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

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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 inverse (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. It has several physiological properties, including maintaining colloidal osmotic pressure, antiplatelet aggregation and anti-inflammatory effects.

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. However, the results of the Albumin in Acute Stroke (ALIAS) trials on intravenous albumin in patients with stroke were negative disappointedly. 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.

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. 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. 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.

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.

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). 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 χ² 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 multivariable logistic model and multivariate Cox model. 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). 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 (YJW). 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

| Variable                                      | Overall   | <35        | 35–39.9    | 40–44.9    | ≥45        | P for trend |
|-----------------------------------------------|-----------|------------|------------|------------|------------|-------------|
| Serum albumin, g/L, mean (SD)                 | N=13618   | n=980      | n=5007     | n=5875     | n=1756     |             |
| 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/m², 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) | <0.0001     |
| Coronary heart disease                        | 1432 (10.5)| 126 (12.9) | 556 (11.1) | 611 (10.4) | 139 (7.9)  | 0.00002     |
| 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     |
| 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
| Variable                                      | Overall       | Serum albumin, g/L |     |     |     |     |     |     |     |     |     |     |
|-----------------------------------------------|---------------|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                                               | N=13618       | <35                | 35–39.9 | 40–44.9 | ≥45 |     |     |     |     |     |     |     |
| 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                   | 13,033 (95.7) | 933 (95.2)         | 4789 (95.7) | 5613 (95.9) | 1698 (96.7) | 0.16  |
| Antiplatelet agents                           | 13,142 (96.5) | 938 (95.7)         | 4816 (96.2) | 5684 (96.8) | 1704 (97.0) | 0.12  |
| Anticoagulant agents                          | 13,72 (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 m², 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.
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 (I²=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 (I²=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

**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). Overall, 980 (7.2%) patients were complicated with hypoproteinemia (defined as serum albumin level <35 g/L) at admission. 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 intracranial arterial stenosis and 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).

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**Clinical outcomes**

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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 thrombosis and inpatient medication (antihypertensive agents, anticoagulant agents). ‡Model 3: adjusted for covariables in model 2, plus TG, TC, LDL, ALT, eGFR and CRP at admission. ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density liprotein; 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 (I²=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.3 Meanwhile, participants in our research were generally younger than in previous studies.8,9 Since recent publications reported that the incidence of hypoproteinemina 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...
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 A2 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

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

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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.

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.
benefit from this treatment. Meanwhile, by careful fluid management and diuretic treatment, common complications included pulmonary oedema and heart failure after albumin infusion could be partially controlled. 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 hypoproteinaemia, 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. 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 pre-clinical 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. 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.

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. 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 β1-globulin and α2-globulin, which might cause a positive bias, especially in severe hypoalbuminemia. Meanwhile, the bromocresol purple assay could avoid this effect. Therefore, our study may reduce the proportion of hypoalbuminemia, and weaken the correlation between low serum albumin 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.
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SUPPLEMENTAL MATERIAL

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

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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

CNSR-III: 15166

Serum albumin unknown: 1139
mRS or mortality in 3 months or 1 year unknown: 409

Data completed: 13618

Serum albumin
<35 g/L : 980
Serum albumin
35-39.9 g/L : 5007
Serum albumin
40-44.9 g/L : 5875
Serum albumin
≥45 g/L : 1756

mRS, modified Rankin Scale.
Figure 2. Flowchart on the selection of eligible articles

Articles from PubMed (N=886)  Articles from Scopus (N=1645)  Articles from Embase (N=1826)

Articles identified through database searching (n=4357)

Duplicates removed (n=1781)

Articles screened (n=2576)

Excluded by title and abstract (n=2531)

Full-text articles assessed for eligibility (n=45)

Excluded (n=41)
  • No assessment of relevant outcomes (15)
  • Population not eligible (9)
  • Ineligible exposure measure (8)
  • Not original data (9)

Reference and citation search (n=2)

Included (n=6)
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)

| Study          | TE  | SE  | Weight | Hazard Ratio IV, Fixed, 95% CI | Hazard Ratio IV, Fixed, 95% CI |
|----------------|-----|-----|--------|-------------------------------|-------------------------------|
| Gariballa, 1998 | 0.03| 0.0418 | 6.2%   | 1.03 [0.95, 1.12]             |                               |
| Cater, 2007     | 0.09| 0.0440 | 5.6%   | 1.09 [1.00, 1.19]             |                               |
| Alcázar, 2013   | 0.07| 0.0264 | 15.6%  | 1.07 [1.02, 1.13]             |                               |
| Zhou, 2020      | 0.04| 0.0122 | 72.6%  | 1.04 [1.02, 1.07]             |                               |
| **Total (95% CI)** | **100.0%** | **1.05 [1.03, 1.07]** | 

Heterogeneity: $\tau^2 = 0$; $\chi^2 = 1.97$, df = 3 ($P = 0.58$); $I^2 = 0$

Test for overall effect: $Z = 4.39$ ($P < 0.01$)
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/m², 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 |
|--------------------------|-------------------|------------------|---------|
| 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 m², 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                      |                         |                                   |                             |                       |                                   |                             |
| <70y                            | 1088/10020 (10.9)       | 1.15(0.96-1.38)                   | 0.56                        | 942/10020 (9.4)       | 1.35(1.12-1.62)                   | 0.16                        |
| ≥70y                            | 783/3598(21.7)          | 1.14(0.90-1.45)                   |                             | 843/3598(23.4)        | 1.48(1.17-1.87)                   |                             |
| Sex                             |                         |                                   |                             |                       |                                   |                             |
| Men                             | 1145/9276(12.3)         | 1.19(0.99-1.42)                   | 0.76                        | 1108/9276(11.9)       | 1.46(1.21-1.75)                   | 0.84                        |
| Women                           | 726/4342(16.7)          | 1.15(0.91-1.46)                   |                             | 677/4342(15.6)        | 1.39(1.09-1.77)                   |                             |
| BMI                             |                         |                                   |                             |                       |                                   |                             |
| <18.5 kg/m²                     | 76/295(25.8)            | 0.99(0.42-2.36)                   | 0.88                        | 77/295(26.1)          | 2.39(0.89-6.43)                   | 0.36                        |
| ≥18.5 kg/m²                     | 1795/13323 (13.5)       | 1.16(1.00-1.34)                   |                             | 1708/13323(12.8)      | 1.39(1.20-1.61)                   |                             |
| TOAST Types                     |                         |                                   |                             |                       |                                   |                             |
| Large-artery atherosclerosis    | 686/3441(19.9)          | 1.07(0.84-1.38)                   | 0.89                        | 631/3441(18.3)        | 1.35(1.05-1.75)                   | 0.94                        |
| Cardiembolism                   | 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        |                         |                                   |                             |                       |                                   |                             |
| ≤3                              | 372/7495(5.0)           | 1.22(0.92-1.62)                   | 0.42                        | 442/7495(5.9)         | 1.65(1.28-2.14)                   | 0.13                        |
| 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 ≤10  | 1320/12630(10.5)        | 1.22(1.05-1.42)                   | 0.04                         | 1284/12630(10.2)       | 1.46(1.25-1.70)                   | 0.09                         |
| >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 m²            |                         | 1.11(0.70-1.78)                   |                              |                        | 1.83(1.18-2.84)                   |                              |
| ≥60 mL/min/1.73 m²            | 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 m²            |                         | 1.13(0.89-1.43)                   |                              |                        | 1.68(1.33-2.12)                   |                              |
| ≥90 mL/min/1.73 m²            | 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/fuller), 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**                  |                           |                                    |                             |                         |                                   |                               |
| <70y                            | 82/10020(0.8)             | 1.61(0.93-2.78)                   | 0.35                        | 185/10020(1.9)          | 1.75(1.23-2.49)                   | 0.35                          |
| ≥70y                            | 113/3598(3.14)            | 1.87(1.16-3.04)                   |                             | 245/3598(6.8)           | 1.33(0.96-1.84)                   |                               |
| **Sex**                         |                           |                                    |                             |                         |                                   |                               |
| Men                             | 115/9276(1.2)             | 1.75(1.11-2.77)                   | 0.72                        | 270/9276(2.9)           | 1.50(1.11-2.02)                   | 0.65                          |
| Women                           | 80/4342(1.8)              | 2.00(1.12-3.56)                   |                             | 160/4342(3.7)           | 1.56(1.03-2.35)                   |                               |
| **BMI**                         |                           |                                    |                             |                         |                                   |                               |
| <18.5 kg/m²                     | 16/295(5.4)               | 2.43(0.30-19.55)                  | 0.48                        | 27/295(9.2)             | 5.23(1.18-23.22)                  | 0.19                          |
| ≥18.5 kg/m²                     | 179/13323(1.3)            | 1.09(0.99-1.21)                   |                             | 403/13323(3.0)          | 1.49(1.16-1.91)                   |                               |
| **TOAST Types**                 |                           |                                    |                             |                         |                                   |                               |
| Large-artery atherosclerosis    | 62/3441(1.8)              | 1.91(1.01-3.61)                   | 0.80                        | 135/3441(3.9)           | 1.43(0.91-2.24)                   | 0.21                          |
| 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**    |                           |                                    |                             |                         |                                   |                               |
| ≤3                              | 57/7495(0.8)              | 1.64(0.85-3.16)                   | 0.40                        | 131/7495(1.8)           | 1.26(0.82-1.93)                   | 0.11                          |
| >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   |                           |                                   |                             |                         |                                   |                             |
| ≤10                        | 116/12630(0.92)           | 2.45(1.56-3.85)                   | 0.02                        | 296/12630(2.34)         | 1.60(1.20-2.13)                   | 0.18                        |
| >10                        | 79/988(8.00)              | 1.03(0.59-1.78)                   |                             | 134/988(13.56)         | 1.15(0.75-1.75)                   |                             |
| eGFR                       |                           |                                   |                             |                         |                                   |                             |
| <60 mL/min/1.73 m²         | 24/718(3.34)              | 0.98(0.30-3.20)                   | 0.34                        | 60/718(8.36)            | 1.33(0.72-2.45)                   | 0.87                        |
| ≥60 mL/min/1.73 m²         | 119/8896(1.34)            | 1.94(1.21-3.10)                   |                             | 248/8896(2.79)         | 1.46(1.05-2.02)                   |                             |
| eGFR                       |                           |                                   |                             |                         |                                   |                             |
| <90 mL/min/1.73 m²         | 92/3978(2.31)             | 1.82(1.10-3.02)                   | 0.37                        | 206/3978(5.18)         | 1.53(1.09-2.15)                   | 0.93                        |
| ≥90 mL/min/1.73 m²         | 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/fulller), 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                               | 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, 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, 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. 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, 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, 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 | No. 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) |
|--------------|---------|----------------|-------------|-----------|-------|---------------|-----------|---------------------|-------------------|-------------|------------------------|-------------------------------|
| 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) | mechanism, coma, DBP, Canadian scale score on admission | 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) | OR:1.04(1.02-1.07) | OR: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

| Study               | Selection | Comparability | Outcome | Total |
|---------------------|-----------|---------------|---------|-------|
| Gariballa SE et al⁵ | *         | *             | *       | 9     |
| Dziedzic T et al⁶   | *         | *             | *       | 9     |
| Carter AM et al²    | *         | *             | *       | 9     |
| Idicula TT et al⁴   | *         | *             | *       | 8     |
| Alcázar Lázaro V et al³ | *     | *             | *       | 9     |
| Babu MS et al³      | *         | *             | *       | 9     |

The Newcastle-Ottawa Quality Scale (NOS) assesses the quality of prospective studies based on the following criteria:

- **Selection**: Representativeness of the exposed cohort, Selection of the non-exposed cohort, Ascertainment of exposure, Outcome not present at baseline
- **Comparability**: Adjustments i) age ii) additional factors, Assessment of outcome, Length of follow-up
- **Outcome**: Adequate follow-up

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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              | 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                                                                              |
| Table Title                      | Number | Description                                                                                                                                                                                                 | Source                           |
|---------------------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| 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      |
| Supplemental Material | Page 22 |
|-----------------------|---------|
| **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 |
| Supplemental Material | Online supplementary figure 4 |
|-----------------------|-----------------------------|
| **Additional analysis** | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | None. |
| **DISCUSSION** | | |
| Summary of evidence | 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 | 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 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Page 14 Paragraph 2 |
| **FUNDING** | | |
| Funding | 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 |
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