

Association Between Total Cholesterol and 5 year Mortality in Patients with Carotid Artery Stenosis and Poststroke Functional Dependence

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Background: Aggressive lipid-lowering treatment reduces the risk of cardiovascular events, but remains controversial in stroke patients. We investigate the influence of total cholesterol level on 5-year outcomes of ischemic stroke patients with high-grade internal carotid artery (ICA) stenosis and poststroke functional dependence.

Methods: One-hundred and ninety-six acute ischemic stroke patients with high-grade ICA stenosis and modified Rankin Scale score ≥ 3 upon discharge were enrolled and prospectively observed for 5 years. Patients were divided into 2 groups according to total cholesterol level at admission: ≥ 200 mg/dL or < 200 mg/dL. Demographic features, vascular risk factors, co-morbidities, and outcomes were compared between the 2 groups. **Results:** 117 (59.7%) patients had higher and 79 (40.3%) patients had lower total cholesterol levels. The prevalence of older age and atrial fibrillation was significantly higher in patients with lower total cholesterol; the prevalence of diabetes mellitus was higher in patients with higher total cholesterol. After adjusting for the established clinical predictors of adverse outcomes, the multivariate Cox regression revealed that lower total cholesterol level is a significant predictor of 5-year mortality (HR (hazard ratio) = 1.88, 95% CI (confidence interval) = 1.09-3.23, $P = .023$). **Conclusions:** Lower total cholesterol level is associated with increased risk of 5-year mortality in ischemic stroke patients with high-grade ICA stenosis and post-stroke functional dependence. Aggressive treatment of hyperlipidemia should be carefully considered in these patients although it could reduce the risk of atherosclerotic cardiovascular diseases and stroke recurrence in some stroke patients.

Key Words: Total cholesterol—lower cholesterol—stroke outcome—mortality—ischemic stroke—carotid artery stenosis—functional dependence

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Introduction

Hyperlipidemia is a well-known risk factor of atherosclerotic carotid artery stenosis and ischemic stroke.¹⁻³ Pharmacologic treatment of hyperlipidemia can not only reduce the risk of atherosclerosis-related stroke, but also reduce cardiovascular events.^{4,5} Although, several previous studies suggested that there was an association between lower cholesterol level and higher risk of hemorrhagic stroke,^{6,7} statin treatment for hyperlipidemia is no longer considered to increase the risk of hemorrhagic stroke.⁸ The recent treatment guidelines of hyperlipidemia suggest more aggressive treatment of hyperlipidemia for reducing the risk of atherosclerotic cardiovascular diseases and ischemic stroke.^{9,10} However, one recent study revealed that low total cholesterol level in patients with atherothrombotic cerebral infarction increased the risk of long-term dependency and stroke recurrence.¹¹

Atherosclerotic carotid artery stenosis is an important cause of cerebral ischemia, and hyperlipidemia is a well-recognized risk factor of carotid stenosis progression.^{12,13} Therefore, lipid-lowering therapy is regarded as an essential component in the management of carotid artery stenosis.¹⁴ However, several population-based cohort studies observed that lower cholesterol level is associated with a higher risk of long-term mortality.¹⁵⁻¹⁹ Whether ischemic stroke patients with high-grade internal carotid artery (ICA) stenosis and lower cholesterol level have a better or worse long-term outcome when compared to those with higher cholesterol level has not been studied before. In addition, whether the influence of cholesterol level on long-term outcomes is different in patients with different functional outcomes is also unclear. Previous study suggests that poststroke functional dependence is associated with long-term mortality.²⁰ In patients with high-grade ICA stenosis and poststroke functional dependence, whether aggressive cholesterol-lowering treatment has positive or negative effects on long-term survival remains unclear.

As a result, the aims of this study were to explore: (1) the differences between patients with high-grade ICA stenosis and poststroke functional dependence (modified Rankin Scale (mRS) score ≥ 3) who had higher total cholesterol level (≥ 200 mg/dL) and lower total cholesterol level (< 200 mg/dL). (2) The association between different total cholesterol levels and 5-year mortality in patients with high-grade ICA stenosis and poststroke functional dependence.

Materials and Methods

Study Patients and Group

The current study is a prospective observational study. We screened all patients with acute first-ever ischemic stroke from the Stroke Unit of the Department of Neurology at Kee-Lung Chang Gung Memorial Hospital from January 2007 to April 2012. The acute ischemic stroke was diagnosed according to the World Health Organization criteria, which was further confirmed by brain computed tomography or magnetic resonance imaging scan.²¹ Bilateral carotid duplex scanning was performed on admission within 7 days after stroke onset for evaluating the degree of ICA stenosis according to the Society of Radiologists in Ultrasound consensus criteria.²² Time-of-flight brain magnetic resonance angiography was done when carotid duplex study revealed 70% or greater stenosis over ICA within 10 days after stroke onset to confirm the ultrasound findings and to evaluate the infarction site and size. The degree of carotid artery stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria.^{23,24} mRS score was evaluated upon discharge for evaluation of poststroke functional status.²⁵ Patients whose stroke symptoms could be correlated with the territory of the unilateral ICA, the

degree of ICA stenosis ranges from 70% to 99% or occlusion, and mRS score greater or equal to 3, were included in this study. Patients were excluded if they had (1) acute infarcts beyond the territory of the ipsilateral ICA (eg, stroke over posterior circulation or contralateral ICA); (2) received revascularization treatments; (3) previous cerebral infarction, cerebral hemorrhage, or stroke of uncertain causes; (4) severe medical problems such as hepatic or renal failure, known malignancy.

Lipid profile evaluation including total cholesterol level was conducted for all of the patients within 1 week after acute stroke onset when fasting at least 8 hours. Patients who were included in the study were divided into 2 groups according to the total cholesterol level: (1) higher cholesterol level (total cholesterol level greater or equal to 200 mg/dL), and (2) lower cholesterol level (total cholesterol level less than 200 mg/dL). This clinical study followed the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital, Taipei, Taiwan (IRB 201800689B0).

Clinical Assessments

Co-morbidities were identified after an in-depth review of the medical records, inclusive of personal history, physical examination, progress notes, discharge summaries, and consultations. Risk factors for cerebrovascular disease included hypertension, diabetes mellitus (DM), smoking, atrial fibrillation (AF), valvular heart disease, coronary artery disease, and peripheral arterial diseases were recorded. Hypertension was defined as known hypertension diagnosed by a clinician, or systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 95 mmHg on 2 different occasions, with the second measurement taken more than 5 days after the stroke.^{26,27} DM was diagnosed in patients with previously treated DM or in patients with fasting plasma glucose ≥ 126 mg/dL, a 2-hour value in the oral glucose-tolerance test or a random plasma glucose concentration ≥ 200 mg/dL, in the presence of symptoms. AF included paroxysmal AF and persistent AF identified by electrocardiography and/or 24-hour electrocardiography monitoring during admission. Cigarette smoking was defined as a current smoker or a smoker with cessation less than 5 years ago. The clinical subtypes of ischemic stroke were rated according to the classification of the Oxfordshire Community Stroke Project classification by 2 neurologists who independently looked at the history, conducted a physical examination, and assessed the patient's symptoms.²⁸ The subtypes were partial anterior circulation infarcts, total anterior circulation infarcts (TACI), and lacunar infarcts.²⁸ Posterior circulation infarcts were excluded. Systematic assessments, including complete blood cell count, blood chemistry studies, lipid level, glycosylated hemoglobin, coagulation testing, urinalysis, chest X-ray, 12-lead electrocardiography, transcranial Doppler, transthoracic

echocardiography, and head computed tomographic scan, were performed on all of the patients within 1 week after acute stroke onset. The scores of National Institutes of Health Stroke Scale, mRS, and Barthel index were recorded at admission and upon discharge.

Follow-up

Patients were followed-up for 5 years after initial assessment. The follow-up was conducted with clinical examinations at the first and the third month after first stroke and then every 3 months. New major medical problems (eg death, recurrent cerebral infarction, cerebral hemorrhage, epilepsy, cancer, cardiovascular diseases, head injury, etc.) were recorded during the follow-up. The primary end point of follow-up is death. Every death occurring during the follow-up was reviewed.

Statistical Analysis

Continuous variables such as age and laboratory measurement values were expressed as median and interquartile range because the values were not normally distributed, and mean length of stay in the acute ward was expressed as mean \pm standard deviation. Categorical variables were expressed as a number, or percentage, for each item. The 2 patient groups (higher and lower cholesterol level) were compared using the chi-square (categorical variables), Mann-Whitney *U* (age and laboratory measurement values) or Student *t* test (mean length of acute ward stay). The independent associations between the variables and the probability of lower total cholesterol were analyzed using logistic regression. All variables with a $P < .10$ in the univariate logistic regression entered a stepwise, backward multivariate logistic regression. The Cox proportional hazards model was used to determine the significance of each variable in predicting the 5-year all-cause mortality. A univariate Cox model, assessing all previously identified variables, was used to measure hazard ratio for mortality. A backward, stepwise multivariate Cox regression model was also used to identify the risk factors for the 5-year mortality. All statistical analyses were performed with IBM SPSS statistics 19 for Windows.

Results

Patient Characteristics

Of 209 acute ischemic stroke patients with greater than or equal to 70% stenosis of ICA and poststroke functional dependence (mRS score ≥ 3), 12 patients were excluded from the study due to receiving carotid artery stenting and 1 patient was excluded due to receiving extracranial-intracranial bypass surgery. A total of 196 patients (136 males, 60 females) were enrolled in the study. Patient characteristics, including age, sex, and co-morbidities, are presented in [Table 1](#). The median age was 75 (63-82) years.

At baseline, 117 (59.7%) patients had higher total cholesterol level, and 79 (40.3%) patients had lower total cholesterol level. The prevalence of DM was significantly higher among patients with higher total cholesterol level ($P = .013$), and AF were significantly higher among patients with lower total cholesterol level ($P = .011$). Of clinical syndromes, there were no differences between the 2 groups. Upon laboratory data, the value of hemoglobin was significantly lower in patients with lower total cholesterol level ($P = .001$), whereas glycohemoglobin was significantly higher in patients with higher total cholesterol level ($P = .001$). The values of total cholesterol, triglyceride, and low density lipoprotein cholesterol were significantly higher in patients with higher total cholesterol level ($P < .001$, $P < .001$, and $P < .001$, respectively).

Determinants of Lower Total Cholesterol Level in Patients with High-Grade ICA Stenosis and Poststroke Functional Dependence

Univariate logistic regression revealed that older age and AF were positively associated with lower total cholesterol level, whereas hemoglobin, glycohemoglobin and DM were negatively associated with lower total cholesterol level ($P < .10$). After adjusting for these potential risk factors ($P < .10$) in a backward, stepwise multivariate logistic regression, only hemoglobin and glycohemoglobin levels were negatively associated with lower total cholesterol in patients with high-grade ICA stenosis and poststroke functional dependence ([Table 2](#)).

Clinical Course of Patients with High-Grade ICA Stenosis and Poststroke Functional Dependence

The mean length of acute ward stay, the occurrences of initial impaired consciousness and stroke in evolution were not different between patients with higher or lower total cholesterol levels ($P = .151$, $P = .191$, and $P = .392$, respectively). Of the occurrence of in-hospital complications, gastrointestinal bleeding was significantly higher in patients with lower total cholesterol level, whereas pneumonia and urinary tract infection were not different between the 2 groups ($P < .001$, $P = .072$, and $P = .226$, respectively). The scores of Glasgow coma scale and National Institutes of Health Stroke were not different between patients with higher and lower total cholesterol levels. The score of Barthel index was lower in patient with lower total cholesterol level. These findings are summarized in [Table 3](#).

Kaplan-Meier Survival Analysis of 5-year Mortality in Patients with High-Grade ICA Stenosis and Poststroke Functional Dependence

At the end of the 5-year observation period, 53 of 196 patients had died (27.0%), including 25 (21.4%) in the

Table 1. Demographic and clinical characteristics of ischemic stroke patients with high-grade internal carotid artery stenosis and poststroke functional dependence, divided according to higher or lower total cholesterol levels

	Higher total cholesterol (n = 117)	Lower total cholesterol (n = 79)	Odds ratio (95% CI)	P value
Age (y)	72 (61-80)	79 (69-83)		.005*
Male	79 (67.5%)	57 (72.2%)	.55 (.32-.96)	.298
Risk factors				
Hypertension	98 (83.8%)	65 (82.3%)	1.11 (.52-2.37)	.466
Diabetes mellitus	63 (53.8%)	29 (36.7%)	2.01 (1.12-3.61)	.013*
Smoking	74 (63.2%)	51 (64.6%)	.95 (.52-1.71)	.487
Coronary artery disease	28 (23.9%)	16 (20.3%)	1.24 (.62-2.48)	.335
Atrial fibrillation	17 (14.5%)	23 (29.1%)	.41 (.20-.83)	.011*
Congestive heart failure	14 (12.0%)	12 (15.2%)	.76 (.33-1.74)	.328
Valvular heart disease	1 (.9%)	3 (3.8%)	.22 (.02-2.14)	.180
Peripheral vascular disease	4 (3.4%)	3 (3.8%)	.90 (.20-4.12)	.589
Chronic kidney disease	24 (20.5%)	22 (27.8%)	.67 (.34-1.30)	.155
Gout	28 (23.9%)	12 (15.2%)	1.76 (.83-3.71)	.094
Clinical syndromes				
TACI	39 (33.3%)	30 (38.0%)	.80 (.44-1.45)	.279
PACI	53 (45.3%)	38 (48.1%)	.92 (.52-1.64)	.449
LACI	25 (21.4%)	11 (13.9%)	1.90 (.83-4.37)	.089
Statin treatment				
Before stroke	7 (6.0%)	2 (2.5%)	2.45 (.50-12.11)	.220
After stroke	85 (72.6%)	9 (11.4%)	11.58 (5.28-25.43)	<.001*
Antithrombotic treatment (before stroke)				
Aspirin	10 (8.5%)	7 (8.9%)	.96 (.35-2.64)	.567
Clopidogrel or ticlopidine	2 (1.7%)	1 (1.3%)	1.34 (.12-15.03)	.649
Warfarin or NOACs	0	0		
Antithrombotic treatment (after stroke)				
Aspirin	77 (65.8%)	40 (50.6%)	1.88 (1.05-3.36)	.024*
Clopidogrel or ticlopidine	22 (18.8%)	30 (38.0%)	.38 (.20-.72)	.003*
Warfarin or NOACs	20 (17.1%)	9 (11.4%)	1.60 (.69-3.73)	.185
Lab data				
Hemoglobin (g/dL)	13.9 (12.3-15.0)	12.6 (11.8-14.0)		.001*
WBC (1000/ μ L)	8100 (6300-10200)	7800 (6400-9200)		.621
Platelet (1000/ μ L)	203 (176-211)	194 (160-253)		.179
Glycohemoglobin (%)	6.2 (5.8-8.0)	5.9 (5.6-6.6)	-	.001*
hs-CRP (mg/L)	5.0 (3.0-12.0)	7.0 (3.5-14.0)		.173
Creatinine (mg/dL)	1.1 (.8-1.4)	1.0 (.8-1.4)		.921
Total cholesterol (mg/dL)	217 (205-235)	154 (134-175)		<.001*
Triglyceride (mg/dL)	126 (80-179)	81 (65-110)		<.001*
LDL (mg/dL)	143 (119-167)	102 (77-117)		<.001*
HDL (mg/dL)	35 (28-43)	35 (27-44)		.829
Uric acid (mg/dL)	6.0 (5.0-7.3)	5.5 (4.7-6.7)		.257

CI, confidence interval; HDL, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LACI, lacunar infarcts; LDL, low density lipoprotein cholesterol; NOAC, Non-vitamin K Antagonist Oral Anticoagulants; PACI, partial anterior circulation infarcts; TACI, total anterior circulation infarcts; WBC, white blood cells.

Data are presented as median (interquartile range) or n (%).

* $P < .05$, chi-square or Mann-Whitney U test.

group of higher total cholesterol level and 28 (35.4%) in the group of lower total cholesterol level. Among the patients of lower total cholesterol level, 1 (3.6%) died within acute stroke stage, 2 (7.1%) died of out of hospital cardiac arrest, 4 (14.3%) died of cardiovascular disease, 2 (7.1%) died of gastrointestinal bleeding and hypovolemic shock, 1 (3.6%) died of uremia, 1 (3.6%) died of gastric cancer, 7 (25%) died of pneumonia and respiratory failure,

9 (32.1%) died of septic shock, and 1 (3.6%) died of intracranial hemorrhage. Among the patients of higher total cholesterol level, 2 (8%) died within acute stroke stage, 2 (8%) died of out of hospital cardiac arrest, 6 (24 %) died of cardiovascular disease, 1 (4%) died of uremia, 2 (8 %) died of lung cancer, 1 (4%) died of multiple myeloma, 4 (16%) died of pneumonia and respiratory failure, 4 (16%) died of septic shock, 1 (4%) died of intracranial hemorrhage,

Table 2. Logistic regression for predictors of lower total cholesterol level in patients with high-grade internal carotid artery stenosis and poststroke functional dependence

Variables	Univariate logistic regression, risk ratio (95% CI)	P value	Stepwise multivariate logistic regression, risk ratio (95% CI)	P value
Age (y)	1.03 (1.01-1.05)	.018*		
Male	1.25 (.67-2.33)	.491		
Hemoglobin	.79 (.68-.92)	.003*	.80 (.67-.94)	.007 [†]
Hypertension	.90 (.42-1.92)	.786		
Diabetes mellitus	.50 (.28-.89)	.019*		
Coronary artery disease	.81 (.40-1.62)	.545		
Congestive heart failure	1.32 (.57-3.02)	.515		
Atrial fibrillation	2.46 (1.21-4.99)	.013*		
Smoking	1.06 (.58-1.92)	.852		
Chronic kidney disease	1.50 (.77-2.91)	.236		
Glycohemoglobin	.74 (.60-.91)	.004*	.76 (.59-.99)	.039 [†]
White blood cell count	1.00 (1.00-1.00)	.593		
Hs-CRP	1.00 (.98-1.02)	.659		

CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein.

* $P < .05$ for the univariate logistic regression.

[†] $P < .05$ for the stepwise multivariate logistic regression.

and 2 (8%) died of recurrent stroke. The Kaplan-Meier survival analysis revealed that of high-grade ICA stenosis patients with poststroke functional dependence, individuals with lower total cholesterol level had a higher rate of mortality than the those with higher total cholesterol level (log rank test: $P = .019$; Fig 1).

Cox Regression Multivariate Analysis for 5-year Mortality in Patients with High-Grade ICA Stenosis and Poststroke Functional Dependence

The univariate Cox regression revealed that older age, chronic kidney disease, hypertension, lower total cholesterol level, coronary artery disease, AF, congestive heart failure, TACI, pneumonia, and gastrointestinal bleeding were potential risk factors ($P < .10$) for a 5-year mortality. These potential variables entered the backward, stepwise multivariate Cox proportional hazards model. We found that lower total cholesterol level (HR = 1.88; 95% CI = 1.09-3.23; $P = .023$) was a significant risk factor for a 5-year all-cause mortality in ischemic stroke patients with high-grade ICA stenosis and poststroke functional dependence even after adjusting for these variables (Table 4).

Discussion

This study demonstrated a novel association between lower total cholesterol level and 5-year mortality in ischemic stroke patients with high-grade ICA stenosis and poststroke functional dependence. This association was significant even after adjusting for the established clinical predictors of adverse outcomes, including older age, chronic kidney disease, hypertension, coronary artery disease, AF, congestive heart failure, TACI, pneumonia, and gastrointestinal bleeding. To our knowledge, this is the first study conducted specifically in ischemic patients

with high-grade ICA stenosis and dependent functional outcome that evaluated the association between total cholesterol level and long-term mortality.

Dyslipidemia is a well-known risk factor for atherosclerotic carotid stenosis progression, and reducing lipid profile to lower targets could result in regression of carotid artery intimal medial thickness.^{12,29} However, previous study did not reveal the association between cholesterol level and mortality rate after ischemic stroke, which might

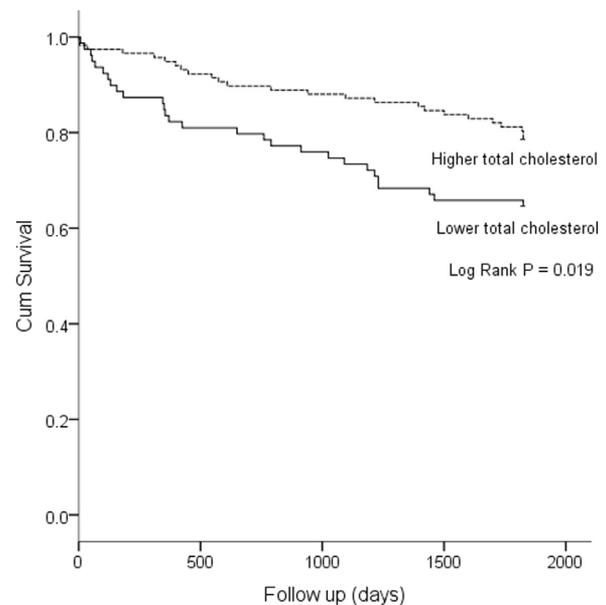


Figure 1. Kaplan-Meier estimates of patient survival (all-cause mortality) during the 5-year study period in patients with high-grade internal carotid artery stenosis and poststroke functional dependence. Symbols are: (●●●●) higher total cholesterol level; (—) lower total cholesterol level. Log Rank $P = .019$.

Table 3. Clinical course of acute stage, mortality, and stroke recurrence within 5 years after stroke onset in patients with high-grade internal carotid artery stenosis and poststroke function dependence, divided according to higher or lower total cholesterol levels

	Higher total cholesterol (n = 117)	Lower total cholesterol (n = 79)	Odds ratio (95% CI)	P value
Mean length of stay in the acute medicine ward (d)	17.0 ± 9.94	19.3 ± 12.73	1.63 (-5.56-87)	.151
Initial impaired consciousness	39 (33.3%)	32 (40.5%)	.73 (.41-1.33)	.191
Course of acute stroke stage				
In evolution	39 (33.3%)	24 (30.4%)	1.15 (.62-2.12)	.392
Complications				
Pneumonia	21 (17.9%)	22 (27.8%)	.57 (.29-1.12)	.072
Gastrointestinal bleeding	18 (15.4%)	30 (38.0%)	.30 (.15-.59)	<.001*
Urinary tract infection	24 (20.5%)	12 (15.2%)	1.44 (.67-3.08)	.226
Glasgow coma scale score				
Upon admission	15 (12-15)	15 (11-15)		.201
Upon discharge	15 (11-15)	15 (11-15)		.163
National Institutes of Health Stroke Scale Score				
Upon admission	8 (6-15)	8 (5-16)		.996
Upon discharge	9 (6-15)	8 (6-16)		.971
Barthel index score				
Upon admission	50 (25-70)	40 (20-60)		.029*
Upon discharge	50 (20-70)	30 (10-60)		.032*
Stroke recurrence	39(22.53%)	23 (31.56%)	1.22 (.66-2.26)	.322
Death	25 (21.4%)	28 (35.4%)	.50 (.26-.94)	.023*

CI, confidence interval.

Data are presented as mean ± SD, median (interquartile range) or n (%).

*P < .05, chi-square, Student t tests, or Mann-Whitney U test.

be partly explained by that high cholesterol levels increase ischemic stroke risk, whereas low levels may increase hemorrhagic stroke risk.^{2,30} In several previous cohort studies, low cholesterol levels were found to be related to high mortality of cardiovascular diseases, which include

patients of ischemic stroke.^{15,16} Low cholesterol levels were also found to be associated with long-term all-cause mortality in other disease populations.³¹⁻³³ Theoretically, in ischemic stroke patients with high-grade ICA stenosis, reducing cholesterol to lower level might reduce the

Table 4. Cox regression analysis of patient survival during the 5-year study period

	Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (y)	1.04 (1.02-1.07)	.002*	1.03 (1.01-1.06)	.012 [†]
Gender (male)	.73 (.42-1.28)	.276		
Chronic kidney disease (yes)	2.38 (1.36-4.15)	.002*	2.13 (.18-3.85)	.012 [†]
Hypertension (yes)	2.17 (.86-5.45)	.099*		
Diabetes mellitus (yes)	.91 (.53-1.57)	.745		
Lower total cholesterol level (yes)	1.89 (1.10-3.24)	.021*	1.88 (1.09-3.23)	.023 [†]
Coronary artery disease (yes)	2.23 (1.27-3.91)	.005*	1.91 (1.06-3.46)	.032 [†]
Atrial fibrillation (yes)	2.22 (1.25-3.96)	.007*		
Congestive heart failure (yes)	1.86 (.96-3.61)	.068*		
Smoking (yes)	1.08 (.61-1.91)	.785		
TACI	2.48 (1.45-4.25)	.001*	3.28 (1.88-5.72)	<.001 [†]
Pneumonia	1.67 (.92-3.03)	.094*		
Gastrointestinal bleeding	1.82 (1.03-3.20)	.041*		

CI, confidence interval; TACI, total anterior circulation infarcts.

*P < .1 for the univariate Cox regression.

[†]P < .05 for the multivariate Cox regression.

progression of carotid artery stenosis and the risk of cardiovascular disease. However, our result found that of patients with poststroke functional dependence, lower total cholesterol levels was associated with increased risk of 5-year all-cause mortality, but the reason remains unclear.

In a previous Japanese cohort study, the relationship between low cholesterol level and mortality is not only limited to noncardiovascular mortality, but also stroke and heart disease mortality.¹⁶ There are several factors that might explain the relationship between low total cholesterol level and high mortality in ischemic stroke patients with high-grade ICA stenosis and dependent functional outcome. Total cholesterol level is generally regarded as a serum marker for assessment of nutrition status, and lower cholesterol level might indicate poor nutrition status.³⁴ Malnutrition is associated with increased mortality in older adults regardless of the cause of death.³⁵ Furthermore, previous studies revealed that low cholesterol level is associated with high cancer mortality.^{16,36} In our study, most patients with lower total cholesterol level died from pneumonia or other infection-related septic shock. Previous study suggested that low cholesterol level is associated with increased risk of fever, sepsis, and malignancy,³⁷ whereas high cholesterol may protect against infections and atherosclerosis.³⁸ In addition, dependent functional outcome increases the risk of infection and is associated with poor long-term survival.²⁰ The synergistic effects of both dependent function outcome and lower total cholesterol level may explain the increased 5-year mortality in ischemic stroke patients with high-grade ICA stenosis, dependent functional outcome, and lower total cholesterol level, especially died from pneumonia or other infection-related septic shock. Of patients with higher total cholesterol level, our result found that a majority of these patients died from cardiovascular diseases or out of hospital cardiac arrest. Previous reports suggested that high serum cholesterol level is associated with an increased risk of cardiovascular diseases, which were in agreement with our study.^{39,40}

We had also analyzed ischemic stroke patients with high-grade ICA stenosis and independent functional outcome upon discharge (mRS score < 3), and found that the association between lower total cholesterol level and 5-year mortality did not exist. This finding suggests that poststroke functional outcome is also an important factor of long-term outcome in patients with high-grade ICA stenosis. Previous study suggests that poor functional status 6 months after ischemic stroke is associated with poor long-term survival, but the reason remains unclear.²⁰ Although reducing cholesterol to lower level might reduce the progression of carotid artery stenosis and the risk of cardiovascular disease, the overall benefit of lipid lowering therapy should be considered together with other factors, such as poststroke functional status, in patients with high-grade ICA stenosis.

This study has several limitations. First, the sample size of this study is relatively small, which may not be able to represent the whole disease group. Second, we did not evaluate the nutritional status of the patients. However, we had excluded patients with known severe medical problems such as malignancy and hepatic or renal failure from the study. Third, this is an observational study of the association between total cholesterol level at stroke onset and 5-year mortality. Therefore, it is difficult to make a conclusion about the positive or negative effects of lipid-lowering treatment in ischemic stroke patients with high-grade ICA stenosis and poststroke functional dependence. However, the finding of this study still provides a hint that aggressive lipid-lower treatment should be carefully considered in ischemic stroke patients with high-grade ICA stenosis, especially in those with dependent functional status.

In conclusion, lower total cholesterol level is associated with increased risk of 5-year mortality in ischemic stroke patients with high-grade ICA stenosis and poststroke functional dependence. Aggressive treatment of hyperlipidemia should be carefully considered in these patients although it could reduce the risk of atherosclerotic cardiovascular diseases and stroke recurrence in some stroke patients.

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