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Prognostic value of serum calprotectin level in elderly diabetic patients with acute coronary syndrome undergoing percutaneous coronary intervention

A Cohort study

Wutang Zhang*, Yongmei Kong, Lizhi Wang, Lizhong Song, Lijuan Tan, Xiaobo Xue

Abstract

Patients with acute coronary syndrome (ACS) have an increased serum level of calprotectin. The purpose of present study was to analyze the prognostic significance of serum calprotectin levels in elderly diabetic patients underwent percutaneous coronary intervention (PCI) due to ACS.

A total of 273 consecutive elderly diabetic patients underwent PCI for primary ACS were enrolled. Serum calprotectin levels were measured before PCI, and baseline clinical characteristics of all patients were collected. All patients were followed up at regular interval for major adverse cardiovascular events (MACEs) during 1 year after PCI. MACEs include cardiovascular death, nonfatal myocardial infarction, and target vessel revascularization (TVR). The predicting value of serum calprotectin for MACEs was analyzed by using univariate and multivariate analysis and receiver-operating characteristic curve (ROC).

At the endpoint of this study, 47 patients of all 273 patients had MACEs. According to optimal cutoff value of calprotectin for predicting MACEs by ROC analysis, all patients were stratified into a high calprotectin group and a low calprotectin group. The incidence rate of MACEs and TVR in high calprotectin group was prominently higher than that in low calprotectin group (21.9% vs 11.5%, $P = .02$). In multivariable COX regression analysis adjusting for potential confounders, serum calprotectin level remains as an independent risk predictor of MACE (hazard ratio, 1.56; 95% confidence interval [CI]: 1.08–4.62; $P = .01$).

In diabetic patients with a comorbidity of ACS, a high serum level of calprotectin is associated to a higher MACE rate after PCI.

Abbreviations: 95%CI = 95% confidence interval, ACS = acute coronary syndrome, DM = diabetes mellitus, HR = hazard ratio, LAD = left atrial diameter, LVEF = left ventricular ejection fractions, MACEs = major adverse cardiovascular events, PCI = percutaneous coronary intervention, ROC = receiver-operating characteristic curve, TIMI = thrombolysis in myocardial infarction flow, TVR = target vessel revascularization.

Keywords: acute coronary syndrome, calprotectin, diabetes mellitus, elderly, percutaneous coronary intervention

1. Introduction

Acute coronary syndrome (ACS) serves as one of the leading contributor of morbidity and mortality worldwide.[1,2] Percutaneous coronary intervention (PCI) has been considered as the most effective treatment approach for ACS.[3] However, the long-term prognosis of ACS following PCI remains poor.[4,5] It has been revealed that both age and diabetes mellitus (DM) are independent prognostic predictors of hospital mortality in ACS.[6] Diabetic elderly patients with ACS frequently have various chronic comorbidity and widely spread atherosclerotic disease, and pathologically present as diffuse and erosive lesion within small vascular, and have a worse outcomes after PCI.[7,8] Therefore, identification of indictors that can improve the risk prediction and stratification is important for improving the clinical efficacy of PCI in diabetic elderly patients with ACS.

Both old age and DM have been evaluated as the risk factors of ACS.[9,10] DM is significantly associated with hypertension, hyperlipidemia, and atherosclerosis, especially for elderly. Meanwhile, inflammation is significantly associated with the development of ACS.[11] Calprotectin, known as S100A8/A9, has been considered as an inflammatory marker mainly expressed in activated human neutrophils, monocytes, and macrophage, which also can promote atherosclerosis.[12] Furthermore, increased calprotectin level has been shown as a predictor for microvascular alterations in patient with diabetes.[13] It has been revealed that a significant higher serum calprotectin level can be observed in patients with ACS compared to patient with stable CAD.[14,15] However, the value of serum calprotectin level in

Editor: Ismaheel Lawal.

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Zhang W, Kong Y, Wang L, Song L, Tan L, Xue X. Prognostic value of serum calprotectin level in elderly diabetic patients with acute coronary syndrome undergoing percutaneous coronary intervention: A Cohort study. Medicine 2020;99:33(e20805).

Received: 28 January 2020 / Received in final form: 26 April 2020 / Accepted: 21 May 2020

http://dx.doi.org/10.1097/MD.0000000000020805

predicting post-PCI outcome for elderly diabetic patients with ACS has not been fully elucidated. Accordingly, the purpose of this study was to evaluate the prognostic value of serum calprotectin levels in elderly diabetic patients undergoing PCI for ACS.

2. Materials and methods

2.1. Patients

This study is a retrospective cohort analysis of a prospective registry database including all consecutive elderly (age ≥70 years) diabetic patients undergoing PCI for ACS between January 2015 and July 2019. The study was conducted according ethical guidelines of the Declaration of Helsinki, and which had also been approved by the ethics committee of the Shanxi Cardiovascular Hospital (No. C2019028). All enrolled participants were required for signed and written informed consents. Data concerning cardiovascular risk factors, previous comorbidities, laboratory tests, PCI, and medication were collected for all enrolled patients. The diagnosis of ACS was based on the European Society of Cardiology guidelines in 2015,[16] including ST-segment elevation myocardial infarction, none-ST-segment elevation myocardial infarction, and unstable angina pectoris. DM was diagnosed according to the Standards of Medical Care in Diabetes in 2016.[17] The exclusion criteria included previous myocardial infarction or coronary artery bypass grafting, history of organic heart disease, comorbidity of infectious or inflammatory disease, other anti-inflammatory drugs administration, acute liver or kidney dysfunctions, incompliance to long-term antiplatelet and anticoagulant treatments. All PCIs was performed by using drug-eluting stent according to the standard approach. The success criteria of PCI were the Thrombolysis in Myocardial Infarction Flow (TIMI) grade 3 and residual stenosis <10%. The perioperative and post-PCI appropriate treatments were conducted according to the discretion of the attending cardiologist. The data of all patients were collected from the hospital information system by 1 author and check by another author. The GRACE score was calculated according to corresponding guidelines.[18,19]

2.2. Laboratory analysis

Peripheral venous blood samples were collected before PCI, thus avoiding contamination with contrast fluid. All blood samples were centrifuged at 4000 rpm for 10 minutes to separate serum. Then, the separated serum was aliquoted into Eppendorf tubes and stored at –80°C for next analysis. The serum calprotectin level was detected by using a commercial calprotectin ELISA (double antibody sandwich ELISA method) test kit (Hycult Biotech Inc) according to the manufacturer's instructions. All routine laboratory tests were performed using the standardized detection methods at the Shanxi Cardiovascular Hospital. Left ventricular ejection fractions (LVEF) and left atrial diameter (LAD) were evaluated by echocardiography on admission.

2.3. Follow-up and clinical evaluation

All 273 patients were regularly followed each month after discharge by telephone communication or face-to-face clinic visiting (median follow-up duration, 12 months). The primary endpoint of this study was evaluated as 12-month major adverse cardiovascular events (MACEs). MACE referred to a composite of nonfatal myocardial infarction, cardiovascular death, and revascularization procedures.

2.4. Statistical analysis

Statistical analysis was conducted by using the SPSS 20.0 (IBM). $P < .05$ (2-sided) was considered as statistically significant. Normal distribution of data was evaluated by the Kolmogorov-Smirnov test. Continuous variables are expressed as mean ± standard deviations (SD), categorical variables as frequencies and percentages. The student t tests were used to compare continuous variables, whereas comparisons of categorical variables were conducted by χ^2 or Fisher exact test. Receiver-operating curves (ROC) were used to analyze the optimal cutoff value of calprotectin predicting 12-month post-PCI MACEs for diabetic patients with ACS. The relationship of clinical variables with MACEs was examined by univariate analysis and multivariate Cox proportional regression model, and an event-free survival curve was build based on the Kaplan-Meier method.

3. Results

3.1. Baseline characteristics

Baseline characteristics of enrolled patient groups based on the serum level of calprotectin were shown were presented in Table 1. During the study period, mean age of all enrolled patients was 63.4 ± 8.5 years, and 62.4% were male. The median level of serum calprotectin level was 4.1 (0.8–11.3) μg/mL. Serum calprotectin level <4.1 μg/mL in 122 patients (44.7%) and ≥4.1 μg/mL in 151 patients (55.3%). The mean value of GRACE risk score was 136.78 ± 38.83. The patients with a high calprotectin level had higher fasting plasma glucose and GRACE scores and lower high-density lipoprotein cholesterol (HDL-C) levels than those with a low calprotectin level (all $P < .05$, see Table 1).

3.2. Incidences of MACEs following PCI

During the 12-month follow-up, in whole group of 273 patients, 47 (17.2%) patients experienced MACEs, including 27 (9.9%) target vessel revascularization (TVR), 13 (4.8%) nonfatal myocardial infarction (MI), and 7 (2.6%) cardiac mortality. Compared with patients with a low calprotectin level, the patients with a high calprotectin level had a higher incidence of MACEs (21.9% vs 11.5%, $P = .02$). In details, there was no significant different was observed between groups regarding cardiac mortality (2.8% vs 2.0%, $P = .92$) and nonfatal MI (4.1% vs 5.3%, $P = .21$), but TVR (4.9% vs 13.9%, $P = .01$).

3.3. Predictive value of calprotectin level for MACEs

ROC analysis showed that area under the curve (AUC) of serum calprotectin level predicting MACEs was 0.79 (95% confidence interval [CI]: 0.63–0.97; $P < .01$), and optimal cutoff value was 3.8 μg/mL (Fig. 1). The Kaplan-Meier curve for MACEs free survival according to serum calprotectin level showed that there was a significant difference between groups ($P = .01$, Fig. 2).

In univariate analyses, serum calprotectin level was significantly associated to MACEs risks following PCI (hazard ratio [HR], 1.56; 95% CI: 1.08–4.62; $P = 0.01$). After adjustment for potential confounding factor including age, BMI, hypertension, hyperlipidemia, insulin therapy, ACEIs/ARBs use, statin use,

Table 1

Baseline characteristics of elderly ACS patients based on serum calprotectin levels.

Variables	Low calprotectin (<4.2 μg/mL, n = 97)	High calprotectin (≥4.2 μg/mL, n = 126)	*P*
General characteristics			
Age, y	78.4 ± 3.2	78.8 ± 4.3	.44
Male	51 (52.6%)	70 (55.6%)	.66
BMI, kg/m^2	25.4 ± 2.7	25.8 ± 3.1	.31
Hypertension	64 (65.9%)	78 (61.9%)	.53
Hyperlipidemia	41 (42.3%)	51 (40.5%)	.79
Chronic kidney disease	30 (45.1%)	48 (48.3%)	.27
Oral medication			
Insulin	21 (21.9%)	32 (25.4%)	.54
ACEIs/ARBs	63 (64.9%)	81 (64.3%)	.92
Statins	87 (92.6%)	114 (92.1%)	.85
Beta-blockers	66 (75.2%)	84 (72.2%)	.83
Laboratory tests			
LDL-C, mmol/L	2.26 ± 0.42	2.48 ± 0.56	<.01
HDL-C, mmol/L	1.31 ± 0.21	1.29 ± 0.21	.48
TC, mmol/L	4.32 ± 1.01	4.35 ± 1.02	.83
TG, mmol/L	2.12 ± 1.11	2.15 ± 1.25	.85
Cr, μmol/L	78.16 ± 12.11	76.42 ± 15.82	.37
eGFR, mL/min/1.73 m^2	72.32 ± 24.41	68.67 ± 18.55	.21
hs-CRP, ng/mL	6.62 ± 4.71	8.62 ± 5.78	<.01
PCI-related data			
Number of stents, per case	1.72 ± 1.12	1.73 ± 1.16	.95
GRACE score	131.26 ± 36.51	144.58 ± 35.61	<.01
LVEF, %	42.23 ± 11.05	43.32 ± 10.11	.44
LAD, mm	29.42 ± 2.62	30.12 ± 2.87	.06

ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin receptor blockers, BMI = body mass index, Cr = creatinine, HDL-C = high-density lipoprotein cholesterol, LAD = left atrial diameter, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fractions, TC = total cholesterol, TG = triglycerides.

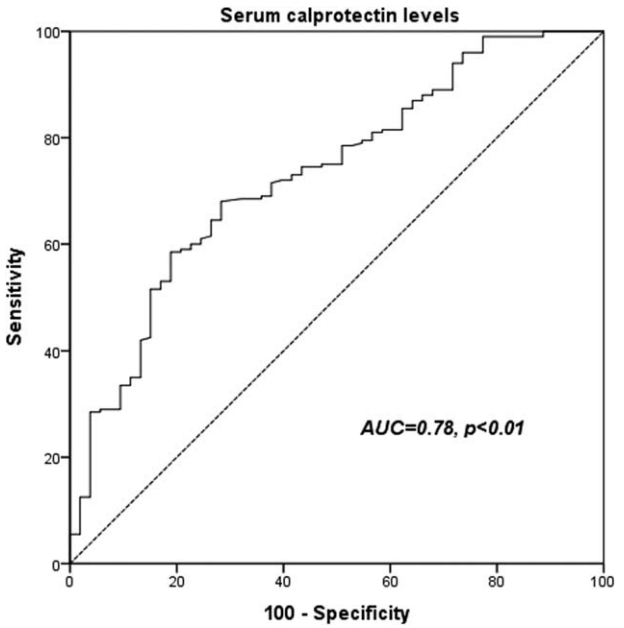

Figure 1. Receiver-operating characteristic curve for serum calprotectin level predicting MACEs. The areas under the curve were 0.79 with a 95% confidence interval (95% CI) for the area between 0.63 and 0.97.

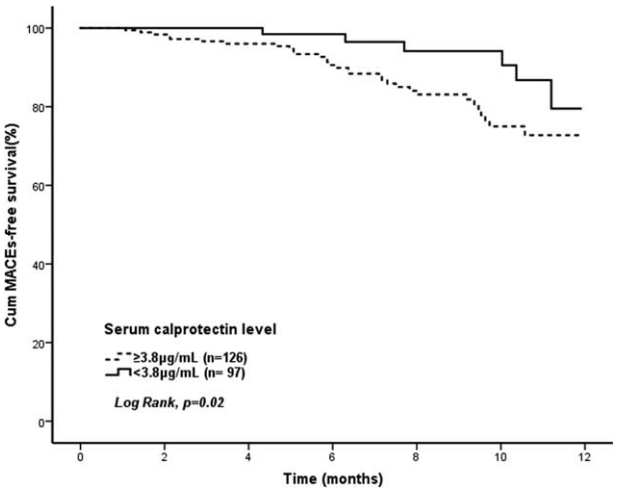

Figure 2. Kaplan-Meier event-free survival curves. The prognostic analysis revealed that patients with a lower serum calprotectin level had a better 12-month major adverse cardiovascular events (MACEs)-free survival than those with a higher serum calprotectin level ($P = .01$).

GRACE score, and LVEF, Cox proportional hazard regression analysis showed serum calprotectin level (HR, 2.11; 95% CI: 1.14–6.65; $P < 0.01$), GRACE score (HR, 2.38; 95% CI: 1.13–9.65; $P = 0.01$), and LVEF (HR, 0.82; 95% CI: 0.78–0.98; $P = .02$) were significant independent predictors for MACEs in DM patients (Table 2).

4. Discussion

In this study, we found that diabetic patients had a significant higher serum calprotectin level, which also significantly associated with plasma glucose, HDL-C, and GRACE score. Furthermore, in prognosis analysis, we found that serum calprotectin level was also significant related to the post-PCI outcome, and diabetics patients with a higher serum calprotectin level were presented as a higher risk level of developing MACEs comparing those with a lower calprotectin. Furthermore, the higher MACEs incidence in the poor glycemic controlled group was mainly contributed from a higher rate of TVR. The findings of our study revealed that serum calprotectin level could be used as an independent predictor for post-PCI outcome in diabetic patients with ACS.

Calprotectin is a heterocomplex of calcium-binding proteins released from neutrophils and monocytes, which has been considered as an effective inflammatory indictor of several inflammatory diseases.[20] As CAD is increasingly considered as a kind of inflammatory disease, calprotectin is associated with development of CAD, and functioned as a mediating factor of atherosclerosis. Viemann et al[21] incubated human microvascular endothelial cells with calprotectin and showed that calprotectin exerts effect on plate aggregation, inflammation, and endothelial permeability were increased. Ehlermann et al[22] showed calprotectin stimulated a proinflammatory response in a dose-dependent way, thus triggering atherosclerosis in diabetes. Such inflammation and atherosclerosis may result from calprotectin-stimulated NF-kappaB (NF-κB) activation induced by interaction of calprotectin and ligands of advanced glycation end products, which may further contribute to ongoing inflammation and vascular complications in CAD patients.[23] It has been

Table 2

Univariate and multivariate analyses of predictors for MACEs after PCI.

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, y	1.01	0.82–1.33	.24			
BMI, kg/m^2	0.99	0.86–1.35	.36			
Hypertension	1.02	0.89–1.47	.94			
Hyperlipidemia	0.85	0.63–1.13	.52			
Chronic kidney disease	1.01	0.98–1.04	.86			
Statin use	0.92	0.65–1.42	.54			
ACEIs/ARBs use	1.01	0.84–2.42	.42			
Number of stents, per case	1.01	0.85–1.12	.86			
GRACE score	2.79	1.01–5.68	.01	2.24	1.03–4.65	.01
LVEF, %	0.88	0.78–0.96	.02	0.72	0.68–0.99	.03
LDL-C, mmol/L	1.01	0.96–1.21	.52			
Calprotectin level	1.36	1.02–5.62	.02	2.23	1.26–7.62	<.01

95% CI = 95% confidence interval, ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin receptor blockers, BMI = body mass index, HR = hazard ratio, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fractions, MACE = major adverse cardiovascular events, PCI = percutaneous coronary intervention.

reported that calprotectin levels were significantly associated with ACS.[24,25] Furthermore, increased calprotectin levels were presented in coronary thrombi or coronary atherosclerotic plaques from patients with ACS.[26,27] In this study, we found that serum calprotectin level was significantly associated with incidence of MACEs following PCI, which was consistent with the conclusion of previous studies mentioned above.

Diabetic patients are generally characterized by chronic inflammation, insulin resistance, prolonged obesity, and dyslipidemia.[28] Catalan et al[29] revealed a potential role of calprotectin as a chemotactic factor in the macrophages recruitment, increased inflammation, and the development of obesity-associated comorbidities. Ortega et al[30] recently showed that serum levels of calprotectin were associated with inflammation independent of obesity in patients with DM. In the present study, we also found that diabetic patients had an increased serum level calprotectin and serum calprotectin level was significantly associated with HDL-C and FPG level, but not with BMI. Pedersen et al[13] reported that patients with DM had higher concentrations of plasma calprotectin, which were associated with myocardial ischemia, which was consistent with the results of our study. Furthermore, hyperglycemia, hyperinsulinemia, chronic inflammation, abnormal platelet function, and insulin resistance may chronically promote vascular neointimal hyperplasia following stent placement in diabetic patients, thereby resulting in development of in-stent restenosis.[31] In this study, we found that a high rate of TVR severs as a main contributor to a high incidence of post-PCI MACEs in diabetic patients, consistently indicting the relationship between in-stent restenosis risk and DM.

In present study, we found that elevated serum calprotectin levels were significantly with MACEs in ASC patients treated with pPCI. Although we did not clearly evaluate the underlying mechanisms of the relationship between serum calprotectin levels and post-PCI outcomes in diabetic patients with ACS, inflammation and atherosclerosis induced by calprotectin may be involved in this association. Meanwhile, we found that patients with a high calprotectin level have higher GRACE scores, indicating that patients with a higher calprotectin may have severer cardiovascular conditions. Furthermore, calprotectin can increase the thrombotic properties of platelets, which can result in additional cardiovascular morbidity.[32]

There were several potential limitations should be considered in the interpretation of the results of our study. The single-center design and short follow-up duration of this study may have influenced the generalization of the conclusion of this study to other centers or hospitals. Moreover, cutoff level of calprotectin was based on a statistic value from ROC analysis. Optimal cutoff level of serum calprotectin predicting clinical outcome after PCI should be evaluated by meta-analysis. Finally, the results of this study should be interpreted cautiously as a relatively small sample volume.

5. Conclusion

In conclusion, our findings demonstrated that diabetic patients with a lower serum level of calprotectin may obtain benefits of a lower risk of restenosis and a better post-PCI clinical outcome over 12-month follow-up.

Author contributions

Clinical studies: Lizhi Wang
Data acquisition: Lijuan Tan
Data analysis: Lizhi Wang
Definition of intellectual content: Wutang Zhang
Experimental studies: Lizhong Song
Guarantor of integrity of the entire study: Wutang Zhang
Literature research: Yongmei Kong
Manuscript editing: Wutang Zhang
Manuscript preparation: Wutang Zhang
Manuscript review: Wutang Zhang
Statistical analysis: Xiaobo Xue
Study concepts: Wutang Zhang
Study design: Wutang Zhang

Corrections

Yongmei Kong's name originally appeared incorrectly as Yongmei Wang and has since been corrected.

The author contributions have been added.

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