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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