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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Serum Alkaline Phosphatase Level is Associated with Angiographic Vasospasm, Delayed Cerebral Ischemia-Caused Clinical Deterioration, and Functional Outcome After Aneurysmal Subarachnoid Hemorrhage

Yu Zhu[1†], Hao Jiang[1,2†], Yongda Li[1†], Yuxiang Weng[1], Kangli Xu[1,3], Lei Zhou[1], Hongwei Lin[1], Tianfu Sun[1], Dexin Cheng[1], Jie Shen[1], Jianping Zeng[1], Di Ye[1], Duanbu Wang[1,4] and Renya Zhan[1*]

Abstract

Background: Alkaline phosphatase (ALP) has been implicated to be associated with poor outcome in ischemic stroke patients, yet its role in aneurysmal subarachnoid hemorrhage (aSAH) patients is unknown. The current study aimed to investigate the on-admission and short-term variation trend of ALP levels in aSAH patients as well as its associations with vasospasm, delayed cerebral ischemia (DCI), and outcome after aSAH.

Methods: Between January 2014 and May 2018, all consecutive aSAH patients were prospectively enrolled. Blood samples from patients and 78 healthy individuals were obtained. Baseline information, clinical data, and radiologic data were collected, and serum ALP levels during hospitalization were measured. Patients were followed up for 6 months.

Results: One hundred and ninety-six aSAH patients were included. The serum ALP levels in aSAH patients were significantly higher compared to controls (71 vs. 61 U/L, $p = 0.0002$), yet did not differ significantly between patients with severe (WFNS 4–5) and mild clinical condition (72 vs. 63 U/L, $p = 0.3362$). However, ALP was significantly higher in patients with severe radiologic status (modified Fisher 3–4) compared to those with mild radiologic status (77 vs. 61.5 U/L, $p = 0.0005$). A significant correlation emerged between modified Fisher score and ALP level ($r = 0.246$, $p = 0.001$). Multivariable analysis found that higher ALP level was associated with angiographic vasospasm (OR 1.019, 95% CI 1.002–1.036, $p = 0.026$) and DCI-caused clinical deterioration (OR 1.019, 95% CI 1.001–1.037, $p = 0.037$), while higher WFNS score, modified Fisher score, and ALP level were independently associated with unfavorable outcome (serum ALP level, OR 1.083, 95% CI 1.041–1.127, $p < 0.001$). Trend analysis of ALP level based on 103 patients' data revealed a significant decrease in ALP level on post-admission day 7–9 (median; on-admission day vs. post-admission day 7–9, 72 vs. 60 U/L, $p = 0.0012$; post-admission day 3–5 vs. day 7–9, 70 vs. 60 U/L, $p = 0.0052$) and subsequent increase in ALP level on post-admission day 12–14 (median, 84 U/L, $p < 0.0001$). Higher ALP levels were observed in

*Correspondence: 1196057@zju.edu.cn
†Yu Zhu, Hao Jiang, and Yongda Li have contributed equally to this work.
[1] Department of Neurosurgery, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou, Zhejiang Province, China
Full list of author information is available at the end of the article

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patients with unfavorable outcome on on-admission day, post-admission day 3–5, and 12–14 (median; unfavorable vs. favorable; on-admission day, 86 vs. 67 U/L, $p = 0.0122$; post-admission day 3–5, 80 vs. 64 U/L, $p = 0.0044$; post-admission day 7–9, 75 vs. 53.5 U/L, $p < 0.0001$) but not on post-admission day 12–14.

Conclusions: Elevated serum ALP level is associated with vasospasm, DCI-caused clinical deterioration, and functional outcome after aSAH. Further studies are required to examine the potential role of serum ALP as an outcome predictor for aSAH patients.

Keywords: Alkaline phosphatase, Angiographic vasospasm, Delayed cerebral ischemia, Outcome, Aneurysmal subarachnoid hemorrhage

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 5–10% of all strokes, with reported incidence varying across the globe, from 2.0 cases per 100,000 persons to 22.5 cases per 100,000 persons [1]. Due to its younger occurrence than other subtypes of stroke such as cerebral infarction, aSAH leads to a greater loss of productive life years with catastrophic fatality rate ranging from 25 to 50%. Among complications arising from aSAH, vasospasm and delayed cerebral ischemia (DCI) remain the major challenge and are the main cause of death and unfavorable outcomes [2].

Alkaline phosphatase (ALP) is an enzyme that catalyzes the hydrolysis of organic pyrophosphate and promotes vascular calcification [3] and has also been implicated in the negative regulation of vascular endothelium-dependent vasodilation [4]. To date, a number of studies found that serum ALP was associated with increased morbidity and mortality in patients with cardiovascular diseases both in community residents and clinic populations [5–9]. Recently, a few researchers have further revealed the association of elevated serum ALP level with increased mortality rate, poor functional outcome, and disease recurrence in stroke patients [10–13]. However, the population in these studies only or mainly consists of ischemic stroke patients. Currently there is lack of data on the association of ALP with outcomes in patients with aSAH, and no published information exists to date about the correlation of ALP with ischemic events after aSAH. As in several aspects, hemorrhagic stroke shares similar pathologic and cellular pathogenesis with ischemic stroke such as vasculopathy and hypertension. We assume that ALP may also play important roles in hemorrhagic stroke and may be correlated with clinical severity and clinical outcomes after aSAH.

In the current study, we investigated the ALP level of aSAH patients on admission as well as its short-term variation trend after admission. The associations/correlations of ALP with on-admission World Federation of Neurological Surgeons (WFNS) score, modified Fisher score, development of vasospasm/DCI complications, and unfavorable functional outcome after aSAH were also analyzed.

Methods

Study Population

Between January 2014 and May 2018, all consecutive patients admitted to Department of Neurosurgery, The First Affiliated Hospital, Zhejiang University School of Medicine, with a diagnosis of aSAH were prospectively enrolled. Inclusion criteria were diagnosis of aSAH, age older than 18 years, and hospital admission within 24 h of aSAH. Exclusion criteria were death within 24 h after admission and heavy alcohol use (defined as > 4 drinks per day for women and > 5 drinks per day for men on 5 or more days in the past month). Clinical management was performed according to international guidelines [14, 15]. Blood samples from 78 healthy individuals were used as controls.

Baseline Data Collection

The following variables were extracted by trained research coordinators: patients' demographics including age, gender, and history of hypertension, diabetes mellitus, stroke, coronary heart disease, dyslipidemia, previous or current smoking, moderate to heavy alcohol consumption, and important laboratory data including blood alanine transaminase, and aspartate transaminase levels. Admission status was evaluated using the WFNS scale and modified Fisher scale.

ALP Testing

Fasting blood samples of healthy individuals and the patients were drawn at study entry or within 24 h of admission, and serum ALP levels were tested using unfrozen samples by automated enzymatic method, according to the recommendation of the International Federation of Clinical Chemistry and Laboratory Medicine in 2011 [16]. Additionally, in 103 patients, the ALP level was tested repeatedly for every 3–5 days before discharge and the ALP data of these 103 patients were further classified into four periods: (1) Day 1 (on admission), (2) Post-admission day 3–5 (Day 3–5, after treatment),

(3) Post-admission day 7–9 (Day 7–9), and (4) post-admission day 12–14 (Day 12–14). Normal ALP values from the laboratory of First Affiliated Hospital, Zhejiang University School of Medicine, who performed the test were 40–150 U/L.

Clinical and Radiological Assessment

Severity of aSAH on admission was recorded according to the WFNS scale [17], and patients were grouped into severe clinical condition (WFNS score of 4 and 5) or mild clinical condition (WFNS score 1–3) category. The extent of hemorrhage was graded on initial computed tomography (CT) scan and was classified using the modified Fisher (mFisher) scale [18], and patients were also grouped into severe aSAH (mFisher score 3–4) or mild SAH (mFisher score 1–2). Angiographic vasospasm and DCI were defined according to the standard definitions proposed by a multidisciplinary research group [19, 20]. Specifically, angiographic vasospasm was defined as observation of arterial diameter > 20% narrowing confirmed by angiography, and DCI was defined separately as cerebral infarction (defined as the identification of cerebral infarction on CT or magnetic resonance imaging within 6 weeks after aSAH which is not attributable to other causes such as surgical clipping or endovascular treatment), and clinical deterioration caused by DCI (defined as the occurrence of focal neurological impairment or a decrease in at least 2 points on Glasgow Coma Scale score after exclusion of other potential causes). The decision of angiographic vasospasm, cerebral infarction, and clinical deterioration caused by DCI were made by at least two senior neurosurgeons in charge of the patient. All clinical and radiological assessments were performed according to the neuroradiology department protocol.

Outcome Assessment

Patients were followed up until death or at 6 months. Outcome was assessed at 6 months after aSAH by telephone interview. Clinical outcome was collected by trained research coordinators who were blinded to patients' clinical information. The unfavorable outcome was defined by modified Rankin score of 3–6 [range from 0 (no symptoms) to 6 (death)] [21].

Statistical Analysis

Statistical analysis was performed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA) and Prism 7 (GraphPad Software, San Diego, CA, USA). Normality of data distribution was assessed by Shapiro–Wilk test. Mann–Whitney test was used for comparing ALP level between aSAH patients and healthy controls, and also for assessing relation of ALP level with WFNS score, modified Fisher score, angiographic vasospasm, cerebral infarction, clinical deterioration caused by DCI and 6-month outcome. Data are presented as scatter-dot plots with medians. Correlation of ALP levels with modified Fisher score was assessed by Spearman's correlation coefficient. A ROC curve was configured for predicting unfavorable outcome (modified Rankin scale of 3–6). Logistic regression model was performed to estimate the association between ALP levels and vasospasm, DCI, and unfavorable outcomes.

Results

Study Population Characteristics

One hundred and ninety-six patients fulfilled the inclusion criteria and were included in this study (Table 1). Sensitivity analyses were performed in which participants with greater than two drinks per day for men and one drink per day for women were excluded; results of regression models with regard to ALP's association with outcomes were not meaningfully changed (data not shown). The mean age was 57.5 years, and 52.6% were female. Fifty-five patients (28.1%) were in severe clinical condition on admission (WFNS score 4–5). One hundred and two (52.0%) patients had severe aSAH (modified

Table 1 Patient characteristics ($n = 196$)

Demographic characteristics	
Age (SD), years	57.5 (± 10.3)
Sex, female	103 (52.6)
Risk factors	
History of smoking	47 (24.0)
Alcohol consumption	20 (10.2)
Hypertension	75 (38.3)
Previous stroke	21 (10.7)
CHD	7 (3.6)
Dyslipidemia	34 (17.3)
Diabetes	21 (10.7)
ALT, U/L, mean (SD)	21.8 (16.9)
AST, U/L, mean (SD)	23.1 (11.0)
Clinical and radiologic characteristics	
Clinical severity on admission	
WFNS grades 1–3	141 (71.9)
WFNS grades 4 and 5	55 (28.1)
Modified Fisher grades 1–2	94 (48.0)
Modified Fisher grades 3–4	102 (52.0)
Treatment	
Clip	75 (38.3)
Coil	121 (61.7)
Angiographic vasospasm	72 (36.7)
Delayed cerebral ischemia	
Cerebral infarction	57 (29.1)
Clinical deterioration caused by DCI	41 (20.9)

ALP alkaline phosphatase, *ALT* alanine transaminase, *AST* aspartate transaminase, *CHD* coronary heart disease, *WFNS* World Federation of Neurosurgical Societies

Fisher score 3–4) detected on admission CT. Aneurysms were treated with surgical clipping in 75 (38.3%) patients, while other 121 (61.7%) received endovascular coiling. During admission, 72 patients (36.7%) developed angiographic vasospasm, 57 (29.1%) developed cerebral infarction and in 41 (20.9%) patients, clinical deterioration caused by DCI was observed. Unfavorable functional outcome at 6 months was observed in 50 (25.5%) patients. Seventy-eight healthy voluntary blood donors served as controls.

ALP Level in aSAH Patients, Healthy Controls, and Its Short-Term Variation Trend in aSAH Patients

Serum ALP levels in both aSAH group and control group did not follow a normal distribution; therefore, all values were expressed as median. The level of serum ALP in patients with aSAH was significantly higher compared to controls (aSAH 71 U/L, controls 61 U/L, $p=0.0002$; Fig. 1a), yet both levels were within normal range. The ALP level measured in aSAH patients was similar to previous data from acute ischemic stroke patients [11].

The overall ALP level trend of 103 patients was shown as Fig. 1b. As ALP levels in all four periods did not follow a normal distribution (Shapiro–Wilk test), therefore all values were expressed as median with interquartile range. The median ALP level of Day 1, Day 3–5, Day 7–9, and Day 12–14 was 72 U/L, 70 U/L, 60 U/L, 84 U/L, respectively. No significant change of ALP level was found between Day 3–5 and Day 1 ($p=0.4376$); however, a significant decrease in ALP level was observed on Day 7–9 (Day 1 vs. Day 7–9, $p=0.0012$; Day 3–5 vs. Day 7–9, $p=0.0052$), and on Day 12–14, we observed a significant increase in ALP level ($p<0.0001$, Mann–Whitney test), even higher than the level on admission ($p=0.0002$).

Association of ALP Level with Clinical and Radiologic Status on Admission

The level of ALP did not differ significantly between patients with severe (WFNS 4–5) and mild clinical condition (WFNS 1–3) on admission (72 vs. 63 U/L, $p=0.3362$; Fig. 2a). However, ALP was significantly higher in patients with severe radiologic status (modified Fisher 3–4) compared to mild radiologic status (modified Fisher 1–2) (77 vs. 61.5 U/L, $p=0.0005$; Fig. 2b). A significant correlation emerged between modified Fisher score and serum ALP level ($r=0.246$, $p=0.001$; Fig. 2c).

ALP Level is Related to Angiographic Vasospasm and DCI-Caused Clinical Deterioration

The ALP level was significantly higher in patients with vasospasm compared with those without (76.5 vs. 67 U/L, $p=0.0028$; Fig. 3a). Higher serum ALP levels were also observed in patients with cerebral infarction and DCI-caused clinical deterioration compared with those without (cerebral infarction 77 vs. 68 U/L, $p=0.0134$; Fig. 3b; clinical deterioration due to DCI: 77 vs. 70 U/L, $p=0.0142$; Fig. 3c). Multivariable analysis revealed that higher WFNS score, modified Fisher score, and ALP level were associated with angiographic vasospasm (Table 2; serum ALP level, OR 1.019, 95% CI 1.002–1.036, $p=0.026$), higher modified Fisher score and ALP level were associated with DCI-caused clinical deterioration (Table 3; serum ALP level, OR 1.019, 95% CI 1.001–1.037, $p=0.037$), while ALP level was not associated with

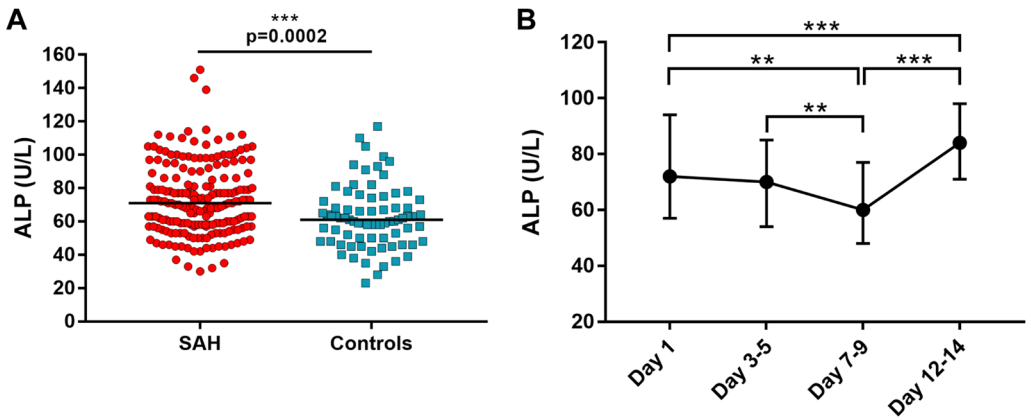

Fig. 1 ALP level in aSAH patients, healthy controls, and its short-term variation trend in aSAH patients. **a** Serum levels of ALP in patients with aSAH ($n=196$) and controls ($n=78$). Data are reported as scatter-dot plots and medians. Mann–Whitney test p value is indicated. **b** Short-term variation trend of ALP level in aSAH patients on Day 1, Day 3–5, Day 7–9, and Day 12–14 ($n=103$). Data are reported as median with interquartile range. Mann–Whitney test p value is indicated. *ALP* Alkaline phosphatase, *SAH* subarachnoid hemorrhage

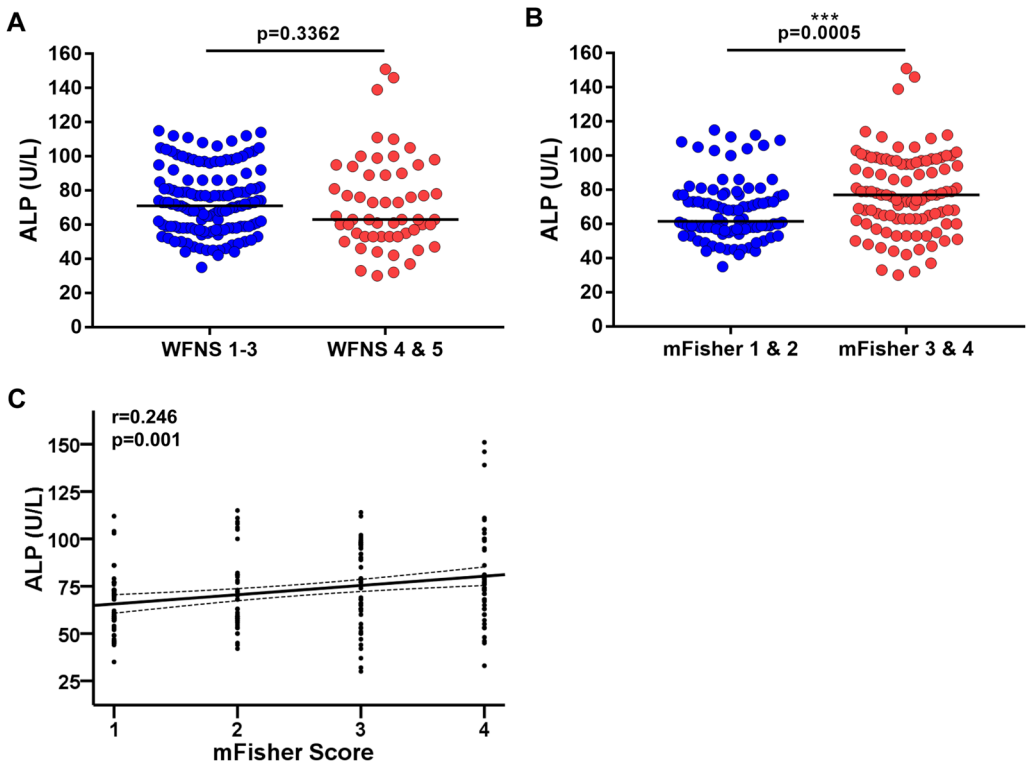

Fig. 2 Association of ALP level with clinical and radiologic status on admission. **a** Serum levels of ALP in patients with mild (WFNS grades 1–3, $n=141$) and severe (WFNS grades 4 and 5, $n=55$) clinical status. **b** Serum levels of ALP in patients with mild (modified Fisher grades 1 and 2, $n=94$) and severe (modified Fisher grades 3 and 4, $n=102$) radiologic status. **c** The correlation of serum ALP level with modified Fisher scale. Data are reported as scatter-dot plots and medians in panel A and B. Mann–Whitney test for assessing relation of ALP level with WFNS score and modified Fisher score. Correlation of ALP levels with modified Fisher score was assessed by Spearman's correlation coefficient. *ALP* Alkaline phosphatase, *WFNS* World Federation of Neurosurgical Societies, *mFisher* modified Fisher scale

cerebral infarction in multivariable analysis (Table 4; OR 1.012, 95% CI 0.996–1.029, $p=0.142$).

Association of ALP Level with Unfavorable 6-Month Functional Outcome

The level of ALP was higher in patients with unfavorable functional outcome compared with those with a favorable functional outcome (79.5 vs. 68 U/L, $p=0.0013$; Fig. 4a). Patients with a serum ALP level higher than 71 U/L (median level of ALP of all patients) were correlated with a more unfavorable 6-month outcome than those with ALP level of ≤ 71 U/L (Fig. 4b). A ROC curve identified that a baseline serum ALP level ≥ 87.5 U/L predicts 6-month unfavorable functional outcome of aSAH patients with 83.56% sensitivity and 46% specificity (area under curve, 0.652; 95% CI 0.559–0.745, $p=0.0014$; Supplementary Figure 1). Multivariable analysis (Table 5) found that higher WFNS score, modified Fisher score, and ALP level were independently associated with unfavorable outcome (serum ALP level, OR 1.083, 95% CI 1.041–1.127, $p<0.001$).

Trend analysis of ALP levels based on 103 patients' functional outcome (66 with favorable outcome and 37 with unfavorable outcome; Fig. 4c) showed that on Day 1, Day 3–5, and Day 12–14, significantly higher ALP levels were observed in patients with unfavorable outcome (median; unfavorable vs. favorable; Day 1, 86 U/L vs. 67 U/L, $p=0.0122$; Day 3–5, 80 U/L vs. 64 U/L, $p=0.0044$; Day 7–9, 75 U/L vs. 53.5 U/L, $p<0.0001$c) but not on Day 12–14 (median; unfavorable vs. favorable; 89 U/L vs. 78.5 U/L, $p=0.0568$).

Discussion

In this preliminary study, we show for the first time that elevated serum ALP level was associated with angiographic vasospasm, clinical deterioration caused by DCI, and unfavorable outcome after aSAH. Our results extend previous findings for the relationship between serum ALP and unfavorable clinical outcome in ischemic stroke patients to patients with hemorrhagic stroke caused by aneurysm rupture. Further, the present study shows a significant correlation between serum ALP level

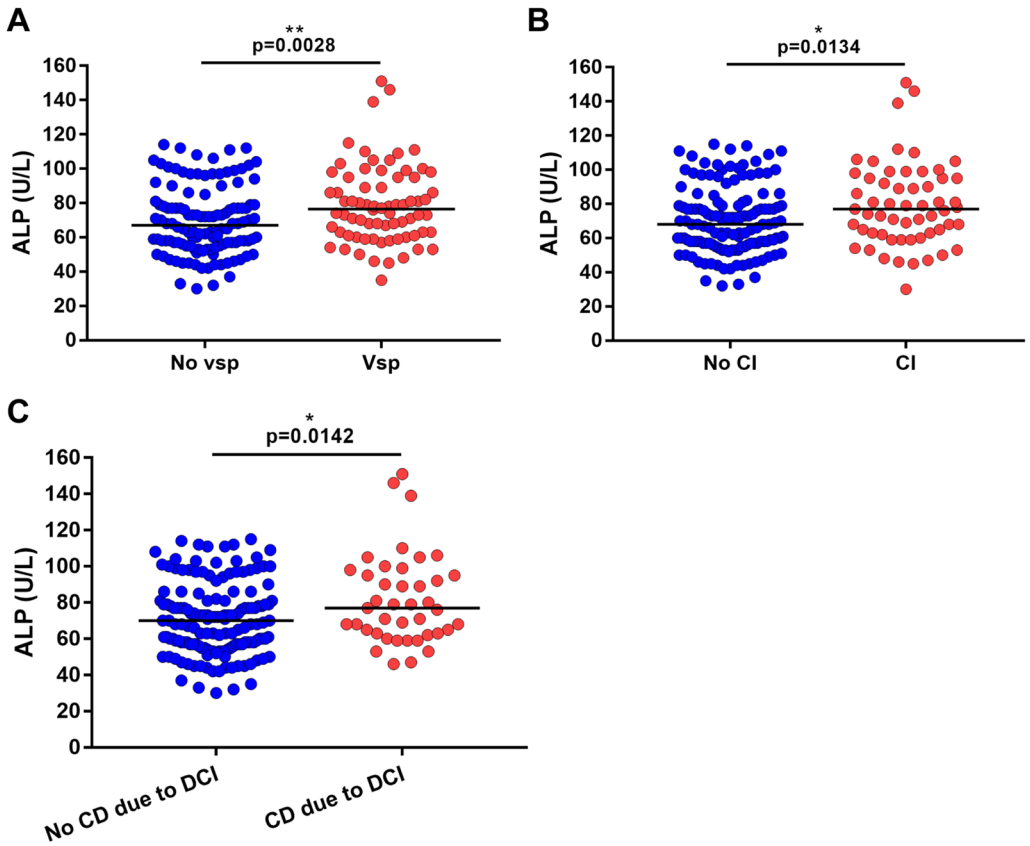

Fig. 3 ALP level is related to angiographic vasospasm and DCI-caused clinical deterioration. **a** Serum levels of ALP in patients with ($n=72$) compared to those without ($n=124$) angiographic vasospasm. **b** Serum level of ALP in patients with ($n=57$) cerebral infarction compared to those without ($n=139$) cerebral infarction. **c** Serum level of ALP in patients with ($n=41$) clinical deterioration compared to those without ($n=155$) clinical deterioration due to DCI. Data are reported as scatter-dot plots and medians. Mann–Whitney test *p* value is indicated. *ALP* Alkaline phosphatase, *vsp* angiographic vasospasm, *CI* cerebral infarction, *CD* clinical deterioration, *DCI* delayed cerebral ischemia

Table 2 Multivariable factors associated with angiographic vasospasm

	Multivariable OR (95% CI)	*p* value
Age	1.000 (0.968–1.033)	0.996
Diabetes	0.631 (0.218–1.823)	0.395
Hypertension	0.912 (0.459–1.812)	0.792
History of smoking	1.296 (0.617–2.721)	0.494
Previous stroke	1.225 (0.434–3.458)	0.702
WFNS on admission	1.314 (1.014–1.704)	0.039
mFisher on admission	1.440 (1.006–2.063)	0.047
ALP on admission	1.019 (1.002–1.036)	0.026

ALP alkaline phosphatase, *mFisher* modified Fisher scale, *WFNS* World Federation of Neurosurgical Societies

and ischemic events after aSAH, which might possibly explain the association between higher ALP level and unfavorable clinical outcome observed in this study.

Previous studies have highlighted the role of ALP in cardiovascular disease to cause higher mortality and morbidity rate [6]. However, relatively quite limited research on the relationship between ALP and outcomes in stroke patients has been conducted. Recently, several studies have demonstrated the association of ALP with all-cause mortality and unfavorable functional outcome in patients with ischemic stroke and only one study further reported that ALP was associated with short-term death and poor outcome in patients with spontaneous intracerebral hemorrhage [22]. To our knowledge, our study is the first to document the association of serum ALP with clinical outcome and ischemic events in patients with aSAH. In the present study, we first observed higher level of serum ALP in patients with aSAH compared to controls, and similar associations were found in patients with higher mFisher scale scores but not in patients with higher WFNS scale scores. As ALP has long been found to be abundantly localized in endothelium and proximal parts of cerebral blood vessels that constitute blood

Table 3 Multivariable factors associated with DCI-caused clinical deterioration

	Multivariable OR (95% CI)	*p* value
Age	0.986 (0.948–1.026)	0.487
Diabetes	1.083 (0.348–3.368)	0.891
Hypertension	1.574 (0.705–3.514)	0.268
History of smoking	0.751 (0.303–1.865)	0.538
Previous stroke	1.005 (0.308–3.282)	0.993
WFNS on admission	1.004 (0.741–1.360)	0.979
mFisher on admission	1.813 (1.143–2.874)	0.011
ALP on admission	1.019 (1.001–1.037)	0.037

ALP alkaline phosphatase, *mFisher* modified Fisher scale, *WFNS* World Federation of Neurosurgical Societies

Table 4 Multivariable factors associated with cerebral infarction

	Multivariable OR (95% CI)	*p* value
Age	0.973 (0.939–1.008)	0.125
Diabetes	0.941 (0.325–2.723)	0.911
Hypertension	1.044 (0.503–2.165)	0.909
History of smoking	0.788 (0.354–1.753)	0.558
Previous stroke	1.124 (0.386–3.275)	0.831
WFNS on admission	0.932 (0.707–1.229)	0.618
mFisher on admission	2.027 (1.346–3.053)	0.001
ALP on admission	1.012 (0.996–1.029)	0.142

ALP alkaline phosphatase, *mFisher* modified Fisher scale, *WFNS* World Federation of Neurosurgical Societies

brain barrier (BBB) [23, 24], elevated serum ALP level might manifest the extent of endothelial damage and BBB destruction after aSAH, which may positively correlate with mFisher score of aSAH patients.

To our knowledge, patients' serum ALP level trend after aSAH has rarely been reported. In the current study, we observed a decrease in ALP level from on-admission day to post-admission day 7–9 with subsequent increase in ALP level on post-admission day 12–14. Although it is unlikely that we elucidate the underling pathologic mechanisms for this ALP level change in the current study, we noticed that in the context of brain trauma, cerebral and plasma ALP level/activity were reported to decrease in acute phase and is associated with neural injury [25]. On the other hand, ALP plays important role in neuronal stem cell-conducted neural regeneration after neurodegenerative injury [26, 27]. It is possible that the decrease in ALP level in acute phase after aSAH may reflect secondary neuronal injury induced by aSAH, while the subacute-phase increase in ALP level may indicate neural repair process after aSAH. Our results offer estimable basis for future studies focusing on the pathological role of ALP in aSAH, and to unveil the underlying pathologic mechanisms of the ALP level change after aSAH, further laboratory investigations are needed.

In this study, we observed increased risk of unfavorable clinical outcome in patients with higher serum ALP, similar to previous findings in the context of ischemic stroke. This correlation was further confirmed in a multivariable regression model, and ALP, along with history of previous stroke, WFNS score, and mFisher score on admission were identified as independent markers to predict 6-month functional outcome. The mechanism underlying the association of serum ALP with increased risk of unfavorable outcomes is poorly understood, but several plausible mechanisms have been proposed in those ischemic stroke-based studies, including induction of systemic inflammation, reflection of malnutrition, and acceleration of atherosclerosis [5, 12, 28, 29]. We assume that these detrimental roles of ALP may also affect patients with hemorrhagic stroke and lead to worse functional outcome after aSAH. The results of trend analysis of serum ALP level based on patients' clinical outcome indicate that except for the single ALP level value on admission, a continuous higher level of ALP during the first week from disease onset is correlated with poorer clinical outcome after aSAH, while the specific results on post-admission day 12–14 may indicate that subacute-phase ALP level is not significantly correlated with clinical outcome and thus can hardly be an effective predictor.

Vasospasm and DCI are considered the main cause of mortality and poor outcome after aSAH. In the present study, higher levels of serum ALP were observed in patients with angiographic vasospasm and clinical deterioration. Two possible mechanisms may partially explain the association between ALP and occurrence of the ischemic events. First, several data have indicated that ALP may be a reflection of inflammation [28, 30], and numerous animal and human studies have provided evidence of inflammation being a vital factor leading to both vasospasm and ischemic brain injury after SAH [31–34]. Second, the role of ALP in negative regulation of vascular endothelium-dependent vasodilation and elevation of blood pressure has been implicated in recent studies [4, 35], and early elevation of blood pressure after aSAH had been found to be associated with vasospasm [36].

This study had some limitations. First, as a preliminary study, the relatively small cohort of patients included in the present analysis needs further confirmation in studies with large sample size. Second, as the current study was designed in a observational manner, we were unable to demonstrate a causal relationship between serum ALP level and various outcomes, and some unmeasured confounding effects may affect the results, which needs to be addressed in experimental settings. Third, testing of

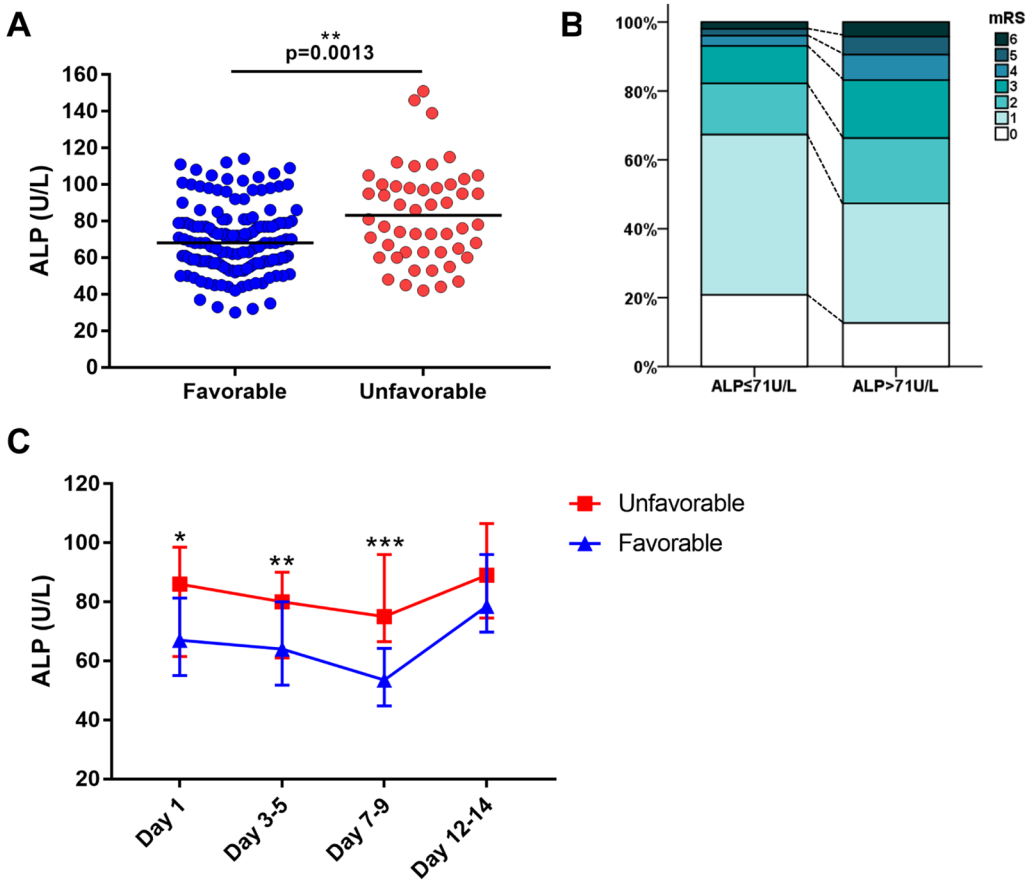

Fig. 4 Association of ALP level with unfavorable 6-month functional outcome. **a** Serum ALP levels in patients with favorable (modified Rankin scale 0–2, $n=146$) and unfavorable (modified Rankin scale 3–6, $n=50$) outcome. **b** Scores on the modified Rankin scale at 6 months for patients with ALP level equal to or lower ($n=101$) and higher ($n=95$) than medium level (71 U/L). **c** Trend analysis of ALP level based on patients' functional outcome (total $n=103$; Favorable outcome, $n=66$; Unfavorable outcome, $n=37$; Fig. 4c). Data are reported as scatter-dot plots and medians in panel A and are reported as median with interquartile range in panel C. Mann–Whitney test for assessing relation of ALP level with unfavorable outcome and for comparing ALP level between patients with favorable and unfavorable outcome. *ALP* Alkaline phosphatase, *mRS* modified Rankin scale

Table 5 Multivariable factors associated with 6-month outcome

	Multivariable OR (95% CI)	*p* value
Age	1.055 (0.989–1.125)	0.103
WFNS on admission	5.441 (2.771–10.683)	< 0.001
mFisher on admission	4.116 (1.852–9.148)	0.001
Previous stroke	3.824 (0.630–23.213)	0.145
Dyslipidemia	1.532 (0.286–8.208)	0.618
Diabetes	2.013 (0.340–11.912)	0.441
Alcohol Consumption	1.707 (0.270–3.991)	0.230
ALT	1.011 (0.970–1.052)	0.614
AST	0.979 (0.922–1.040)	0.499
ALP	1.083 (1.041–1.127)	< 0.001

ALT alanine transaminase, *ALP* alkaline phosphatase, *AST* aspartate transaminase, *mFisher* modified Fisher scale, *WFNS* World Federation of Neurosurgical Societies

ALP isozymes was not performed so more detailed information on relationship between subtypes of ALP and adverse outcomes was unavailable.

Conclusions

In conclusion, the results in the present study suggest that elevated serum ALP level is associated with angiographic vasospasm, DCI-caused clinical deterioration, and unfavorable outcome after aSAH. Further studies are required to examine the potential role of serum ALP as an outcome predictor for aSAH patients.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-019-00714-7) contains supplementary material, which is available to authorized users.

Author details
[1] Department of Neurosurgery, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou, Zhejiang Province, China. [2] Department of Neurosurgery, Shulan Hospital, 848 Dongxin Road, Hangzhou, Zhejiang Province, China. [3] Emergency Department Trauma Center, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou, Zhejiang Province, China. [4] Department of Neurosurgery, Sanmen People's Hospital, Sanmen, Zhejiang Province, China.

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Author Contributions
YZ: project development, data collection and management, data analysis, manuscript writing. HJ: data collection and management, manuscript writing. YL: data collection and management, manuscript writing. YW: data collection and management. KX: data collection and management. LZ: data collection and management. HL: data collection and management. TS: data collection. DC: data management. JS: data collection and management. JZ: data management. DY: data management. DW: data management. RZ: project development, manuscript writing and editing.

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Conflicts of Interest
All authors declare that there are no competing interests with regard to publication of this paper.

Ethical Approval/Informed Consent
This study was approved by the Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine. Informed consent was obtained from study population or family members in all cases.

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