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Predictive value of the apolipoprotein B/A1 ratio in intracerebral hemorrhage outcomes

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Abstract

Background and Aims: The apolipoprotein B (apoB)/apolipoprotein A1 (apoA1) ratio is a key indicator in predicting future cardiovascular outcomes. However, it is still unclear whether the ratio of apoB/apoA1 is a better predictor of the outcomes after intracerebral hemorrhage (ICH). Therefore, we aimed to assess the relationships between the ratio of apoB/apoA1 and functional outcomes, all-cause mortality, and stroke recurrence in ICH patients.

Methods: Two hundred and sixteen Chinese ICH patients participated in this study from December 2018 to December 2019. Laboratory routine tests including hematology analysis, coagulation tests, and lipid levels were examined. The clinical outcomes included functional outcomes evaluated by the modified Rankin Scale score (mRS), all-cause death, and stroke recurrence 1 year after discharge. Associations between the apoB/apoA1 ratio and the outcomes were evaluated using logistic regression analysis. Based on multivariate analysis, we constructed a nomogram. Univariate survival analysis was performed by the Kaplan–Meier method and log-rank test. All the patients were classified into two groups by the median value of the apoB/apoA1 ratio: B1 < 0.8 and B2 ≥ 0.8.

Results: Of the 216 patients, 107 had an apoB/apoA1 ratio ≥ 0.8. Eighty-five patients had poor functional outcomes (mRS ≥ 3), and 32 patients had severe functional outcomes (mRS ≥ 4). During the 1-year follow-up, a total of 18 patients died, and 13 patients had apoB/apoA1 ratio levels ≥0.8 during the 1-year follow-up period. Moreover, 16 recurrent strokes were recorded. Adjustments for age, sex, smoking, alcohol, body mass index, lipid levels, and hematoma site and volume showed that a high apoB/apoA1 ratio was significantly related to adverse functional outcomes and all-cause mortality. The ORs for B2 versus B1 were 3.76 (95% CI: 1.37 to 10.40, $p = 0.010$), 22.74 (95% CI: 1.08 to 474.65, $p = 0.044$), and 7.23 (95% CI: 1.28 to 40.88, $p = 0.025$) for poor functional outcomes with mRS ≥ 3, mRS ≥ 4, and all-cause mortality, respectively.

Rasha Alsamani and Zhang Limin contributed equally to this work.

Conclusion: An increased apoB/apoA1 ratio at admission was independently related to poor functional outcome and all-cause mortality in ICH patients at the 1-year follow-up.

KEYWORDS
apoB/apoA1 ratio, intracerebral hemorrhage, mortality, outcome

1 | INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is the most lethal type of stroke, causing severe disability among survivors. The high 1-month case fatality rate and poor long-term outcomes make it a driver of morbidity and mortality worldwide.[1,2] The SINO-MONICA-Beijing study reported that Chinese ICH patients have a higher mortality rate than patients from other countries.[3] Therefore, it is vital to identify biomarkers that can predict the prognosis of ICH at an early stage to improve outcomes. Lipid parameters are recognized as risk factors for cardiovascular events. However, the predictive value of the lipid profile for cardiovascular disease does not appear to be the same.[4–6] The ratio of apolipoprotein (apo) B/apoA1 could be a marker of the balance between pro-atherogenic and antiatherogenic lipoprotein particles.[7] Over the past few years, evidence has shown that an increased apoB/apoA1 ratio is a valuable predictor of stroke and is associated with cardiovascular outcomes.[8,9] It has been shown that the apoB/apoA1 ratio has a greater prognostic value than other traditional cardiovascular risk factors, including conventional lipid profile abnormalities.[10,11] Some studies have revealed that the apoB/apoA1 ratio exhibits a greater ability to predict acute ischemic stroke.[5] However, the value of the apoB/apoA1 ratio in ICH prognosis is still obscure. Moreover, to date, data on the apoB/apoA1 ratio as a predictor of intracerebral hemorrhage outcomes are still scarce.

This study aimed to investigate the relationships between the apoB/apoA1 ratio and poor clinical outcomes in a cohort of patients suffering from acute ICH.

2 | MATERIALS AND METHODS

2.1 | Patient enrollment

This was a retrospective, observational study. Our study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Beijing Tiantan Hospital of Capital Medical University, China (KY 2020–076-02). Written informed consent was obtained from all patients or their relatives. We enrolled consecutive ICH patients older than 18 years who presented directly to Beijing Tiantan Hospital of Capital Medical University at the emergency department between December 2018 and December 2019. Patients with ICH attributed to trauma, brain tumors, hemorrhagic transformation of ischemic stroke, aneurysm, cerebral vascular malformations, hepatic disease, renal diseases, impaired coagulation, and sepsis were excluded. All patients underwent cranial magnetic resonance imaging (MRI) during hospitalization to clarify the etiology of ICH. Patients were also excluded if ICH was induced by cerebral amyloid angiopathy (CAA).

In total, 916 ICH patients were enrolled. Among these patients, we excluded patients whose time since clinical onset of stroke exceeded 24 h (n = 285), patients who did not take initial NCCT within 24 h (n = 196), and patients who did not take follow-up NCCT within 48 h (n = 83). Of the remaining 348 patients, we excluded five patients who were younger than 18 years, 101 patients without follow-up records, and 30 patients without apo A1 and apo B values. Finally, 216 patients with ICH were analyzed in the present study (Figure 1).

2.2 | Baseline information

Demographic and clinical data were collected in detail by interviews with patients and their family members and a review of hospital medical records by attending physicians. All patients underwent a brain CT at admission. Follow-up CT scans were performed at the hospital within 48 h of admission or if the clinical condition worsened. The time of ICH onset and National Institutes of Health Stroke Scale (NIHSS) scores were recorded. On the initial CT scan, we evaluated hematoma volume, bleeding site, and the presence of intraventricular hemorrhage (IVH). The bleeding sites were categorized as basal ganglia, lobar, cerebellum, and brainstem. Hematoma volume was measured using the ABC/2 method (where A is the largest CT-measured bleeding diameter, B is the diameter 90 degrees from A, and C is the approximate number of CT slices with hemorrhage multiplied by slice thickness).[12]

2.3 | Outcome assessment

During the follow-up, patient functional outcomes were evaluated by the modified Rankin Scale (mRS) through a clinical assessment or telephone interview at the 1-year follow-up by trained personnel who were blinded to the detailed clinical data and used standardized questionnaires to contact the patients or their caregivers. An mRS score of ≥3 was defined as an unfavorable functional outcome.[13] As an mRS score of 3 is a moderate disability, we also observed a group with an mRS score ≥ 4, which was recognized as a severe prognosis.

FIGURE 1 Enrollment flow chart for analysis. ICH, intracerebral hemorrhage; NCCT, noncontrast CT
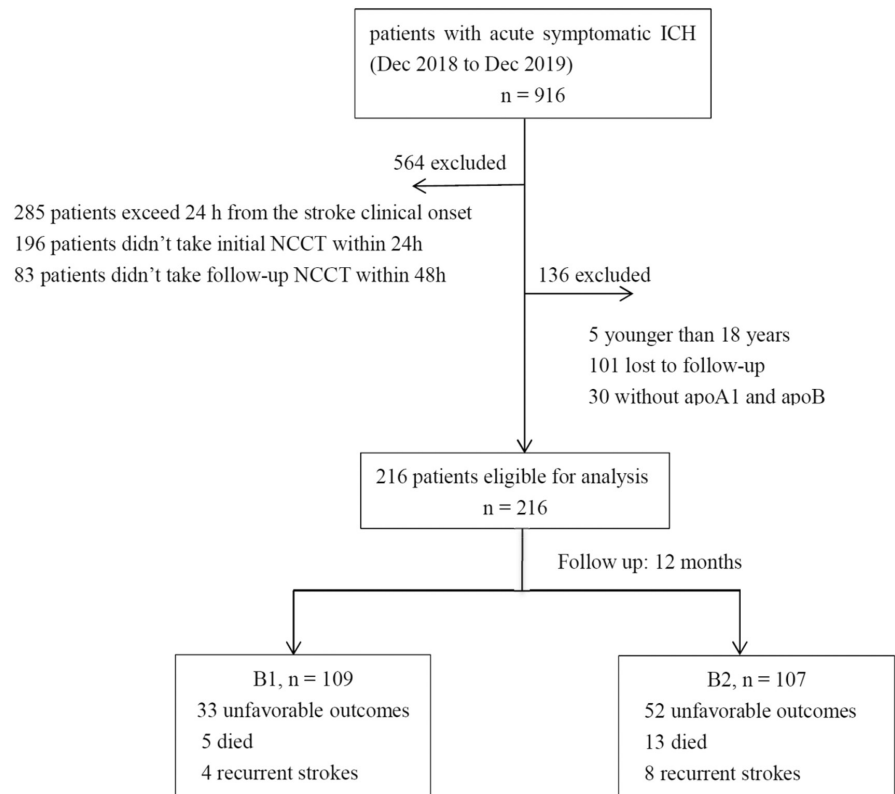
All-cause death was reported by family members or workers and/or death certificates and medical records. The definitions of recurrent stroke in this study included ischemic stroke and hemorrhagic stroke. A recurrent event was verified at the hospital the patient attended based on new neurological deficit documents in the medical record with CT scan or MRI.

2.4 | Laboratory tests and classification of the apoB/apoA1 ratio

All patients underwent routine blood tests for the measurement of white blood cell count (WBC), neutrophil granulocyte count (NEU), lymphocyte count (LYM), neutrophil/lymphocyte ratio (N/L), biochemical tests, including triglyceride (TG), cholesterol (CHO), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (apo A1), and apolipoprotein B (apoB) levels, and blood coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), and D-dimer (DD) at the emergency clinic or during admission. Blood samples were withdrawn from the antecubital vein and collected into tubes with ethylenediaminetetraacetic acid, potassium citrate, or separating gel separately. The tests were performed within 2 h after sampling. The WBC and differential counts were processed on a BC-6900 auto hematology analyzer (Mindray, China), biochemical tests were processed on a 008 automatic biochemical analyzer (Hitachi, Japan), and coagulation tests were performed on an ACL TOP 700 automatic coagulometer (IL company, USA) using the original reagents. The

ratio of apoB/apoA1 was calculated and determined according to the median value of the apoB/apoA1 ratio of the whole cohort with a value of 0.8. At the 3-month follow-up, patients came to the outpatient service, and venous blood was extracted for apoA1 and apoB detection.

2.5 | Statistical analysis

All patients were divided into two groups according to the median apoB/apoA1 ratio: B1 < 0.8 and B2 ≥ 0.8. Categorical variables were expressed as frequencies and percentages and analyzed by chi-squared tests. The results were expressed as the means and standard deviations (SDs) and analyzed by Student's t tests for normally distributed continuous variables. They were expressed as medians and interquartile ranges for continuous variables that were not normally distributed using Wilcoxon rank-sum tests to evaluate differences in different patient categories according to the apoB/apoA1 ratio. The correlations between apoB/apoA1 ratios and the outcomes were assessed by logistic regression analyses. To adjust in the multivariable analyses, variables with a $p < 0.1$ in the univariate analysis and the well-established predictors of the outcomes were selected. Additionally, the results of unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were obtained. Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, smoking, and alcohol. Model 3 was further adjusted for cholesterol and triglycerides. Model 4 was further adjusted for LDL-C, HDL-C, FIB, baseline hematoma site, and volume. A nomogram was built according to the results of the multivariate analysis. Univariate

survival analysis was compared by Kaplan–Meier analysis and log-rank testing.

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, USA), Empower Stats, and R software, version 3.3.1. All statistical analyses were two-tailed, and a value of $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline patient characteristics

Two hundred sixteen primary ICH patients were recruited for this study (Figure 1). The median (IQR) apoB/apoA1 ratio of all the patients was 0.8 (0.62, 0.96), and the mean ± SD value was 0.82 ± 0.26.

One hundred seven patients had an apoB/apoA1 ratio ≥0.8. The baseline characteristics of all patients based on apoB/apoA1 ratio levels are shown in Table 1. The median NIHSS score for the whole study cohort was 7 (4, 12). The median hematoma volume at baseline was 20.9 (9.17, 34.80) ml. A total of 138 patients had hematomas located in the supratentorial deep gray matter (63.9%), and 37 patients had hematomas located in lobar locations (17.1% of the cohort). Hematoma expansion was observed in 9 patients (4.2%). Eighty-five patients (39.4%) had poor clinical outcomes with mRS 3–6, and 51 patients (23.6%) had a severe prognosis with mRS 4–6 one year after ICH. The mRS score distribution stratified by the median apoB/apoA1 ratio is shown in Figure 2. It was obvious that the proportion of mRS scores 3–6 or 4–6 in the B2 group was higher than that in the B1 group. Those patients with a higher apoB/apoA1 ratio at admission were mostly male and had a history of alcohol consumption. These patients also more frequently suffered from mortality after ICH.

Eighteen patients died within 1 year of ICH, and thirteen of these 18 patients had apoB/apoA1 ratio levels ≥0.8. Of the 18 deaths, 13 were caused by cardiovascular disease, including 8 hemorrhage strokes, 2 ischemic strokes, 2 myocardial infarctions, and 1 heart failure, 2 were due to infectious disease, and 3 were caused by other reasons.

A total of 16 patients experienced recurrent stroke, including 8 (7.5%) in Group B2 and 4 (3.7%) in Group B1. Regarding lipid levels, significant intergroup differences were noted for all types of lipids, including TG, CHO, LDL-C, HDL-C, apoA1, and apoB ($p < 0.001$). At 3 months after discharge, the B2 group had a high apoB/apoA1 ratio and apoB level compared with the B1 group.

3.2 | The correlations between lipid parameters and coagulation

As shown in Table 2, apoA1 was strongly correlated with HDL-C and the apoB/apoA1 ratio ($r = 0.835$ and -0.567, respectively). ApoB was strongly correlated with LDL-C, CHO and the apoB/apoA1 ratio ($r = 0.664$, 0.807 and 0.728, respectively). However, each lipid parameter was relatively weakly correlated with fibrinogen (Table 2).

3.3 | The correlations between the apoB/apoA1 ratio and clinical outcomes

As shown in Table 3, a higher median apoB/apoA1 ratio was used for further logistic regression analysis to investigate the influence of apoB/apoA1 ratio on clinical outcomes. All risk factors with p-values smaller than 0.1 on admission, as shown in Table 1, were selected for regression analysis. In addition, variables related to poor clinical outcomes were also included in the regression analysis even if they did not meet the p-value standard in statistics such as age, sex, smoking status, and hematoma site and volume. When the cutoff value of the apoB/apoA1 ratio was 0.8, a significant association was noted between the apoB/apoA1 ratio and the clinical outcomes. Despite the adjustment in Models 2, 3, and 4, the apoB/apoA1 ratio was still related to mRS and all-cause mortality (Table 3). As shown in Model 4, the ORs for B2 versus B1 were 3.76 (95% CI: 1.37 to 10.40, $p = 0.010$), 22.74 (95% CI: 1.08 to 474.65, $p = 0.044$), and 7.23 (95% CI: 1.28 to 40.88, $p = 0.025$) for mRS 3–6, mRS 4–6 and all-cause mortality, respectively. The survival curves showed that the overall survival rate of the B2 group was dramatically lower than that of the B1 group ($p = 0.044$) at 1 year (Figure 3). The survival rates assessed at the end of 3, 6, and 12 months were 99.1, 97.2, and 95.4% in the B1 group, respectively. Meanwhile, the rates in the B2 group were 96.2, 93.4, and 87.8%. Moreover, these results also suggested that apoA1 correlated with mRS ($p = 0.000$, OR = 0.10, 95% CI: 0.03 to 0.34) in Model 1 even after adjusting for confounding factors in Models 2, 3 and 4. There was no correlation between apoB and each variable in Models 1–4 (Table 3).

3.4 | A predictive model for 1-year outcomes

A noninvasive nomogram was drawn by data from all patients according to five parameters using logistic regression analysis to further explore the predictive significance of the apoB/apoA1 ratio with clinical outcomes in patients with ICH (Figure 4). It is predicted that the higher the total nomogram score is, the higher the likelihood of a poor functional outcome in mRS 3–6 stratification.

The key variables are marked in the diagram by a line. Each variable receives a point based on its value. Total scores for each variable are added and matched with the probability of an adverse outcome.

4 | DISCUSSION

The present study determined the relationships between the serum apoB/apoA1 ratio and ICH patient characteristics. We found that a higher ratio of apoB/apoA1 at admission is strongly correlated with poor functional outcomes and all-cause mortality in ICH patients

TABLE 1 Baseline characteristics of individuals stratified by the median apoB/apoA1 ratio

Variables	All (n = 216)	apoB/apoA1		p-value
		<0.80 (n = 109)	≥0.80 (n = 107)	
Male gender	175 (81.0)	86 (78.9)	89 (83.2)	0.423
Age, year	54.38 ± 13.55	54.96 ± 12.98	53.79 ± 14.14	0.380
BMI	25.71 (23.44,27.76)	25.31 (3.83)	26.12 (24.22,28.40)	**0.005**
Smoking history	101 (46.8)	50 (45.9)	51 (47.7)	0.792
Alcohol history	123 (56.9)	55 (50.5)	68 (63.9)	0.052
History of hypertension	158 (73.1)	80 (73.4)	78 (72.9)	0.934
History of dyslipidemia	47 (21.8)	25 (22.91)	22 (20.6)	0.672
History of diabetes	34 (15.7)	18 (16.5)	16 (15.0)	0.753
History of stroke	27 (12.5)	16 (14.7)	11 (10.3)	0.328
Coronary heart disease	23 (10.6)	11 (10.1)	12 (11.2)	0.789
Antihypertensive medication	72 (33.3)	32 (29.4)	40 (37.4)	0.211
Lipid-lowering medicine	21 (9.7)	11 (10.1)	10 (9.3)	0.853
Antidiabetic	17 (7.9)	8 (7.3)	9 (8.4)	0.770
Antiplatelet medication	18 (8.3)	11 (10.1)	7 (6.5)	0.345
Anticoagulants	8 (7.3)	3 (2.8)	5 (47)	0.496
NIHSS score	7 (4,12)	7 (3,12)	7 (4,11)	0.747
Time from onset to initial NCCT (h)	5.75 (3,8.37)	6 (3,8)	5 (3,9)	0.939
Baseline hematoma volume (ml)	20.90 (9.17,34.80)	20.8 (9.7,34.6)	21.00 (8.16,36.0)	0.998
Hematoma expansion	9 (4.2)	6 (5.5)	3 (2.8)	0.499
Hematoma location				0.482
Basal ganglia	138 (63.9)	75 (68.8)	63 (58.9)	
Lobar	37 (17.1)	18 (16.5)	19 (17.8)	
Brainstem	11 (5.1)	6 (5.5)	5 (4.7)	
Cerebellum	15 (6.9)	5 (4.6)	10 (9.3)	
IVH	7 (3.2)	2 (1.8)	5 (4.7)	
Basal ganglia and lobar	8 (3.7)	3 (2.8)	5 (4.7)	
mRS 3–6 at 1 year	85 (39.4)	33 (30.3)	52 (48.6)	**0.006**
mRS 4–6 at 1 year	51 (23.6)	19 (17.4)	32 (29.9)	**0.031**
Recurrence of stroke at 1 year	12 (5.6)	4 (3.7)	8 (7.5)	0.222
Mortality	18 (8.3)	5 (4.6)	13 (12.1)	**0.044**
TG (mmol/L)	1.25 (0.87,1.69)	1.03 (0.78,1.39)	1.50 (1.13,2.05)	**<0.001**
CHO (mmol/L)	4.53 (3.90,5.20)	4.18 (3.73,4.75)	4.95 (4.25,5.79)	**<0.001**
LDL-C (mmol/L)	2.98 ± 0.93	2.66 ± 0.72	3.31 ± 1.00	**<0.001**
HDL-C (mmol/L)	1.19 ± 0.30	1.31 ± 0.29	1.06 ± 0.26	**<0.001**
apoA1 (g/L)	1.29 ± 0.26	1.41 ± 0.24	1.17 ± 0.23	**<0.001**
apoB (g/L)	1.02 ± 0.27	0.86 ± 0.18	1.18 ± 0.24	**<0.001**
PT (s)	11.48 ± 1.01	11.56 ± 1.04	11.40 ± 0.97	0.237
APTT (s)	29.08 ± 3.16	29.41 ± 3.27	28.74 ± 3.03	0.117
FIB (g/L)	2.90 (2.52,3.38)	2.76 (2.38,3.29)	2.99 (2.61.3.53)	**0.018**
DD (ug/ml)	0.60 (0.40,0.96)	0.60 (0.40,1.10)	0.60 (0.43,0.90)	0.632
WBC (×10⁹/L)	9.26 (7.40,11.43)	8.94 (6.78,11.13)	9.57 (7.78,12.27)	0.100
NEU (×10⁹/L)	7.29 (5.40,9.86)	7.01 (4.94,9.80)	7.48 (5.84,9.87)	0.085
LYM (×10⁹/L)	1.28 (0.91,1.66)	1.26 (0.91,1.64)	1.30 (0.92,1.79)	0.539
N/L	5.80 (3.56,9.99)	5.83 (3.22,9.89)	5.60 (3.84,10.23)	0.581

(Continues)

TABLE 1 (Continued)

Variables	All (n = 216)	apoB/apoA1		p-value
		<0.80 (n = 109)	≥0.80 (n = 107)	
apoA1 at 3 months (g/L)	1.26±0.28	1.30±0.31	1.22±0.24	0.240
apoB at 3 months (g/L)	0.88±0.23	0.82±0.24	0.96±0.20	**0.012**
apoB/apoA1 at 3 months	0.73±0.24	0.66±0.310.24	0.81±0.310.23	**0.009**

Note: Data are expressed as the mean±standard deviation (SD), median (IQR), or n (%) as appropriate.

Abbreviations: apoA1, apolipoprotein A1; apoB, apolipoprotein B; APTT, activated partial thromboplastin time; CHO, cholesterol; DD, D-dimer; FIB, fibrinogen; HDL-C, high-density lipoprotein cholesterol; IVH, intraventricular hemorrhage; LDL-C, low-density lipoprotein cholesterol; LYM, lymphocyte count; mRS, modified Rankin Scale; NEU, neutrophil granulocyte count; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; TG, triglyceride; WBC, white blood cell count.

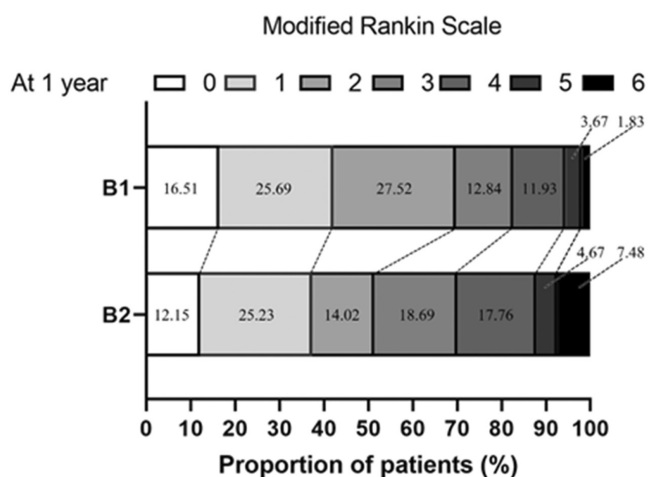Bold indicates the *p* less than 0.05.

FIGURE 2 mRS score distribution stratified by the median apoB/apoA1 ratio. The figure shows the distribution of scores on the mRS. Scores range from 0 to 6, with 0 indicating no symptoms, 1 indicating no clinically significant disability, 2 indicating slight disability, 3 indicating moderate disability, 4 indicating moderately severe disability, 5 indicating severe disability and 6 indicating death. mRS, modified Rankin Scale. B1: apoB/apoA1 ratio <0.80. B2: apoB/apoA1 ratio ≥0.80

after 1year of follow-up. Many studies have been conducted to identify risk factors for life-threatening complications and reliable prognostic criteria for ICH. Compared with neuroradiological findings, laboratory test parameters are relatively objective and easy to identify, enhancing the ability to predict hematoma expansion and ICH outcome.[14]

There are relatively few published studies about the apoB/apoA1 ratio and ICH outcomes in the literature. Our results support a study in which the apoB/apoA1 ratio was found to predict poor prognosis and mortality in metastatic renal cell carcinoma after a 1-year follow-up.[15] Data on the apoB/apoA1 ratio concerning stroke risk are not consistent. Previous studies reported that the ratio of apoB/apoA1 is a useful predictor of the risk of stroke, especially ischemic stroke.[16] In a long-term study, the apoB/apoA1 ratio was the most potent independent risk factor for ischemic stroke, followed by apoB.[17] Compared with the TC/HDL-C ratio, the apoB/

apoA1 ratio level has recently been reported to be more accurate in predicting clinical outcomes and first ischemic stroke in individuals over 70years old.[5,18] However, our findings are consistent with more recent studies that reported a relationship between the ratio of apoB/apoA1 and outcomes. Therefore, the apoB/apoA1 ratio may provide a more accurate method to evaluate the balance of the pro-atherogenic properties of LDL-C particles and the antiatherogenic properties of HDL-C particles. At the 3-month follow-up, the ratio value of apoB/apoA1 in the B2 group was still higher than that in the B1 group, and so were the apoB levels. This suggests that patients with poor prognosis had poor lipid control to some extent, which may be related to metabolic function or lifestyle changes.

An increase in the apoB/apoA1 ratio indicates an increase in the degree of atherosclerosis.[19,20] Using AMORIS data, Walldius G found that a high apoB/apoA1 ratio as well as high levels of TC and TG were associated with fatal stroke.[21] Sato Y's study showed that for hemodialysis patients, a higher apoB/apoA1 ratio was positively correlated with increased all-cause and mortality of cardiovascular risk.[22] In a large study, the apoB/apoA1 ratio was related to mortality in coronary heart disease.[23] In Model 4, we concluded that there was an independent association between the apoB/apoA1 ratio and all-cause mortality after 1year (*p* = 0.025), even after adjusting for age, sex, smoking, BMI, alcohol, baseline hematoma site and volume, and other lipid levels.

The relationships between apoA1 and apoB levels and outcomes were also studied. ApoA1 was strongly linked to HDL-C and the apoB/apoA1 ratio, and apoB was correlated with LDL-C, CHO, and the apoB/apoA1 ratio. Previous research has shown that the apoB/apoA1 ratio along with apoB and apoA1 levels are better at predicting stroke than traditional lipid profile components.[24] A strong correlation between apoA1 and coronary heart disease has been found in prospective studies of the general population.[25] In our research, we discovered that apoA1 exhibited a greater correlation with functional outcomes (mRS ≥3 or 4) in unadjusted and adjusted models. We propose that in the adjustment and application of apoA1, the follow-up time and the population differences are essential.

ApoB, but not apoA1, was a strong predictor of mortality and cardiovascular risk in multiple studies.[26,27] In contrast to these studies, we found no evidence that apoB was linked to those incidents.

TABLE 2 Correlations between the apoB/apo A1 ratio and the parameters of lipids and coagulation

	apoB/apoA1	TG	CHO	LDL-C	HDL-C	apoA1	apoB
TG	0.240[**]						
CHO	0.465[**]	0.514[**]					
LDL-C	0.664[**]	0.055	0.486[**]				
HDL-C	−0.464[**]	−0.073	0.249[**]	0.148[*]			
apoA1	−0.567[**]	0.062	0.259[**]	0.103	0.835[**]		
apoB	0.728[**]	0.383[**]	0.807[**]	0.664[**]	0.086	0.099	
FIB	0.217[**]	0.043	0.114	0.010	−0.169[*]	−0.183[**]	0.111

Abbreviations: apoA1, apolipoprotein A1; apoB, apolipoprotein B; CHO, cholesterol; FIB, fibrinogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

* Correlation is significant at the 0.01 level (two-tailed).; ** Correlation is significant at the 0.05 level (two-tailed).

TABLE 3 Associations between apoA1 levels, apoB levels, and the apoB/apoA1 ratio and mRS, all-cause mortality and stroke recurrence

	apoA1		apoB		apoB/apoA1 ratio[e]	
Variables	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
mRS 3–6						
Model 1[a]	0.10 (0.03,0.34)	**0.000**	1.23 (0.44,3.45)	0.689	2.18 (1.25,3.80)	**0.006**
Model 2[b]	0.11 (0.03,0.48)	**0.003**	2.37 (0.67,8.46)	0.183	2.57 (1.27,5.22)	**0.009**
Model 3[c]	0.02 (0.10,0.44)	**0.002**	8.96 (0.89,90.05)	0.063	2.75 (1.28,5.89)	**0.009**
Model 4[d]	0.003 (0.00,0.06)	**0.000**	1.18 (0.05,24.01)	0.910	3.76 (1.37,10.40)	**0.010**
mRS 4–6						
Model 1[a]	0.09 (0.02,0.36)	**0.001**	0.85 (0.26,2.77)	0.791	5.02 (1.54,16.39)	**0.007**
Model 2[b]	0.07 (0.01,0.37)	**0.002**	1.03 (0.99,1.05)	0.106	8.50 (1.92,37.68)	**0.005**
Model 3[c]	0.06 (0.01,0.35)	**0.002**	2.44 (0.23,25.35)	0.453	17.64 (3.14,98.92)	**0.001**
Model 4[d]	0.01 (0.00,0.23)	**0.007**	0.06 (0.00,3.20)	0.165	22.74 (1.08,474.65)	**0.044**
All-cause mortality						
Model 1[a]	0.22 (0.03,1.66)	0.142	2.95 (0.51,17.15)	0.228	2.87 (0.98,8.37)	0.053
Model 2[b]	0.19 (0.02,2.27)	0.193	6.29 (0.85,47.73)	0.072	6.37 (1.31,30.96)	**0.022**
Model 3[c]	0.12 (0.01,1.60)	0.109	5.24 (0.19,145.54)	0.328	5.49 (1.06,28.39)	**0.042**
Model 4[d]	0.37 (0.005,27.08)	0.655	26.35 (0.19,3488.04)	0.189	7.23 (1.28,40.88)	**0.025**
Stroke recurrence						
Model 1[a]	0.15 (0.01,1.65)	1.121	2.55 (0.32,20.23)	0.375	2.12 (0.62,7.27)	0.231
Model 2[b]	0.17 (0.01,2.60)	0.204	4.09 (0.41,40.52)	0.228	2.05 (052,8.08)	0.304
Model 3[c]	0.08 (0.00,1.72)	0.106	12.17 (0.20,725.91)	0.231	2.11 (0.47,9.50)	0.331
Model 4[d]	0.09 (0.004,2.09)	0.133	13.43 (0.05,3416.32)	0.358	2.35 (0.40,13.68)	0.341

Abbreviations: 95% CI, 95% confidence intervals; apo A1, apolipoprotein A1; apo B, apolipoprotein B; mRS, modified Rankin Scale; OR, odds ratio.

[a] Model 1: unadjusted.

[b] Model 2: adjusted for age, sex, BMI, smoking, and alcohol.

[c] Model 3: Model 2 adjusted for cholesterol and triglyceride.

[d] Model 4: Model 3 adjusted for LDL-C, HDL-C, FIB, and baseline hematoma site and volume.

[e] B2 versus B1; B1: apoB/apoA1 ratio <0.80.; B2: apoB/apoA1 ratio ≥0.80.

Bold indicates the *p* less than 0.05.

It is worth further exploring the differences between our research results and those of other studies. The follow-up period in this study was just 1 year. This is much shorter than the follow-up periods in other studies, which were longer than 7 years. In addition, increased apoB levels were only associated with the first ischemic stroke. Future research should focus on elucidating these inconsistencies.

In various studies, the correlations between total cholesterol, triglyceride, LDL-C, and HDL-C levels and stroke risk are less robust than that noted for coronary heart disease. In a previous study, hypercholesterolemia was correlated with poor outcome in stroke at both admission and discharge. High LDL-C, low HDL-C, and high triglyceride levels were associated with a high mRS score at admission

and severe stroke in the same population.[28] In a case–control study, the ratio of apoB/apoA1 and apoB, total cholesterol, LDL-C, and triglyceride levels were significantly increased in stroke cases compared with controls.[29] Yuwei Chen confirmed the association between low cholesterol levels and poor outcomes after a 3-month follow-up in ICH patients.[30] After 90 days of follow-up, Hao Feng et al. reported higher non-HDL-C levels and a decreased prevalence of poor functional outcomes.[31]

It should be noted that this is a single-center study. The enrolled patients only represented the northern area around Beijing. Table 1 shows that the median NIHSS score for both groups was 7, which
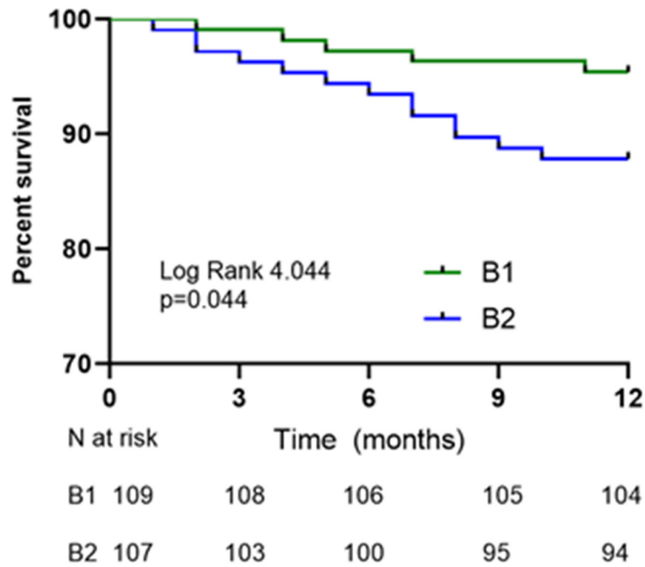
mean that the whole cohort had a moderate stroke. Therefore, patients may have a relatively long survival time, and it is essential for us to find early potential biomarkers to predict outcomes to elevate the quality of life at an early stage. However, this can also explain why the mortality is lower than that in other similar studies. Table 1 also shows that there was some unbalanced distribution of the hematoma site, although the p-value was over 0.05. To exclude the influence of the bleeding site, we first adjusted the results during logistic regression analysis. Second, we statistically analyzed the site distribution between the groups with good (mRS < 3) and poor functional outcomes (mRS ≥ 3). The results showed that the bleeding site had no significant differences between the groups (Table S1).

It is crucial to consider the relative strengths and weaknesses of the study. The study samples were representative of the adult population in North China, and the study employed a retrospective design. As a result, the current findings cannot be applied to the entire adult Chinese population. The apoB/apoA1 ratio was an important predictor of ICH outcome and mortality, and apoA1 was also a better predictor of functional outcomes. These findings suggest that apolipoprotein testing is superior to routine clinical lipid testing in identifying patients at risk of poor outcomes. However, some limitations must still be considered. Because this was a real-world retrospective study, we were not sure how many cases could be enrolled. Therefore, we did not calculate the sample size. Additionally, the number of patients was relatively small, and we did not evaluate the outcome at discharge. Our study did not exclude patients taking lipid-lowering drugs but only applied baseline data. Moreover, this cohort study did not adjust for potential risk factors due to the sample size being limited. As a consequence, there is little possibility to eliminate those residual confounding factors. The improvement of these issues will be the focus of our future studies.
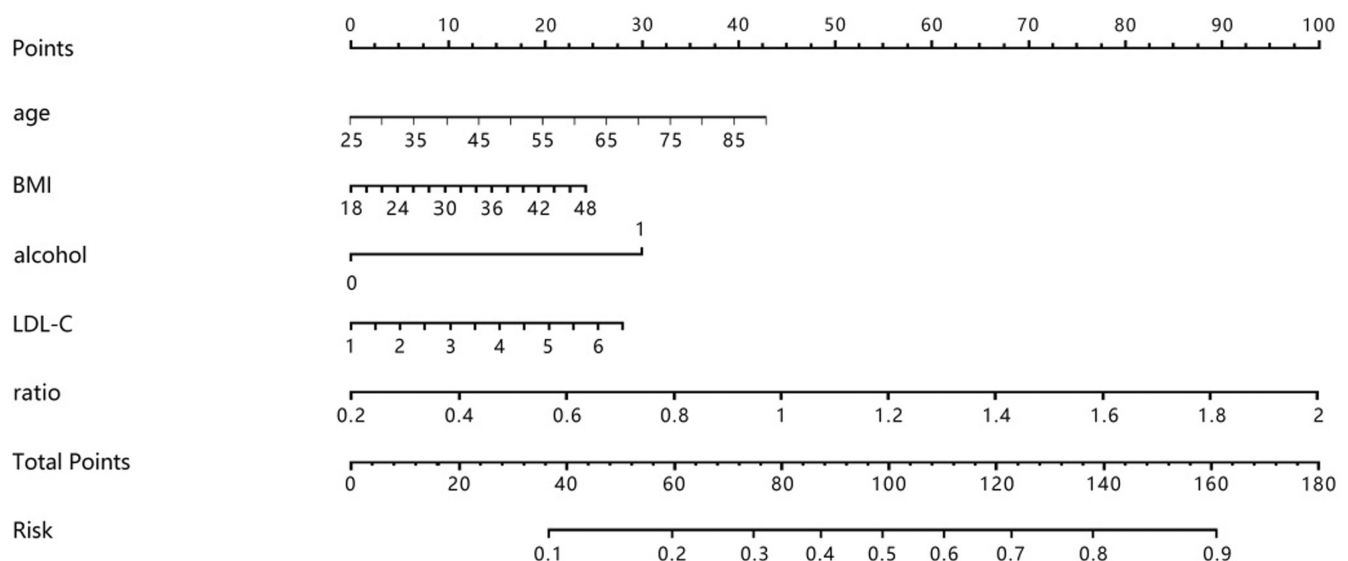

FIGURE 3 Survival curves for patients stratified by the apoB/apoA1 ratio. B1: apoB/apoA1 ratio <0.80. B2: apoB/apoA1 ratio ≥0.80

FIGURE 4 Nomogram developed by logistic regression. Each selected variable is represented by a line in the figure. Total points are added for each variable and matched with the probability of poor functional outcome of mRS 3–6. Ratio, apoB/apoA1 ratio

5 | CONCLUSIONS

In summary, strong associations between the apoB/apoA1 ratio and the functional outcomes (calculated by mRS) and all-cause mortality in ICH patients were found in this study. The apoB/apoA1 ratio is a potential marker that can reflect the risk of poor outcomes, including functional outcomes and all-cause mortality, in ICH patients at a 1-year follow-up.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data in this study are available upon request to the corresponding author.

INFORMED CONSENT

Written informed consent was obtained from all participants or their legal representatives.

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