Serum Alkaline Phosphatase, Phosphate, and In-Hospital Mortality in Acute Ischemic Stroke Patients

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Background: The clinical impacts of serum alkaline phosphatase (ALP) and phosphate on early death are not fully understood in patients with acute ischemic stroke. We examined the associations between serum ALP, phosphate, and in-hospital mortality after ischemic stroke. *Methods:* Serum ALP and phosphate were measured in 2944 ischemic stroke patients from 22 hospitals in Suzhou City from December 2013 to May 2014. Cox proportional hazard models and restricted cubic splines were used to estimate the relationships between serum ALP and phosphate (both as categorical and continuous variables) and risk of in-hospital mortality. *Results:* During hospitalization, 111 patients (3.7%) died from all causes. After multivariable adjustment, the hazard ratio (HR) of the highest quartile compared with the lowest quartile of ALP was 2.19 (95% confidence interval [CI], 1.20-4.00) for early death. Restricted cubic spline analysis indicated a significant linear association between ALP and death (*P*-linearity = .017). A U-shaped association of phosphate with in-hospital mortality was observed (*P*-nonlinearity = .011). Compared with the third quartile of phosphate (1.08-1.21 mmol/L), HRs of the lowest and highest quartiles for early death were 2.17 (1.15-4.08) and 1.70 (.88-3.30), respectively. Sensitivity analyses further confirmed our findings. *Conclusions:* We observed a graded relationship between serum ALP levels and risk of early death in patients with

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acute ischemic stroke. There was a U-shaped association between phosphate and all-cause mortality with significantly increased risk among patients with lower phosphate levels. **Key Words:** Alkaline phosphatase—phosphate—ischemic stroke—mortality.

Introduction

Stroke is one of the leading causes of death and long-term neurological disability in adults worldwide.[1] The in-hospital mortality rate of stroke remains high. Early identification of risk factors for mortality during hospitalization would contribute to reduce death rate after ischemic stroke by aggressively monitoring and enhancing the application of effective therapeutic strategies to patients at high risk of dying.[2] Alkaline phosphatase (ALP) and phosphate are commonly used in clinical practice as markers of liver or bone disease.[3,4] It is shown that ALP can promote vascular calcification by catalyzing the hydrolysis of organic pyrophosphate, an inhibitor of vascular calcification.[5] Numerous studies found that ALP was associated with an increased risk of cardiovascular disease (CVD), total mortality, and hospitalization in the general population and in subjects with myocardial infarction or chronic kidney disease.[6-9] However, little is known about the relation of serum ALP with very early death among patients with ischemic stroke.

Elevated phosphate has been shown to have an important role in the induction of vascular calcification, myocardial fibrosis, and atherosclerosis,[10-12] while a low serum phosphate level correlated with hypertension and metabolic syndrome in the general population[13-15] or with an increased risk of brain infarction in hemodialysis patients.[16] Prior studies have reported conflicting findings on the associations of serum phosphate with mortality and CVD risk. Some studies suggested that high serum phosphate increased the risk of CVD and all-cause mortality,[17] whereas others indicated that it had no such effect,[18,19] and there were some pieces of evidence showing that a low serum phosphate level was also associated with increased risk of cardiovascular events.[15,16] It is unknown how serum phosphate levels affect early death in patients with ischemic stroke.

We therefore examined the associations of serum ALP and phosphate with all-cause mortality based on multicenter data of acute ischemic stroke patients. We first treated serum ALP and phosphate as categorical variables for the main analysis, and then we performed restricted cubic spline analyses as the secondary analysis to provide more precise estimates and the exact shape of the relationship between serum ALP and phosphate and early death.

Methods

Study Populations

From December 2013 to May 2014, we recruited patients with acute ischemic stroke or transient ischemic attack admitted to the 22 hospitals in Suzhou, China. A diagnosis of acute ischemic stroke was made according to World Health Organization criteria based on patient history and clinical data, and was confirmed by computed tomography scan or magnetic resonance imaging. A total of 3720 potentially eligible patients were enrolled.[20] The additional exclusion criteria of this analysis were as follows: (1) final diagnosis of transient ischemic attack (n = 206); (2) time from onset to admission over 7 days (n = 64); and (3) lack of serum ALP and phosphate concentration (n = 506). As a result, 2944 ischemic stroke patients were finally included in this study (Fig 1).

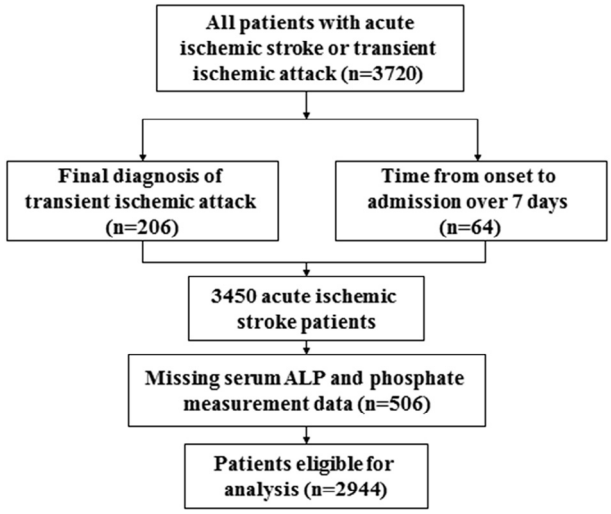

Figure 1. *Flowchart of participants' selection.*

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University, as well as ethical committees at the participating hospitals. Written consent was obtained from all study participants or their immediate family members.

Data Collection and Outcome Assessment

Data on demographic characteristics, lifestyle risk factors, medical history, and medication history were collected at the time of enrollment. Information on these factors was obtained by interviews with patients or their family members (if patients were not able to communicate). Routine laboratory determinations (plasma glucose, blood lipids, etc.) were performed for all enrolled patients using standard procedures in each participating hospital at admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) by trained