Alkaline Phosphatase and Outcomes in Patients With Preserved Renal Function

Results From China National Stroke Registry

Lixia Zong, MD, PhD*; Xianwei Wang, MD, MHSc*; Zixiao Li, MD, PhD; Xingquan Zhao, MD, PhD; Liping Liu, MD, PhD; Hao Li, PhD; Xia Meng, MD, PhD; Yilong Wang, MD, PhD; Yongjun Wang, MD

Background and Purpose—Alkaline phosphatase (ALP) is associated with risk of adverse cardiovascular events in patients with kidney failure. However, there is little data about effects of ALP on stroke outcomes in patients with preserved kidney function. The study aimed to explore the association between serum ALP level and clinical outcomes after stroke in patients with preserved kidney function.

Methods—We included 16 367 stroke patients with preserved kidney function from the China National Stroke Registry for current analysis. Serum ALP levels were tested by automated enzymatic method using unfrozen samples in each center. Participants were divided into 5 groups according to ALP quintiles. Composite end point comprised of recurrent stroke, myocardial infarction, other ischemic vascular events, and all-cause mortality. Poor functional outcome is defined as modified Rankin Scale score of 3 to 6. Multivariable logistic regression was used to evaluate the independent association of serum ALP with 1-year all-cause mortality, recurrent stroke, composite end point, and poor functional outcome.

Results—The mean age of the included 16 367 patients was 63.9 years, and 63.3% of them were men. Among the top ALP quintile (>98.0 U/L), 1-year incidences of all-cause mortality, recurrent stroke, composite end point, and poor functional outcome were 12.6%, 5.7%, 14.4%, and 27.0%, respectively. Compared with the lowest ALP quintile (≤59.0 U/L), the adjusted odds ratios of the top quintile were 1.36 (1.10–1.68) for all-cause mortality, 1.45 (1.11–1.90) for stroke recurrence, 1.35 (1.12–1.63) for composite end point, and 1.36 (1.17–1.60) for poor functional outcome. There was no significant interaction between age, sex, or alcohol consumption and ALP (P for interaction ≥0.10) for all outcomes.

Conclusions—In patients with preserved kidney function, ALP may be an independent predictor of all-cause mortality, stroke recurrence, composite end point, and poor functional outcome after stroke. **(*Stroke*. 2018;49:1176-1182. DOI: 10.1161/STROKEAHA.118.020237.)**

Key Words: alkaline phosphatase ■ China ■ mortality ■ recurrence ■ stroke

Alkaline phosphatase (ALP) is an enzyme that catalyzes the hydrolysis of the calcification inhibitor pyrophosphate.[1,2] Serum ALP has been implicated in the pathogenesis of vascular calcification and subclinical atherosclerotic burden measured by ankle–brachial index or carotid intima–media thickness.[3,4] The associations of serum ALP with cardiovascular morbidity and mortality have been suggested in patients with end-stage renal disease, who were at high risk for vascular calcification because of disorders of mineral metabolism.[5–7]

Recently, some researchers also investigated the relationship of ALP with cardiovascular events in community residents, clinic populations, and myocardial infarction survivors.[8–12] Moreover, a few studies reported that elevated ALP was associated with increased risk of all-cause mortality and 3-month disability in patients after a stroke.[13–15] However, there is a lack of data on the association of ALP with recurrent stroke or other incident cardiovascular disease in stroke patients. We assumed that serum ALP would serve as a predictor of stroke outcomes and then explored the associations of serum ALP levels with adverse outcomes in stroke patients. Given that chronic kidney disease is independently associated with adverse cardiovascular events, including stroke,[16,17] the current study focused on patients with preserved kidney function defined as estimated glomerular filtration rate (eGFR) >60 mL/min per 1.73 m2.

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From the Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, China; China National Clinical Research Center for Neurological Diseases, Beijing; Center of Stroke, Beijing Institute for Brain Disorders, China; and Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, China.

*Drs Zong and X. Wang contributed equally.

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Correspondence to Yongjun Wang, MD, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 6 Tian Tan Xi Li, Dongcheng District, Beijing, China 100050, E-mail yongjunwang1962@gmail.com, or Yilong Wang, MD, PhD, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 6 Tian Tan Xi Li, Dongcheng District, Beijing, China 100050, E-mail yilong528@gmail.com

Methods

Study Population

The data that support the findings of this study are available from the corresponding author on reasonable request. This study was conducted on the basis of the CNSR II study (China National Stroke Registry II), which was a nationwide, hospital-based, prospective cohort study launched in 2012 in China. Patients were eligible if they met the following criteria: age 18 years or older; diagnosis within 7 days of the index event of ischemic stroke, transient ischemic attack (TIA), spontaneous intracerebral hemorrhage, or subarachnoid hemorrhage confirmed by brain imaging; or direct hospital admission from a physician's clinic or emergency department. Among the 25 018 patients in the registry, 16 367 were analyzed after excluding patients with self-reported liver disease or kidney disease or eGFR <60 mL/min per 1.73 m2 (n=2643), missing ALP values (n=3718), and lost during the 1-year follow-up (n=2299; Figure 1). The CNSR II study was approved by the Central Institutional Review Board at the Beijing Tiantan Hospital, and written informed consent was obtained from patients or their legally authorized representatives.

Baseline Data Collection

Baseline information, including patients' demographics, vascular risk factors, important laboratory data, diagnosis, treatment, and complications were collected by trained research coordinators at each study center. Risk factors contained history of stroke or TIA, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, previous or current smoking, and moderate or heavy alcohol consumption. Hypertension, diabetes mellitus, and dyslipidemia were defined according to (1) documented or self-reported history or (2) receiving medication for corresponding diseases or (3) clinical or laboratory examination (blood pressure >140/90 mm Hg on repeated measurements for a diagnosis of hypertension, fasting glucose level ≥126 mg/dL or the nonfasting glucose concentration ≥200 mg/dL for diabetes mellitus, serum triglyceride ≥150 mg/dL or low-density lipoprotein cholesterol ≥130 mg/dL or high-density lipoprotein cholesterol ≤40 mg/dL for dyslipidemia), or (4) new diagnosis at discharge. Moderate or heavy alcohol consumption was defined as consuming ≥2 standardized alcohol drinks per day. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation with adjusted coefficient of 1.1 for the Asian population.[18,19]

ALP Testing

Fasting blood samples were drawn within 24 hours of admission, and serum ALP levels were tested using unfrozen samples by automated enzymatic method at each study center. The measurement of ALP was performed according to the recommendation of the International Federation of Clinical Chemistry and Laboratory Medicine in 2011.[20]

Outcome Assessment

Patients were followed up by telephone interview at 12-month after disease onset. Data on clinical outcomes were collected by trained research coordinators who were blinded to patients' baseline clinical status. We defined adverse clinical outcomes as recurrent stroke, all-cause mortality, and poor functional outcome. Recurrent stroke includes ischemic stroke, intracranial hemorrhage, and subarachnoid hemorrhage. Composite end point comprised of recurrent stroke, myocardial infarction, other ischemic vascular events, and all-cause mortality. Poor functional outcome is defined as modified Rankin Scale score of 3 to 6 (modified Rankin Scale score range from 0 [no symptoms] to 6 [death]).

Statistical Analysis

Categorical variables are described as proportions, and continuous variables are presented as mean with SD or medians with interquartile ranges. Baseline characteristics and adverse clinical outcomes grouped by ALP quintiles were compared using χ^2 test or 1-way ANOVA as appropriate.

Logistic regression model was performed to estimate the association between ALP levels and adverse outcomes, with the first quintile of ALP as a reference group. We adjusted covariates that may be associated with adverse clinical outcomes or ALP levels. Variables included in the multivariable models were selected a priori based

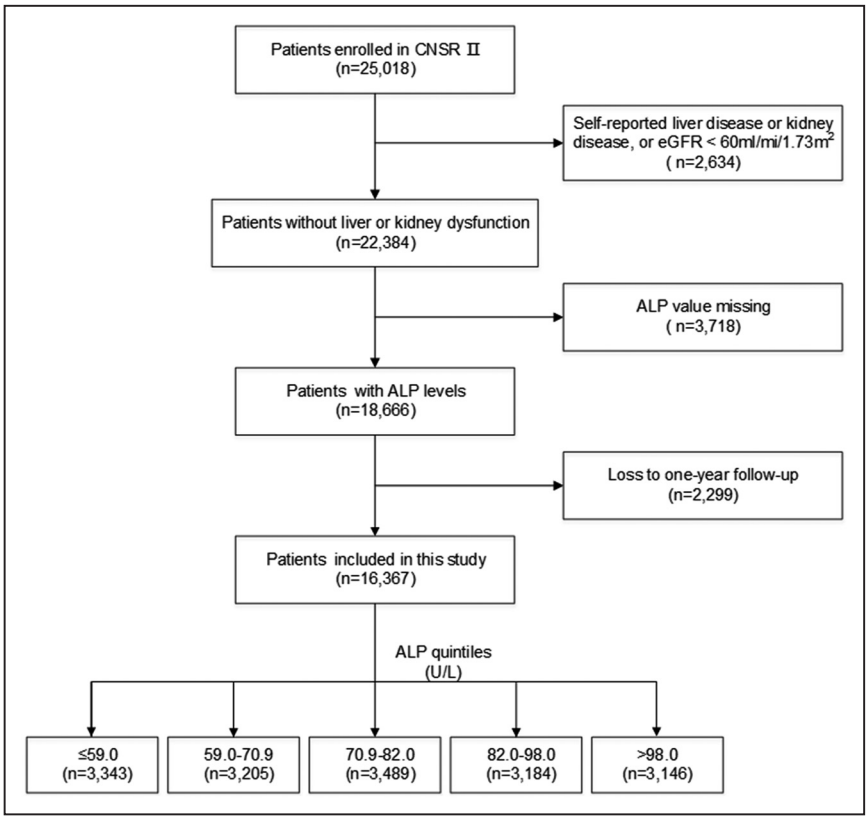

Figure 1. Patient flow diagram. ALP indicates alkaline phosphatase; CNSR II, China National Stroke Registry II; and eGFR, estimated glomerular filtration rate.

Table 1. Baseline Characteristics of the Patients According to Quintiles of ALP Levels

Characteristics	Overall (n=16 367)	ALP Quintiles, U/L					*P* Value
		Q1 (≤59.0); (n=3343)	Q2 (59.0–70.9); (n=3205)	Q3 (70.9–82.0); (n=3489)	Q4 (82.0–98.0); (n=3184)	Q5 (>98.0); (n=3146)	
Age (SD), y	63.9 (12.0)	63.5 (12.5)	64.0 (11.9)	63.9 (11.9)	63.9 (11.9)	64.1 (11.6)	0.33
Male sex, n (%)	10 367 (63.3)	2326 (69.6)	2206 (68.8)	2241 (64.2)	1943 (61.0)	1651 (52.5)	<0.0001
Risk factors, n (%)							
Previous stroke	5570 (34.0)	1155 (34.5)	1091 (34.0)	1180 (33.8)	1115 (35.0)	1029 (32.7)	0.37
Hypertension	12 190 (74.5)	2392 (71.6)	2342 (73.1)	2631 (75.4)	2417 (75.9)	2408 (76.5)	<0.0001
Diabetes mellitus	2917 (17.8)	620 (18.5)	538 (16.8)	607 (17.4)	553 (17.4)	599 (19.0)	0.11
Dyslipidemia	1688 (10.3)	384 (11.5)	316 (9.9)	370 (10.6)	332 (10.4)	286 (9.1)	0.03
CHD	1975 (12.1)	453 (13.6)	361 (11.3)	439 (12.6)	366 (11.5)	356 (11.3)	0.01
Current or previous smoking	7069 (43.2)	1508 (45.1)	1472 (45.9)	1495 (42.8)	1401 (44.0)	1193 (37.9)	<0.0001
Moderate to heavy alcohol consumption	4658 (28.5)	1056 (31.6)	1024 (32.0)	982 (28.1)	861 (27.0)	735 (23.4)	<0.0001
ALT, U/L, median (IQR)	19.0 (13.2–27.0)	17.0 (13.0–24.0)	17.6 (13.0–25.0)	19.0 (13.3–26.1)	19.3 (14.0–28.0)	21.0 (15.0–32.0)	<0.0001
AST, U/L, median (IQR)	21.0 (17.0–27.0)	20.0 (16.0–25.3)	20.0 (17.0–26.0)	21.0 (17.0–26.4)	21.7 (17.0–28.0)	23.0 (18.0–32.0)	<0.0001
WBC (SD), 10^9/L	7.4 (2.8)	7.0 (2.6)	7.2 (2.6)	7.4 (2.6)	7.6 (2.9)	7.7 (3.1)	<0.0001
BMI, median (IQR)	23.9 (22.0–25.7)	23.9 (22.0–25.7)	24.1 (22.0–25.9)	24.0 (22.1–25.7)	23.9 (22.0–25.6)	23.8 (21.7–25.7)	0.17
NIHSS score at admission, median (IQR)	3 (1–7)	3 (1–6)	3 (1–6)	3 (1–7)	4 (1–7)	4 (2–8)	<0.0001
mRS score at discharge							
0–2	12 433 (77.0)	2657 (80.3)	2540 (80.0)	2637 (76.3)	2359 (75.3)	2240 (72.8)	<0.0001
3–5	3717 (23.0)	651 (19.7)	634 (20.0)	821 (23.7)	773 (24.7)	838 (27.2)	
Medication during hospitalization							
Antihypertensive drugs	8016 (49.0)	1545 (46.2)	1520 (47.4)	1765 (50.6)	1622 (50.9)	1564 (49.7)	<0.001
Hypoglycemia drug	2904 (17.7)	563 (16.8)	549 (17.1)	624 (17.9)	562 (17.7)	606 (19.3)	0.1
Lipid-lowering drugs	7367 (45.0)	1434 (42.9)	1457 (45.5)	1599 (45.8)	1466 (46.0)	1411 (44.9)	0.07
Pneumonia during hospitalization	1366 (8.3)	249 (7.4)	236 (7.4)	262 (7.5)	287 (9.0)	332 (10.6)	<0.0001

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHD, coronary heart disease; IQR, interquartile range; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; Q, quintile; and WBC, white blood cells.

on differences in baseline characteristics between patients with different ALP levels or based on theoretical considerations. These variables were age, sex, history of stroke, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, current or previous smoking, moderate or heavy alcohol consumption, serum ALT levels, serum aspartate aminotransferase levels, white blood cell count, drugs used during hospitalization (antihypertensive agents, lipid-lowering agents, and hypoglycemic agents), baseline National Institutes of Health Stroke Scale score, body mass index, modified Rankin Scale score at discharge, and pneumonia during hospitalization.

We also performed a series of stratified analyses by age (≤70 versus >70 years), sex, and alcohol consumption. To examine effect modification by age, sex, and alcohol consumption, we used a postestimation Wald test in multivariable-adjusted logistic model to get an omnibus *P* value for interaction between ALP quintiles and variables of interest. In addition, we further explored the pattern of association between ALP and risk of stroke outcomes using a logistic regression model with restricted cubic splines for ALP adjusting for covariates. Reference is the mean serum ALP value (75 U/L), and 9 knots for ALP levels are placed at 40, 50, 60, 70, 80, 90, 100, 110, and 120 U/L. All analyses were conducted with SAS version 9.3 software (SAS institute), and 2-tailed *P* values of <0.05 were considered to be statistically significant.

Results

Baseline Characteristics

Baseline characteristics are summarized in Table 1. Of the total 16 367 patients included, the mean age was 63.9 years, and 63.3% were men. Among patients with higher quintiles of ALP, there were more females, nonsmokers, and nondrinkers

Table 2. Rates of 1-y Outcomes According to Quintiles of ALP Levels

Outcomes	Overall	ALP Quintiles					*P* Value
		Q1 (≤59.0)	Q2 (59.0–70.9)	Q3 (70.9–82.0)	Q4 (82.0–98.0)	Q5 (>98.0)	
All-cause mortality, n (%)	1484 (9.1)	241 (7.2)	229 (7.1)	297 (8.5)	321 (10.1)	396 (12.6)	<0.0001
Recurrent stroke, n (%)	629 (4.2)	103 (3.3)	115 (3.8)	124 (3.9)	126 (4.3)	161 (5.7)	<0.001
Composite end point, n (%)	1759 (10.7)	289 (8.6)	282 (8.8)	356 (10.2)	378 (11.9)	454 (14.4)	<0.0001
Poor functional outcome, n (%)	3532 (21.6)	586 (17.5)	582 (18.2)	757 (21.7)	760 (23.9)	847 (27.0)	<0.0001

ALP indicates alkaline phosphatase; and Q, quintile.

and more patients with history of hypertension, dyslipidemia, coronary heart disease, pneumonia during hospitalization, and functional disability at discharge, and they also have a higher National Institutes of Health Stroke Scale score at baseline. The levels of serum ALT, aspartate aminotransferase, and white blood cell increased along with the levels of serum ALP. Age, body mass index, history of stroke, and diabetes mellitus were not significantly different among the quintiles.

One-Year Outcomes Among Patients Grouped by Quintiles of ALP

The 1-year incidences of clinical outcomes are shown in Table 2. The 1-year rates of all outcomes increased by ALP quintiles (P<0.0001 for all-cause mortality, composite end point, and poor functional outcome; P<0.001 for recurrent stroke). In the top ALP quintile, the incidence rates of all outcomes including all-cause mortality, recurrent stroke, composite end point, and poor functional outcome were 12.6%, 5.7%, 14.4%, and 27.0%, respectively.

Association of ALP Levels With Adverse Clinical Outcomes

Crude and adjusted odds ratios with 95% confidence intervals of ALP levels for adverse clinical outcomes are presented in Figure 2. Compared with the first ALP quintile, the adjusted odds ratio of the highest quintile was 1.36 (1.10–1.68) for all-cause mortality, 1.45 (1.11–1.90) for stroke recurrence, and 1.35 (1.12–1.63) for composite end point. For poor functional outcome, the adjusted odds ratio of the third ALP quintile was 1.21 (1.03–1.41), of the fourth quintile was 1.24 (1.06–1.45). and of the fifth quintile was 1.36 (1.17–1.60), compared with the first quintile of ALP levels (P for trend <0.0001).

In subgroup analysis, the associations between ALP levels and adverse clinical outcomes were not significantly altered by age, sex, and alcohol consumption (P for interaction ≥0.10 for all outcomes; Table I in the online-only Data Supplement). Further analyses using restricted cubic spline regression showed that elevated ALP levels (especially >120 U/L) were significantly associated with increased risk of adverse stroke outcomes (Figure 3).

Discussion

In this large cohort study of stroke patients with eGFR ≥60 mL/min per 1.73 m2, elevated serum ALP levels >98 U/L were associated with ≈1.4-fold higher risk for all-cause mortality, stroke recurrence, composite end point, and poor functional outcomes after stroke, compared with ALP levels <59 U/L. The associations were not changed significantly by age, sex, and alcohol consumption. Our results provide new evidence for the known relationships between serum ALP levels and clinical outcomes in stroke patients and extend previous findings to patients with preserved kidney function.

Recently, the role of ALP has been highlighted in terms of its effects in cardiovascular disease, and the activity of ALP is

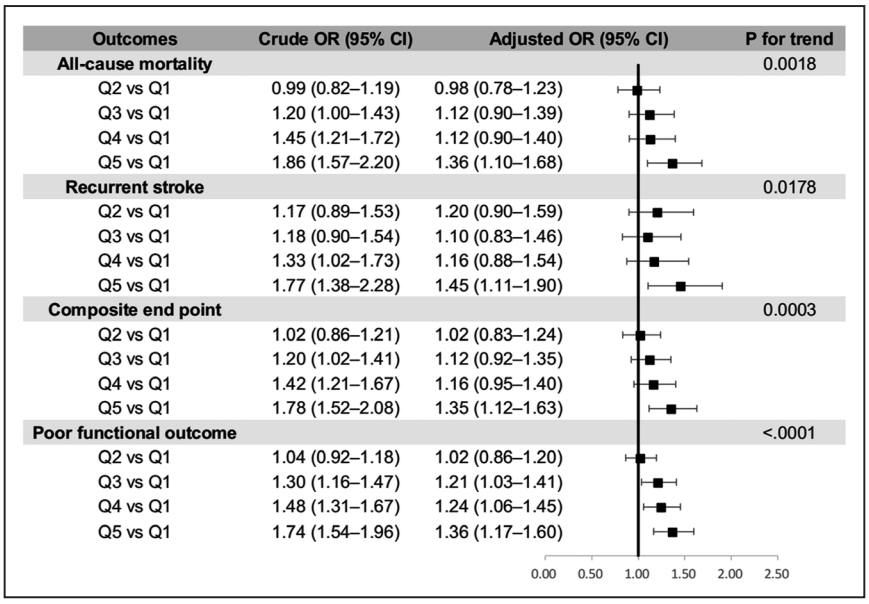

Figure 2. Crude and adjusted odds ratios (OR) of alkaline phosphatase (ALP) levels for 1-year all-cause mortality, recurrent stroke, composite end point, and functional outcome. In multivariable analysis, adjusted variables included age, sex, history of stroke, diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, coronary heart disease, current or previous smoking, moderate or heavy alcohol, baseline National Institutes of Health Stroke Scale score, modified Rankin Scale score at discharge, body mass index, ALT levels, aspartate aminotransferase levels, white blood cell count, antihypertensive drugs, lipid-lowering drugs, hypoglycemia drugs, and pneumonia during hospitalization. CI indicates confidence interval; and Q, quintile.

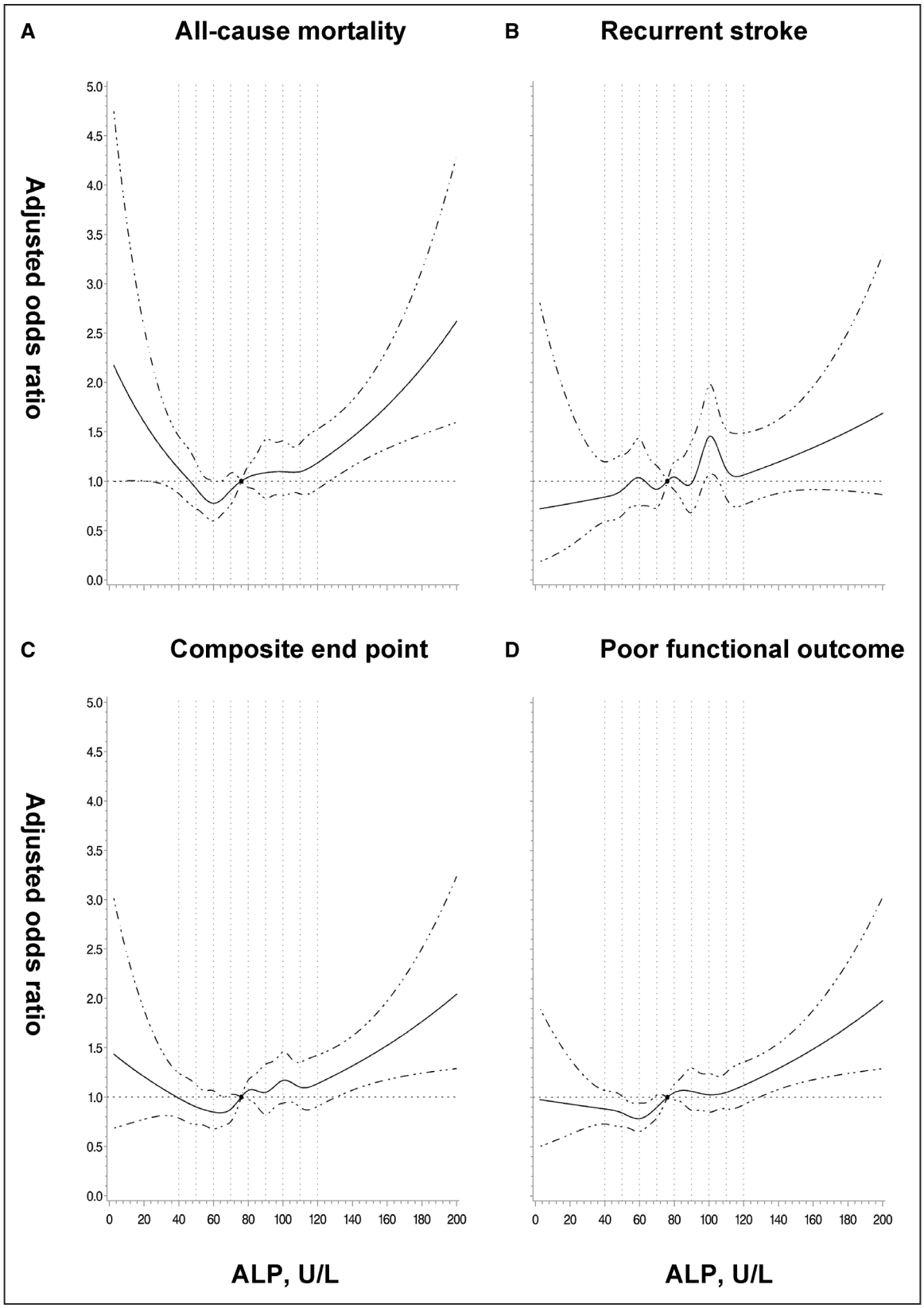

Figure 3. Adjusted dose–response association between alkaline phosphatase (ALP) levels and adverse clinical outcomes. **A**, All-cause mortality. **B**, Recurrent stroke. **C**, Composite end point. **D**, Poor functional outcome. The solid lines indicate adjusted odds ratios (ORs), and the dashed lines indicate the 95% confidence interval bands. ORs were obtained by restricted cubic spline logistic regression after adjustment for confounding factors, with knots placed at 40, 50, 60, 70, 80, 90, 100, 110, and 120 U/L of ALP levels and the average serum ALP value (75 U/L) as the reference.

often used as a molecular marker of vascular calcification.[21,22] Vascular calcification plays significant role in the process of atherosclerosis and also leads to increased vascular stiffness and reduced vascular compliance. Patients with vascular calcification are at high risk for adverse cardiovascular events.[23,24] Thus, ALP may be associated with major adverse cardiovascular events through the acceleration of vascular calcification. Several studies have reported that elevated serum ALP levels were related with increased incidence of cardiovascular disease.[8,12] In our study, high ALP levels were associated with increased risk of stroke recurrence and composite end point, which were consistent with previous results. A study of 10 754 community-dwelling subjects reported that low ALP levels were also associated with risk of stroke.[10] However, we did not find a significant association between low ALP levels and stroke recurrence in the present study. The impact of low ALP levels on vascular system warrants further research.

Elevated ALP was related with increased risk of all-cause mortality in patients with end-stage renal disease and in general populations.[7,8] In stroke patients, a study of 2029 subjects with ≈2.5 years of follow-up reported that the top quintile of ALP levels (≥97 IU/L) was associated with ≈2.8-fold increased risk of all-cause mortality, compared with the lowest quintile of ALP.[13] The risk of the top ALP quintile (>98 U/L) for 1-year all-cause mortality increased only 1.4 times in the present study. This discrepancy might be because of different follow-up period and study populations (our study excluded patients with eGFR<60 mL/min per 1.73 m2). Additionally, this study also demonstrates that elevated serum ALP levels were associated with increased risk of 1-year poor functional outcome. Two previous studies suggested that ALP might predict 3-month functional outcome after cerebral infarction or spontaneous intracerebral hemorrhage.[14,15] Elevated serum ALP may be a reflection of inflammation and malnutrition, which could lead to worse functional outcomes after stroke.[8,13,25]

ALP levels and activity might differ by sex and alcohol consumption.[10,26] In the CIRCS study (Circulatory Risk in Communities Study), the associations between ALP and stroke risks were confined primarily to nondrinkers, and the strengths of the associations varied by sex.[10] But in our subgroup analysis, the effects of ALP on adverse clinical outcomes were not changed by sex or alcohol consumption. Thus, the associations between ALP and stroke outcomes in subjects stratified by alcohol and sex should be assessed in future studies.

The study had some limitations. First, serum ALP testing was performed at each study site. However, the results of ALP testing across the involved sites would be comparable because the procedure of ALP measurement in all sites was based on the recommendation of International Federation of Clinical Chemistry and Laboratory Medicine (2011). Second, ALP isozymes were unavailable in this stroke registry, so we could not evaluate which types of ALP were associated with adverse stroke outcomes. Third, we did not exclude patients with obstructive biliary disease because the biliary levels were not recorded in the study. Fourth, given that we excluded patients lacking baseline ALP value and follow-up information, the selection bias might occur. Finally, some unmeasured or residual confounding effects may still exist because of the nature of the observational study.

In summary, in stroke patients with preserved kidney function, high serum ALP levels were associated with increased risk of all-cause mortality, stroke recurrence, composite end point, and poor functional outcomes. Serum ALP might serve as a predictor for stroke outcomes in patients with preserved kidney function.

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Disclosures

None.

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Alkaline Phosphatase and Outcomes in Patients With Preserved Renal Function: Results From China National Stroke Registry

Lixia Zong, Xianwei Wang, Zixiao Li, Xingquan Zhao, Liping Liu, Hao Li, Xia Meng, Yilong Wang and Yongjun Wang

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Table I. Adjusted associations of ALP levels with adverse outcomes in each subgroup.

Outcome	Subgroup	ALP quintiles*					p for interaction
		Q1	Q2	Q3	Q4	Q5	
All-cause mortality	Age						0.45
	<70	1 (reference)	1.10 (0.77-1.57)	0.99 (0.70-1.41)	1.24 (0.88-1.74)	1.31 (0.94-1.84)	
	≥70	1 (reference)	0.94 (0.71-1.26)	1.25 (0.95-1.63)	1.11 (0.84-1.46)	1.48 (1.13-1.95)	
	Sex						0.36
	Male	1 (reference)	0.93 (0.69-1.25)	1.05 (0.78-1.39)	1.17 (0.88-1.55)	1.36 (1.03-1.80)	
	Female	1 (reference)	0.76 (0.52-1.09)	1.21 (0.86-1.69)	0.88 (0.62-1.24)	1.22 (0.88-1.70)	
	Alcohol consumption						0.12
	Yes	1 (reference)	1.05 (0.65-1.69)	0.77 (0.47-1.28)	1.22 (0.76-1.94)	1.50 (0.95-2.38)	
	No	1 (reference)	0.95 (0.73-1.23)	1.26(0.99-1.62)	1.09 (0.85-1.40)	1.32 (1.04-1.68)	
Recurrent stroke	Age						0.68
	<70	1 (reference)	1.26 (0.84-1.89)	1.17 (0.78-1.74)	1.37 (0.92-2.03)	1.41 (0.95-2.09)	
	≥70	1 (reference)	1.18 (0.78-1.78)	1.08 (0.72-1.63)	1.04 (0.69-1.58)	1.58 (1.07-2.34)	
	Sex						0.25
	Male	1 (reference)	1.03 (0.72-1.48)	0.86 (0.60-1.25)	0.93 (0.65-1.34)	1.21 (0.85-1.70)	
	Female	1 (reference)	1.36 (0.84-2.19)	1.40 (0.88-2.24)	1.71 (1.09-2.69)	1.46 (0.92-2.31)	
	Alcohol consumption						0.94
	Yes	1 (reference)	1.11 (0.61-2.04)	1.00 (0.54-1.83)	1.00 (0.54-1.83)	1.45 (0.82-2.56)	
	No	1 (reference)	1.12 (0.81-1.55)	1.06 (0.76-1.47)	1.18 (0.85-1.62)	1.34 (0.98-1.82)	
Composite endpoint	Age						0.11

	<70	1 (reference)	1.09 (0.81-1.46)	1.00 (0.75-1.33)	1.32 (1.00-1.75)	1.26 (0.95-1.67)	
	≥70	1 (reference)	1.00 (0.76-1.30)	1.29 (1.00-1.66)	1.10 (0.84-1.42)	1.53 (1.19-1.98)	
	Sex						0.55
	Male	1 (reference)	1.01 (0.78-1.31)	1.03 (0.80-1.33)	1.16 (0.91-1.49)	1.32 (1.03-1.68)	
	Female	1 (reference)	0.86 (0.62-1.19)	1.23 (0.91-1.67)	1.07 (0.79-1.46)	1.24 (0.92-1.68)	
	Alcohol consumption						0.19
	Yes	1 (reference)	1.29 (0.86-1.93)	0.93 (0.61-1.42)	1.21 (0.80-1.81)	1.38 (0.93-2.06)	
	No	1 (reference)	0.95 (0.75-1.19)	1.22 (0.98-1.52)	1.17 (0.94-1.46)	1.33 (1.07-1.65)	
Poor functional outcome	Age						0.53
	<70	1 (reference)	1.06 (0.84-1.33)	1.16 (0.93-1.44)	1.18 (0.94-1.47)	1.45 (1.17-1.81)	
	≥70	1 (reference)	1.02 (0.82-1.27)	1.32 (1.06-1.63)	1.37 (1.10-1.71)	1.38 (1.10-1.73)	
	Sex						0.52
	Male	1 (reference)	0.96 (0.78-1.18)	1.13 (0.92-1.39)	1.15 (0.94-1.41)	1.25 (1.02-1.54)	
	Female	1 (reference)	1.06 (0.81-1.38)	1.43 (1.11-1.85)	1.23 (0.95-1.60)	1.59 (1.23-2.06)	
	Alcohol consumption						0.94
	Yes	1 (reference)	0.88 (0.63-1.22)	1.11 (0.80-1.52)	1.06 (0.77-1.47)	1.24 (0.90-1.71)	
	No	1 (reference)	1.04 (0.86-1.25)	1.29 (1.08-1.55)	1.23 (1.02-1.49)	1.42 (1.19-1.71)	

*For subgroups stratified by age and alcohol consumption, ALP quintiles refer to age-specific and alcohol-specific quintiles of ALP levels. Sex-specific cut-points for ALP per quintile are <58 [men], <62 [women] for Q1; 58-68 [men], 62-74 [women] for Q2; 68-79 [men], 74-87 [women] for Q3; 79-94 [men], 87-103 [women] for Q4; ≥94 [men], ≥103 [women] for Q5. Alcohol-specific cut-points for ALP per quintile are <58 [drinkers], <60 [non-drinkers] for Q1; 58-68 [drinkers], 60-71.4 [non-drinkers] for Q2; 68-79 [drinkers], 71.4-83 [non-drinkers] for Q3; 79-94 [drinkers], 83-99 [non-drinkers] for Q4; ≥94 [drinkers], ≥99 [non-drinkers] for Q5.