Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Serum Prealbumin Levels and Risks of Adverse Clinical Outcomes After Ischemic Stroke

Mengyao Shi[1,*], Xueyu Mao[2,*], Xuechun Wu[2], Min Chu[2], Huicong Niu[2], Lulu Sun[1], Xinyue Chang[1], Yu He[1], Yi Liu[1], Daoxia Guo[3], Yonghong Zhang[1], Zhengbao Zhu[1], Jing Zhao[2,4]

[1]Department of Epidemiology, School of Public Health, Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, MOE Key Laboratory of Geriatric Diseases and Immunology, Suzhou Medical College of Soochow University, Suzhou, People's Republic of China; [2]Department of neurology, Minhang Hospital, Fudan University, Shanghai, People's Republic of China; [3]School of Nursing, Suzhou Medical College of Soochow University, Suzhou, People's Republic of China; [4]Institute of Healthy Yangtze River Delta, Shanghai Jiao Tong University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jing Zhao, Department of Neurology, Minhang Hospital, Fudan University, Shanghai, People's Republic of China, Email zhao_jing@fudan.edu.cn; Zhengbao Zhu, Department of Epidemiology, School of Public Health and Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Suzhou Medical College of Soochow University, 199 Renai Road, Industrial Park District, Suzhou, Jiangsu Province, 215123, People's Republic of China, Email zbzhu@suda.edu.cn

Background: Prealbumin is a symbol of protein nutrition and is involved in anti-inflammatory and neuron regeneration, but its association with the prognosis of ischemic stroke remains unclear. We aimed to prospectively explore the associations between serum prealbumin levels and adverse clinical outcomes after ischemic stroke in a large-scale cohort study.

Methods: We measured serum prealbumin levels among 6609 ischemic stroke patients admitted at Minhang hospital. The primary outcome was composite of death and major disability (modified Rankin Scale [mRS] score ≥ 3) at 3 months after stroke onset, and secondary outcomes included death and the ordered 7-level categorical score of mRS.

Results: During 3 months of follow-up, a total of 2118 patients developed the primary outcome. After multivariable adjustment, high prealbumin levels were associated with a decreased risk of primary outcome (odds ratio, 0.71; 95% CI, 0.59–0.85; P_{trend}< 0.0001) when 2 extreme quartiles were compared. Each unit increase of log-transformed prealbumin was associated with a 42% (95% CI, 28-53%) decreased risk of primary outcome. There was a better shift in the distribution of mRS score at 3 months with higher quartiles of serum prealbumin in ischemic stroke patients (P_{trend}< 0.0001). Multivariable-adjusted spline regression model showed a linear relationship between prealbumin and the risk of primary outcome (P for linearity = 0.0036).

Conclusion: High serum prealbumin level was independently associated with decreased risks of adverse clinical outcomes among ischemic stroke patients. Our findings suggested that prealbumin may be a valuable prognostic biomarker and indicated the importance of keeping nourished in the daily life.

Keywords: prealbumin, ischemic stroke, prognosis, cohort study

Background

Stroke is the third most common causes of mortality and disability combined globally.[1] With the aging population and accumulating environmental risk factors, the absolute number of incident strokes increased by 70% in the past three decades.[1] Consistent with the global trend, stroke is a major public health challenge in China. As estimated by national representative surveys, there were about 3.4 million incident stroke cases in 2020,[2] causing 2.3 million deaths and about 12.5% survivors were left disabled.[3] More than 85% of stroke cases were ischemic stroke.[3] Therefore, it is crucial to identify novel blood biomarkers that could aid in a better understanding of the ischemic stroke pathogenesis and provide new insights into potential preventive strategies.

Prealbumin, also named transthyretin, is synthesized in liver and serves as the transport protein for thyroxine and vitamin A.[4] Due to its short half-life (2 to 3 days), prealbumin has been proposed as a sensitive and accurate marker for nutritional balance.[5] Besides this, previous studies have found that prealbumin is actively involved in multiple biological

Received: 24 April 2024
Accepted: 20 September 2024
Published: 9 October 2024

processes, including anti-inflammatory response,[6,7] cleavage of neuropeptide,[8,9] and neuron regeneration after brain injury.[10,11] These biological features indicated that prealbumin may be implicated in the prognosis of ischemic stroke. Prospective studies have reported that high prealbumin levels were associated with good prognosis at discharge[12] and lower 1-year mortality rate among stroke patients.[13] Consistently, lower prealbumin level was related to worse clinical outcomes at 3 months in stroke patients treated with thrombolysis or mechanical thrombectomy.[14,15] Of note, the existing studies were based on relatively small sample sizes and several important prognostic factors (eg stroke subtype, time from onset to hospitalization, and personal medical history) were not considered. Therefore, the evidence for the association between serum prealbumin and the prognosis of ischemic stroke was limited.

To fill these gaps, well-designed large-scale prospective studies with comprehensive information about potential confounders are needed to extend our knowledge on the associations between prealbumin and prognosis of ischemic stroke. Herein, we prospectively explore the associations of serum prealbumin levels at admission with death and major disability at 3 months among 6609 ischemic stroke patients from Minhang Stroke Cohort.

Methods

Study Participants

The study participants in the present study were from the Minhang Stroke Cohort study, which was a prospective cohort study for ischemic stroke patients presenting to Minhang hospital in Shanghai, China. Briefly, from January 2018 to December 2022, a total of 7323 consecutive patients aged ≥18 years with a clinical diagnosis of ischemic stroke were enrolled from the Department of Neurology at Minhang hospital. Diagnosis of ischemic stroke was made according to World Health Organization criteria based on patient history and clinical data, and was confirmed by computed tomography scan or magnetic resonance imaging. Additional exclusion criteria were as follows: (1) time from onset to admission over 7 days (n = 263) and (2) diagnosis of cancer (n = 168). A total of 6892 eligible patients were enrolled in Minhang Stroke Cohort. For the present study, 283 patients were further excluded because of lack of serum prealbumin level at baseline, and 6609 patients were finally included.

Data Collection

Baseline data on demographic characteristics, clinical features, medical history, and imaging data were collected at the time of enrollment using a standard questionnaire. Information on these factors was obtained through face-to-face interviews by a trained interviewer. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) by trained neurologists during hospital admission.[16] Three blood pressure (BP) measurements were obtained at admission by trained nurses using a standard mercury sphygmomanometer according to a standard protocol adapted from procedures recommended by the American Heart Association.[17] Based on the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria,[18] ischemic stroke was classified as large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology according to the symptoms and imaging data of the patients. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L, history of diabetes, or use of glucose-lowering medications.[19] Dyslipidemia was defined as triglyceride ≥2.26 mmol/L, total cholesterol ≥6.22 mmol/L, low-density lipoprotein cholesterol ≥4.14 mmol/L, high-density lipoprotein cholesterol <1.04 mmol/L, history of dyslipidemia, or use of lipid-lowering medications according to Chinese guidelines on the prevention and treatment of dyslipidemia.[20]

Fasting blood samples were collected after at least 8 hours of fasting within 24 hours of hospital admission. All serum and plasma samples were separated and immediately frozen at −80°C until laboratory testing. Routine laboratory determinations (blood glucose, blood lipids, etc) were performed for all enrolled patients at Minhang hospital. Serum prealbumin concentration at baseline was measured with a Cobas 8000 automatic analyzer (Roche Diagnostics, Indianapolis, Indiana). Laboratory technicians who performed these measurements were blind to the clinical characteristics and outcomes of the study participants.

Outcome Assessment

Participants were followed up in person at 3 months after ischemic stroke by trained neurologists. The primary outcome was the composite of death and major disability (modified Rankin Scale [mRS] score, 3–6) at 3 months after ischemic

stroke. The secondary outcome was death, and death certificates were obtained for deceased patients. We also included an ordered 7-level categorical score of the mRS as a secondary outcome for neurological functional status based on the recommendation from the European Stroke Organization Outcomes Working Group.[21] All study outcomes were reviewed and adjudicated by the outcome assessment committee that was blinded to participants' clinical characteristics.

Statistical Analysis

Baseline characteristics of the study participants were presented according to the quartiles of baseline serum prealbumin levels. Tests for linear trend of baseline characteristics across prealbumin quartiles were performed using the generalized linear regression analysis for continuous variables and the Cochran-Armitage trend χ^2 test for categorical variables. Multivariable logistic regression analyses were used to assess the associations between serum prealbumin and adverse outcomes after ischemic stroke. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for higher quartiles of prealbumin compared with the lowest quartile and for each SD increment of log-transformed prealbumin. Important covariates for adverse outcomes after ischemic stroke were selected based on our prior knowledge. The covariates included in the multivariable models were age, sex, smoking, drinking, education, time from onset to hospitalization, baseline body mass index, baseline NIHSS score, baseline systolic BP, diabetes, dyslipidemia, history of hypertension, family history of stroke, ischemic stroke subtypes, intravenous thrombolysis and mechanical thrombectomy. The effects of serum prealbumin on mRS shift were analyzed using multivariable ordinal logistic regression model with adjustment for the aforementioned variables.

We further used restricted cubic splines to provide more precise estimates and to explore the shapes of the associations between serum prealbumin and adverse outcomes after ischemic stroke, with 4 knots defined at the 5th, 35th, 65th, and 95th percentiles of prealbumin.[22] In addition, subgroup analyses were carried out to investigate the effect modification of age, sex, smoking, drinking, time from onset to hospitalization, baseline systolic BP, and baseline NIHSS score on the associations between serum prealbumin and prognosis of ischemic stroke. Interactions between serum prealbumin and subgroup variables on the primary outcome were tested in the models with interaction terms by the likelihood ratio test, adjusting for the aforementioned covariates. Two-tailed $P<0.05$ was considered to be statistically significant. All statistical analyses were performed with SAS software version 9.4 (Cary, NC).

Results

Baseline Characteristics

The flow-chart of the current study was shown as Supplementary Figure 1. All baseline characteristics were well balanced between participants who were assayed for serum prealbumin and all participants in Minhang Stroke Cohort (Supplementary Table 1), indicating that those assayed could represent the total participants of Minhang Stroke Cohort. A total of 6609 patients (4200 males and 2409 females) were included in the present study, and the average age was 70 years. The median serum prealbumin level was 218 mg/L (interquartile range, 180–251 mg/L). Compared with patients with lower prealbumin level, patients with higher prealbumin level were more likely to be younger, male, drinker, and smoker; have higher education, systolic BP, diastolic BP, total cholesterol, triglyceride, and low-density lipoprotein cholesterol; have longer time from onset to hospitalization; have higher prevalence of history of dyslipidemia, family history of stroke, large-artery atherosclerosis stroke, small-vessel occlusion stroke, stroke of other determined etiology, and intravenous thrombolysis; have lower body mass index, high-density lipoprotein cholesterol and NIHSS score; and have lower prevalence of history of diabetes, cardioembolism stroke, and mechanical thrombectomy (Table 1).

Serum Prealbumin Levels and Clinical Outcomes

Within 3 months after ischemic stroke, 474 participants (7.17%) were lost to follow-up. As shown in Supplementary Table 2, most of the baseline characteristics were well balanced between participants who had complete follow-up and participants who lost to follow-up. Among the remaining 6135 participants, a total of 2118 participants (34.5%) developed the primary outcome (671 deaths and 1447 major disabilities) (Table 2). The cumulative incidence rates of primary outcome at 3 months from the lowest quartile to the highest quartile of prealbumin were 50.51%, 35.31%, 29.97% and 23.18%, respectively ($P <$

Table 1 Baseline Characteristics of the Study Participants According to the Quartiles of Serum Prealbumin

Characteristics*	Prealbumin (mg/L)				P_{trend}
	<180	180–217	218–251	≥252	
No. of patients	1627	1673	1610	1699	
Demographics					
Age, y	78.66 (10.58)	71.98 (11.61)	67.49 (11.16)	62.47 (11.76)	<0.0001
Male	830 (51.01)	973 (58.16)	1081 (67.14)	1316 (77.46)	<0.0001
Drinking	57 (3.50)	103 (6.16)	165 (10.25)	322 (18.95)	<0.0001
Smoking	142 (8.73)	279 (16.68)	398 (24.72)	520 (30.61)	<0.0001
Education					
Less than high school	1157 (71.11)	1137 (67.96)	1013 (62.92)	1059 (62.33)	<0.0001
High school graduate	305 (18.75)	329 (19.67)	376 (23.35)	389 (22.90)	0.0003
College graduate or higher	165 (10.14)	207 (12.37)	221 (13.73)	251 (14.77)	<0.0001
Medical history					
History of diabetes	520 (31.93)	545 (32.58)	484 (30.06)	496 (29.19)	0.0323
History of hypertension	1052 (64.66)	1104 (65.99)	1061 (65.90)	1118 (65.80)	0.5280
History of dyslipidemia	7 (0.43)	10 (0.60)	10 (0.62)	28 (1.65)	0.0002
Family history of stroke	12 (0.74)	14 (0.84)	23(1.43)	28 (1.65)	0.0048
Clinical features					
Time from onset to hospitalization, h	6.50 (2.17–25.75)	7.92 (2.20–26.37)	8.15 (2.17–28.50)	9.58 (2.50–29.05)	0.0002
BMI, kg/m^2	23.51 (3.78)	24.25 (3.58)	24.54 (3.45)	24.94 (3.48)	<0.0001
Systolic BP, mm Hg	142.63 (21.81)	143.69 (21.57)	143.43 (19.61)	144.69(20.74)	0.0101
Diastolic BP, mm Hg	79.77 (11.55)	81.55 (11.57)	82.06 (11.15)	84.08 (11.80)	<0.0001
FPG, mmol/L	5.80 (4.90–7.60)	5.70 (4.90–7.70)	5.60 (4.90–7.26)	5.60 (5.00–7.10)	0.1861
Total cholesterol, mmol/L	3.78 (3.12–4.41)	4.16 (3.46–4.84)	4.28 (3.68–4.97)	4.49 (3.87–5.19)	<0.0001
Triglyceride, mmol/L	1.07 (0.83–1.38)	1.27 (0.97–1.68)	1.47 (1.13–1.97)	1.78 (1.34–2.47)	<0.0001
LDL-C, mmol/L	2.37 (1.82–3.00)	2.77 (2.15–3.37)	2.86 (2.29–3.54)	2.99 (2.40–3.64)	<0.0001
HDL-C, mmol/L	1.09 (0.90–1.30)	1.06 (0.90–1.28)	1.03 (0.88–1.24)	1.03 (0.88–1.22)	<0.0001
NIHSS score	4.00 (2.00–10.00)	3.00 (1.00–5.00)	3.00 (1.00–5.00)	2.00 (1.00–4.00)	<0.0001
Stroke subtype					
Large-artery atherosclerosis	866 (53.23)	1025 (61.27)	1011(62.80)	1062 (62.51)	<0.0001
Cardioembolism	398 (24.46)	241 (14.41)	160 (9.94)	84 (4.94)	<0.0001
Small-vessel occlusion	322 (19.79)	380 (22.71)	398 (24.72)	598 (29.31)	<0.0001
Stroke of other determined etiology	4 (0.25)	5 (0.30)	8 (0.50)	11 (0.65)	0.0485
Stroke of undetermined etiology	37 (2.27)	22 (1.32)	33 (2.05)	44 (2.59)	0.2648
Endovascular treatment					
Intravenous thrombolysis	132 (8.11)	159 (9.50)	170 (10.56)	179 (10.54)	0.0109
Mechanical thrombectomy	109 (6.70)	92 (5.50)	80 (4.97)	56 (3.30)	<0.0001

Notes: *Continuous variables are expressed as mean ± SD or as median (interquartile range). Categorical variables are expressed as frequency (%).
Abbreviations: BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NIHSS, NIH Stroke Scale.

0.0001). After adjusting for age, sex, baseline NIHSS score, and other important prognostic factors, the ORs associated with highest quartile of prealbumin were 0.71 (95% CI, 0.59–0.85; P_{trend}= 0.0006) for primary outcome and 0.36 (95% CI, 0.25–0.49; P_{trend}<0.0001) for death. On continuous analyses, each unit increase of log-transformed prealbumin was associated with a 42% (95% CI, 28–53%) decreased risk of primary outcome and a 74% (95% CI, 65–80%) decreased risk of death. Multivariable ordinal logistic regression analyses showed a significantly better shift in the distribution of mRS score at 3 months with higher quartiles of serum prealbumin in ischemic stroke patients (P_{trend}< 0.0001; Figure 1). In addition, multivariable-adjusted restricted cubic spline analyses showed linear associations of serum prealbumin with primary outcome (P for linearity = 0.0036) and death (P for linearity < 0.0001) (Figure 2).

We further conducted subgroup analyses to examine potential modified effect of age, sex, smoking, drinking, time from onset to hospitalization, baseline systolic BP, and baseline NIHSS score on the association between serum prealbumin and primary outcome. In subgroup analyses, we found that high serum prealbumin level was significantly

Table 2 Associations Between Serum Prealbumin Level and Adverse Outcomes at 3 Months After Ischemic Stroke

	Prealbumin (mg/L)				P_{trend}	Each Unit Increase In Log-Prealbumin
	<180	180–217	218–251	≥252		
Primary outcome: death or majordisability (mRS score 3–6)						
Cases, N (%)	747 (50.51)	549 (35.31)	455 (29.97)	367 (23.18)		2118 (34.52)
Unadjusted OR	1.00 (reference)	0.54 (0.46, 0.62)	0.42 (0.36, 0.49)	0.30 (0.25, 0.35)	<0.0001	0.20 (0.17, 0.25)
Multiple-adjusted OR*	1.00 (reference)	0.81 (0.69, 0.95)	0.81 (0.69, 0.96)	0.71 (0.59, 0.85)	0.0006	0.58 (0.47, 0.72)
Secondary outcomes						
Death						
Cases, N (%)	363 (24.54)	164 (10.35)	82 (6.06)	55 (3.47)		671 (10.94)
Unadjusted OR	1.00 (reference)	0.36 (0.29, 0.43)	0.20 (0.16, 0.25)	0.11 (0.08, 0.15)	<0.0001	0.09 (0.07, 0.11)
Multiple-adjusted OR*	1.00 (reference)	0.58 (0.46, 0.72)	0.45 (0.34, 0.59)	0.36 (0.25, 0.49)	<0.0001	0.26 (0.20, 0.35)
Modified Rankin Scale score						
Unadjusted OR†	1.00 (reference)	0.50 (0.44, 0.57)	0.38 (0.33, 0.43)	0.32 (0.28, 0.36)	<0.0001	0.20 (0.17, 0.23)
Multiple-adjusted OR*†	1.00 (reference)	0.77 (0.67, 0.87)	0.72 (0.63, 0.83)	0.75 (0.65, 0.87)	0.0003	0.56 (0.47, 0.66)

Notes: *Adjusted for age, sex, smoking, drinking, education, time from onset to hospitalization, baseline body mass index, baseline NIHSS score, baseline systolic blood pressure, diabetes, dyslipidemia, history of hypertension, family history of stroke, ischemic stroke subtype, intravenous thrombolysis and mechanical thrombectomy. † Odds of 1-unit higher modified Rankin Scale score.

associated with a decreased risk of primary outcome in most subgroups (Table 3). There was no significant interaction between serum prealbumin levels and these subgroup factors in the risk of primary outcome (all $P_{interaction} > 0.05$).

Discussion

In this large-scale prospective study, we found linear dose–response associations between serum prealbumin and adverse outcomes after ischemic stroke. Ischemic stroke patients in the highest quartile of serum prealbumin level at baseline was associated with a 29% decreased risk of the composite outcome of death and major disability at 3 months compared with those in the lowest quartile. This linear dose–response relationship was independent of traditional prognostic factors for ischemic stroke, and subgroup analyses further confirmed these findings. These findings suggested that serum prealbumin might play an important role in the prognosis of ischemic stroke.

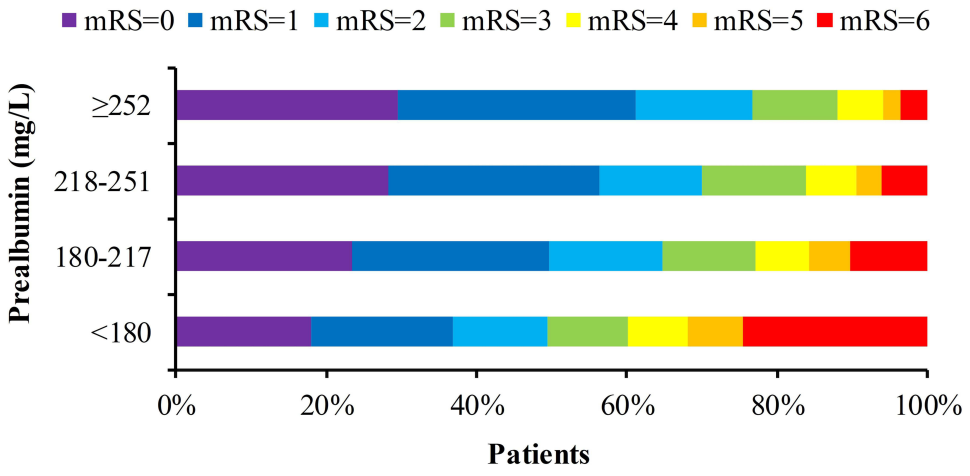

Figure 1 Distribution of 3-month mRS score according to prealbumin quartiles in ischemic stroke patients. Multivariable-adjusted odds ratio of ordinal logistic regression analysis was 0.71 (95% CI, 0.59, 0.85) for patients in the highest quartile of serum prealbumin compared with the patients in the lowest quartile (*P* for trend < 0.0001). Multivariable model adjusted for age, sex, smoking, drinking, education, time from onset to hospitalization, baseline body mass index, baseline NIHSS score, baseline systolic blood pressure, diabetes, dyslipidemia, history of hypertension, family history of stroke, ischemic stroke subtype, intravenous thrombolysis and mechanical thrombectomy.

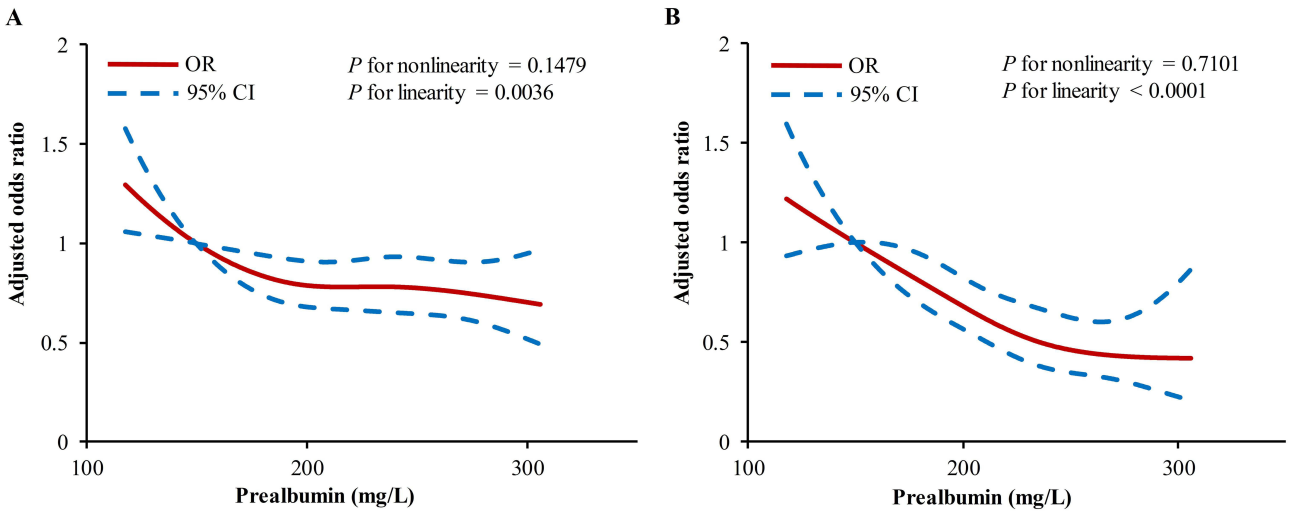

Figure 2 Associations between serum prealbumin at baseline and adverse outcomes at 3 months among patients with ischemic stroke. Adjusted odds ratios and 95% CIs derived from restricted cubic spline regression, with knots placed at the 5th, 35th, 65th, and 95th percentiles of serum prealbumin levels. Odds ratios were adjusted for age, sex, smoking, drinking, education, time from onset to hospitalization, baseline body mass index, baseline NIHSS score, baseline systolic blood pressure, diabetes, dyslipidemia, history of hypertension, family history of stroke, ischemic stroke subtype, intravenous thrombolysis and mechanical thrombectomy. (**A**) Death or major disability; (**B**) death.

To date, there is limited research on the role of serum prealbumin in ischemic stroke prognosis. In an analysis based on the 585 young cerebral infarction patients, serum prealbumin at baseline was an independent predictor of good functional outcome at discharge.[12] One study explored the association between prealbumin and long-term prognosis

Table 3 Subgroup Analyses of the Association Between Serum Prealbumin and the Primary Outcome

Subgroup	No. of Outcomes/Patients (%)	Prealbumin (mg/L)				$P_{interaction}$
		<180	180–217	218–251	≥252	
Age, y						
<65	366/1856 (19.72)	Ref.	1.00 (0.61, 1.64)	0.84 (0.52, 1.36)	0.69 (0.43, 1.11)	0.5578
≥65	1752/4279 (40.94)	Ref.	0.68 (0.58, 0.81)	0.66 (0.55, 0.79)	0.55 (0.45, 0.67)	
Sex						
Female	919/2236 (41.10)	Ref.	0.91 (0.72, 1.16)	0.91 (0.70, 1.19)	0.87 (0.64, 1.18)	0.5929
Male	1199/3899 (30.75)	Ref.	0.74 (0.60, 0.92)	0.76 (0.61, 0.96)	0.64 (0.50, 0.81)	
Smoking						
No	1834/4876 (37.61)	Ref.	0.81 (0.69, 0.96)	0.85 (0.70, 1.02)	0.73 (0.60, 0.90)	0.3338
Yes	284/1259 (22.56)	Ref.	0.72 (0.44, 1.18)	0.65 (0.40, 1.06)	0.58 (0.35, 0.97)	
Drinking						
No	1972/5528 (35.67)	Ref.	0.81 (0.69, 0.95)	0.80 (0.68, 0.96)	0.71 (0.58, 0.86)	0.6394
Yes	146/607 (24.05)	Ref.	0.37 (0.16, 0.82)	0.42 (0.19, 0.90)	0.35 (0.17, 0.74)	
Time from onset to hospitalization, h						
<12	1282/3526 (36.36)	Ref.	0.89 (0.72, 1.10)	0.88 (0.71, 1.10)	0.73 (0.57, 0.93)	0.0577
≥12	836/2609 (32.04)	Ref.	0.68 (0.53, 0.88)	0.70 (0.54, 0.92)	0.68 (0.51, 0.90)	
Baseline systolic BP, mm Hg						
<160	1543/4712 (32.75)	Ref.	0.77 (0.64, 0.92)	0.80 (0.66, 0.97)	0.69 (0.56, 0.86)	0.3335
≥160	575/1423 (40.41)	Ref.	0.97 (0.69, 1.35)	0.92 (0.64, 1.33)	0.80 (0.55, 1.16)	
Baseline NIHSS score						
<4	925/3293 (25.74)	Ref.	0.94 (0.75, 1.17)	0.87 (0.69, 1.11)	0.75 (0.58, 0.97)	0.8456
≥4	1193/2542 (47.93)	Ref.	0.63 (0.51, 0.79)	0.67 (0.53, 0.86)	0.59 (0.45, 0.77)	

Notes: Adjusted for age, sex, smoking, drinking, education, time from onset to hospitalization, baseline body mass index, baseline NIHSS score, baseline systolic blood pressure, diabetes, dyslipidemia, history of hypertension, family history of stroke, ischemic stroke subtype, intravenous thrombolysis and mechanical thrombectomy, unless the variable was used as a subgroup variable.

among 81 ischemic stroke patients and Kaplan–Meier survival analysis revealed that patients with higher baseline prealbumin had lower 1-year mortality rate.[13] Another study of 234 ischemic stroke patients undergoing intravenous thrombolysis showed that higher globulin-to-prealbumin ratio was associated with worse functional outcome at 3 months.[14] Similarly, in another cohort of 319 stroke patients treated with mechanical thrombectomy, low prealbumin levels were independently associated with higher risk of death at 3 months.[15] In addition, Ye et al analyzed the data of 104 consecutive ischemic stroke patients and suggested that lower serum prealbumin level was associated with a higher rate of infection after stroke.[23] Meanwhile, He et al recruited 637 ischemic stroke patients and found that prealbumin levels were inversely associated with intracranial atherosclerotic stenosis lesions.[24]

Different from the existing literatures, the current study was based on Minhang Stroke Cohort, a prospective study with over 6000 ischemic stroke patients. The large sample size guaranteed the statistical power of the analyses. Furthermore, the restricted cubic spline analyses confirmed the inverse linear association between baseline prealbumin and poor prognosis. Standardized protocols and rigid quality control procedures were also used for data collection and outcome assessment. Thus, comprehensive information about potential confounders was collected and controlled for in the multivariable models to ensure the independence of the observed associations. Additionally, the subgroup analysis proved the robustness of the results. In a word, the method used in this study was appropriate and rigorous, and our study will provide a more valid appraisal of the association between serum prealbumin and adverse outcomes among ischemic stroke patients.

Low prealbumin level was closely related to malnutrition and was a useful indicator of lean body mass among elderly subjects.[25,26] As a symbol of nutrition status and frailty, low prealbumin levels have been reported to be associated with poor prognosis of multiple diseases.[27–30] In real life, malnutrition is a common and unrecognized problem among elder population.[31,32] As estimated by the Third China National Stroke Registry, the prevalence of malnutrition risk ranged from 16% to 58% among Chinese ischemic stroke patients.[33] Consistently, our results also found that serum prealbumin levels were significantly lower in ischemic stroke patients with older ages, especially among female patients. Despite the importance of maintaining adequate nutrition, randomized control trials studies have found that neither albumin supplementation alone[34,35] nor composite nutritional therapies[36] after disease could successfully improve clinical outcomes among severely ill patients. On the other side, these disappointing results might indicate the importance of keeping nourished in the daily life and highlighted the importance of routine evaluation of nutrition status among elder population.

Additionally, previous studies have suggested that serum prealbumin is actively involved in the anti-inflammation responses via cytokine network.[6,7] Data from animal studies also indicated that prealbumin could reduce the risk of cardiovascular diseases through the cleavage of neuropeptide Y, a neuropeptide that involved in the increased platelet aggregation and macrophage activation.[8,9,37] Furthermore, animal models of middle cerebral artery occlusion (MCAO) proved that serum prealbumin was directly involved in nerve regeneration and could repair the function of injured neurons.[38,39] Finally, thyroxine can enhance recovery of lost neurological functions after ischemic stroke,[40,41] and vitamin A has properties of anti-oxidation and anti-inflammation.[42,43] As the transport protein for thyroxine and vitamin A, prealbumin level may inhibit oxidative stress and inflammation, and thus improve neurological impairment. These biological mechanisms supported the observed protective effect of prealbumin, and prealbumin might serve as a biomarker to help early select ischemic stroke patients at high risk of poor prognosis.

Our study has several limitations that need to be considered. First, although multiple important confounders have been controlled in the multivariable analysis, there is also a possibility of residual confounding in our observational study. Second, serum prealbumin level was only measured once at admission, so we were unable to investigate the influence of thrombolysis or mechanical thrombectomy on prealbumin, and we could not explore the effect of prealbumin changes on ischemic stroke prognosis. Further studies are needed to investigate this issue. Third, we only followed up participants once at 3 months after stroke, so we could not assess the association of baseline prealbumin with the long-term prognosis of stroke. Fourth, all patients in the current study were Chinese, so prospective studies conducted among different populations are needed to replicate our findings.

Conclusion

High serum prealbumin level was independently associated with decreased risks of adverse clinical outcomes among ischemic stroke patients. Our findings suggested that serum prealbumin may be a useful prognostic biomarker for ischemic stroke and avoiding undernourished may be a valuable preventive strategy among elder population.

Data Sharing Statement

The data that support the findings of this study and additional data are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Minhang Hospital (IRB:008-01K). The patients or their immediate family members were fully informed about the purpose of the study and signed the informed consents, in accordance with the Declaration of Helsinki.

Acknowledgments

We thank the study participants and their relatives and the clinical staff at all participating hospitals for their support and contribution to this project.

Funding

JZ was supported by the National Natural Science Foundation of China (grant: 81973157 and 82173646) and Public Health Discipline Construction project of Shanghai Minhang District Health Commission (grant: MGWXK2023-04); XW was supported by the Clinic Youth Talent Fund of Minhang Hospital, Fudan University (grant: 2021MHLC01); HN was supported by Fundamental Medical Project of Minhang Hospital of Fudan University Project Foundation (grant: 2023MHBJ02); ZZ was supported by the National Natural Science Foundation of China (grant: 82103917); MS was supported by the Jiangsu Funding Program for Excellent Postdoctoral Talent; DG was supported by the Natural Science Foundation of Jiangsu Province (grant: BK20210716).

Disclosure

None of the authors have any competing interests.

References

1. Valery LF, Stark BA, Catherine OJ, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795–820. doi:10.1016/s1474-4422(21)00252-0
2. Tu WJ, Zhao Z, Yin P, et al. Estimated Burden of Stroke in China in 2020. *JAMA Network Open*. 2023;6:e231455. doi:10.1001/jamanetworkopen.2023.1455
3. Tu WJ, Wang LD. China stroke surveillance report 2021. *Mil Med Res*. 2023;10(1):33. doi:10.1186/s40779-023-00463-x
4. Keller U. Nutritional Laboratory Markers in Malnutrition. *J Clin Med*. 2019;8(6):775. doi:10.3390/jcm8060775
5. Davis CJ, Sowa D, Keim KS, Kinnare K, Peterson S. The use of prealbumin and C-reactive protein for monitoring nutrition support in adult patients receiving enteral nutrition in an urban medical center. *JPEN J Parenter Enteral Nutr*. 2012;36(2):197–204. doi:10.1177/0148607111413896
6. Lögdberg L, Wester L. Immunocalins: a lipocalin subfamily that modulates immune and inflammatory responses. *Biochim Biophys Acta*. 2000;1482(1–2):284–297. doi:10.1016/s0167-4838(00)00164-3
7. Wang L, Xu H, Ren W, et al. Low serum prealbumin levels in post-stroke depression. *Psychiatry Res*. 2016;246:149–153. doi:10.1016/j.psychres.2016.09.021
8. Nunes AF, Saraiva MJ, Sousa MM. Transthyretin knockouts are a new mouse model for increased neuropeptide Y. *FASEB j*. 2006;20(1):166–168. doi:10.1096/fj.05-4106fje
9. Liz MA, Fleming CE, Nunes AF, et al. Substrate specificity of transthyretin: identification of natural substrates in the nervous system. *Biochem J*. 2009;419(2):467–474. doi:10.1042/bj20082090
10. Fleming CE, Mar FM, Franquinho F, Saraiva MJ, Sousa MM. Transthyretin internalization by sensory neurons is megalin mediated and necessary for its neuritogenic activity. *J Neurosci*. 2009;29(10):3220–3232. doi:10.1523/jneurosci.6012-08.2009
11. Fleming CE, Saraiva MJ, Sousa MM. Transthyretin enhances nerve regeneration. *J Neurochem*. 2007;103(2):831–839. doi:10.1111/j.1471-4159.2007.04828.x
12. Gao C, Zhang B, Zhang W, Pu S, Yin J, Gao Q. Serum prealbumin (transthyretin) predict good outcome in young patients with cerebral infarction. *Clin Exp Med*. 2011;11(1):49–54. doi:10.1007/s10238-010-0103-8

13. Ambrosius W, Michalak S, Kazmierski R, Andrzejewska N, Kozubski W. Predictive value of serum transthyretin for outcome in acute ischemic stroke. *PLoS One*. 2017;12:e0179806. doi:10.1371/journal.pone.0179806
14. Li C, Yang C, Zhu J, et al. Predictive Value of Globulin to Prealbumin Ratio for 3-Month Functional Outcomes in Acute Ischemic Stroke Patients. *Dis Markers*. 2022;2022:1120192. doi:10.1155/2022/1120192
15. López B, Castañón-Apilánez M, Molina-Gil J, et al. Serum Prealbumin Levels on Admission as a Prognostic Marker in Stroke Patients Treated with Mechanical Thrombectomy. *Cerebrovasc Dis Extra*. 2022;12(3):103–108. doi:10.1159/000526354
16. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864–870. doi:10.1161/01.str.20.7.864
17. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111(5):697–716. doi:10.1161/01.Cir.0000154900.76284.F6
18. Adams HP Jr, 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(1):35–41. doi:10.1161/01.str.24.1.35
19. Association. Standards of medical care in diabetes--2010. *Diabetes Care*. 2010;33(Suppl 1):S11–61. 10.2337/dc10-S011
20. Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults. 2007;35(5)390–419.
21. Bath PM, Lees KR, Schellinger PD, et al. Statistical analysis of the primary outcome in acute stroke trials. *Stroke*. 2012;43(4):1171–1178. doi:10.1161/strokeaha.111.641456
22. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8(5):551–561. doi:10.1002/sim.4780080504
23. Ye S, Lin SP, Wu K, Fan Y, Xu M. Serum prealbumin is a predictive biomarker for stroke-associated infection after an ischemic stroke. *Int J Neurosci*. 2017;127(7):601–605. doi:10.1080/00207454.2016.1218874
24. He J, Zhu J, Zhang W, Zhan Z, Fu F, Bao Q. Association between serum transthyretin and intracranial atherosclerosis in patients with acute ischemic stroke. *Front Neurol*. 2022;13:944413. doi:10.3389/fneur.2022.944413
25. Sergi G, Coin A, Enzi G, et al. Role of visceral proteins in detecting malnutrition in the elderly. *Eur J Clin Nutr*. 2006;60(2):203–209. doi:10.1038/sj.ejcn.1602289
26. Ingenbleek Y. Why should plasma transthyretin become a routine screening tool in elderly persons? *J Nutr Health Aging*. 2009;13(7):640–642. doi:10.1007/s12603-009-0175-x
27. Dávalos A, Ricart W, Gonzalez-Huix F, et al. Effect of malnutrition after acute stroke on clinical outcome. *Stroke*. 1996;27(6):1028–1032. doi:10.1161/01.str.27.6.1028
28. Matsui R, Ida S, Ri M, et al. Impact of preoperative prealbumin levels on long-term prognosis in patients with gastric cancer after gastrectomy: a retrospective cohort study. *Gastric Cancer*. 2024;27(3):611–621. doi:10.1007/s10120-024-01472-y
29. Cui N, Tong H, Li Y, et al. Role of Prealbumin in Predicting the Prognosis of Severely and Critically Ill COVID-19 Patients. *Am J Trop Med Hyg*. 2021;105(3):718–726. doi:10.4269/ajtmh.21-0234
30. Godala M, Gaszyńska E, Walczak K, Małecka-Wojciesko E. Evaluation of Albumin, Transferrin and Transthyretin in Inflammatory Bowel Disease Patients as Disease Activity and Nutritional Status Biomarkers. *Nutrients*. 2023;15. doi:10.3390/nu15153479
31. Dent E, Wright ORL, Woo J, Hoogendijk EO. Malnutrition in older adults. *Lancet*. 2023;401(10380):951–966. doi:10.1016/s0140-6736(22)02612-5
32. Norman K, Haß U, Pirlich M. Malnutrition in Older Adults-Recent Advances and Remaining Challenges. *Nutrients*. 2021;14(1):13. doi:10.3390/nu13082764
33. Zhang G, Pan Y, Zhang R, et al. Prevalence and Prognostic Significance of Malnutrition Risk in Patients With Acute Ischemic Stroke: results From the Third China National Stroke Registry. *Stroke*. 2022;53(1):111–119. doi:10.1161/strokeaha.121.034366
34. Rubin H, Carlson S, DeMeo M, Ganger D, Craig RM. Randomized, double-blind study of intravenous human albumin in hypoalbuminemic patients receiving total parenteral nutrition. *Crit Care Med*. 1997;25(2):249–252. doi:10.1097/00003246-199702000-00009
35. Golub R, Sorrento JJ Jr, Cantu R Jr, Nierman DM, Moideen A, Stein HD. Efficacy of albumin supplementation in the surgical intensive care unit: a prospective, randomized study. *Crit Care Med*. 1994;22(4):613–619. doi:10.1097/00003246-199404000-00017
36. Sakai K, Niimi M, Momosaki R, et al. Nutritional therapy for reducing disability and improving activities of daily living in people after stroke. *Cochrane Database Syst Rev*. 2024;8:Cd014852. doi:10.1002/14651858.CD014852.pub2
37. Zoccali C, Mallamaci F, Tripepi G, et al. Prospective study of neuropeptide y as an adverse cardiovascular risk factor in end-stage renal disease. *J Am Soc Nephrol*. 2003;14(10):2611–2617. doi:10.1097/01.asn.0000089026.28617.33
38. Gomes JR, Nogueira RS, Vieira M, et al. Transthyretin provides trophic support via megalin by promoting neurite outgrowth and neuroprotection in cerebral ischemia. *Cell Death Differ*. 2016;23(11):1749–1764. doi:10.1038/cdd.2016.64
39. Santos SD, Lambertsen KL, Clausen BH, et al. CSF transthyretin neuroprotection in a mouse model of brain ischemia. *J Neurochem*. 2010;115(6):1434–1444. doi:10.1111/j.1471-4159.2010.07047.x
40. Baksi S, Pradhan A. Thyroid hormone: sex-dependent role in nervous system regulation and disease. *Biol Sex Differ*. 2021;12(1):25. doi:10.1186/s13293-021-00367-2
41. Talhada D, Santos CRA, Gonçalves I, Ruscher K. Thyroid Hormones in the Brain and Their Impact in Recovery Mechanisms After Stroke. *Front Neurol*. 2019;10:1103. doi:10.3389/fneur.2019.01103
42. Takahashi N, Saito D, Hasegawa S, Yamasaki M, Imai M. Vitamin A in health care: suppression of growth and induction of differentiation in cancer cells by vitamin A and its derivatives and their mechanisms of action. *Pharmacol Ther*. 2022;230:107942. doi:10.1016/j.pharmthera.2021.107942
43. Marie A, Darricau M, Touyarot K, Parr-Brownlie LC, Bosch-Bouju C. Role and Mechanism of Vitamin A Metabolism in the Pathophysiology of Parkinson's Disease. *J Parkinsons Dis*. 2021;11(3):949–970. doi:10.3233/jpd-212671