



OPEN Impact of non-traditional lipid profiles on 1-year vascular outcomes in ischemic stroke patients with prior statin therapy and LDL-C < 100 mg/dL

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This study aimed to investigate the association between non-traditional lipid profiles and the risk of 1-year vascular events in patients who were already using statins before stroke and had admission LDL-C < 100 mg/dL. This study was an analysis of a prospective, multicenter, nationwide registry of consecutive patients with acute ischemic stroke patients who treated with statin before index stroke and LDL-C < 100 mg/dL on admission. Non-traditional lipid profiles including non-HDL, TC/HDL ratio, LDL/HDL ratio, and TG/HDL ratio were analyzed as a continuous or categorical variable. The primary vascular outcome within one year was a composite of recurrent stroke (either hemorrhagic or ischemic), myocardial infarction (MI) and all-cause mortality. Hazard ratios (95% Cis) for 1-year vascular outcomes were analyzed using the Cox PH model for each non-traditional lipid profiles groups. A total of 7028 patients (age 70.3 ± 10.8years, male 59.8%) were finally analyzed for the study. In unadjusted analysis, no significant associations were observed in the quartiles of LDL/HDL ratio and 1-year primary outcome. However, after adjustment of relevant variables, compared with Q1 of the LDL/HDL ratio, Q4 was significantly associated with increasing the risk of 1-year primary outcome (HR 1.48 [1.19–1.83]). For the LDL/HDL ratio, a linear relationship was observed (P for linearity < 0.001). Higher quartiles of the LDL/HDL ratio were significantly and linearly associated with increasing the risk of 1-year primary vascular outcomes. These findings suggest that even during statin therapy with LDL-C < 100 mg/dl on admission, there should be consideration for residual risk based on the LDL/HDL ratio, following stroke.

Keywords Non-traditional lipid profiles, Lipid ratio, LDL/HDL ratio, LDL-cholesterol, Acute ischemic stroke, Vascular outcome, Residual cardiovascular risk

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Stroke constitutes a significant cause of morbidity and mortality, especially among the elderly population. Lowering low-density lipoprotein cholesterol (LDL-C) through statin treatment is crucial for preventing atherosclerotic cardiovascular diseases, including stroke¹. For secondary prevention, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial emphasized the benefit of high-dose statin therapy for stroke patients with admission LDL-C > 100 mg/dL². Additionally, the Treat Stroke to Target (TST) trial demonstrated that maintaining LDL-C < 70 mg/dL significantly reduces the risk of long-term vascular events compared to keeping LDL-C in the range of 90–110 mg/dL in atherosclerotic ischemic stroke³.

In addition to LDL-C, non-traditional lipid profiles, such as non-high density lipoprotein (non-HDL) cholesterol and lipid ratios, have been recognized as contributors to residual vascular risk⁴. Previous studies have considered non-HDL cholesterol, triglyceride (TG)/HDL ratio, and LDL/HDL ratio as residual risk factors for cardiovascular diseases in patients with coronary artery diseases^{5,6}. Elevated lipid ratios in patients with general risk factors have been also associated with an increased risk of stroke⁷.

Among ischemic stroke patients, with the escalating use of cholesterol-lowering therapy for primary and secondary prevention, there is an increasing proportion of patients who were already on statin treatment before the index event and had well-controlled LDL-C levels (< 100 mg/dL) upon admission. In a previous study, there was a relationship between admission LDL-C levels and early vascular outcomes for patients not taking a statin at the time of the index event but not for patients already on statins⁸. Therefore, the best post-stroke target lipid level for patients who were already on statins and had well-controlled LDL-C levels at the time of their index stroke remains unclear. In such cases, the impact of non-traditional lipid profiles on outcome might need consideration. Research on the prognostic implications and targets for treatment of non-traditional lipid profiles for patients with statin pretreatment and baseline LDL-C < 100 mg/dL remains limited. While statin therapy may be associated with the reduced risk of vascular outcome for these patients with low LDL-C on admission⁹, understanding the clinical significance of non-traditional lipid profiles beyond LDL-C could hold importance.

Therefore, this study aimed to investigate the association between non-traditional lipid profiles and the risk of 1-year vascular events in patients who were already using statins before index stroke and had admission LDL-C < 100 mg/dL.

Methods

Subjects

This study was an analysis of a prospective, multicenter, nationwide registry of consecutive patients with acute stroke or transient ischemic attack (TIA) admitted to 18 academic hospitals in South Korea, the Clinical Research Center for Stroke-Korea (CRCS-K) registry. Detailed methodologic information about the CRCS-K registry has been reported previously^{10,11}. We identified patients with acute cerebrovascular events admitted between January 2011 and July 2020 ($N = 75690$). Among the patients with acute cerebrovascular events, we included ischemic stroke or TIA with lesion-positive on diffusion weighted imaging (DWI) within 7 days of onset ($N = 68468$), patients classified as non-cardioembolic ischemic stroke according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria ($N = 52878$), statin pretreatment before index stroke ($N = 10189$) and admission LDL-C < 100 mg/dL ($N = 7063$). Patients without information on fasting lipid profiles at admission were excluded. A detailed patient selection flowchart is shown in Supplemental Fig. 1.

Ethics statement

Clinical information was collected from the CRCS-K registry with approval from the local institutional review boards of all the participating centers, including Seoul National University Bundang Hospital and Chonnam National University Hospital. A waiver for informed consent was provided by the Institutional Review Board of Seoul National University Bundang Hospital and Chonnam National University Hospital due to study subject anonymity and minimal risk to the participants. The data used in this study are available upon reasonable request following the submission of a legitimate academic research proposal to be assessed by the CRCS-K steering committee and all research was performed in accordance with relevant guidelines and regulations.

Ethics approval

The current study was approved by local institutional review boards at all participating centers, including Chonnam National University Hospital (CNUH-2024-032).

Data collection

Demographic, clinical, imaging, and laboratory data were prospectively collected. Lipid profiles, including LDL-C, total cholesterol (TC), HDL-C, and TG levels, were obtained during the first fasting period after admission. Four non-traditional lipid profile parameters, non-HDL, TC/HDL ratio, LDL/HDL ratio, and TG/HDL ratio, were analyzed as continuous and categorical variables. The patients were classified into quartiles, with each quartile representing 25% of the distribution, for each non-traditional lipid profile for comparison: Q1 (0–25.0%), Q2 (25.1–50.0%), Q3 (50.1–75.0%) and Q4 (75.1–100%). Ischemic stroke subtypes were classified according to the TOAST criteria, which were refined to incorporate additional information based on modern imaging studies^{12,13}. We analyzed non-cardioembolic etiologies, including large artery atherosclerosis (LAA), small vessel occlusion (SVO), other determined etiology (OD), and undetermined etiology (UD), according to each lipid profiles.

Outcomes

The primary vascular outcome within one year was a composite of recurrent stroke (either hemorrhagic or ischemic), myocardial infarction (MI) and all-cause mortality. The secondary vascular outcomes were the individual outcomes of (a) all-cause mortality, (b) stroke (either ischemic or hemorrhagic), and (c) MI. Detailed definitions of the vascular outcome events and methods of outcome capture used in the current study are described in the Supplemental Methods and previous reports^{10,11}.

Statistical analysis

Baseline characteristics and outcomes were compared among each non-traditional lipid profiles quartiles by using the chi-square test, ANOVA, or Kruskal–Wallis test according to the type of variable. The event probability of 1-year vascular outcomes according to the non-traditional lipid profiles quartiles in all patients and in patients by stroke subtype was calculated by using the Kaplan–Meier method, and the log-rank test was performed to analyze differences among the groups. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for 1-year vascular outcomes were analyzed using the Cox proportional hazards model for each non-traditional lipid profiles groups. Adjustments were made for the following 18 predetermined variables with clinically relevant associations with the outcome variables; age, male sex, BMI, NIHSS score, history of stroke, history of coronary artery diseases, HTN, DM, dyslipidemia, smoking, prior antiplatelet, in-hospital anti-diabetic treatment, in-hospital antihypertensive treatment, statin, glucose, creatinine, LDL-C and SBP. In the analysis of the LDL/HDL ratio, although LDL-C has been restricted to less than 100 mg/dl, it remains a crucial risk marker with significant variability. To investigate whether the LDL/HDL ratio has independent clinical significance, LDL-C was included as an adjusted variable. The modifying effect of stroke subtype on the relationships between each non-traditional lipid profiles groups and clinical outcomes was explored by separately introducing an interaction term of ischemic stroke subtype and LDL/HDL ratio quartile groups (and TC/HDL ratio) into the models.

Two-sided *p* values < 0.05 were considered indicative of significance. Given the known insensitivity of interaction testing, evidence of heterogeneity was considered present with *p* values ≤ 0.10. In addition, the goodness of fit of the four models were compared using the Akaike (AIC) and Bayesian information criterion (BIC). Lower AIC and BIC indicate a better fit. Statistical analyses were performed with R software using the “rms” package (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

General characteristics

A total of 7,028 patients (mean age 70.3 ± 10.8 years, male 59.8%) met study entry criteria. The median NIHSS score was 3 (IQR 1–6) and the mean LDL-C level on admission was 69.7 ± 17.3 mg/dL. For lipid profiles at admission, the mean levels of HDL-C, TG, TC, and non-HDL were 43.2 ± 12.5 mg/dL, 116.4 ± 72.1 mg/dL, 130.4 ± 24.8 mg/dL, and 87.2 ± 22.3 mg/dL, respectively. The mean LDL-C/HDL-C ratio, TG/HDL ratio, and TC/HDL ratio was 1.72 ± 0.61, 3.06 ± 2.63, and 3.20 ± 1.08, respectively. Non-statin lipid-lowering agents, in addition to statins, were used in 6.5% of patients before index stroke. At discharge, 92.2% of the study subjects received statin treatment.

The demographic and clinical characteristics of subjects according to the quartiles of non-traditional lipid profiles (LDL/HDL ratio, TC/HDL ratio, TG/HDL ratio, and non-HDL) are presented in Table 1 and Supplemental Tables 1–3. As the quartile of the LDL/HDL ratio increased, there were significant trends of decreasing age and increasing body weight and BMI. Additionally, the frequency of DM, HTN, and history of CAD significantly increased as the quartile of LDL/HDL ratio increased (Table 1).

One-year vascular outcomes

The mean follow-up duration was 330 ± 88.9 days, and 91.5% of the study subjects completed 1-year of follow-up. The 1-year cumulative incidences of the composite of stroke, MI and all-cause mortality was 14.5%; all-cause mortality, 8.9%; stroke (either ischemic or hemorrhagic), 7.2%; and MI, 0.5%. In crude analysis, the 1-year cumulative incidences of the composite of stroke, MI, and all-cause mortality did not significantly differ among the quartiles of the LDL/HDL ratio: 14.9% in the lowest quartile (Q1) of the LDL/HDL ratio, 13.4% in the second quartile (Q2), 14.1% in the third quartile (Q3), and 15.7% in the highest quartile (Q4) (Table 2, *p* for trend = 0.59). The 1-year cumulative incidences of stroke, all-cause mortality, and MI as individual outcomes also did not show significant differences according to the quartiles of LDL/HDL ratio. Similar observations with no significant differences were made for 1-year cumulative incidences of vascular events according to the quartiles of TG/HDL ratio and TC/HDL ratio (Supplemental Table 4).

	All	Q1 (0.20–1.29)	Q2 (1.30–1.66)	Q3 (1.67–2.08)	Q4 (2.09–7.29)	P†	P _{trend} ‡
N	7028	1767	1738	1751	1772		
LDL/HDL ratio		0.20–1.29	1.30–1.66	1.67–2.08	2.09–7.29		
Age, mean ± SD	70.3 ± 10.8	70.9 ± 11.0	70.4 ± 10.6	70.5 ± 10.6	69.5 ± 11.1	0.001	0.001
Male, n (%)	4206 (59.8)	1000 (56.6)	962 (55.4)	1055 (60.3)	1189 (67.1)	<0.0001	<0.0001
Onset-to-arrival							
Within 24 h, n (%)	4432 (63.1)	1151 (65.1)	1125 (64.7)	1108 (63.3)	1048 (59.1)	0.001	0.0002
Height, cm, mean ± SD	161.8 ± 8.8	161.3 ± 8.9	160.9 ± 8.7	161.9 ± 8.8	163.0 ± 8.9	<0.0001	<0.0001
Weight, kg, mean ± SD	63.3 ± 11.3	61.4 ± 11.0	62.3 ± 10.7	63.9 ± 11.2	65.3 ± 11.8	<0.0001	<0.0001
BMI, %	24.1 ± 3.4	23.5 ± 3.4	24.0 ± 3.3	24.3 ± 3.3	24.5 ± 3.4	<0.0001	<0.0001
NIHSS, med (IQR)	3 (1–6)	3 (1–6)	3 (1–6)	3 (1–6)	3 (1–6)	0.82	0.06
Premorbid mRS 0–1	5629 (80.1)	1376 (77.9)	1417 (81.5)	1419 (81.0)	1417 (80.0)	0.033	0.17
History of stroke	3222 (45.8)	900 (50.9)	826 (47.5)	742 (42.4)	754 (42.6)	<0.0001	<0.0001
History of TIA	285 (4.1)	71 (4.0)	69 (4.0)	71 (4.1)	74 (4.2)	0.99	0.79
History of PAD	98 (1.4)	18 (1.0)	25 (1.4)	29 (1.7)	26 (1.5)	0.43	0.21
History of CAD	1476 (21.0)	333 (18.8)	352 (20.3)	391 (22.3)	400 (22.6)	0.02	0.002
HTN	5851 (83.3)	1450 (82.1)	1449 (83.4)	1475 (84.2)	1477 (83.4)	0.38	0.23
DM	3637 (51.8)	820 (46.4)	858 (49.4)	921 (52.6)	1038 (58.6)	<0.0001	<0.0001
Dyslipidemia	5108 (72.7)	1262 (71.4)	1270 (73.1)	1310 (74.8)	1266 (71.4)	0.07	0.71
Smoking						<0.0001	0.003
Never	4559 (64.9)	1199 (67.9)	1175 (67.6)	1133 (64.7)	1052 (59.4)		
Current	1228 (17.5)	244 (13.8)	273 (15.7)	316 (18.0)	395 (22.3)		
Ex (beyond 5 year)	821 (11.7)	202 (11.4)	209 (12.0)	198 (11.3)	212 (12.0)		
Recent (within 5 year)	420 (6.0)	122 (6.9)	81 (4.7)	104 (5.9)	113 (6.4)		
Medication history							
Antihypertensive	5402 (76.9)	1306 (73.9)	1324 (76.2)	1394 (79.6)	1378 (77.8)	0.001	0.001
Anti-diabetics	3226 (45.9)	748 (42.3)	771 (44.4)	806 (46.0)	901 (50.8)	<0.0001	<0.0001
Lipid lowering agents	455 (6.5)	128 (7.2)	120 (6.9)	88 (5.0)	119 (6.7)	0.04	0.19
Antiplatelet	4909 (69.8)	1263 (71.5)	1218 (70.1)	1190 (68.0)	1238 (69.9)	0.16	0.16
Aspirin	3332 (47.4)	825 (46.7)	827 (47.6)	803 (45.9)	877 (49.5)	0.16	0.21
Clopidogrel	2426 (34.5)	628 (35.5)	599 (34.5)	576 (32.9)	623 (35.2)	0.36	0.59
Reperfusion therapy						0.07	0.01
No	6215 (88.4)	1537 (87.0)	1531 (88.1)	1553 (88.7)	1594 (90.0)		
IVT	441 (6.3)	120 (6.8)	107 (6.2)	111 (6.3)	103 (5.8)		
EVT	216 (3.1)	69 (3.9)	61 (3.5)	41 (2.3)	45 (2.5)		
IV + EVT	156 (2.2)	41 (2.3)	39 (2.2)	46 (2.6)	30 (1.7)		
Laboratory findings							
WBC counts	8.1 ± 3.1	8.0 ± 3.3	8.0 ± 3.2	8.0 ± 3.0	8.3 ± 3.1	0.02	0.0062
Platelet counts	227.4 ± 77.6	220.0 ± 81.5	227.4 ± 78.5	227.5 ± 72.5	234.6 ± 76.9	<0.0001	<0.0001
Hemoglobin	13.0 ± 2.0	12.9 ± 1.9	13.0 ± 2.0	13.1 ± 2.0	13.2 ± 2.2	0.002	0.0001
Glucose	152.2 ± 68.2	147.5 ± 68.0	147.8 ± 61.5	153.0 ± 67.3	160.2 ± 74.6	<0.0001	<0.0001
BUN	18.6 ± 10.0	18.6 ± 10.2	18.2 ± 9.0	18.6 ± 9.6	19.2 ± 10.9	0.03	0.0439
Creatinine	1.2 ± 1.3	1.1 ± 1.0	1.1 ± 0.9	1.1 ± 1.1	1.3 ± 1.9	<0.0001	<0.0001
LDL-cholesterol	69.7 ± 17.3	54.4 ± 15.2	67.9 ± 14.5	74.6 ± 13.4	81.7 ± 12.8	<0.0001	<0.0001
TC	130.4 ± 24.8	122.5 ± 26.8	129.3 ± 25.2	133.0 ± 22.9	136.9 ± 21.9	<0.0001	<0.0001
TG	116.4 ± 72.1	91.5 ± 57.4	106.0 ± 59.9	121.6 ± 71.5	146.2 ± 84.4	<0.0001	<0.0001
HDL	43.2 ± 12.5	53.9 ± 14.0	45.8 ± 9.8	40.3 ± 7.5	32.9 ± 6.3	<0.0001	<0.0001
Non-HDL	87.2 ± 22.3	68.6 ± 18.1	83.4 ± 17.6	92.7 ± 17.7	103.9 ± 19.1	<0.0001	<0.0001
SBP	146.5 ± 25.9	146.0 ± 25.8	146.8 ± 26.4	147.5 ± 25.7	145.6 ± 25.8	0.14	0.83
In-hospital treatment							
Aspirin	5934 (84.4)	1444 (81.7)	1496 (86.1)	1481 (84.6)	1513 (85.4)	0.002	0.01
Clopidogrel	4183 (59.5)	1028 (58.2)	1054 (60.6)	1040 (59.4)	1061 (59.9)	0.51	0.46
Other antiplatelet	743 (10.6)	226 (12.8)	171 (9.8)	174 (9.9)	172 (9.7)	0.01	0.01
Anti-diabetics	2710 (38.6)	616 (34.9)	649 (37.3)	693 (39.6)	752 (42.4)	<0.0001	<0.0001
Anti-hypertensives	3645 (51.9)	890 (50.4)	882 (50.7)	943 (53.9)	930 (52.5)	0.14	0.08
Lipid lowering agents other than statin	165 (2.3)	47 (2.7)	34 (2.0)	35 (2.0)	49 (2.8)	0.24	0.82
Statin	6483 (92.2)	1606 (90.9)	1613 (92.8)	1628 (93.0)	1636 (92.3)	0.08	0.12

Table 1. General characteristics of subjects according to the quartiles of LDL/HDL ratio. [†]P-value by Chi-square test, ANOVA and Kruskal-Wallis test. [‡]P-value by Cochran-Armitage trend test, Cochran-Mantel-Haenszel test and linear contrasts test in ANOVA.

	All	Q1 (0.20–1.29)	Q2 (1.30–1.66)	Q3 (1.67–2.08)	Q4 (2.09–7.29)	<i>P</i> _{trend} ^b
N	7028	1767	1738	1751	1772	
Primary outcome						
No. of events	963	249	221	231	262	
1-year event rate (%; 95% CI) ^a	14.52 (13.67–15.38)	14.88 (13.17–16.59)	13.42 (11.77–15.08)	14.05 (12.36–15.74)	15.70 (13.94–17.45)	0.59
Stroke						
No. of events	463	111	113	123	116	
1-year event rate (%; 95% CI) ^a	7.24 (6.60–7.88)	6.88 (5.64–8.12)	6.95 (5.70–8.19)	7.80 (6.47–9.14)	7.30 (6.01–8.60)	0.68
All-cause mortality						
No. of events	572	155	122	131	164	
1-year event rate (%; 95% CI) ^a	8.91 (8.21–9.61)	9.55 (8.11–10.99)	7.80 (6.46–9.13)	8.18 (6.83–9.52)	10.09 (8.62–11.56)	0.60
MI						
No. of events	33	6	8	9	10	
1-year event rate (%; 95% CI) ^a	0.54 (0.35–0.72)	0.38 (0.08–0.69)	0.52 (0.16–0.89)	0.57 (0.20–0.94)	0.68 (0.26–1.10)	0.33

Table 2. One-year vascular outcomes according to the quartiles of the LDL/HDL ratio. ^aBased on the Kaplan-Meier estimates. ^bP-value by log-rank test for trend.

However, non-HDL showed a significant association of increasing quartile levels with decreased event rates of 1-year composite vascular events and secondary outcome variables (Supplemental Table 4).

The unadjusted and adjusted associations of LDL/HDL ratio with 1-year vascular outcomes are shown in Table 3. In unadjusted analysis, no significant associations were observed in the quartiles of LDL/HDL ratio and 1-year primary outcome and secondary outcomes. However, after adjustment for the 18 prespecified clinically relevant variables, compared with Q1 of the LDL/HDL ratio, Q4 of the LDL/HDL ratio was significantly associated with increasing the risk of 1-year composite of stroke, MI, and all-cause mortality (HR 1.48 [1.19–1.83]). Similarly, compared with Q1 of the TC/HDL ratio, Q2, Q3, and Q4 of the TC/HDL ratio were significantly associated with increasing the risk of 1-year primary outcome (aHR 1.21 [1.00–1.45], 1.26 [1.04–1.53], and 1.40 [1.15–1.70], respectively) (Supplemental Table 5). For TG/HDL ratio, Q4 of the TG/HDL ratio, compared with Q1, was more likely to occur to 1-year primary outcome (aHR 1.30 [1.08–1.57]) (Supplemental Table 6). However, there were no significant associations between the quartiles of non-HDL and 1-year primary outcome (Supplemental Table 7). Kaplan-Meier survival plots for these are presented in Fig. 1 and Supplemental Fig. 2A–C.

Adjusted HR plots for each non-traditional lipid profiles as continuous variables are presented in Fig. 2 and Supplemental Fig. 3A–C. For the LDL/HDL ratio, a linear relationship was observed (*P* for linearity < 0.001), and the cut-off value associated with significant increase in the composite outcome within 1-year was 2.09 of LDL/HDL ratio. For other lipid profiles of TC/HDL ratio and TG/HDL ratio, non-linear associations were observed. Among the four lipid profiles models, the model for the LDL/HDL ratio had the lowest Akaike Information Criteria and Bayes Information Criterion (Supplemental Table 8).

TOAST subgroup analysis

There were significant interactions between LDL/HDL ratio and TOAST subgroups with 1-year primary outcome (*P* interaction = 0.01). Among the LAA and SVO subtypes, compared with Q1 of LDL/HDL ratio, higher quartiles were more likely to be associated with increasing the risk of 1-year primary vascular outcomes, while no associations were observed among UD subtype (Fig. 3). For other lipid ratios and non-HDL cholesterol, there were no potential interactions of stroke subtypes with 1-year primary outcome (Supplemental Fig. 4).

Discussion

Our study, which focused on over 7,000 patients with acute ischemic stroke who were treated with statins before the index stroke and had LDL-cholesterol levels < 100 mg/dl upon admission, demonstrated an association between non-traditional lipid profiles and an increased risk of 1-year vascular outcomes. Higher quartiles of the LDL/HDL ratio, TC/HDL ratio, and TG/HDL ratio, though not non-HDL levels, were significantly associated with increasing the risk of 1-year composite vascular events. These findings suggest that even during statin therapy with LDL-C < 100 mg/dl on admission, there should be consideration for residual risk based on non-traditional lipid profiles.

Among the parameters examined in this study, the best performance model was the LDL/HDL ratio, which is the most widely used in clinical practice. Our study is noteworthy of finding a linear relationship between the LDL/HDL ratio and the increasing risk of 1-year vascular events in ischemic stroke patients under statin

		Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Primary outcomes	Q1	1 (Ref)		1 (Ref)	
	Q2	0.89 (0.74–1.06)	0.19	1.09 (0.90–1.32)	0.39
	Q3	0.92 (0.77–1.10)	0.37	1.22 (1.00–1.49)	0.05
	Q4	1.04 (0.87–1.23)	0.68	1.48 (1.19–1.83)	0.0004
Stroke	Q1	1 (Ref)		1 (Ref)	
	Q2	1.02 (0.78–1.32)	0.89	1.14 (0.86–1.51)	0.36
	Q3	1.10 (0.85–1.42)	0.46	1.34 (1.00–1.80)	0.05
	Q4	1.03 (0.80–1.34)	0.81	1.33 (0.95–1.84)	0.09
All-cause mortality	Q1	1 (Ref)		1 (Ref)	
	Q2	0.79 (0.62–1.00)	0.05	1.03 (0.80–1.32)	0.81
	Q3	0.84 (0.66–1.06)	0.14	1.16 (0.89–1.50)	0.27
	Q4	1.04 (0.84–1.30)	0.72	1.50 (1.15–1.97)	0.003
MI	Q1	1 (Ref)		1 (Ref)	
	Q2	1.33 (0.46–3.83)	0.60	1.16 (0.38–3.51)	0.80
	Q3	1.48 (0.53–4.17)	0.45	1.06 (0.34–3.37)	0.92
	Q4	1.64 (0.60–4.51)	0.34	1.06 (0.30–3.69)	0.93

Table 3. Associations of LDL/HDL ratio with one-year vascular outcomes. Adjusted variable: age, male, NIHSS, BMI, LDL-C, history of stroke, history of CAD, HTN, DM, dyslipidemia, smoking status, prior antiplatelet, creatinine, glucose, SBP, in-hospital anti-hypertensive, in-hospital antidiabetics, in-hospital lipid lowering agents.

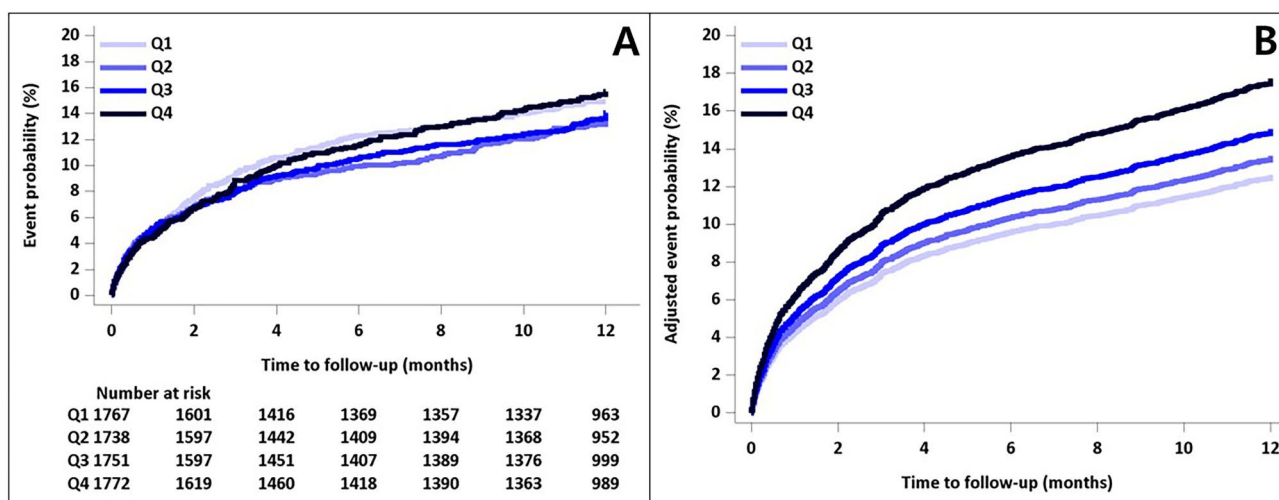


Fig. 1. Kaplan-Meier survival plots for 1-year primary outcome according to the LDL/HDL ratio, unadjusted (A) and adjusted plots (B).

treatment and admission LDL-C < 100 mg/dl. Compared with the lowest quartile of the LDL/HDL ratio, the highest quartile of was more likely to be associated with increasing the risk of 1-year composite of vascular events and all-cause mortality by relatively 48% and 50%, respectively. In a prior study, when statins had already been taken before index stroke and LDL-C levels were well controlled at admission, LDL-C levels had little association with early vascular outcomes in ischemic stroke⁸. Therefore, our study provides important insights that even in patients undergoing appropriate LDL-C lowering treatment before index stroke, there could still be residual risk, which may be predicted through lipid ratio like the LDL/HDL ratio. While the reduction of LDL-C through statin therapy diminishes a patient's cardiovascular risk, a residual risk persists even when LDL-C levels are adequately controlled¹⁴. In such cases, non-traditional lipid profiles may serve as clinical targets for this residual risk. Emerging evidence from various studies indicates that the assessment of cardiovascular residual risk through non-traditional lipid parameters is gaining increasing importance^{15–18}. For instance, when LDL-C levels are well controlled with statins, it may be advisable to consider additional lipid-lowering therapy, targeting non-HDL as a therapeutic goal¹⁹.

This finding is consistent with findings in other cardiovascular diseases. Several studies have found associations between the LDL/HDL ratio, and cardiovascular event risk in patients with coronary artery diseases^{20,21}. Additionally, a previous study found that an elevated LDL/HDL ratio could be a positive predictor

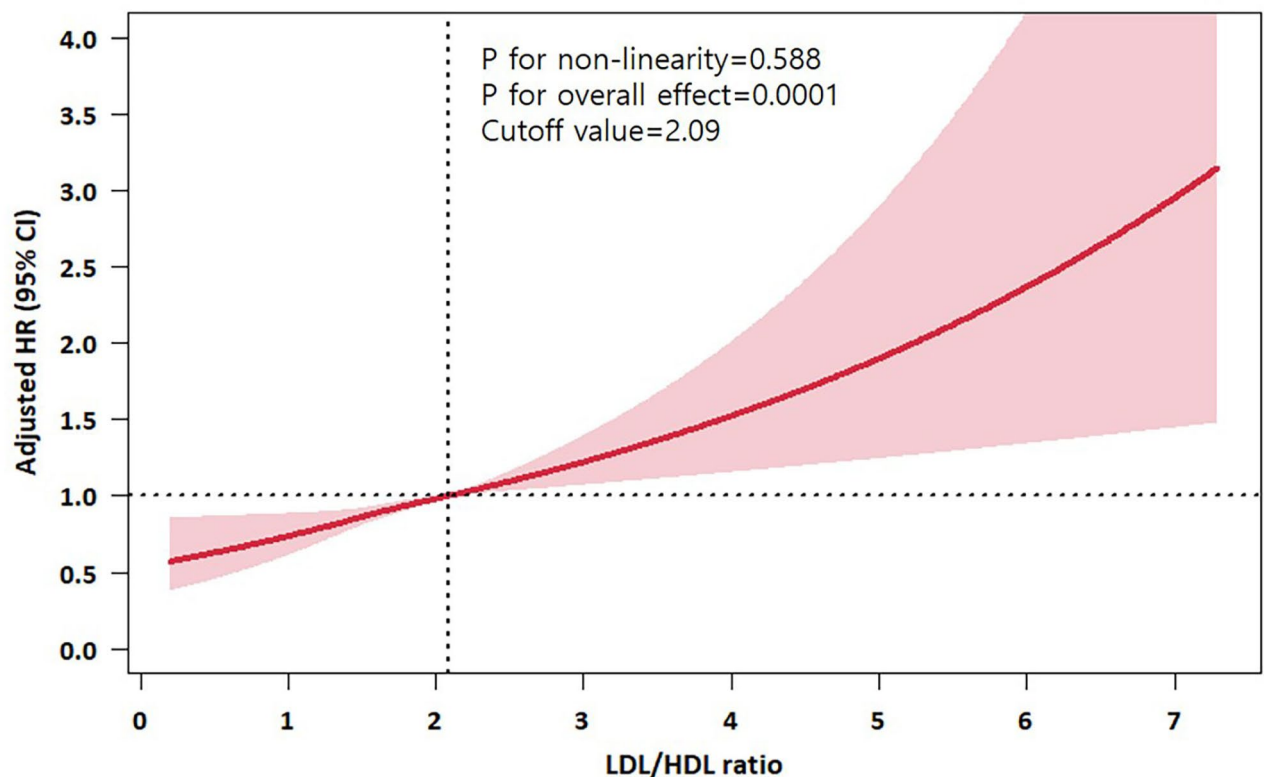


Fig. 2. Adjusted HR of continuous LDL/HDL ratio for primary outcome within 1 year.

of aortogenic cerebral embolism²². In contrast, some studies found an opposing finding that a high LDL/HDL ratio protected against death, recurrence, and moderate disability within 3 months following stroke onset²³. However, the population in these studies differed from the current investigation as were not confined to patients who were already taking statins and had their LDL-C levels appropriately controlled. In a previous study of general population without DM or cardiovascular diseases, when LDL-C was controlled below 100 mg/dL by statin therapy, the LDL/HDL ratio had an HR for cardiovascular diseases event and death of 1.43 and 1.34, respectively²⁴. In our study, beyond LDL-C, the risk of 1-year composite of stroke, MI, and all-cause mortality significantly and linearly increased when the LDL/HDL ratio surpassed 2.09. Currently, guidelines for dyslipidemia in stroke patients specify a target goal for LDL-C levels, but do not clearly define targets for other lipid profiles²⁵.

We included patients with the LDL-C level at < 100 mg/dl on admission, not < 70 mg/dl, based on current stroke guidelines that use LDL-C > 100 mg/dl as the criterion for high-intensity statin therapy²⁵. The SPARCL study included patients with acute ischemic stroke and LDL-C > 100 mg/dl³. Recent guidelines mention LDL targets of < 70 mg/dl or even < 55 mg/dl^{19,25}, but these targets primarily guide atherosclerotic stroke management. The applicability to other stroke mechanism or etiologies such as SVO or UD remains uncertain and requires further research. Initiating lipid-lowering treatment in non-CE stroke may be considered when LDL-C is > 100 mg/dl.

In a previous meta-analysis, the TC/HDL ratio demonstrated a linear correlation with stroke outcomes²⁶. For each 1-unit increase in the TC/HDL ratio, the risk of stroke increased by 16%. In contrast, we found a non-linear relationship of the TC/HDL ratio and 1-year composite of stroke, MI, and all-cause mortality, with lower risk with a lower TC/HDL ratio. In addition, compared with Q1 of the TC/HDL ratio, higher quartiles were significantly associated with increasing risk of 1-year composite of stroke, MI, and all-cause mortality (adjusted HR 1.21, 1.26, and 1.40 in Q2, Q3, and Q4, respectively) after adjustments of relevant variables. When the TC/HDL ratio was 3.65 or lower, there was a reduced HR for a one-year composite of stroke, MI, and all-cause mortality.

Our study also revealed a non-linear relationship for the TG/HDL ratio, with the highest risk observed at 3.6. The highest quartile of the TG/HDL ratio, compared with lowest quartile, was associated with relative 30% increased risk of composite vascular events within 1 year. In a meta-analysis investigating the TG/HDL ratio and stroke risk, it was found that the highest category had a 1.24 times greater risk of stroke compared to the lowest category²⁶. However, it's worth noting that other studies have reported inconsistent findings, with some suggesting that higher TG/HDL ratio is linked to favorable outcomes²⁷.

In our study, we found that non-HDL does not have a strong association with predicting residual risk, similar to LDL-C. While dyslipidemia guidelines recommend maintaining non-HDL below 100 mg/dl for ASCVD

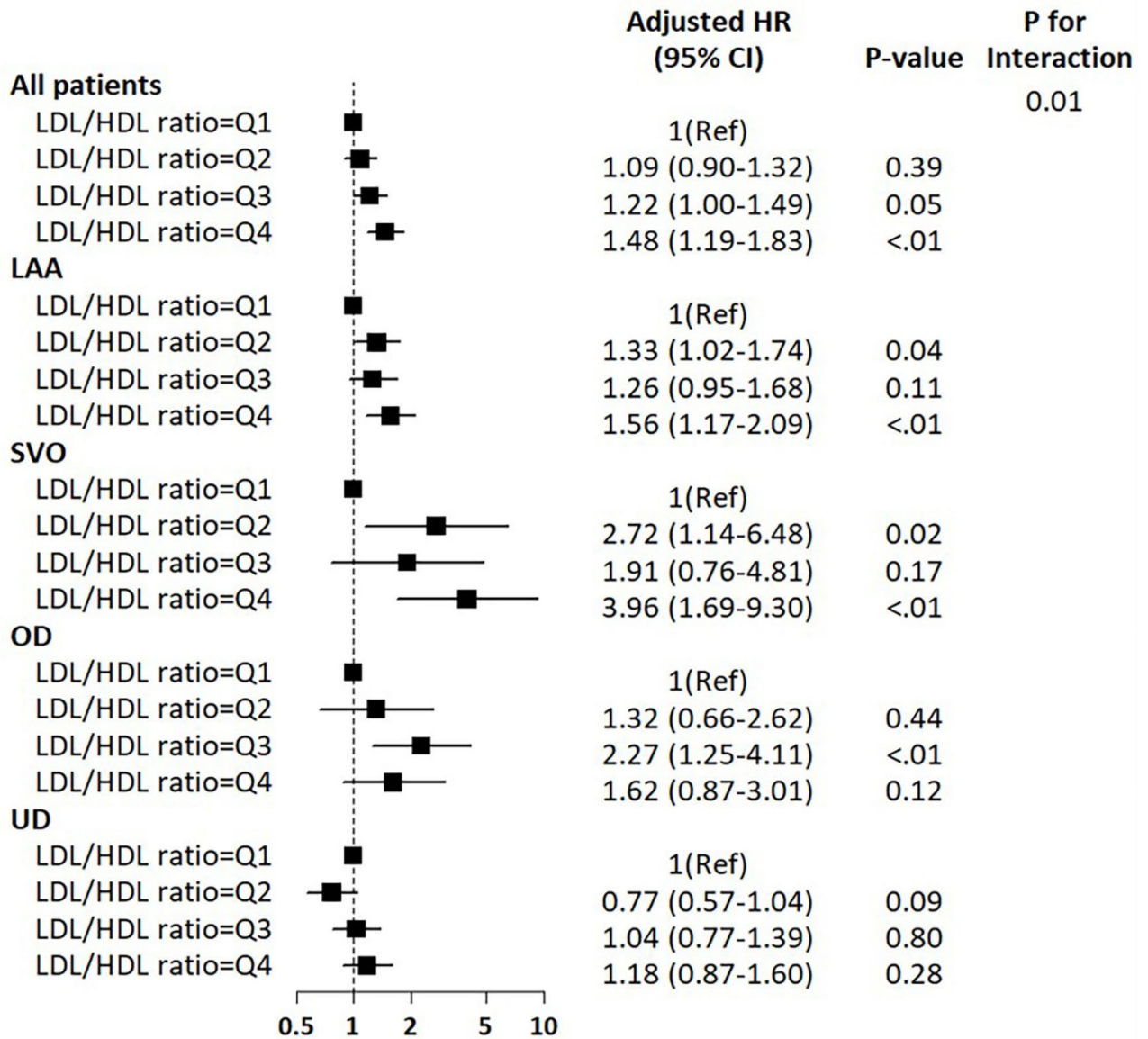


Fig. 3. Associations of LDL/HDL ratio with one-year vascular outcomes according to the ischemic stroke subtypes.

patients, when stroke patients are already on statins and have LDL levels below 100 mg/dl, it appears that lipid ratios may be more helpful in predicting the risk of vascular events than non-HDL.

There are several limitations of this study. First, information regarding aspects of statin pretreatment were lacking. Details such as intensity, duration, type of statin, or dose of statin pretreatment were not available. Second, it was not possible to determine the medication status or lipid profiles and ratio during the follow-up periods. Third, as a registry-based retrospective study, there are inherent limitations of observational data to consider. Despite adjustment for various variables, the potential impact of unmeasured or residual confounding variables may not be entirely eliminated. Fourth, this study was conducted in only South Korea, which could introduce an additional element of confounding when considering differences in lipid profiles among different ethnic groups. Fourth, there is a possibility of index event bias in the analysis of stroke patients who received statin treatment with LDL-C levels of 100 or lower²⁸. This might affect the relationship between baseline risk factors and the outcome of interest. However, the findings of this study would still be applicable to patients matching those analyzed.

In conclusion, our study found that, in ischemic stroke patients whose LDL-C levels were already controlled with statin, higher LDL/HDL ratio, TC/HDL ratio, and TG/HDL ratio, though not non-HDL levels, were associated with residual risk of 1-year composite of stroke, MI, and all-cause mortality. The risk with LDL/

HDL particularly increased when the ratio value reached 2.09 or higher and showed a linear association with the 1-year primary vascular outcome. Our results suggest that non-traditional lipid profiles, particularly the LDL/HDL ratio, may be helpful in predicting the risk of subsequent vascular events for patients with ischemic stroke occurring despite well-controlled LDL with statin pretreatment. Based on our research findings, the patients with abnormal non-traditional lipid profiles may warrant more stringent lipid management and tighter cardiovascular risk control.

Data availability

Data used in this study are available upon reasonable request following submission of a legitimate academic research proposal to be assessed by the CRCS-K steering committee. One may request to contact the corresponding author regarding data availability.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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