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The clinical value of triglyceride to high-density lipoprotein cholesterol ratio for predicting stroke-associated pneumonia after spontaneous intracerebral hemorrhage

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Abstract

Objective Stroke-associated pneumonia (SAP) is relevant to the poor functional outcomes of patients with spontaneous intracerebral hemorrhage (SICH). It is unclear if the triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio (TG/HDL-C) is related to the risk of SAP in SICH patients. This study aimed to investigate the association between TG/HDL-C and SAP in SICH patients.

Methods Consecutive patients with SICH were enrolled in this retrospective study. Relevant clinical variables were extracted from electronic medical records. All enrolled participants were divided into SAP ($n = 71$) and non-SAP ($n = 187$) groups. Multivariate binary logistic regression analysis was used to explore the association between TG/HDL-C and SAP. The optimal cutoff value of TG/HDL-C was defined by the receiver operating characteristic (ROC).

Results Among 258 patients, 71 (27.5%) had SAP. Patients with SAP were older (72.75 ± 11.10 vs. 64.81 ± 12.70 years), with a lower TG, higher HDL-C, and lower TG/HDL-C than participants in the non-SAP group. TG/HDL-C was an independent protective factor for SAP (adjusted OR 0.516, 95% CI 0.339–0.784) after adjusting for relevant risk factors. According to ROC analysis, the optimal cutoff value was a TG/HDL-C > 1.09 for decreased SAP [area under the ROC curve (AUC) 0.705; sensitivity 76.1% and specificity 59.4%]. Patients with a TG/HDL-C of > 1.09 were independently associated with decreased SAP (adjusted OR 0.285, 95% CI 0.138–0.591) after adjustment.

Conclusion This study suggests that a lower TG/HDL-C is independently associated with increased SAP after SICH.

Keywords Intracerebral hemorrhage, Stroke-associated pneumonia, Triglyceride, High-density lipoprotein cholesterol

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Introduction

Spontaneous intracerebral hemorrhage (SICH) is a neurovascular emergency with high rates of mortality and disability, accounting for 20–30% of all strokes [1–3]. SICH contributes substantially to the global burden of disease. Currently, there is still a lack of specific treatment available for SICH.

Stroke-associated pneumonia (SAP) is one of the most common respiratory complications after stroke and is related to poor outcomes and increased risk of post-stroke mortality [4–6]. SAP can cause brain hypoxia and inflammatory responses, which contribute to secondary brain injury, increasing the length of the hospital stay and treatment expenses [7, 8]. Furthermore, it has been reported that the incidence of SAP is higher in SICH than after acute ischemic stroke [5]. Therefore, SAP poses a severe threat to SICH patients' safety and care. The search for new objective and conveniently accessible biomarkers for predicting SAP may aid clinicians in diagnosing these patients in need of early and aggressive therapy.

Several studies have speculated that severe stroke, aspiration, dysphagia, nasogastric tubing, impaired bulbar reflexes, and end-stage renal disease are essential predictors of SAP after stroke [9–11]. Besides, dysregulation of lipid metabolism has been reported to be closely relevant to sepsis secondary to hospital-acquired pneumonia [12]. Triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio (TG/HDL-C), an atherogenic dyslipidemia parameter, is connected to metabolic syndrome, atherosclerosis, and cardio-cerebrovascular disease [13–15]. Previous studies have suggested that TG/HDL-C is relevant to hemorrhagic transformation and adverse clinical outcomes in acute cerebral infarction patients [16]. However, studies on the effects of TG/HDL-C on SAP after SICH are rarely reported. This study aimed to investigate the association of the TG/HDL-C with SAP after SICH.

Patients and methods

Study design and participants

In this retrospective study, we collected 258 consecutive patients with SICH presented at the Department of Neurology of Affiliated Hospital 2 of Nantong University between January 2019 and January 2023. Inclusion criteria: (1) diagnosis of intracerebral hemorrhage according to the 2013 AHA definition for hemorrhagic stroke [17]; (2) confirmed by computed tomography (CT) within 72 h of symptom onset; (3) available chest CT imaging; (4) aged ≥ 18 years. Exclusion criteria: (1) infratentorial intracerebral hemorrhage; (2) other types of intracerebral hemorrhage (aneurysm or arteriovenous malformation, trauma, tumor, primary ventricular hemorrhage, acute thrombolysis, and hemorrhagic cerebral infarction); (3) with pre-pneumonia before admission; (4) mechanical ventilation; (5) with serious systemic diseases such as severe hepatic, renal and cardiovascular dysfunction. All study data were analyzed in anonymized form. This study was approved by the Ethics Committee of Affiliated Hospital 2 of Nantong University, and the committee exempted the patient informed consent because the study had a retrospective design.

Clinical information and classification

In this study, the age, gender, and medical history (diabetes, hypertension, hyperlipidemia, smoking status, alcohol drinking status, anticoagulant and antiplatelet agent, and statin agent) were recorded for each subject. Measurement of blood pressure and peripheral venous blood samples after overnight fasting were obtained within 24 h of hospitalization. Plasma fasting blood glucose (FBG), TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and HDL-C were detected. Stroke severity and neurological deficits at admission were estimated by the National Institutes of Health Stroke Scale (NIHSS) [18]. The baseline hematoma volume was estimated based on the admission computed tomography using the ABC/2 method [19].

Study grouping

Patients were divided into two groups (SAP or non-SAP group) according to the presence or absence of SAP. SAP was defined as infections of the lower respiratory tract during the first seven days after SICH onset without mechanical ventilation, according to the modified Centers for Disease Control and Prevention criteria [20]. SAP was diagnosed independently by two experienced clinicians blinded to the clinical and laboratory results. Any discrepancies were resolved following discussions with a senior clinician.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) for normally distributed variables or median (interquartile range, IQR) for variables with skewed distribution. Categorical variables were represented as counts (percentages). Baseline characteristics between SAP and no-SAP were compared using chi-square tests for categorical variables and analysis of variance (normal distribution) or Mann-Whitney U test (skewed distribution) for continuous variables. The multivariable binary logistic regression analyses were used to explore the independent factors associated with SAP. The receiver operating characteristic (ROC) curves and the areas under the curve (AUC) were constructed to determine the predictive values of TG, HDL-C, and TG/HDL-C. The cutoff value of TG/HDL-C was also calculated to better distinguish the risk of SAP according to the highest Youden index values (Youden

Table 1 Baseline characteristics between patients with and without SAP

	Total ($n = 258$)	No-SAP ($n = 187$)	SAP ($n = 71$)	*p*
Demographic				
Age, years, mean ± SD	66.99 ± 12.76	64.81 ± 12.70	72.75 ± 11.10	<0.001
Sex, male, *n*(%)	180(69.8%)	127(67.9%)	53(74.6%)	0.293
Medical history				
Smoking, *n*(%)	56(21.7%)	41(21.9%)	15(21.1%)	0.890
Alcohol drinking, *n*(%)	64(24.8%)	44(23.5%)	20(28.2%)	0.441
Diabetes, *n*(%)	52(20.2%)	39(20.9%)	13(18.3%)	0.649
Hypertension, *n*(%)	212(82.2%)	154(82.4%)	58(81.7%)	0.901
Hyperlipidemia, *n*(%)	112(43.4%)	91(48.7%)	21(29.6%)	0.006
Antiplatelet medication, *n*(%)	31(12.0%)	24(12.8%)	7(9.9%)	0.512
Anticoagulant medication, *n*(%)	8(3.1%)	4(2.1%)	4(5.6%)	0.148
Statin medication, *n*(%)	30(11.6%)	23(12.3%)	7(9.9%)	0.585
Clinical features				
SBP, mmHg, mean ± SD	156.14 ± 19.51	154.80 ± 19.99	159.89 ± 17.69	0.071
DBP, mmHg, mean ± SD	89.52 ± 13.28	89.49 ± 12.88	89.60 ± 14.46	0.954
NIHSS, median(IQR)	6(3–13)	5(2–9)	14(6–25)	<0.001
Hematoma volume, ml, median(IQR)	6.55(2.85–14.11)	5.89(2.68–12.42)	8.83(4.44–18.74)	<0.001
Laboratory examination				
FBG, mmol/L, median(IQR)	5.57(5.05–6.76)	5.54(5.04–6.60)	5.82(5.09–6.92)	0.279
TC, mmol/L, median(IQR)	4.34(3.85–4.87)	4.36(3.88–4.95)	4.34(3.70–4.78)	0.238
TG, mmol/L, median(IQR)	1.31(0.94–1.93)	1.44(1.03–2.13)	1.19(0.70–1.56)	<0.001
HDL-C, mmol/L, median(IQR)	1.22(1.07–1.44)	1.19(1.04–1.40)	1.33(1.12–1.60)	0.002
LDL-C, mmol/L, mean ± SD	2.74 ± 0.94	2.81 ± 0.98	2.53 ± 0.78	0.029
TG/HDL-C, median(IQR)	1.07(0.72–1.71)	1.27(0.81–1.94)	0.84(0.46–1.13)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; FBG, plasma fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG/HDL-C, TG to HDL-C ratio. *P* values were calculated using the variance (normal distribution) and Mann-Whitney U test (skewed distribution) for continuous variables or the χ2 test for categorical variables

index = sensitivity + specificity −1). $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 23.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics between patients with or without SAP

The baseline characteristics of all patients are shown in Table 1. In total, 258 patients suffering from SICH were enrolled in the analysis; the mean age was 66.99 ± 12.76 years old (range 31–97 years), and 180 (69.8%) patients were male. For vascular risk factors, 212 patients (82.2%) had hypertension, 52 patients (20.2%) had diabetes mellitus, 112 patients (43.4%) had hyperlipidemia, 56 (21.7%) were former or current smokers and 64 (24.8%) had a history of alcohol consumption. The admission NIHSS score was 6(3–12) and the baseline hematoma volume was 6.55 mL (2.85–14.11 mL). Compared with participants in the non-SAP group, those in the SAP group were more likely to be older (p<0.001), to have higher NIHSS scores (p<0.001), concentrations of HDL-C ($p = 0.002$) and larger hematoma volume (p<0.001), to have lower TG (p<0.001) and TG/HDL-C (p<0.001) levels.

Table 2 Multiple analyses between TG/HDL-C and SAP

	Unadjusted		Adjusted*	
	OR(95%CI)	***P***	**OR(95%CI)**	***P***
TG	0.400(0.252–0.635)	<0.001	0.497(0.323–0.766)	0.002
HDL-C	5.413(2.168–13.514)	<0.001	3.171(1.134–8.870)	0.028
TG/HDL-C	0.397(0.251–0.630)	<0.001	0.516(0.339–0.784)	0.002

TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG/HDL-C, TG to HDL-C ratio

*Adjusted for age, NIHSS, Hematoma volume, histories of diabetes, hypertension, LDL-C, and statin use

Association between lipid profiles and SAP

As shown in Table 2, after adjusting for age, admission NIHSS, baseline hematoma volume, histories of diabetes, hypertension, LDL-C, and statin use, per unit increment of TG (adjusted OR:0.497, 95%CI: 0.323–0.766) and TG/HDL (adjusted OR: 0.516, 95% CI 0.339–0.784) were negatively associated with the risk of SAP. While a positive association between HDL-C and SAP was observed both in unadjusted(p<0.001) and adjusted models($p = 0.028$).

Predictive performance of lipid profiles for SAP

For SAP, TG/HDL-C had an AUC of 0.723(95% CI 0.655–0.791), whereas independent TG and HDL-C had AUC of 0.692 (95% CI 0.620–0.764) and 0.624 (95% CI 0.546–0.702), respectively. The optimal cutoff point for

TG/HDL-C was 1.09 (sensitivity 76.1%, specificity 59.4%, positive predictive value 41.5%, and `negative predictive value 86.7%) for the prediction of SAP. The ROC curves and AUC for predicting SAP after SICH are depicted in Fig. 1.

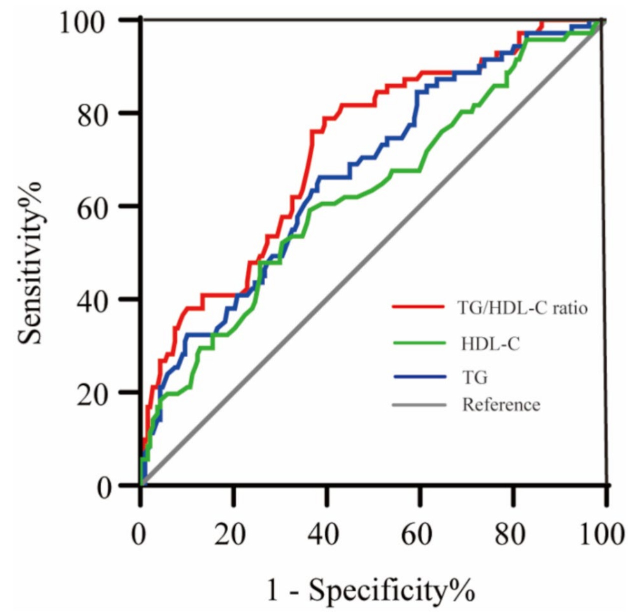

Fig. 1 Predictive values of TG, HDL-C, and TG/HDL-C ratio for SAP in patients with SICH. Receiver operating characteristic curves for SAP. Areas under the curves: 0.723 (95% CI 0.655–0.791) for TG/HDL-C ratio, 0.692 (95% CI 0.620–0.764)for TG, 0.624 (95% CI 0.546–0.702) for HDL-C

Multivariate logistic regression for SAP according to dichotomized values of TG/HDL-C

We dichotomized patients into groups of high TG/HDL-C (>1.09) and low TG/HDL-C (≤ 1.09) according to the optimal cutoff values. As shown in Fig. 2, in the low TG/HDL-C group, 54(41.5%) patients had SAP, while 17(13.3%) patients were in the high TG/HDL-C group. For the binary logistic regression analyses, the SAP was defined as the dependent variable, and the TG/HDL-C dichotomized was described as an independent variable. As shown in Table 3, the result revealed that a TG/HDL-C value >1.09 was independently associated with decreased SAP (adjusted OR 0.285, 95% CI 0.138–0.591) after adjustment for the confounding factors.

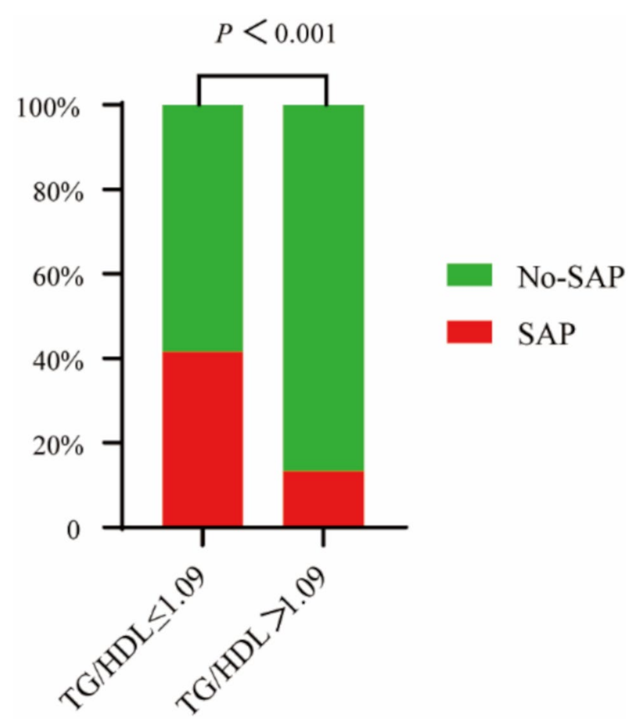

Fig. 2 Stacked bar plots for the prevalence of SAP after SICH according to dichotomized values of TG/HDL-C. *P* value was calculated using the $\chi 2$ test. *P*<0.001

Discussion

In this study, we found that TG/HDL-C was independently associated with SAP after SICH, after adjustment for age, admission NIHSS, baseline hematoma volume, and histories of diabetes, hypertension, LDL-C, and statin use, which suggested that an early low TG/HDL-C had a predictive effect on the occurrence of SAP in patients with SICH. The AUC value of TG/HDL-C for SAP was better than that of isolated concentrations of TG or HDL-C. The optimal cutoff point of TG/HDL-C was 1.09 for the prediction of SAP after SICH. To our knowledge, this is the first time to explore the relationship between TG/HDL-C and SAP after SICH.

Our result showed that the incidence of SAP after SICH was 27.5%. This is in accordance with previous reports [5, 7]. However, the enrolled patients in our study had a relatively lower initial NIHSS score and hematoma volume, with a relatively older age when compared to a previous report [5]. This could be due to the fact that we only enrolled non-surgical patients. Some young patients with larger hematoma volumes who underwent surgical intervention were not included in this study. The TG/HDL-C is a relatively conveniently accessible and cost-effective value in daily clinical practice. Our study provides new evidence suggesting that low TG/HDL-C is connected to the occurrence of SAP after SICH. However, the mechanism of low TG/HDL-C on SAP is unclear, and several speculative hypotheses can be formulated to explain this finding.

A major considerable speculation is the role of a low TG concentration. First, as we know, pulmonary surfactant is a lipid-rich secreted material. The major 90% of its weight is lipids, and the remaining 10% is proteins [21].

Table 3 Multiple logistic regression for SAP according to dichotomized values of TG/HDL-C

TG/HDL-C	Unadjusted		Adjusted*	
	OR(95%CI)	*p*	OR(95%CI)	*p*
≤ 1.09	1.0(reference)	-	1.0(reference)	-
>1.09	0.216(0.116-0.400)	<0.001	0.285(0.138–0.591)	0.001

TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG/HDL-C, TG to HDL-C ratio

*Adjusted for age, NIHSS, Hematoma volume, histories of diabetes, hypertension, LDL-C, and statin use

Metabolic parameters, such as lipids and lipoproteins, vary during bacterial and viral infections, as reported in the literature [22, 23]. Lipids play a central role in lung physiology and the pathology of infectious diseases [24]. For example, lipids are involved in various pathologic processes in viral infection, such as host-viral cell membrane fusion, viral replication, endocytosis, and exocytosis [25]. As the primary component of the cell membrane, the TG plays an essential role in the cell membrane. Second, SICH causes an elevation of the metabolic state accompanied by high-energy requirements. As a biomarker of nutritional status, triglycerides likely play an essential role in energy storage and supply, which excess calories and provide the necessary energy for metabolic stress conditions [26]. Malnutrition is considered a major risk factor for the prognosis of infectious diseases, including pneumonia [27–30]. A low level of TG is usually an indicator of malnutrition, which may be detrimental to early function repair in SICH. Therefore, low TG could increase the risk of SAP. In addition, TG is also an integral part of the innate and adaptive immune systems in the context of infections [31, 32]. Collectively, this analysis shows that TG might play a protective role in the anti-infective effects. Therefore, these could explain, at least in part, why low TG concentrations could increase the incidence of SAP after SICH. Our results showed that TG levels in the SAP group were lower than those in the non-SAP group. Indeed, some studies have documented the protective value of TG in infective disease [32, 33]. An experimental animal study showed that triglyceride-rich lipoprotein-bound endotoxin inhibits the host's innate immune response to sepsis, which could attenuate the deleterious effects of proinflammatory molecules like tumor necrosis factor-a on endothelial permeability [32]. Another study has also reported that a low TG level was relevant to length in intensive care and mortality in patients with coronavirus disease 2019(COVID-19) [33]. However, a large longitudinal cohort in the United States reported that higher TG level was strongly related to an increased long-term pneumonia hospitalization risk [34]. This seems contradictory to our results and may be due to different subject populations. The previous paper studied the non-stroke population and observed community-acquired pneumonia for a long-term observation [34], while our study was limited to SICH and assessed SAP after SICH for a short observation time. The present study shows that high TG concentrations may be protective against SAP, and further adjustment for age, initial NIHSS, initial hematoma volume, diabetes, hypertension, LDL-C, and statin use does not appreciably alter the relationship.

Another possible explanation is related to a high concentration of HDL-C. HDL-C is involved in innate immunity in different infectious diseases. A recent study has reported the interaction between HDL-C and *Mycobacterium avium*. HDL-C attenuates the engulfment of *Mycobacterium avium* by THP-1 macrophages. Besides, HDL is involved in the formation of lipid droplets in THP-1 macrophages infected by *Mycobacterium avium*. Therefore, HDL may facilitate *Mycobacterium avium* to escape from the host's innate immunity [35]. Our results showed that HDL-C concentration in the SAP group was higher than in the non-SAP group, and we found a positive association between HDL-C and SAP after further adjustment. Previous literature has reported that a high concentration of HDL-C is positively associated with COVID-19-related mortality [33]. This is consistent with our results. Another study also reported that at the admission of COVID-19 pneumonia, HDL-C levels were higher in severe cases compared with common cases [31]. Nevertheless, one study has found that a low HDL-C level is a risk factor for the development of severe sepsis [36]. Lower baseline HDL-C was relevant to an increased risk of future pneumonia hospitalization [34]. Another population-based cohort study in Copenhagen has reported a U-shaped relationship between HDL-C and the risk of infectious disease; that is, high or low HDL-C levels are related to an increased risk of infection, particularly gastroenteritis and bacterial pneumonia [37]. These discordant results may be due to different study populations and relatively small sample sizes in our study.

At the same time, one additional explanation merits our attention. TG/HDL-C could be a simple surrogate marker of subjects with numerous risk factors for poor outcomes of stroke. For example, a retrospective cohort study including 1006 acute ischemic stroke (AIS) patients found that a lower TG/HDL-C was related to poor prognosis and mortality three months after AIS [35]. Besides, stroke severity is a decisive risk factor for SAP [38, 39]. Taking together, the above explanations may explain the relationship between low TG/ HDL-C and increased SAP risk.

Our research indicated that TG/HDL-C value is a better predictor for the occurrence of SAP after SICH, compared with isolated levels of TG or HDL-C. Participants with high TG/HDL-C(> 1.09) had a 71.5% reduction of SAP(adjusted OR = 0.285, 95%CI 0.138–0.591, P = 0.001), compared with participants with low TG/HDL-C(≤ 1.09) after adjustment. The TG/HDL-C value was inversely relevant to the occurrence of SAP after SICH.

This observational study has several potential limitations. Firstly, the possibility of patient selection bias still exists as this was a retrospective single-center study with a relatively limited sample size. Secondly, a definite causal-effect relationship between TG/HDL-C and the risk of SAP could not be established owing to the nature of the cross-sectional study. In order to help establish causal relations, further prospective randomized trials are necessary to confirm causality between TG/HDL and SAP. Besides, future research could investigate the underlying mechanisms linking the TG/HDL-C ratio with the risk of SAP in patients with SICH, which can provide valuable insights into pathophysiological mechanisms and help develop practical SAP prediction tools. Thirdly, we only measured TG/HDL-C at admission and not repeated thereafter. However, the blood lipid parameters are dynamic. The dynamic changes of TG/HDL-C may be a more effective parameter for the prognosis of the disease. This is an exciting topic for future research. Fourthly, some parameter information was incomplete. For example, although we considered the effect of statins in this study, other lipid-lowering medications, such as fenofibrate, which could also affect the connection between SAP and TG/HDL, were not considered. In future studies, we may consider collecting more detailed variable information. Fifthly, we did not explore the association between lobar versus deep subcortical hemorrhages and SAP. As it has been reported that acute lobar intracerebral hemorrhage exhibits a distinct clinical profile and is associated with a more severe early prognosis compared to deep subcortical intracerebral hemorrhage [40]. Future research could benefit from examining how the location of intracerebral hemorrhages influences SAP and other clinical outcomes. Moreover, it is imperative to consider the specific etiologies of intracerebral hemorrhage, such as hematologic disorders, as they necessitate distinct therapeutic approaches and present varying risks of recurrence and outcomes [41].

In conclusion, a lower TG/HDL-C is strongly related to the occurrence of SAP in patients with SICH. A TG/HDL-C $\leq$ 1.09 is connected to a markedly increased occurrence of SAP than a TG/HDL-C > 1.09. The TG/HDL-C value may be readily available in clinical practice for predicting SAP, which may aid clinicians in distinguishing patients in need of early and aggressive treatment.

Abbreviations

SICH	Spontaneous intracerebral hemorrhage
SAP	Stroke-associated pneumonia
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
TG/HDL-C	Triglyceride to high-density lipoprotein cholesterol ratio
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
FBG	Plasma fasting blood glucose
ROC	Receiver operating characteristic
AUC	Areas under the curve
NIHSS	National Institutes of Health Stroke Scale

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Author contributions
Jiawei Yang, Chengwei Duan and Qiuhong Ji conceived and designed the study; Jiawei Yang and Jiabing Shen interpreted data; Jiawei Yang and Jiabing Shen wrote the manuscript; Jiawei Yang and Jiabing Shen prepared figures and tables; Jiawei Yang, Xiangyang Zhu and Jiabing Shen did the statistical analyses; Xiangyang Zhu, Jiabing Shen and Qiuhong Ji supervised the study. All authors have made an intellectual contribution to the manuscript and approved the submission.

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Data availability
The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate
This study was in line with the Helsinki Declaration and was approved by the ethics committees of Affiliated Hospital 2 of Nantong University(2023KT047), and the committee exempted the patient informed consent because the study had a retrospective design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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