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

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ABSTRACT

Introduction: The serum alkaline phosphatase (ALP) level has 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 the study were to investigate serum ALP levels in patients with AMI, and determine its value in predicting the extent and severity of CAD.

Materials and Method: A total of 200 patients with AMI were included in this study. Serum ALP levels higher than 120 mg/dl were defined as the elevated ALP group. Extent and severity of CAD was assessed by 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 Gensini score in study population. Patients were grouped according to the Gensini score (Gensini score ≤40 and Gensini score >40). There was no difference between the groups in terms of ALP level. However, ALP levels were significantly higher in diabetic patients, and in patients with NSTEMI. Parathormone levels and neutrophil counts were significantly higher in advanced CAD group.

Conclusion: ALP level does not indicate the extent and severity of CAD in patients with AMI. However, ALP levels are higher in diabetic patients and in patients with NSTEMI compared to patients with STEMI. Higher parathormone level and neutrophil count are related to the extent and severity of CAD in AMI.

Keywords: Coronary Angiography; Myocardial Infarction; Coronary Artery Disease; Parathyroid Hormone; Alkaline Phosphatase

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

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ÖZET

Giriş: Serum alkalen fosfataz (ALP) seviyesi, vasküler kalsifikasyon üzerine olan tetikleyici etkisinden dolayı akut miyokard infarktüsünde (AMİ) ve stabil koroner arter hastalığında (KAH) 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 Metod: 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 NSTEMI'lı 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 STEMI hastalarıyla kıyaslandığında NSTEMI hastalarında daha yüksektir. Yüksek parathormon düzeyi ve nötrofil sayısı, AMİ'de KAH yaygınlığı ve ciddiyeti ile ilişkilidir.

Anahtar Kelimeler: Alkalen Fosfataz; Koroner Anjiyografi; Miyokard İnfarktüsü; Koroner Arter Hastalığı; Paratiroid Hormon

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INTRODUCTION

Acute myocardial infarction (AMI) indicates 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 people with various population subgroups[3]. Vascular calcification is recognized both in early and late stages of atherosclerosis. Serum alkaline phosphatase (ALP) is a membrane-bound metalloenzyme that liberating 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 over the pyrophosphate pathway[5]. Circulating ALP and phosphate concentrations often increase in end-stage renal disease. Several clinical and epidemiological studies have linked higher serum ALP and phosphate levels to increased coronary calcification and increased risk of cardiovascular disease events and total mortality in patients with chronic kidney disease[6,7]. Also higher levels of serum phosphate are associated with adverse outcomes among people with normal kidney function[8]. Higher level of ALP is associated with adverse outcomes among survivors of AMI and stroke which was partially explained by its association with established risk factors and inflammation[9]. Higher serum ALP level is 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 the extent and severity of CAD in patients with AMI has not been

evaluated previously. The objective of the study was to investigate serum ALP level, and its relation between the extent and severity of CAD in patients with AMI who were underwent primary PCI.

PATIENTS and METHODS

Study design and patient population

The study was a prospective and single-center study conducted on 200 patients (140 males, 60 females, age range 33–91 years) with AMI. All patients underwent emergency angiography immediately after admission. Exclusion criteria included patients with any history of cardiovascular event, chronic renal failure, malabsorption syndrome, liver and biliary system diseases, active infection, cancer, chronic inflammatory diseases involving the skeletal system, heart failure, and those taking calcium and/or vitamin D supplementation previously 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. Departmental 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 lesion with a visual diameter stenosis of 50% was considered significant. The severity of CAD was calculated for each patient by 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 (LMCA), 2.5 for the proximal left anterior descending coronary artery (LAD) or proximal left circumflex artery (LCX), 1.5 for the mid-region of the LAD artery, 1 for the distal LAD, the mid-distal region of the LCX or right coronary artery (RCA), and 0.5 for other segments. The Gensini score was expressed as the total of the scores for all coronary arteries and a score greater than 40 was defined as advanced CAD.

The possible scores of number of vessel-disease range 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 the LAD, LCX, or RCA. Our study complies with the World Health Organization Declaration of Helsinki and the World Psychiatric Association, Good Clinical Practices and Good Laboratory Practice rules. Departmental ethical committee approved the study protocol.

Laboratory measurements

Venous blood samples were obtained at admission before emergency coronary angiography was performed. Complete blood cell counts were analyzed in the whole blood samples by 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 UniCel DxI 800 immunoassay analyzer (Beckman Coulter, Miami, FL, USA) by chemiluminescence immunoassay using original assay reagents (Beckman Coulter, Miami, FL, USA). The normal range of ALP measurements was 30–120 U/l. Patients with serum ALP levels higher than 120 U/l were defined as the elevated ALP groups.

Statistical analysis

The normal distributions of continuous variables were evaluated with the 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 (25–75th percentiles) for

continuous variables. Categorical variables were expressed as percentages. Statistical analyses were performed by using SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA). For continuous variables, the differences between 2 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 by Chi-square test. Correlation was assessed with 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. LAD was infarct related artery in 42% of patients while RCA was in 33% and LCX in 25% of patients. Primary PCI was performed in 84.5% of patients (n=169) and 13% of patients (n=26) were underwent coronary artery bypass grafting. The 2.5% of patients (n=5) 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 defined to have advanced CAD (Gensini score >40). The median ALP level was 80 IU/l in study population (ranging from 3 to 349 U/l). ALP levels outside the normal range (<30 or >120 IU/l) were observed in 26 patients (13%) including 3 patients (1.5%) having ALP <30 IU/l and 23 patients (11.5%) having ALP >120 IU/l. There was no relationship between the ALP level and Gensini score in study population ($r = -0.063$, $p = 0.38$) (Figure 1). The demographic and clinical characteristics of groups in terms of Gensini score (≤40 and >40) are shown in Table 2. Patients with advanced CAD (Gensini score >40) were more elderly than those without advanced CAD (Gensini score ≤40) ($p=0.040$). There was no difference between the groups in terms of ALP level ($p=0.906$). In patients with advanced CAD, STEMI were more common, neutrophil count and parathormone (PTH) level were significantly higher. When patients were grouped according to the number of vessel-disease, still

there was no difference in terms of ALP levels between three groups (Figure 2). Patients with non-ST-segment elevation myocardial infarction (NSTEMI) have significantly higher ALP levels than STEMI patients [8 (71-110) IU/l vs. 77 (64-97) IU/l, p=0.015)]. There were 85 patients (42.5%) with diabetes mellitus in study population. The median Gensini scores and the proportions of patients with advanced CAD were similar in diabetic and non-diabetic patients groups. In the diabetic group, the frequency of hypertension was higher, and the frequencies of male gender and smokers were lower (Table 3). Serum glucose, hemoglobin A1c, triglyceride, ALP levels were significantly higher and vitamin D levels were significantly lower in the diabetic group.

DISCUSSION

The present study aimed to evaluate the association of ALP level and the severity and extent of atherosclerotic lesions of coronary arteries in patients with AMI. The main finding of our study is that ALP level was not associated with the extent and severity of CAD assessed by Gensini score in patients with AMI.

Early risk stratification in patients with AMI is essential to identify those patients at 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 a number of 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 after PCI with drug eluting stents[10]. All of these results have led to a focus on ALP in patients with CAD. Sahin et al. showed that elevated ALP levels are associated with higher Gensini scores and a more severe form of CAD[11]. However, whether ALP is associated with extent and severity of CAD in AMI patients was unknown. For the first time, our study has demonstrated the absence of such a relationship by using Gensini score 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[7,16]. In our study, we determined PTH and vitamin D status of patients, which have been suggested to affect ALP levels. Unlike the ALP and 25(OH)D levels, PTH level was significantly higher in 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, higher PTH level may be a predictor of extent and severity of CAD in AMI.

Inflammation has 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 short-term prognosis and infarct size and neutrophil mediate the inflammatory response resulting from acute myocardial damage. In our study, neutrophil count was higher in 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 tip 2 diabetes mellitus[19]. This was also observed in diabetic animal models and suggests that in the diabetic rat intestine, ALP may increase while its degradation may decrease[20]. In our study, we found that serum ALP levels were significantly higher in diabetic patients. Additionally, serum 25(OH)D levels were significantly lower in diabetic group. In the National Health and Nutrition Examination Study (NHANES), the prevalence of CAD (angina, myocardial infarction) was more common in adults with lower vitamin D levels[21]. Low vitamin D concentrations are associated with an increased risk of macrovascular and microvascular disease events in type 2

diabetes[22]. Vitamin D status is lower in individuals with type 2 diabetes, but the causality of this relationship is unknown. Low level of vitamin D is proposed to be associated with insulin resistance and insulin secretion derangements resulting in the development of diabetes mellitus[23]. The relation between high ALP levels and low 25(OH)D levels in tip 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 to 4%) compared to patients with STEMI (3 to 8%)[24]. In contrast to the short-term outcomes, long-term outcomes have been similar or worse with NSTEMI when compared to STEMI[25-27]. We know that high ALP levels are associated with adverse outcomes among survivors of AMI[9]. But in our study, patients with NSTEMI have higher ALP levels than STEMI patients. This conflicting result may indicate that ALP is not sufficient in determining the mortality risk after AMI alone.

CONCLUSIONS

In this study, we found that serum ALP level does not correlate with the extent and severity of CAD in patients with AMI. However, ALP level is higher in diabetic patients and in patients with NSTEMI. Higher PTH level and neutrophil count 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.

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Legends for Figures:

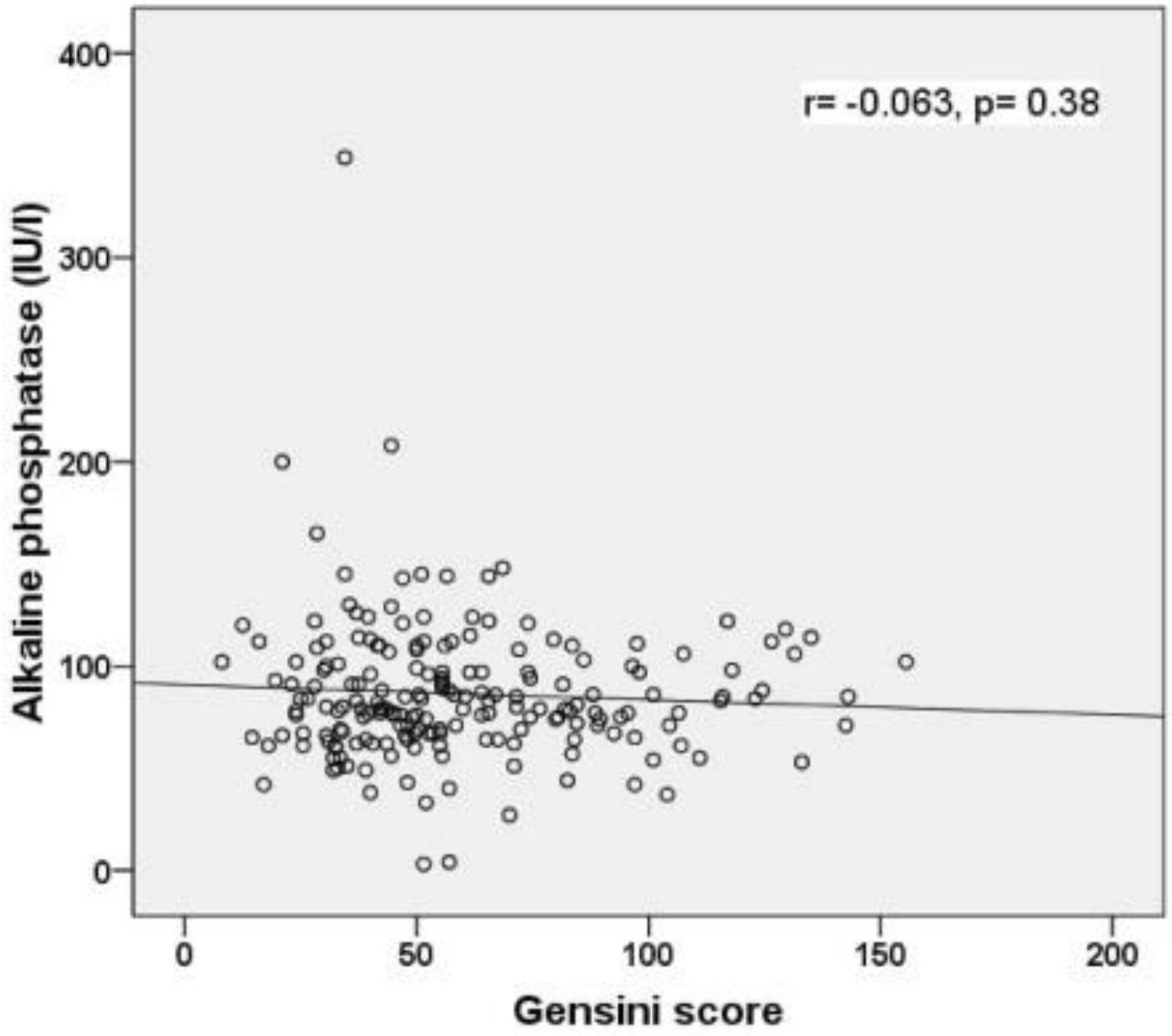

Figure 1. The correlation between alkaline phosphatase levels and Gensini scores of the study population.

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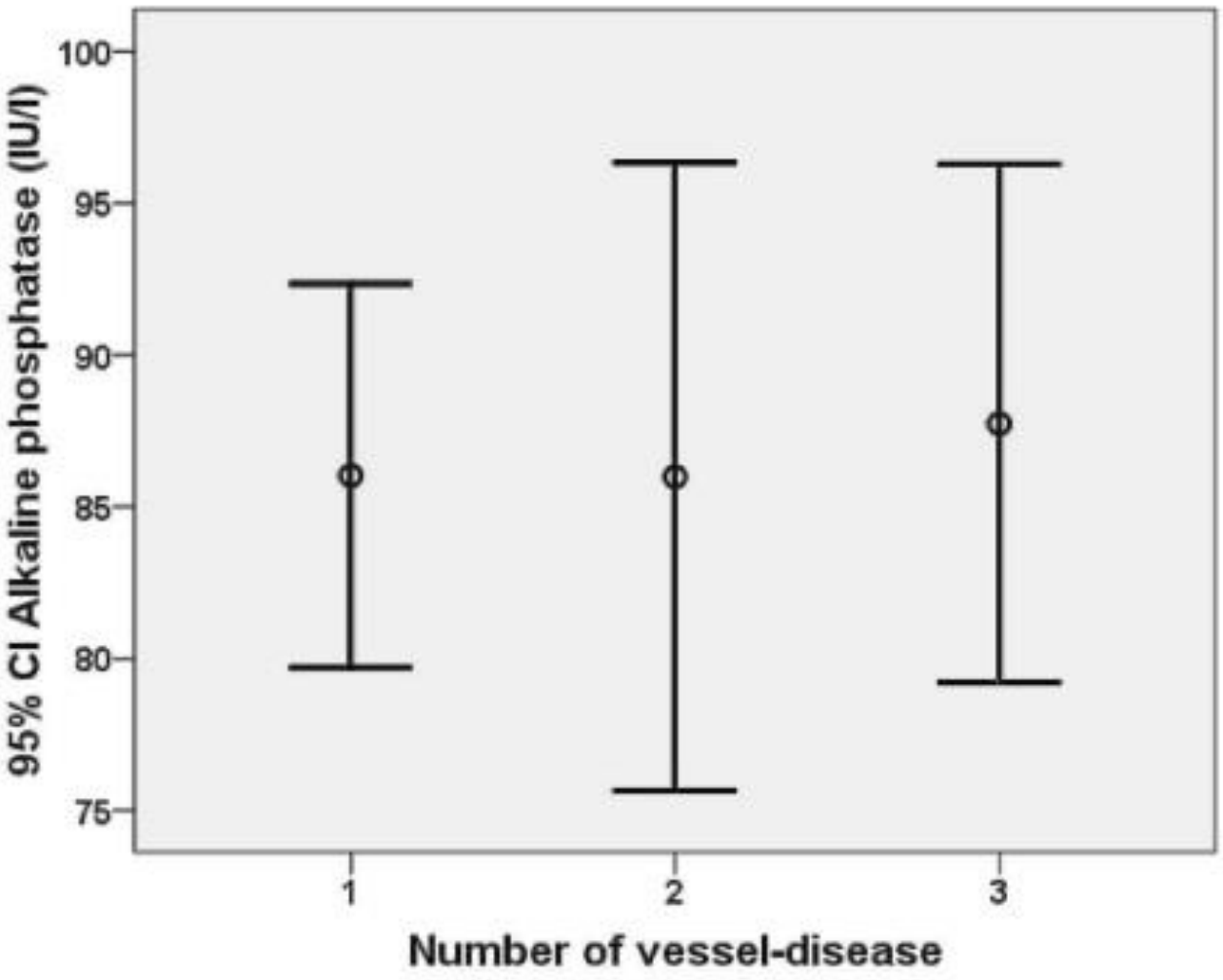

Figure 2. Alkaline phosphatase levels and standard error for numbers of vessel-disease.