Research Square

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Increased Admission Serum Total Bile Acids can be Associated with Decreased 3-month Mortality in Patients with Acute Ischemic Stroke

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Research

Keywords: Total bile acids, Acute ischemic stroke, Stroke severity, In-hospital complications, Mortality

Posted Date: November 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1045356/v1

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Version of Record: A version of this preprint was published at Lipids in Health and Disease on January 22nd, 2022. See the published version at https://doi.org/10.1186/s12944-021-01620-8.

Abstract

Background: Bile acids not only play an important role in lipid metabolism and atherosclerosis, but also have anti-apoptosis and neuroprotective effects. However, few studies have focused on the relationship of TBA levels with the severity and prognosis of AIS.

Objectives: The aim of this study is to investigate the potential associations of admission fasting serum TBA levels with stroke severity, in-hospital complication incidence and 3 -month all-cause mortality in patients of AIS.

Methods: A total of 777 AIS patients were finally enrolled in this study and divided into four groups according to the quartiles of serum TBA levels on admission.

Results: Patients in group Q3 had the lowest risk of severe AIS (NIHSS > 10) regardless of the adjustments for confounders ($P < 0.05$). During hospitalization, 115 patients (14.8%) had stroke progressed (NIHSS score increased by ≥ 2), and 222 patients (28.6%) developed at least one complication, with no statistical difference among the four groups ($P > 0.05$). There was no significant difference in the incidence of pneumonia, urinary tract infection (UTI), hemorrhagic transformation (HT), gastrointestinal bleeding (GIB), seizures and renal insufficiency (RI) among the four groups ($P > 0.05$). A total of 114 patients (14.7%) died from various causes (including in-hospital deaths) at 3-month follow-up, respectively 42 (21.3%), 26 (13.3%), 19 (9.9%) and 27 (13.9%) in groups Q1, Q2, Q3 and Q4 with statistical difference ($P = 0.013$). After adjustments for confounding factors, the risk of death decreased (P-trend < 0.05) in groups Q2, Q3, and Q4 progressively compared with group Q1, with OR values of 0.36 (0.16-0.80), 0.30 (0.13-0.70), and 0.29 (0.13-0.65), respectively.

Conclusions: TBA level presents no significant association with the severity of stroke and incidence of complications in patients of AIS, but negatively correlates to the risk of death within 3 months of onset.

Introduction

As the population aging goes increasingly intensive, stroke has become the second cause of death worldwide after ischemic heart disease[1], and is also associated with a high rate of disability and recurrence, which brings a great burden to society and families, especially in low- and middle-income countries[2]. Ischemic stroke is the most prevailing type in all stroke events. In 2017, acute ischemic stroke (AIS) was reported to take up 65% of all stroke events globally, primary intracerebral hemorrhage (PICH) for approximately 26%, and subarachnoid hemorrhage (SAH) for 9%[3–5]. Managements like early intravenous thrombolysis and endovascular treatment can allow the occluded blood vessels to be recanalized leading to blood reperfusion, which may reduce the infarct volume and effectively improve the overall prognosis of stroke patients. Besides, the therapeutic time window of reperfusion for AIS continuous to extend along with the development of neuroimaging techniques, while most patients fail to receive reperfusion treatment as they are out of the time window, which affects the prognosis[6–12].

Moreover, patients suffering from AIS, especially the elderly, are commonly accompanied with certain complications, such as post-stroke pneumonia and gastrointestinal bleeding, leading to a higher risk of early death as a result of a joint effect together with AIS[13–15].

Hypercholesterolemia is a major risk factor for atherosclerosis as well as a common cause of coronary heart disease, stroke, peripheral vascular disease, aortic aneurysm, and renal artery stenosis[16,17]. In the human body, cholesterol excretion is completed following a conversion into bile acids, which are essential in the body's lipid metabolism and cholesterol homeostasis[18]. Previous research found that increased bile acid excretion indicated a reduced risk of coronary heart disease[19], and lower fasting serum total bile acid (TBA) was closely associated with the progress of coronary heart disease, myocardial infarction, and coronary artery disease[20]. Additionally, a 20-year prospective follow-up study identified that reduced bile acid excretion was an independent risk factor for stroke incidence and death[21].

In addition to being associated with lipid metabolism, bile acids were also reported to be active in cellular protection and anti-apoptosis in rats of acute stroke and acute myocardial infarction[22–25], as well as in the reduction of glial cell activation in animal models of acute neuroinflammation[26]. A clinical trial found that there is a potential relationship between increased serum TBA levels and a smaller hematoma volume during cerebral hemorrhage as well as a better outcome[27]. Ursodeoxycholic acid (UDCA) can be used to treat chronic heart failure by improving peripheral blood flow[28], while tauroursodeoxycholic acid (TUDCA) has anti-apoptotic effects on a number of neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease[29].

To our knowledge, no one has probed into serum TBA levels for associations with the clinical manifestations and early prognosis of patients with AIS. Here, we try to fill the gap by initially exploring the relationship between fasting TBA levels on admission and several AIS-related targets including stroke severity, in-hospital complications, and 3-month mortality.

Materials And Methods

Study population

A total of 777 AIS patients treated in the Department of Neurology, Zhangjiagang Hospital of Traditional Chinese Medicine affiliated to Nanjing University of Chinese Medicine in China from April 2012 to January 2016 were eventually included in the study. Diagnosis of AIS was made by two or more neurologists after admission to our hospital based on the patient's medical history, clinical presentation, and brain computed tomography (CT) or magnetic resonance imaging (MRI) manifestations, according to World Health Organization (WHO) standards as follows: clinical pictures of sudden focal or complete neurological deficit, or neurological deficit lasting more than 24 h, exclusion of brain dysfunction caused by other non-vascular factors, along with diagnosis evidenced by brain CT or MRI. All patients enrolled (n=983) had stable vital signs on admission without severe disturbance of consciousness or severe

dysfunction of other organs. Patients with more than 72 h from onset to admission (n=102) and those without TBA measurements within 24 h of admission (n=45) were excluded. Besides, patients who had severe hepatobiliary or renal disease prior to or on admission (n=17), underlying blood disease or cancer (n=16), current any infections or immune system disease (n=12) or were lost to follow-up at 3 months of admission (n=14) were excluded as well (Figure 1).

Ethics statement

Approval of the Ethics Committee of Zhangjiagang TCM Hospital Affiliated to Nanjing University of Chinese Medicine in China, was gained before starting the study, regardless of the retrospective nature, while written informed consent was waived. The study was fully complied with the Declaration of Helsinki and obtained required data from the clinical records without any clinical intervention for the protection of patient privacy.

Data collection

Baseline information comprised demographic characteristics (such as gender, age) and known risk factors for cerebrovascular disease (such as stroke, hypertension, diabetes, atrial fibrillation, coronary heart disease, heart failure, smoking and drinking history). The time from onset to admission, stroke severity (National Institutes of Health Stroke Scale, NIHSS), previous thrombolytic therapy, clinical data and laboratory indexes on admission (such as systolic blood pressure, diastolic blood pressure, blood routine, serum TBA, liver function, blood glucose, blood lipid, creatinine, uric acid) and in-hospital complications were recorded. Laboratory data were obtained in the emergency department before hospital admission or in the ward within 24 h after hospital admission. Blood routine data were obtained by XE-5000 (Mindray, China). Biochemical data were obtained from fasting blood samples with Olympus AU5400 Automatic Analyzer (First Chemical Co., Ltd, Japan). All the tests were completed by the experts from the Laboratory Department of our hospital.

Outcome evaluation

The NIHSS score on admission was used to represent the severity of stroke on admission. A NIHSS score greater than 10 was defined as severe stroke, and a NIHSS score increased by more than 2 points was defined as progressive AIS during the hospitalization. Six complications of relatively high incidence, including pneumonia, urinary tract infection (UTI), hemorrhagic transformation (HT), gastrointestinal bleeding (GIB), seizures, and renal insufficiency, were included in the study. Definitions for these complications are depicted in Table 1. Three-month death was determined by telephone interviews of the patients or their families three months after onset.

Table 1
Definitions of progressive cerebral infarction and in-hospital complications.

Complications	Definitions
Progressive cerebral infarction	The patients whose NIHSS score increased more than two points after hospitalization.
Pneumonia	Presented at least 3 of the following manifestations: new or aggravated cough and expectoration; increased respiratory rate (≥22 times/min); fever (temperature>38°C); peripheral blood WBC count decreased (<4×10^9/L), or increased (>11×10^9/L), or increased neutrophil ratio; Auscultatory respiratory moist rales; abnormal chest radiology (patchy infiltration, lobar consolidation, or pleural effusion).
Urinary tract infection	Clinical symptoms of urinary tract infection combined with an increase in white blood cell and bacterial counts on routine urine tests, or bacterial growth in urine culture.
Hemorrhagic transformation	Hemorrhage in the infarct area or other parts of the brain parenchyma.
Gastrointestinal bleeding	Having coffee-ground emesis, hematemesis, and blood in nasogastric tube, melena, or blood in rectum, accompanied by blood routine tests showing a decrease in hemoglobin than before, or vomit, fecal occluded blood test is positive.
Seizures	Previously nonepileptic patients presented focal seizure and/or generalized seizure.
Renal insufficiency	Estimated glomerular filtration rate (eGFR)<60 mL/min.

Statistical analysis

The quartiles of TBA levels on admission were referenced to divide patients into four groups (Q1, ≤3.0 μmol/L; Q2, 3.0-5.7 μmol/L; Q3, 5.7-9.5 μmol/L; Q4, >9.5 μmol/L). SPSS software (Version 23.0; IBM, Armonk, NY, USA) was operated for statistical analysis, and a two-tailed P value <0.05 was a statistically significant event.

Since four groups were generated with the total sample size ≥200 (each >100), continuous variables were analyzed in normality with the Kolmogorov-Smirnov test, and represented by mean (standard deviation) via one-way ANOVA in cases of all four groups are in normal distribution or median (interquartile range) via Kruskal-Wallis test when one of the four groups does not conform to the normal distribution. Categorical variables were compared by Chi-square test or Fisher's exact probability method.

Correlation analysis for serum TBA with severe AIS on admission and 3-month all-cause mortality was run on univariate and multivariate logistic regression models. In the multivariate logistic regression model, the independence of TBA was identified following adjustments for covariates. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each group using the lowest quartile (Q1) of TBA as

a reference. The *P*-trend in trend test was obtained by involving the median value of Q1, Q2, Q3 and Q4 groups into regression analysis.

Results

Baseline characteristics

Totally, 777 eligible patients (420 males and 357 females) with AIS were enrolled in the study, with a mean age of 71 (62-78) years and a mean NIHSS score of 4 (3-8) on admission. Patients were assigned into groups Q1 (≤ 3.0 μmol/L, n = 197), Q2 (3.0-5.7 μmol/L, n = 195), Q3 (5.7-9.5 μmol/L, n = 191) and Q4 (> 9.5 μmol/L, n = 194) according to the quartiles of fasting serum TBA concentration on admission, associated with NIHSS scores of 5, 5, 4 and 4, respectively, with no significant differences (p = 0.389) (Table 2). No significant differences were noted in baseline demographic, clinical and laboratory parameters (including blood lipid) (p > 0.05), except for the history of atrial fibrillation (AF) and admission white blood cell (WBC) count (p < 0.05), among the four groups.

Table 2
Baseline characteristics of AIS patients according to quartiles of admission serum TBA.

Variables	Total (777)	Q 1 ≤3.0 (197)	Q 2 3.0-5.7 (195)	Q 3 5.7-9.5 (191)	Q 4 >9.5 (194)	*P*-value
Age (years), median (IQR)	71 (62-78)	69 (61-77)	70 (62-78)	71 (62-78)	72 (63-79)	0.623
Gender (male), n (%)	420 (54.1%)	104 (52.8%)	100 (51.3%)	109 (57.1%)	107 (55.2%)	0.677
Time from onset to admission (hours), median (IQR)	11 (3-25)	9 (3-22)	13 (4-28)	12 (4-27)	8 (3-27)	0.156
NIHSS score on admission, median (IQR)	4 (3-8)	5 (3-8)	5 (3-8)	4 (3-6)	4 (3-8)	0.389
Thrombolytic therapy, n (%)	31 (4.0%)	11 (5.6%)	2 (1.0%)	7 (3.7%)	11 (5.7%)	0.064
SBP (mmHg), median (IQR)	150 (140-170)	155 (140-170)	150 (140-163)	150 (140-170)	150 (130-170)	0.861
DBP (mmHg), median (IQR)	89 (80-95)	87 (80-95)	90 (80-95)	90 (80-98)	89 (80-95)	0.929
Previous stroke, n (%)	185 (23.8%)	42 (21.3%)	50 (25.6%)	45 (23.6%)	48 (24.7%)	0.769
Hypertension, n (%)	547 (70.4%)	139 (70.6%)	143 (73.3%)	129 (67.5%)	136 (70.1%)	0.667
Diabetes, n (%)	179 (23.0%)	43 (21.8%)	49 (25.1%)	43 (22.5%)	44 (22.7%)	0.876
Coronary heart disease, n (%)	37 (4.8%)	9 (4.6%)	13 (6.7%)	8 (4.2%)	7 (3.6%)	0.516
Atrial fibrillation, n (%)	113 (14.5%)	28 (14.2%)	27 (13.8%)	18 (9.4%)	40 (20.6%)	0.020
Heart failure, n (%)	23 (3.0%)	4 (2.0%)	5 (2.6%)	5 (2.6%)	9 (4.6%)	0.443
Smoking history, n (%)	210 (27.0%)	51 (25.9%)	47 (24.1%)	58 (30.4%)	54 (27.8%)	0.548
Drinking history, n (%)	166 (21.4%)	42 (21.3%)	39 (20.0%)	48 (25.1%)	37 (19.1%)	0.487
WBC ($\times 10^9$/L), median (IQR)	6.4 (5.3-8.1)	6.8 (5.6-8.5)	6.3 (5.0-7.8)	6.7 (5.4-8.3)	6.3 (5.1-7.9)	0.032

Variables	Total (777)	Q 1 ≤3.0 (197)	Q 2 3.0-5.7 (195)	Q 3 5.7-9.5 (191)	Q 4 >9.5 (194)	*P* value
Platelet (×10^9/L), median (IQR)	178 (143-217)	185 (150-225)	173 (139-217)	182 (151-216)	170 (138-205)	0.072
Hemoglobin concentration (g/L), median (IQR)	135 (123-146)	134 (121-145)	134 (123-146)	136 (127-146)	134 (124-145)	0.373
ALB (g/L), mean (SD)	38.5 (3.3)	38.6 (3.3)	38.8 (3.3)	38.6 (3.4)	38.3 (3.2)	0.666
ALT (U/L), median (IQR)	19 (13-26)	19 (13-25)	19 (13-27)	18 (14-25)	19 (14-28)	0.941
AST (U/L), median (IQR)	23 (19-28)	23 (19-28)	23 (19-28)	22 (19-27)	23 (19-27)	0.546
Blood glucose (mmol/L), median (IQR)	5.5 (4.9-6.7)	5.7 (5.0-6.9)	5.6 (4.8-7.0)	5.4 (4.9-6.3)	5.5 (5.0-6.7)	0.537
TG (mmol/L), median (IQR)	1.3 (0.9-1.8)	1.2 (0.9-1.7)	1.3 (0.9-1.9)	1.4 (1.0-1.9)	1.3 (0.9-1.9)	0.173
TC (mmol/L), median (IQR)	4.6 (3.9-5.3)	4.7 (3.9-5.2)	4.6 (3.9-5.3)	4.5 (3.9-5.3)	4.5 (3.9-5.2)	0.976
LDL-C (mmol/L), mean (SD)	2.7 (0.9)	2.7 (0.8)	2.8 (1.0)	2.7 (0.9)	2.6 (0.9)	0.577
HDL-C (mmol/L), median (IQR)	1.3 (1.0-1.5)	1.3 (1.0-1.5)	1.2 (1.1-1.5)	1.2 (1.0-1.5)	1.3 (1.0-1.6)	0.510
SCr (μmol/L), median (IQR)	72 (60-84)	70 (59-84)	72 (62-83)	72 (61-82)	71 (57-85)	0.900
Uric acid (μmol/L), median (IQR)	304 (234-381)	287 (223-379)	303 (238-387)	308 (237-380)	310 (238-381)	0.655

Correlation between serum TBA and AIS severity

The numbers and proportions of severe AIS cases (NIHSS > 10) among the four groups were statistically different (p = 0.029), much higher in groups Q1 (n = 41, 20.8%) and Q4 (n = 36, 18.6%), and lower in groups Q2 (n = 28, 14.4%) and Q3 (n = 20, 10.5%) (Table 3). Binary logistic regression analysis showed that, patients in group Q3 had a significantly lower risk of severe AIS than those in group Q1 (OR, 0.45; 95% CI, 0.25-0.79) before adjustments. While in multivariate-adjusted models (Model 1 for age and gender, and Model 2 for age, gender, thrombolytic therapy, history of AF, WBC count, platelet count), as compared to group Q1, patients in groups Q2 and Q3 had a lower risk of severe AIS, which was not

reflected in group Q4. Besides, and p-trend was greater than 0.05 regardless of adjustment for other confounding factors, and no significant trend was displayed.

Table 3
Odds ratios and 95% confidence intervals of severe AIS by quartiles of admission serum TBA (n=125).

TBA quartiles (μmol/L), range (median)	severe AIS, n (%)	Unadjusted OR (95% CI)	Model 1 Adjusted OR (95% CI)	Model 2 Adjusted OR (95% CI)
Q 1 ≤3.0 (1.8)	41 (20.8%)	1 (reference)	1 (reference)	1 (reference)
Q 2 3.0-5.7 (4.4)	28 (14.4%)	0.64 (0.38-1.08)	0.57 (0.33-0.99)	0.65 (0.36-1.19)
Q 3 5.7-9.5 (7.3)	20 (10.5%)	0.45 (0.25-0.79)	0.42 (0.23-0.76)	0.40 (0.21-0.78)
Q 4 >9.5 (12.7)	36 (18.6%)	0.87 (0.53-1.43)	0.79 (0.47-1.32)	0.76 (0.43-1.37)
P-trend	*P*=0.029	0.708	0.544	0.378
Model 1, adjusted for age and gender.				

Model 2, adjusted for age, gender, thrombolytic therapy, history of atrial fibrillation, admission WBC and platelet count.

Association between serum TBA and in-hospital complications

During hospitalization, 115 (14.8%) of the 777 patients had aggravated AIS (NIHSS score increased by ≥ 2 points), showing no significant difference among the four groups (p = 0.584). There were 222 (28.6%) cases developing at least one complication, with no significant difference among the groups (p = 0.906), and the incidence rates of pneumonia, UTI, HT, GIB, seizures, and renal insufficiency were 11.7%, 9.1%, 9.5%, 2.1%, 0.9%, 2.4%, respectively, still with no significant difference among the four groups (all p > 0.05). The detailed results are shown in Table 4.

Table 4
Proportions of progressive cerebral infarction and different in-hospital complications after AIS according to quartiles of serum TBA.

Variables	Total	Q 1 ≤3.0 (1.8)	Q 2 3.0-5.7 (4.4)	Q 3 5.7-9.5 (7.3)	Q 4 >9.5 (12.7)	*P*-value
Progressive cerebral infarction, n (%)	115 (14.8%)	28 (14.2%)	30 (15.4%)	33 (17.3%)	24 (12.4%)	0.584
At least one complication, n (%)	222 (28.6%)	59 (29.9%)	57 (29.2%)	51 (26.7%)	55 (28.4%)	0.906
Pneumonia, n (%)	91 (11.7%)	27 (13.7%)	26 (13.3%)	16 (8.4%)	22 (11.3%)	0.343
UTI, n (%)	71 (9.1%)	15 (7.6%)	19 (9.7%)	17 (8.9%)	20 (10.3%)	0.808
HT, n (%)	74 (9.5%)	24 (12.2%)	20 (10.3%)	19 (9.9%)	11 (5.7%)	0.163
GIB, n (%)	16 (2.1%)	3 (1.5%)	2 (1.0%)	4 (2.1%)	7 (3.6%)	0.344
Seizures, n (%)	7 (0.9%)	1 (0.5%)	2 (1.0%)	3 (1.6%)	1 (0.5%)	0.585
Renal insufficiency, n (%)	19 (2.4%)	1 (0.5%)	7 (3.6%)	6 (3.1%)	5 (2.6%)	0.143

Correlation between serum TBA and 3-month all-cause mortality

The follow-up visit in 3 months witnessed 114 deaths (14.7%) from various causes (including hospital deaths), respectively 42 (21.3%), 26 (13.3%), 19 (9.9%) and 27 (13.9%) in groups Q1, Q2, Q3 and Q4, indicating statistical differences (p = 0.013) (Table 5). In Model 2 with adjustments for gender, age, NIHSS score on admission, AIS progress and occurrence of at least one complication during hospitalization, the 3-month all-cause mortality decreased with the increase of serum TBA content. The OR values of groups Q2, Q3, and Q4 compared to group Q1 were 0.36 (0.16-0.80), 0.35 (0.16-0.78), and 0.30 (0.14-0.66), respectively. In addition to the factors adjusted in Model 2, baseline indicators which affected the unadjusted OR value by more than 10% after addition were included, and finally a total of 7 covariates were included in Model 3 as a result of indicator selection and adjustments for history of AF and baseline WBC count. In this case, the OR values of groups Q2, Q3, and Q4 were 0.36 (0.16-0.80), 0.30 (0.13-0.70), and 0.29 (0.13-0.65), respectively, as compared to group Q1. In Model 2 and Model 3, both p-trend values were less than 0.05, indicating a decreased risk of 3-month mortality in reaction to the increase of serum TBA levels.

Table 5
Odds ratios and 95% confidence intervals of all-cause mortality at 3 months by quartiles of admission serum TBA (n=114).

TBA quartiles (μmol/L), range (median)	Death in 3 months, n (%)	Unadjusted OR (95% CI)	Model 1 Adjusted OR (95% CI)	Model 2 Adjusted OR (95% CI)	Model 3 Adjusted OR (95% CI)
Q 1 ≤3.0 (1.8)	42 (21.3%)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q 2 3.0-5.7 (4.4)	26 (13.3%)	0.57 (0.33-0.97)	0.44 (0.24-0.80)	0.36 (0.16-0.80)	0.36 (0.16-0.80)
Q 3 5.7-9.5 (7.3)	19 (9.9%)	0.41 (0.23-0.73)	0.34 (0.18-0.64)	0.35 (0.16-0.78)	0.30 (0.13-0.70)
Q 4 >9.5 (12.7)	27 (13.9%)	0.60 (0.35-1.01)	0.45 (0.25-0.82)	0.30 (0.14-0.66)	0.29 (0.13-0.65)
P-trend	*P*=0.013	0.072	0.021	0.007	0.005
Model 1, adjusted for age and gender.					
Model 2, adjusted for age, gender, NIHSS score on admission, progressive cerebral infarction and at least one complication during hospitalization.					
Model 3, adjusted for age, gender, NIHSS score on admission, progressive cerebral infarction and at least one complication during hospitalization, history of atrial fibrillation, admission WBC count.					

Discussion

Lipid metabolism disorders can cause cholesterol overload leading to excessive deposition of lipid substances, such as low-density lipoprotein cholesterol (LDL-C), within the intima of the large and medium-sized arteries, which is considered the culprit of atherosclerosis incidence and the main risk factor of coronary heart disease, cerebral infarction and other cardiovascular and cerebrovascular diseases[16,30–32]. Studies have shown that excessive cholesterol in human body can convertes into bile acids and finally be discharged from feces in the form of bile salts[30,33,34]. Large amounts of bile acid excretion can prevent atherosclerosis incidence, while the reduction can reversely lead to increased risk of atherosclerosis and coronary heart disease[19,35,36]. UDCA facilitates to prevent the occurrence of atherosclerosis and promote plaque regression with dissolved cholesterol crystals[37]. Gideon et al.[21] studied into in-hospital bile acid excretion in 68 men and 35 women admitted to hospital between 1996 and 1998 for chest pain and suspected cardiac events and followed for up to 20 years. They found a significant higher average bile acid excretion in subjects without stroke relative to those with stroke, while

those with lower bile acid excretion had higher stroke incidence and mortality, suggesting that reduced bile acid excretion was also an independent risk factor for stroke incidence and death.

In many animal experiments, bile acids, in addition to being a regulator for blood lipid and cholesterol content by participating in lipid metabolism, also act as a signal molecule that activates different nuclear receptors, such as farnesoid X receptor (FXR), pregnane X receptor (PXR), vitamin D receptor (VDR), and transmembrane G protein-coupled receptor 5 (TGR5), which reduces the risk of atherosclerosis via a variety of metabolic pathways in diverse tissues[20,32,33,38,39]. Bile acid chelates, such as coleswelen hydrochloride, can not only reduce LDL-C content, but also decrease hypersensitive C-reactive protein (hs-CRP) content to prevent atherosclerosis incidence[40].

Bile acids also show effects on anti-apoptosis and cellular protection. Andrew L. Rivard et al.[24] found reduced apoptosis and improved cardiac function in rats by TUDCA administration before myocardial infarction. In a rat model of acute stroke, bile acids TUDCA presented neuroprotective effects, and the underlying mechanism was proven with the involvement of enhanced cell apoptosis in response to inhibited mitochondrial disturbance and subsequent caspase activation[22]. Besides, TUDCA was found to negatively regulate Nrf2 signaling pathway to decrease lipid peroxidation, inflammation and apoptosis in ACI rats[41]. TUDCA can not only reduce the cell apoptosis of rats with acute hemorrhagic stroke and protect the nerve from being damaged[23], but also reduce the activation of glial cells in animal models of acute neuroinflammation[26]. Joana D. Amaral et al.[25] reviewed the role of bile acids in the regulation process of apoptosis, which highlighted the anti-apoptotic effects of UDCA and TUDCA, as well as their potential application as new and alternative drugs for the treatment of apoptosis-related diseases. All these certain evidences provide some basis for the conjecture that serum TBA may have a protective effect on AIS. However, to our knowledge, the relationship between serum TBA level and the severity of AIS, in-hospital complications, and short-term prognosis in patients with AIS has not been reported.

In our study, fasting serum TBA levels were found independent of the severity of AIS on admission, and there was no significant difference in NIHSS scores among patients with different TBA concentrations ($p = 0.389$). Additionally, the fasting serum TBA on admission also showed no correlation with the progress of AIS symptoms or the occurrence of in-hospital complications, but a certain relationship with the 3-month clinical outcome. Following adjustments for confounding factors, such as gender, age, NIHSS score on admission, in-hospital AIS progress and occurrence of at least one complication, AF, and baseline WBC count, low serum TBA levels were still an independent risk factor for death within 3 months in patients of AIS. Patients with higher serum TBA levels on admission had a lower risk of death within 3 months, and this trend was statistically significant (P-trend < 0.05). We speculated that this may be related to the neuroprotective and anti-apoptotic effects of bile acids, yet the specific mechanism remains to be clarified.

Here, we identified an association between high fasting serum TBA levels on admission and reduced mortality within three months after stroke in patients of AIS, yet the underlying causal relationship cannot be explained as this is only a single-center retrospective study with small sample size. Although we

adjusted for several covariates that might have an impact on the outcomes, there are still many possible influencing factors which have not been collected. Besides, we did not follow up the functional outcomes in patients with AIS who survived more than 3 months, thus we were unable to determine the effect of serum TBA on functional recovery. Different from other studies, our research did not observe significant correlations between serum TBA levels and serum lipid levels, including triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol[27,41], while evident associations with AF incidence and WBC count, which may require further large-scale studies to determine the reliability of our conclusion.

Conclusion

This study shows that admission fasting serum TBA levels were inversely associated with 3-month mortality of AIS patients, but not significant associated with the severity of stroke and incidence of complications. It suggests that serum TBA level may be a simple, cost-effective and readily available biomarker with additional predictive value for the prognosis of patients with AIS.

Abbreviations

AIS, acute ischemic stroke; PICH, primary intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TBA, total bile acid; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; UDCA, Ursodeoxycholic acid; TUDCA, tauroursodeoxycholic acid; CT, computed tomography; MRI, magnetic resonance imaging; WHO, World Health Organization; NIHSS, National Institutes of Health Stroke Scale; UTI, urinary tract infection; HT, hemorrhagic transformation; GIB, gastrointestinal bleeding; OR, Odds ratios; 95%CI, 95% confidence intervals; AF, atrial fibrillation; WBC, admission white blood cell; FXR, farnesoid X receptor; PXR, pregnane X receptor; VDR, vitamin D receptor; TGR5, transmembrane G protein-coupled receptor 5.

Declarations

Acknowledgements

N/A

Funding

This work was supported by Special research of Suzhou industrial technology Innovation (SYSD2017006).

Availability of data and materials

All data generated or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RZ and YS provided funding and designed the study. GX, FL and YW collected the data. LH, FL and JJ were involved in data cleaning, follow-up and verification. YS revised the article. All authors have read and approved the final manuscript.

Ethics approval

The retrospective cohort study was approved by the Ethics Committee of the Zhangjiagang TCM Hospital affiliated to the Nanjing University of Chinese Medicine.

Consent for publication

All authors agree to publish this article in the journal of Lipids in Health and Disease.

Competing interests

The authors declare that they have no competing interest.

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Figures

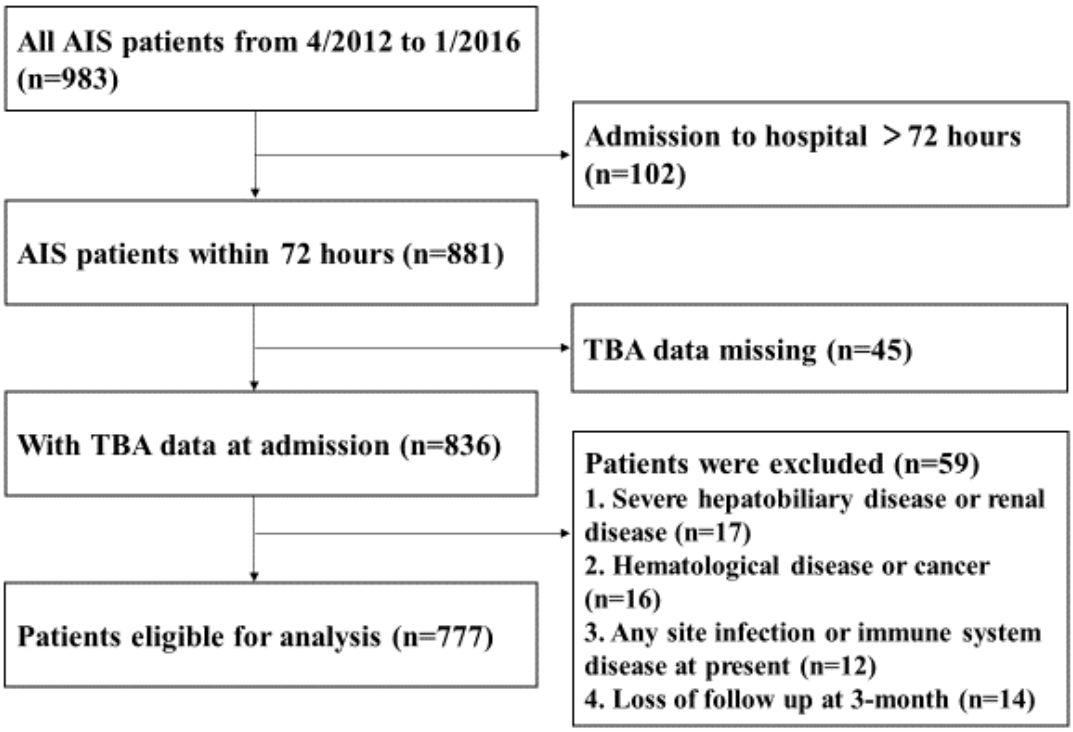

Figure 1

Research flowchart.

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