SVN Stroke and Vascular Neurology

Low serum albumin levels predict poor outcome in patients with acute ischaemic stroke or transient ischaemic attack

Hongyu Zhou ,[1,2] Anxin Wang ,[1,2] Xia Meng,[1,2] Jinxi Lin,[1,2] Yong Jiang,[1,2] Jing Jing,[1,2,3] Yingting Zuo,[1,2] Yilong Wang,[1,2] Xingquan Zhao,[1,2] Hao Li ,[1,2] Yongjun Wang [1,2,4]

To cite: Zhou H, Wang A, Meng X, *et al*. Low serum albumin levels predict poor outcome in patients with acute ischaemic stroke or transient ischaemic attack. *Stroke & Vascular Neurology* 2021;**6**: e000676. doi:10.1136/svn-2020-000676

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2020-000676).

HZ and AW contributed equally.

Received 10 October 2020
Revised 6 January 2021
Accepted 24 January 2021
Published Online First 25 February 2021

For numbered affiliations see end of article.

Correspondence to
Dr Yongjun Wang;
yongjunwang@ncrcnd.org.cn

ABSTRACT

Background To examine the relationship of serum albumin with poor functional outcome and mortality in patients with acute ischaemic stroke (AIS) or transient ischaemic attack (TIA), and perform a meta-analysis to summarise the association.

Methods We analysed data from the Third China National Stroke Registry (CNSR-III). Patients were divided into four groups based on serum albumin levels at admission. The outcomes included poor functional outcome (modified Rankin Scale (mRS) score of 3 to 6) and mortality at 3 months and 1 year. Multiple logistic regression models and Cox regression models were used to evaluate the association, respectively. We used a fixed-effect model to calculate the risk ratio for poor functional outcome and a random-effect model for mortality in the meta-analysis.

Results A total of 13 618 patients were enrolled. During the 3-month follow-up period, compared with 40 to 44.9 g/L group, patients in <35 g/L group had an increased risk of poor functional outcome and mortality (adjusted OR 1.37 (95% CI 1.12 to 1.67); adjusted HR 2.13 (95% CI 1.41 to 3.23)). The relationship in per 10 g/L decreased serum albumin with prognosis was consistently inversed (adjusted OR 1.17 (95% CI 1.01 to 1.35); adjusted HR 1.86 (95% CI 1.30 to 2.64)). Also, low serum albumin levels were independently correlated with clinical outcomes at 1 year. In the meta-analysis, the OR for poor functional outcome pooled 3 studies per 1 g/L decrease was 1.03 (95% CI 1.02 to 1.05), and the HR for mortality pooled 5 studies was 1.07 (95% CI 1.03 to 1.11).

Conclusions Low serum albumin levels predict poor functional outcome and mortality in patients with AIS or TIA.

INTRODUCTION

Albumin is the most abundant serum protein synthesised primarily in the liver and regulated by multiple physiological mechanisms.[1 2] It has several physiological properties, including maintaining colloidal osmotic pressure, antiplatelet aggregation and anti-inflammatory effects.[3]

Recent pre-clinical research found that moderate-dose albumin therapy after vascular recanalisation remarkably reduced infarction volume and brain swelling, and improved neurological function, suggesting that serum albumin has a neuroprotective effect.[4 5] However, the results of the Albumin in Acute Stroke (ALIAS) trials on intravenous albumin in patients with stroke were negative disappointedly.[6] This apparent paradox between the strong basic evidence and the failure in translation to humans brings great confusion. In the past, several studies have discussed the relationship between serum albumin and stroke prognosis, while the sample size was limited and lack long-term follow-up.[7–11]

Our study aimed to assess the correlation between low serum albumin level and poor functional outcome and mortality in patients with acute ischaemic stroke (AIS) or transient ischaemic attack (TIA) in a large, long-term follow-up, prospective registry. Furthermore, we performed a meta-analysis to summarise the association.

METHODS

Study design and participants

The Third China National Stroke Registry (CNSR-III) was an ongoing, nationwide, prospective stroke registry enrolling patients with AIS or TIA (≥18 years old; within 7 days from the onset) between August 2015 and March 2018. A total of 201 hospitals from 22 provinces and 4 municipalities in China participated. We collected aetiology, imaging and biology data, and tried to clarify the pathogenesis and prognostic factors of ischaemic cerebrovascular disease. Details on the design of the CNSR-III have been published previously.[12] The study protocol was approved by the ethics committee of all participating study centres. Each participant signed informed consent before enrolment, and was followed up at 3 months and 1 year. An independent

contract research organisation performed data monitoring throughout the study period.

Data collection

Baseline information was recorded on admission by trained research coordinators. Some information, like patient demographics, medical history, primary diagnosis, acute recanalisation therapy, inpatient medication and laboratory tests, were extracted from medical records. Other parts were obtained from face-to-face interviews, such as the pre-stroke modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) scores. The aetiological classification was conducted by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[13] All images were stored in DICOM format on disks and centrally interpreted by two neurologists. Disagreements were resolved by discussion with a third reviewer. The presence of intracranial arterial stenosis and extracranial arterial stenosis was defined as 50%–99% stenosis or occlusion of any intracranial and extracranial artery.[14 15]

Serum albumin and alanine aminotransferase (ALT) were tested in sub-centres within the first 24 hours after admission. Bromocresol purple assay or bromocresol green assay were used to measure the serum albumin levels, which depended on the test reagent of sub-centres. High-sensitivity C reactive protein (hs-CRP), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG) and serum creatinine were tested in the central laboratory of Beijing Tiantan Hospital. The blood samples were collected at admission and frozen in the cryotube at −80°C refrigerator, then transported through the cold chain to the central laboratory. The estimated glomerular filtration rate (eGFR) was calculated by Chronic Kidney Disease Epidemiology Collaboration equations.[16]

Outcomes

The clinical outcomes included functional outcome and mortality, which were obtained through face-to-face interviews at 3 months and 1 year. The poor functional outcome was defined as mRS score of 3 to 6 (disability/death), and the good functional outcome was defined as mRS score of 0 to 2 (independence).[17] Mortality included death from all causes.

Statistical analysis

Continuous variables were presented as mean±SD or median with IQR, and categorical variables as percentages. The baseline characteristics of different groups were compared by Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. We used ordinal logistic regression to compare the disparity in mRS scores between different groups at 3 months and 1 year. The proportional hazards assumption of mortality was eligible for Cox regression. The association of serum albumin with poor functional outcome and mortality was analysed in logistic regression models for ORs and Cox proportional hazards models for HRs, respectively. Moreover, the relationship was tested by two types of data, four groups as categorical variable and every 10 g/L as continuous variable. Adjusted ORs, adjusted HRs and their 95% CI were calculated on three models. In the first model, we adjusted age and sex, which are demographic characteristics. In the second model, we added body mass index (BMI), medical history, index event, TOAST types, pre-stroke mRS score 0~2, NIHSS scores at admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis and inpatient medication, which were statistically significant in the baseline characteristics comparison. In the third model, we further adjusted the laboratory test, including TG, LDL, HDL, TC, ALT, eGFR and hs-CRP.

Restricted cubic splines were presented as the graphical representation of the associations. The interaction of age, sex, BMI, TOAST types, baseline NIHSS scores and eGFR were analysed by the multivariate logistic model and multivariate Cox model.[9 10 18 19] Statistical significance was determined as p values <0.05, two-sided. All statistical analyses were performed with SAS software, V.9.4 (SAS Institute, Cary, NC).

Meta-analysis

The meta-analysis was conducted following the Preferred Reporting in Systematic Reviews and Meta-Analyses statement and the Meta-analysis Of Observational Studies in Epidemiology guidelines (online supplemental table 8).[20 21] We searched PubMed, Scopus and Embase up to 22 May 2020, using the following combination of search terms: (“albumin” OR “hypoalbuminemia”) AND (“stroke” OR “cerebral ischemia” OR “cerebral ischaemia” OR “cerebral infarction” OR “transient ischemic attack” OR “transient ischaemic attack” OR “TIA”) AND (“outcome” OR “functional” OR “dependency” OR “mortality” OR “prognosis”). Articles were eligible if (1) the subjects were patients with AIS or TIA, (2) the design was a prospective study, (3) the exposure was serum albumin level (either categorised or continuous), (4) the outcome was poor functional outcome or mortality, and (5) an effect estimate with a 95% CI was reported. Two reviewers (HZ and AW) examined the retrieved papers based on the inclusion criteria mentioned previously. Disagreements were resolved by discussion with a third senior reviewer (Y-JW). The most adjusted ORs or HRs were extracted. We used the Newcastle-Ottawa Scale, the funnel plots, Begg’s tests and Egger’s tests to assess the bias risk of included studies (online supplemental table 7). We performed a fixed-effect model for poor functional outcome and a random-effect model for mortality according to the test of heterogeneity. All analyses were performed using R software V.3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). More details of statistical analysis are shown in online supplemental material.

Table 1 Baseline characteristics of patients according to serum albumin levels

		Serum albumin, g/L				
	Overall	<35	35–39.9	40–44.9	≥45	
Variable	N=13618	n=980	n=5007	n=5875	n=1756	P for trend
Serum albumin, g/L, mean (SD)	40.5±4.1	32.7±2.6	37.9±1.4	42.1±1.4	47.1±2.3	<0.0001
Age, years, mean (SD)	62.2±11.3	68.2±11.3	64.4±10.7	60.8±10.8	57.2±11.3	<0.0001
Men, n (%)	9276 (68.1)	664 (67.8)	3352 (67.0)	4027 (68.5)	1233 (70.2)	0.06
BMI, kg/m^2, mean (SD)	24.7±3.3	23.8±3.6	24.4±3.3	24.9±3.3	25.2±3.2	<0.0001
Medical history, n (%)						
Hypertension	8503 (62.4)	573 (58.5)	3005 (60.0)	3765 (64.1)	1160 (66.1)	<0.0001
Diabetes mellitus	3135 (23.0)	260 (26.5)	1153 (23.0)	1357 (23.1)	365 (20.8)	0.01
Dyslipidemia	1070 (7.9)	64 (6.5)	378 (7.6)	475 (8.1)	153 (8.7)	0.16
Stroke or TIA	3005 (22.1)	244 (24.9)	1127 (22.5)	1291 (22.0)	343 (19.5)	0.01
Coronary heart disease	1432 (10.5)	126 (12.9)	556 (11.1)	611 (10.4)	139 (7.9)	0.0002
Atrial fibrillation/flutter	911 (6.7)	121 (12.4)	424 (8.5)	304 (5.2)	62 (3.5)	<0.0001
Peripheral vascular disease	90 (0.7)	12 (1.2)	34 (0.7)	35 (0.6)	9 (0.5)	0.13
Index event, n (%)						
Ischaemic stroke	12690 (93.2)	941 (96.0)	4711 (94.1)	5433 (92.5)	1605 (91.4)	<0.0001
TIA	928 (6.8)	39 (4.0)	296 (5.9)	442 (7.5)	151 (8.6)	
TOAST types, n (%)						
Large-artery atherosclerosis	3441 (25.3)	277 (28.3)	1330 (26.6)	1416 (24.1)	418 (23.8)	<0.0001
Cardioembolism	824 (6.1)	90 (9.2)	375 (7.5)	299 (5.1)	60 (3.4)	
Small-vessel occlusion	2836 (20.8)	132 (13.5)	988 (19.7)	1319 (22.5)	397 (22.6)	
Other determined aetiology	173 (1.3)	20 (2.0)	54 (1.1)	75 (1.3)	24 (1.4)	
Undetermined aetiology	6344 (46.6)	461 (47.0)	2260 (45.1)	2766 (47.1)	857 (48.8)	
Smoking status, n (%)						
Never	7674 (56.4)	574 (58.6)	2839 (56.7)	3272 (55.7)	989 (56.3)	0.53
Previous	1674 (12.3)	120 (12.2)	625 (12.5)	725 (12.3)	204 (11.6)	
Current	4270 (31.4)	286 (29.2)	1543 (30.8)	1878 (32.0)	563 (32.1)	
NIHSS score at admission, median (IQR)	3 (1–6)	4 (2–7)	3 (1–6)	3 (1–6)	3 (1–5)	<0.0001
Pre-stroke mRS 0~2, n (%)	13044 (95.8)	912 (93.1)	4764 (95.2)	5658 (96.3)	1710 (97.4)	<0.0001
Arterial stenosis, n(%)						
ICAS	3382/11 689 (28.9)	299/849 (35.2)	1320/4327 (30.5)	1371/5019 (27.3)	392/1494 (26.2)	<0.0001
ECAS	529/11 689 (4.5)	58/849 (6.8)	204/4327 (4.7)	218/5019 (4.3)	49/1494 (3.3)	0.0009

Continued

Table 1 Continued

Variable	Overall N=13618	Serum albumin, g/L <35 n=980	35–39.9 n=5007	40–44.9 n=5875	≥45 n=1756	P for trend
Acute recanalisation therapy, n (%)						
Intravenous thrombolysis	1146 (8.4)	122 (12.5)	474 (9.5)	442 (7.5)	108 (6.2)	<0.0001
Endovascular therapy	85 (0.6)	10 (1.0)	24 (0.5)	42 (0.7)	9 (0.5)	0.15
Inpatient medication, n (%)						
Antihypertensive agents	6237 (45.8)	391 (39.9)	2147 (42.9)	2821 (48.0)	878 (50.0)	<0.0001
Hypoglycaemic agents	3374 (24.8)	262 (26.7)	1216 (24.3)	1461 (24.9)	435 (24.8)	0.44
Cholesterol-lowering agents	13033 (95.7)	933 (95.2)	4789 (95.7)	5613 (95.5)	1698 (96.7)	0.16
Antiplatelet agents	13142 (96.5)	938 (95.7)	4816 (96.2)	5684 (96.8)	1704 (97.0)	0.12
Anticoagulant agents	1372 (10.1)	130 (13.3)	562 (11.2)	535 (9.1)	145 (8.3)	<0.0001
Laboratory tests						
TC, mmol/L, mean (SD)	4.13±1.23	3.90±1.47	4.05±1.18	4.18±1.21	4.33±1.30	<0.0001
LDL, mmol/L, mean (SD)	2.45±1.08	2.34±1.21	2.42±1.04	2.47±1.08	2.54±1.13	<0.0001
HDL, mmol/L, mean (SD)	0.97±0.30	0.94±0.29	0.97±0.30	0.97±0.30	0.97±0.30	0.03
TG, mmol/L, mean (SD)	1.60±0.92	1.43±1.01	1.52±0.85	1.65±0.92	1.75±0.99	<0.0001
eGFR, mL/min/1.73 m^2, mean (SD)	92.0±33.7	84.1±37.9	89.4±28.5	94.1±35.2	97.0±38.8	<0.0001
ALT, U/L, median (IQR)	18.0 (13.0–25.7)	15.0 (11.0–20.0)	16.5 (12.0–23.0)	19.0 (13.9–26.6)	22.0 (16.0–32.0)	<0.0001
hs-CRP, mg/L, median (IQR)	1.7 (0.8–4.6)	3.5 (1.2–8.3)	1.9 (0.8–5.2)	1.6 (0.8–3.9)	1.4 (0.7–3.4)	<0.0001

ALT, alanine aminotransferase; BMI, body mass index; ECAS, extracranial arterial stenosis; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; ICAS, intracranial arterial stenosis; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TC, total cholesterol; TG, triglyceride; TIA, transient ischaemic attack; TOAST, the Trial of Org 10172 in Acute Stroke Treatment.

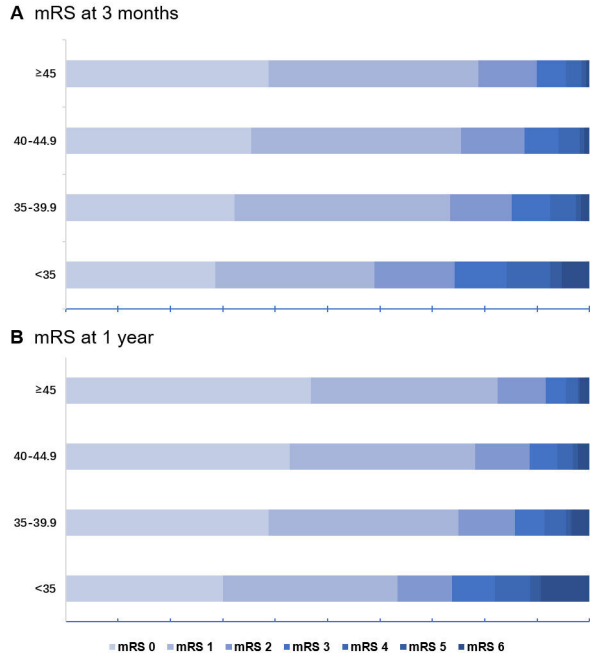


Figure 1 Distribution of mRS score at (A) 3 months and (B) 1 year. mRS, modified Rankin Scale.

RESULTS

Baseline characteristics

Among the 15166 patients in the CNSR-III, a total of 13618 (89.8%) participants completed serum albumin measurement and 3-month and 1-year follow-up (online supplemental table 1). They were divided into four groups based on serum albumin levels according to the previous literature: <35 g/L, 35~39.9 g/L, 40~44.9 g/L and ≥45 g/L (online supplemental figure 1).[22] Overall, 980 (7.2%) patients were complicated with hypoproteinemia (defined as serum albumin level <35 g/L) at admission.[23] The demographics and clinical characteristics of the study population are shown in table 1. Compared with the higher serum albumin groups, participants in the lower groups were inclined to be older, had lower BMI, TC, LDL, HDL, TG, eGFR and ALT level, but higher hs-CRP level, higher proportion of large-artery atherosclerosis (LAA) and cardioembolism (CE) in TOAST types, higher proportion of intracranial arterial stenosis and extracranial arterial stenosis, higher percentage of receiving intravenous thrombolysis and anticoagulant agents, and lower percentage of receiving antihypertensive agents. Meanwhile, patients with low serum albumin were more likely to suffer from diabetes mellitus, stroke or TIA, coronary heart disease and atrial fibrillation at baseline, and be dependent before the onset, more severe at admission (table 1).

Clinical outcomes

As shown in figure 1, the distribution of 3-month and 1-year mRS scores for four groups was significantly different (p<0.0001). During the 3-month follow-up period, 1871 (13.7%) patients had poor functional outcome and 195 (1.4%) patients died. Disability/died patients had lower serum albumin levels compared with independent patients (39.6±4.4 g/L vs 40.6±4.0 g/L, p<0.0001). For serum albumin level <35 g/L versus 40 to 44.9 g/L, crude OR for poor functional outcome was 2.14 (95% CI 1.81 to 2.52) and crude HR for mortality was 5.03 (95% CI 3.42 to 7.39). After adjustment for age, sex, BMI, medical history (hypertension, diabetes mellitus, stroke or TIA, coronary heart disease and atrial fibrillation), index event, TOAST types, pre-stroke mRS 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication, serum TG, TC, LDL, HDL, ALT, eGFR and hs-CRP level, the strong association still persisted (adjusted OR 1.37 (95% CI 1.12 to 1.67); adjusted HR 2.13 (95% CI 1.41 to 3.23)). In addition, the risk of poor functional outcome and mortality increased 17% and 86% for every 10 g/L decrease in serum albumin levels (adjusted OR 1.17 (95% CI 1.01 to 1.35); adjusted HR 1.86 (95% CI 1.30 to 2.64)) (figure 2).

Furthermore, low serum albumin levels also independently predicted poor functional outcome and mortality at 1 year, whether it was a comparison in categorical variables or continuous variables (figure 2). As shown in figure 3, restricted cubic spline similarly confirmed the inverse association of decreased serum albumin levels with disability and mortality.

Subgroup analysis was stratified by age, sex, BMI, TOAST types, NIHSS score on admission and baseline eGFR. There were almost no variables that interacted with albumin and clinical outcome, except NIHSS score at admission ≤10 with 3-month poor functional outcome (adjusted OR 1.22 (95% CI 1.05 to 1.42); p for interaction=0.04) and 3-month mortality (adjusted HR 2.45 (95% CI 1.56 to 3.85); p for interaction=0.02) (online supplemental tables 2 and 3).

Meta-analysis

We identified 4357 relevant articles in initial. There was no meta-analysis of this issue conducted before. After removing 1781 duplicates and excluding 2531 references by title and abstract, 45 articles remained for the second evaluation. Based on the full text, we included six eligible studies in the final (online supplemental figure 2, tables 5 and 6).

There were three studies (n=14937) that reported the association of serum albumin with poor functional outcome. For per 1 g/L lower plasma albumin, risk ratio (RR_{pooled}) of poor functional outcome obtained by a fixed-effect model was 1.03 (95% CI 1.02 to 1.05), without evidence of statistical heterogeneity (I^2=0%; p for heterogeneity=0.49) and publication bias based on Begg's tests (p=0.33) and Egger's tests (p=0.24), whereas our research accounted for 80.8% of the weight (figure 4). Five studies (n=15092) were included to explain the relationship between serum albumin and mortality. Due to the significance of statistical heterogeneity (I^2=63%; p for heterogeneity=0.03), we used a random-effect model to calculate RR_{pooled} of mortality (1.07 (95% CI 1.03 to

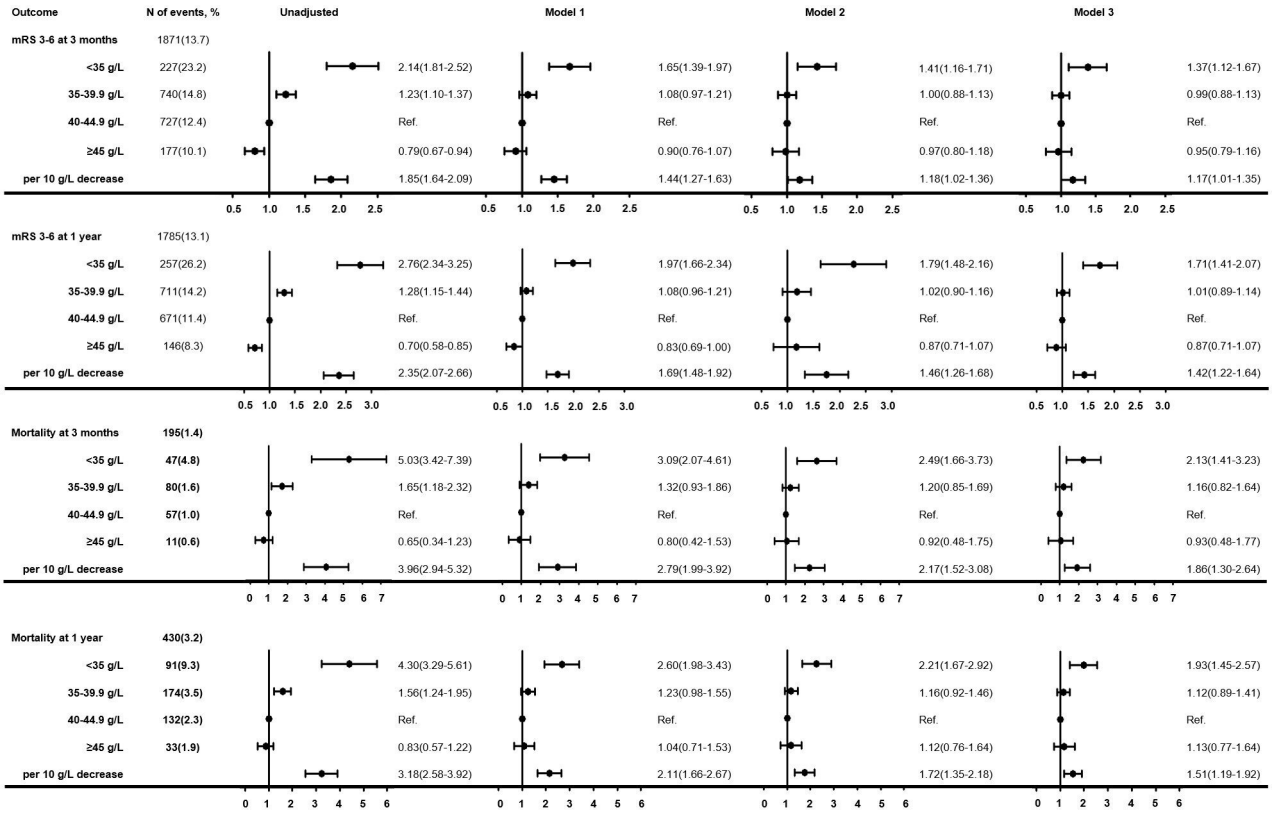


Figure 2 Association of serum albumin with clinical outcomes: HR/OR (95% CI). *Model 1: adjusted for age and sex. †Model 2: adjusted for covariables in model 1, plus BMI, medical history (hypertension, diabetes mellitus, stroke or TIA, coronary heart disease and atrial fibrillation/flutter), index event, TOAST types, NIHSS score on admission, pre-stroke mRS 0~2, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis and inpatient medication (antihypertensive agents, anticoagulant agents). ‡Model 3: adjusted for covariables in model 2, plus TG, TC, LDL, HDL, ALT, eGFR and CRP at admission. ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TC, total cholesterol; TG, triglyceride; TIA, transient ischaemic attack; TOAST, the Trial of Org 10172 in Acute Stroke Treatment.

1.11)) (figure 4). No publication bias was observed according to Begg's tests (p=0.48) and Egger's tests (p=0.74). After excluding Idicula *et al*,[10] which had fewer factors to adjusted HR value, there was no statistical heterogeneity (I^2=0%; p for heterogeneity=0.58), and RR_{pooled} of mortality was still significant (1.05 (95% CI 1.03 to 1.07)) (online supplemental figure 3). The funnel plots are shown in online supplemental figure 4.

DISCUSSION

In this prospective study, we confirmed that low serum albumin levels increased the risk of poor functional outcome and mortality in patients with AIS or TIA at 3 months and 1 year, especially in patients accompanying with hypoproteinemia. The results of the meta-analysis were additionally consistent.

In our population, hypoproteinemia accounted for only 7.2% of patients and varied from the previous data of 33.6%, which may be attributed to improved nutritional status and economic development, as well as the disparity in the inclusion criteria and sample size.[7] Meanwhile, participants in our research were generally younger than in previous studies.[8 9] Since recent publications reported that the incidence of hypoproteinemia in Chinese people over 65 years is 10.1%, and in the white Danish general population is 10.8%, ethnic differences of disease susceptibility cannot be excluded.[22 24] Mild patients were more likely to be affected by albumin. We speculated that patients with severe illness may have more comorbidities or complications, which might mask the role of albumin.[9]

Previous research showed an association between low serum albumin and the incidence of CE and cryptogenic stroke, but not LAA.[18] It was well established that low serum albumin levels were linked to many heart diseases, including atrial fibrillation, which was the main cause for CE,[25] whereas in our study population, the proportion of CE and LAA both gradually increased with the decrease of serum albumin. Also, the average serum albumin level of patients with CE or LAA was all lower than that of other types (online supplemental table 4). This discrepancy may be partially explained by the different aetiological classification characteristics of patients with stroke in the East and the West.[26] Even though our research may amplify the effect, there was some relevant evidence supporting

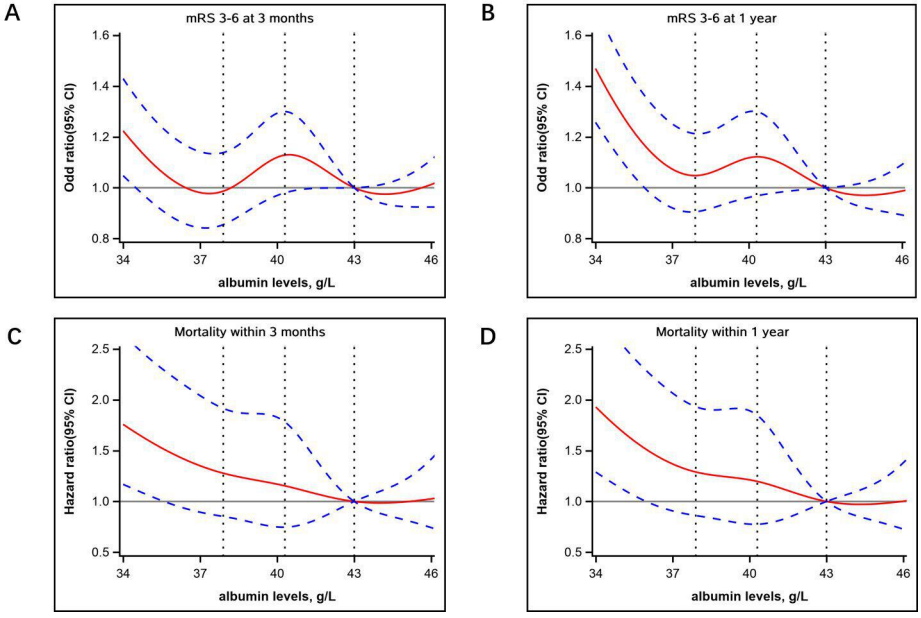


Figure 3 Spline models in the association between serum albumin and clinical outcomes The association with serum albumin level and poor functional outcome (mRS score of 3–6) at (A) 3 months and (B) 1 year. The association with serum albumin level and mortality at (C) 3 months and (D) 1 year. The red line indicates adjusted OR/HR, and the blue lines indicate the 95% CI. Data were fitted with a Cox regression model with adjustment for age, sex, BMI, medical history (hypertension, diabetes mellitus, stroke or transient ischaemic attack, coronary heart disease and atrial fibrillation/flutter), index event, TOAST types, pre-stroke mRS score 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), serum TG, TC, LDL, HDL, ALT, eGFR and hs-CRP. ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TC, total cholesterol; TG, triglyceride; TOAST, the Trial of Org 10172 in Acute Stroke Treatment.

the assumption that serum albumin was associated with LAA. Based on the prior basic medical studies, the weakening anti-inflammatory function, antioxidant effect and endothelial protection of low serum albumin might indirectly promote the development of atherosclerosis.[27–29]

We speculated that the powerful predictive function on poor functional outcome and mortality would be explained by three plausible pathophysiological mechanisms. First, because of a long circulatory half-life, serum albumin might serve as a biomarker of some pre-stroke pathological states, which seriously affect the prognosis, such as malnutrition.[30] Nevertheless, we did not find the interaction between BMI and albumin, suggesting that there may be other likely diseases declining serum albumin levels and preventing the rehabilitation, such as kidney disease and cancer.[19 31] Second, serum albumin deficiency may impair the balance of coagulation and anticoagulation. Early studies have shown that albumin is a cofactor mediating the binding of plasminogen to fibrin, and further participating in the interaction of tissue plasminogen activator.[32] Also, serum albumin prevented arachidonic acid oxidation and inhibited thromboxane A_2 synthesis, which is a potent stimulator of platelet aggregation.[33] The decrease of serum albumin might weaken the anticoagulant effect and strengthen the coagulation function, and thrombus would be more likely to form.[34] Besides, the excessive production for fibrinogen, and coagulation factors V and VIII by the liver as compensation for hypoproteinemia might enlarge the coagulation pathway.[35] Third, hypoalbuminemia increased the risk of stroke complications such as pneumonia, which significantly impaired survival status and functional recovery.[36]

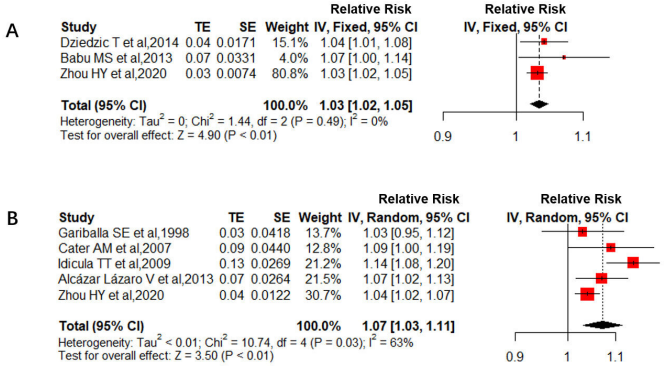


Figure 4 Forest plot of the meta-analysis showed relative risk and 95% CI of (A) poor functional outcome and (B) mortality in every 1 g/L decreased serum albumin. TE, treatment effect.

In a recent subgroup analysis of the ALIAS trials, for patients with CE in the middle cerebral artery (NIHSS score ≥15), there was a trend to be effective when high-dose albumin therapy was started within 2 hours after onset, indicating that some specific subgroups might

benefit from this treatment.[37] Meanwhile, by careful fluid management and diuretic treatment, common complications included pulmonary oedema and heart failure after albumin infusion could be partially controlled.[6] These remarkable findings indicated that a more precise and individualised application of albumin might be needed to re-examine the neuroprotection hypothesis. For patients with hypoproteinemia, positive therapy should be initiated as soon as possible. Also, the therapeutic options would be more effective by treating the underlying cause simultaneously, rather than mere albumin supplement.[8] For patients with normal albumin, it might be more beneficial to take an appropriate dose of albumin infusion to specific subgroups of patients representative of preclinical settings while actively controlling complications.

Some prior studies have shown that high albumin level is associated with a better prognosis. However, it was based on comparison with low albumin level.[10] Given the multiple physiological effects of albumin, there might be a ceiling effect in albumin therapy. More research is needed to find the sweet spot of serum albumin therapy. Furthermore, since albumin could pass through the blood–brain barrier, the strong adsorption function of albumin to transport relevant drugs to local damaged brain tissue will also have extraordinary effects on promoting functional recovery.[38]

This study has some limitations. First, only one period of serum albumin was measured, and there was no follow-up on the changes in albumin levels. Second, the serum albumin level was not tested immediately after the stroke. A previous study found that serum albumin levels might change during the first days after stroke, especially in patients with poor outcome.[39] Therefore, our data may partially magnify the negative relationship between hypoalbuminemia and outcome. Third, serum albumin measurement of sub-centres was not uniform. In fact, the bromocresol green assay is a common method to measure albumin, but is affected by α1-globulin and α2-globulin, which might cause a positive bias, especially in severe hypoalbuminemia. Meanwhile, the bromocresol purple assay could avoid this effect.[40] Therefore, our study may reduce the proportion of hypoalbuminemia, and weaken the correlation between low serum albumin level and poor prognosis. Fourth, there may be a selection bias when patients were enrolled. Some older patients with severe illness at the time of onset were more likely to refuse admission. However, they may be closely related to hypoalbuminemia. Fifth, despite no statistical bias, few studies were included in the meta-analysis, and the definition of poor functional outcome varied. More prospective studies are needed to validate the findings in the future.

CONCLUSIONS

In summary, low serum albumin level was a robust, independent predictor in poor functional outcome and mortality of patients with AIS or TIA. As a promising neuroprotective agent, serum albumin requires more further investigation.

Author affiliations
[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[3]Tiantan Neuroimaging Center of Excellence, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[4]Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China

Twitter Yilong Wang @yilong

Acknowledgements We thank the staff and participants of the CNSR-III studies for their contribution.

Contributors Y-JW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y-JW designed the study. HZ, AW and XM collected the data. HZ and AW wrote the manuscript. HZ, AW and YZ completed the statistical analysis. JL, YJ, JJ, Y-LW, XZ and HL reviewed, edited and approved the final version.

Funding This work was supported by grant from National Key R&D Program of China (2018YFC1312903), grant from the National Natural Science Foundation of China (81870905), grant from Beijing Municipal Science & Technology Commission (Z181100001818001), grant from Beijing Municipal Administration of Hospitals Incubating Program (PX2020021) and grant from Beijing Excellent Talents Training Program (2018000021469G234).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Anonymised data are available to other researchers on request for the sole purpose of replicating procedures or reproducing the results by directly contacting the corresponding author and their institutions.

ORCID iDs
Hongyu Zhou http://orcid.org/0000-0002-9130-889X
Anxin Wang http://orcid.org/0000-0003-4351-2877
Hao Li http://orcid.org/0000-0002-8591-4105
Yongjun Wang http://orcid.org/0000-0002-9976-2341

REFERENCES

1 Boldt J. Use of albumin: an update. *Br J Anaesth* 2010;104:276–84.
2 Lang J, Katz R, Ix JH, *et al*. Association of serum albumin levels with kidney function decline and incident chronic kidney disease in elders. *Nephrol Dial Transplant* 2018;33:986–92.
3 Arques S. Human serum albumin in cardiovascular diseases. *Eur J Intern Med* 2018;52:8–12.
4 Belayev L, Liu Y, Zhao W, *et al*. Human albumin therapy of acute ischemic stroke: marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. *Stroke* 2001;32:553–60.
5 Belayev L, Pinard E, Nallet H, *et al*. Albumin therapy of transient focal cerebral ischemia: in vivo analysis of dynamic microvascular responses. *Stroke* 2002;33:1077–84.
6 Martin Renee' H, Yeatts SD, Hill MD. ALIAS (Albumin in Acute Ischemic Stroke) trials: analysis of the combined data from parts 1 and 2. *Stroke* 2016;47:2355–9.
7 Famakin B, Weiss P, Hertzberg V, *et al*. Hypoalbuminemia predicts acute stroke mortality: Paul Coverdell Georgia stroke registry. *J Stroke Cerebrovasc Dis* 2010;19:17–22.
8 Seet RCS, Lim ECH, Chan BPL, *et al*. Serum albumin level as a predictor of ischemic stroke outcome. *Stroke* 2004;35:2435–6. author reply -6.

9 Babu MS, Kaul S, Dadheech S, *et al*. Serum albumin levels in ischemic stroke and its subtypes: correlation with clinical outcome. *Nutrition* 2013;29:872–5.
10 Idicula TT, Waje-Andreassen U, Brogger J, *et al*. Serum albumin in ischemic stroke patients: the higher the better. The Bergen stroke study. *Cerebrovasc Dis* 2009;28:13–7.
11 Kimura Y, Ohji S, Ishiyama D, *et al*. Factors associated with functional recovery in Japanese patients with convalescent stroke stratified by age: a multicenter observational study. *Int J Rehabil Res* 2019;42:249–55.
12 Wang Y, Jing J, Meng X, *et al*. The third China national stroke registry (CNSR-III) for patients with acute ischaemic stroke or transient ischaemic attack: design, rationale and baseline patient characteristics. *Stroke Vasc Neurol* 2019;4:158–64.
13 Adams HP, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. definitions for use in a multicenter clinical trial. TOAST. trial of org 10172 in acute stroke treatment. *Stroke* 1993;24:35–41.
14 Samuels OB, Joseph GJ, Lynn MJ, *et al*. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol* 2000;21:643–6.
15 North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, *et al*. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445–53.
16 Inker LA, Astor BC, Fox CH, *et al*. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014;63:713–35.
17 Chen W, Pan Y, Zhao X, *et al*. Totaled health risks in vascular events score predicts clinical outcome and symptomatic intracranial hemorrhage in Chinese patients after thrombolysis. *Stroke* 2015;46:864–6.
18 Xu W-H, Dong C, Rundek T, *et al*. Serum albumin levels are associated with cardioembolic and cryptogenic ischemic strokes: Northern Manhattan study. *Stroke* 2014;45:973–8.
19 Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol* 2014;13:823–33.
20 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1–34.
21 Stroup DF, Berlin JA, Morton SC. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
22 Ronit A, Kirkegaard-Klitbo DM, Dohlmann TL, *et al*. Plasma albumin and incident cardiovascular disease: results from the CGPS and an updated meta-analysis. *Arterioscler Thromb Vasc Biol* 2020;40:473–82.
23 Dziedzic T, Pera J, Slowik A, *et al*. Hypoalbuminemia in acute ischemic stroke patients: frequency and correlates. *Eur J Clin Nutr* 2007;61:1318–22.
24 Lyu YB, Zhou JH, Duan J, *et al*. [Association of plasma albumin and hypersensitive C-reactive protein with 5-year all-cause mortality among Chinese older adults aged 65 and older from 8 longevity areas in China]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2019;53:590–6.
25 Liao L-Z, Zhang S-Z, Li W-D, *et al*. Serum albumin and atrial fibrillation: insights from epidemiological and Mendelian randomization studies. *Eur J Epidemiol* 2020;35:113–22.
26 Wang Y, Zhao X, Liu L, *et al*. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese intracranial atherosclerosis (CICAS) study. *Stroke* 2014;45:663–9.
27 Fanali G, di Masi A, Trezza V, *et al*. Human serum albumin: from bench to bedside. *Mol Aspects Med* 2012;33:209–90.
28 Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res* 2016;118:620–36.
29 Geovanini GR, Libby P. Atherosclerosis and inflammation: overview and updates. *Clin Sci (Lond)* 2018;132:1243–52.
30 Gariballa SE, Parker SG, Taub N, *et al*. Influence of nutritional status on clinical outcome after acute stroke. *Am J Clin Nutr* 1998;68:275–81.
31 O'Neal WT, Claxton J'Neka S, Sandesara PB, *et al*. Provider specialty, anticoagulation, and stroke risk in patients with atrial fibrillation and cancer. *J Am Coll Cardiol* 2018;72:1913–22.
32 He H, Guo J. Serum albumin: a risk of stroke? *Am J Emerg Med* 2017;35:186–7.
33 Mikhailidis DP, Ganotakis ES. Plasma albumin and platelet function: relevance to atherogenesis and thrombosis. *Platelets* 1996;7:125–37.
34 Gyamlani G, Molnar MZ, Lu JL, *et al*. Association of serum albumin level and venous thromboembolic events in a large cohort of patients with nephrotic syndrome. *Nephrol Dial Transplant* 2017;32:157–64.
35 Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. *Thromb Res* 2006;118:397–407.
36 Dziedzic T, Pera J, Klimkowicz A, *et al*. Serum albumin level and nosocomial pneumonia in stroke patients. *Eur J Neurol* 2006;13:299–301.
37 Khatri R, Afzal MR, Rodriguez GJ, *et al*. Albumin-induced neuroprotection in focal cerebral ischemia in the ALIAS trial: does severity, mechanism, and time of infusion matter? *Neurocrit Care* 2018;28:60–4.
38 Eady TN, Khoutorova L, Obenaus A, *et al*. Docosahexaenoic acid complexed to albumin provides neuroprotection after experimental stroke in aged rats. *Neurobiol Dis* 2014;62:1–7.
39 Makris K, Koniari K, Spanou L, *et al*. Prognostic significance of serum albumin level changes in acute ischemic stroke: the role of biological and analytical variation. *Clin Chem Lab Med* 2016;54:143–50.
40 Ueno T, Hirayama S, Sugihara M, *et al*. The bromocresol green assay, but not the modified bromocresol purple assay, overestimates the serum albumin concentration in nephrotic syndrome through reaction with α2-macroglobulin. *Ann Clin Biochem* 2016;53:97–105.

SUPPLEMENTAL MATERIAL

Low Serum Albumin Levels Predict Poor Outcome in Patients with Acute Ischemic Stroke or Transient Ischemic Attack

Catalogs

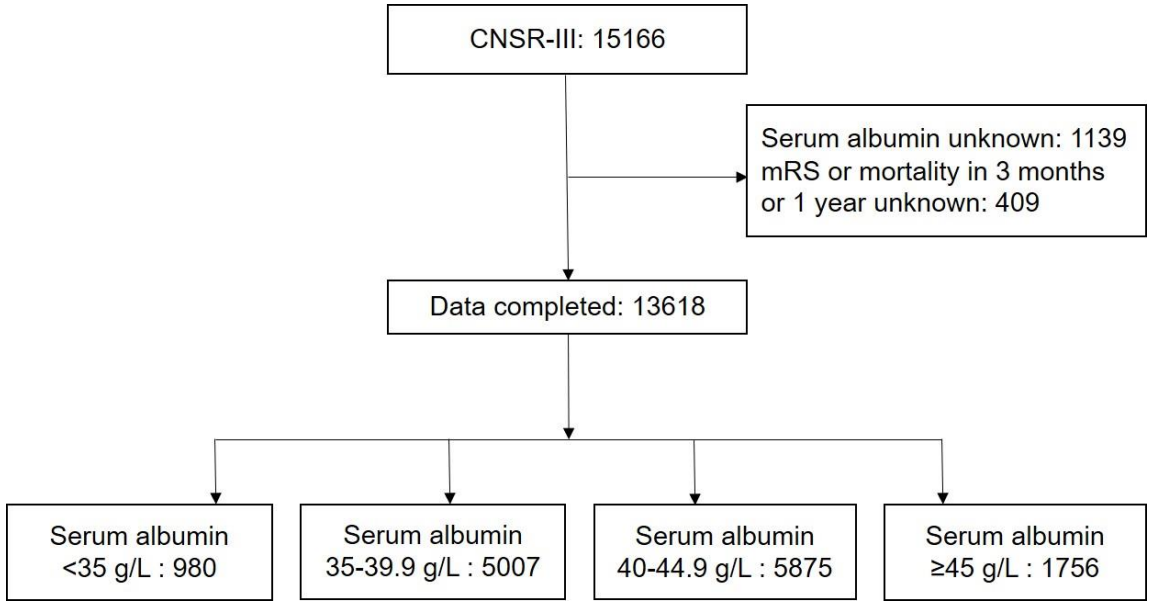
Supplementary Methods

Statistical analysis for the meta-analysis

Details of the included studies were shown in online supplementary table 6 and 7. Including our study, there was five research with poor functional outcome, and three research with mortality. Two studies had to convert serum albumin unit to g/L.[1] Only one paper needed to be converted into the continuous scale (g/L) based on the previous literature.[2, 3] The OR/HR per 1g/L serum albumin increase was converted to per 1g/L serum albumin decrease by reverse calculation.[4-6] In our study, the risk of poor functional outcome and mortality increased 3% and 4% for every 1 g/L decrease in serum albumin levels (adjusted OR, 1.03; 95%CI, 1.02-1.05; adjusted HR, 1.04, 95%CI, 1.02-1.07) (online supplementary table 5). We combined the odds ratio (OR) and hazard ratio (HR) for prospective studies for a risk ratio (RR_{pooled}). The poor functional outcome was analysed by the fixed-effect model, while mortality by the random-effect model according to heterogeneity assessed with the I^2 statistic and the Q statistic.[7] Furthermore, we evaluated potential publication bias by the funnel plots, the Begg's tests and the Egger's tests.

Supplementary Figures

Figure 1. Study flowchart and numbers of eligible patients in each group



mRS, modified Rankin Scale.

Figure 2. Flowchart on the selection of eligible articles

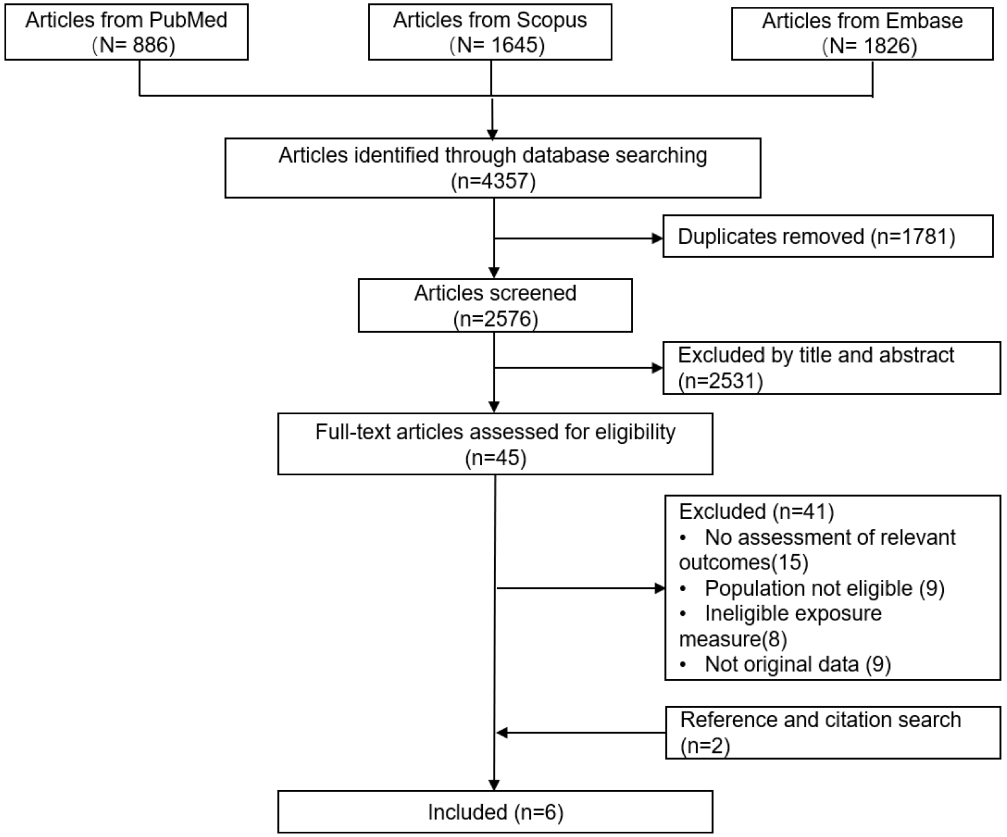


Figure 3. Forest plot of the meta-analysis showed relative risk and 95% CI of mortality in every 1 g/L decreased serum albumin (excluding Idicula, 2009)

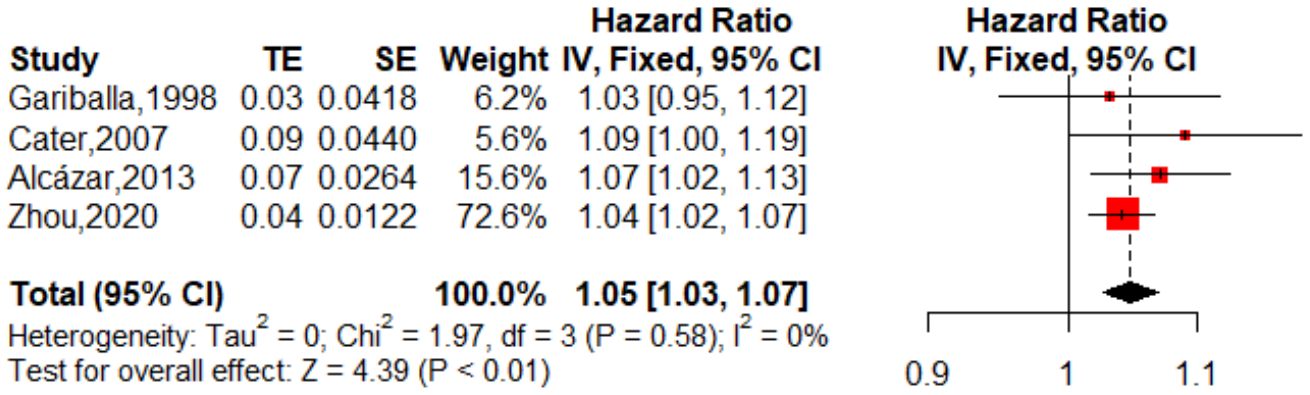
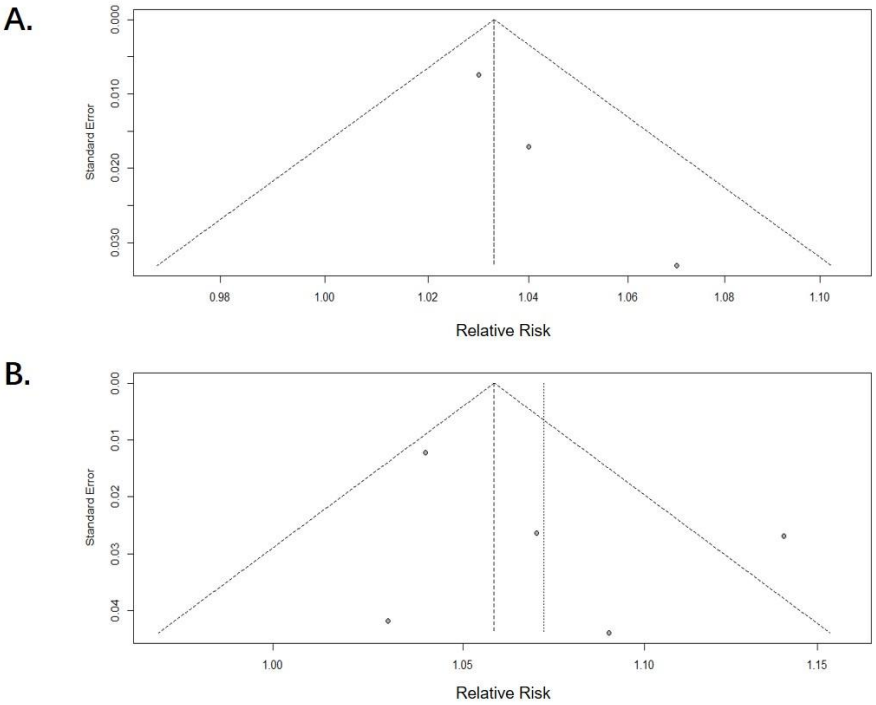


Figure 4. Funnel plots of studies reporting on the association of serum albumin level with (A) poor functional outcome and (B) mortality



Supplementary Tables

Table 1. Baseline characteristics of patients between included and excluded patients

Variable	Included	Excluded	P Value
	n=13618	n=1548	
Age, y, mean (SD)	62.2±11.3	62.7±11.6	0.07
Men, n (%)	9276(68.1)	1088(70.3)	0.08
BMI, kg/m^2, mean (SD)	24.7±3.3	24.9±3.5	0.16
Medical history, n (%)			
Hypertension	8503(62.4)	991(64.0)	0.22
Diabetes mellitus	3135(23.0)	375(24.2)	0.29
Dyslipidemia	1070(7.9)	121(7.8)	0.96
Stroke or TIA	3005(22.1)	350(22.6)	0.63
Coronary heart disease	1432(10.5)	176(11.4)	0.30
Atrial fibrillation/ flutter	911(6.7)	108(7.0)	0.67
Peripheral vascular disease	90(0.7)	28(1.8)	<0.0001
Index event, n (%)			
Ischemic stroke	12690(93.2)	1456(94.1)	0.19
TIA	928(6.8)	92(5.9)	
TOAST types, n (%)			
Large-artery atherosclerosis	3441(25.3)	415(26.8)	0.12

Variable	Included	Excluded	P Value
	n=13618	n=1548	
Cardioembolism	824(6.1)	93(6.0)	
Small-vessel occlusion	2836(20.8)	329(21.3)	
Other determined etiology	173(1.3)	9(0.6)	
Undetermined etiology	6344(46.6)	702(45.4)	
Smoking status, n (%)			
Never	7674(56.4)	832(53.8)	0.005
Previous	1674(12.3)	234(15.1)	
Current	4270(31.4)	482(31.1)	
NIHSS score on admission, median (IQR)	3(1-6)	4(2-6)	<0.0001
Pre-stroke mRS 0~2, n (%)	13044(95.8)	1465(94.6)	0.04
Arterial stenosis, n (%)			
ICAS	3382/11689(28.9)	431/1323(32.6)	0.006
ECAS	529/11689(4.5)	67/1323(5.1)	0.37
Acute recanalization therapy, n (%)			
Intravenous thrombolysis	1146(8.4)	157(10.1)	0.02
Endovascular therapy	85(0.6)	10(0.7)	0.92
Inpatient medication, n (%)			
Antihypertensive agents	6237(45.8)	763(49.3)	0.009
Hypoglycemic agents	3374(24.8)	418(27.0)	0.06
Cholesterol-lowering agents	13033(95.7)	1473(95.2)	0.32
Antiplatelet agents	13142(96.5)	1471(95.0)	0.003
Anticoagulant agents	1372(10.1)	174(11.2)	0.15
Laboratory tests			

Variable	Included	Excluded	P Value
	n=13618	n=1548	
TC, mmol/L, mean (SD)	4.13±1.23	4.07±1.12	0.27
LDL, mmol/L, mean (SD)	2.45±1.08	2.40±1.00	0.40
HDL, mmol/L, mean (SD)	0.97±0.30	0.95±0.29	0.19
TG, mmol/L, mean (SD)	1.60±0.92	1.58±0.90	0.36
eGFR, mL/min/1.73 m^2, mean (SD)	92.0±33.7	92.0±37.7	0.37
ALT, U/L, median (IQR)	18.0(13.0-25.7)	18.0(13.6-27.0)	0.11
hs-CRP, mg/L, median (IQR)	1.7(0.8-4.6)	2.1(0.9-5.6)	<0.0001

BMI, body mass index; TIA, transient ischemic attack; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; ICAS, intracranial arterial stenosis; ECAS, extracranial arterial stenosis; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; SD, standard deviation.

Table 2. Association of plasma albumin with poor functional outcome (mRS of 3-6) at 3 months and 1 year in analyses stratified for risk factors

Variable	mRS 3-6 at 3 months (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*	mRS 3-6 at 1 year (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*
Age, Years			0.56			0.16
<70y	1088/10020 (10.9)	1.15(0.96-1.38)		942/10020 (9.4)	1.35(1.12-1.62)	
⩾70y	783/3598(21.7)	1.14(0.90-1.45)		843/3598(23.4)	1.48(1.17-1.87)	
Sex			0.76			0.84
Men	1145/9276(12.3)	1.19(0.99-1.42)		1108/9276(11.9)	1.46(1.21-1.75)	
Women	726/4342(16.7)	1.15(0.91-1.46)		677/4342(15.6)	1.39(1.09-1.77)	
BMI			0.88			0.36
<18.5 kg/m^2	76/295(25.8)	0.99(0.42-2.36)		77/295(26.1)	2.39(0.89-6.43)	
⩾18.5 kg/m^2	1795/13323 (13.5)	1.16(1.00-1.34)		1708/13323(12.8)	1.39(1.20-1.61)	
TOAST Types			0.89			0.94
Large-artery atherosclerosis	686/3441(19.9)	1.07(0.84-1.38)		631/3441(18.3)	1.35(1.05-1.75)	
Cardioembolism	156/824(18.9)	1.22(0.71-2.09)		161/824(19.5)	1.37(0.79-2.36)	
Small-vessel occlusion	200/2836(7.1)	1.34(0.88-2.04)		184/2836(6.5)	1.49(0.97-2.29)	
Other determined etiology	29/173(16.8)	0.92(0.24-3.59)		30/173(17.3)	0.89(0.22-3.70)	
Undetermined etiology	800/6344(12.6)	1.18(0.96-1.46)		799/6344(12.3)	1.47(1.19-1.82)	
NIHSS score on admission			0.42			0.13
≤3	372/7495(5.0)	1.22(0.92-1.62)		442/7495(5.9)	1.65(1.28-2.14)	

Variable	mRS 3-6 at 3 months (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*	mRS 3-6 at 1 year (%)	Adjusted OR of per 10 g/L decrease	Adjusted *P* for interaction*
>3	1499/6123(24.5)	1.14(0.97-1.33)		1343/6123(21.9)	1.29(1.09-1.52)	
NIHSS score on admission			0.04			0.09
≤10	1320/12630(10.5)	1.22(1.05-1.42)		1284/12630(10.2)	1.46(1.25-1.70)	
>10	551/988(55.8)	0.92(0.65-1.31)		501/988(50.7)	1.13(0.79-1.62)	
eGFR			0.80			0.25
<60 mL/min/1.73 m^2	156/718(21.7)	1.11(0.70-1.78)		168/718(23.4)	1.83(1.18-2.84)	
⩾60 mL/min/1.73 m^2	1153/8896(13.0)	1.19(0.99-1.44)		1072/8896(12.1)	1.46(1.20-1.76)	
eGFR			0.56			0.13
<90 mL/min/1.73 m^2	669/3978(16.8)	1.13(0.89-1.43)		690/3978(17.4)	1.68(1.33-2.12)	
⩾90 mL/min/1.73 m^2	640/5636(11.4)	1.31(1.02-1.69)		550/5636(9.8)	1.40(1.08-1.82)	

*Adjustment model: age, sex, BMI, medical history (hypertension, DM, stroke or TIA, coronary heart disease and atrial fibrillation/fullter), index event, TOAST types, pre-stroke mRS 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), serum TG, TC, LDL, HDL, ALT, eGFR, and hs-CRP.

BMI, body mass index; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio.

Table 3. Association of plasma albumin with mortality at 3 months and 1 year in analyses stratified for risk factors

Variable	Mortality at 3 months (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*	Mortality at 1 year (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*
Age, Years			0.35			0.35
<70y	82/10020(0.8)	1.61(0.93-2.78)		185/10020(1.9)	1.75(1.23-2.49)	
⩾70y	113/3598(3.14)	1.87(1.16-3.04)		245/3598(6.8)	1.33(0.96-1.84)	
Sex			0.72			0.65
Men	115/9276(1.2)	1.75(1.11-2.77)		270/9276(2.9)	1.50(1.11-2.02)	
Women	80/4342(1.8)	2.00(1.12-3.56)		160/4342(3.7)	1.56(1.03-2.35)	
BMI			0.48			0.19
<18.5 kg/m^2	16/295(5.4)	2.43(0.30-19.55)		27/295(9.2)	5.23(1.18-23.22)	
⩾18.5 kg/m^2	179/13323(1.3)	1.09(0.99-1.21)		403/13323(3.0)	1.49(1.16-1.91)	
TOAST Types			0.80			0.21
Large-artery atherosclerosis	62/3441(1.8)	1.91(1.01-3.61)		135/3441(3.9)	1.43(0.91-2.24)	
Cardioembolism	25/824(3.0)	2.38(0.77-7.41)		57/824(6.9)	1.53(0.72-3.26)	
Small-vessel occlusion	9/2836(0.3)	0.96(0.18-5.19)		32/2836(1.1)	1.02(0.42-2.49)	
Other determined etiology	3/173(1.7)	-		11/173(6.4)	0.54(0.09-3.36)	
Undetermined etiology	96/6344(1.5)	1.78(1.07-2.96)		195/6344(3.1)	1.70(1.20-2.41)	
NIHSS score on admission			0.40			0.11
≤3	57/7495(0.8)	1.64(0.85-3.16)		131/7495(1.8)	1.26(0.82-1.93)	
>3	138/6123(2.3)	1.89(1.24-2.88)		299/6123(4.9)	1.64(1.23-2.19)	

Variable	Mortality at 3 months (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*	Mortality at 1 year (%)	Adjusted HR of per 10 g/L decrease	Adjusted *P* for interaction*
NIHSS score on admission			0.02			0.18
≤10	116/12630(0.92)	2.45(1.56-3.85)		296/12630(2.34)	1.60(1.20-2.13)	
>10	79/988(8.00)	1.03(0.59-1.78)		134/988(13.56)	1.15(0.75-1.75)	
eGFR			0.34			0.87
<60 mL/min/1.73 m^2	24/718(3.34)	0.98(0.30-3.20)		60/718(8.36)	1.33(0.72-2.45)	
⩾60 mL/min/1.73 m^2	119/8896(1.34)	1.94(1.21-3.10)		248/8896(2.79)	1.46(1.05-2.02)	
eGFR			0.37			0.93
<90 mL/min/1.73 m^2	92/3978(2.31)	1.82(1.10-3.02)		206/3978(5.18)	1.53(1.09-2.15)	
⩾90 mL/min/1.73 m^2	51/5636(0.90)	1.62(0.76-3.44)		102/5636(1.81)	1.66(0.98-2.83)	

*Adjustment model: age, sex, BMI, medical history (hypertension, DM, stroke or TIA, coronary heart disease and atrial fibrillation/fullter), index event, TOAST types, pre-stroke mRS 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), serum TG, TC, LDL, HDL, ALT, eGFR, and hs-CRP.

BMI, body mass index; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio.

Table 4. Serum albumin levels in different TOAST types

Variable	Large-artery atherosclerosis	Cardioembolism	Small-vessel occlusion	Other determined etiology	Undetermined etiology	*P* for trend
	n= 3441	n= 824	n= 2836	n=173	n=6344	
Serum albumin, g/L, mean (SD)	40.3±2.0	39.3±3.8	41.0±3.9	40.2±4.9	40.6±4.1	<0.0001

TOAST, the Trial of Org 10172 in Acute Stroke Treatment.

Table 5. The association of serum albumin with outcomes (poor functional outcome and mortality) in 1 year : HR/OR（95%CI）

Outcomes	N of events, %	Every 1 g/L decrease after adjustment*
mRS 3-6 at 1 year	1785(13.1)	1.03(1.02-1.05)
Mortality in 1 year	430(3.2)	1.04(1.02-1.07)

*Adjustment model: age, sex, BMI, medical history (hypertension, DM, stroke or TIA, coronary heart disease and atrial fibrillation/fullter), index event, TOAST types, pre-stroke mRS 0~2, NIHSS scores on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), serum TG, TC, LDL, HDL, ALT, eGFR, and hs-CRP.

mRS, modified Rankin Scale; HR, hazard ratio; OR, odds ratio.

Table 6. Summary of the studies exploring an association between serum albumin and poor functional outcome or mortality

Author, year	Country	N0. of subjects	Participants	Age, years	Men,%	Follow-up time	NOS score	Albumin comparison	Study outcome(no.)	Adjustments	Effect estimate (95% CI)	Unified effect estimate (95% CI)
Gariballa SE *et al*[5] 1998	UK	225	Acute ischemic stroke	77.6±9.4	96(42.7)	3 months	9	Per +1 g/L	Mortality	Age, sex, mRS, previous illnesses, drugs, smoking	HR:0.91(0.84-0.99)	HR:1.03(1.01-1.19)
Dziedzic T *et al*[6], 2004	Poland	759	Acute ischemic stroke	68.3±12	372(49.0)	3 months	9	Per +1g/L	Poor outcome (mRS 4~6)	Age, sex, atrial fibrillation, ischemic heart disease, smoking, SSS score on admission, infarct size, TC	OR:0.96(0.93-0.99)	OR:1.04(1.01-1.08)
Carter AM *et al*[2],2007	UK	545	Acute ischemic stroke	-	274(50.3)	7.4 years(median)	9	>43 g/L vs <38 g/L	Mortality	Age, stroke subtype, previous stroke/TIA, atrial fibrillation, creatinine, haemoglobin, fibrinogen, FVIII, FXIIIA, β-TG, vWF, tPA	HR:0.65(0.44-0.96)	HR:1.09(1.01-1.20)
Idicula TT *et al*[4], 2009	Norway	444	Acute ischemic stroke	70.3±14.4	250(56.3)	2 years	8	Per +1g/L	Mortality	Age, sex and NIHSS score on admission	OR:0.88(0.83-0.93)	OR:1.14(1.08-1.20)
Alcázar Lázaro V *et al*[1], 2013	Spain	260	Acute ischemic stroke	-	127 (48.8)	5 years	9	Per -1 g/dL	Mortality	Age, BMI, cardiopathy, atrial fibrillation, urea, calcemia, total proteins, cholesterol, glycemia, embolic	OR:2.00(1.12-3)	OR:1.07(1.01-1.12)

Author, year	Country	N0. of subjects	Participants	Age, years	Men,%	Follow-up time	NOS score	Albumin comparison	Study outcome(no.)	Adjustments	Effect estimate (95% CI)	Unified effect estimate (95% CI)
										mechanism, coma, DBP, Canadian scale score on admission		
Babu MS *et al*[8], 2013	India	560	Acute ischemic stroke	-	401(71.6)	3 months	9	Per -1 g/dL	Poor outcome (mRS 4~6)	Age, sex, smoking, diabetes, hypertension, alcoholism, TC, HDL-C, LDL-C and TG	OR:1.972(1.103- 4.001)	OR:1.07(1.01-1.15)
Zhou HY *et al, 2020*	China	13618	Acute ischemic stroke or transient ischemic attack	62.17±11.26	9276(68.12)	1 year	9	Per -1g/L	Poor outcome (mRS 3~6)	Age, sex, BMI, medical history (hypertension, diabetes mellitus, stroke or TIA, coronary heart disease and atrial fibrillation/flutter), diagnosis type, TOAST type, NIHSS score on admission, Pre-stroke mRS 0~2 on admission, intracranial arterial stenosis, extracranial arterial stenosis, intravenous thrombolysis, inpatient medication (antihypertensive agents, anticoagulant agents), TG, TC, LDL, HDL, ALT, eGFR, hs-CRP	OR:1.03(1.02-1.05)	OR:1.03(1.02-1.05)
									Mortality		HR:1.04(1.02-1.07)	HR:1.04(1.02-1.07)

BMI, body mass index; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; vWF, von Willebrand factor; tPA, tissue-type plasminogen activator; OR, odds ratio; HR, hazard ratio; NOS, the Newcastle-Ottawa Scale.

Table 7. The Newcastle-Ottawa Quality Scale (NOS) for prospective studies

	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Adjustments i) age ii) additional factors	Assessment of outcome	Length of follow-up	Adequate follow-up	
Gariballa SE *et al*[5]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Dziedzic T *et al*[6]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Carter AM *et al*[2]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Idicula TT *et al*[4]	✸	✸	✸	✸	✸✸	✸		✸	8
Alcázar Lázaro V *et al*[1]	✸	✸	✸	✸	✸✸	✸	✸	✸	9
Babu MS *et al*[8]	✸	✸	✸	✸	✸✸	✸	✸	✸	9

Table 8. PRISMA Checklist

PRISMA Checklist	#	Checklist item	Reported on page #
TITLE			
title	1	Identify the report as a systematic review, meta-analysis, or both.	Because the meta-analysis was added after the original analysis, and the title had a word limit, it was not reflected in the title.
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 6 Paragraph 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3 Paragraph 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6 Paragraph 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 Paragraph 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 Paragraph 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6 Paragraph 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 Paragraph 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6 Paragraph 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6 Paragraph 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Online supplementary Page 3 Paragraph 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6 Paragraph 3
Synthesis of results	14	Describe the methods of handling data and combining results of	Online supplementary Page 3

		studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Paragraph 1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Online supplementary Page 3 Paragraph 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Online supplementary Page 3 Paragraph 1
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Online supplementary figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Online supplementary table 6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Online supplementary table 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Online supplementary table 8 figure 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	figure 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	figure 4 Page 10 Paragraph 1

			Online supplementary figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10 Paragraph 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14 Paragraph 1
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14 Paragraph 2
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Complete draft Page 14 Paragraph 5

e-references

1. Alcázar Lázaro V, del Ser Quijano T, Barba Martín R. Hypoalbuminemia and other prognostic factors of mortality at different time points after ischemic stroke. *Nutr Hosp* 2013;28:456-63
2. Carter AM, Catto AJ, Mansfield MW*, et al.* Predictive variables for mortality after acute ischemic stroke. *Stroke* 2007;38:1873-80
3. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135:1301-9
4. Idicula TT, Waje-Andreassen U, Brogger J*, et al.* Serum albumin in ischemic stroke patients: The higher the better. The bergen stroke study. *Cerebrovasc Dis* 2009;28:13-7
5. Gariballa SE, Parker SG, Taub N*, et al.* Influence of nutritional status on clinical outcome after acute stroke. *Am J Clin Nutr* 1998;68:275-81
6. Dziedzic T, Slowik A, Szczudlik A. Serum albumin level as a predictor of ischemic stroke outcome. *Stroke* 2004;35:e156-8
7. Higgins JP, Thompson SG, Deeks JJ*, et al.* Measuring inconsistency in meta-analyses. *Bmj* 2003;327:557-60
8. Babu MS, Kaul S, Dadheech S*, et al.* Serum albumin levels in ischemic stroke and its subtypes: Correlation with clinical outcome. *Nutrition* 2013;29:872-5