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Relationship between alkaline phosphatase and impaired coronary flow in patients with ST-segment elevated myocardial infarction

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Abstract

Objective: Recent studies have shown that alkaline phosphatase (ALP) might play a negative role in clinical outcomes of patients with peripheral and coronary artery disease. This study aimed to investigate the relationship between serum ALP levels and coronary thrombolysis in myocardial infarction (TIMI) frame counts in patients with ST-segment elevated myocardial infarction undergoing primary percutaneous coronary intervention (PCI).

Methods: A total of 198 patients were enrolled in the current study. Serum ALP levels were measured in lithium-heparin plasma samples via a standardized, colorimetric enzyme assay. Coronary TIMI flow was evaluated by counting the number of cine frames that were required for contrast to reach a standardized distal coronary landmark in the culprit vessel.

Results: The Spearman correlation coefficient test showed strong positive relationships between coronary TIMI frame counts after primary PCI and serum ALP levels on admittance for the left anterior descending, circumflex, and right coronary arteries ($r = 0.774$, $r = 0.831$, and $r = 0.730$, respectively).

Conclusion: Elevated serum ALP levels appear to be a predictor of impaired coronary TIMI frame count in patients suffering from ST-segment elevated myocardial infarction.

Keywords

Alkaline phosphatase, myocardial infarction, atherosclerosis, percutaneous coronary intervention, thrombolysis in myocardial infarction, artery

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Background

Serum alkaline phosphatase (ALP) is a metalloenzyme that catalyses the hydrolysis of organic pyrophosphate. Vascular calcification is a major component of atherosclerosis, and pyrophosphate provides integrity for vessels by inhibiting medial vascular calcification.[1] Advanced vascular calcification adversely affects the coronary thrombolysis in myocardial infarction (TIMI) frame count after reperfusion therapy in acute myocardial infarction.[2] Elevated total serum ALP levels are associated with mortality in patients with chronic kidney failure.[3] Recent studies have shown that elevated ALP levels are associated with negative clinical outcomes in patients with coronary artery disease and peripheral artery disease.[4,5] The current study investigated the relationship between serum ALP levels and the coronary TIMI frame count. We assessed angiographic results after performing primary percutaneous coronary intervention (PCI) during the course of ST-segment elevated myocardial infarction (STEMI).

Material and methods

Study population and definitions

The current retrospective study was performed in a single centre. The study protocol was approved by the local ethics committee. All of the patients provided verbal informed consent. A total of 198 patients who underwent primary PCI because of STEMI between January 2013 and December 2016 in our clinic were enrolled in the study. On admission, a loading dose of 600 mg of clopidogrel and 300 mg of acetylsalicylic acid was applied to the patients followed by a daily regimen of 75 mg of clopidogrel and 100 mg of acetylsalicylic acid.

Patients' demographic, biochemical, and clinical variables, including age, sex, diabetes mellitus (DM), hypertension, and smoking status, were recorded. DM was defined as having a glycated haemoglobin level $\geq$6.5%, fasting plasma glucose level $\geq$126 mg/dL during hospitalization, or on anti-diabetic treatment.[6] Hypertension was defined as having a systolic blood pressure level of at least 130 mmHg and/or a diastolic blood pressure level of at least 80 mmHg during hospitalization or using an antihypertensive treatment.[7] A detailed physical examination was performed for all of the patients who were included in the study. STEMI was defined as acute chest pain and persistent ST segment elevation $\geq$2 mm (>20 min) in at least two contiguous leads.

Patients with advanced clinical conditions, which may potentially increase serum ALP levels, including a history of malignancy, acute or chronic biliary system disease, chronic liver disease, active hepatitis, decompensated heart failure, chronic renal disease, and chronic inflammatory diseases of the skeletal system, were excluded from the study.

Study protocol

Participants' medical data of demographic features and laboratory parameters, including ALP levels, were carefully recorded during each patient's enrolment. Blood for ALP measurement was taken on admission before angiography. Activity of ALP was measured in lithium-heparin plasma samples via a standardized, colorimetric enzyme assay on an automatized Cobas c 501 system (Roche Diagnostics GmbH, Mannheim, Germany) according to the International Federation of Clinical Chemistry and Laboratory Medicine method.[8] The imprecision of the method was indicated by coefficients of variation between 0.9% and 2.4% for between-day

comparison using assay controls and human serum samples, as provided by the manufacturer.

Angiographic data from catheter laboratory records were evaluated by four interventional cardiologists. Coronary TIMI flow for each patient was evaluated by counting the number of cine frames that were required for contrast to reach a standardized distal coronary landmark in the culprit vessel. The count number was based on a cine film rate of 30 frames/second; therefore, a frame count of 30 indicated that 1 second was required for dye to traverse an artery.[9] TIMI frame counts were calculated directly from cine frames. Therefore, the corrected TIMI frame count was not used. Interobserver and intraobserver intraclass correlation coefficients for interventional cardiologists who assessed the cine films were 79.1% (good) and 78.3% (good), respectively.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, Version 20.0 (IBM, Armonk, NY, USA). Data are presented as mean, standard deviation, median, minimum, maximum, percent, and number. The normality of distribution for continuous variables was confirmed with the Kolmogorov–Smirnov test. The Mann–Whitney U test was also used according to the distribution pattern of continuous variables. Cross tables were constructed for qualitative variables and their distribution was assessed by the chi-square test. The Spearman correlation coefficient test was used if normal distribution conditions were not met when two continuous variables were compared. Multivariate regression analysis was performed with the backward stepwise Wald method. A p value of <0.05 was considered a statistically significant difference for the 95% confidence interval (CI).

Results

A total of 198 patients with STEMI (men, 70.7%) were enrolled in the study. The culprit artery was the circumflex artery (CX) in 42 (21.2%) patients, the right coronary artery (RCA) in 76 (38.3%) patients, and the left anterior descending artery (LAD) in 80 (40.5%) patients. The mean age of the study population was 58.6 ± 16.0 years. Demographic, biochemical, and clinical characteristics of the study group are shown in Table 1. Among the study population, 71 (%35.9) patients had a smoking history, 64 (%32.3) had a history of hypertension, and 52 (%26.3) had a previous diagnosis of DM. The mean coronary

Table 1. Demographic, biochemical, and clinical characteristics of the study group

	Mean ± standard deviation
Age (years)	58.6 ± 16.0
Glucose (mg/dL)	135.7 ± 61.8
Creatinine (mg/dL)	1.1 ± 0.5
Na (meq/L)	138.6 ± 5.0
K (meq/L)	4.3 ± 0.4
AST (mg/dL)	42.9 ± 13.8
ALT (mg/dL)	25.4 ± 11.9
GGT (mg/dL)	24.3 ± 9.2
Lipase (mg/dL)	28.2 ± 11.6
LDL (mg/dL)	129.9 ± 35.2
TG (mg/dL)	159.7 ± 35.5
HDL (mg/dL)	43.1 ± 15.0
Troponin I (ng/mL)	4.2 ± 0.80
CK-MB (IU/mL)	57.8 ± 20.6
Haemoglobin (g/dL)	14.2 ± 5.4
Total bilirubin (mg/dL)	0.52 ± 0.30
Direct bilirubin (mg/dL)	0.17 ± 0.10
LDH (mg/dL)	300.6 ± 178.5
TIMI frame count	13.12 ± 8.51
ALP (mg/dL)	67.5 ± 42.3

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CK-MB: creatine kinase-MB, GGT: gamma-glutamyl transferase, HDL: high-density lipoprotein, K: potassium, LDH: lactate dehydrogenase, LDL: low-density lipoprotein, Na: sodium, TG: triglycerides, TIMI: thrombolysis in myocardial infarction.

TIMI frame count was 13.1 ± 8.5 and ALP levels were 67.5 ± 42.3 mg/dL. The presence of DM was significantly associated with increased coronary TIMI frame counts and serum ALP levels (both $p \leq 0.001$).

The Spearman correlation coefficient test showed strong positive relationships between coronary TIMI frame counts after primary PCI and serum ALP levels on admittance for each coronary artery. Figures 1, and 2 and 3 show strong positive relationships in the LAD, CX, and RCA ($r = 0.774$, $p \leq 0.001$; $r = 0.831$, $p \leq 0.001$; and $r = 0.730$, $p \leq 0.001$, respectively). Receiver operator characteristics curve analysis showed that ALP values > 79 mg/dL predicted a TIMI frame count ≥ 20 with a sensitivity of 94.4% and a specificity of 97.2% (+likelihood ratio: 34, −likelihood ratio: 0.057; 95% CI = 19.996–506.615, $p \leq 0.001$; area under the receiver operator characteristics curve: 0.969) (Figures 4–6). Multivariate regression analysis in the whole study group showed that ALP values >79 mg/dL were an independent risk factor for impaired coronary TIMI frame count (TIMI frame count ≥ 20) after percutaneous revascularization in patients with STEMI ($p \leq 0.001$, odds ratio: 595.0, 95% CI: 128.72–2750.25) (Table 2).

Discussion

Calcification of coronary arteries indicates atherosclerosis. Extension and severity of

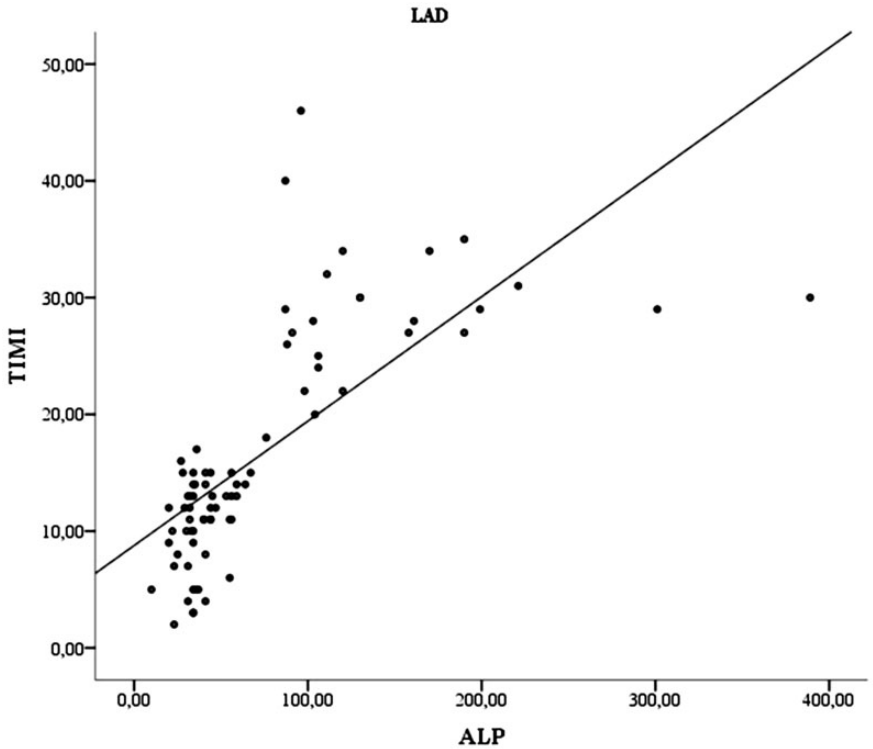

Figure 1. Strong positive correlation between admittance serum ALP levels and coronary TIMI frame counts in patients who underwent primary PCI in the LAD ($r = 0.774$, $p \leq 0.001$, $N = 80$).
TIMI: thrombolysis in myocardial infarction, PCI: percutaneous coronary intervention, ALP: alkaline phosphatase, LAD: left anterior descending artery.

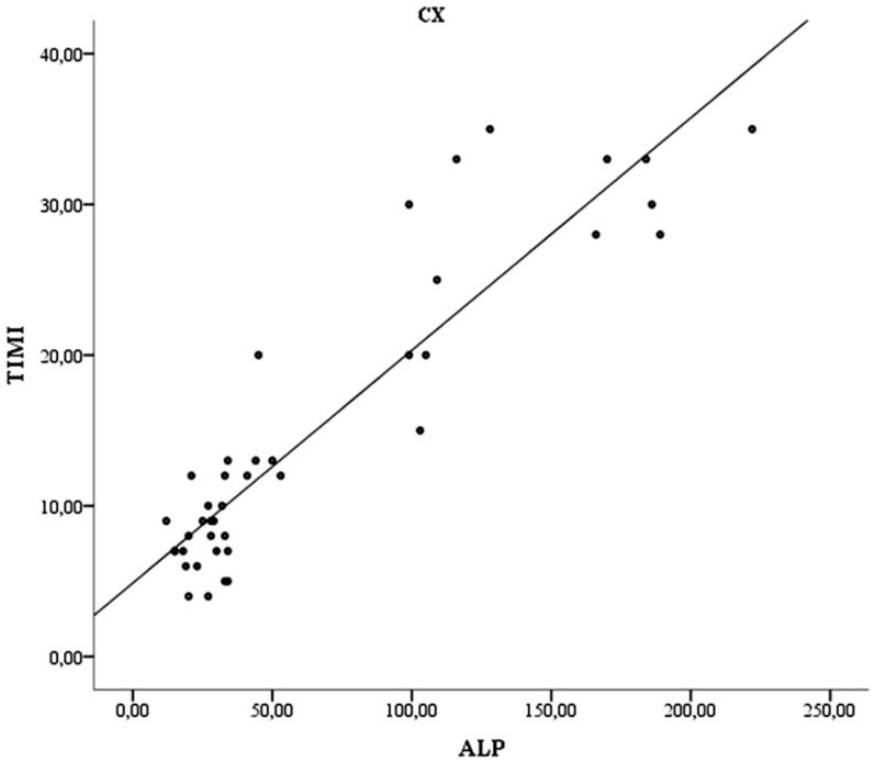

Figure 2. Strong positive correlation between admittance serum ALP levels and coronary TIMI frame counts in patients who underwent primary PCI in the CX ($r = 0.831$, $p \leq 0.001$, $N = 42$).
TIMI: thrombolysis in myocardial infarction, PCI: percutaneous coronary intervention, ALP: alkaline phosphatase, CX: circumflex artery.

coronary artery calcification are used to make predictions about future cardiovascular events.[10] Vascular calcium deposits lead to transformation of the arterial wall into a bone-like matrix.[11] Increased ALP activity is associated with excessive arterial calcification. This eventually leads to premature atherosclerosis and cardiovascular events, which can be seen in Hutchinson–Gilford progeria syndrome or generalized arterial calcification of infancy syndrome.[10,12–14] High ALP levels are also a predictor of increased coronary artery calcification in patients undergoing haemodialysis.[15] A study conducted by Park et al.[4] in patients with implantation of drug-eluting stents showed that the incidence of adverse events, involving stent thrombosis, myocardial infarction, and mortality, was evident in patients with the highest ALP levels. In 2017, Ndrepepa et al.[16] showed that in patients who presented with acute coronary syndrome and then underwent PCI, elevated ALP activity was related to an increased risk of subsequent mortality.[15]

Transformation in the arterial walls due to endothelial and smooth muscle cell dysfunction is the principal characteristic of diabetic vasculopathy, resulting in an inflammatory condition, which results in a thrombotic state. Increased ALP levels are related to higher levels of C-reactive protein,[17] which is the most broadly investigated marker of inflammation. Some

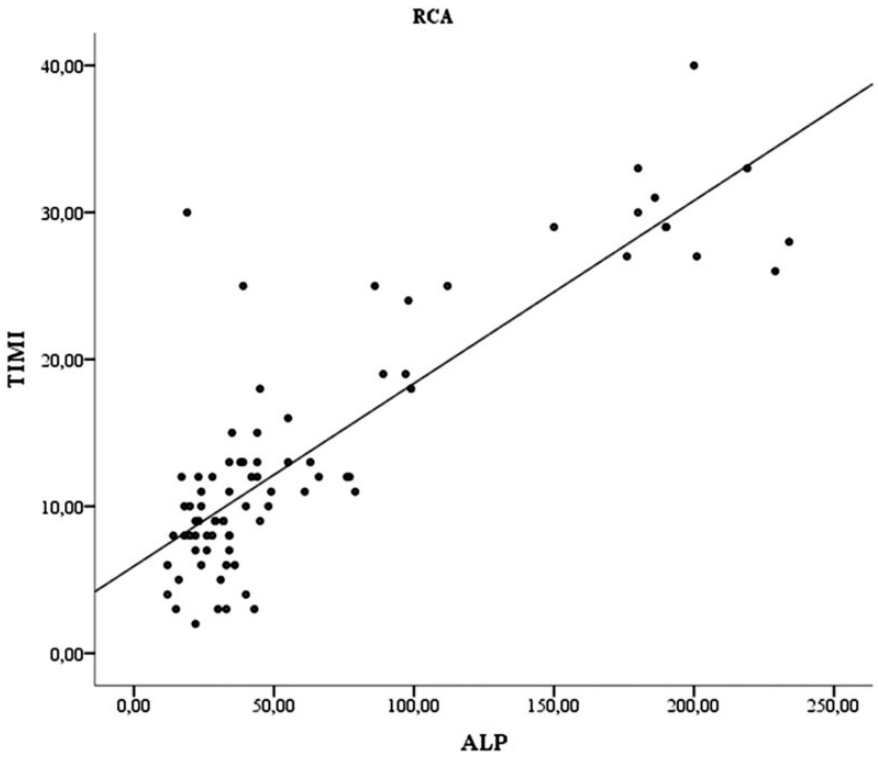

Figure 3. Strong positive correlation between admittance serum ALP levels and coronary TIMI frame counts in patients who underwent primary PCI in the RCA ($r = 0.730$, $p \leq 0.001$, $N = 76$).
TIMI: thrombolysis in myocardial infarction, PCI: percutaneous coronary intervention, ALP: alkaline phosphatase, RCA: right coronary artery.

mediators of inflammation, such as oxidation, cytokines, and C-reactive protein, may directly provoke arterial calcification. Arterial calcification is an active cell-derived process, and likely reflects a change in vascular smooth muscle cells into osteoblast-like cells. In the current study, we demonstrated significant relationships between the presence of DM and elevated coronary TIMI frame counts and serum ALP levels. Because high serum ALP levels reflect inflammation, this could explain the relationships found in our study population.[15]

The coronary TIMI frame count is a quantitative and reproducible variable, which can be used to compare flow data between angiographic trials. The TIMI frame count predicts in-hospital mortality. Decreased flow grade in coronary vessels leads to a poor clinical prognosis and fatal complications. During primary PCI, physicians should be aware of factors that might affect coronary TIMI frame counts for patients' clinical outcomes. A previous study showed that the coronary TIMI frame count for RCA culprit lesions was significantly higher than that for the LAD and CX because of the large thrombus burden of the RCA after STEMI.[18] Recently, Liang et al.[19] suggested that patients who showed coronary no-reflow phenomenon during PCI for acute coronary syndrome were older, their reperfusion

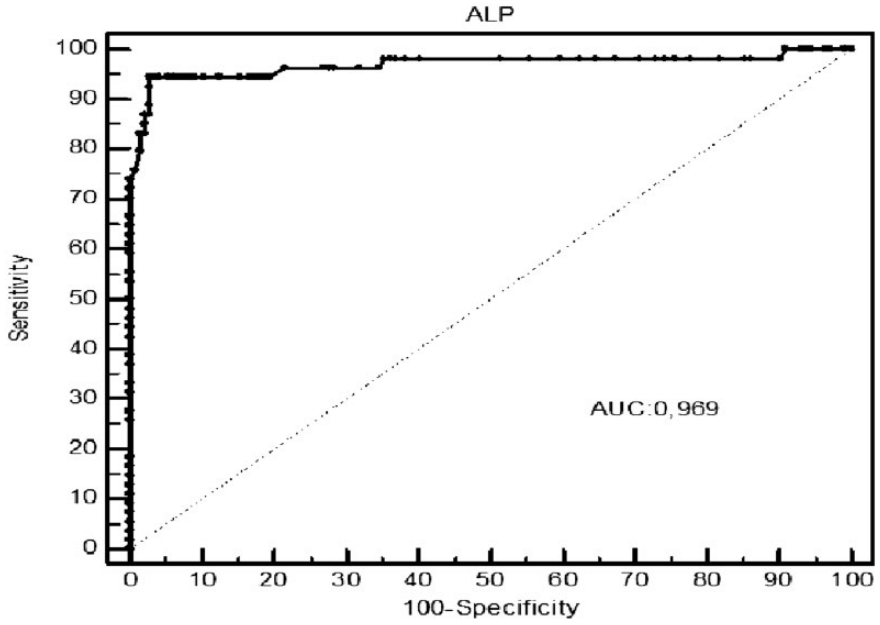

Figure 4. ROC curve analysis shows that ALP values > 79 mg/dL predict a TIMI frame count ≥20 with a sensitivity of 94.4% and a specificity of 97.2% (+LR: 34, −LR: 0.057; 95% confidence interval = 19.996–506.615, p ≤ 0.001; area under receiver operator curve: 0.969).
ALP: alkaline phosphatase, TIMI: thrombolysis in myocardial infarction, LR: likelihood ratio, ROC: receiver operator characteristics.

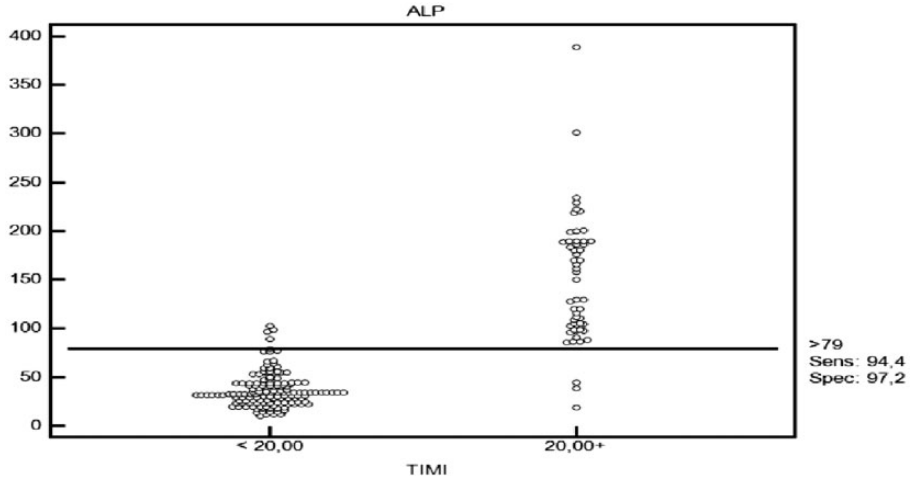

Figure 5. Graph showing that ALP values > 79 mg/dL predict a TIMI frame count ≥20 with a sensitivity of 94.4% and a specificity of 97.2%.
ALP: alkaline phosphatase, TIMI: thrombolysis in myocardial infarction, ROC: receiver operator characteristics.

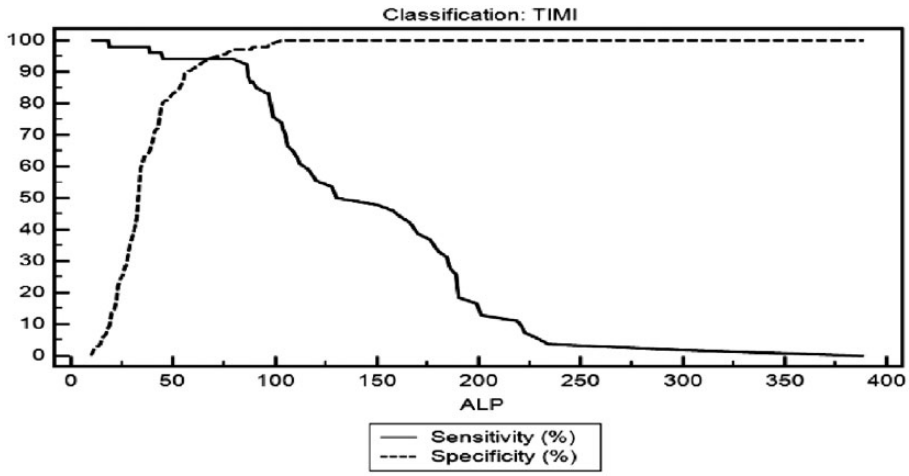

Figure 6. Youden index shows that ALP values > 79 mg/dL predict a TIMI frame count ≥20 with a sensitivity of 94.4% and a specificity of 97.2%.
ALP: alkaline phosphatase, TIMI: thrombolysis in myocardial infarction, ROC: receiver operator characteristics.

Table 2. Effect of ALP and other parameters on impaired coronary thrombolysis in myocardial infarction frame count (≥20) after primary percutaneous coronary intervention for the left anterior descending, circumflex, and right coronary arteries

	OR	p value	95% CI
ALP	595.0	≤0.001	128.72–2750.25
RCA	0.53	0.430	0.11–2.58
DM	2.03	0.547	0.20–20.22
HT	0.31	0.385	0.02–4.33
Smoking	0.94	0.971	0.04–21.59

ALP: alkaline phosphatase, OR: odds ratio, CI: confidence interval, DM: diabetes mellitus, HT: hypertension, RCA: right coronary artery.

time was significantly longer, preoperative systolic pressure was lower, and troponin and creatine kinase enzyme peaks were significantly higher compared with patients with normal reflow. In 2015, Modolo et al.[2] showed that a high coronary artery calcium score was associated with impaired coronary flow in patients with STEMI who underwent primary PCI. There are several underlying mechanisms that contribute to impaired coronary TIMI frame counts after reperfusion of STEMI, such as embolization of thrombotic debris, vasoconstriction of the microcirculation induced by endothelin, and aggregation of platelets in the microcirculation. A high level of ALP is associated with enhanced vascular calcification, and enhanced vascular calcification leads to poor coronary flow and prognosis. Therefore, in the current study, we investigated a new parameter, serum ALP levels, which can predict impaired coronary flow after primary PCI and are easily measured on admittance by simple blood sampling. We observed that elevated serum ALP levels were an independent biomarker for predicting impaired coronary TIMI frame counts of the LAD, CX, and RCA during the course of primary PCI for STEMI.

Conclusions

This study shows that elevated serum ALP levels appear to be an independent predictor of impaired coronary TIMI frame count in patients suffering from STEMI.

Therefore, serum ALP levels on admittance could be used to identify high-risk patients for an impaired coronary TIMI frame count in patients with STEMI. Further large-scale studies are required to determine the role of ALP levels for predicting angiographic coronary TIMI frame counts in patients undergoing primary PCI.

Study limitations

Three limitations of this study should be mentioned. One limitation is the retrospective design of the study. Another limitation is that the sample size was not sufficiently powered to assess the predictive role of ALP levels on the coronary TIMI frame count after reperfusion therapy. Multivariate regression analysis could not be performed for each vessel separately because of the limited number of patients in each artery group. Finally, the data of the current study were obtained from a single centre. Therefore, our findings must be considered as hypothesis generating, and larger studies are required to confirm our findings.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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