Neurology Asia 2024; 29(3) : 525 – 533

Triglyceride-HDL index as a predictor of post-stroke outcomes: A retrospective analysis of 6,235 ischemic stroke patients from the Qatar Stroke Database

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Abstract

Objectives:. In this study, we explored the Qatar stroke database to study the independent effect of sex-specific TG-HDL index on neurologic and cardiovascular outcomes following stroke in a predominantly Arab and Southeast Asian population. *Methods:* All patients admitted with acute ischemic stroke between 2014-2022 were included. TG-HDL index on admission was calculated and patients were stratified into sex-specific quartiles. We studied the 90-day modified Rankin Score (mRS), and 1-year major cardiac adverse events (MACE). Multivariate linear and binary logistic regression analyses were performed to identify the independent effect of TG-HDL index on short- and long-term outcomes. *Results:* A total of 6,235 stroke patients were identified. Overall, mean age was 55±13 years; 5,122 patients (82%) male; 1,989(32%) Arab; 1,628(26%) BMI ≥30; 3,526 (57%) diabetes mellitus; 4,598 (74%) hypertension, 3,158 (51%) dyslipidemia, and 1,876 (30%) smokers. The median TG levels were 1.5 (1.0-2.3), HDL levels 1.0 (0.8-1.2), and TG-HDL index was 1.5 (1.0-2.3). On long term follow-up, 120 (2%) had a recurrent stroke, 314 (5.1%) had MACE, 38 (0.6%) had post-stroke MI, and 37 (0.6%) had post-stroke cardiac revascularization procedures. On multivariate analyses, higher sex-specific TG-HDL index was independently associated with lower adjusted odds of severe stroke and lower inpatient mortality, and higher 1-year adjusted odds of post-stroke MI (p<0.05).
Conclusion: TG-HDL was strongly associated with in-patient mortality and long-term post-stroke cardiovascular outcomes but not long-term stroke recurrence. Our finding of an independently increased 1-year risk of post-stroke MI with higher TG-HDL index may warrant consideration of this index as a cardiac risk stratification tool for stroke patients.

Keywords: High density lipoprotein, triglyceride and HDL ratio, stroke, post-stroke outcomes, MACE

INTRODUCTION

Stroke is the second leading cause of death and a major cause of disability worldwide. With an aging population, the incidence of stroke is increasing - a large proportion of which are ischemic strokes. It is a preventable disease with multiple modifiable risk factors. Over the years, there has been a rising incidence of stroke among more younger age groups, a finding which can be partly attributed to rising cardiovascular risk factors in young adults.[1]

The association between low density lipoprotein cholesterol (LDL-C) and stroke is well established, with higher levels being directly related to cerebral infarction and with lipid lowering therapy being used as a preventive strategy to mitigate stroke risk.[2] A recent meta-analysis demonstrated a significant association between triglyceride level (TG) and ischemic stroke[3], whereas another meta-analysis demonstrated that elevated high density lipoprotein cholesterol (HDL-C) levels are associated with reduced risk of total stroke and ischemic stroke (IS) and an increased risk of intra-cerebral hemorrhage (ICH).[4]

More recently, the TG-to-HDL-C (TG/HDL-C) ratio was investigated as a clinical biomarker of vascular risk. It has shown promise as an indicator of cardiovascular disease onset[5], insulin resistance[6] and metabolic syndrome.[7] TG/HDL-C ratio's association with stroke is however not completely understood.[2,8,9,10] While it has proven to

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Date of Submission: 6 April 2024; Date of Acceptance: 22 April 2024

https://doi.org/10.54029/2024tic

be effective in showing an association with stroke outcomes in some studies, it has also not proven effective in others.[11] The aim of our study was to evaluate the independent effect of sex-specific TG-HDL index on both short- and long-term neurologic and cardiovascular outcomes following stroke in a predominantly Arab and South Asian population. We hypothesize that a higher sex-specific TG/HDL index is associated with better neurological inpatient and post-discharge long-term outcomes and worse cardiovascular outcomes following a stroke.

METHODS

This is a retrospective cohort analysis of stroke patients from a large prospectively maintained database. All patients admitted as acute stroke to Hamad General Hospital (HGH), Doha, Qatar between 2014 and 2022 were enrolled in the HGH Stroke database and trained stroke coordinators prospectively entered data into the database starting upon hospital admission, including patient characteristics such as age, sex, nationality, medical comorbidities and prior medications. Upon identification in the emergency department, data was collected once confirmation of diagnosis of ischemic stroke was made using the *International Classification of Disease, 10th Edition,* definitions (H34·1, I63.x, I64.x, I61.x, I60.x, G45.x). Data from emergency medical services/paramedics, immediate emergency department care, NIHSS score, length of stay (LOS), neuroimaging, post-stroke complications, in-hospital mortality, and recurrences were recorded.

Inclusion criteria were: (i) admission within 24 h of symptom onset; (ii) confirmed ischaemic stroke; (iii) age more than 18 years (iv) all stroke severity; Exclusion criteria: (i) severe inflammatory, infective diseases and malignancies; (ii) a serum lipid level measured more than 24 hours after symptom onset. (iii) patients with missing data. Finally, a total of 6,235 patients met these criteria.

Dyslipidemia was defined as a LDL level ≥ 3.62 mmol/L, HDL level ≤ 1.03 mmol/L, triglycerides ≥ 1.69 mmol/L, or current treatment with a cholesterol-lowering drug (12) .TG-HDL index on admission was calculated by dividing TG levels in mmol/L by HDL levels in mmol/L. Patients were stratified into 4 sex-specific quartiles [Low (L) males: ≤1.06, females : ≤0.81; Low-normal (LN) males: 1.07-1.60, females: 0.82-1.18; High-normal (HN) males: 1.61-2.44, females: 1.19-1.88; and High (H) males: >2.44, females: >1.88). We chose these quartiles because there was no standardised threshold for the Arab population.

Atrial fibrillation (AF) was diagnosed based on electrocardiographic findings on admission or on Holter monitoring during hospitalization. Smoking was defined as current cigarette smoking. Diabetes was diagnosed according to the American Diabetes Association(ADA) and WHO recommendations and included patients with a previous diagnosis of DM, on medication for DM or a HbA1c ≥6.5% and the diagnosis of pre-DM was based on a HbA1c of 5.7 - 6.4 % as per 2015 ADA clinical practice recommendations.[13] Hypertension was defined as a previous systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg, or current treatment with antihypertensive drugs. Complications monitored and recorded included aspiration pneumonia, urinary tract infection, bedsores, deep venous thrombosis, and sepsis during hospitalization.

Inpatient outcome measures were National Institute of health Stroke Scale (NIHSS) on admission, in-hospital mortality, ICU admission, major complications, in-hospital interventions including thrombolysis and mechanical thrombectomy, and survivor-only hospital length of stay (LOS). Long-term outcome measures among survivors of index admission with adequate follow-up data available were mortality and modified Rankin Score (mRS) at 90 days of discharge, stroke recurrence, post-stroke MI, post-stroke major cardiac adverse events (MACE), and post-stroke cardiac revascularization procedures within 1 year of discharge. To achieve this, the Cerner electronic medical systems were used to track patient admissions throughout the state of Qatar.

Descriptive results for all continuous variables were reported as mean ± standard deviation (SD) when normally distributed or as medians with interquartile ranges (IQR) when non-normally distributed. The distribution of continuous variables was assessed by applying Kolmogorov Smirnov tests prior to using statistical tools. Descriptive results for all categorical variables were reported as numbers and percentages. ANOVA test was used to compare normally distributed continuous variables between groups. Kruskall-Wallis h test was used to compare non-parametric continuous variables between groups. Chi-square or Fisher's exact test were used to compare categorical variables between groups where appropriate.

Multivariate binary logistic regression analyses

were performed to determine the independent effect of sex-specific TG-HDL indices on outcomes: LOS, NIHSS, in-hospital mortality, in-hospital major complications, 1-year stroke recurrence, 90-day mortality, 1-year post-stroke MI, and 1-year post-stroke cardiac revascularization. Multiple linear regression analyses were performed to determine the independent effect of sex-specific TG-HDL indices on outcomes (Hospital LOS and NIHSS on admission).

Multivariate analyses adjusted for potential confounders, including patient demographics (age, sex, ethnicity), emergency department vitals (systolic blood pressure), comorbidities (diabetes, hypertension, dyslipidemia, coronary artery disease, atrial fibrillation, prior stroke history, obesity, smoking status), stroke severity, and in-hospital interventions (thrombolysis or thrombectomy). Covariates for multivariate analyses were chosen from an initial bivariate analysis as well as from prior literature demonstrating effect on stroke outcomes. Alpha was set at 5% and a *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM Statistical Product and Service Solutions (SPSS) version 28.

RESULTS

A total of 6,235 stroke patients were identified (1,541 L, 1,574 LN, 1,545 HN, and 1,575 H). The mean age was 55 ± 13 years. 5,122 patients were male accounting for 82% of the study population, reflecting the high percentage of male expatriate workers in Qatar (14). Of the 6,235 patients, 1,989 (32%) were Arab and 3,294 (52.8%) were South Asian; 3,526 (57%) had diabetes mellitus, 4,598 (74%) had hypertension, and 3,158 (51%) had dyslipidemia. The median TG levels were 1.5 [1.0-2.3], HDL levels 1.0 [0.8-1.2], and TG-HDL index 1.5 [1.0-2.3]. All ethnicities had a higher number of patients with low TG/HDL apart from the South Asian and Arab cohorts which had a greater number of patients with a high TG/HDL index (p<0.001). Further baseline characteristics of our study are summarized in Table 1.

We evaluated the effects of TG-HDL ratio on the type of stroke according to the TOAST classification. We found an increase in small vessel disease with increasing TG-HDL quartiles (<0.001). There was no association noted with any of the other stroke types.

Overall, 758 (12%) patients received thrombolysis, 278 (5%) thrombectomy, 295 (5%) were admitted to ICU, 395 (6%) suffered major complications, median survivor-only LOS was 4 [3-6] days, and 61 (1%) died during their index hospitalizations. On univariate analysis, admission NIHSS, LOS and In-hospital mortality, all decreased with increasing sex-specific TG-HDL quartiles (p=0.001, p=0.029, p=0.004). A similar decrease in the rate of ICU admissions and In-hospital complications was also observed (p=0.021, p=0.017). (Table 2)

Among 6,174 survivors of index admission who had 1-year follow-up data available, a MACE was noted in 314 (5.1%) patients. This included 120 (2%) with a recurrent stroke (most commonly ischemic), 38 (0.6%) with post-stroke MI, and 37 (0.6%) with post-stroke cardiac revascularization procedure. Mortality within 90 days of discharge was 1.6%. An increasing number of patients suffered from a post-stroke MI as TG-HDL increased (p=0.011) but the increase in post-stroke cardiac revascularization procedures was not statistically significant (p=0.228).

On multiple linear regression analysis, higher sex-specific TG-HDL index was independently associated with lower NIHSS on admission (β -0.198 [95% CI -0.307-{-0.089}], *p*<0.001) and shorter hospital LOS (β -0.229 [95% CI -0.364-{-0.094}], *p*=0.001). On multivariate binary logistic regression analyses, higher sex-specific TG-HDL index was independently associated with lower adjusted odds of inpatient mortality and higher 1-year adjusted odds of post-stroke MI (*p*<0.05) (Table 3). On multivariate cox regression analysis, prior stroke history (aOR 1.765, p=0.012) and history of CAD (aOR 1.655, p=0.029) were the only factors significantly predictive of stroke recurrence within one year. Higher sex-specific TG/HDL quartile was also associated with a statistically but not clinically significant improvement in mRS scores at 90 days after discharge (ß-0.057, 95% CI -0.014 to -0.100, p=0.009).

DISCUSSION

In this large prospectively collected data set, we studied the relationship between TG/HDL index and short – and – long term outcomes post-stroke in a large cohort of patients. We observed that increasing sex-specific TG/HDL index was associated with higher rates of small vessel disease, lower NIHSS at presentation, and shorter LOS. One potential explanation for observed increased rates of small vessel disease and not the other stroke subtypes could be

Table 1: Baseline characteristics stratified by sex-specific TG-HDL index quartiles

	Overall (n=6,235)	**Low TG-HDL Index** (n=1,541)	**Low-Normal TG-HDL Index** (n=1,574)	**High-Normal TG-HDL Index** (n=1,545)	**High TG-HDL Index** (n=1,575)	***p*-value**
Sex-specific TG-HDL Cut-offs		M: ≤1.06 F: ≤0.81	M: 1.07-1.60 F: 0.82-1.18	M: 1.61-2.44 F: 1.19-1.88	M: >2.44 F: >1.88	
Baseline Characteristics						
Patient Demographics						
Age, years, mean ± SD	55 ± 13	56 ± 14	55 ± 13	54 ± 12	53 ± 12	<0.001*
Age > 55 years, n (%)	2,989 (47.9)	789 (51.2)	755 (48.0)	743 (48.1)	702 (44.6)	0.003*
Male Sex, n (%)	5,122 (82.1)	1,266 (82.2)	1,298 (82.5)	1,265 (81.9)	1,293 (82.1)	0.979
Ethnicity, n (%)						<0.001*
Arab	1,989 (31.9)	519 (33.7)	471 (29.9)	472 (30.6)	537 (33.5)	
South Asian	3,294 (52.8)	721 (46.8)	844 (53.6)	861 (55.7)	868 (55.1)	
Far Eastern	539 (8.6)	156 (10.1)	162 (10.3)	122 (7.9)	99 (6.3)	
African	267 (4.3)	102 (6.6)	63 (4.0)	52 (3.4)	50 (3.2)	
Caucasian	146 (2.3)	43 (2.8)	34 (2.2)	38 (2.5)	31 (2.0)	
BMI, mean ± SD	28 ± 5	27 ± 5	28 ± 5	28 ± 5	29 ± 5	<0.001*
Patient Comorbidities						
Diabetes Mellitus, n (%)	3526 (56.6)	677 (43.9)	847 (53.8)	939 (60.8)	1063 (67.5)	<0.001*
Hypertension, n (%)	4598 (73.7)	1083 (70.3)	1201 (76.3)	1156 (74.8)	1158 (73.5)	<0.001*
Atrial Fibrillation, n (%)	461 (7.4)	153 (9.9)	127 (8.1)	112 (7.2)	69 (4.4)	<0.001*
Prior Stroke History, n (%)	710 (11.4)	174 (11.3)	183 (11.6)	182 (11.8)	171 (10.9)	0.855
CAD, n (%)	737 (11.8)	169 (11.0)	185 (11.8)	184 (11.9)	199 (12.6)	0.552
Smoking History, n (%)	1876 (30.1)	351 (22.8)	442 (28.1)	495 (32.0)	588 (37.3)	<0.001*
Obesity, n (%)	1628 (26.1)	311 (20.2)	387 (24.6)	425 (27.5)	505 (32.1)	<0.001*
Dyslipidemia, n (%)	3158 (50.6)	654 (42.4)	791 (50.3)	824 (53.3)	889 (56.4)	<0.001*
Admission Vitals						
SBP, mm Hg, mean ± SD	158 ± 30	156 ± 31	159 ± 31	158 ± 29	158 ± 30	0.101
DBP, mm Hg, mean ± SD	91 ± 19	91 ± 19	92 ± 20	91 ± 19	91 ± 19	0.430
Admission Labs						
RBS, mmol/L, median [IQR]	7.7 [5.9-11.8]	6.9 [5.8-9.8]	7.4 [5.8-10.9]	7.9 [6.0-12.4]	9.0 [6.4-13.8]	<0.001*
HbA1C, %, median [IQR]	6.5 [5.6-9.0]	5.9 [5.5-7.4]	6.3 [5.6-8.5]	6.8 [5.8-9.3]	7.7 [5.9-10.2]	<0.001*
TG, mmol/L, median [IQR]	1.5 [1.1-2.1]	0.9 [0.7-1.0]	1.3 [1.1-1.5]	1.7 [1.5-2.0]	2.7 [2.2-3.4]	<0.001*
HDL, mmol/L, median [IQR]	1.0 [0.8-1.2]	1.2 [1.1-1.4]	1.0 [0.9-1.2]	0.9 [0.8-1.1]	0.8 [0.7-0.9]	<0.001*
LDL, mmol/L, median [IQR]	3.0 [2.3-3.8]	2.8 [2.1-3.6]	3.1 [2.3-3.8]	3.1 [2.4-3.9]	3.0 [2.2-3.8]	<0.001*
Chol, mmol/L, median [IQR]	4.8 [4.0-5.6]	4.5 [3.7-5.2]	4.7 [3.9-5.5]	4.9 [4.1-5.7]	5.2 [4.2-6.0]	<0.001*
Stroke Characteristics						
NIHSS, median [IQR]	3 [2-6]	3 [2-7]	3 [2-7]	3 [2-6]	3 [2-6]	0.004*
TOAST Classification, n (%)						<0.001*
Small-vessel Disease	3009 (48.3)	668 (43.3)	755 (48.0)	748 (48.4)	838 (53.2)	
Large-vessel Disease	1320 (21.2)	328 (21.3)	326 (20.7)	344 (22.3)	322 (20.4)	
Cardioembolic Stroke	1169 (18.7)	337 (21.9)	312 (19.8)	273 (17.7)	247 (15.7)	
Determined Origin	454 (7.3)	129 (8.4)	119 (7.6)	102 (6.6)	104 (6.6)	
Undetermined Origin	283 (4.5)	79 (5.1)	62 (3.9)	78 (5.0)	64 (4.1)	

TG=triglyceride; HDL=high density lipoprotein; M=males; F=females; SD=standard deviation; BMI=body mass index; CAD=coronary artery disease; SBP=systolic blood pressure; DBP=diastolic blood pressure; RBS=random blood sugar; HbA1C=glycosylated hemoglobin; LDL=low density lipoprotein; Chol=cholesterol; NIHSS=National Institutes on Health Stroke Severity Scale; TOAST=trial of ORG 10172 in Acute Stroke Treatment Classification

Table 2: Univariate Analysis of Outcomes Stratified by Sex-Specific TG-HDL Index Quartiles

	Low TG-HDL Index (n=1,541)	**Low-Normal TG-HDL Index** (n=1,574)	**High-Normal TG-HDL Index** (n=1,545)	**High TG-HDL Index** (n=1,575)	***p*-value**
Sex-specific TG-HDL Cut-offs	M: ≤1.06 F: ≤0.81	M: 1.07-1.60 F: 0.82-1.18	M: 1.61-2.44 F: 1.19-1.88	M: >2.44 F: >1.88	
Inpatient Outcomes					
LOS, d, median [IQR]	4 [3-7]	4 [3-6]	4 [2-6]	4 [2-6]	0.001*
In-hospital Mortality, n (%)	21 (1.4)	19 (1.2)	15 (1.0)	6 (0.4)	0.029*
NIHSS, median [IQR]	3 [2-7]	3 [2-7]	3 [2-6]	3 [2-6]	0.004*
Thrombolysis, n (%)	197 (12.8)	196 (12.5)	189 (12.2)	176 (11.2)	0.546
Thrombectomy, n (%)	75 (4.9)	82 (5.2)	72 (4.7)	49 (3.1)	0.023*
ICU Admission, n (%)	89 (5.8)	84 (5.3)	62 (4.0)	60 (3.8)	0.021*
In-hospital Complications, n (%)	119 (7.7)	102 (6.5)	96 (6.2)	78 (5.0)	0.017*
Post-discharge Long-term Outcomes					
1-y Stroke Recurrence, n (%)	21 (1.8)	33 (2.7)	30 (2.5)	36 (2.8)	0.377
mRS at 90 days, median [IQR]	1 [0-3]	1 [0-3]	1 [0-3]	1 [0-3]	0.164
90-Day Mortality, n (%)	27 (2.3)	27 (2.3)	18 (1.5)	26 (2.1)	0.495
1-y Post-stroke MACE, n (%)	70 (4.6)	81 (5.2)	76 (5.0)	87 (5.5)	0.681
1-y Post-stroke MI, n (%)	3 (0.3)	6 (0.5)	16 (1.3)	13 (1.0)	0.011*
1-y Post-stroke Cardiac Revascularization, n (%)	6 (0.5)	6 (0.5)	13 (1.1)	12 (0.9)	0.228

TG=triglyceride; HDL=high-density lipoprotein; LOS=length of stay; d=days; y=year; IQR=interquartile range; ICU=intensive care unit; MRS=modified Rankin Scale; MACE=major adverse cardiac event; MI=myocardial infarction; M=males; F=females

Long-term outcomes and in-hospital LOS were assessed among survivors of index hospital admission.

that TG/HDL ratio is closely related to insulin resistance and metabolic syndrome, which induce a high inflammatory state and promotes oxidative stress, causing vascular endothelial dysfunction and accelerating arteriosclerosis.[2] A lower TG/HDL was also found to be statistically significantly associated with the development of myocardial infarction (MI) within one year following the stroke event, a finding which can be explained by the already established association between dyslipidemia and adverse cardiovascular outcomes[15], but one which has not been studied in stroke previously. Our finding of an increased cardiovascular risk after stroke with TG-HDL index is an interesting finding that can carry prognostic and management implications. Another important feature of our study is the evaluation of the detrimental effects of dyslipidemia in patients from the Middle East and South Asia, a cohort which has not been previously extensively studied. In these populations, dyslipidemia is very common and stroke and CAD presents at an earlier age.[16]

Dyslipidemia is frequently seen in association with cardiovascular disease and diabetes mellitus and new evidence suggests that it is also associated with stroke. We used the TG/HDL index as a marker of dyslipidemia. Basic lipid indices such as triglycerides (TG) HDL-C have been historically used when assessing the relationship between dyslipidemia and insulin resistance, obesity and metabolic syndrome.[17] More recently, the TG to high-density lipoprotein cholesterol (HDL-C) ratio (TG/HDL-C) has been utilized. It has shown promise in predicting cardiovascular events and cerebrovascular events[18], and it has also proven to be more beneficial than isolated lipid levels as it is able to account for complex metabolic lipid interactions.[17] Deng *et al*. found via ROC analyses that the AUC of TG/HDL-C index for outcome measures of excellent and good outcomes and mortality was greater than that of the other lipid variables alone, namely triglyceride (TG), total cholesterol (TC), HDL-C, LDL, Non-HDL-C.[17] The current study aimed to extend these observations to a predominantly Arab and South Asian population, groups in which insulin resistance, accompanied by high TG and low HDL-C, occurs more commonly than in European

Table 3: Multivariate Binary Logistic Regression Analysis of Outcomes Stratified by Sex-Specific TG-HDL Index Quartiles

	Low TG-HDL Index		**Low-Normal TG-HDL Index**		**High-Normal TG-HDL Index**		**High TG-HDL Index**	
Sex-specific TG-HDL Cut-offs	M: ≤1.06 F: ≤0.81		M: 1.07-1.60 F: 0.82-1.18		M: 1.61-2.44 F: 1.19-1.88		M: >2.44 F: >1.88	
Inpatient Outcomes			aOR [95% CI]	*p*	aOR [95% CI]	*p*	aOR [95% CI]	*p*
In-hospital Mortality	Ref.	-	0.84 [0.43-1.63]	0.609	0.82 [0.40-1.67]	0.575	0.33 [0.13-0.84]	0.021*
In-hospital Complications	Ref.	-	0.83 [0.61-1.13]	0.230	0.94 [0.69-1.28]	0.682	0.78 [0.56-1.10]	0.151
Long-term Outcomes			aOR [95% CI]	*p*	aOR [95% CI]	*p*	aOR [95% CI]	*p*
1-year Stroke Recurrence	Ref.	-	1.53 [0.87-2.68]	0.138	1.36 [0.76-2.41]	0.303	1.53 [0.86-2.70]	0.147
90-Day Mortality	Ref.	-	1.07 [0.60-1.92]	0.821	0.83 [0.43-1.59]	0.570	1.35 [0.73-2.50]	0.335
1-year Post-stroke MI	Ref.	-	1.80 [0.44-7.31]	0.411	4.76 [1.36-16.7]	0.015*	3.29 [0.91-11.9]	0.070
1-year Post-stroke Cardiac Revascularization	Ref.	-	1.11 [0.28-4.34]	0.887	2.77 [0.82-9.35]	0.101	1.98 [0.59-6.64]	0.267

TG=triglyceride; HDL=high-density lipoprotein; LOS=length of stay; d=days; IQR=interquartile range; ICU=intensive care unit; MRS=modified Rankin Scale; MACE=major adverse cardiac event; MI=myocardial infarction; aOR=adjusted odds ratio; 95% CI=95% confidence interval; M=males; F=females

Multivariate analyses adjusted for patient demographics (age, sex, ethnicity), emergency department vitals (systolic blood pressure), comorbidities (diabetes, hypertension, dyslipidemia, coronary artery disease, atrial fibrillation, prior stroke history, obesity, smoking status), stroke severity, and in-hospital interventions (thrombolysis or thrombectomy)

Long-term outcomes were assessed among survivors of index hospital admission.

patients.[19]

We found higher TG-HDL indices to be independently associated with lower rates of inpatient mortality on multivariate analysis. One explanation for this finding could be that increasing levels of sex-specific TG/HDL ratios were associated with higher percentages of small vessel disease in the population. From a pathophysiological perspective, the exact reason still remains uncertain. Some studies have suggested that low TG/HDL may aggravate neuronal damage, leading to poor outcomes in ischemic stroke patients. A potential explanation for that being that low serum cholesterol levels may affect cell membrane fluidity and result in the failure of neuronal cells to resist local hypertonicity and acidosis under ischemic stress.[20] In a retrospective study conducted by Deng *et al*. on a total of 1006 acute ischemic stroke (AIS) patients, a clear association was demonstrated between increasing TG/HDL ratio and 0.34-fold decreased risk of death and a 2-fold or more increased probability of good or excellent outcomes. They did not account for stroke severity or stroke sub-type however.[17] Similar results were obtained when the same authors replicated their findings two years later and used the X-tile software rather than ROC analysis and concluded that the discriminatory ability (sensitivity 82.5% and specificity 73.4%) of TG/HDL index was significantly greater than that in their prior study (sensitivity 67.8% and specificity 60.6%).[21] Luo *et al*. similarly demonstrated an increased risk of hemorrhagic transformation (HT) after AIS in patients with low TG/HDL-C and showed that low TG/HDL was associated with an increased risk of poor outcome even after adjusting for stroke severity and stroke sub-type per TOAST criteria.[20] Conversely, an inverse relation was reported by Choi *et al*. who showed that high TG/HDL-C levels were significantly associated with early poor prognoses in 736 patients with AIS.[22] The Northern Manhattan study[23] and the Iwate-Kenpoku cohort study[24] however indicated no association b/w lipid ratios and stroke, which in part could be explained by the small number of ischemic strokes in the Manhattan study and utilization of only LDL/HDL ratio and TC/HDL ratio, and not the TG/HDL ratio in the Iwate-Kenpoku cohort. Since the TG/HDL ratio is an accurate predictor of cardiometabolic outcomes, we believe its application in the latter study might have yielded different results. Furthermore, the discrepancy in these results can also be attributed to different study sample sizes, study designs, and inclusion and exclusion criteria.

A major finding of our paper is the association between TG/HDL and new onset 1-year post-stroke myocardial infarction (MI). While TG/HDL-C has been known to predict cardiovascular events in hypertension and diabetes mellitus[25], we were able to demonstrate that TG/HDL can also be used to predict cardiovascular events - specifically MI, in stroke patients within a specific time frame (1 year) after stroke onset. Lars Lind et al. reported a more adverse cardiometabolic profile at baseline and increased development of cardiovascular disease (CVD) over the next 40 years in patients with the highest TG/HDL-C ratio. They reported an increased HR for total CVD ($p<0.001$) and MI ($p<0.001$) but a decreased HR for Stroke in all three high risk groups - a finding which only remained statistically significant in persons with MetS ($p<0.008$) (18). Alberto Cordero *et al*. similarly concluded that a high TG/HDL ratio increased the risk of a first coronary event regardless of BMI by approximately 50%.[15] Moreover, Park *et al*. in a post-hoc analysis of a randomized control trial (RCT) demonstrated an association between rising TG/HDL quintiles and stroke (1.56, 1.05-2.32; $p=0.002$) and stroke/coronary heart disease (CHD) including MI, cardiac revascularization, cardiac resuscitation, and fatal CHD/vascular death (1.39, 1.05-1.83; $p<0.001$) after adjusting for multiple confounders.[26] TG/HDL ratio was similarly able to precede IHD in a Korean cohort.[27] Keeping these findings in mind, using TG/HDL as a cardiac risk stratification tool in stroke patients holds significant potential.

There was no elevated 1-year stroke recurrence with increased TG/HDL ratio in our population. In a post-hoc analysis of a randomized clinical trial, Park *et al*. demonstrated a significant association between increasing TG/HDL-C ratio and risk of recurrent stroke.[26] A likely explanation for this difference could be the possibility of unmeasured confounding in the VISP study as they had been unable to adjust for metabolic syndrome or diabetes due to non-availability of serum glucose levels, or that their study comprised of 80% Caucasians, while ours comprised of a combined 84.8% Arabs and South Asians, a completely different cohort in whom lipid abnormalities are very common. In our study, prior stroke history (aOR 1.765, $p=0.012$) and history of CAD (aOR 1.655, $p=0.029$) were the only factors significantly predictive of stroke recurrence within one year, as demonstrated on multivariate cox regression analysis.

Higher sex-specific TG/HDL quartile was also associated with a statistically but not clinically significant improvement in mRS scores at 90 days after discharge (ß-0.057, 95% CI -0.014 to -0.100, p=0.009). This is likely related to the higher rates of small vessel disease and milder stroke severity noted in our subjects. A retrospective follow-up study involving 1006 patients concluded similar findings and stated that higher TG/HDL was strongly associated with excellent and good outcomes (OR 2.34, OR 4.12) and death (OR 0.26). They were able to show that increasing levels of TG/HDL were inversely correlated with mRS at 90 days (ϱ = -0.259; P < 0.001).[17]

In conclusion, TG-HDL was strongly correlated with in-patient mortality and long-term post-stroke cardiovascular outcomes but not long-term stroke recurrence. Our study contributes to the growing literature regarding the complex relationship between TG-HDL index and neurologic outcomes following stroke. Our finding of an independently increased 1-year risk of post-stroke MI with higher TG-HDL index may warrant consideration of this index as a cardiac risk stratification tool for stroke patients. Given that lipid levels are obtained on all stroke patients on admission, the utilization of this index can aid clinicians in appropriate follow up and surveillance.

There are some limitation of our study including, its retrospective design, unavailability of fasting glucose levels due to which we had to utilize random glucose levels, and our study being predominantly limited to Arab and South Asian populations, due to which its generalizability to other populations is limited. The study comprised of 82% males, and hence the findings cannot be generalized to females. Data on prior stroke history was not available. Strengths of our study include a large patient population and availability of data points on all patients which were collected prospectively by trained personnel.

DISCLOSURE

Ethics: The study was approved by the Committee for Human Ethics Research, Academic Health Service at HMC (MRC-01-20-1135).

Data availability: Original data is available and can be accessed by direct request from the corresponding author, Dr Naveed Akhtar.

Financial support: None

Conflict of interest: None

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