Original Article

Hemorrhagic stroke and atherogenic markers – is there any relation?

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Abstract

Background: The triglyceride/high-density lipoprotein (TG/HDL) ratio emerges as a promising marker for cardiovascular risk. However, the relationship between overall serum lipid levels and hemorrhagic stroke (HS) remains uncertain. Therefore, our study aims to explore the association between this novel index and mortality in HS patients. **Methods:** Utilizing a retrospective-prospective framework from January 2020 to August 2023, we scrutinized data from 104 hospitalized patients diagnosed with HS, with particular attention to their medical backgrounds and lipid profiles. **Results:** Age (odds ratio [OR], 1.078; 95% confidence interval [CI], 1.032–1.125; $P = 0.001$), atrial fibrillation (OR, 0.237; 95% CI, 0.074–0.760; $P = 0.015$), glucose level (OR, 1.121; 95% CI, 1.007–1.247; $P = 0.037$), and TG/HDL index (OR, 0.368; 95% CI, 0.173–0.863; $P = 0.020$) emerged as independent predictors for in-hospital mortality, as determined by both univariable and multivariable logistic regression analyses. **Conclusion:** Our results add weight to the growing evidence backing the utility of the TG/HDL index in assessing cardiovascular risk among HS patients. They emphasize the necessity of adopting a comprehensive risk assessment and management strategy that incorporates both traditional markers and novel indicators.

Keywords: Hemorrhage, predictors, stroke

Introduction

Stroke remains one of the most common causes of death and disability worldwide and as such represents a significant burden on the public health system.[1] The World Stroke Organization estimates the global cost of stroke to be over 721 billion US$ (0.66% of the global gross domestic product (GDP)), while lower-income and lower-middle-income countries account for the majority of the burden.[2] Hemorrhagic strokes (HSs) represent 13% of all stroke cases, including intracerebral hemorrhage with 10%, and aneurysmal subarachnoid hemorrhage representing 3% of stroke cases.[3] Risk factors for both ischemic and hemorrhagic subtypes of stroke can be categorized as modifiable and nonmodifiable. Age, sex, and race/ethnicity are well-established nonmodifiable risk factors,[4] while hypertension, hyperlipidemia, diabetes, smoking, and atrial fibrillation (AF) are considered potentially modifiable risk factors.[5]

While dyslipidemia is considered a major risk factor for ischemic stroke (IS), the effects of serum lipid levels on HS are still unclear.[6,7] An inverse relationship between total serum cholesterol levels and the prevalence of HS has been proven

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in several studies.[8] On the contrary, several other studies have shown no clear association between cholesterol and HS.[9,10] The risk of both IS and HS seems to increase in patients with higher triglyceride (TG) levels, while lower high-density lipoprotein (HDL)-cholesterol levels are significantly higher in patients with IS than in those with HS.[11]

A possible explanation for the inverse relationship between HS and serum cholesterol relies on the role of lipids in the cell membrane structure, namely, cholesterol and TGs.[12] Decreased platelet aggregability as well as increased erythrocyte fragility were observed *in vitro* and *in vivo* with reduced levels of cholesterol. Furthermore, lower cholesterol leads to a weakened endothelium and the development of arterial fragility, hemorrhages, and ultimately slower vascular repair after smaller hemorrhages.[13]

One of the rapidly emerging markers of atherogenic dyslipidemia is the combination of increased plasma TGs and low HDL-cholesterol.[14] The TG/HDL index is a novel indicator of cardiovascular risk.[15] Several studies have demonstrated a direct correlation between TG and HDL level ratio (THR) with small, dense LDL particles. This indicates that THR could be used as an atherogenic dyslipidemia index in routine clinical examinations.[15,16]

Deng *et al.*[17] indicated a positive correlation between low levels of TG/HDL-C and mortality as well as worse short-term outcomes after acute ischemic stroke (AIS). Further studies have shown that lower levels of TG/HDL-C are correlated with a greater risk of HT (hemorrhagic transformation) after AIS attributable to LAA (large artery atherosclerosis). TC/HDL-C has been proven to have a higher AUC as a stroke predictor than other lipid variables, indicating it may be a more potent predictor of cardiovascular risk than TC, LDL-C, or HDL-C alone.[18]

Aim

Regarding the unclear relationship between the overall serum lipid status and HS, this study aimed to assess the correlation between the novel THR and mortality in patients with this subtype of stroke.

Methods

Patients and study design

The research had a retrospective-prospective design and covered the period from January 2020 to August 2023. The study included 104 patients diagnosed with HS who were hospitalized at the Clinic for Neurology, Clinical Center of the University of Sarajevo. Anamnestic data of the included patients were analyzed, including the presence of AF in the medical history, and the values of their lipid profile were also analyzed. Inclusion criteria were acute spontaneous HS confirmed by a computed tomography (CT) scan. Exclusion criteria were HS secondary to trauma, thrombolysis, or an underlying structural abnormality such as tumor, venous thrombosis, aneurysm, or arteriovenous malformation, patients who underwent a neurosurgical intervention, as well as insufficient

Table 1: Baseline characteristics of subjects

Variables	Survivors (n=65)	Deceased (n=39)	P
Age (years)	67.0 (57.0–76.0)	77.0 (67.0–84.0)	**0.001**
Gender (male/female)	41 (63.1%)/24 (36.9%)	19 (48.7%)/20 (51.3%)	0.151
Hypertension	61 (93.8%)	37 (94.9%)	0.597
DM	22 (33.8%)	12 (30.8%)	0.746
AF	5 (7.8%)	10 (26.3%)	**0.013**

P<0.05 level of significance, Results are expressed as absolute numbers and percentage values and as median and interquartile range (25–75 percentiles). DM=diabetes mellitus, AF=atrial fibrillation

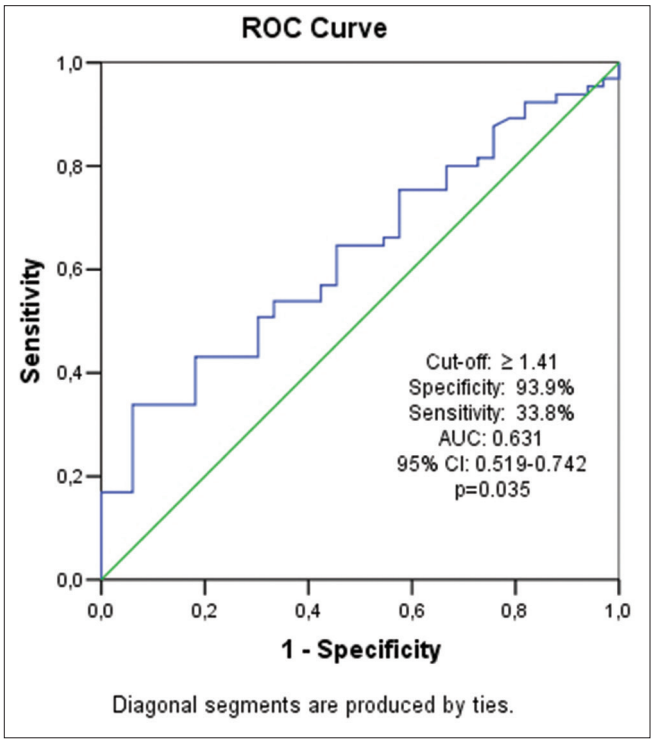

Figure 1: ROC curve of the TG/HDL in the prediction of the mortality in patients with CVI

data from available medical records. All patients who met the diagnostic criteria were included in the study. All patients underwent clinical, neurological, and psychological examinations. The ethical approval was obtained from the Ethical Committee of the Clinical Centre of the University of Sarajevo.

Methods

Brain images were obtained with a Toshiba Astelion CT scanner, a multidetector 16-slice CT, with a minimum slice thickness of 0,5 mm, minimum scan time of 0.6 s, maximum field of scanning 500, and scan time from 10 to 12 s. A routine brain image acquisition protocol, starting from the lower most part of the skull (base) to the vertex, was used to acquire all the brain images.

Measurement of serum lipid and glucose concentrations

Venous blood samples were drawn within 72 h from the onset of symptoms. The samples were processed as per the laboratory

protocol, and the blood glucose levels as well as lipid-profile parameters, namely, total cholesterol (TC), HDL, and serum TG were tested on the same day, using Cobas C system by Roche.

The Cobas Pro Integrated Solutions (Cobas Pro) is a fully automated, random-access, software-controlled system intended for in-vitro quantitative analysis of analytes in body fluids. The system consolidates clinical chemistry, homogenous, and heterogeneous immunoassays as well as electrolyte testing within one workplace.

Glucose levels were measured using a UV test (enzymatic reference method with hexokinase). Lipid profile fractions (HDL, LDL, TGL, and total cholesterol) were measured using enzymatic colorimetric tests. Information on demographic data, lifestyle factors, and use of medications (e.g., antihypertensives) as well as AF presence was collected from medical records.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 21.0. The data were presented as mean value ± standard deviation, absolute value (*N*), percentage (%), and the median and interquartile range (25th–75th percentiles). The significance of the divergence from the normal distribution was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. The Mann–Whitney *U* test and Student's *t*-test were used to compare the groups based on the distribution of variables. The χ^2 and Fisher's exact tests were used to analyze the dependence between categorical variables. To determine optimal cut-off values of potential biomarkers for differentiation between surviving and deceased patients, receiver-operating characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used. The accuracy rate for ROC curves was calculated with a 95% confidence interval (95% CI). Logistic regression analyses were performed to predict mortality in patients with stroke. A P <0.05 was considered statistically significant.

Results

The age of the survivors was 67.0 (57.0–76.0), and that of the deceased was 77.0 (67.0–84.0) years [Table 1]. The established difference in age was significant (P = 0.001). Gender distribution, frequency of hypertension, and frequency of diabetes mellitus between the studied groups did not differ significantly. The frequency of AF in the group of survivors was 5 (7.8%) and 10 (26.3%) in those who died. The determined difference in the frequency of AF between the studied groups was significant (P = 0.013).

The value of glucose in the group of survivors was 6.85 (5.70–9.50) mmol/L and was significantly lower compared with the value of glucose in the group of deceased 8.85 (6.07–11.90) mmol/L (P = 0.033). The value of TG/HDL in the group of survivors was 1.08 (0.72–1.74) and was significantly higher than the ratio in the group of deceased 0.80 (0.62–1.18) (P = 0.035). Other biochemical parameters did not significantly differentiate between the investigated groups [Table 2].

An optimal cut-off value of TG/HDL in the prediction of the mortality in patients with CVI was ≥1.41. The AUC for a determined cut-off value was 0.631 with 95% CI of 0.519–0.742 (P = 0.035). For a calculated optimal TG/HDL cut-off value of ≥1.41, the maximal specificity was 93.9% and maximal sensitivity 33.8%.

Age (odds ratio [OR], 1.078; 95% CI, 1.032–1.125; P = 0.001), AF (OR, 0.237; 95% CI, 0.074–0.760; P = 0.015), glucose (OR, 1.121; 95% CI, 1.007–1.247; P = 0.037), and TG/HDL (OR, 0.368; 95% CI, 0.173–0.863; P = 0.020) were found to be independent predictors for in-hospital mortality by univariable logistic regression analysis. Age (OR, 1.173; 95% CI, 1.004–1.354; P < 0.001), AF (OR, 0.267; 95% CI, 0.073–0.759; P = 0.046), glucose (OR, 1.226; 95% CI, 1.062–1.415; P = 0.006), and TG/HDL (OR, 0.301; 95% CI, 0.119–0.759; P = 0.011) were found to be independent predictors for in-hospital mortality by multivariable logistic regression analysis [Table 3].

Discussion

Lipid profile fractions and HS

While traditionally more focused on atherosclerotic diseases, our study extends its relevance to the realm of HS. The present observational study explored the association between the TG/HDL index and mortality among patients with HS, unveiling notable insights into cardiovascular risk predictors. Our findings suggest that a TG/HDL index cut-off value of ≥1.41 serves as a significant prognostic marker for mortality in CVIs. The derived cut-off demonstrated an AUC of 0.631, indicating a moderate predictive value, with high specificity and lower sensitivity [Figure 1]. These results align with the emerging perspective in research that underscores the TG/HDL ratio as a critical indicator of atherogenic dyslipidemia and its role in cardiovascular risk assessment.[19,20] The study's multivariable and univariable logistic regression analyses further illuminated the complex interplay of various factors with in-hospital mortality. Age, AF, glucose levels, and the TG/HDL index were all identified as independent

Table 2: Biochemical parameters in patients with CVI in relation to disease outcome

Variables	Survivors (*n*=65)	Deceased (*n*=39)	*P*
Total cholesterol (mmol/L)	5.05 (4.40–5.62)	5.10 (3.90–6.12)	0.584
HDL-cholesterol (mmol/L)	1.23 (1.08–1.41)	1.34 (1.12–1.60)	0.119
LDL-cholesterol (mmol/L)	3.35±1.17	3.20±1.29	0.594
Triglycerides (mmol/L)	1.24 (0.93–1.99)	1.13 (0.84–1.44)	0.062
Glucose (mmol/L)	6.85 (5.70–9.50)	8.85 (6.07–11.90)	**0.033**
TyG index	1.42 (1.16–1.93)	1.44 (1.15–1.90)	0.784
TG/HDL	1.08 (0.72–1.74)	0.80 (0.62–1.18)	**0.035**
TC/HDL	4.11 (3.22–4.89)	3.59 (2.91–4.50)	0.064
LDL/HDL	2.76 (1.95–3.43)	2.35 (1.63–2.98)	0.131

P<0.05 level of significance, Results are expressed as median and interquartile range (25–75 percentiles) and as mean±standard deviation (x±SD). TyG=triglyceride glucose index

Table 3: The logistic regression analysis predicting mortality in patients with CVI

Variables	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.078	1.032–1.125	0.001*	1.173	1.004–1.354	<0.001*
Gender	0.556	0.249–1.244	0.153	–	–	–
Hypertension	0.814	0.144–4.724	0.828	–	–	–
DM	0.141	0.491–2.699	0.746	–	–	–
AF	0.237	0.074–0.760	0.015*	0.267	0.073–0.759	0.046*
Total cholesterol (mmol/L)	0.878	0.618–1.247	0.467	–	–	–
HDL-cholesterol (mmol/L)	1.459	0.555–3.837	0.444	–	–	–
LDL-cholesterol (mmol/L)	0.905	0.628–1.303	0.590	–	–	–
Triglycerides (mmol/L)	1.069	0.556–2.054	0.842	–	–	–
Glucose (mmol/L)	1.121	1.007–1.247	0.037*	1.226	1.062–1.415	0.006*
TyG index	1.069	0.556–2.054	0.842	–	–	–
TG/HDL	0.368	0.173–0.863	0.020*	0.301	0.119–0.759	0.011*
TC/HDL	0.690	0.474–1.004	0.053	–	–	–
LDL/HDL	0.732	0.489–1.097	0.131	–	–	–

*Significant value, DM=diabetes mellitus, AF=atrial fibrillation, TyG=triglyceride glucose index

predictors. This multifaceted view is consistent with literature indicating the multifactorial nature of cardiovascular risks and the importance of comprehensive assessments.[21]

The strength of the TG/HDL ratio lies in its reflection of atherogenic dyslipidemia, which is characterized by elevated TGs and low HDL-cholesterol levels, a combination known to exacerbate cardiovascular risk.[16] Research suggested that a higher TG/HDL ratio is associated with an increased risk of cardiovascular events.[22] The potential prognostic value of the TG/HDL-C ratio for future cardiovascular events is supported by the high frequency of high-risk vulnerable plaques in patients with a higher TG/HDL-C ratio.[23,24] It has been revealed that the TG/HDL-C ratio is a reliable predictor of major adverse cardiovascular events in patients with acute coronary syndrome undergoing percutaneous coronary intervention and in postmenopausal women, as well as an effective indicator of the presence of coronary artery calcification.[25-28] The TG/HDL-C ratio is also a reliable and easily accessible marker for predicting cardiovascular events and mortality in patients undergoing maintenance hemodialysis, even in those without diabetes,[29-33] and has been strongly associated with metabolic syndrome, particularly with insulin resistance and central obesity.[34-38] While other studies have highlighted the TG/HDL ratio's predictive value in cardiovascular risk, the present study provides novel insights into its specific application in the HS population, suggesting a broader, perhaps more nuanced role for lipids in cerebrovascular diseases. Increased TG/HDL-C is linked to a higher risk of intracerebral hemorrhage and cerebral infarction, particularly in individuals with a healthy body mass index (BMI).[39] A study further confirmed an association between low TG/HDL-C levels and increased case fatality at three months after AIS.[34] It was also revealed that a low TG/HDL-C ratio was significantly linked to an increased risk of hemorrhagic transformation due to large artery atherosclerosis in individuals with AIS, but not in those with cardio-embolism or small-vessel occlusion.[35] Furthermore, research by Han *et al.*[36] revealed that in patients with AIS, a TG/HDL-C ratio lower than 3.515 was significantly negatively correlated with the risk of unfavorable outcomes, whereas a TG/HDL-C ratio greater than 3.515 was positively correlated with the risk of unfavorable outcomes. In addition, a study suggested that TC levels below 120 mg/dL were associated with an increased risk of HS, while HDL-C levels below 50 mg/dL might increase the risks for both ischemic and HSs.[37] Moreover, a significant association was noted between an increased TG/HDL-C ratio and the risk of recurrent stroke in a randomized controlled trial.[38] The specific cut-off value (≥1.41) identified in our study offers a practical and potentially impactful tool for early intervention strategies and risk stratification in patients with HS. This is particularly intriguing considering the relatively underexplored role of lipid profiles in HS prognosis. These findings are supported by not only confirming the significance of the TG/HDL ratio as a predictor of mortality in this specific patient population but also providing a concrete cut-off value for clinical use. Comparing the sensitivity and specificity of this ratio with other studies can help validate its utility and encourage its integration into clinical practice.

Age and HS

Age is widely recognized as a fundamental predictor of mortality in across different patient populations, including those affected by stroke. Research consistently indicates that older age is associated with higher mortality rates and poorer outcomes following stroke occurrences.[40] The reasons may be multifactorial, including the presence of comorbidities, a decreased physiological reserve, or differences in treatment response in the elderly. Our study identifies age as an independent predictor of in-hospital mortality in patients with HS, with an increasing odds ratio indicating higher risk as age increases. This finding is consistent with existing literature.[41-44] Moreover, Sagui *et al.*[45] found that the mean age for HS was 51 years, and the mortality rate at one month was 56%. Additionally, older age, specifically age >75 years, has been identified as an independent predictor of in-hospital mortality for individuals with HS.[46] Similarly, a significant association between older age and

in-hospital mortality was also observed in individuals with IS.[47-49] Our study adds to this narrative by quantifying this risk specifically in HS patients, reinforcing the need for age-tailored management strategies in this vulnerable group.

Glucose levels and HS

Studies on acute stroke (both ischemic and hemorrhagic subtypes) have demonstrated that higher glucose levels are associated with worse clinical outcomes and mortality.[50-54]

Literature has long suggested that high blood glucose at the time of stroke is associated with worse outcomes, potentially due to increased brain damage and a higher likelihood of complications.[55,56] Our findings regarding glucose in patients with HS align with the concept that acute hyperglycemia is a bad prognostic factor in stroke patients. Our study's identification of glucose as an independent predictor provides valuable, targeted insight into its impact on HS patients, highlighting the need for stringent glucose monitoring and management in the acute care of stroke patients to potentially improve outcomes.

Atrial fibrillation and HS

The presence of AF is associated with reduced odds of in-hospital mortality in our patient population. This is a somewhat counterintuitive finding, as AF is generally associated with increased morbidity and mortality in patients with stroke.[57,58] Other studies have revealed that AF is associated with higher mortality outcomes in patients with HS, reflecting the traditional view of AF as a risk factor.[58] Our findings with regard to AF could be attributed to several possible reasons. In this context, this finding could be due to treatment effects, given that patients with known AF might receive more aggressive monitoring and antithrombotic therapy, thus potentially leading to more favorable outcomes. It is also possible that the lower number in the OR in our study reflects a protective effect from treatments associated with AF management rather than AF itself.

Limitations of study

However, our findings must be interpreted within the context of their limitations and the broader literature. The moderate AUC indicates that while the TG/HDL ratio is a significant marker, it is not definitive and should be considered alongside other clinical factors. Furthermore, the discrepancy between specificity and sensitivity highlights the potential for missed cases if relying solely on this threshold.

Although previous studies have shown a well-established significance of higher TG/HDL ratio as a negative outcome predictor in cardiovascular diseases, the dispute regarding the increased risk of cerebral hemorrhage at lower levels of serum lipids remains unsolved. While several studies showed no correlation between low cholesterol and hemorrhagic stroke, others have proved a clearly positive correlation.[59,60]

One of the widely accepted theories on molecular mechanisms of the increase in cerebral hemorrhages at low levels of cholesterol suggests that adequate cholesterol levels may maintain the cerebral small vessels integrity.[61]

Future directions

Taking into consideration the unclear and controversial effect of lipid status on different stroke subtypes, further research is needed to establish therapeutic options and guidelines in order to reduce worsening effects on the IS risk while maintaining potential beneficial effects on reducing the HS risk.[11]

Future studies should aim to validate these findings in larger, more diverse populations and explore mechanisms underlying the relationship between TG/HDL ratio and stroke outcomes.

Conclusion

In conclusion, our study contributes to the growing body of evidence supporting the TG/HDL index as a valuable component of cardiovascular risk assessment in patients with HS. It underscores the need for a multifactorial approach to risk prediction and management, integrating traditional markers with novel indicators like the TG/HDL ratio. As personalized medicine continues to advance, understanding and utilizing comprehensive lipid profiles will be crucial in improving patient outcomes and guiding therapeutic decisions.

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Conflicts of interest

There are no conflicts of interest.

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