



Positive Association Between Serum Alkaline Phosphatase and First Stroke in Hypertensive Adults

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The relation of alkaline phosphatase (ALP) with stroke risk remains uncertain. We aimed to examine the association between serum ALP and the risk of first stroke, and explore the possible effect modifiers in the association, among adults with hypertension. A total of 19,747 participants with baseline ALP measurements and without liver disease at baseline from the China Stroke Primary Prevention Trial (CSPPT) were included. The primary outcome was a first stroke. Over a median follow-up of 4.5 years, there was a positive association between serum ALP levels and the risk of first stroke (per SD increment, adjusted HR, 1.10; 95%CI: 1.01, 1.20). When serum ALP was evaluated as quartiles, a significantly higher risk of first stroke was observed in those in quartile 2–4 (ALP ≥ 79 IU/L; adjusted HR, 1.38; 95% CI: 1.11, 1.71), compared with participants in quartile 1 (ALP < 79 IU/L). Similar results were found for first ischemic or hemorrhagic stroke. Similar findings were also found in those with a normal range of baseline ALP levels (20–140 IU/L) (per SD increment, adjusted HR, 1.15; 95%CI: 1.05, 1.27). None of the variables, including sex, age, body mass index, smoking, alcohol drinking, blood pressure, total cholesterol, fasting glucose levels at baseline, and blood pressure levels during the treatment period, significantly modified the association. In summary, our study suggests that higher serum ALP levels, even in normal range, were significantly related to higher risk of first stroke among Chinese hypertensive adults.

Keywords: alkaline phosphatase, first ischemic stroke, first stroke, hypertension, cohort study

INTRODUCTION

Stroke has become a worldwide public health concern worldwide (1, 2). Previous studies had reported that traditional risk factors could not explain all first stroke risk (3–5). Therefore, it is important to identify more risk factors to further lower residual risk of first stroke.

Alkaline phosphatase (ALP) is a clinical marker of bone or hepatic disease (6). Previous studies have found that higher ALP was related to vascular calcification by

catalyzing the hydrolysis of organic pyrophosphate, which is an inhibitor of vascular calcification (6). This indicated that ALP may have an important role in the development of vascular disease. Accordingly, previous studies showed that higher serum ALP was related to higher cardiovascular disease (CVD) (7–9), and cerebral small vessel disease (10–12). However, data from prospective studies on the relation of ALP with stroke risk are limited and inconclusive (8, 9, 13). Moreover, few previous studies have fully examined the potential effect modifiers on the relationship of ALP with the risk of first stroke.

Hypertension has been shown to be one of the most important modifiable risk factors of stroke (14, 15). Therefore, using data from the China Stroke Primary Prevention Trial (CSPPT) (16), we aimed to investigate the association between serum ALP and the risk of first stroke and examine the possible effect modifiers for the association in adults with hypertension.

MATERIALS AND METHODS

Study Design and Participants

The detailed methods and major findings of the CSPPT (ClinicalTrials.gov identifier NCT00794885) have been reported previously elsewhere. (16–19) Briefly, the CSPPT was a randomized, double-blind, controlled trial conducted in 20,702 45–75 years adults with hypertension from May 19, 2008 to August 24, 2013 in 32 communities in Anhui and Jiangsu provinces of China.

Our current study, as a *post-hoc* analysis of the CSPPT, included a total of 19,747 participants with complete data on ALP measurements and without liver disease, including self-reported chronic hepatitis, hepatic adipose infiltration, or cirrhosis at baseline (**Supplementary Figure 1**).

The CSPPT and the current study were approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263). All participants provided written informed consent.

Intervention and Follow-Up

In the CSPPT, eligible participants were randomly assigned, in a 1:1 ratio, to one of two treatment groups: a daily oral dose of one tablet containing 10 mg enalapril and 0.8 mg folic acid (the enalapril-folic acid group), or one tablet containing 10 mg enalapril only (the enalapril-only group).

Participants were followed up every 3 months. BP was measured; usage of concomitant medications, adverse events, study drug compliance and possible endpoint events were documented at each follow-up visit.

Laboratory Assessment

Serum concentrations of fasting ALP, alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), total bilirubin (TBIL), aspartate aminotransferase (AST), total homocysteine (tHcy), lipids, creatinine, glucose, albumin, and fasting glucose were measured using automatic clinical analyzers (Beckman Coulter) at the core laboratory of the National Clinical

Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China.

Study Outcomes

The primary outcome was a first, nonfatal or fatal stroke, excluding subarachnoid hemorrhage and silent stroke. Secondary outcomes included a first ischemic stroke and a first hemorrhagic stroke. The study outcomes were adjudicated by an independent Endpoint Adjudication Committee, whose members were unaware of treatments assignments (16).

Statistical Analysis

Means \pm standard deviations (SDs) or medians [interquartile range (IQR)] for continuous variables and proportions for categorical variables, were calculated for population characteristics by baseline serum ALP quartiles (<79 IU/L, 79 to <96 IU/L, 96 to <118 IU/L, ≥ 118 IU/L). Differences in baseline characteristics was compared using ANOVA tests or chi-square tests, accordingly.

The association between baseline serum ALP and the risk of first stroke were estimated with the use of Cox proportional hazards models [hazards ratio (HR) and 95% confidence interval (CI)] without and with adjustments for study centers, treatment groups, age, sex, systolic blood pressure (SBP), smoking, body mass index, alcohol drinking, fasting glucose, total cholesterol, triglyceride, albumin, creatinine, tHcy, methylenetetrahydrofolate reductase (*MTHFR*) C677T genotypes and antihypertensive treatment at baseline, as well as time-averaged SBP during the follow up. Moreover, the possible effect modifiers in the association between serum ALP and the risk of stroke were evaluated by stratified analyses and their interactions were assessed.

A two-tailed $P < 0.05$ was considered statistically significant in all the analyses. R software, version 3.6.1 (<http://www.R-project.org/>) was used for all analyses.

RESULTS

Study Participants and Baseline Characteristics

As illustrated in the flow chart (**Supplementary Figure 1**), in the current study, 19,747 participants with baseline ALP measurements and without baseline liver disease, were included.

The median and mean serum ALP levels were 96 IU/L and 100.7 IU/L (SD, 31.2), respectively. Characteristics of participants by ALP quartiles are presented in **Table 1**. Participants with higher ALP levels were older and more likely to be female; had higher HDL-C, TG, FG, SBP, albumin, folate at baseline and time-averaged SBP levels during the follow-up; had lower DBP, BMI, total cholesterol, tHcy, creatinine at baseline and time-averaged DBP levels during the follow up; and had lower frequency in the antiplatelet and antihypertensive drugs usage, as well as lower frequency in C677 TT genotype, current smoking, alcohol drinking consumptions at baseline (**Table 1**).

In addition, those with higher ALP levels had a lower frequency usage of diuretics and a higher frequency

TABLE 1 | Characteristics of the study participants by baseline serum alkaline phosphatase quartiles.

Variables ^a	Baseline serum alkaline phosphatase quartiles, IU/L				P-value
	Q1 (<79)	Q2 (79–<96)	Q3 (96–<118)	Q4 (≥118)	
N	4,695	49,19	5,182	4,951	
Male, No. (%)	2,422 (51.6)	2,235 (45.4)	1,987 (38.3)	1,390 (28.1)	<0.001
Age, year	58.3 ± 8.2	59.7 ± 7.6	60.6 ± 7.2	61.3 ± 6.8	<0.001
Body mass index, kg/m ²	25.4 ± 3.6	25.1 ± 3.6	24.9 ± 3.7	24.5 ± 3.7	<0.001
Current smoking, No. (%)	1324 (28.2)	1269 (25.8)	1152 (22.2)	866 (17.5)	<0.001
Current alcohol drinking, No. (%)	1576 (33.6)	1291 (26.2)	1122 (21.7)	750 (15.2)	<0.001
MTHFR 677 TT, No. (%)	1205 (25.7)	1210 (24.6)	1198 (23.1)	1102 (22.3)	<0.001
Enalapril-folic acid, No. (%)	2375 (50.6)	2454 (49.9)	2561 (49.4)	2493 (50.4)	0.661
BP, mmHg					
SBP at baseline	165.6 ± 20.6	167.3 ± 20.5	167.4 ± 20.6	168.2 ± 20.3	<0.001
DBP at baseline	95.3 ± 12.0	94.5 ± 12.0	94.1 ± 11.7	93.1 ± 11.9	<0.001
Time-averaged on-treatment SBP	139.3 ± 11.3	140.0 ± 11.2	139.7 ± 11.4	140.5 ± 11.9	<0.001
Time-averaged on-treatment DBP	84.3 ± 7.5	83.5 ± 7.7	82.8 ± 7.4	82.0 ± 7.8	<0.001
Laboratory results					
Total cholesterol, mmol/L	5.6 ± 1.2	5.6 ± 1.2	5.5 ± 1.2	5.4 ± 1.2	<0.001
HDL-C, mmol/L	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	<0.001
Triglycerides, mmol/L	1.6 ± 1.7	1.6 ± 1.0	1.7 ± 0.9	1.8 ± 1.0	<0.001
Fasting glucose, mmol/L	5.8 ± 1.4	5.8 ± 1.5	5.8 ± 1.7	5.9 ± 2.1	0.034
Creatinine, μmol/L	68.6 ± 16.5	66.7 ± 17.2	65.2 ± 16.9	63.4 ± 25.2	<0.001
Folate, ng/mL	7.9 ± 3.3	8.3 ± 3.8	8.6 ± 3.9	9.4 ± 4.4	<0.001
Total homocysteine, μmol/L	14.9 ± 10.0	14.5 ± 8.6	14.5 ± 8.1	14.1 ± 7.0	<0.001
Albumin, g/L	47.8 ± 5.6	48.8 ± 4.9	49.4 ± 5.5	50.3 ± 6.9	<0.001
Alkaline phosphatase, IU/L	65.9 ± 10.4	87.1 ± 4.8	105.6 ± 6.3	142.3 ± 24.8	<0.001
Alanine transaminase, IU/L	11.0 (9.0, 15.0)	12.0 (9.0, 16.0)	13.0 (10.0, 17.0)	14.0 (11.0, 19.6)	<0.001
Aspartate transaminase, IU/L	21.4 (18.0, 26.1)	22.8 (19.2, 27.8)	24.0 (19.9, 29.5)	26.6 (21.6, 33.4)	<0.001
Gamma glutamyl transpeptidase, IU/L	19.6 (14.5, 28.7)	19.8 (14.8, 28.5)	19.9 (14.9, 29.4)	20.5 (15.2, 30.2)	<0.001
Medication use, No. (%)					
Antihypertensive drugs	2,399 (51.1)	2,315 (47.1)	2,371 (45.8)	2,062 (41.6)	<0.001
Glucose-lowering drugs	59 (1.3)	84 (1.7)	75 (1.4)	86 (1.7)	0.175
Lipid-lowering drugs	46 (1.0)	43 (0.9)	32 (0.6)	35 (0.7)	0.171
Antiplatelet drugs	196 (4.2)	164 (3.3)	143 (2.8)	92 (1.9)	<0.001

^aContinuous variables are presented as Mean ± SD or IQR (25th, 75th), categorical variables are presented as n (%).

BP, blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure.

usage of glucose-lowering drugs during the follow up (Supplementary Table 1).

Baseline Serum ALP and the Risk of First Stroke

We first evaluated the association of ALP with other covariates at baseline, and found that age, sex, BMI, SBP, current smoking, alcohol drinking, total cholesterol, triglycerides, fasting glucose, tHcy, creatinine, albumin and time-averaged SBP levels were significantly associated with ALP levels (all $P < 0.05$) (Supplementary Table 2). As such, we included all above covariates in the regression models for the association between serum ALP and the risk of first stroke.

During the median follow-up duration of 4.5 years (25th-75th percentile, 4.2–4.7), there was a significant positive relation of serum ALP with first total stroke (per SD increment, adjusted HR, 1.10; 95%CI: 1.01, 1.20) (Table 2). When serum ALP was evaluated as quartiles, the adjusted HRs (95%CI) were 1.00 (ref.), 1.28 (1.00, 1.64), 1.44 (1.13, 1.85), 1.47 (1.13, 1.93), according to quartile 1 (<79 IU/L), quartile 2 (79 to <96 IU/L), quartile 3 (96 to <118 IU/L), quartile 4 (≥118 IU/L), respectively. Consistently, a higher risk of first total stroke was observed in those in quartile 2-4 (ALP ≥79 IU/L; 3.2% vs. 2.6%; adjusted HR, 1.38; 95% CI: 1.11, 1.71), compared with participants in quartile 1 (ALP <79 IU/L) (Table 2). Similar trends were observed for first ischemic stroke (ALP ≥79 vs. <79 IU/L; adjusted HR, 1.37; 95% CI: 1.08, 1.73), and first hemorrhagic stroke (ALP

TABLE 2 | The association between baseline alkaline phosphatase and the risk of first stroke.

ALP, IU/L	N	No. of events (%)	Crude model		Adjusted model ^a	
			HR (95% CI)	P-value	HR (95% CI)	P-value
First total stroke						
Continuous, per SD increment	19,747	606 (3.1)	1.04 (0.96, 1.13)	0.311	1.10 (1.01, 1.20)	0.036
Quartiles						
Q1 (<79)	4,695	123 (2.6)	1.00		1.00	
Q2 (79–<96)	4,919	154 (3.1)	1.20 (0.95, 1.52)	0.133	1.28 (1.00, 1.64)	0.047
Q3 (96–<118)	5,182	172 (3.3)	1.26 (1.00, 1.59)	0.049	1.44 (1.13, 1.85)	0.004
Q4 (≥118)	4,951	157 (3.2)	1.21 (0.95, 1.53)	0.116	1.47 (1.13, 1.93)	0.004
P for trend			0.114		0.003	
Categories						
Q1 (<79)	4,695	123 (2.6)	1.00		1.00	
Q2–4 (≥79)	15,052	483 (3.2)	1.22 (1.00, 1.49)	0.046	1.38 (1.11, 1.71)	0.003
First ischemic stroke						
Continuous, per SD increment	19,747	493 (2.5)	1.04 (0.95, 1.13)	0.369	1.12 (1.02, 1.24)	0.020
Categories						
Q1 (<79)	4,695	101 (2.2)	1.00		1.00	
Q2–4 (≥79)	15,052	392 (2.6)	1.21 (0.97, 1.51)	0.088	1.37 (1.08, 1.73)	0.010
First hemorrhagic stroke						
Continuous, per SD increment	19,747	111 (0.6)	1.05 (0.88, 1.26)	0.577	1.05 (0.85, 1.29)	0.644
Categories						
Q1 (<79)	4,695	21 (0.4)	1.00		1.00	
Q2–4 (≥79)	15,052	90 (0.6)	1.33 (0.83, 2.14)	0.239	1.57 (0.91, 2.72)	0.103

^aAdjusted for study centers, treatment groups, age, sex, body mass index, smoking, alcohol drinking, systolic blood pressure (SBP), albumin, total cholesterol, triglyceride, fasting glucose, creatinine, total homocysteine, methylenetetrahydrofolate reductase (MTHFR) C677T genotypes and antihypertensive treatment at baseline, as well as time-averaged SBP during the treatment period.
ALP, alkaline phosphatase.

≥79 vs. <79 IU/L; adjusted HR, 1.57; 95% CI: 0.91, 2.72) (Table 2).

Moreover, similar findings were also observed in those with a normal range of serum ALP (20–140 IU/L) (20) levels (per SD increment, adjusted HR, 1.15; 95%CI: 1.05, 1.27) (Supplementary Table 3). More importantly, further adjustments for diuretics, calcium channel blockers, and glucose-lowering drugs during the follow-up (ALP ≥79 vs. <79 IU/L; adjusted HR, 1.38; 95%CI: 1.12, 1.72) (Supplementary Table 4), or other liver enzymes, including AST, ALT and GGT (ALP ≥79 vs. <79 IU/L; adjusted HR, 1.40; 95% CI: 1.12, 1.75) (Supplementary Table 5) did not materially alter the findings.

Stratified Analyses

Considering the substantial ALP difference between men and women, we investigated the ALP-stroke association stratified by sex. In males, compared to participants with ALP <79 IU/L, a higher risk of first stroke was observed in those in quartile 2–4 (ALP ≥79 IU/L; adjusted HR, 1.38; 95%CI: 1.04, 1.82). Similar results were found in females (adjusted HR, 1.39; 95%CI: 1.00, 1.91; P for interaction = 0.979) (Table 3).

Other variables, including treatment group (enalapril vs. enalapril-folic acid), age (≥60 vs. <60 years), BMI (≥24 vs. <24 kg/m²), current smoking (yes vs. no), current alcohol drinking (yes vs. no), SBP (<160 vs. ≥160 mmHg), total cholesterol (<6.2

vs. ≥6.2 mmol/L), fasting glucose (<6.1 vs. 6.1–<7.0 mmol/L vs. diabetes), tHcy [<12.5 (median) vs. ≥12.5 μmol/L], albumin [<48.3 (median) vs. ≥48.3 g/L] at baseline, as well as time-averaged SBP (≥140 vs. <140 mmHg), diuretics usage (yes vs. no), calcium channel blockers usage (yes vs. no) and over during the follow-up period, also did not significantly modified the association between baseline serum ALP and first total stroke (all P-interactions > 0.05) (Table 3).

Sensitivity Analysis

We first explored the effects of folic acid treatment on ALP levels, and found that there was no significant difference of ALP levels between the 2 treatment groups (enalapril-folic acid group vs. enalapril only group; P = 0.669) (Supplementary Table 6). Furthermore, we also did not find the substantial difference in the efficacy of folic acid treatment in prevention of first stroke among participants with different ALP levels (<79 vs. ≥79 IU/L; P-interaction = 0.597) (Supplementary Table 7).

DISCUSSION

Our study first found that among hypertensive adults, those participants with higher serum ALP, even in normal range, had a significantly higher risk of first total stroke. This study has adjusted for a comprehensive range of covariables/ confounders,

TABLE 3 | The association between baseline alkaline phosphatase and the risk of first stroke in various subgroups.

Subgroups	N	Q1 (<79) Events (%)	Q2-4 (≥79) Events (%)	Adjusted HR(95%CI) *	P-interaction ^a
Sex					0.979
Male	8,034	73 (3.0)	212 (3.8)	1.38 (1.04, 1.82)	
Female	11,713	50 (2.2)	271 (2.9)	1.39 (1.00, 1.91)	
Age, year					0.143
<60	10,000	47 (1.7)	186 (2.6)	1.69 (1.21, 2.36)	
≥60	9,747	76 (3.9)	297 (3.8)	1.24 (0.94, 1.62)	
BMI, kg/m ²					0.250
<24	8,087	47 (2.8)	185 (2.9)	1.18 (0.84, 1.65)	
≥24	11,653	76 (2.5)	298 (3.4)	1.51 (1.15, 1.98)	
Treatment group					0.597
Enalapril	9,864	66 (2.8)	272 (3.6)	1.45 (1.09, 1.93)	
Enalapril-folic acid	9,883	57 (2.4)	211 (2.8)	1.30 (0.95, 1.77)	
Current smoking					0.381
No	15,135	75 (2.2)	352 (3.0)	1.48 (1.13, 1.95)	
Yes	4,611	48 (3.6)	131 (4.0)	1.23 (0.87, 1.72)	
Current Alcohol drinking				0.340	
No	15,004	71 (2.3)	376 (3.2)	1.49 (1.14, 1.96)	
Yes	4,739	52 (3.3)	107 (3.4)	1.21 (0.86, 1.70)	
SBP at baseline, mmHg				0.296	
<160	7,389	26 (1.4)	108 (2.0)	1.69 (1.08, 2.64)	
≥160	12,358	97 (3.5)	375 (3.9)	1.30 (1.02, 1.65)	
Time-averaged SBP during the treatment period, mmHg			0.974		
<140	10,884	38 (1.4)	142 (1.7)	1.38 (0.96, 1.99)	
≥140	8,862	85 (4.3)	341 (4.9)	1.39 (1.08, 1.80)	
Total cholesterol, mmol/L				0.577	
<6.2	14,389	81 (2.4)	313 (2.8)	1.32 (1.02, 1.71)	
≥6.2	5,114	36 (2.8)	160 (4.2)	1.50 (1.03, 2.16)	
Fasting glucose, mmol/L				0.948	
<6.1	14,526	78 (2.3)	321 (2.9)	1.40 (1.08, 1.81)	
6.1–<7.0	2,765	21 (2.8)	60 (3.0)	1.28 (0.76, 2.14)	
Diabetes	2,221	19 (4.0)	92 (5.3)	1.41 (0.85, 2.36)	
Total homocysteine, μmol/L				0.690	
<12.5	9,786	45 (1.9)	201 (2.7)	1.45 (1.04, 2.04)	
≥12.5	9,809	73 (3.1)	276 (3.7)	1.33 (1.02, 1.75)	
Albumin, g/L					0.566
<48.3 (median)	9,811	81 (3.1)	257 (3.6)	1.31 (1.00, 1.71)	
≥48.3	9,931	42 (2.1)	226 (2.9)	1.48 (1.05, 2.10)	
Calcium channel blockers usage during the treatment period			0.787		
No	4,114	18 (1.7)	77 (2.5)	1.48 (0.87, 2.51)	
Yes	15,633	105 (2.9)	406 (3.4)	1.36 (1.08, 1.72)	
Diuretics usage during the treatment period			0.817		
No	9,978	52 (2.4)	213 (2.7)	1.35 (0.97, 1.87)	
Yes	9,769	71 (2.8)	270 (3.7)	1.42 (1.07, 1.87)	

^aIf not stratified, adjusted for study centers, treatment groups, age, sex, body mass index, smoking, alcohol drinking, systolic blood pressure (SBP), albumin, total cholesterol, triglyceride, fasting glucose, creatinine, total homocysteine, methylenetetrahydrofolate reductase (MTHFR) C677T genotypes and antihypertensive treatment at baseline, as well as time-averaged SBP during the treatment period.

BMI, body mass index.

and multiple subgroup analyses and sensitivity analyses were conducted to ensure the robustness of the study findings.

The association between serum ALP and stroke have been reported by previous cohort studies, but the results have been

inconclusive. A recent prospective study, including 2,578 Iranian participants without prevalent CVD at baseline (mean ALP levels: 210.5 IU/L), showed that per one SD increase in ALP level was related to higher risk of stroke (adjusted HR, 1.20;

95%CI: 0.97, 1.49) (8). However, another study reported that there was no obvious relationship between serum ALP and stroke in 3,381 men, aged 60 to 79 years, without a history of MI or stroke at baseline (9). In addition, Shimizu Y et al. (13) reported that for nondrinkers, compared with participants in quintile 3 of ALP levels, higher ALP levels were related to higher risks of ischemic stroke for men and hemorrhagic stroke for women. However, lower ALP levels were related to higher risks of ischemic and hemorrhagic strokes in both men and women among 10,754 Japanese subjects (13). Overall, these studies showed that the relation of ALP and the risk of stroke is still uncertain. Of note, only part of the participants had hypertension in the previous studies. More importantly, there was no information about BP levels during the follow-up period in all of the previous studies. Therefore, the results cannot be generalized to adults with hypertension. Our study provided an opportunity to examine the dose-response association between circulating ALP and first stroke in hypertensive adults receiving standard antihypertensive treatments.

In contrast to the prior studies, our study provides some novel findings. It is by far the first and largest study of its kind demonstrating a positive relation between serum ALP and first stroke during a follow-up period of 4.5 years in general hypertensive adults. This significant association remained with adjustments for comprehensive covariables, including sex, age, BP, BMI, *MTHFR* C677T, smoking, alcohol drinking, lipids, FG, creatinine, albumin, tHcy and antihypertensive drug usage at baseline, and the time averaged BP during the follow-up period. Moreover, we have fully explored possible effect modifiers on the serum ALP-stroke association in general hypertensive adults, the findings suggested that the association between serum ALP and first stroke was consistent in these subgroups.

The exact mechanisms by which higher serum ALP was related to higher risk of stroke remains to be delineated. However, our study's findings are biologically plausible based on the available evidence. First, higher ALP has been reported to be related to vascular calcification by increased bone metabolism (7, 11). An animal experiment in the mouse had found a positive association of serum total ALP activity with bone-type ALP activity in calcified vascular lesions (21). Second, impaired vascular homeostasis may be another possible mechanism. Hematopoietic stem cells derived from bone marrow have an important role in vascular homeostasis (22, 23). Previous studies have reported that osteoblasts, whose activity was positively associated with bone-type ALP expression (24), may regulate the production of hematopoietic stem cells in bone marrow (25–27). As such, serum ALP level may be associated with vascular homeostatic activity. In addition, hematopoietic stem cells play a major role in the pathogenesis of atherosclerosis and may promote angiogenesis (22). Thus, higher ALP might constitute a risk factor for stroke owing to the progressive atherosclerosis. Furthermore, a previous study conducted in hypertensive individuals revealed that higher serum ALP increased the risk of endothelial dysfunction (28). Some possible mechanisms for this may be that ALP was related to reduced nitric oxide (NO) bioavailability by inhibiting tyrosine kinase activity into

endothelial cells (29, 30). Taken together, we hypothesized that vascular calcification, atherosclerosis, and endothelial dysfunction associated with higher serum ALP may all be involved in the pathogenesis of first stroke. However, the detailed underlying mechanisms still need to be further examined in future studies.

Limitations of the current study should also be noted. First, our study is a *post-hoc* analysis of the CSPPT. Although a broad array of covariates had been adjusted in the regression models, the residual confounding remains possible. Second, our study was conducted in Chinese adults with hypertension. Caution is needed when generalizing to other populations. Third, the small events of hemorrhagic stroke limited the statistical power of our analysis. Fourth, in our current study, most of the participants had normal ALP levels. Therefore, we could not investigate the possible increased stroke risk associated with relatively very low ALP levels. Fifth, in the present study, we measured total serum ALP rather than ALP isozymes. Finally, the ALP levels were assessed only at baseline and the exit visit. More frequent assays of ALP levels would allow for a more accurate assessment of its progression over time. Therefore, our current study could not provide a causal relationship between ALP and an increased risk of stroke. Overall, our results were just hypothesis generating. All findings need to be further confirmed in more studies.

In summary, our study suggests that higher serum ALP levels, even in normal range, were significantly related to higher risk of first stroke in general hypertensive adults. If our findings were further confirmed, identifying hypertensive patients with higher serum ALP levels may help detect those individuals who are at high risk of first stroke.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YuZ, XX, and XQ designed research. YuZ, JL, YaZ, BW, YH, FH, XX, and XQ conducted research. YuZ, HL, DX, JL, YaZ, BW, CL, YS, XW, YH, FH, XX, and XQ contributed to acquisition, analysis, or interpretation of data. YuZ, HL, and XQ performed statistical analysis. YuZ and XQ wrote the paper. All authors revised the manuscript and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2021.749196/full#supplementary-material>

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