Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.10.678 2020;27(1):164-9

Original Article

Severity of coronary artery disease is associated with contrast induced nephropathy in patients with impaired renal function

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Abstract

Aim: Patients with acute coronary syndrome who underwent percutaneous coronary intervention (PCI) constitute the group with the highest risk of contrast-induced nephropathy development. Contrast media exposure might increase in patients who have lesions with >70% stenosis in the major epicardial arteries. Also, the impaired kidney function is associated with severity of coronary artery disease. We evaluated the relationship with severity of coronary artery disease (CAD) calculated by Gensini score and contrast induced nephropathy (CIN) in patients with mild renal insufficiency in acute coronary syndrome (ACS).

Material and Methods: We enrolled 227 patients with ACS who underwent percutaneous coronary intervention. Patients were divided into groups according to CIN development. Severity of CAD was evaluated by Gensini score. Logistic regression analysis (univariate and multivariate) was performed to evaluate the predictors of CIN using variables that are clinically related to CIN. The 95% confidence interval (CI) and odds ratios (OR) were presented. Receiver–operating characteristic (ROC) curve was performed to demonstrate the sensitivity and specificity of the Gensini score.

Results: A total of 69 (30.1%) patients with ACS had CIN. Compared to CIN (-) patients, CIN (+) patients had higher Gensini score, incidence of diabetes mellitus and amount of contrast media. Multivariate logistic regression analyses demonstrated that Gensini score, DM and amount of contrast media were independent risk factors for CIN development ($p < 0.05$ for all parameters).

Conclusion: Gensini score, which simply shows severity of CAD, may be helpful in the determination of CIN risk in patients with ACS.

Keywords: Acute renal injury; SYNTAX; severity of coronary artery disease

INTRODUCTION

Contrast-induced nephropathy (CIN) is defined as the impairment of renal function within 48-72 hours after the administration of intravenous or intra-arterial contrast media. (1). CIN incidence varies with a wide range of 4% to 24% following interventional cardiac procedures depending on the patients' risk factors (2). Patients undergoing percutaneous coronary intervention (PCI) due to acute coronary syndrome (ACS) are at high risk of CIN development (3). It is known that CIN is associated with increased in-hospital mortality and long-term adverse clinical events. Several new potential biomarkers of CIN have been reported, but the pathophysiological mechanism of CIN development is not clear (4). Patients' pre procedural renal functions and the type and amount of contrast media are well-known predictors of CIN (5). It is thought that there might be different mechanisms about CIN development after coronary procedures in patient with ACS. Recently, there have been shown that the contrast media exposure increased in patients who have lesions with >70% stenosis in the major epicardial arteries (6). Also, it has been investigated that there is a significant relationship between impaired kidney function and severity of coronary artery disease (CAD) (7). Gensini Score (GS) which defines the grade of stenosis starting with 25 % obstruction to total occlusion of the coronary artery and including the anatomical location is a widely used for quantifying the severity of CAD (8). In our study, we aimed to evaluate the association between GS and CIN development in patients with ACS undergoing PCI.

Received: 29.10.2019 **Accepted:** 17.12.2019 **Available online:** 18.02.2020
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MATERIAL and METHODS

Study Population

We retrospectively reviewed 416 patients who were admitted to our hospital with ACS who underwent percutaneous coronary intervention (PCI) within 24 hours after admission. Acute coronary syndrome included ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina pectoris (UA). The fourth universal definition of myocardial infarction was used for diagnosis of ACS (9). There was no sex or age restriction. The exclusion criteria were cardiogenic shock on admission, thrombolytic therapy within 24 hours, hypotension (<90/60mmHg), and administration inotropic therapy, history of hemodialysis treatment, admission glomerular filtration rate (GFR) < 60 or >90 mL/min/1.73 m2, contrast media exposure within 10 days, steroid usage, malignancy, systemic inflammatory disease, autoimmune disease, liver disease and undergoing emergency cardiac surgery, prior history of coronary artery bypass grafting (CABG) and known severe CAD. The final study population consisted of 227 patients. The study protocol was approved by our local Institutional Ethics Committee and performed in accordance with the Declaration of Helsinki.

Study protocol

Baseline characteristics such as history, coronary angiography data, and blood biochemical indicators of all patients were collected from our hospital electronic data system. The presence of comorbidities was determined by directly taking the patients' histories. Venous blood was drawn from a vein at the time of hospital admission. Baseline hemoglobin, urea, creatinine levels, lipid parameters were measured on admission. Estimated GFR (eGFR) was calculated using the Cockcroft-Gault formula at admission. Serum creatinine levels were measured at 24th, 48th, and 72th h during hospitalization. CIN was defined as increase in serum creatinine level ≥0.3 mg/dL or 25% compared with admission level within 72 h after the contrast media exposure (10). Patients who had blood pressures ≥ 140/90 mm Hg in repeated measurements, and antihypertensive drug users were considered as hypertensive patients. Patients with HgbA1c ≥ 6.5 mg/dL or who used antidiabetic medications were considered as diabetic patients.

The coronary angiographies were performed and interpreted experienced interventional cardiologists. The PCI was performed using the standard Judkins technique via femoral or radial approach. In addition to 300 mg of chewable aspirin, each patient was given 600 mg of clopidogrel or 60 mg of prasugrel or 180 mg of ticagrelor. All patients with STEMI were treated with primary PCI. We used a nonionic low-osmolality contrast media for all patients during PCI and amount of contrast media was noted per each patient. CAD was defined as ≥50% narrowing in the luminal diameter of the left main artery or ≥70% narrowing in other coronary artery branches. Gensini score was calculated in all the participants for quantifying the degree of coronary artery lesions by two cardiologists who did not know the patient's clinic. Gensini score was calculated by grading each coronary stenosis as follows: 1 point for ≤25% narrowing, 2 points for 26 to 50% narrowing, 4 points for 51 to 75% narrowing, 8 points for 76 to 90% narrowing, 16 points for 91 to 99% narrowing, and 32 points for total occlusion (8).

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are expressed as a percentage. Comparisons between two groups were made using the T-tests for continuous variables and chi-square tests for categorical variables. Logistic regression analysis (univariate and multivariate) was performed to evaluate the predictors of CIN using variables that are clinically related to CIN. The 95% confidence interval (CI) and odds ratios (OR) were presented. Receiver–operating characteristic (ROC) curve was performed to demonstrate the sensitivity and specificity of the Gensini score and the cutoff value for predicting CIN. Two-tailed p values < 0.05 were considered statistically significant. Statistical Package for the Social Sciences software version 20.0 (SPSS Institute Inc, Chicago, Illinois) was used for all statistical analyses.

RESULTS

A total of 227 patients with ACS who underwent PCI were included in the study (mean age 65.9 +10.8 years; 71.4% male). CIN was defined in 69 (30.4%) patients (mean age 66.1±10.8 and 69.6% men). There were 158 (69.6%) patients without CIN (mean age 65.8 ± 10.8 and 72.2% men). Totally, 37 (16.2%) patients were had STEMI (27 patients [17.2%] in CIN (-) and 10 patients [14.5%] in CIN (+) group). There were 64 patients with NSTEMI and remaining 126 patients were unstable angina. The demographic, clinical, angiographic and procedural characteristics of the study groups are summarized in Table 1. Both study groups were similar concerning age, sex, body mass index (BMI), hypertension (HT), dyslipidemia, and smoking habits (for all variables p values were > 0.05).

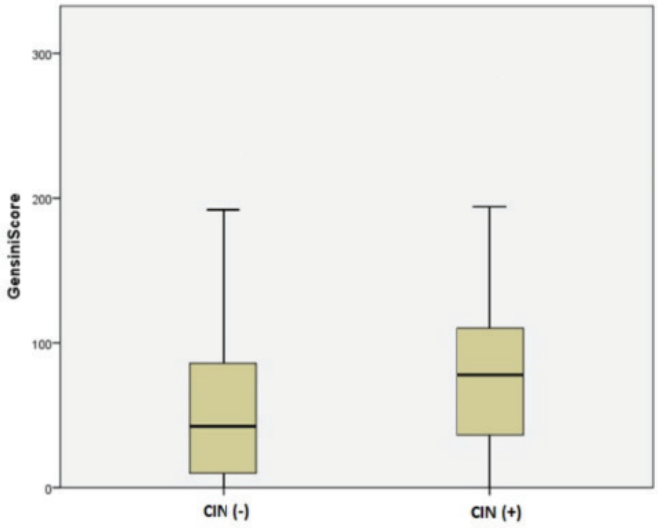

Figure 1. Gensini scores between contrast induced nephropathy (-) and (+) groups. Abbreviations: CIN, contrast induced nephropathy

Gensini scores were significantly higher in patients with CIN compared to without CIN (Figure 1). Patients with CIN had a significantly higher prevalence of diabetes mellitus (DM), and the amount of contrast media (p = 0.019 and p < 0.001, respectively). There were no differences between two groups in albumin levels, cholesterol panels, admission levels of serum creatinine, glucose and hemoglobin, and ejection fractions at 24th hour.

The well-known predictors of CIN (age, presence of DM and HT, hemoglobin levels, admission creatinine levels, amount of contrast media) and Gensini score were included in the regression analyses (Table 2). Gensini score (odds ratio [OR]: 1.009, 95% confidence interval [CI]: 1.003-1.014, p = 0.002), DM (OR: 2.003, 95% CI: 1.127-3.561, p = 0.018) and amount of contrast media (OR: 1.056, 95% CI: 1.023 -1.089, p = 0.001) were univariantly associated with development of CIN.

Table 1. Baseline Clinical, Laboratory and Angiographic Characteristics According to Contrast-Induced Nephropathy

Variables	CIN (-) n: 158	CIN (+) n: 69	P
Age, years	65.8 ± 10.8	66.1 ± 10.8	0.866
Sex, male %	114 (72.2)	49 (69.6)	0.750
BMI, kg/cm2	28.3 ± 4.5	30.2 ± 6.0	0.055
DM, n (%)	55 (35.3)	36 (52.2)	**0.019**
HT, n (%)	117 (75.5)	56 (81.2)	0.392
Dyslipidemia, n (%)	76 (48.1)	33 (47.8)	0.970
Smoking, n (%)	65 (41.4)	21 (30.4)	0.138
Gensini Score	53.8 ± 49.7	79.4 ± 58.1	**0.001**
Amount of Contrast Media, mL	158.46 ± 55.2	186.6 ± 53.4	<0.001
Hgb, g/dL	12.9 ± 2.0	12.7 ± 1.8	0.570
Admission Crea, mg/dL	1.2 ± 0.2	1.2 ± 0.3	0.831
Admission GFR, mL/min/1.73m2	58.5 ± 14.1	58.6 ± 17.0	0.986
Crea, 72th hour, mg/dL	1.16 ± 0.24	1.6 ± 0.71	<0.001
Admission Urea, mg/dL	49.9 ± 19.2	51.1 ± 21.9	0.675
Glucose, mg/dL	134.8 ± 71.7	149.3 ± 70.3	0.162
Albumin, mg/dL	4.1 ± .04	4.0 ± 0.4	0.190
Total protein, mg/dL	7.2 ± 0.6	7.0 ± 0.8	0.254
Total cholesterol, mg/dL	176.3 ± 49.3	183.7 ± 46.6	0.290
HDL, mg/dL	41.0 ± 11.5	40.2 ± 10.4	0.603
LDL, mg/dL	105.3 ± 36.8	110.9 ± 37.0	0.296
Triglyceride, mg/dL	164.1 ± 109. 1	160.9 ± 111.2	0.841
EF, %	48.9 ± 11.4	46.0 ± 12.2	0.102
STEMI, n (%)	27 (17.2)	10 (14.5)	0.699

CIN, contrast induced nephropathy; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; Hgb, hemoglobin; Crea, creatinine; GFR, glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; EF, ejection fraction; STEMI, ST elevation myocardial infarction

Table 2. Univariate and Multivariate Logistic Regression Analysis Showing Independent Predictors of Contrast-Induced Nephropathy

Variables	Univariate			Multivariate		
	OR	(95% CI)	p	OR	(95% CI)	p
Age	1.002	0.976–1.029	0.865	1.007	0.975–1.039	0.684
HT	1.339	0.691–2.834	0.351	1.079	0.478–2.437	0.854
DM	2.003	1.127–3.561	**0.018**	2.730	1.378–5.409	**0.004**
Gensini Score	1.009	1.003–1.014	**0.002**	1.010	1.004–1.016	**0.002**
Hgb	0.959	0.829–1.109	0.569	0.973	0.814–1.163	0.763
Admission Crea	1.147	0.328–4.011	0.830	1.529	0.339–6.897	0.580
Amount of Contrast Media	1.056	1.023–1.089	**0.001**	1.063	1.026–1.100	**0.002**
Media						

Abbreviations: HT, hypertension; DM, diabetes mellistus; Hgb, hemoglobin; Crea, creatinine

Multivariate logistic regression analysis demonstrated that higher Gensini score, presence of DM and higher amount of contrast media were independent predictors of CIN (OR: 1.010, 95% CI: 1.004-1.016, p = 0.002; OR: 2.730, 95% CI: 1.378-5.409, p = 0.004; OR: 1.063, 95% CI: 1.026 -1.100, p = 0.002, respectively). The cutoff value of Gensini score was defined as 76.5 with a sensitivity of 50% and specificity of 70.1% for CIN prediction (AUC, 0.635; 95% CI: 0.556 - 0.713; p = 0.001; Figure 2).

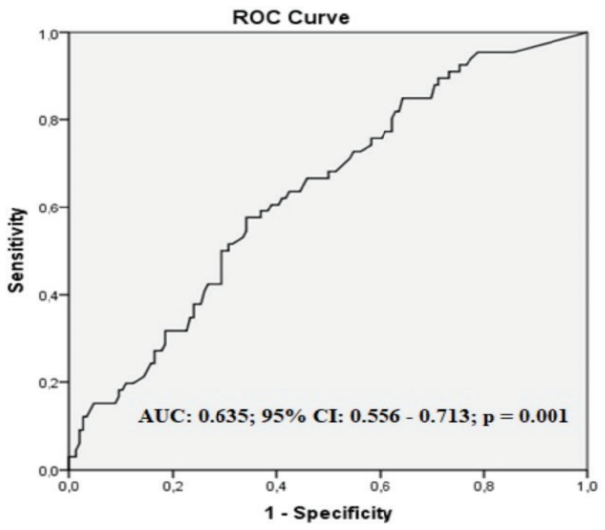

Figure 2. The receiver–operating characteristic (ROC) curve of Gensini Score for Predicting Contrast Induced Nephropathy. Abbreviations: AUC, area under curve; CI, confidence interval

DISCUSSION

Our current study demonstrated an association between contrast-induced nephropathy and the severity of CAD in patients with mildly impaired renal function who underwent percutaneous coronary intervention. Also, the presence of DM and a higher amount of contrast agent were the other independent predictors in our multivariate analysis. It was previously shown that the severity of CAD was associated with CIN but to our best knowledge, this study is the first that demonstrated the relation with severity of CAD as quantified using Gensini scores which is well known and simple scoring system and CIN (11). In contrast to other studies, the presence of hypertension and admission eGFR cannot reach significance in our study group. These results may be depended on our inclusion criteria about mild renal insufficiency.

The prevalence of CIN development was relatively high in our study group. The incidence of CIN varies between 4% and 24% depending on the type of procedure (2). While radio diagnostic procedures cause CIN development around 5%, CIN incidence can increase up to 34% after invasive coronary procedures depending on the patients' comorbidities (12). It was demonstrated that renal insufficiency and acute myocardial infarction represent a high-risk combination in CIN development, also as seen in our study (13,14). Many studies recently established that CIN development after ACS is strongly associated with adverse cardiac events and mortality (15,16). In a recent randomized trial, Schönenberger E. at al. investigated the relationship between intravenous versus intra-arterial contrast agent administration and to acute kidney injury in patients with atypical chest pain and suspected coronary artery disease. They concluded that obstructive CAD is a strong predictor of CIN whether the administration way of contrast agent (17). In another study, Caspi et al. compared patients with STEMI who underwent reperfusion therapy with fibrinolytic and primary percutaneous intervention. They found that there was not a significant relationship between contrast media exposure and acute

kidney injury, there might be different mechanisms in ACS (18). Consequently, these studies suggest that CIN after cardiac procedures has a multifactorial nature. Thrombus burden in infarct-related artery, the myocardial area under infarct risk, pre-procedural hyperglycemia, and the higher inflammatory condition might be related to the acute kidney injury in patients with ACS (19-21).

Scoring systems are used to determine the severity and complexity of coronary artery disease. Gensini score (GS) and SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) scores are the most commonly used systems for this purpose. While the GS is used means of quantifying severity of angiographic atherosclerosis, the SYNTAX Score evaluates complexity and clinical impact of CAD (8,22). Gensini score is older but simpler and more suitable for quantifying the severity of CAD.

The pathophysiology of CIN involves a complex interaction of several mechanisms. Although the pathophysiological mechanisms are not completely explained, free radical damage by oxidative stress, vasoconstriction and endothelial dysfunction in renal vessels are thought to play key roles in acute renal injury (23). According to our results, two possible mechanisms may be thought between the severity of CAD and CIN development in patients with ACS: first, increased concentrations of inflammatory cytokines additional to chronic inflammation of atherosclerosis; second, systemic endothelial dysfunction during ACS in patients with severe CAD. Atherosclerosis is a chronic subclinical inflammatory arterial disease, characterized by an impaired lipid metabolism and immune response. Numerous studies have found that inflammation is involved in the development and progression of CAD (24). It has been shown that higher inflammatory cytokines are related to the extent, complexity, and severity of coronary atherosclerosis (25). Systemic inflammation leads to cytokine release. These cytokines cause renal medullary vasoconstriction and disturb renal medullary blood flow and consequently, renal hypoxia and injury occur (26). In a recent study, Díez-Delhoyo F at al. showed that microvascular and endothelial dysfunction in the non-culprit artery in patients with STEMI who have the multi-vessel disease is very common. They found functional abnormalities in 93% of the patients (27). ACS that is added to an existing inflammatory condition in patients with severe CAD might cause systemic endothelial dysfunction and cause acute kidney injury (28,29).

The major limitation of our study is retrospective and single centered design. For this reason, we did not achieve enough data about previous medications (Renin–angiotensin–aldosterone system blockers, etc.). Another limitation is that there was no data about acute inflammatory cytokines and endothelial dysfunction markers. In addition, patients with severely decreased renal function (eGFR <30 mL/min/1.73m2) and normal/high renal function (> 90 mL/min/1.73m2) were not enrolled in our study. So, our results may not represent these patients.

CONCLUSION

The development of contrast-induced nephropathy due to percutaneous coronary intervention in patients with impaired renal function is related to high Gensini score, presence of DM and higher amount of contrast agent. Gensini score which is calculated simply after coronary angiography may be used to predict contrast-induced nephropathy.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Approval was obtained from the Ethics Committee of Şişli Hamidiye Etfal Hospital (Date: 28.05.2019, Decision no: 2411)

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