI. Patients who had high V/GFR ratio should be followed closely to avert CIN especially in older patients with lower GFR. The impact of close follow-up on mortality and adverse events in high-risk population is unknown and needs further studies.

Conflict of interest: None declared

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