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Relationship of serum phosphorus level with acute cerebrovascular disease

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There are no sufficient studies on laboratory parameters associated with acute stroke. Laboratory parameters associated with acute stroke may become important in the prevention or follow-up of the disease. To investigate the relationship between cerebrovascular disease (CVD) and serum phosphorus levels. This study was conducted prospectively to evaluate the relationship between cerebrovascular disease and phosphorus in patients who applied to the Emergency Medicine Clinic of the Faculty of Medicine Hospital and underwent central imaging between March 1, 2023, and December 31, 2023. 299 patients who applied to the university emergency department were prospectively included in the study with brain computed tomography (CT) and diffusion magnetic resonance imaging (MRI). The lactate, white blood cell, hgb, neutrophil, lymphocyte, urea, creatine and phosphorus values of the patients at their first admission were recorded. The patients were divided into two groups: CVD group and control group. The laboratory parameters of the patients were compared according to the groups. In the ROC analysis performed to evaluate the power of laboratory parameters in predicting the diagnosis of CVD, the AUC value of phosphorus was obtained as 0.935, lactate as 0.620 and urea as 0.596. The optimum cut-off value for phosphorus was calculated as 3.47 (mg/dl) and the sensitivity of this cut-off value was found to be 89%, specifically 86.9%, positive predictive value (ppv) as 77.4% and negative predictive value (npv) as 94%. Lactate, urea and phosphorus values were found to be significantly higher in the CVD group compared to the control group. With this study, we found that serum phosphorus levels were higher than our cut-off value in patients with acute ischemic CVD. We believe that serum phosphorus level will be useful in excluding acute cerebrovascular disease due to its high negative predictive value when evaluated according to the cut-off value of 3.47 (mg/dl).

Keywords Phosphorus, Stroke, Ischemic CVD, Laboratory

Neurological diseases are also an important cause of mortality and morbidity associated with the increase in the elderly population. Cerebrovascular disease (CVD) has the largest share among neurological diseases with a rate of 47–67%[1]. Stroke, which accounts for 11.6% of deaths in the world, ranks 2nd in mortality and 3rd in disability, according to the report of the Global Burden of Disease Survey[2]. Classifying stroke is important for reasons such as determining the treatment method to be applied and grouping patients in studies. National Institute of Neurological Disorders and Stroke (UNBIE, NINDS) Stroke Data Bank has divided stroke into five main groups; cerebral hemorrhages, cerebral infarctions (atherothrombotic and tandem arterial pathologies), cardioembolic stroke, lacunar stroke, undetermined or rare causes[3].

Phosphorus takes part in various functions in the body such as cell metabolism, intercellular communication, and osteoblast production[4]. The plasma level of phosphorus, whose serum concentrations show a circadian rhythm, is at its highest concentration in infants (Normal; 4.5–8.3 mg/dl) and decreases with age (Normal; 2.5–4.5 mg/dl). In addition to hormones such as thyrocalcitonin, parathormone (PTH) and calcitriol (1,25-dihydroxycholecalciferol/1,25(OH) 2D3), fibroblast growth factor-23 (FGF-23) and α-klotho, which started to attract attention in the last century, also play a role in phosphorus homeostasis[5]. Recent studies have shown that a decrease in α-klotho levels, an increase in FGF-23 levels and hyperphosphatemia play a role in vascular calcification through various mechanisms. It has also been shown that phosphate causes vascular calcification and apoptosis in a time-dependent manner[6]. High serum phosphorus levels have been associated with mortality in studies on myocardial infarction (MI), as phosphorus has been shown to cause vascular pathologies[7].

Dyslipidemia, a risk factor for stroke, causes stroke through different mechanisms. While high serum HDL levels protect against stroke, triglyceride triggers atherosclerosis and atherothrombosis. High serum LDL

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cholesterol levels cause endothelial dysfunction[8]. There are studies that show that dysnatremia and dyskalemia are associated with acute CVD. In addition, studies have shown that dysnatremia has a significant relationship with stroke severity[9].

Although there are many studies on phosphorus levels and MI, there are few studies on the relationship between CVD and phosphorus. In this study, we wanted to examine the relationship between phosphorus levels, mortality and morbidity in CVD patients, to see whether phosphorus can be used as a prognostic marker in CVD, and to examine the gender-related level difference of phosphorus in patients with CVD because of gender on phosphorus.

Methods

Study design

This study was conducted prospectively to evaluate the relationship between cerebrovascular disease and phosphorus in patients who presented it to the Emergency Medicine Department of the Medical Faculty Hospital between March 1, 2023, and December 31, 2023. Patients who applied to the emergency department with CVD were included in the study.

The age, gender, comorbidities, phosphorus, lactate, and creatinine parameters of the patients included in the study were recorded in the patient files. The patients included in the study were divided into two groups, ischemic cerebrovascular event patients and a control group based on the results of brain CT and brain diffusion MRI. Using the hospital information management system, it was noted whether there was an emergency department outcome, hospital outcome, and in-hospital mortality for both groups.

Exclusion and acceptance criteria

Patients aged 18 and above who were presented to the emergency department and agreed to participate in the study were included. Patients under 18 years old, pregnant, diagnosed with trauma or acute mesenteric ischemia, diagnosed with acute myocardial infarction, presence of diabetes mellitusic ketoacidosis, respiratory alkalosis, acute or chronic renal failure, liver failure, use of bisphosphonates, diuretics, glucocorticoids, vitamin D, calcium preparations, diagnosed with hypothyroidism or hyperthyroidism were excluded from the study. A total of 299 patients were included in the study, with 199 of them being taken as the control group. Patients in the control group did not meet the exclusion criteria and were those who underwent central imaging in the emergency department for any reason. Since we thought that serum phosphorus levels were affected by infarction caused by atherothrombosis, only patients with cerebral infarction were included in the CVD group and patients belonging to the other four groups specified by the NINDS Stroke Data Bank were not included.

Ethical process

Approval was received from the Non-Pharmaceutical and Medical Device Research Ethics Committee.

Statistical analysis

The data analysis was conducted using IBM SPSS Statistics ver. 25 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation, median, and percentage distribution. For comparison of normally distributed parametric variables, the Student T test was used. For non-normally distributed variables, the Mann–Whitney U test was used. For comparison of nominal data, the Chi-Square test and Fisher's Exact test were used. ROC analysis was used to evaluate the ability of laboratory parameters to predict clinical diagnosis. Pearson and Spearman correlation tests were used for correlation analysis. A p-value < 0.05 was considered statistically significant for all analyses.

Results

A total of 299 patients were included in our study. 164 (54.8%) of all patients were male. In the control group, 116 (58.3%) of the patients were male. In the CVD group, 48 (48%) of the patients were male. There was no statistically significant difference between the groups according to gender distribution (p:0.092). The mean age of all patients was 60.92 ± 17.86 and the mean age of the control group was 57.27 ± 19.04. The average age of the CVD group was found to be 68.18 ± 12.46. A statistically significant difference was found between the groups in mean age ($p < 0.01$). When the medical history of all patients is questioned, the most common comorbidities are hypertension (39.8%) and diabetes mellitus (22.7%). In the control group, the most common comorbidities were hypertension (28.6%) and diabetes mellitus (14.6%). Similarly, in patients in the CVD group, the most common orders were hypertension (62%) and diabetes mellitus (39%). The detailed characteristics of the patients and their comparison between groups are presented in Table 1.

When examining the hemogram values of all patients, the mean WBC was found to be 8.94 ± 3.71 (10^3/mm^3), and the mean hemoglobin was 13.5 ± 2.26 g/dl. In the control group, the median WBC value was 8.03 (6.41–9.82) (10^3/mm^3), and the median hemoglobin value was 13.9 (12.8–15.1). In the CVD group, the median WBC value was 8.65 (6.76–10.82) (10^3/mm^3), and the median hemoglobin value was 13.9 (11.95–15) (g/dl). There was no statistically significant difference between the groups in terms of WBC and hemoglobin values (p: 0.137, p: 0.173). The urea, lactate, and creatinine values in the control group were found to be 31.7 (24.6–43.8) (mg/dl), 1.3 (1–2) (mmol/L), and 0.84 (0.73–1.02) (mg/dl), respectively. In the CVD group, urea, lactate, and creatinine values were found to be 37.8 (29.07–49.62) (mg/dl), 1.65 (1.22–2.17) (mmol/L), and 0.89 (0.76–1.06) (mg/dl), respectively. There was a statistically significant difference between the groups in terms of urea, lactate, and creatinine values (p: 0.007, p: 0.001, p: 0.037). The phosphorus value in the control group was found to be 2.96 ± 0.54 (mg/dl). In the CVD group, the phosphorus value was found to be 3.96 ± 0.52 (mg/dl). There was a

Variables	All patients N = 299	Control group N = 199	CVD group N = 100	*P* value
Age	60.92 ± 17.86	57,27 ± 19,04	68,18 ± 12,46	**< 0,001**
Male	164	116	52	0,092
Female	135	83	48	0,092
Diabetes mellitus	68	29	39	**< 0,001**
Hypertension	119	57	62	**< 0,001**
CAD	42	16	26	**< 0,001**
CHF	9	6	3	0,989
Asthma-COPD	21	12	9	0,061
Malignancy	29	25	4	**< 0,001**

Table 1. Demographic characteristics and comorbidities of all patients, control group and CVD group. Significant values are in bold. *CAD: Coronary Artery Disease,* CHF: Congestive Heart Failure * COPD: Chronic Obstructive Pulmonary Disease.

Laboratory parameters	All patients N = 299	Control group N = 199	CVD group N = 100	*P* value
Wbc(10^3/uL)	8,21(6,56–10,31)	8,03(6,41–9,82)	8,65(6,76–10,82)	0,137
Neu(10^3/uL)	5,34(3,90–7,53)	5,29(3,72–7,07)	5,62(4,23–8,11)	0,093
Lyn(10^3/uL)	1,79(1,19–2,37)	1,79(1,17-–2,37)	1,75(1,21–2,45)	0,670
Hgb(g/dl)	13,8(12,3–15,0)	13,9(12,8–15,1)	13,4(11,9–15,0)	0,173
Nlr	2,96(1,84–5,09)	2,76(1,90–5,03)	3,30(1,83–5,79)	0,388
Urea (mg/dl)	34,0(26,5–45,6)	31,7(24,6–43,8)	37,8(29,1–49,6)	**0,007**
Creatine (mg/dl)	0,86(0,73–1,04)	0,84(0,73–1,02)	0,89(0,76–1,06)	**0,037**
Lactate (mmol/L)	1,4(1,1–2,1)	1,3(1,0–2,0)	1,7(1,3–2,2)	**0,001**
Phosphorus (mg/dl)	3,29 ± 0,71	2,96 ± 0,54	3,96 ± 0,52	**< 0,001**

Table 2. Comparison of laboratory values of patients. Significant values are in bold. *Neu: neutrophil, Lyn: lymphocyte, Hgb: hemoglobin Nlr: neutrophil lymphocyte ratio.

	Phosphorus
AUC(95% CL)	0,935(0,904–0,967)
Cut-off value	> 3,47
Sensitivity	%89
Specificity	%86,9
Ppv	%77,4
Npv	%94
Plr	6,739
Nlr	0,126

Table 3. Cut-off, specificity, sensitivity, ppv and npv value of phosphorus.

statistically significant difference between the groups in terms of phosphorus values ($p < 0.001$). The comparison of laboratory parameters between groups is indicated in Table 2.

In the ROC analysis conducted to evaluate the power of laboratory parameters in predicting the diagnosis of CVD, phosphorus, lactate, and urea had AUC values of 0.935, 0.620, and 0.596, respectively. The optimal cut-off value for phosphorus was calculated to be 3.47 (mg/dl). At this cut-off value, the sensitivity was found to be 89%, specificity was 86.9%, positive predictive value (PPV) was 77.4%, negative predictive value (NPV) was 94%, positive likelihood ratio (PLR) was 6.793, and negative likelihood ratio (NLR) was 0.126. The likelihood of diagnosing CVD was found to be 53.83 times higher when phosphorus levels were above 3.47 (mg/dl) compared to when they were below this value. The cut-off value, specificity, sensitivity, PPV, and NPV of phosphorus are shown in Table 3. The ROC curve for predicting phosphorus, lactate, and urea in CVD is shown in Fig. 1.

When examining the correlation between serum phosphorus levels and age, no correlation was found in either group (CVD group p: 0.865, control group p: 0.551). To investigate the relationship between gender and serum phosphorus levels, the serum phosphorus levels of male and female patients were compared separately in both groups, and no statistically significant difference was found in either group (control group p: 0.530, CVD group p: 0.946).

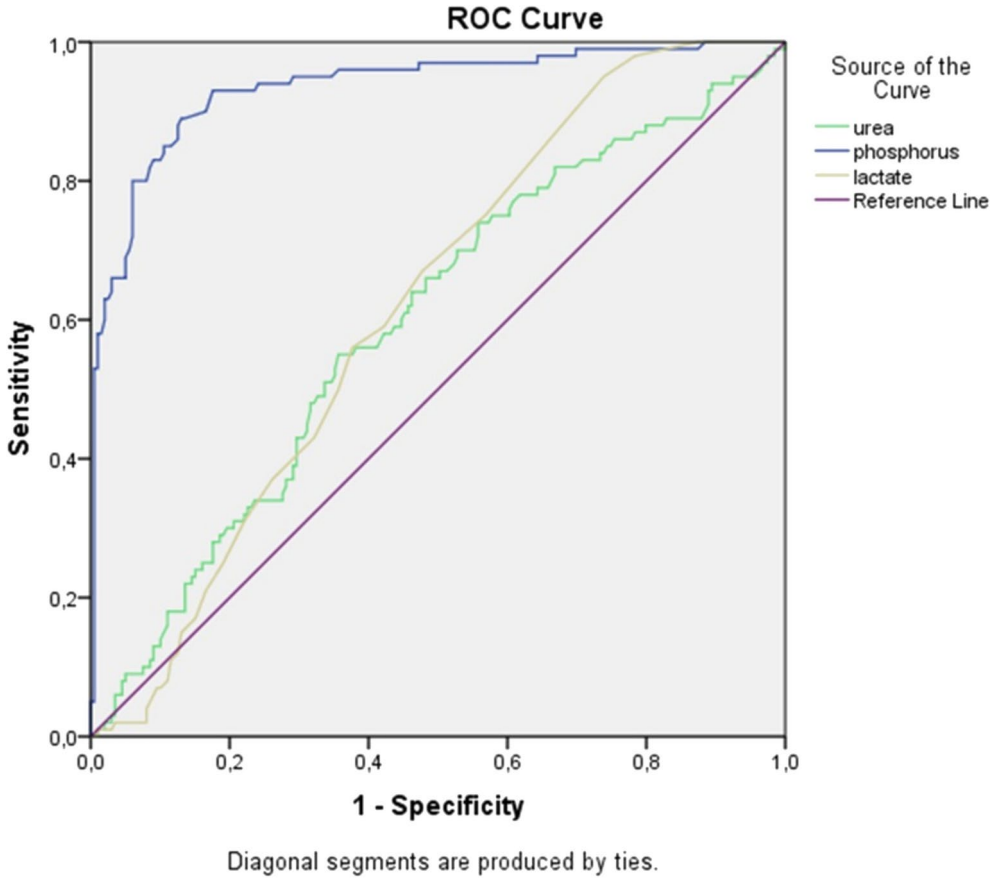

Fig. 1. ROC curve for the predictive power of phosphorus, lactate, urea in CVO.

Discussion

This study focused on the relationship between acute cerebrovascular disease and serum phosphorus levels. In instance, we would like to point out that phosphorus levels are higher in acute CVD. We also determined the cut-off value for phosphorus levels in the acute period as 3.47 (mg/dl).

Phosphorus is one of the macro elements that regulate the acid–base balance in the body[10]. Phosphorus plays an active role in energy production in ATP, one of the fundamental building blocks of life. Serum phosphorus levels vary depending on biological and environmental factors. There are studies indicating that high serum phosphorus levels are a risk factor for vascular calcification[11,12]. In vitro studies have shown that vascular smooth muscle cells do not mineralize spontaneously in culture; however, when the phosphorus level in the culture medium is increased to the level found in hyperphosphatemic patients (>2 mmol), mineralization begins[11–16]. These studies have found that high phosphate levels increase osteochondrogenic markers and induce a transition to a bone-forming phenotype and apoptosis due to phosphate accumulation[17,18]. Kidney functions are important in phosphorus metabolism. In acute or chronic kidney failure, serum phosphorus levels increase. In a study conducted by Park et al. involving 6,329 patients with normal kidney function, they investigated the relationship between serum phosphorus levels and coronary atherosclerosis. They found that an increase in serum phosphorus levels was associated with a higher risk of developing coronary calcified plaques[19]. Park et al. observed a positive correlation between serum phosphorus levels and in-hospital heart failure, heart failure at discharge, in-hospital mortality, and mortality at discharge in patients who had experienced acute myocardial infarction[7]. In a study by Karabulut et al. on the relationship between mesenteric ischemia and serum phosphorus levels in experimental animals, a statistically significant difference in serum phosphorus levels was found between the control group and the ischemia group[20]. There are not many studies in the literature investigating the relationship between serum phosphorus levels and CVD. In a study by Talebi et al. examining the relationship between CVD and phosphorus, they found the average serum phosphorus level to be 4.2 mg/dl in the control group and 3.6 mg/dl in the SVO group[21]. In our study, we found the average serum phosphorus level to be 2.96 mg/dl in the control group and 3.96 mg/dl in the SVO group. The results of our study are not consistent with the results of this literature. We believe this difference is due to the insufficient exclusion criteria in the study conducted by Talebi et al.It is likely that patients with acute or chronic kidney failure, liver failure, hypothyroidism or hyperthyroidism (which can alter phosphorus metabolism), and those using bisphosphonates, diuretics, glucocorticosteroids, vitamin D, or calcium preparations were not excluded from their study. Additionally, we observed that the control group in Talebi et al. 's study consisted of patients selected for cataract surgery. Studies have shown that patients with cataracts tend to have higher serum phosphorus levels[22].

The use of laboratory analyses for diagnostic purposes in ischemic CVD is not common. Generally, laboratory parameters are used to determine the suitability for thrombolytic therapy or mechanical thrombectomy. In our study, a statistically significant difference was found in urea values between the CVD group and the control group (p: 0.007). Upon reviewing the literature, we found that there are not many studies investigating the relationship between urea and the diagnosis of CVD. Jingfeng et al. in a study examining risk factors between a known type 2 diabetes mellitus complication group with CVD and a control group, did not find a significant difference in urea values between the two groups[23]. In a study by Swerdel et al. they investigated the relationship between dehydration and CVD in patients with atrial fibrillation, and found a short-term association between dehydration and CVD[24]. There are studies indicating that urea levels not only increase in renal failure but also in conditions such as sepsis and dehydration[25]. In a study by Li et al., it was found that patients with low urea levels had a higher risk of experiencing CVD compared to patients with high urea levels[26]. In our study, patients with laboratory values of urea and creatinine above the upper limit were excluded from the study as acute or chronic kidney failure can alter the phosphorus shift and thus change the statistical analysis of the phosphorus-CVD relationship, which is our main objective. More studies are needed to understand the relationship between urea and CVD diagnosis. Lactic acid is a molecule that rises in the body due to tissue hypoxia and poor tissue perfusion. Several studies indicate significantly elevated levels of lactic acid in necrosis and ischemia[27,28]. We found higher lactate levels in our study compared to the control group. Studies have been conducted on lactate as a predictor of disease severity and mortality in various conditions such as trauma, dehydration, shock, hyperthermia, epilepsy, sepsis, and hypoxia[29–34].

In the study conducted by Altıparmak et al. on SVO patients, 56% of the patients were found to be male[35]. In the study conducted by Betaş et al., 53% of the patients who experienced ischemic CVD were found to be male[36]. In our study, we found a higher proportion of female patients in the CVD group compared to the literature. We attributed this to the higher prevalence of major risk factors for ischemic CVD, such as diabetes mellitus, hypertension, and coronary artery disease, among the female patients in the CVD group. In our study, the mean age of the control group was 57.3, while the mean age of the CVD group was 68.1. There was a statistically significant difference in the mean age between the groups ($p < 0.01$). In a study by Altıparmak et al. regarding the prognosis of ischemic CVD patients, the mean age was found to be 67.6[35]. In a study by Karpal et al. regarding CVD, the mean age was found to be 71[37]. Our study is consistent with the literature. The higher average age of the SVO group compared to the control group is thought to be due to the increase in CVD frequency with age. It has been reported that the risk of ischemic CVD increases by 1.66 times in men and 1.93 times in women every 10 years of age[38]. In the 2012 update of the American Heart Association's guidelines on CVD, it was reported that the incidence of CVD increases with age, doubling every 10 years after the age of 55[39]. In our study, the most common comorbidities in the control group were hypertension (28.6%) and diabetes mellitus (14.6%), respectively. Similarly, in the CVD group, the order was the same with hypertension (62%) and diabetes mellitus (39%). Hypertension is the most important modifiable risk factor for ischemic CVD[40]. It is the second most important risk factor after age for ischemic SVO among all risk factors[41]. In individuals with normal blood pressure, an increase in mean arterial pressure causes vasoconstriction in the cerebral arteries. This keeps cerebral blood flow constant and maintains blood flow at the blood–brain barrier. In hypertensive patients, however, this autoregulation mechanism operates at higher mean arterial pressure values[41]. Li et al. conducted a study with 223,097 patients hospitalized with a diagnosis of hypertension. In this study, 4.99% of the patients experienced cerebrovascular events as complications, and 71.18% of these were classified as ischemic CVD[42]. In a retrospective study conducted by Chang et al., hypertension was found in 59.7% of the ischemic CVD patient group as an additional disease, while this rate was found to be 43.3% in the control group[43]. Diabetes mellitus is one of the most important modifiable risk factors for ischemic CVD. Chronic hyperglycemia leads to endothelial damage and sets the stage for atherosclerosis. Diabetes mellitus cause oxidative stress, protein kinase C activation, and advanced glycation product receptor activation, along with hyperglycemia, increased free fatty acids, and insulin resistance. Due to these molecular products, the risk of vasoconstriction, inflammation, and thrombosis increases[44]. In the Framingham study, the incidence of ischemic stroke was found to be 2.5 times higher in diabetes mellitusic men and 3.6 times higher in diabetes mellitusic women[45]. In studies, patients with known diabetes mellitus who experienced ischemic CVD had a significantly higher rate of comorbid hypertension[46,47]. In a study investigating the relationship between diabetes mellitus and CVD, the incidence of CVD was found to be 0.538% in those with diabetes mellituses and 0.151% in those without diabetes mellituses[48]. In a study by Kuusisto et al., the rate of experiencing CVD in patients with diabetes mellituses was found to be 6.1%, while in those without diabetes mellituses, this rate was found to be 3.4%[49]. Additionally, in this study, the incidence of SVO was found to be significantly higher in women with diabetes mellituses compared to those without diabetes mellituses[49]. In a study by Banerjee et al., diabetes mellituses was found to be associated with an increased risk of ischemic stroke[50]. Our study is consistent with the literature.

Limitations

Our study had some limitations. The first limitation was that there was a statistically significant age difference between the CVD group and the control group. Studies without an age difference between groups would yield more accurate data. However, when the phosphorus levels were examined according to age between the groups, no correlation was found between phosphorus and age.

Secondly, the patients' serum phosphorus levels were measured from blood samples taken at the time of admission. Due to the emergency department's workflow, follow-up serum phosphorus levels were not monitored. It was not checked how long the serum phosphorus levels remained elevated after the onset of symptoms.

To associate serum phosphorus levels with CVD, the serum phosphorus levels of the patients in the CVD group during their healthy period before the onset of symptoms could not be evaluated. Knowing the basal

serum phosphorus levels of the patients would contribute to the literature to investigate whether CVD causes increased serum phosphorus levels or whether high serum phosphorus levels cause CVD.

Conclusion

In our study, we investigated the relationship between acute ischemic cerebrovascular disease and serum phosphorus levels. We demonstrated that serum phosphorus levels were higher in patients who experienced an acute cerebrovascular disease.

When evaluating our study based on the serum phosphorus level cut-off value of 3.47 (mg/dl), we found that serum phosphorus levels below this value had a 94% NPV. This suggests that low serum phosphorus levels could be used to exclude acute CVD.

In our study, serum phosphorus levels were measured from blood samples taken at the time of admission, and no repeated measurements were made. Further studies on this subject could show whether repeated serum phosphorus measurements are useful in the diagnosis of CVD. To understand the relationship between CVD and phosphorus, multi-center studies need to be conducted.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Received: 28 February 2025; Accepted: 29 April 2025
Published online: 09 May 2025

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Author contributions

S.A prepared figure and all tables S.A. and AS.G. wrote the main manuscript MK.A and K.K performed the statistical analysis All authors reviewed the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Drugs and Medical Devices Non-Interventional Research of Necmettin Erbakan University Faculty of Medicine on 06/03/2023 with decision number 2023/4235.

Consent for publication

Patients and/or their relatives were informed that the data obtained from the patients would be used for the article without their names being added and that it could be published in journals worldwide, and written informed consent was obtained from each patient.

Human and animal rights

During the research, the World Medical Association (WMA) Declaration of HELSINKI and/ or the World Psychiatric Association HAWAII Declaration of Good Clinical Practice rules were complied with.

Additional information

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