Value of Alkaline Phosphatase in Predicting the Extent and Severity of Coronary Artery Disease in Acute Myocardial Infarction

Celal Kilit
Dumlupınar University Faculty of Medicine, Department of Cardiology, Kütahya, Turkey

ABSTRACT

Introduction: The serum alkaline phosphatase (ALP) level has been shown to be a prognostic factor in stable coronary artery disease (CAD) and acute myocardial infarction (AMI) by its promoting effect on vascular calcification. The objectives of this study were to investigate serum ALP levels and to determine their value in predicting the extent and severity of CAD in patients with AMI.

Patients and Methods: A total of 200 patients with AMI were included in this study. Patients with serum ALP levels higher than 120 mg/dL were classified as elevated ALP group. The extent and severity of CAD was assessed using Gensini score and number of vessel disease. Patients with a Gensini score greater than 40 were included in advanced CAD group.

Results: There was no relationship between the ALP level and the Gensini score in study population. Patients were grouped according to the Gensini score (Gensini scores ≤ 40 and > 40). There was no difference between the groups in terms of ALP levels. However, ALP levels were significantly higher in diabetic patients and in patients with non—ST-segment elevation myocardial infarction (NSTEMI). Parathormone levels and neutrophil counts were significantly higher in the advanced CAD group.

Conclusion: ALP levels do not indicate the extent and severity of CAD in patients with AMI. However, these levels are higher in diabetic patients and in patients with NSTEMI than in patients with ST-segment elevation myocardial infarction. Higher parathormone levels and neutrophil counts are related to the extent and severity of CAD in patients with AMI.

Key Words: Alkaline phosphatase; coronary angiography; myocardial infarction; coronary artery disease; parathyroid hormone

Akut Miyokart İnfarktüsünde Koroner Arter Hastalığının Yaygınlığını ve Ciddiyetini Tahmin Etmede Alkalen Fosfatazın Değeri

ÖZET

Giriş: Serum alkalen fosfataz (ALP) seviyesi, vasküler kalsifikasyon üzerine olan tetikleyici etkisinden dolayı akut miyokart infarktüsü (AMİ)'nde ve stabil koroner arter hastalığı (KAH)'nda prognostik bir faktör olarak gösterilmiştir. Çalışmanın amacı, AMİ hastalarında serum ALP seviyelerini araştırmak ve KAH'ın yaygınlığı ve ciddiyetini tahmin etmedeki değerini saptamaktır.

Hastalar ve Yöntem: Bu çalışmaya AMİ geçiren toplam 200 hasta dahil edildi. Serum ALP düzeyleri 120 mg/dL'den yüksek olanlar, yükselmiş ALP grubu olarak tanımlandı. KAH'ın yaygınlığı ve ciddiyeti, Gensini skoru ve hasta damar sayısı ile değerlendirildi. Gensini skoru 40'ın üzerinde olan hastalar, ilerlemiş KAH grubuna dahil edildi.

Bulgular: Çalışma popülasyonunda ALP düzeyi ve Gensini skoru arasında ilişki yoktu. Hastalar Gensini skorlarına göre gruplandırıldı (Gensini skoru ≤ 40 ve Gensini skoru > 40). Gruplar arasında ALP düzeyi açısından fark yoktu. Bununla birlikte, ALP düzeyleri diyabetik hastalarda ve ST elevasyonsuz miyokart infarktüsü (NSTEMİ) olan hastalarda anlamlı derecede daha yüksekti. Parathormon düzeyleri ve nötrofil sayıları, ilerlemiş KAH grubunda anlamlı olarak yüksek bulundu.

Sonuç: ALP düzeyi, AMİ'li hastalarda KAH yaygınlığı ve ciddiyetini göstermemektedir. Bununla birlikte ALP düzeyleri, diyabetik hastalarda ve ST elevasyonlu miyokart infarktüsü (STEMİ) hastalarıyla kıyaslandığında NSTEMİ hastalarında daha yüksektir. Yüksek parathormon düzeyi ve nötrofil sayısı, AMİ'de KAH yaygınlığı ve ciddiyeti ile ilişkilidir.

Anahtar Kelimeler: Alkalen fosfataz; koroner anjiyografi; miyokart infarktüsü; koroner arter hastalığı; paratiroid hormon

Correspondence

Celal Kilit

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INTRODUCTION

Acute myocardial infarction (AMI) indicates a serious clinical manifestation of coronary artery disease (CAD) and is the major cause of morbidity and mortality worldwide[1]. The severity of CAD is associated with cardiovascular prognosis in patients with AMI[2]. Prediction and diagnosis of the extent of coronary lesion in AMI are important for clinical management of this disease.

Atherosclerosis is by far the most frequent underlying cause of CAD. Vascular calcification constitutes a basic pathway in the progression of atherosclerosis, and it contributes to cardiovascular risk in various population subgroups[3]. Vascular calcification has been recognized both in early and late stages of atherosclerosis. Serum alkaline phosphatase (ALP) is a membrane-bound metalloenzyme that liberates inorganic phosphate by catalyzing the hydrolysis of organic pyrophosphate, which is an inhibitor of vascular calcification[4]. Pyrophosphate was shown to be a protective factor for vascular integrity, and an elevated ALP level may promote vascular calcification via the pyrophosphate pathway[5]. Circulating ALP and phosphate concentrations often increase in the end-stage renal disease. Several clinical and epidemiological studies have linked higher serum ALP and phosphate levels to increased coronary calcification, increased risk of cardiovascular disease events, and total mortality in patients with chronic kidney disease[6,7]. Also, higher serum phosphate levels are associated with adverse outcomes among people with a normal kidney function[8]. High ALP levels are associated with adverse outcomes among survivors of AMI and stroke; this has been partially explained by the association of high ALP levels with established risk factors and inflammation[9]. High serum ALP levels are an independent predictor of mortality, AMI, and stent thrombosis in CAD patients after percutaneous coronary intervention (PCI) with drug-eluting stents[10]. Elevated ALP levels were associated with more advanced forms of CAD in patients with stable angina pectoris[11]. To the best of our knowledge, the relationship between ALP and extent and severity of CAD in patients with AMI has not been evaluated previously. The objectives of this study were to investigate serum ALP levels and to determine their relation with the extent and severity of CAD in patients with AMI who underwent primary PCI.

PATIENTS and METHODS

Study Design and Patient Population

This was a prospective, single-center study conducted on 200 patients (140 males and 60 females; age range 33-91 years) with AMI. All patients underwent emergency angiography immediately after admission. Exclusion criteria included patients with history of cardiovascular events, chronic renal failure, malabsorption syndrome, liver and biliary system diseases, active infection, cancer, chronic inflammatory diseases involving the skeletal system, and heart failure and those with history of intake of calcium and/or vitamin D supplements at any time. Our study complies with the World Health Organization Declaration of Helsinki and the World Psychiatric Association, Good Clinical Practices, and Good Laboratory Practice rules. Dumlupınar University ethical committee approved the study protocol.

Angiographic Data

All coronary angiograms were recorded using Siemens Artis Zee (Siemens AG, Munich, Germany) and Shimadzu (Shimadzu Corporation, Kyoto, Japan) devices. Angiographic data were evaluated by two experienced interventional cardiologists who were blinded to the clinical history and laboratory test results of the patients. All obstructive lesions were visualized in two orthogonal views, and a lesion with a visual diameter stenosis of 50% was considered significant. The severity of CAD was calculated for each patient using the Gensini score system and number of vessel disease(12). Gensini score grades the narrowing of the lumen of the coronary arteries as 1 for 1%-25% narrowing, 2 for 26%-50% narrowing, 4 for 51%-75% narrowing, 8 for 76%-90% narrowing, 16 for 91%-99% narrowing, and 32 for total occlusion. The stenosis score was multiplied by a factor taking into account the position of the coronary lesions: 5 for the left main coronary artery, 2.5 for the proximal left anterior descending coronary artery (LAD) or the proximal left circumflex artery (LCX), 1.5 for the mid-region of LAD, 1 for the distal region of LAD and the mid-distal region of LCX or right coronary artery (RCA), and 0.5 for other segments. The Gensini score was expressed as the sum of the scores for all coronary arteries, and a score greater than 40 was defined as advanced CAD.

The number of vessel disease score ranges from one- to three-vessel disease(13). The criterion for one-, two-, or three-vessel disease is a 50% or more reduction in the internal diameter of LAD, LCX, or RCA.

Laboratory Measurements

Venous blood samples were obtained at admission before emergency coronary angiography was performed. Complete blood cell counts were analyzed from the whole-blood samples using a Beckman Coulter LH 780 Gen-S automated hematology instrument (Beckman Coulter, Miami, FL, USA) with original reagents. Serum biochemical parameters were measured using a Beckman Coulter AU680 instrument (Beckman Coulter, Miami, FL, USA) with original reagents. Serum hormone levels were measured on Beckman Coulter UniCelDxI 800 immunoassay analyzer (Beckman Coulter, Miami, FL, USA) with chemiluminescence immunoassay using original assay reagents (Beckman Coulter, Miami, FL, USA). The normal range of measured ALP levels was 30-120 U/L. Patients with serum ALP levels higher than 120 U/L were classified as elevated ALP group.

Statistical Analysis

The normal distributions of continuous variables were evaluated using Shapiro-Wilk test. The results with normal distribution were expressed as mean ± standard deviation, while non-normal distribution data were expressed as median with interquartile range (25^{th}-75^{th} percentiles) for continuous variables. Categorical variables were expressed as percentages. Statistical analyses were performed using SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA). For continuous variables, the differences between two groups were compared using Student's t-test for normally distributed data and Mann-Whitney U-test for non-parametric data. Categorical parameters were analyzed using $\chi 2$ test. Correlation was assessed using Pearson's correlation coefficient. $p< 0.05$ was considered as statistically significant for all tests.

RESULTS

Table 1 shows the demographic characteristics, clinical features, and laboratory findings of the study population. A total of 200 patients with a mean age of 63.8 ± 12.2 years (ranging from 33 to 91 years) were enrolled in the study. The infarct-related artery was LAD in 42% of patients and RCA and LCX in 33% and 25% of patients, respectively. Primary PCI was performed in 84.5% of patients (n= 169), and 13% of patients (n= 26) underwent coronary artery bypass grafting; 2.5% of patients (n= 5) were treated without reperfusion therapy. Nearly half of the patients (57%, n= 114) had ST-segment elevation myocardial infarction (STEMI). The median Gensini score was 52, and 71% (n= 142) of the patients were found to have advanced CAD (Gensini score > 40). The median ALP level was 80 IU/L in the study population (ranging from 3 to 349 U/L). ALP levels outside the normal range (< 30 or > 120 IU/L) were observed in 26 (13%) patients including 3 (1.5%) having ALP < 30 IU/L and 23 (11.5%) having ALP > 120 IU/L. There was no relationship between the ALP level and the Gensini score in the study population (r= –0.063, p= 0.38) (Figure 1). The demographic and clinical characteristics of groups in terms of the Gensini score (≤ 40 and > 40) are shown in Table 2. Patients with advanced CAD (Gensini score > 40) were more elderly than

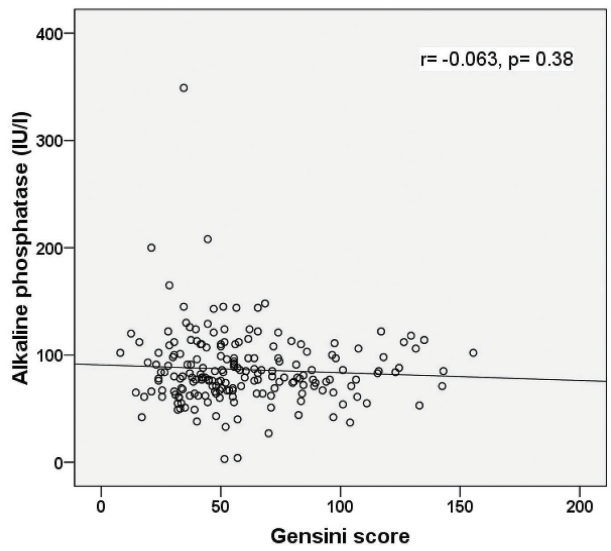

Figure 1. Correlation between alkaline phosphatase levels and Gensini scores of the study population.

Table 1. Demographic characteristics, clinical features, and laboratory results of the study population

Parameters	n= 200
Age (years)	63.8 ± 12.2
Gender, male, n (%)	140 (70%)
Hypertension, n (%)	91 (46%)
Diabetes mellitus, n (%)	85 (43%)
Smoking, n (%)	73 (37%)
STEMI, n (%)	114 (57%)
Glucose, mg/dL	141 (110-200)
Hemoglobin A1c, %	6.1 (5.6-7.9)
Creatinine, mg/dL	0.94 (0.81-1.08)
Uric acid, mg/dL	5.3 (4.5-6.2)
Calcium, mg/dL	9.2(8.9-9.6)
Phosphate, mg/dL	3.1 ± 0.7
Total cholesterol, mg/dL	192 (166-229)
Triglyceride, mg/dL	144 (94-212)
HDL-C (mg/dL)	40 (32-48)
LDL-C, mg/dL	124 ± 38
CRP, mg/L	2.8 (0.8-6.5)
Hemoglobin, g/dL	14.0 ± 1.7
Hematocrit, %	42.2 ± 4.7
Platelet, ×1000/μL	244 (198-296)
Neutrophil, ×1000/μL	7.0 (5.1-9.2)
Lymphocyte, ×1000/μL	2.0 (1.4-2.7)
Neutrophil-to-Lymphocyte ratio	3.55 (1.92-5.82)
Alkaline phosphatase, U/L	80 (67-102)
Elevated alkaline phosphatase, n (%)	23 (12%)
Parathormone, pg/mL	53 (37-78)
25(OH)D, ng/mL	10.0 (6.0-15.8)
Gensini score	52 (38-76)
Gensini score > 40, n (%)	142 (71%)
1-vessel disease, n (%)	75 (38%)
2-vessel disease, n (%)	73 (36%)
3-vessel disease, n (%)	52 (26%)

Values are presented as mean ± standard deviation or median with interquartile range. STEMI: ST-segment elevation myocardial infarction, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CRP: C-reactive protein, 25(OH)D: 25-hydroxyvitamin D.

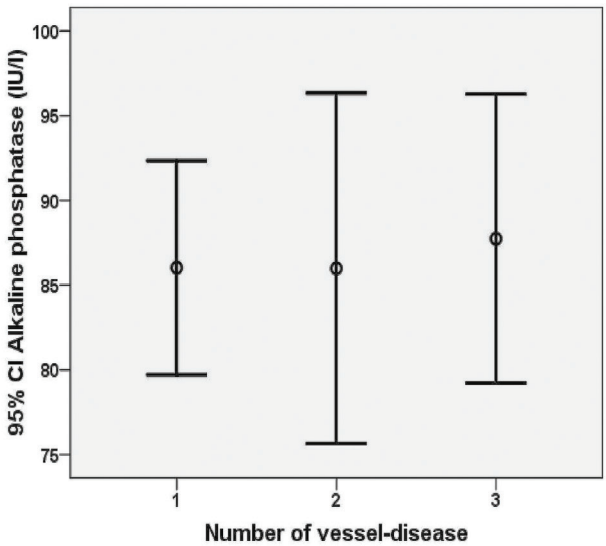

Figure 2. Alkaline phosphatase levels and standard error for number of vessel disease.

those without advanced CAD (Gensini score ≤ 40) (p= 0.040). There was no difference between the groups in terms of ALP levels (p= 0.906). In patients with advanced CAD, STEMI was more common and neutrophil count and parathormone (PTH) levels were significantly higher than those in patients without advanced CAD. When patients were grouped according to the number of vessel disease, still no difference was found in terms of ALP levels between one-, two-, three-vessel groups (Figure 2). Patients with non–ST-segment elevation myocardial infarction (NSTEMI) had significantly higher ALP levels than those with STEMI [8 (71-110) IU/L vs. 77 (64-97) IU/L; p= 0.015)]. There were 85 patients (42.5%) with diabetes mellitus in the study population. The median Gensini scores and the proportions of patients with advanced CAD were similar in the diabetic and nondiabetic patient groups. In the diabetic group, the frequency of hypertension was higher and number of males and smokers were lower (Table 3). Serum glucose, hemoglobin A1c, triglyceride, and ALP levels were significantly higher and vitamin D levels were significantly lower in the diabetic group than in the non-diabetic group.

DISCUSSION

The present study aimed to evaluate the association between ALP levels and the severity and extent of atherosclerotic lesions of coronary arteries in patients with AMI. The main finding of our study is that ALP levels were not associated with the extent and severity of CAD assessed using Gensini scores in patients with AMI.

Early risk stratification in patients with AMI is essential to identify those at the highest risk for further cardiac events who may benefit from a more aggressive therapeutic approach. Analyses from several large clinical trials and registries have established numerous clinical predictors of adverse outcomes among patients with AMI. ALP is a relatively new risk marker predicting adverse outcomes among survivors of AMI[9]. It is also an independent predictor of mortality, myocardial infarction, and stent thrombosis in CAD patients who undergo PCI with drug-eluting stents[10]. These results have led to a focus on ALP in patients with CAD. Sahin et al. showed that elevated ALP levels are associated with high Gensini scores and a more severe form of CAD[11]. However, whether ALP is associated with the extent and severity of CAD in AMI patients was unknown. Our study is the first to demonstrate the absence of such a relationship using Gensini scores and number of vessel disease.

Abnormalities in bone mineral metabolism parameters such as plasma phosphate, PTH, and 25-hydroxyvitamin D [25(OH)D] are associated with cardiovascular outcomes not only in patients with end-stage renal disease but also in subjects with CAD[14,15]. Previous studies showed that the association between ALP and mortality was independent of PTH or vitamin D status[7,16]. In our study, we determined PTH and vitamin D status of patients, which have been suggested to affect ALP levels. Unlike ALP and 25(OH)D levels, PTH levels were significantly higher in the advanced CAD group. PTH can stimulate insulin resistance, inflammation, and renin–angiotensin aldosterone system. These metabolic changes upregulate the process of atherosclerosis, leading to CAD[9]. Therefore, high PTH levels may be a predictor of the extent and severity of CAD in AMI.

Inflammation plays an important role in the evolution of atherosclerosis, and white blood cell count is a proven biomarker of inflammation. Neutrophils are associated with increased blood viscosity and hypercoagulability, and increased neutrophil count was shown to be related to the presence and severity of coronary atherosclerosis[17,18]. Increase in neutrophil count in patients with STEMI is associated with a short-term prognosis and infarct size, and neutrophils mediate the inflammatory response resulting from acute myocardial damage. In our study, neutrophil count was higher in the advanced CAD group. Therefore, neutrophil count seems to be related to the severity of CAD in AMI.

Chen at al. found that compared with the nondiabetic controls, serum ALP levels were increased in patients with type 2 diabetes mellitus[19]. This was also observed in diabetic animal models, and it was suggested that in the diabetic rat intestine, ALP levels may increase, while ALP degradation may decrease[20]. In our study, we found that serum ALP levels were significantly higher in diabetic patients than in non-diabetic patients. Additionally, serum 25(OH)D levels were significantly lower in the diabetic group. In the National Health and Nutrition Examination Study, the prevalence of CAD (angina, myocardial infarction) was more common in adults with low vitamin D levels[21]. Low vitamin D concentrations

Table 2. Distribution of the clinical and demographic characteristics of patients according to the severity of coronary artery disease

Parameters	Gensini ≤ 40 (n= 58)	Gensini > 40 (n= 142)	p
Age, years	60.9 ± 13.1	65.0 ± 11.7	0.040
Gender, male, n (%)	44 (76%)	96 (68%)	0.248
Hypertension, n (%)	28 (48%)	63 (44%)	0.705
Diabetes mellitus, n (%)	25 (43%)	60 (42%)	0.949
Smoking, n (%)	20 (34%)	54 (38%)	0.392
STEMI, n (%)	25 (43%)	89 (63%)	0.024
Glucose, mg/dL	129 (102-199)	143 (114-210)	0.105
Hemoglobin A1c, %	6.0 (5.5-8.3)	6.1 (5.7-7.7)	0.762
Creatinine, mg/dL	0.92 (0.77-1.10)	0.95 (0.40-1.07)	0.265
Uric acid, mg/dL	5.4 (4.4-5.9)	5.3 (4.7-6.4)	0.439
Calcium, mg/dL	9.4 (8.9-9.6)	9.2 (8.9-9.5)	0.546
Phosphate, mg/dL	3.1 ± 0.7	3.1 ± 0.7	0.749
Total cholesterol, mg/dL	194 (165-218)	191 (166-236)	0.734
Triglyceride, mg/dL	171 (100-248)	152 (93-194)	0.422
HDL-C, mg/dL	36 (30-44)	38 (33-51)	0.716
LDL-C, mg/dL	120 ± 36	125 ± 38	0.389
CRP, mg/L	2.9 (0.4-6.6)	2.8 (1.0-6.1)	0.795
Hemoglobin, g/dL	14.2 ± 1.6	14.0 ± 1.7	0.286
Hematocrit, %	42.9 ± 4.4	41.9 ± 4.9	0.153
Platelet, ×1000/μL	253 (196-290)	241 (199-300)	0.956
Neutrophil, ×1000/μL	6.0 (4.7-8.3)	7.3 (5.3-9.7)	0.034
Lymphocyte, ×1000/μL	1.9 (1.4-2.8)	2.0 (1.4-2.7)	0.573
Neutrophil-to-Lymphocyte ratio	3.31 (1.74-5.11)	3.6 (2.0-6.4)	0.373
Alkaline phosphatase, U/L	80 (63-102)	81 (69-100)	0.906
Parathormone, pg/mL	48 (33-63)	54 (39-80)	0.030
25(OH)D, ng/mL	9.0 (6.4-14.0)	10.0 (6.0-17.0)	0.551
Gensini score	32 (25-37)	65 (51-86)	< 0.001
1-vessel disease, n (%)	41 (71%)	34 (24%)	< 0.001
2-vessel disease, n (%)	15 (26%)	58 (41%)	0.046
3-vessel disease, n (%)	2 (3%)	50 (35%)	< 0.001

Values are presented as mean ± standard deviation or median with interquartile range. STEMI: ST-segment elevation myocardial infarction, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CRP: C-reactive protein; 25(OH)D: 25-hydroxyvitamin D.

are associated with an increased risk of macrovascular and microvascular disease events in patients with type 2 diabetes[22]. Vitamin D levels are lower in individuals with type 2 diabetes, but the causality of this relationship is unknown. Low vitamin D levels are proposed to be associated with insulin resistance and insulin secretion derangements, resulting in the development of diabetes mellitus[23]. The relationship between high ALP levels and low 25(OH) D levels in type 2 diabetes mellitus and the clinical significance of this association in AMI patients should be investigated in future studies.

It is known that short-term mortality is lower in patients with NSTEMI (2%-4%) than in those with STEMI (3%-8%)[24]. In contrast to the short-term outcomes, long-term outcomes have been similar or worse with NSTEMI compared with that with STEMI[25-27]. High ALP levels are known to be associated with adverse outcomes among survivors of AMI[9]. But in our study,

Table 3. Distribution of the clinical and demographic characteristics of patients according to the presence of diabetes mellitus

Parameters	DM group (n= 85)	Non-DM group (n= 115)	p
Age, years	65.2 ± 11.2	62.9 ± 12.9	0.183
Gender, male, n (%)	51 (60%)	89 (77%)	0.008
Hypertension, n (%)	56 (66%)	35 (30%)	< 0.001
Smoking, n (%)	26 (31%)	45 (39%)	0.048
STEMI, n (%)	42 (49%)	67 (58%)	0.214
Glucose, mg/dL	213 (153-273)	117 (102-140)	< 0.001
Hemoglobin A1c, %	8.4 (6.9-9.7)	5.7 (5.4-6.0)	< 0.001
Creatinine, mg/dL	0.93 (0.79-1.17)	0.94 (0.85-1.05)	0.950
Uric acid, mg/dL	5.2 (4.3-6.2)	5.4 (4.7-6.2)	0.330
Calcium, mg/dL	9.2 (8.9-9.6)	9.3 (8.9-9.5)	0.490
Phosphate, mg/dL	3.2 ± 0.8	3.1 ± 0.7	0.106
Total cholesterol, mg/dL	195 ± 51	199 ± 43	0.512
Triglyceride, mg/dL	167 (103-221)	133 (90-182)	0.020
HDL-C, mg/dL	38 (30-47)	41 (35-49)	0.085
LDL-C, mg/dL	119 ± 43	128 ± 33	0.103
CRP, mg/L	2.8 (1.0-7.3)	2.8 (0.8-5.7)	0.507
Hemoglobin, g/dL	14.0 (12.9-15.2)	14.3 (12.8-15.3)	0.349
Hematocrit, %	41.8 ± 4.8	42.5 ± 4.7	0.333
Platelet, ×1000/μL	260 (196-302)	232 (199-291)	0.190
Neutrophil, ×1000/μL	7.4 (5.5-9.5)	6.4 (4.8-9.2)	0.184
Lymphocyte, ×1000/μL	2.1 (1.5-2.8)	1.9 (1.3-2.6)	0.339
Neutrophil-to-Lymphocyte ratio	3.6 (1.9-6.0)	3.5 (2.1-5.6)	0.865
Alkaline phosphatase, U/L	86 (71-110)	78 (65-96)	0.022
Parathormone, pg/mL	53 (35-80)	53 (39-73)	0.777
25(OH)D, ng/mL	7.8 (5.0-11.8)	11.0 (7.3-18.5)	< 0.001
Gensini score	52 (38-76)	53 (39-80)	0.964
Gensini score > 40, n (%)	60 (71%)	82 (71%)	0.912
1-vessel disease, n (%)	26 (31%)	49 (43%)	0.083
2-vessel disease, n (%)	31 (36%)	42 (36%)	0.994
3-vessel disease, n (%)	28 (33%)	24 (21%)	0.054

Values are presented as mean ± standard deviation or median with interquartile range. STEMI: ST-segment elevation myocardial infarction, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CRP: C-reactive protein, 25(OH)D: 25-hydroxyvitamin D.

patients with NSTEMI had higher ALP levels than those with STEMI. This conflicting result may indicate that ALP levels alone are not sufficient in determining the mortality risk after AMI.

CONCLUSION

In this study, we found that serum ALP levels do not correlate with the extent and severity of CAD in patients with AMI. However, ALP levels are higher in diabetic patients and in patients with NSTEMI. Higher PTH levels and neutrophil counts are related to the extent and severity of CAD in AMI.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: CK
Analysis/Interpretation: CK
Data Acquisition: CK
Writing: CK
Critical Revision: CK
Final Approval: CK

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