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# The utility of serum calcium and phosphate levels for determining mortality in patients with acute ischemic stroke

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**Abstract**

The most common form of stroke presents as ischemic stroke. For these patients, the primary goals of stroke management in the emergency department are revascularization and minimizing secondary neuronal damage via thrombolytic therapy and/or endovascular thrombectomy. However, in addition to improvements in the treatment of stroke, preventive measures to avoid stroke occurrence have been the focus of considerable recent research interest. Calcium and phosphorus are important elements in many structural components and cellular processes in the body. The aim of the study was to evaluate the role of serum calcium and phosphorus levels on the mortality of patients with acute ischemic stroke (AIS). The data of 1,204 patients admitted to the emergency department of our secondary state hospital between 2019 and 2021, and subsequently hospitalized for diagnosis of AIS, were analyzed. Our results showed that low serum calcium levels associated with mortality in AIS patients, but phosphate levels have no effect on mortality of patients with AIS.

**Keywords:** Acute schemic stroke, mortality, calcium, phosphate

## Introduction

Stroke is a cause of death and disability in underdeveloped countries [1]. Studies conducted in recent years have shown an increase in the frequency of stroke. In fact, stroke is the second cause of death and the third cause of long-term acquired disability worldwide [2]. Therefore, stroke is a global public health problem that imposes a considerable economic burden on patients, their families, and society [3]. The implementation of stroke prevention programs and the early diagnosis and treatment of stroke should thus be prioritized. The most common form of stroke is ischemic stroke [4]. For these patients, the primary goals of stroke management in the emergency department (ED) are revascularization and minimizing secondary neuronal damage, achieved with thrombolytic therapy and/or endovascular thrombectomy. However, in addition to improvements in the treatment of stroke, measures aimed at stroke prevention have been the focus of growing research attention.

Calcium and phosphorus are essential to many structural components and cellular processes in the body. Calcium is required for intracellular signal transmission, muscle contraction, coagulation pathways, and bone structure [5], whereas phosphorus serves to cellular signal mechanism, mineral metabolism, and energy pathways, among other processes. However, increased calcium and phosphate levels cause vascular calcification and endothelial dysfunction, while decreased calcium levels cause coagulopathy, leading to vascular diseases [6]. There are a few studies about the relationship between serum calcium and phosphate levels with acute ischemic stroke (AIS) [5,7]. In our study, we measured serum calcium and phosphorus levels on admision to investigate their effects on mortality in patients diagnosed with AIS in the ED.

## Material and Methods

This was a retrospective, observational, single-center study that included patients admitted for AIS to Tokat State Hospital Emergency Service between 2019 and 2021. Ethics committee of Tokat Gaziosmanpasa University approved the study (22-KAEK-133, date 13.03.2023).

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Patients with malignancy, neoplastic hematological diseases, or immunosuppressant drug use were excluded, as were patients who had suffered a major trauma or undergone surgery in the last 3 months, patients with renal failure or liver failure, and patients whose blood test results and other data were missing from the hospital information system.

### Statistical Analysis

Data were analyzed using SPSS for Windows software (version 15.0; IBM Corp.,USA). Categorical variables are expressed as numbers with percentage, whereas numerical variables are expressed as medians with range. P-values < 0.05 were considered indicative of statistical significance.

## Results

This study included 621 women (51.6%), 583 men (48.4%) totally 1,204 patients with a median age of 74 (range: 20–100) years, of whom 190 (15.8%) died due to AIS and 1,014 (84.2%) were survived. The median age was significantly higher for patients who non-survived than those who survived (78 [range: 29–95] and 73 [range: 20–100] years, respectively; p<0.001; Table 1).

**Table 1.** Comparison of demographic and clinical characteristics in survivors and non-survivors

| Characteristic | | Total n=1204 | Non-survivors n=190 (15.8%) | Survivors n=1014 (84.2%) | p* |
|---|---|---|---|---|---|
| Gender n (%) | Male | 583 (48.4) | 87 (45.8) | 496 (48.9) | 0.429 |
| | Female | 621 (51.6) | 103 (54.2) | 518 (51.1) | |
| Age Median (Min-Max) | | 74 (20-100) | 78 (29-95) | 73 (20-100) | <0.001 |
| Comorbidity n (%) | No | 153 (12.7) | 25 (13.2) | 128 (12.6) | 0.839 |
| | Yes | 1051 (87.3) | 165 (86.8) | 886 (87.4) | |
| | CAD | 289 (24.0) | 51 (26.8) | 238 (23.5) | 0.318 |
| | Arrhythmia | 176 (14.6) | 26 (13.7) | 150 (14.8) | 0.691 |
| | HT | 817 (67.9) | 126 (66.3) | 691 (68.1) | 0.62 |
| | DM | 298 (24.8) | 39 (20.5) | 259 (25.5) | 0.141 |
| | Hiperlipidemia | 129 (10.7) | 25 (13.2) | 104 (10.3) | 0.235 |
| | CVD | 376 (31.2) | 76 (40.0) | 300 (29.6) | 0.004 |
| | Other | 54 (4.5) | 13 (6.8) | 41 (4.0) | 0.087 |

CAD: coronary artery disease, HT: hypertension, DM: diabetes mellitus, CVD: cerebrobascular disease, Data are expressed as number (n), percentage (%), median, *Intergroup comparisons (Non-Survivors vs. Survivors) were conducted by chi-squared and Mann–Whitney U tests, as appropriate.

Within the study population, 153 (12.7%) patients had no comorbidities and 1,051 (87.3%) had at least one comorbidity, including hypertension (67.9%), cerebrovascular disease (31.2%), diabetes (24.8%), coronary artery disease (24%), arrhythmia (14.6%), and hyperlipidemia (10.7%).

The median calcium level of the patients was 8.91 mg/dL. In the subgroup of patients who had non-survived, median calcium level was 8.1 mg/dL, whereas in the subgroup of patients who were survived it was 8.97 mg/dL. The calcium and corrected calcium levels were significantly lower among the patients who had non-survived due to AIS than among those who were survived after AIS (p<0.001; Table 2). Simlarly, the mean levels of albumin were significantly lower among the patients who had non-survived due to AIS than among those who were survived after AIS (p<0.001; Table 2).

The median serum phosphate level of patients was 3.42 mg/dL. It was 3.3 mg/dL in the subgroup of patients who had non-survived, whereas in the subgroup of survived patients it was 3.44 mg/dL. There was no difference between the two subgroups (p=0.163; Table 2).

Among the 1,204 patients, 817 (67.9%) were admitted by the neurology service and 387 (32.1%) to the intensive care unit (ICU). Among the patients who non-survived, 23 had been admitted to the neurology service and 167 to the ICU (Table 2). The number of patients who died in the ICU was found to be statistically significantly higher than the number of patients who died in the ward (p<0.001).

**Table 2.** Laboratory characteristics of study population

| Laboratory | Total N=1204 | Non-survivors n=190 (15.8%) | Survivors n=1014 (84.2%) | p* |
|---|---|---|---|---|
| Calcium (mg/dL) | 8.91 (5.92-10.97) | 8.1 (5.92-10.21) | 8.97 (6.7-10.97) | <0.001 |
| Corrected calcium (mg/dL) | 9.27 (6.33-11.94) | 9.19 (6.33-11.05) | 9.28 (6.84-11.94) | <0.001 |
| Phosphate (mg/dL) | 3.42 (0.7-12.6) | 3.3 (0.7-12.56) | 3.44 (1.48-9.86) | 0.163 |
| Albumin (g/dL) | 3.54 (1.2-5.11) | 2.69 (1.2-4.22) | 3.61 (1.5-5.11) | <0.001 |

Data are expressed as numbers (n), percentages (%), or median, *Intergroup comparisons (Non-Survivors vs. Survivors) were conducted by chi-squared and Mann–Whitney U tests, as appropriate.

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The median duration of hospitalization was 6 (range: 1–136) days, and the duration was significantly longer for the patients who non-survived than for those who were survived (11 [range: 1–136] and 5 [range: 1–90] days, respectively; p<0.001).

## Discussion

Acute stroke is the second common cause of death in the world [1]. In developed countries, nearly half of patients with acute stroke are aged 80 years or over, with men and women being similarly affected [8]. In our study, the number of female and male patients was roughly the same (51.6% vs. 48.4%), but the median age was 74 years.

Studies on serum calcium levels and AIS have reported different results. In the study of Zhang et al. [9] they found a positive correlation between serum calcium levels and stroke severity, with calcium levels increasing as stroke severity increased. Excitotoxicity and calcium overload, which are one of the molecular mechanisms of ischemic stroke pathophysiology, are thought to be related to this result [10].

In another study, Zhang et al. [5] found that neither high nor low serum calcium levels were associated with recurrent ischemic stroke or poor outcomes in their study. However, when differentiated by sex, high calcium levels in females were associated with both recurrent ischemic stroke and poor outcomes. On the other hand, in the study by Ishfag et al. [11], clinical findings were more serious in stroke patients with low serum calcium levels. In the study by Buck et al. [12] AIS patients with higher serum calcium levels had smaller cerebral infarct volumes. These results suggest that the serum calcium can serve as a determinant of prognosis and mortality after stroke. In addition, Bawiskar et al. [13], in their study comparing serum calcium and infarct size, concluded that higher normal levels of serum calcium and albumin-corrected calcium are associated with a smaller-sized infarct and had less severity index among patients with AIS. Similarly, in our study, the serum calcium levels of patients who did not survive were significantly lower than survived patients. A serum calcium level within the high–normal range may thus be associated with a good prognosis and lower mortality risk following AIS.

Zhang et al. [7] also examined serum phosphate levels and concluded that low levels were associated with recurrent stroke and poor outcome in AIS and patients with transient ischemic attack. In their study, high phosphate levels were also associated with an increased risk of poor outcomes. Jia et al. [14] investigated the relationship between phosphate levels and prognosis in young AIS and showed a potential associations of low phosphate levels with more serious stroke findings. Zhong et al. in their study, found a U-shaped association between phosphate and mortality with significantly increased risk among patients with lower phosphate levels [15]. However, another study found no evidence of a relationship between phosphate levels and AIS [16,17]. Similarly, in our research, there was no significant difference in serum phosphate levels or in mortality between survived patients and those who non-survived due to AIS.

In addition, from the data we included to determine the corrected calcium level in our study, albumin levels were found to be significantly lower in patients who non-survived. A meta-analysis data examining albumin treatment in AIS patients showed that albumin therapy had satisfactory effectiveness with proper use [18].

This study had some limitations. It was a single-center retrospective research. Also the effects of treatments, such as thrombolytic agents, antiplatelets, and statins, were not evaluated. Finally, calcium and phosphate were determined at the admission and were not subsequently rechecked. Prospective multicenter studies are therefore needed to verify our findings.

## Conclusion

Our data indicate that low serum calcium levels are associated with mortality in AIS patients Moreover, we suggest that the level of serum calcium levels in conjunction with stroke severity scoring systems, but not serum phosphate levels, might be a useful biomarker to predict mortality in patients with AIS.

**Conflict of Interests**
*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**
*The authors declare that they have received no financial support for the study.*

**Ethical Approval**
*The study was commenced after receiving Tokat Gaziosmanpaşa University ethics committee approval, numbered 22-KAEK-133, date 13.03.2023.*

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