Alkaline phosphatase and mortality in stroke patients: a systematic review

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Background: Increased plasma levels of alkaline phosphatase (ALP) have been associated to a worse prognosis in several types of diseases. In the present review, the authors aimed to study the relationship between plasma levels of ALP and overall mortality in patients with stroke.

Methods: A systematic review was carried out, searching two databases: Web of Science and Medline/PubMed.

Results: A total of nine studies that included data on overall mortality in stroke patients were selected. The selected studies were published between 2010 and 2022 and were predominantly from Asia. The articles reviewed quantified ALP levels through different methods: highest versus lowest quintiles of plasma ALP (three reports); highest versus lowest quartiles of plasma ALP (four reports); and plasma ALP levels in deceased versus in surviving patients (two reports). All selected studies showed an increased mortality associated to elevated ALP levels, irrespective of stroke type and length of follow-up, from a mean of 10 days to 2.5 years. The studies comparing the highest to the lowest ALP quintiles showed an aggregate value of 1.8 times greater risk of mortality for the former, when compared to the latter. Whereas, the studies comparing the highest to the lowest ALP quartiles showed an aggregate value of 2.4 times greater risk of mortality for the former, when compared to the latter.

Conclusions: Elevated ALP levels are associated with increased mortality in stroke patients and provide cost effective prognostic indicators of mortality in stroke.

Keywords: Alkaline phosphatase (ALP); mortality; stroke; systematic review

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Introduction

Stroke is a major cause of death and the leading cause of disability worldwide. Stroke-related complications occur most frequently during the first week after stroke and are associated with higher mortality risk during hospital stay and a longer hospital stay (1). The risk for death is highest in the acute phase of a stroke and then gradually declines. A study from the Danish MONICA project (2) found that the most frequent cause of death in patients with non-fatal strokes was cardiovascular disease, with 32.1% of deaths due to cerebrovascular disease and 22.7% to ischemic heart disease.

Different predictive models for mortality in stroke have been developed (3), but none of them are routinely used in clinical practice. These models include clinical

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variables, such as age and stroke severity, as predictors of poor outcome and mortality (4). It has been suggested that the addition of blood biomarkers to clinical models might improve their prediction capacity. Over 150 candidate stroke biomarkers have been studied (5). However, there is still a lack of trackable biomarkers capable of predicting the risk and prognosis of stroke, and that may play a role in stroke mortality prevention. Biomarkers could be used to help identify high-risk patients, allowing more aggressive therapeutic strategies targeted at those most likely to benefit. One possible candidate as a diagnostic and prognostic biomarker for stroke is alkaline phosphatase (ALP). This enzyme is responsible for catalyzing the hydrolysis of organic pyrophosphate, an inhibitor of vascular calcification, thus promoting the enhancement of vascular calcification, accelerating the stiffening of vessels, decreasing vascular compliance and consequently promoting atherosclerosis (6). The possible involvement of the serum ALP levels in the risk of cardiac and cerebrovascular diseases as well as in poor outcomes and all-cause mortality after stroke has been under study in recent years.

Given these considerations, we aimed to conduct a systematic review concerning the association between ALP levels and all-cause mortality after stroke and its use as a possible predictor of mortality in this context. We present this article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1627/rc) (7).

Highlight box

Key findings

- Elevated alkaline phosphatase (ALP) levels are associated with increased mortality in stroke patients.

What is known and what is new?

- No predictive models for mortality in stroke are routinely used in clinical practice. The addition of blood biomarkers to clinical models might improve their prediction capacity. Over 150 candidate stroke biomarkers have been studied. However, there is still a lack of trackable biomarkers capable of predicting stroke mortality, and that may play a role in its prevention.
- This review has demonstrated that the elevation of ALP levels is consistently associated to increased mortality after stroke. Studies comparing the highest to the lowest ALP quintiles and quartiles showed that the mortality risk is 1.8 and 2.4 times, respectively.

What is the implication, and what should change now?

- ALP levels may provide a cost-effective prognostic indicator of stroke-related mortality. This finding warrants further investigation in future primary studies that follow standardized methodologies.

Methods

Eligibility criteria

We searched for original studies focused on the impact of ALP levels on overall mortality, in patients who had a past diagnosis of stroke event of any type (ischemic or hemorrhagic) or a transient ischemic attack (TIA).

Articles that only analyzed the incidence of stroke or TIA in the general population (patients without previous stroke events) or that did not present data on mortality were excluded. Case reports, systematic reviews, review articles and studies including animal models were not considered for this study.

No specific limit of time after stroke was defined in which our primary outcome (mortality) had to occur. With this in mind, follow-up time was not considered as an exclusion criterion.

No articles were excluded based on publication date or the language in which the studies were written.

Search strategy

A comprehensive literature search was carried out to identify all reported articles relating the impact of ALP levels on mortality after stroke. This search was conducted on the databases Medline (PubMed) and Web of Science.

The search took place on the 30th of October 2022 in the Web of Science database and on the 31st of October 2022 in the Medline database, using the following query: ("alkaline phosphatase" [MeSH Terms]) OR ("alkaline phosphatase"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]).

Additionally, to avoid missing reports, we manually scanned the list of references from the included studies and of the previous review focusing on the relation between ALP and stroke (8).

Selection process

Eligibility was evaluated by four investigators, who independently assured that all the inclusion and exclusion criteria were met. In the screening phase, only the title and the abstract were analyzed. After this process, 22 articles were considered eligible. Full-text critical assessment of the 22 articles followed and 9 articles were included in

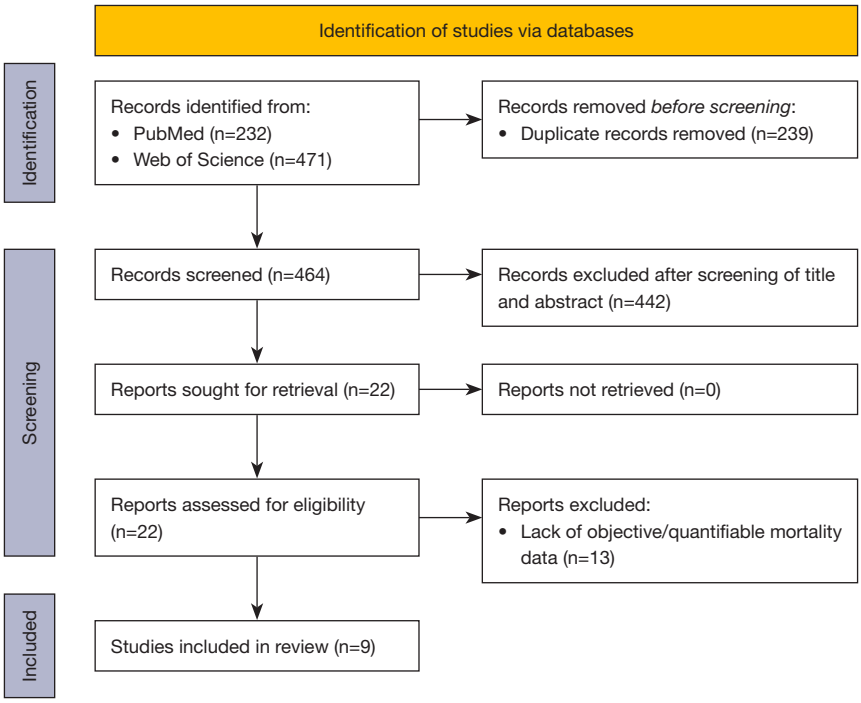

Figure 1 Flowchart showing literature search method.

this systematic review. Divergent opinions regarding the relevance of articles were solved by consensus between the authors.

Data collection process and data item

Data extraction was individually done, by the four above mentioned authors, from the data published in the selected articles, and then compared between the investigators. Any doubtful situation was solved by consensus between the authors.

Study quality assessment

Global article quality assessment was carried out according to the National Heart, Lung and Blood Institute study quality assessment tools (available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) and is presented in Table S1.

Outcome measures

Our primary outcome was the association between the level of ALP and the risk for all-cause mortality, in the period after a stroke event, either ischemic or hemorrhagic, or after a TIA. No statistical analysis was carried out. Arithmetic analysis of the number of deceased patients in studies comparing the highest to the lowest ALP quintiles and in studies comparing the highest to the lowest ALP quartiles was made by retrieving the data from the original reports.

Results

Study selection

In the screening phase, only original observational articles, involving either prospective or retrospective data collection, were included and also a letter to the editor, since it was possible to extract relevant association data from it (9). After applying our inclusion and exclusion criteria, 22 articles were selected for full-text analysis, which was independently performed by four different reviewers. This process is further detailed in *Figure 1*. The data extracted from the thirteen articles excluded after full-text analysis is exposed in the Table S2.

The process of article selection was finalized with a total number of nine articles selected for the purpose of the present study (10-18) (*Figure 1*). The complete set of studies is presented in *Table 1*.

Table 1 Summary of included articles and its main mortality findings

Author (year, country)	Study type	Number of pts (recruitment time period)	Stroke type	Follow-up	ALP levels (IU/L)	Main mortality findings
Ryu *et al.* (10) (2010, Korea)	Prospective	2,029 (from October 2002 to September 2008)	Ischemic (89%) and hemorrhagic (11% SAH excluded)	2.5 years (mean of 923 days), with 3-month intervals	Quintiles (Q1, <57; Q2, 57–69; Q3, 70–81; Q4, 82–97; Q5, >97)	Mortality outcome: all-cause mortality and vascular death Kaplan-Meier survival analysis: • All-cause mortality: In patients with ischemic stroke, the difference of all-cause death among the quintiles was significant In patients with hemorrhagic stroke, the mortality rate appeared to be different among groups, but the difference failed to reach statistical significance • Vascular death: The differences in vascular death rate were significant in all patients and those exhibiting ischemic stroke, but not in those who had had hemorrhagic stroke Cox regression models: • All-cause mortality: Compared with Q1, adjusted hazard ratios of the Q3, Q4 and Q5 for all-cause death were 1.67 (95% CI: 1.12–2.49), 1.79 (95% CI: 1.20–2.67), and 2.83 (95% CI: 1.95–4.10), respectively The top quintile of ALP levels (Q5, ≥97 IU/L) was associated with ~2.8-fold increased risk of all-cause mortality, compared with the lowest quintile of ALP. This association was also significant irrespective of stroke types: ischemic stroke (HR 2.51) or hemorrhagic stroke (HR 5.79) • Vascular death: The independent predictive power was similar (HR for all strokes, 2.78; for ischemic stroke, 2.53; for hemorrhagic stroke, 11.37) Inclusion of ALP improved the predictive value of the initial model, with an increase in AUC from 0.762 to 0.789 (95% CI: 0.762–0.817; P for difference =0.003)
Gupta *et al.* (11) (2012, India)	Prospective	111 (from April 2008 to July 2009)	Hemorrhagic (acute hypertensive intracerebral hemorrhage)	30 days	–	Mortality outcome: all-cause mortality Elevated serum ALP correlated significantly with death Mean ± SD ALP: Expired pts (n=54): 133.1±122.0 versus Survived pts: 119.6±108.8 P=0.02

Table 1 (*continued*)

Table 1 (*continued*)

Author (year, country)	Study type	Number of pts (recruitment time period)	Stroke type	Follow-up	ALP levels (IU/L)	Main mortality findings
Pratibha *et al.* (12) (2014, India)	Prospective	60 (from June 2011 to November 2011)	Ischemic and hemorrhagic (SAH excluded)	1 year at least, with 3-month intervals	Quintiles (Q1, <60; Q2, 60–79; Q3, 80–99; Q4, 100–119; Q5, >120)	Mortality outcome: all cause deaths Patients with higher ALP had higher incidence of all cause deaths and vascular deaths P value for: All cause deaths: P=0.01 Vascular deaths: P=0.02
Tan *et al.* (13) (2016, China)	Retrospective	639 (from January 2013 to December 2013)	Hemorrhagic (ICH-SAH and hemorrhagic transformation of ischemic stroke excluded)	–	Quartiles (Q1, 31–63; Q2, 64–77; Q3, 78–95; Q4, 96–700)	Mortality outcome: 30-day death and 90-day death (death defined as all-cause case fatality) Q2: 30-day death: 35 (22.7); OR (95% CI): 2.074 (1.126–3.820) 90-day death: 39 (25.3); OR (95% CI): 2.392 (1.310–4.368) Q4: 30-day death: 48 (29.8); OR (95% CI): 2.996 (1.665–5.390) 90-day death: 51 (31.7); OR (95% CI): 3.270 (1.823–5.864) ALP was independently associated with all outcomes, even after data adjustment
Zhong *et al.* (14) (2017, China)	Prospective	2,944 (from December 2013 to May 2014)	Ischemic (final diagnosis of TIA was excluded)	Hospitalization period of each patient, a mean of 10.0 (8.0–14.0) days of hospital-stay	Quartiles (Q1, <65; Q2, 65–78; Q3, 78–96; Q4, >96)	Mortality outcome: in-hospital mortality (death from any cause during hospitalization) Patients in the highest ALP quartile had the highest cumulative incidence of in-hospital mortality (log-rank P=0.012) In age- and sex-adjusted Cox model, the HR of early death was significantly higher among study participants with ALP in the highest quartile (≥96 IU/L) compared with those in the lowest quartile <65 IU/L). After additional adjustment for admission NIHSS score, baseline estimated glomerular filtration rate, medical history, and other covariates, HR (95% CI) for the highest quartile of ALP was 2.19 (1.20–4.00) for in-hospital mortality compared with the lowest quartile A linear relationship between ALP and in-hospital mortality was suggested

Table 1 (*continued*)

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Author (year, country)	Study type	Number of pts (recruitment time period)	Stroke type	Follow-up	ALP levels (IU/L)	Main mortality findings
Zong *et al.* (15) (2018, China)	Retrospective	16,367	Ischemic and hemorrhagic stroke (SAH and spontaneous intracerebral hemorrhage confirmed by brain imaging) or TIA	1 year	Quintiles (Q1, ≤59.0; Q2, 59.0–70.9; Q3, 70.9–82.0; Q4, 82.0–98.0; Q5, >98.0)	Mortality outcome: all-cause mortality The 1-year rates of all outcomes increased by ALP quintiles (P<0.0001 for all-cause mortality) In the top ALP quintile, the incidence rates of all-cause mortality were 12.6%. Compared with Q1, the adjusted odds ratio of the highest quintile was 1.36 (1.10–1.68) for all-cause mortality Elevated serum ALP levels >98 IU/L were associated with ~1.4-fold higher risk for all-cause mortality, compared with ALP levels <59 IU/L
Liu *et al.* (16) (2020, China)	Prospective	1,922 (from January to December, 2015)	Ischemic (MIS defined by a NIHSS score at admission ≤3)	1, 3, 6 and 12 months	–	Mortality outcome: all-cause mortality The results of univariate analysis showed that the factors associated with death included ALP (ALP, IU/L in the dead patients of 87.2±43.7, versus ALP, IU/L in the non-dead patients of 77.2±24.7, P=0.012) ALP levels (OR =1.01; 95% CI: 1.00–1.02; P=0.023) were independent risk factors associated with all-cause mortality at 1 year after MIS onset
Nezu *et al.* (17) (2020, Japan)	Retrospective	1,484 (from October 2009 to September 2018)	Ischemic	–	Quartiles (Q1, ≤192; Q2, 193–238; Q3, 239–296; Q4, ≥297)	Mortality outcome: death at 3 months. The mortality outcome was a secondary outcome The patients who had died by 3 months had higher ALP levels than survivors (412.6±565.2 versus 254.4±107.0 IU/L, P value <0.001)
Guo *et al.* (18) (2022, China)	Prospective	2,799 (from January to December 2015)	Ischemic or hemorrhagic stroke (SAH and spontaneous intracerebral hemorrhage confirmed by CT or MRI) or TIA	1 and 3 months	Quartiles (Q1, ≤62.9; Q2, 63.0–76.7; Q3, 76.8–92.9; Q4, ≥93.0)	Mortality outcome: all-cause mortality In Q4 group, the incidence of all-cause mortality was 7.8%. After being adjusted for confounding variables, patients in Q4 had an increased risk of all-cause mortality (OR =2.17, 95% CI: 1.19–3.96; P=0.011) The optimal range of ALP for all-cause mortality was seen in Q2, with a nadir level of 70 IU/L A continuous variable analysis demonstrated that the risk of death increases by 7% after being adjusted for potential confounding variables (adjusted OR =1.07, 95% CI: 1.01–1.14; P=0.03) when ALP rises per 10 IU/L

pts, patients; ALP, alkaline phosphatase; SAH, subarachnoid hemorrhage; Q, quartiles; CI, confidence interval; HR, hazard ratio; AUC, area under the curve; SD, standard deviation; ICH, intracerebral hemorrhage; OR, odds ratio; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; MIS, minor ischemic stroke; CT, computed tomography; MRI, magnetic resonance imaging.

Study characteristics

Stroke was defined by the World Health Organization (WHO) clinical criteria (19) in five of the nine articles (10,11,13,14,16), as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than of vascular origin. Five studies (13-16,18) confirmed the clinical diagnosis through brain imaging [computed tomography (CT) or magnetic resonance imaging (MRI) scan]. Not all articles studied populations with the same type of stroke. Three studies (14,16,17) focused on mortality purely after ischemic stroke, two (11,13) purely after hemorrhagic stroke and four (10,12,15,18) after either hemorrhagic or ischemic stroke. Regarding the studies that considered patients who suffered a hemorrhagic stroke, three studies excluded hemorrhagic strokes caused by subarachnoid hemorrhage (SAH) (10,12,13), while the other two (15,18) included both SAH and spontaneous intracerebral hemorrhage as hemorrhagic strokes. From those that focused solely on ischemic stroke, two (15,18) also included TIA, whilst Zhong *et al.* (14) excluded patients diagnosed with TIA. Liu *et al.* (16) specifically evaluated patients with minor ischemic stroke, defined as a National Institutes of Health Stroke Scale (NIHSS) score at admission lower or equal to 3. Two articles (10,17) detailed the aetiology of the ischemic stroke events according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (20). Still concerning the seven ischemic stroke focused articles (*Table 1*), not all apply the same criteria regarding the inclusion of patients who underwent thrombolytic treatment. Ryu *et al.* (10) included 159 patients (7.8%) that had been submitted to thrombolytic treatment. Zhong *et al.* (14) included 70 patients (2.4%) who have received thrombolytic therapy, but also conducted a sensitivity analysis excluding these patients. Nezu *et al.* (17) excluded all patients that underwent either intravenous thrombolysis or endovascular treatment. The remaining four ischemic stroke focused articles, during their population selection process, do not conduct any type of restriction regarding thrombolytic therapy.

An acceptable period of time, after onset of stroke symptoms and until admission, was defined for each study, except for Liu *et al.* (16) in which the only criteria for enrollment was a NIHSS lower or equal to 3 at admission. The time of onset of the stroke was defined as the time in which the patient or observer first became aware of the symptoms. One article (12) considered patients eligible for enrollment if they were admitted within 2 weeks from symptom onset, six articles (10,13-15,17,18) within 7 days and one article (11) within 3 days. It is thus expected that the levels of ALP at admission of some patients might not accurately reflect the levels at stroke onset. For this reason, Zhong *et al.* (14) restricted their analysis to patients with time from onset to admission inferior to 2 days and their findings remained unaltered.

Of the nine included articles, three were retrospective analyses (13,15,17) and six were prospective studies (10-12,14,16,18). All the studies were published between 2010 and 2022.

China contributed with most of the studies (n=5). The remaining studies were conducted in Korea (n=1), Japan (n=1), and in India (n=2). The sample size included in the studies varied from 60 to 16,367 patients.

Available demographics and comorbidities data were extracted and are presented in *Table 2*.

Since liver disease might affect ALP levels, five studies (10-13,15) excluded patients with established liver disease. Additionally, as alcohol consumption, even in small amounts, can cause derangement in liver function, Pratibha *et al.* (12) defined alcohol consumption within the previous 3 months as an exclusion criterion. In contrast, six articles (13-18) included data on alcohol consumption, and it ranged from 9.6% (14) to 29.7% of patients (17) (*Table 3*).

Synthesis of results

As depicted on *Table 1*, the nine studies included in this review defined mortality after stroke as one of their outcomes. Nevertheless, not all studies have the same follow-up period, allowing for mortality to be accounted, as an outcome, at different time intervals post stroke occurrence. Ryu *et al.* (10) followed their enrolled patients for a maximum period of 2.5 years, three studies (12,15,16) for 1 year, two studies (17,18) for 3 months, one study (13) for 90 days, one study (11) for 30 days and one study (14) only for the hospitalization period of each patient, a mean of 10.0 (8.0–14.0) days of hospital stay.

Elevated serum ALP correlated significantly and independently with all-cause mortality in all the studies included in our systematic review, even after data adjustment for potential confounding variables (*Table 1*), and specifically with vascular death, defined as death caused by stroke, myocardial infarction, heart failure, pulmonary

Table 2 Comorbidities data on the nine included studies

Author	Age, years	Male sex	Hypertension	Diabetes	Dyslipidemia	Current smoking	Previous stroke	Heart disease	BMI on admission, kg/m^2
Ryu *et al.* (10)	65.2±12.4	1,243 (61.3)	1,385 (68.3)	654 (32.2)	435 (21.4)	410 (20.2)	479 (23.6)	575 (28.3)	–
Gupta *et al.* (11)	66.4 (expired pts) versus 64.5 (survived pts)	72 (64.9)	34 (30.6)	20 (18.0)	–	32 (28.9)	Excluded	–	–
Pratibha *et al.* (12)	–	35 (58.3)	37 (61.7)	21 (12.6)	–	16 (26.7)	10 (16.7)	18 (10.8)	–
Tan *et al.* (13)	54.87±16.37	414 (64.8)	421 (65.9)	143 (22.4)	172 (26.9)	120 (18.8)	–	–	–
Zhong *et al.* (14)	68.7±12.9	1,697 (57.6)	2,291 (77.8)	757 (25.7)	–	578 (19.6)	661 (22.5)	167 (5.7)	–
Zong *et al.* (15)	63.9	10,360 (63.3)	12,109 (74.5)	2,917 (17.8)	1,688 (10.3)	7,069 (43.2)	5,570 (34)	1,975 (12.1)	23.9 (22.0–25.7)
Liu *et al.* (16)	64.0	1,195 (62.2)	768 (68.5)	242 (21.6)	77 (6.9)	287 (25.6)	297 (26.5)	–	23.9 (22.2–25.6)
Nezu *et al.* (17)	73.24 (Q1, 71.8±12.8; Q2, 73.0±11.6; Q3, 74.1±10.8; Q4, 74.1±10.5)	924 (62.3)	1,029 (69.3)	514 (34.7)	734 (49.6)	313 (21.4)	407 (27.4)	160 (10.8)	–
Guo *et al.* (18)	63.9±12.5	1,740 (62.2)	2,004 (71.6)	603 (1.5)	–	671 (24.0)	769 (7.5)	–	28.3±3.5

Values are presented as n (%), mean ± SD or median (IQR). BMI, body mass index; pts, patients; Q, quartiles; n, number; SD, standard deviation; IQR, interquartile range.

Table 3 Liver disease and alcohol consumption data on the nine included studies

Author	Liver disease	Alcohol consumption, n (%)
Ryu *et al.* (10)	Excluded (self-reported or increased total bilirubin level >1.3 mg/dL)	–
Gupta *et al.* (11)	Excluded (previous episodes of jaundice or documented deranged liver function tests)	Excluded (alcoholic patients, significant alcohol intake "defined as consumption of up to 1 drink per day for women and up to 2 for men. Twelve fluid ounces of regular beer, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof distilled spirits is taken as one drink. This definition is not intended as an average over several days but rather as the amount consumed on any single day")
Pratibha *et al.* (12)	Excluded (increased total bilirubin level >1.3 mg/dL)	Excluded (within past 3 months)
Tan *et al.* (13)	Excluded (if severe or manifest liver-related syndrome)	90 (14.1)
Zhong *et al.* (14)	–	283 (9.6)
Zong *et al.* (15)	Excluded (self-reported)	Moderate to heavy, 4,658 (28.5)
Liu *et al.* (16)	–	271 (24.2)
Nezu *et al.* (17)	–	434 (29.7)
Guo *et al.* (18)	–	Moderate to heavy, 664 (3.7)

Table 4 Stroke severity data on the 9 included articles

Author	Initial neurological severity	
	NIHSS	GCS
Ryu *et al.* (10)	Median value of 4 with an IQR of 2–8	–
Gupta *et al.* (11)	–	Expired patients, mean ± SD: 6.6±2.8 versus survived patients, mean ± SD: 11.2±3.2
Pratibha *et al.* (12)	According to ALP levels quintiles, mean ± SD: Q1 (<60), 3.5±0.5774; Q2 (60–79), 5.87±3.6; Q3 (80–99), 6.0±2.93; Q4 (100–119), 13.86±6.56; Q5 (>120), 9.27±6.42	–
Tan *et al.* (13)	–	Median value of 11 with an IQR of 7–15
Zhong *et al.* (14)	Median value of 4 with an IQR of 2–7	–
Zong *et al.* (15)	Median value of 3 with an IQR of 1–7	–
Liu *et al.* (16)	Median value of 1 with an IQR of 0–2	–
Nezu *et al.* (17)	Median value of 3 with an IQR of 1–7.5	–
Guo *et al.* (18)	Median value of 4 with an IQR of 2–7	–

NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; IQR, interquartile range; SD, standard deviation; ALP, alkaline phosphatase; Q, quartiles.

embolism, cardiac arrhythmia, or other definite vascular causes, in two studies (10,12).

The studies comparing the highest to the lowest ALP quintiles (10,12,15) showed an aggregate value of 1.8 times greater risk of mortality for the former, when compared to the latter. The studies comparing the highest to the lowest ALP quartiles for which data were available (13,18) showed an aggregate value of 2.4 times greater risk of mortality for the former, when compared to the latter.

All of the nine studies included in this systematic review estimated, at admission, the severity of neurologic impairment using either the NIHSS or the Glasgow Coma Scale (GCS), as shown in *Table 4*. Seven of the nine studies (10,13-18) conducted data adjustment for the NIHSS or GCS score at admission. This covariate was selected to integrate multivariable adjusted models since stroke severity has been associated with mortality after stroke and ALP levels (21,22). ALP remained independently associated with mortality after adjustment for admission NIHSS or GCS score and this association was not weakened.

From the six above mentioned studies that included data on alcohol consumption, all included this variable in their multivariable models. Zong *et al.* (15) even conducted a stratified analysis by alcohol consumption that showed that the effects of ALP on mortality were not changed by alcohol consumption.

Data concerning other main prognostic findings, besides mortality, were available for six studies (12,13,15-18) (*Table 5*). Elevated ALP levels were significantly associated with increased risk of adverse stroke outcomes, except for two studies (16,18).

Risk of bias in the included studies

Five studies (10,14,15,17,18) excluded patients due to lack of serum ALP concentration values (selection bias), limiting the generalizability of the findings.

As demonstrated in *Table 3*, three articles (10,11,15) excluded liver disease through self-reported questionnaires, which may lead to reporting bias. Additionally, Zong *et al.* (15) did not exclude patients with obstructive biliary disease for lack of biliary levels data registration and Nezu *et al.* (17) did not evaluate detailed information on liver diseases that affect serum ALP levels. However, Nezu *et al.* (17) conducted multivariable analysis for both daily alcohol intake and other liver enzymes, adjusting for these influences.

Discussion

In the present report, the association of ALP levels and mortality after stroke was under review.

ALP is a key regulator of the phosphate/pyrophosphate

Table 5 Summary of other main prognostic findings, besides mortality, extracted from the nine included studies

Author	Other main prognostic findings	
	Poor functional outcome defined by a mRS score >2 (3 to 6)	Poor prognosis otherwise defined
Pratibha *et al.* (12)	–	Poor prognostic outcome: vascular events
		"Vascular event may be stroke, myocardial infarction, heart failure, pulmonary embolism, cardiac arrhythmia, or other definite vascular causes"
		"Patients with higher ALP had higher incidence of recurrent vascular events without death (P=0.008)"
Tan *et al.* (13)	Poor prognosis outcome: 90-day poor functional outcome after ICH	–
	90-day poor outcome:	
	Q2: 85 (55.2); OR (95% CI) 1.909 (1.213–3.007)	
	Q4: 100 (62.1); OR (95% CI) 2.541 (1.613–4.004)	
	ALP in Q2 and Q4 had significantly higher incidence of all outcomes when compared to that in Q1	
	ALP, in this study, was independently associated with all outcomes, even after data adjustment	
Zong *et al.* (15)	Poor prognosis outcome: poor functional outcome	Poor prognosis outcomes: recurrent stroke
	"The 1-year rates of all outcomes increased by ALP quintiles (P<0.0001) for poor functional outcome"	Recurrent stroke defined as ischemic stroke, intracranial hemorrhage and SAH
	In the top ALP quintile, the incidence rates of poor functional outcome were 27.0%	"The 1-year rates of all outcomes increased by ALP quintiles (P<0.001 for recurrent stroke)"
	"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<0.0001)"	In the top ALP quintile, the incidence rates of recurrent stroke were 5.7%
	"Elevated ALP levels (especially >120 IU/L) were significantly associated with increased risk of adverse stroke outcomes"	Compared with the first ALP quintile, the adjusted OR of the highest quintile was 1.45 (1.11–1.90) for stroke recurrence
	"Elevated serum ALP levels >98 IU/L were associated with ~1.4-fold higher risk for poor functional outcomes after stroke, compared with ALP levels <59 IU/L"	"Elevated serum ALP levels >98 IU/L were associated with ~1.4-fold higher risk for stroke recurrence, compared with ALP levels <59 IU/L"
Liu *et al.* (16)	Poor prognosis outcome: 1-year stroke disability	Poor prognosis outcome: 1-year stroke recurrence
	Results of univariate analysis showed "there was no significant difference between patients with versus without 1-year disability in the ALP levels (P=0.165)"	Stroke recurrence included cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage
		Results of univariate analysis showed "there was no significant difference between patients with versus without 1-year stroke recurrence in the ALP levels (P=0.104)"

Table 5 (*continued*)

Table 5 (*continued*)

Author	Other main prognostic findings	
	Poor functional outcome defined by a mRS score >2 (3 to 6)	Poor prognosis otherwise defined
Nezu *et al.* (17)	Poor prognosis outcome: poor functional outcome. The poor prognosis outcome was a primary outcome	–
	"The patients with poor outcomes had higher ALP levels than those with good outcomes (294.3±259.5 *vs.* 246.3±92.5 IU/L, P<0.001)"	
	"The optimal cutoff ALP level to predict patients with poor outcomes was ≥288 U/L, with a sensitivity of 55%, a specificity of 59%, and an area under the ROC curve of 0.578"	
	"Multivariable analysis revealed that increased ALP levels were independently associated with poor stroke outcome after adjusting for several baseline characteristics and laboratory findings"	
	"Conversely, a 1–SD increase in ALP levels was independently associated with mRS scores of 3–6 at 3 months among patients with a premorbid mRS score of 0–1 in each model (OR 1.32 95% CI: 1.10–1.59, P<0.001, model 1, OR 1.24, 95% CI: 1.01–1.53, P=0.041, model 2 and OR 1.34, 95% CI: 1.09–1.66, P=0.002, model 3)"	
Guo *et al.* (18)	Poor prognosis outcome: poor functional outcomes	Poor prognosis outcome: recurrent stroke
	The rates of "poor functional outcome at 3 months were higher in the Q4 group when compared with the Q1, Q2, and Q3 groups (P<0.001)"	"Recurrent stroke included a new occurrence of ischemic stroke, TIA, spontaneous intracranial hemorrhage or SAH during the follow-up"
	In the Q4 (≥93.0 U/L) group, the incidences of poor functional outcomes were 24.9%	At 3 months, "there was no significant difference in recurrent stroke among different ALP quartiles (P=0.097)"
	"However, differences were statistically insignificant between ALP levels and poor functional outcomes (P>0.05)"	In the Q4 (≥93.0 U/L) group, the incidences of recurrent stroke were 2.7%
	In the multivariate logistic regression, the risk of "poor functional outcomes (adjusted OR =1.04, 95% CI: 0.98–1.08; P=0.086) did not increase with ALP levels"	After being adjusted for confounding variables, "patients in Q3 (76.8–92.9 U/L) were related to a lower risk of recurrent stroke (OR =0.37, 95% CI: 0.14–0.97; P=0.043) at the 3-month time point, compared to those in Q2 (63.0–76.7 U/L)"
		In the multivariate logistic regression, "the risk of recurrent stroke (adjusted OR =1.00, 95% CI: 0.91–1.10; P=0.978) did not increase with ALP levels"
		The optimal range for reducing recurrent stroke was Q3 (76.8–92.9 U/L)
		"In addition, the Kaplan-Meier curves of 3-month cumulative rates of recurrent stroke differ significantly in different stroke subtypes, providing a new direction for investigating ALP levels with all-cause mortality and recurrent stroke in different stroke types"

mRS, modified Rankin Scale; ALP, alkaline phosphatase; ICH, intracerebral hemorrhage; Q, quartiles; OR, odds ratio; CI, confidence interval; SAH, subarachnoid hemorrhage; ROC, receiver operating characteristic; SD, standard deviation; TIA, transient ischemic attack.

ratio (23), by catalyzing the hydrolysis of organic pyrophosphate, which plays a role in vascular calcification (23). Increased ALP levels have been proposed to accelerate this process therefore decreasing vascular compliance, which in turn results in vascular aging.

Therefore, serum ALP has been progressively accepted as a marker of vascular calcification and, consequently, might constitute a risk factor for ischemic stroke. Also, through the above-mentioned vascular aging, these weakened vessels might be more prone to rupture potentially increasing the risk of hemorrhagic stroke too. Indeed, elevated ALP levels have been demonstrated to be associated with stroke recurrence and other cardiovascular diseases—both known causes of post-stroke mortality.

Plausible mechanisms through which ALP detrimentally affects survival post-stroke may thus include increased vascular calcification, an association with other cardiovascular diseases, an association with liver disease, and changes in cholesterol metabolism (24).

Concerning the risk of post-stroke mortality over time, Brønnum-Hansen *et al.* (2) demonstrated that 72% survived their first stroke by 27 days and 41% died after 1 year. The risk of death between 4 weeks and 12 months after the first stroke was 18.1%. After the first year, the annual risk for death was approximately 10% and remained almost constant.

The 28-day mortality of intracerebral haemorrhage has been shown to be considerably higher than that of ischaemic stroke. We analyzed data concerning the two main types of stroke and also ischemic stroke subtypes. From the four studies (10,12,15,18) that included both ischemic and hemorrhagic stroke, only Ryu *et al.* (10) compared the association of ALP levels and all-cause mortality after an ischemic versus hemorrhagic stroke, showing that this association was significant irrespective of stroke subtypes, although it has a greater impact on haemorrhagic stroke (ischemic stroke hazard ratio 2.51 versus hemorrhagic stroke hazard ratio 5.79). Guo *et al.* (18) concluded that Kaplan-Meier curves of 3-month cumulative rates of all-cause mortality differ significantly in different stroke subtypes, demonstrating that spontaneous intracerebral hemorrhage and subarachnoid hemorrhage might have higher mortality rates than TIA and ischemic stroke, providing a new direction for investigating the association of ALP levels and different stroke types.

A biomarker providing strong prognostic indications could help identify high-risk patients that could benefit from different therapeutic approaches. Accordingly, an ideal stroke biomarker should be capable of predicting stroke prognosis and facilitating therapeutic stratification and monitoring (5), for example by indicating risk of hemorrhagic transformation after stroke or after tissue type plasminogen activator treatment (rt-PA). In fact, Zhu *et al.* (25) already demonstrated that higher serum ALP levels were independently associated with a poor outcome in patients after intravenous thrombolysis.

Mechanical thrombectomy has become the standard of care for acute ischemic stroke due to large vessel occlusions. However, up to 29% of all mechanical thrombectomies fail (26). Recently, acute intracranial stenting has been reported to be a highly promising bailout strategy for these thrombectomy cases with predictably poor outcomes (27-29). Park *et al.* (30) has already demonstrated that high levels of total ALP activity predicted coronary stent thrombosis. In the future, it would be interesting to study ALP levels as a possible predictor of intracranial stent thrombosis.

In the future, it would be interesting to define the timeline of influence of ALP levels in mortality post-stroke. Indeed, as time passes by, since stroke onset, the risk of mortality and the corresponding promoting causes vary. Regarding post-stroke mortality causes over time, Viitanen *et al.* (31) showed that the dominant causes of death were cerebrovascular disease (90%) in the first week and later than 3 months after stroke, cardiac disease, mainly myocardial infarction dominated.

When attempts are made to reduce mortality after stroke, there seems to be a considerable potential for prevention and early treatment of complications, such as cardiac disorders. Mortality rate due to all cardiovascular diseases in stroke populations is almost four times higher than that in the general population (8). Myocardial infarction is one of the leading causes of death during long-term follow-up in patients with an ischemic stroke, since it shares common risk factors with coronary artery disease (32). Liu *et al.* (33) found that higher serum ALP levels, even within the normal range, were significantly and linearly associated with higher risks of cardiovascular disease in both men and women, without previous stroke. Moreover, their analyses showed that each per unit increment in natural log-transformed ALP levels was independently associated with 31%, 61%, and 206% greater risks of acute coronary syndrome, ischemic stroke and hemorrhagic stroke, respectively, in men. This review has demonstrated that the elevation of ALP levels is consistently associated to increased mortality after stroke, however it is not known if it represents short-

term or long-term mortality and, consequently, the specific cause of death that lies behind it.

It is possible that the underlying cause of the higher mortality 3 months after stroke is the higher risk of cardiovascular disease, which these patients have, since cardiovascular disease starts to dominate as the main post-stroke mortality cause.

The regulation of ALP is already a potential novel treatment strategy that might reduce vascular calcification and improve cardiovascular outcomes (34). The mechanisms suggested are mainly two: inhibition of ALP activity and the modulation of its expression. A novel direct ALP inhibitor, SBI-425, effectively inhibits vascular calcification in animal models at doses that do not alter bone mineralization. Interestingly, two phase II trials showed that apabetalone (a novel bromo-domain and extra-terminal motif inhibitor RVX-208) administration reduced circulating levels of ALP, which was associated with a marked reduction of major cardiovascular events (34,35).

Limitations

The limitations for the present report include the heterogeneity in the studies characteristics, namely concerning the types of stroke under study and length of follow-up. A further limitation is that the reviewed studies come predominantly from Asia.

In the nine studies reviewed, measurement of ALP was carried out exclusively at admission. Since no serial measurements of serum ALP were conducted, the association between ALP changes during hospitalization and all-cause mortality could not be examined. Likewise, Guo *et al.* (18) stated that because the study was only focused on the association of serum ALP levels within 24 h of admission and the 3-month outcome, the potential influence of changes in ALP levels after discharge was not analyzed. Besides Guo *et al.*, two other authors (10,14) presented this fact as a possible limitation. Ryu *et al.* (10) states that changes of serum ALP levels during the acute period of stroke have not yet been understood, and therefore, it is possible that an acute phase reaction accompanying stroke or in-hospital complications may be behind the elevation of ALP levels. Additionally, since ALP was only measured in the acute stroke period, they were unable to rule out post-stroke cholestasis that can, although rarely, lead to death after stroke.

Two authors (10,12) identified the time interval until death as a possible limitation. On one hand, due to the previously mentioned possible acute phase reaction accompanying stroke, Ryu *et al.* (10) conducted a subsequent analysis excluding early mortality (inferior to 1 month), but no variations concerning the association between ALP and mortality after stroke were verified. On the other hand, Pratibha *et al.* (12) suggested that a longer follow up time would have yielded much more information regarding long term mortality.

Conclusions

ALP was demonstrated to be a promising biological marker for improving the predictive ability for stroke outcomes (17). Serum ALP measurement requires a routinely available blood test, which is simple, low-cost, and standardized, and our review indicates that it may be a potential test to predict stroke outcomes, namely mortality.

In conclusion, measuring ALP levels may provide a cost-effective prognostic indicator of stroke-related mortality (17). A finding that warrants further investigation in future primary studies that follow standardized methodologies.

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Footnote

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Supplementary

Table S1 Quality assessment tool for observational cohort and cross-sectional studies

Criteria	Ryu *et al.*	Gupta *et al.*	Pratibha *et al.*	Tan *et al.*	Zhong *et al.*	Zong *et al.*	Liu *et al.*	Nezu *et al.*	Guo *et al.*
Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the participation rate of eligible persons at least 50%?	Y	NR	NR	NR	NR	Y	NR	Y	Y
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was a sample size justification, power description, or variance and effect estimates provided?	NR	NR	NR	NR	NR	NR	NR	NR	NR
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	NA	Y	Y	Y	NA	Y
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	NR	Y	Y	Y	Y	Y	Y
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	NR	Y	Y	Y	Y	NR	NR	Y
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the exposure(s) assessed more than once over time?	NR	NR	NR	NR	NR	NR	NR	NR	NR
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcome assessors blinded to the exposure status of participants?	NA	NA	NA	NA	NA	NA	Y	NA	NA
Was loss to follow-up after baseline 20% or less?	Y	Y	Y	NA	Y	Y	NR	NA	Y
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y	Y	NR	Y	Y	Y	Y	Y	Y
Quality rating	Good	Fair	Fair	Good	Good	Good	Good	Good	Good

Y, yes; NR, not reported; NA, not applicable.

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Table S2 Summary of the articles excluded for not presenting objective mortality data

Source (year, country)	Study type	Main prognostic findings	
		Poor functional outcome defined by a mRS score >2 (3 to 6)	Poor prognosis otherwise defined
Kim *et al.* (2013, Korea)	Retrospective	Poor prognosis outcome: poor functional outcome "Elevated ALP levels were associated with a poor functional outcome (61.17±17.24 versus 66.66±25.51 IU/L; P=0.002)" "After adjustment for sex, age, and other covariates that had a P<0.05 on univariate analysis, OR for 1 increase of SD in ALP (19.61 IU/L) was 1.25 (95% CI: 1.04–1.50; P=0.017)" "Penalized-spline curve demonstrated a positive relationship between levels of ALP and an increased risk for poor functional outcomes"	–
Liu *et al.* (2016, China)	Prospective	–	Poor prognosis outcome: HT) "HT was defined as hemorrhage in the infarct zone not detected by CT immediately after stroke, but observed later during MRI" "HT was defined as symptomatic when it was associated with early neurologic deterioration" "Neurologic deterioration was diagnosed when the NIHSS worsened by greater than or equal to 4" Pts in T3 (>92 IU/L) were more likely to have symptomatic HT (OR: 8.96; 95% CI: 1.33–60.21; P=0.02) compared with pts in T1 (<70 IU/L) T3 had about 8.96 times greater risk of symptomatic HT compared with T1
Uehara *et al.* (2018, Japan)	Retrospective	–	Poor prognosis outcome: "occurrence of ischemic stroke within 90 days of the onset of the TIA" Ischemic stroke was defined as "a focal neurological deficit lasting for more than 24 hours" "The serum ALP levels on admission of pts with ischemic stroke were significantly higher than those of pts without ischemic stroke (P=0.0020)" "ALP>292 U/L on admission (HR, 6.77; 95% CI: 2.10-23.53; P=0.002) was found to be a significant independent predictor of ischemic stroke events"
Liu *et al.* (2018, China)	Prospective	Poor prognosis outcome: poor functional outcome "There was no difference in ALP concentration between the favorable functional group and unfavorable functional outcome group (81.76±20.60 versus 81.70±20.54 U/L, P=0.802)" "This suggests that ALP has no effect on functional outcomes after 1 year, which differs from some previous reports. ALP may be partially used for the diagnosis of ischemic stroke, but may be meaningless for the assessment of prognosis"	Poor prognosis outcome: neurological deficit The degree of neurological deficit was evaluated through NIHSS in pts with ischemic stroke, during blood sampling "Serum ALP concentration was not significantly correlated with NIHSS (P=0.085)"
Liang *et al.* (2018, China)	Prospective	Poor prognosis outcome: poor functional outcome ALP was prominently higher in the poor prognosis group (89.28±24.75) than in the good prognosis group (74.11±22.81), P<0.001 "Based on the ROC curve, the cutoff value of logistic regression model for predicting of poor outcome was 0.787: more than 0.787 considered as poor outcome, and less than 0.787 considered as good outcome" In conclusion, the model combining age, FFA, Hcy and ALP showed better performance in predicting the poor prognosis of ischemic stroke pts	–
Xu *et al.* (2019, China)	Retrospective	–	Poor prognosis outcome: "occurrence of ischemic stroke or TIA readmission within 90-day after discharge" Result showed that "ALP, hypertension and pneumonia were consistently highly associated with the readmission event in each prediction model" The logistic regression analysis revealed that "ALP (OR 1.003, 95% CI: 1.00–1.005), hypertension (OR 4.60, 95% CI: 3.80–5.58), and pneumonia (OR 1.46, 95% CI: 1.07–1.97) were independently associated with stroke patient readmission" ALP importance score is 14 (out of the 10, maximum is hypertension with 32 and minimum is K+ with 9)
Zhu *et al.* (2019, China)	Prospective	Poor prognosis outcome: poor functional outcome "Level of serum ALP in patients with SAH was significantly higher compared to controls (SAH 71 IU/L, controls 61 IU/L, P=0.0002), yet both levels were within normal range" "The level of ALP was higher in pts with unfavorable functional outcome compared with those with a favorable functional outcome (79.5 versus 68 IU/L, P=0.0013)" Pts "with a serum ALP level higher than 71 U/L (median level of ALP of all pts) were correlated with a more unfavorable 6-month outcome than those with ALP level of ≤71 U/L" "A ROC curve identified that a baseline serum ALP level ≥87.5 U/L predicts 6-month unfavorable functional outcome of SAH pts with 83.56% sensitivity and 46% specificity (area under curve, 0.652; 95% CI: 0.559–0.745, P=0.0014)" Multivariable analysis found that higher ALP level was independently associated with unfavorable outcome (OR 1.083, 95% CI: 1.041–1.127, P<0.001)	Poor prognosis outcome: severe radiological status, angiographic vasospasm and delayed cerebral ischemia (DCI) - caused clinical deterioration Radiological status "ALP was significantly higher in pts with severe radiologic status (modified Fisher 3–4) compared to mild radiologic status (modified Fisher 1–2) (77 *vs.* 61.5 IU/L, P=0.0005). A significant correlation emerged between modified Fisher score and serum ALP level (r=0.246, P=0.001)" Angiographic Vasospasm ALP was significantly higher in pts with vasospasm compared with those without (76.5 *vs.* 67 IU/L, P=0.0028) DCI-caused clinical deterioration "Higher serum ALP levels were also observed in pts with cerebral infarction and clinical deterioration caused by DCI compared with those without (cerebral infarction 77 *vs.* 68 IU/L, P=0.0134; clinical deterioration due to DCI: 77 *vs.* 70 IU/L, P=0.0142)"
Jia *et al.* (2020, China)	Retrospective	–	Poor prognosis outcome: cognitive impairment Cognitive impairment was evaluated with the Chinese version of the Mini-Mental State Examination (MMSE) "A significant positive relationship was observed between ALP and cognitive impairment severity (P<0.05)" "In the model adjusted for all variables, the ALP level was positively associated with cognitive impairment, evidenced by a change of −0.54 to −0.16 per unit (IU/L) increase" "The logistic regression indicated that elevated ALP levels increased the risk of cognitive impairment in pts with ischaemic stroke" "The univariate analyses suggested that the increased ALP level was positively associated with the risk of cognitive function decline (OR =4.21, 95% CI: 2.37–7.21, P<0.001)" Odds of cognitive impairment increased by 42 % when ALP concentration increased by 1 IU/L (OR =1.42, 95% CI: 1.17–3.09, P=0.012) "After adjusting for potential confounding factors, the spline regression model further confirmed the dose-response relationships between ALP levels and three-month cognitive impairment (P for nonlinear trend =0.012)"
Uehara *et al.* (2020, Japan)	Retrospective	–	Poor prognosis outcome: Early Neurological Deterioration (END) END was defined as an increase of ≥2 in the NIHSS "Serum ALP level was an independent predictor of END (OR: 1.0120, 95% CI: 1.0027–1.0235, P=0.0109) after adjusting for age, sex and baseline NIHSS" "Serum ALP levels on admission were significantly higher among patients with, than without END {median [interquartile range], 313 [280–338] *vs.* 216 [187.5–261.75] IU/L, P=0.0008} in cases with stenosis" "On the other hand, there was no difference in serum ALP levels on admission between patients with and without END {median [interquartile range], 224.5 [165.5–327.75] *vs.* 215 [125–270] U/L, P=0.7055} in cases with occlusion"
Naito *et al.* (2021, Japan)	Retrospective	Poor prognosis outcome: poor functional status "Reference: lowest quartiles of ALP for patients with an ABI of >0.9" Serum ALP levels were higher in patients with a poor outcome than in those with a good outcome "In the multivariable analysis adjusted for confounding factors, serum ALP levels and a low ABI were independently associated with poor functional outcome at 3 months (OR: 1.21, 95% CI: 1.07–1.38, P=0.003, and OR: 2.00, 95% CI: 1.40–2.84, P<0.001, respectively)" "Regardless of renal function, a low ABI and increased serum ALP levels were independently associated with a poor outcome at 3 months among patients with and without CKD" "The highest quartiles of ALP levels for patients with a low ABI showed a remarkable association with a poor outcome, which was not observed with the lowest quartiles of ALP levels for patients with a normal ABI (OR: 3.75, 95% CI: 1.96–7.20)"	Poor prognosis outcome: low ABI "The patients with the highest quartile of ALP levels had the highest frequency of a low ABI (30.4%, P<0.001)" "Higher ALP levels were independently associated with a low ABI in patients with ischemic stroke"
Li *et al.* (2021, China)	Prospective	Poor prognosis outcome: 30-day, 90-day and 1-year poor functional outcome Compared with patients in Q4 of ALP, "the adjusted odds ratio of the highest quartile (>94.8 U/L) was 2.16 (1.32–3.55) for the 30-day poor functional outcome, 1.86 (1.12–3.10) for the 90-day poor functional outcome, and 2.26 (1.34–3.80) for 1-year poor functional outcome. However, a serum ALP in the lowest quartile (≤58.0 U/L) was not significantly correlated with 30-day, 90-day, and 1-year poor functional outcomes" High ALP level (>94.8 U/L) was independently associated with 30-day, 90-day, and 1-year poor functional outcomes in ICH patients	–
Liu *et al.* (2022, China)	Retrospective	Poor prognosis outcome: 3-month poor functional outcome "For every 10-unit increase (10 U/L) in ALP, the risk of a poor 3-month prognosis increased by 6% in the crude model and model I (crude model and Model I: OR 1.06, 95% CI: 1.02–1.11, P=0.007)" "After being adjusted for potential confounding factors, the risk of having a poor 3-month prognosis increased by 4% in model II (OR 1.04, 95% CI: 1.01–1.09, P=0.041)" "Patients in Q1, Q2, Q3 and Q5 had a higher risk of having a poor 3-month prognosis than those in Q4 being as the reference quintile. The highest risk was noted in Q5 (OR 2.21, 95% CI: 1.32–3.73, P=0.003)" "J-shaped-curve relationship between ALP levels and a poor 3-month prognosis in AIS pts with preserved renal function: to the left of the threshold value, the risk of a poor 3-month prognosis was not significantly associated with ALP levels (per 10 IU/L increase) until it was up to 90 IU/L (OR 0.99, 95% CI: 0.87–1.12, P=0.857); whereas to the right of the optimal threshold value, the risk of a poor 3-month prognosis significantly increased (OR 1.57, 95% CI: 1.27–1.93, P<0.001)" "ALP levels higher than 90 IU/L could cause an increased risk of a poor 3-month prognosis"	–
Zhu *et al.* (2022, China)	Retrospective	Poor prognosis outcome: 3-month after thrombolysis poor functional outcome "This study found that ALP level was an independent risk factor for a poor outcome" "We divided all eligible patients into poor outcome and favorable outcome groups: ALP (76.6 *vs.* 71.4, respectively, P=0.002)" "In multivariate analysis, ALP was independently associated with poor outcome adjusted by Model 1 (OR =1.010; 95% CI: 1.003–1.016; P=0.003), Model 2 (OR =1.010; 95% CI: 1.004–1.016; P=0.002), Model 3 (OR =1.011; 95% CI: 1.005–1.018; P=0.001), and Model 4 (OR =1.009; 95% CI: 1.002–1.016; P=0.010)" "Full ROC area was 0.723, and the test ROC area was 0.708, indicating that the present model was stable"	Poor prognosis outcome: HT observed during cranial CT 24 hours "This study found that ALP level was not an independent risk factor for HT after thrombolysis" "ALP levels were not significantly different between the HT and no-HT groups (75.1 *vs.* 76.3, P=0.617)"

mRS, modified Rankin scale; ALP, alkaline phosphatase; OR, odds ratio; SD, standard deviation; CI, confidence interval; HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; T, tertiles; TIA, transient ischemic attack; HR, hazard ratio; FFA, free fatty acid; Hcy, homocysteine; ROC, plot receiver operating characteristic; DCI, delayed cerebral ischemia; END, Early Neurological Deterioration; ABI, Ankle-brachial Index; CKD, chronic kidney disease; ICH, intracerebral hemorrhage; Q, quartiles; pts, patients.

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