Original Article

Calprotectin Correlates with Reduced Level of LVEF and Occurrence of Cardiac Arrhythmia in STEMI Patients

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Abstract

Background: Calprotectin is recognized as a promising prognostic as well as a diagnostic marker of cardiac disorders. In the present study, we aimed to survey the efficiency of serum calprotectin levels in anticipating the severity of coronary artery disease (CAD) along with in-hospital major adverse cardiovascular events (MACE) in patients with ST-segment elevation (STEMI) underlying primary percutaneous coronary intervention (PCI).

Materials and Methods: A total of 97 patients with STEMI participated and were evaluated for in-hospital MACE for possible correlation with serum calprotectin.

Results: Increased levels of serum calprotectin showed positive and negative correlation with severity of coronary arteries and left ventricular ejection fraction (LVEF) of STEMI patients, respectively. Regarding in-hospital MACE, only arrhythmia showed a significant relationship in patients with high calprotectin levels.

Conclusion: High calprotectin levels may be a prognostic marker for occluded artery and LVEF in STEMI patients.

Keywords: Coronary occlusion, leukocyte L1 antigen complex, risk factors, ST-elevation myocardial infarction

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Introduction

Coronary artery disease (CAD) is mostly considered a coronary atherosclerotic disorder that leads to the narrowing of coronary artery, resulting in insufficient blood supply to the myocardium; myocardial infarction (MI) with ST-segment elevation (STEMI) is found to be its utmost acute advent.[1] Most of the time, a thorough thrombotic obstruction extending from an atherosclerotic plaque in a coronary vessel is implicated in the development of STEMI.[2] Moreover, primary percutaneous coronary intervention (PCI) has been introduced as a preferable reperfusion approach in patients presenting with STEMI but it is of note that it is not available for all clinics and hospitals, especially in marginal areas.[3] On the other hand, individual risk classification is vital to recognize high-risk patients for in-hospital major adverse cardiac events (MACE) after STEMI.[4] Therefore, early diagnosis of vascular anatomy including the number of involved coronary arteries and the severity of vascular occlusion along with early understanding of cardiac function serve as the most efficient approaches to restrict myocardial ischemia as well as infarct size, thereby decreasing the likelihood of post-STEMI problems such as MACE and finally heart failure.[1]

Currently, cardiac troponin has become a gold standard and dominant indicator for MI, but its limitation is that it does not show the injured area.[5,6] Calprotectin is a heterodimer protein also known as S100A8/A9, myeloid-related protein 8/14 or

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leukocyte L1 antigen complex, which is extensively localized in the cytosol of white blood cells, including monocytes and neutrophils. It is a useful marker of inflammation in inflammatory bowel disease. In recent decades, calprotectin has been found to be a promising marker of cardiovascular disorders.[7] In coronary arteries, calprotectin levels have been reported to elevate in vulnerable atherosclerotic plaques, which correlated with remarkable cardiac death and MI in patients suffering from acute coronary syndrome (ACS).[8] In addition, in patients presenting with comorbidity of diabetes and ACS, high levels of serum calprotectin were shown to be correlated with a significant risk of MACE.[9,10]

In spite of such findings, the correlation between serum calprotectin with severity and number of coronary stenosis, heart function, and in-hospital MACE among STEMI patients undergoing primary PCI is not clear. The aim of the present study was to survey the association between calprotectin with severity and number of injured vascular arteries, ejection fraction, and in-hospital MACE and also evaluate the significance of serum calprotectin in predicting the development of vascular occlusion in STEMI patients undergoing primary PCI.

Material and Methods

Patients and study design

The study cohort of this cross-sectional analysis comprised 97 STEMI patients aged 18–80 years who underwent primary PCI and had their possible in-hospital MACE evaluated between September 2022 and February 2023. Inclusion criteria were patients aged 18 to 80 years with STEMI, patients who have indications for angiography and primary PCI and those who give permission before blood sampling. Candidates fewer than 18 years and above 80 years, absence of ST-elevation, failure to perform angiography, candidates with current infection, missing demographic features, or written informed consent for sampling were excluded from the research. For this study, data of participants with STEMI was verified by a cardiologist. The study procedure was approved by the local Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1401.133). Written informed consent was provided by all participants.

Serum calprotectin measurement

Five mL of whole blood sample was collected instantly before coronary angioplasty for the analysis of calprotectin. The blood was left to clot prior to serum separation using centrifugation at 2400×g for 10 min at 4°C. Serum was frozen at -80°C until further evaluation. An enzyme-linked immunosorbent assay (ELISA) kit was utilized to measure the concentration of serum calprotectin.

Echocardiography

Left ventricular ejection fraction (LVEF) measurement was done by end-systolic as well as end-diastolic diameters using transthoracic echocardiograms,[11] which was performed and interpreted by a specialist in cardiology. A GE vivid E9 ultrasound machine was used for transthoracic echocardiography.

Outcome assessment

Demographic and clinical risk factors, including previous history of diabetes and incidence of gastrointestinal (GI)[1] bleeding, were inquired from all patients. The coronary angiography was done using the Artis Zee machine (Ziemens, Germany), and the data including severity and number of diseased vessels was collected during the angiography procedures. Other considered outcomes were in-hospital MACE, including cerebrovascular accident (CVA), death, stent thrombosis, and arrhythmia incidence, which were collected for all patients.

Statistical analysis

All variables of the recent analysis were evaluated for normality using Kolmogorov-Smirnov test. Data with normal distribution was shown as mean ± standard deviation (SD) for continuous parameters and percentages for categorical ones. The independent Chi-squared test was used to compare categorical parameters. To specify the correlation among variable parameters and serum calprotectin, Pearson's correlation coefficient analysis was performed. P value <0.05 was considered the statistical significance level. All data analyses were conducted using SPSS (version 23).

Results

A total of 97 STEMI patients participated in the present study and were distributed in two groups based on the median of serum calprotectin identified in this analysis (4.8 ± 2.5 μg/ml). A total of 37 STEMI patients (mean age of 54.24 ± 9.01 with 73% male) were included in the group with low calprotectin (i.e., group 1, patients who had calprotectin level lower than the mean level of calprotectin in this study, <4.8 μg/ml) and 60 patients (mean age of 59.16 ± 10.36 with 61.7% male) in the high calprotectin group (i.e., group 2, patients who had calprotectin level higher than the mean level of calprotectin in this study, ≥4.8 μg/ml). Coronary risk factors, baseline demographic, echocardiographic, and angiographic characteristics are presented in Table 1. The results of independent *t*-test showed indicated a significant difference in serum calprotectin levels between young and elderly STEMI patients, so that the patients who were older had a higher level of calprotectin; however, the level of serum calprotectin was not significantly associated with gender (P = 0.254). With respect to coronary risk parameters, there was a high prevalence of diabetes among patients with both lower and higher calprotectin levels (32.4% and 83.3%, respectively), which was significantly different; however, the incidence of GI bleeding was observed in only 2.7% of patients with low calprotectin levels, which did not show a significant difference. In terms of echocardiographic findings, LVEF was reported to be 41.62 ± 5.28 in lower calprotectin group and 26.16 ± 6.53 in higher calprotectin group, which was significant between the two groups. The results of Pearson's test also showed an

inverse correlation between serum calprotectin levels and LVEF. In other words, patients with higher serum calprotectin levels had a lower mean of LVEF ($P < 0.05$).

Regarding coronary artery occlusion, single vessel disease (SVD) showed the highest percentage of artery occlusion in patients with lower calprotectin levels; nevertheless, in patients with higher calprotectin levels, 3-vessel disease (3VD) had the highest percentage, both of which were statistically significant. In this study, left anterior descending artery (LAD) was the most frequently occluded coronary artery in patients (67%), followed by right coronary artery (RCA) in 12.4%, the left circumflex artery (LCX) in 8.2%, the patent ductus arteriosus (PDA) in 7.2%, and the obtuse marginal (OM) in 5.2%. In other words, the results of Chi-squared test showed that patients with higher serum calprotectin levels were more likely to present with higher severity of diseased vessels ($P < 0.001$).

The incidence of in-hospital MACE is also shown in Table 2. For the in-hospital MACE, neither lower calprotectin group nor higher calprotectin patients reported in-hospital stent thrombosis, in-hospital death, and in-hospital CVA. Moreover, the results of Chi-squared test showed that there was a significant relationship between high levels of calprotectin and the incidence of in-hospital arrhythmia in patients that occurred on the first day of hospitalization, so that 80% of patients with high calprotectin levels had in-hospital cardiac arrhythmia ($P < 0.001$). Premature ventricular contraction (PVC) and atrial fibrillation (AF) were the most and the least frequent type of cardiac arrhythmia in patients, respectively.

Table 1: General features of STEMI patients undergoing PCI according to serum calprotectin levels

Variables	Serum calprotectin levels		*P*
	Low calprotectin group <4.8 μg/ml (*n*=37)	High calprotectin group ≥4.8 μg/ml (*n*=60)	
Baseline demographic characteristics			
Age (years)	9.01±54.24	10.36±59.16	
Male	27 (73%)	37 (61.7%)	0.254
Underlying disorders			
Diabetes	12 (32.4%)	50 (83.3%)	0.001
GI bleeding	1 (2.7%)	0 (0%)	0.2
Echocardiographic data			
LVEF (%)	41.62±5.28	26.16±6.53	<0.001
Angiographic data			
Stent length	27.67±5.26		
Stent diameter	3.08±0.26		
SVD	22 (59.5%)	7 (11.7%)	0.001
2VD	10 (27%)	11 (18.3%)	0.001
3VD	5 (13.5%)	42 (70%)	0.001

GI: Gastrointestinal; LVEF: Left ventricular ejection fraction; SVD: Single vessel disease; 2VD: Two-vessel disease; 3VD: Three-vessel disease

Table 2: In-hospital MACE in STEMI patients undergoing PCI according to serum calprotectin levels

Variables	Serum calprotectin levels		*P*
	Low calprotectin group <4.8 μg/ml (*n*=37)	High calprotectin group ≥4.8 μg/ml (*n*=60)	
In-hospital MACE			
Arrhythmia	0 (0%)	48 (80%)	0.001
Stent thrombosis	---	---	---
CVA	1 (2.7%)	1 (1.7%)	0.727

CVA: Cerebrovascular accident; MACE: Major adverse cardiovascular events

Discussion

In the present study, we have shown that STEMI patients with higher serum calprotectin levels had a higher severity of diseased vessels. The serum calprotectin level was also inversely associated with LVEF level in patients with STEMI. Despite the fact that MACE was correlated with the inevitable outcome of STEMI, only serum calprotectin and cardiac arrhythmia acted as significant predictors of in-hospital MACE among patients with STEMI as shown in the present study.

Calprotectin is known as an inflammation-correlated peptide along with pro-inflammatory characteristics, which is mostly released from activated monocytes and neutrophils under diverse circumstances.[12] Calprotectin is typically considered to be involved in the pathophysiology of various inflammatory conditions like rheumatoid arthritis.[13] Nevertheless, current investigations have mentioned that calprotectin may be involved in the pathogenesis of cardiovascular disorders.[14-16]

High levels of calprotectin were reported in patients with STEMI who died after a mean follow-up interval of 12 months in comparison to patients who survived.[11] A study demonstrated that calprotectin is correlated with an elevated risk of cardiac death and MI in ACS patients.[17]

More interestingly, calprotectin was shown to be associated with first as well as recurrent cardiac events in middle-aged healthy participants. Moreover, an inverse correlation was also found between calprotectin and LVEF in a previous study.[15] Similarly, our finding revealed that serum calprotectin negatively correlated with LVEF but there was no correlation between serum calprotectin levels and in-hospital cardiovascular death. Inconsistent with our findings regarding the possible correlation of calprotectin and in-hospital stent thrombosis, a high concentration of calprotectin was shown in the culprit ACS lesions that correlated with thrombosis.[18] Such difference may be logical due to the limited number of our STEMI patients and shorter in-hospital median follow-up period. Consistent with the present study, Zhang *et al*.[10] reported that the prevalence rate of MACE was remarkably higher in ACS patients who had high calprotectin levels

compared to those who had low calprotectin levels. It is of note that serum calprotectin did not show any significant correlation with in-hospital CVA in STEMI patients of the present study.

Despite the vital role of calprotectin in cardiovascular diseases, its involvement in coronary artery occlusion of STEMI patients has not been investigated. Our study showed that 3VD was more prevalent in STEMI patients who had higher levels of serum calprotectin compared with SVD in STEMI patients who had lower levels of it, indicating that serum calprotectin may be a promising vital prognostic biomarker of severity of diseased vessels in STEMI patients.

Cardiac risk factors such as diabetes mellitus, smoking, hyperlipidemia, and other inflammatory markers are believed to be risk predictors of coronary heart disease.[19,20] In this regard, diabetes and hypercholesterolemia are regarded as pivotal risk factor of ACS, which were associated with coronary thrombosis.[21,22] In the present investigation, diabetes was significantly more prevalent than other risk factors in both patients with low and high levels of serum calprotectin. It can be hypothesized that in patients suffering from cardiovascular risk factors like diabetes with a comorbidity of cardiovascular disorders like STEMI, a high level of serum calprotectin can be correlated with higher rate of arrhythmia as an MACE indicator as well as a higher rate of coronary artery occlusion.

Conclusion

Calprotectin shows direct correlation with reduced levels of LVEF and the occurrence of cardiac arrhythmia but it does not have any relationship with in-hospital CVA. It may be due to the fact that we examined the patients only during hospitalization. The present investigation was a pilot study, and such effective correlation can contribute to planning for further studies in this regard. In the next study, long follow-up period and larger number of patients will be considered.

Limitation

Small sample size is among the limitations of the present study. As a result, planning a future research with larger number of patients is required. Factors such as nutrition, smoking, sex, and lipid profile which are regarded as confounding variables should be investigated in future experiments to check their changes in calprotectin levels. Evaluating the relationship between long follow-up with the level of calprotectin and in-hospital MACE is also suggested.

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Data availability

All data are included in the manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. Vogel B, Claessen BE, Arnold SV, Chan D, Cohen DJ, Giannitsis E, *et al*. ST-segment elevation myocardial infarction. Nat Rev Dis Primers 2019;5:39.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, *et al*. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
3. Zubaid M, Khraishah H, Alahmad B, Rashed W, Ridha M, Alenezi F, *et al*. Efficacy and safety of pharmacoinvasive strategy compared to primary percutaneous coronary intervention in the management of ST-segment elevation myocardial infarction: A prospective country-wide registry. Ann Glob Health 2020;86:13.
4. Huseynov A, Baumann S, Becher T, Koepp J, Lang S, Jabbour C, *et al*. Liver and cholestatic parameters as prognostic biomarkers of in-hospital MACE in patients with STEMI. Eur J Clin Investig 2016;46:721-9.
5. Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: What do we gain and what are the challenges? Eur Heart J 2012;33:579-86.
6. Fathil M, Arshad MM, Gopinath SC, Hashim U, Adzhri R, Ayub R, *et al*. Diagnostics on acute myocardial infarction: Cardiac troponin biomarkers. Biosens Bioelectron 2015;70:209-20.
7. Kunutsor SK, Flores-Guerrero JL, Kieneker LM, Nilsen T, Hidden C, Sundrehagen E, *et al*. Plasma calprotectin and risk of cardiovascular disease: Findings from the PREVEND prospective cohort study. Atherosclerosis 2018;275:205-13.
8. Zhen X-W, Song N-P, Ma L-H, Ma L-N, Guo L, Yang X-D. Calprotectin and neutrophil gelatinase-associated lipocalin as biomarkers of acute kidney injury in acute coronary syndrome. Am J Med Sci 2021;361:736-43.
9. Wang C, Kong Y, Ding Y, Sun J, Chen T. Serum calprotectin levels and outcome following percutaneous coronary intervention in patients with diabetes and acute coronary syndrome. Med Sci Monit 2019;25:9517-23.
10. 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:e20805.
11. Jensen LJ, Pedersen S, Bjerre M, Mogelvang R, Jensen JS, Flyvbjerg A. Plasma calprotectin predicts mortality in patients with ST segment elevation myocardial infarction treated with primary percutaneous coronary intervention. J Interv Cardiol 2010;23:123-9.
12. Jukic A, Bakiri L, Wagner EF, Tilg H, Adolph TE. Calprotectin: From biomarker to biological function. Gut 2021;70:1978-88.
13. Jarlborg M, Courvoisier DS, Lamacchia C, Martinez Prat L, Mahler M, Bentow C, *et al*. Serum calprotectin: A promising biomarker in rheumatoid arthritis and axial spondyloarthritis. Arthritis Res Ther 2020;22:1-11.
14. Iqbal M, Alakwe-Ojimba CE, Omeludike EK, Abung A, Ahmed K, Fasoranti-Sowemimo OF, *et al*. Calprotectin as biomarker in cardiovascular disease: A systematic review. J Adv Med Med Res 2023;35:219-29.
15. Song N-P, Zhen X-W, Li L-D, Zhong L, Wang H, An Y. Plasma calprotectin was associated with platelet activation and no-reflow phenomenon in acute coronary syndrome. BMC Cardiovasc Disord 2020;20:1-10.
16. Mahendra J, Muralidharan J, Srinivasan S, Mahendra L, Cherian SM, Fathima L, *et al*. Calprotectin and periostin levels in periodontitis patients with coronary artery disease. Oral Dis 2023.
17. Mjelva ØR, Brügger-Andersen T, Pönitz V, Grundt H, Kontny F, Staines H, *et al*. Long-term prognostic utility of PAPP-A and calprotectin in suspected acute coronary syndrome. Scand Cardiovasc J 2013;47:88-97.

18. Sakuma M, Tanaka A, Kotooka N, Hikichi Y, Toyoda S, Abe S, *et al*. Myeloid-related protein-8/14 in acute coronary syndrome. Int J Cardiol 2017;249:25-31.
19. Tahir A, Martinez PJ, Ahmad F, Fisher-Hoch SP, McCormick J, Gay JL, *et al*. An evaluation of lipid profile and pro-inflammatory cytokines as determinants of cardiovascular disease in those with diabetes: A study on a Mexican American cohort. Sci Rep 2021;11:2435.
20. Dugani SB, Moorthy MV, Li C, Demler OV, Alsheikh-Ali AA, Ridker PM, *et al*. Association of lipid, inflammatory, and metabolic biomarkers with age at onset for incident coronary heart disease in women. JAMA Cardiol 2021;6:437-47.
21. Schneider DJ. Diabetes and thrombosis. InDiabetes and cardiovascular disease 2023 Jun 2 (pp. 99-127). Cham: Springer International Publishing.
22. Vuorio A, Watts G, Schneider W, Tsimikas S, Kovanen P. Familial hypercholesterolemia and elevated lipoprotein (a): Double heritable risk and new therapeutic opportunities. J Intern Med 2020;287:2-18.