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ORIGINAL RESEARCH

Elevated Albumin to Globulin Ratio on Day 7 is Associated with Improved Function Outcomes in Acute Ischemic Stroke Patients with Intravenous Thrombolysis

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Background and Purpose: Albumin to globulin ratio (A/G) has been established as a representative biomarker for assessing inflammation and nutritional status. However, the prognostic value of A/G has rarely been reported in acute ischemic stroke (AIS) patients with intravenous thrombolysis (IVT).

Methods: A total of 311 AIS patients who had undergone IVT and completed 3-month follow-up were retrospectively recruited in this study. Albumin (Alb), globulin (Glb) and A/G on admission, within 24 hours after IVT and on day 7 were recorded. Poor outcome was defined as death or major disability (modified Rankin Scale, 3–6) at 3 months.

Results: Among the 311 cases, 260 patients had admission blood samples, 296 cases had blood samples within 24 hours after IVT and 126 cases had blood samples on day 7. The patients with and without available blood samples were well-balanced. During the first 24 h, we observed A/G to increase significantly compared with baseline whereas at day 7 it was almost back to baseline in patients with a poor outcome. Receiver operating characteristic (ROC) curves analysis showed that A/G had a better performance in discriminating patients at high risk and low risk of a poor outcome than either Alb or Glb alone and carried the highest predictive ability on day 7 (AUC = 0.807). Lower 7-day A/G was independently associated with a poor outcome (per-SD increase, OR = 0.182, 95% CI: 0.074–0.446).

Conclusion: A/G is an important prognostic indicator for AIS outcomes and merits dynamic monitoring.

Keywords: ischemic stroke, albumin-globulin ratio, intravenous thrombolysis

Introduction

Acute ischemic stroke (AIS), a type of acute cerebrovascular disease, caused by obstruction of blood vessels, is a primary disease contributing to adult morbidity and mortality. Intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator (rt-PA) within 4.5 hours after AIS onset is accepted as a standard therapy for AIS patients nowadays. However, nearly two-thirds of AIS patients do not experience clinical benefit after IVT. This situation creates a need for prognostic factors that would help clinicians identify those AIS patients who are more likely to have poor function outcomes.

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Blood biochemistry tests are one of the most commonly prescribed tests. Blood samples could be obtained from AIS patients at an early stage. Total serum protein is composed of albumin (Alb) and globulins (Glb), and abnormalities in the albumin/globulin ratio (A/G) have been observed in different clinical states including malnutrition, cancer, severe liver disease and rheumatic diseases.[1–3] A recent study reported that higher serum A/G is associated with better cognitive function in community-dwelling older people.[4] Besides, A/G showed a good prognostic value and remained an independent predictor of 90-day and 1-year mortality in patients with chronic heart failure.[5] Beamer et al.[6] suggested that lower levels of A/G are associated with increased risk for recurrent vascular events after AIS. However, few studies have examined the prognostic value of A/G in AIS patients with r-tPA administration. In the present study, considering Alb, Glb and A/G might be dynamic variables during hospitalization, we aimed to investigate (1) the dynamic profile of Alb, Glb and A/G in AIS patients during the first 7 days; (2) the association between Alb, Glb, A/G and 3-month clinical outcome; and (3) the predictive ability and incremental predictive ability of Alb, Glb and A/G for poor function outcomes in AIS patients treated with IVT r-tPA.

Materials and Methods

Study Population

A total of 458 patients consecutively diagnosed as AIS and treated with IVT r-tPA from January 2016 to September 2019 in the Third Affiliated Hospital of Wenzhou Medical University were initially enrolled in this retrospective study. Within 4.5 h of AIS onset, IVT r-tPA (0.9 mg/kg, maximum of 90 mg) was adopted for therapy with 10% of the total as a bolus and 90% by a 60-min infusion. The exclusion criteria were as follows: (1) undergoing mechanical embolectomy followed by IVT; (2) with recent or concurrent infections; (3) with immunological disease; (4) with tumor; (5) with cirrhosis or renal failure; (6) missing follow-up data. Finally, 311 cases were available for analysis. The flow chart is shown in Figure 1. After the initial peer review of the manuscript, data of 206 ischemic stroke patients treated between January 2020 and June 2020 in our hospital (ward 3) were additionally obtained to investigate the role of Alb, Glb and A/G in ischemic stroke patients without IVT. After excluding patients with recent or concurrent infections and/or with immunology disease and/or with tumor and/or with cirrhosis or renal failure and/or missing follow-up data, 142 ischemic stroke patients without IVT therapy were finally included for analysis.

Data Collection and Outcome Assessments

Data of AIS patients were gathered from medical records including demographics (age and sex), medical history (smoking, drinking, atrial fibrillation, hypertension, diabetes, hyperlipidemia and prior stroke), clinical data (admission blood pressure, door to needle time, onset to needle time), and National Institutes of Health Stroke Scale (NIHSS) on admission, 24 hours after IVT and day 7. Blood glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) measurements after overnight fasting were performed within 24 hours after IVT; data of serum Alb and Glb were collected on admission, within 24 hours after IVT and day 7, measured by ARCHITECT c16000 (Abbott Laboratories, Illinois, USA). A/G was calculated automatically, under the formula of Alb concentration divided by Glb concentration. AIS etiologies were classified as large artery atherosclerosis (LAA), small artery occlusion (SAO), cardioembolic (CE), stroke of other determined etiology (SOE), and stroke of undetermined etiology (SUE) according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[7] Other than that, 3-month Modified Rankin Scale (mRS) after onset of AIS, as a variable for outcome, was collected by two trained physicians on phone interviews. Death or major disability (mRS, 3–6) were defined as ta poor outcome.

Statistical Analysis

All statistical analyses were performed via SPSS Statistics 25.0.0.0, MedCalc Statistical Software version 15.2.2. and R version 4.1.0. Continuous variables were expressed as mean with standard deviation (mean ± SD) or medians and interquartile range (median, IQR) appropriately and compared using Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were presented as number and percentages (n, %) and the intergroup difference were tested

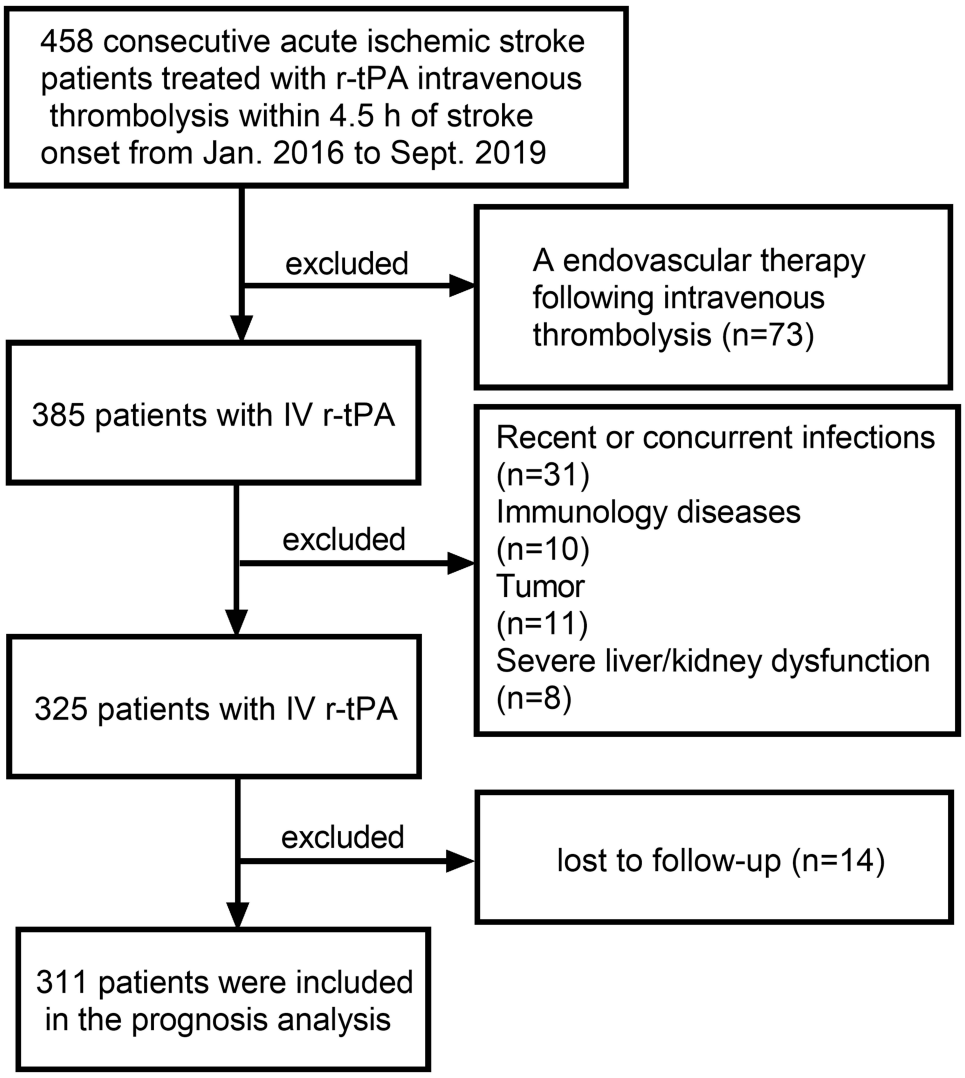

Figure 1 Flow chart for patients' selection.

using Chi-square test. The relationship between biomarkers (Alb, Glb, A/G) and AIS outcomes was analyzed by univariate and multivariable logistic regression, variables with p <0.1 in the univariate analysis were included in the multivariable model. In the regression models, the Alb, Glb, A/G were examined continuously and as quartiles to investigate a potential dose-response relationship with the AIS outcomes. The receiver operating characteristic curve (ROC) analysis was employed to evaluate the predictive ability of Alb, Glb and A/G for AIS outcomes and the maximum Youden index was used to determine the optimal cut-off values. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were further used to test the incremental predictive ability of A/G. A two-tailed p <0.05 were considered as statistically significant.

Results

Characteristics of the Study Subjects

A total of 311 consecutive AIS patients with r-tPA IVT were enrolled in this study, among which 260 (83.60%) patients had available admission blood samples, 296 (95.18%) patients had available 24 h blood samples, and 126 (40.51%) patients had available blood samples on day 7 for Alb and Glb measurement. Table 1 shows the characteristics of the enrolled patients. The patients with available blood samples and those without available blood samples were well balanced except that those without admission blood samples had a higher proportion of

Table 1 Characteristics of AIS Patients with or Without Available Blood Samples in Each Time Point

Characteristics	Admission			24 Hours			7 Days		
	Without (n = 51)	With (n = 260)	*p* value	Without (n = 15)	With (n = 296)	*p* value	Without (n = 185)	With (n = 126)	*p* value
Demographic data									
Age, (years)	69.08 ± 12.55	67.90 ± 13.06	0.555	67.13 ± 14.77	68.15 ± 12.90	0.769	67.16 ± 13.31	69.47 ± 12.37	0.124
Sex, (male, n.%)	27 (52.94)	169 (65.00)	0.103	8 (53.33)	188 (63.51)	0.426	123 (66.84)	73 (57.48)	0.093
Stroke risk factors									
Current smoking, n (%)	12 (23.53)	68 (26.15)	0.695	4 (26.67)	76 (25.68)	1.000	47 (25.54)	33 (25.98)	1.000
Hypertension, n (%)	36 (70.59)	169 (65.00)	0.441	9 (60.00)	196 (66.21)	0.620	125 (67.93)	80 (62.99)	0.366
Diabetes, n (%)	11 (21.57)	52 (20.00)	0.799	1 (6.67)	62 (20.95)	0.311	34 (18.48)	29 (22.83)	0.347
Hyperlipidemia, n (%)	16 (31.37)	22 (8.46)	< 0.001	3 (20.00)	35 (11.82)	0.590	24 (13.04)	14 (11.02)	0.593
Atrial fibrillation, n (%)	16 (31.37)	54 (20.76)	0.097	5 (33.33)	65 (21.96)	0.476	43 (23.37)	27 (21.26)	0.661
Prior stroke, n (%)	3 (5.88)	36 (13.85)	0.116	1 (6.67)	38 (12.84)	0.761	19 (10.33)	20 (15.75)	0.156
Laboratory data									
TC (mmol/L)	4.84 ± 1.07	4.59 ± 1.09	0.151	NA	4.63 ± 1.09		4.62 ± 1.02	4.65 ± 1.17	0.848
TG (mmol/L)	1.69 ± 1.54	1.49 ± 1.07	0.272	NA	1.51 ± 1.15		1.56 ± 1.13	1.45 ± 1.19	0.406
HDL (mmol/L)	1.15 ± 0.22	1.10 ± 0.28	0.222	NA	1.10 ± 0.27		1.11 ± 0.28	1.09 ± 0.25	0.557
LDL (mmol/L)	3.00 ± 0.95	2.91 ± 0.95	0.559	NA	2.93 ± 0.94		2.88 ± 0.87	3.00 ± 1.03	0.303
FBG (mmol/L)	6.20 ± 2.53	6.27 ± 2.49	0.874	6.94 ± 1.39	6.24 ± 2.50	0.633	6.27 ± 2.58	6.24 ± 2.37	0.905
Clinical data									
SBP (mmHg)	161.60 ± 27.28	163.83 ± 26.36	0.585	173.93 ± 30.66	163.00 ± 26.19	0.117	164.35 ± 26.70	162.16 ± 26.21	0.474
DBP (mmHg)	88.75 ± 16.26	90.63 ± 16.43	0.454	94.87 ± 18.29	90.09 ± 16.29	0.271	91.49 ± 16.25	88.60 ± 16.51	0.126
DNT (minute)	60 (50–72)	55 (44–73)	0.183	63 (57–69)	56 (45–73)	0.523	59 (46–73)	54 (43–73)	0.132
ONT (minute)	158 (124–213)	154 (125–197)	0.714	145 (114–194)	155 (126–200)	0.279	150 (120–195)	161 (130–209)	0.123
NIHSS at admission	7 (5–9)	7 (5–12)	0.530	11 (6–17)	7 (5–11)	0.055	7 (4–11)	7 (5–11)	0.930
NIHSS at 24 h	4 (2–8)	5 (2–9)	0.457	21 (12–35)	4 (2–8)	< 0.001	4 (2–9)	5 (2–9)	0.644
Stroke subtype, n (%)			0.543			0.290			0.618
CE	18 (35.29)	90 (34.72)		5 (33.33)	103 (34.80)		64 (34.78)	44 (34.65)	
LAA	19 (37.25)	109 (41.94)		7 (46.67)	121 (20.88)		77 (41.85)	51 (40.16)	
SAO	6 (11.76)	37 (14.23)		0 (0)	43 (14.53)		28 (15.22)	15 (11.81)	
SOE/SUE	8 (15.69)	24 (9.23)		3 (20.00)	29 (9.80)		16 (8.70)	16 (12.60)	

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; DNT, Door to needle time; ONT, Onset to needle time; NIHSS, National Institute of Health Stroke Scale; LAA, large artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology.

hyperlipidemia and those without 24 h blood samples had higher 24 h NIHSS scores compared with the patients with available blood samples.

Among the total 311 AIS patients, the mean age was 68, and 196 (63.02%) patients were male. Altogether 101 (35.48%) patients either died or had a major disability during the 3-month follow-up. Compared with patients with mRS 0–2, those patients with death or major disability were older, had lower proportion of male and current smoking, had higher proportion of hypertension, atrial fibrillation, prior stroke and CE etiology, had higher blood glucose, systolic blood pressure, admission and 24 h NIHSS, had lower admission Alb (39.59 ± 3.68 vs 41.31 ± 2.90, p <0.001), 7-day Alb (35.14 ± 3.05 vs 37.50 ± 3.15, p <0.001), admission A/G (1.18 ± 0.21 vs 1.27 ± 0.18, p <0.001), 24 h A/G (1.33 ± 0.27 vs 1.46 ± 0.24, p <0.001), 7-day A/G (1.15 ± 0.19 vs 1.41 ± 0.25, p <0.001), higher 24 h Glb (29.36 ± 4.85 vs 26.77 ± 4.12, p <0.001) and 7-day Glb (31.26 ± 4.78 vs 27.42 ± 4.63, p <0.001) (Table 2).

Serial Changes of Albumin, Globulin and A/G Ratio

The dynamic profile of Alb, Glb and A/G during the first 7 days of AIS are visualized in Figure 2. The results of paired *t*-tests comparing admission and 24 h data in 249 patients who received both admission and 24 h blood tests, and the results of paired *t*-tests comparing 24 h and 7-day data in 124 patients who received both 24 h and 7-day blood tests are listed in Table S1. At 24 h and on day 7, a significant decline in Alb was observed. During the first 24 h Glb dropped significantly compared with baseline whereas at day 7 it was almost back to baseline. In contrast, A/G peaked at 24 h and remained at high levels in the non-poor outcome group (admission vs 24 h [n = 172]: 1.27 ± 0.18 vs 1.46 ± 0.25, p < 0.001; 24 h vs day 7 [n = 85]: 1.42 ± 0.24 vs

Table 2 Characteristics of AIS Patients with or Without Poor Function Outcomes

Characteristics	Available Cases	Function Outcomes		
		mRS 0–2 (n = 210)	mRS 3–6 (n = 101)	*p* value
Demographic data				
Age (years)	311 (100)	65.24 ± 12.71	74.04 ± 11.43	< 0.001
Sex (male, n, %)	311 (100)	141 (67.14)	55 (54.46)	0.030
Stroke risk factors				
Current smoking, n (%)	311 (100)	66 (31.43)	14 (13.86)	0.001
Hypertension, n (%)	311 (100)	130 (61.90)	75 (74.26)	0.031
Diabetes, n (%)	311 (100)	43 (20.48)	20 (19.80)	0.890
Hyperlipidemia, n (%)	311 (100)	21 (10.00)	17 (16.83)	0.085
Atrial fibrillation, n (%)	311 (100)	39 (18.57)	31 (30.69)	0.017
Prior stroke, n (%)	311 (100)	19 (9.05)	20 (19.80)	0.007
Laboratory data				
TC (mmol/L)	286 (91.96)	4.61 ± 1.03	4.69 ± 1.21	0.556
TG (mmol/L)	286 (91.96)	1.58 ± 1.26	1.37 ± 0.82	0.152
HDL (mmol/L)	286 (91.96)	1.10 ± 0.26	1.12 ± 0.30	0.634
LDL (mmol/L)	286 (91.96)	2.89 ± 0.91	3.04 ± 1.01	0.236
FBG (mmol/L)	294 (94.53)	5.79 ± 1.97	7.36 ± 3.17	< 0.001
Admission-Alb (g/L)	260 (83.60)	41.31 ± 2.90	39.59 ± 3.68	< 0.001
Admission-Glb (g/L)	260 (83.60)	33.18 ± 4.64	34.39 ± 4.78	0.053
Admission-A/G	260 (83.60)	1.27 ± 0.18	1.18 ± 0.21	< 0.001
24 h-Alb (g/L)	296 (95.18)	38.08 ± 3.03	37.90 ± 3.49	0.624
24 h-Glb (g/L)	296 (95.18)	26.77 ± 4.12	29.36 ± 4.85	< 0.001
24 h-A/G	296 (95.18)	1.46 ± 0.24	1.33 ± 0.27	< 0.001
7 day-Alb (g/L)	126 (40.51)	37.50 ± 3.15	35.14 ± 3.05	< 0.001
7 day-Glb (g/L)	126 (40.51)	27.42 ± 4.63	31.26 ± 4.78	< 0.001
7 day-A/G (g/L)	126 (40.51)	1.41 ± 0.25	1.15 ± 0.19	< 0.001
Clinical data				
SBP (mmHg)	311 (100)	161.29 ± 26.40	168.40 ± 26.08	0.022
DBP (mmHg)	311 (100)	90.96 ± 16.58	88.98 ± 15.99	0.319
DNT (minute)	311 (100)	55 (45–73)	60 (46–74)	0.334
ONT (minute)	311 (100)	150 (124–196)	159 (127–200)	0.413
NIHSS at admission	310 (99.68)	6 (4–8)	13 (7–18)	< 0.001
NIHSS at 24 h	295 (94.86)	4 (2–6)	12 (7–19)	< 0.001
Stroke subtype, n (%)	311 (100)			< 0.001
CE		57 (27.14)	51 (50.49)	
LAA		88 (41.90)	40 (39.60)	
SAO		43 (20.48)	0 (0)	
SOE/SUE		22 (10.47)	10 (9.90)	

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBG, fasting blood glucose; Alb, albumin; Glb, globulin; A/G, albumin to globulin ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; DNT, Door to needle time; ONT, Onset to needle time; NIHSS, National Institute of Health Stroke Scale; LAA, large artery atherosclerosis; CE, cardioembolism; SAO, small-artery occlusion; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology.

1.42 ± 0.25, $p = 0.318$). In the poor outcome group, A/G reached a maximum value at 24 h and was back to approximately admission level at day 7 (admission vs 24 h [n = 77]: 1.18 ± 0.20 vs 1.33 ± 0.28, $p < 0.001$; 24 h vs day 7 [n = 39]: 1.23 ± 0.15 vs 1.13 ± 0.18, $p < 0.001$).

Association Between A/G Ratio and Stroke Prognosis

The relationships between Alb, Glb, A/G and stroke prognosis are shown in Table 3. Among 260 patients with available admission blood samples, 85 patients had died or hadmajor disability, of whom 29 patients had died. In the 296 patients with available 24h blood samples, 89 patients had died or had major disability, of whom 25 patients had

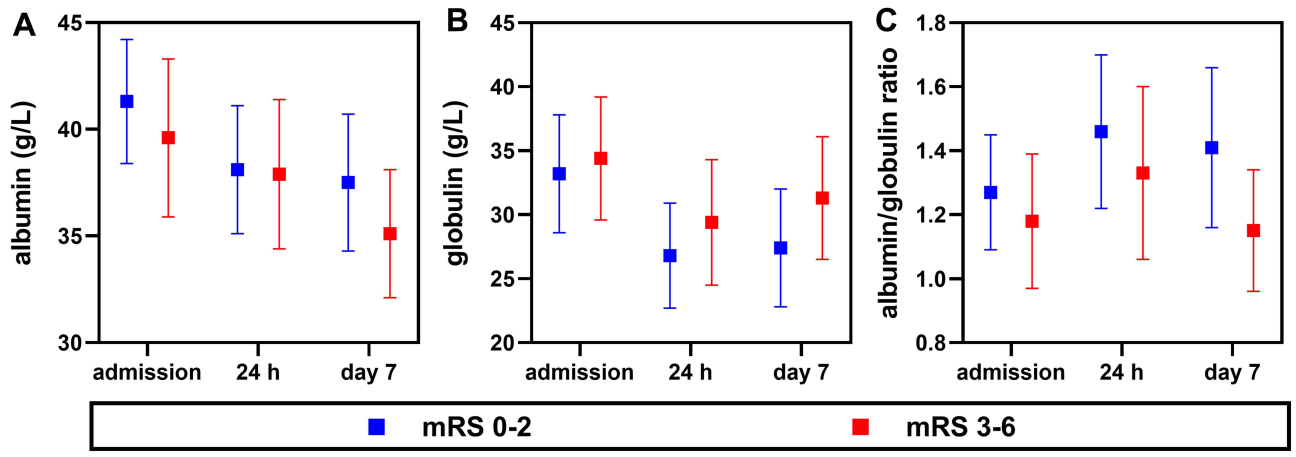

Figure 2 Dynamic changes in concentration (mean ± SD) of (**A**) albumin; (**B**) globulin and (**C**) albumin-globulin ratio (A/G) according to AIS outcomes. The data are summarized in Tables 2 and S1.

died. Besides, 41 patients had died or were with major disability, of whom 8 patients had died, in the group of patients with available 7-day blood samples (n = 126). No association between admission blood indicators (Alb, Glb, A/G) and a poor outcome was observed after adjusting for potential confounders. AIS patients with higher 24 h-Glb (OR = 1.499, 95% CI: 1.057–2.126) and lower 24 h-A/G (OR = 0.694, 95% CI: 0.469–1.027) tended to have higher risk of death or major disability at 3months. On day 7 after AIS, Alb (OR = 0.401, 95% CI: 0.202–0.794), Glb (OR = 2.489, 95% CI: 1.285–4.823) and A/G (OR = 0.182, 95% CI: 0.074–0.446) were all independent factors associated with death or major disability at 3 months. However, a statistically significant associationwas not found between Alb, Glb, A/G and death status at 3 months after AIS.

Table 3 Association Between Albumin, Globulin, Albumin/Globulin Ratio in Different Time Points and Function Outcomes After AIS

Characteristics	Death or Major Disability (mRS 3–6)		
	Events	OR* (95% CI)	*p* value
Admission-Albumin			
Q1, n = 69 [< 38.6]	35	1	
Q2, n = 61 [38.6–41.0]	19	0.462 (0.174–1.228)	0.122
Q3, n = 66 [41.1–43.0]	15	0.477 (0.180–1.263)	0.136
Q4, n = 64 [> 43.0]	16	0.701 (0.256–1.917)	0.489
Per 1-SD increase		0.476 (0.490–1.135)	0.171
Admission-Globulin			
Q1, n = 65 [< 30.2]	17	1	
Q2, n = 65 [30.2–32.9]	13	0.932 (0.315–2.756)	0.898
Q3, n = 65 [33.0–36.4]	29	1.636 (0.658–4.401)	0.330
Q4, n = 65 [> 36.4]	26	1.564 (0.541–4.520)	0.409
Per 1-SD increase		1.062 (0.732–1.542)	0.751
Admission-A/G ratio			
Q1, n = 68 [< 1.12]	39	1	
Q2, n = 64 [1.12–1.24]	19	0.486 (0.191–1.237)	0.130
Q3, n = 64 [1.25–1.35]	12	0.173 (0.059–0.508)	0.001
Q4, n = 64 [> 1.35]	15	0.459 (0.161–1.313)	0.147
Per 1-SD increase		0.816 (0.544–1.223)	0.325

(*Continued*)

Table 3 (Continued).

Characteristics	Death or Major Disability (mRS 3–6)		
	Events	OR* (95% CI)	*p* value
24 h-Albumin			
Q1, n = 76 [< 36.1]	27	1	
Q2, n = 72 [36.1–37.8]	19	0.682 (0.256–1.756)	0.427
Q3, n = 76 [37.9–40.1]	20	0.949 (0.364–2.474)	0.915
Q4, n = 72 [> 40.1]	23	1.477 (0.598–3.650)	0.398
Per 1-SD increase		1.138 (0.810–1.598)	0.457
24 h-Globulin			
Q1, n = 74 [< 24.3]	13	1	
Q2, n = 75 [24.3–27.3]	15	1.309 (0.458–3.737)	0.615
Q3, n = 74 [27.4–30.0]	27	2.986 (1.112–8.021)	0.030
Q4, n = 73 [> 30.0]	34	3.455 (1.258–9.485)	0.016
Per 1-SD increase		1.499 (1.057–2.126)	0.023
24 h-A/G ratio			
Q1, n = 74 [< 1.25]	38	1	
Q2, n = 76 [1.25–1.40]	20	0.388 (0.162–0.931)	0.034
Q3, n = 74 [1.41–1.58]	19	0.328 (0.131–0.826)	0.018
Q4, n = 72 [> 1.58]	12	0.279 (0.098–0.790)	0.016
Per 1-SD increase		0.694 (0.469–1.027)	0.067
7 day-Albumin			
Q1, n = 32 [< 34.5]	17	1	
Q2, n = 32 [34.5–36.8]	11	0.438 (0.110–1.742)	0.241
Q3, n = 32 [36.9–39.1]	8	0.229 (0.052–1.007)	0.051
Q4, n = 30 [> 39.1]	5	0.196 (0.035–1.082)	0.062
Per 1-SD increase		0.401 (0.202–0.794)	0.009
7 day-Globulin			
Q1, n = 33 [< 25.5]	4	1	
Q2, n = 31 [25.5–28.6]	8	3.902 (0.427–35.659)	0.228
Q3, n = 32 [28.7–31.8]	11	8.496 (0.932–77.451)	0.058
Q4, n = 30 [> 31.8]	18	22.598 (2.415–211.6)	0.006
Per 1-SD increase		2.489 (1.285–4.823)	0.007
7 day-A/G ratio			
Q1, n = 32 [< 1.14]	22	1	
Q2, n = 32 [1.14–1.34]	12	0.268 (0.069–1.041)	0.057
Q3, n = 34 [1.34–1.51]	4	0.059 (0.011–0.316)	0.001
Q4, n = 29 [> 1.51]	3	0.008 (0.000–0.177)	0.002
Per 1-SD increase		0.182 (0.074–0.446)	< 0.001

Notes: *Adjusted for age, sex, current smoking, hyperlipidemia, atrial fibrillation, prior stroke, systolic blood pressure, fasting glucose and NIHSS at admission.

Predictive Ability of A/G Ratio for a Poor Outcome

The ROC curve analysis was employed to test the discriminative ability of Alb, Glb and A/G for a poor outcome in AIS patients. Results are shown in Table 4. On the same time-points, A/G had a better performance in discriminating patients at high risk and low risk of a poor outcome than either Alb or Glb alone. An optimal cut-off of <1.11 was derived for admission A/G in predicting death or major disability (area under the curve 0.653, 95% CI: 0.591–0.710, p <0.001). The optimal cut-off value for 24 h-A/G as a predictor of death or major disability was determined as 1.35 in the ROC curve analysis with the AUC at 0.677 (95% CI: 0.620–0.730). 7-day A/G had the highest area under the curve (0.807) among the three time points, with an optimal cut-off value of 1.20 to distinguish the presence of a poor outcome, yielding a sensitivity of 73.17% and a specificity of 78.82%.

Table 4 Diagnostic Values of the Albumin, Globulin and Albumin/Globulin Ratio for Death or Major Disability (mRS 3–6)

	AUC (95% CI)	*p* value	Cut-off Value	Sensitivity (%)	Specificity (%)
Admission-Albumin	0.644 (0.583–0.702)	< 0.001	40.5	62.35	66.29
Admission-Globulin	0.589 (0.527–0.650)	0.019	32.8	67.06	57.14
Admission-A/G ratio	0.653 (0.591–0.710)	< 0.001	1.11	45.88	83.43
24 h-Albumin	0.513 (0.454–0.571)	0.732			
24 h-Globulin	0.672 (0.615–0.725)	< 0.001	27.9	62.92	66.97
24 h-A/G ratio	0.677 (0.620–0.730)	< 0.001	1.35	62.92	68.12
7 day-Albumin	0.695 (0.606–0.773)	< 0.001	34.9	53.66	78.82
7 day-Globulin	0.731 (0.645–0.806)	< 0.001	27.8	80.49	58.82
7 day-A/G ratio	0.807 (0.727–0.872)	< 0.001	1.20	73.17	78.82

Incremental predictive ability of 7-day A/G ratio was further investigated. When adding 7-day A/G (as a continuous variable) into the established model (including age, sex, current smoking, hyperlipidemia, atrial fibrillation, prior stroke, systolic blood pressure, fasting glucose and NIHSS at admission), we found a significant improvement in the AUC (0.844 vs 0.913, $p = 0.013$). In addition, both continuous NRI (1.072, 95% CI: 0.758–1.387, $p < 0.001$) and IDI (0.153, 95% CI: 0.087–0.220, $p < 0.001$) showed a significant advancement to risk stratification of a poor outcome. Adding 7-day A/G (as a categorical variable) into the established model yielded a similar result (Table S2).

Results in Ischemic Stroke Patients without Intravenous Thrombolysis

Characteristics of 142 ischemic stroke patients without intravenous thrombolysis are listed in Table S3. Admission and 24 h A/G levels were significantly lower in patients with a poor outcome. However, results of multivariate logistic regression show that A/G at any time-point was not a significant predictor of poor outcome in ischemic stroke patients without intravenous thrombolysis (Table S4). ROC curve analysis (Table S5) suggested that a cut-off value of A/G 1.38 on hospital admission can predict a poor outcome with good sensitivity (90.00%) but with poor specificity (40.85%).

Discussion

To the extent of our knowledge, our study is the first to evaluate the prognostic value of A/G in AIS patients with r-tPA IVT. Our study showed that Alb, Glb and A/G were dynamic variables during the first 7 days after onset of AIS, and A/G on day 7 had the highest predictive ability of 3-month poor outcome. In addition, higher Glb and lower A/G tested within 24 h after IVT and on day 7, and lower Alb tested on day 7 were independent predictors of 3-month poor outcome in AIS patients with r-tPA IVT. Furthermore, adding the A/G ratio measured on the seventh day to the conventional model can significantly optimize the risk stratification of a poor outcome.

Inflammation and malnutrition play important roles in the initiation and progression of AIS. A/G, the composite biomarker of Alb and Glb, reflects both the inflammation and nutrition status. After stroke onset, the inflammatory cascade is activated immediately in response to ischemic injury. Through the disrupted blood–brain barrier (BBB) or the cerebrospinal fluid (CSF) drainage system, damage-associated molecular patterns (such as purines, heat shock proteins, peroxiredoxins) and cytokines expressed during the acute phase of stroke can influx into the systemic circulation, trigger an immune system response in lymphoid organs, and consequently cause a systemic inflammation.[8] Aggravated systemic inflammatory response to AIS could be a hazard for the neurovascular unit, sensitizing cells to ischemic brain injury and further increasing BBB permeability.[9] Globulins, including C-reactive protein, α2 macroglobulin, fibrinogen, and many other proteins are typically considered as acute phase proteins. Cytokines such as IL-6 can act on liver and contribute to the globulin synthesis in the acute phase of AIS.[10] IL-6 is strongly associated with the risk of incident stroke, recurrence of vascular events and poor outcomes after stroke.[11,12] An elevated globulin level is independently associated with hemorrhagic transformation in stroke patients receiving intra-arterial thrombolysis.[13] Non-infective C-reactive protein level is an independent risk factor for poor prognosis in AIS patients with IVT treatment.[14] Besides, previous literatures also suggested that increased plasma fibrinogen was associated with reduced chance of favorable outcome in ischemic

stroke patients.[15,16] Consistent with the previous data, our study demonstrated that AIS patients with poor outcome tended to have lower globulin levels.

Malnutrition is a well-known risk factor for poor outcome after stroke.[17–20] The AHA/ASA Guidelines for the early management of acute ischemic stroke patients recommend timely enteral diet and nutritional supplements for acute ischemic stroke patients with (or at risk of) malnutrition.[21] Serum albumin also acts as a required component of many nutritional screening tools (e.g., controlling nutritional status score,[22] prognostic nutritional index,[23] geriatric nutritional risk index).[24] Albumin is a carrier for various molecules and plays a vital role in maintaining normal microvascular permeability. Albumin could alleviate the inflammatory response after AIS through inhibiting neutrophil-endothelial adhesion.[25] Lower serum Alb concentrations could lead to a decreasing plasma osmotic pressure, and consequently cause coagulation abnormalities. In addition, Alb is a specific inhibitor of human endothelial cell apoptosis[26] and an important antioxidant.[27] Albumin from the blood can gain access to the CSF via the BBB and the choroid plexus. Since albumin is not synthesized in the central nervous system, CSF albumin concentration/serum albumin concentration (Qalb) is suggested as an indicator of BBB permeability.[28] Statistics show that serum albumin drops significantly during the first 24 h in AIS patients with IVT, which might be attributed to the disrupted BBB during the acute phase of stroke. Besides, malnutrition during hospitalization might be the most probable explanation for the continuous decreasing albumin level during the first 7 days. A decreasing trend in Alb after AIS was also reported by Makris et al.[29]

Previous literatures suggested that lower serum Alb level was associated with worse neurological state and poor function outcomes in all the AIS subtypes classified based on TOAST[30,31] and higher odds of hemorrhagic transformation post-AIS.[32] However, the second analysis of ALIAS (Albumin in Acute Ischemic Stroke) Trials and the latest meta-analysis suggested that albumin therapy was not associated with improved outcome at 3 months but associated with higher risks of pulmonary edema and other complications.[33,34] In our study, the level of albumin was lower in patients with a poor outcome, though albumin at any time-point (admission, 24 h, and day 7) was not a significant predictor of a poor outcome after adjusting for potential confounders.

The A/G ratio, the combination of Alb and Glb, was one of the concise and representative parameters used for evaluation of nutritional and systemic inflammatory status. The longitudinal analysis was the advantage of our study. As we mentioned above, A/G had a higher predictive value for post-AIS death and major disability than either Alb or Glb alone in different time points. The addition of A/G measured in day 7 to the conventional stroke prognostic model improved significantly in C statistics, NRI and IDI for predicting 3-month functional outcomes. Therefore, monitoring A/G in every AIS patient with IVT might be suggested as a routine item in a future stroke prevention and control system, which would help to establish the risk stratification models, make clinical decisions, and ultimately relieve the burden of AIS patients.[35] Inevitably, there were several limitations in our study. First, our study was a single-center study with small sample sizes, which meant that only a small number of patients died during the 3-month follow-up. Second, for various reasons, only 260 (83.60%) blood samples on admission, 296 (95.18%) blood samples within 24 h after IVT and 126 (40.51%) blood samples on day 7 were available. However, AIS patients with available blood samples in our study were highly representative of the entire cohort. Third, our study only collected blood samples at three time points (admission, 24 h and day 7). Fourth, the prognostic value of A/G in ischemic stroke patients without IVT was limited as reperfusion therapies might influence the kinetics of A/G. Besides, the time measured from stroke onset to recruitment/admission was not limited. In our study, A/G at any time-point was not a significant predictor of a poor outcome in ischemic stroke patients without IVT. Finally, this study was observational and retrospectively designed. Cytokines (e.g., IL-1, IL-6, TNF-A) were not measured in the present study, and a causal association between A/G and AIS function outcome could not be established. Future prospective studies with larger sample sizes to examine the kinetics of A/G in ischemic stroke patients are warranted.

Conclusion

In AIS patients treated with r-tPA IVT, A/G has a higher predictive ability for a poor outcome than either Alb or Glb alone and yields the highest predictive ability on day 7. Lower 24 h A/G and 7-day A/G are independent risk factors for a poor outcome. Dynamic monitoring of A/G might be helpful for AIS risk stratifications and clinical management.

Data Sharing Statement

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

Ethics Statement

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University (YJ2020034) and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

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Disclosure

The authors report no conflicts of interest for this work.

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