



Combination of High-Density Lipoprotein Cholesterol and Lipoprotein(a) as a Predictor of Collateral Circulation in Patients With Severe Unilateral Internal Carotid Artery Stenosis or Occlusion

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Background and Purpose Collateral circulation is considered an important factor affecting the risk of stroke, but the factors that affect collateral circulation remain unclear. This study was performed to identify the factors associated with collateral circulation, especially blood lipids.

Methods The study involved patients who had undergone digital subtraction angiography and were confirmed as having severe unilateral stenosis or occlusion of the internal carotid artery (ICA). We classified the collateral circulation status of each patient as good (Grade 3 or 4) or poor (Grade 0, 1, or 2) according to the grading system of the American Society of Interventional and Therapeutic Neuroradiology/American Society of Interventional Radiology. We collected data on patients' characteristics and identified the factors that affect collateral circulation.

Results This study included 212 patients. The multivariate logistic regression analysis showed that the high-density lipoprotein cholesterol (HDL-C) concentration and a complete anterior half of the circle of Willis were independent protective factors for good collateral circulation, whereas elevated lipoprotein(a) [Lp(a)] and serum creatinine concentrations were independent risk factors for good collateral circulation. The area under the receiver operating characteristics curve (AUC) was 0.68 (95% confidence interval [CI], 0.61–0.76) for HDL-C and 0.69 (95% CI, 0.62–0.76) for Lp(a). A binary logistic regression model analysis of the joint factor of HDL-C and Lp(a) yielded an AUC of 0.77 (95% CI, 0.71–0.84).

Conclusions In patients with severe unilateral ICA stenosis or occlusion, the combination of HDL-C and Lp(a) is a useful predictor of collateral circulation.

Keywords internal carotid artery stenosis; cerebrovascular occlusion; collateral circulation; high-density lipoprotein cholesterol; lipoprotein(a).

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INTRODUCTION

Stenosis or occlusion of the internal carotid artery (ICA) caused by atherosclerosis is very common, and incidence rates of stroke in patients with severe ICA stenosis of 9.3% and 16.6% have been reported at 10- and 15-year follow-ups, respectively.¹ In addition, the severity of the clinical manifestations of severe ICA stenosis or occlusion varies markedly, ranging from no symptoms to transient ischemic attack or stroke.² Collateral circulation is considered an important factor affecting the risk of stroke and the heterogeneity of the severity and prognosis of stroke in patients with severe ICA stenosis or occlusion.^{3,4}

The compensatory ability of collateral circulation is mainly determined by the integrity of

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the circle of Willis and changes in blood flow dynamics.^{5,6} Some studies have suggested that age,⁷⁻⁹ the blood creatinine concentration,⁸ metabolic syndrome,⁹ hyperuricemia,⁹ blood lipid levels,⁸ and the use of statins⁷ affect the prevalence of collateral circulation, and that angiogenic factors¹⁰ and microRNAs¹¹ are related to cerebral angiogenesis. Although some researchers have studied the relationships between blood lipids and collateral circulation, they have focused only on triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), while ignoring the functions of apolipoprotein and lipoprotein(a) [Lp(a)]. Increasingly more attention has been given to the function of apolipoprotein and Lp(a). One meta-analysis found that an elevated Lp(a) concentration was an independent risk factor for ischemic stroke.¹² Apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB) are also considered to be related to the risk of atherosclerotic cardiovascular and cerebrovascular disease (ASCCVD).¹³ Moreover, it is believed that apoB can replace LDL-C as a clinical marker for risk predictions of ASCCVD.¹⁴

The present study was performed to clarify the factors affecting the compensatory ability of patients with severe ICA stenosis or occlusion induced by atherosclerosis, and to determine the role of blood lipids in collateral circulation, especially apoA-I, apoB, and Lp(a). Knowledge of the risk factors that can be changed will help clinicians to predict the occurrence of collateral circulation and determine whether interventions are available to improve the compensatory ability in patients with severe ICA stenosis or occlusion. Moreover, such findings could help clinicians to enhance collateral circulation in patients before or after the onset of stroke, thus improving the prognosis of patients with severe ICA stenosis or occlusion.

METHODS

Study population

This study retrospectively included patients confirmed as having severe stenosis ($\geq 70\%$ stenosis) or occlusion of the ICA by digital subtraction angiography (DSA) at the Department of Neurology, The Second Affiliated Hospital of Xi'an Jiaotong University from May 2017 to April 2021. The degree of stenosis was determined according to the definition in the North American Symptomatic Carotid Endarterectomy Trial.¹⁵ The exclusion criteria were 1) $\geq 50\%$ stenosis of the contralateral ICA, bilateral common carotid arteries, vertebral artery, external carotid artery, anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), or basilar artery found in DSA; 2) no history of carotid atherosclerosis and < 7 days from a transient ischemic attack or

acute cerebral infarction to DSA; 3) absence of atherosclerotic occlusion and stenosis, including arterial dissection, vascular disease caused by radiation, and arteritis; 4) atrial fibrillation; 5) a history of endovascular treatment; or 6) Moyamoya disease.

The flow chart of patient inclusion is shown in Fig. 1. This study was approved by the Ethics Committee of Xi'an Jiaotong University (NO. 2020060), and all patients provided informed consent.

DSA and collateral circulation

The imaging device used was a Philips Allura systems (Philips Medical limited company, Suzhou, Jiangsu, China) or Siemens Artis Q Biplane large-scale DSA machine (Artis Q; Siemens Medical Systems limited company, Shanghai, China). The modified Seldinger method was used to puncture the femoral artery, and a high-pressure injection gun (Medrad Stellant CT double-barrel syringe; Medrad Inc., Indianola, PA, USA) was used to inject iomeprol or iodixanol so that anatomical images of the aortic arch and supra-arch artery could be obtained. Whole-brain angiography was performed, and at least three neuroradiologists blinded to the clinical information of the patients jointly evaluated the results.

Collateral circulation in the patients was rated according to the collateral circulatory grading system of the American Society of Interventional and Therapeutic Neuroradiology/American Society of Interventional Radiology (ASITN/SIR)¹⁶ as follows: Grade 0, no collateral blood vessel on the ischemic side; Grade 1, low collateral blood flow around the ischemic side but no blood flow in some areas; Grade 2, high collateral blood flow around the ischemic side but only partial continuous blood flow without collateral flow and only partial blood flow in the ischemic focus; Grade 3, low but complete blood flow in the ischemic focus in the late stage of the venous phase; and Grade 4, high collateral blood flow supplying the entire vascular area. Grades 3 and 4 were considered good collateral circulation, and Grades 0 to 2 were considered poor collateral circulation.

The circle of Willis was divided into four types: Type I, complete circle of Willis; Type II, complete anterior half and incomplete posterior half of the circle of Willis; Type III, incomplete anterior half and complete posterior half of the circle of Willis; and Type IV, incomplete anterior half and complete posterior half of the circle of Willis.¹⁷ The blood vessels in the anterior half of the circle of Willis include the anterior communicating artery, bilateral ACA A1, and the end of the ICA. The blood vessels in the posterior half include the bilateral posterior communicating artery, the PCA P1, and the basilar artery.

This study used DSA to assess the presence of leptomen-

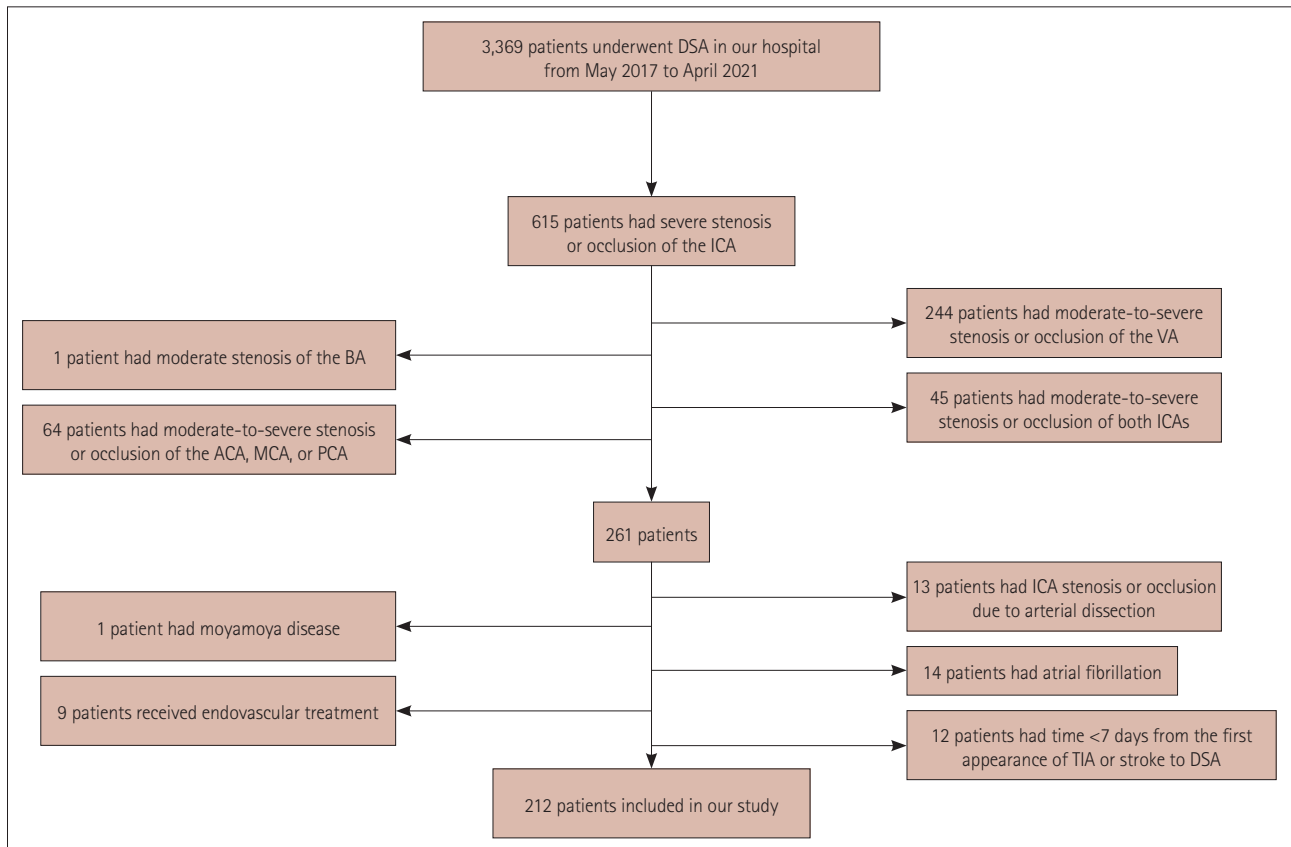


Fig. 1. Flow chart of patient inclusion. ACA, anterior cerebral artery; BA, basilar artery; DSA, digital subtraction angiography; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; TIA, transient ischemic attack; VA, vertebral artery.

ing collateral circulation based on whether the M3 segment of the MCA was anastomosed with the leptomeningeal arteries of the ACA or PCA, and the collateral area was the blood supply area of the ICA on the diseased side. In patients with severe ICA stenosis, the late stage of ICA angiography on the diseased side showed reverse blood flow in the leptomeningeal collateral circulation.

Risk factor assessment

Hypertension was defined as a history of hypertension or treatment with antihypertensive medication and a systolic blood pressure (SBP) of ≥ 140 mm Hg or a diastolic blood pressure of ≥ 90 mm Hg measured in the morning on 3 consecutive days after admission. Diabetes was defined as a history of diabetes or use of insulin or oral glucose-lowering medications and a measured fasting blood glucose level of ≥ 7.0 mmol/L or random blood glucose level of ≥ 11.1 mmol/L. A history of coronary atherosclerotic heart disease was defined as $\geq 50\%$ stenosis measured in a major coronary blood vessel. A history of stroke was defined as the presence of at least one infarcted lesion with a diameter of ≥ 1.5 cm visible on magnetic resonance imaging with or without neurological deficits. Smok-

ing was defined as self-reported current smoking or any history of smoking regardless of the amount. A drinking history was defined as consuming ≥ 50 g of alcohol per week. A history of antiplatelet drugs was defined as having taken antiplatelet drugs regularly for >3 months. A history of statin medication was defined as having taken statin drugs regularly for >3 months.

Laboratory parameters

Early in the morning on the day after admission, 5 mL of peripheral venous blood was drawn from all patients in a fasted state. The blood samples were centrifuged for 5 min in a centrifugation machine at a centrifuge radius of 10 cm and rotating speed of 3,000 revolutions/min. An automatic biochemical analyzer (Beckman AU5800; Beckman Coulter, Inc. Brea, CA, USA) was used to determine the serum levels of TC, TG, LDL-C, HDL-C, apoA-I, apoB, and Lp(a). The serum levels of TC, TG, LDL-C, and HDL-C were also measured using an enzyme-linked immunosorbent assay, while those of apoA-I, apoB, and Lp(a) levels were also measured using an immunoturbidimetric method. The kits were purchased from Shanghai Langdon Company (Blood Lipid Bio-

chemical Test Kit; Shanghai, China), and the measurements were carried out strictly in accordance with the manufacturer's instructions.

Statistical analyses

Standard statistical software (SPSS version 20.0; IBM Corp., Armonk, NY, USA) was used for the statistical analyses of the data, and all data were tested for whether they conformed to a normal distribution. There were missing values for the laboratory parameters due to the retrospective nature of the analyses; however, the proportion of missing values was <3% for all variables, and expectation-maximization imputation was used to assign missing values. Measurement data not conforming to a normal distribution are presented as median and interquartile-range values, and the Mann–Whitney U test was used for comparisons between two groups. Categorical variables are presented as number and percentage values, and the chi-square test was used for comparisons between groups.

We conducted univariate analyses followed by a multivariate logistic regression analysis that included variables for which $p < 0.1$ in the univariate analyses. The variance inflation factor was calculated before the regression analysis, with a value of <10 taken to indicate that multicollinearity was not present between the variables. Moreover, variables that were independent and with similar research significance were selected for inclusion in the final multivariate logistic regression model.

A receiver operating characteristics curve was used to analyze the predictive effects of HDL-C and Lp(a) on collateral circulation, and the area under the receiver operating characteristics curve (AUC) was used to indicate the probability of a prediction being accurate. Delong's test was performed using MedCalc software (version 19.4.1; <https://www.medcalc.org>) to assess differences in the AUC values. A two-sided test was used, and a p -value of <0.05 was used as the criterion for statistical significance.

RESULTS

Baseline characteristics

This study included 212 patients: 123 with good collateral circulation and 89 with poor collateral circulation. Their baseline characteristics are listed in Table 1. The univariate analyses revealed statistically significant differences between patients with good and poor collateral circulation in the HDL-C level, apoA-I level, Lp(a) level, white blood cell count, blood creatinine level, SBP on admission, and the integrity of the circle of Willis. There were no statistically significant differences between patients with good and poor collateral circulation in the blood glucose level, history of diabetes, history of smok-

ing, history of statin use, degree of ICA stenosis, sex, age, or TC, LDL-C, and blood uric acid levels.

Binary logistic regression analysis

Sex, SBP on admission, history of diabetes, history of smoking, history of statin use, degree of ICA stenosis, integrity of the circle of Willis, blood creatinine level, white blood cell count, and HDL-C, apoA-I, and Lp(a) levels were included in the multivariate logistic regression analysis. As indicated in Table 2, the HDL-C level and a complete circle of Willis or a complete anterior half of the circle of Willis were associated with good collateral circulation, while the Lp(a) and blood creatinine levels were associated with poor collateral circulation.

HDL-C, Lp(a), and ASITN/SIR grading system

Rank-sum tests were applied to the HDL-C level, Lp(a) level, and ASITN/SIR grade. For patients with different ASITN/SIR grades, the distributions of HDL-C and Lp(a) among the subgroups were analyzed to detect statistically significant differences. The relationships among the HDL-C level, Lp(a) level, and ASITN/SIR grade are presented as box plots in Fig. 2.

Prediction of collateral circulation using the combination of HDL-C and Lp(a)

As shown in Fig. 3, the AUC was 0.68 (95% confidence interval [CI], 0.61–0.76) for HDL-C and 0.69 (95% CI, 0.62–0.76) for Lp(a). Using a cutoff value of 0.96 mmol/L for the HDL-C level to predict good collateral circulation provided a sensitivity of 69.11% and a specificity of 65.17%. Using a cutoff value of 19.55 mg/dL for the Lp(a) level to predict poor collateral circulation provided a sensitivity of 62.92% and a specificity of 71.54%. A binary logistic regression model analysis that calculated the joint factor of $\text{HDL-C}^{-0.026} \times \text{Lp(a)}^{3.737}$ yielded an AUC of 0.77 (95% CI, 0.71–0.84). Using a cutoff value of 0.80 for the joint factor to predict good collateral circulation provided a sensitivity of 72.36% and a specificity of 74.16%. There was no significant difference between the AUC values for the HDL-C and Lp(a) levels, whereas the AUC value for the joint factor differed significantly from those for the HDL-C level and the Lp(a) level.

DISCUSSION

This retrospective study included 212 patients with severe unilateral ICA stenosis or occlusion, and performed DSA to determine the status of their collateral circulation. We collected clinical information and laboratory parameters on the patients to identify the predictive factors for collateral circulation. We found that the HDL-C level and a complete circle of Willis, and especially a complete anterior half of the circle

Table 1. Baseline characteristics of the patients with good or poor collateral circulation included in the study

Variables	Good collateral circulation (ASITN/SIR Grade 3/4) (n=123)	Poor collateral circulation (ASITN/SIR Grade 0/1/2) (n=89)	<i>p</i>
Age (yr)	63 [14]	63 [16]	0.807
Sex, male	90 (73.2)	74 (83.1)	0.087
SBP (mm Hg)	137 [29]	145 [26]	0.030
DBP (mm Hg)	79 [18]	82 [18]	0.154
Premorbid risk factors			
Hypertension	65 (52.8)	56 (62.9)	0.144
Diabetes	35 (28.5)	35 (39.3)	0.097
Coronary arterial disease	22 (18.0)	16 (17.9)	0.986
Previous stroke*	22 (17.9)	17 (19.1)	0.822
Time from stroke onset (days)	35 [32.5]	30 [40.0]	0.279
Previous TIA*	16 (13.0)	12 (13.5)	0.920
Smoking	61 (49.6)	55 (61.8)	0.078
Drinking	38 (30.9)	31 (34.8)	0.546
Medication history			
Antiplatelet drugs	23 (18.7)	13 (14.6)	0.433
Statins	22 (17.9)	8 (9.0)	0.067
Laboratory parameters			
Blood glucose (mmol/L)	5.25 [1.85]	5.48 [2.50]	0.075
Hemoglobin (g/L)	143.00 [24.00]	144.66 [23.00]	0.865
White blood cell count ($\times 10^9/L$)	6.31 [2.47]	6.86 [3.29]	0.026
Platelet count ($\times 10^9/L$)	198.50 [82.00]	191.00 [83.00]	0.720
Total bilirubin (mmol/L)	13.03 [6.66]	13.70 [7.28]	0.378
Blood creatinine (mmol/L)	59.85 [17.63]	62.00 [23.60]	0.022
Blood uric acid (mmol/L)	300.00 [103.80]	282.00 [106.20]	0.152
TC (mmol/L)	3.72 [1.48]	3.79 [1.82]	0.661
TG (mmol/L)	1.30 [0.80]	1.26 [0.86]	0.601
HDL-C (mmol/L)	1.05 [0.29]	0.90 [0.25]	<0.001
LDL-C (mmol/L)	2.30 [1.04]	2.40 [1.34]	0.440
apoA-I (g/L)	1.18 [0.24]	1.04 [0.27]	<0.001
apoB (g/L)	0.68 [0.29]	0.76 [0.41]	0.165
Lp(a) (mg/dL)	12.70 [18.80]	31.00 [45.25]	<0.001
Homocysteine (mmol/L)	15.50 [12.80]	17.10 [8.75]	0.559
Angiography			
Stenosis in extracranial segment	90 (73.2)	73 (82.0)	0.131
Occlusion or Stenosis	69 (56.1)	39 (43.8)	0.078
Circle of Willis			
Type I	53 (43.1)	12 (13.5)	
Type II	53 (43.1)	27 (30.3)	
Type III	8 (6.5)	14 (15.7)	
Type IV	9 (7.3)	36 (40.4)	<0.001
Ophthalmic artery	25 (20.3)	12 (15.6)	0.195
Leptomeningeal collateral	30 (24.4)	14 (15.7)	0.125

Data are median [interquartile range] or *n* (%) values. Stenosis, patients with severe stenosis ($\geq 70\%$ stenosis) or occlusion according to the definition in the North American Symptomatic Carotid Endarterectomy Trial. *p*<0.05 indicates that the difference is statistically significant.

*Previous stroke and TIA were related to internal carotid artery disease.

apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/American Society of Interventional Radiology; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; TIA, transient ischemic attack.

Table 2. Logistic regression analysis results

Variable	OR	95% CI	p
Male	1.56	0.49–4.92	0.451
History of diabetes	1.86	0.84–4.11	0.128
History of smoking	0.66	0.28–1.58	0.354
History of statin use	0.62	0.20–1.89	0.396
Stenosis or occlusion	1.42	0.63–3.19	0.394
HDL-C	21.61	2.12–219.92	0.009
Lp(a)	0.97	0.96–0.99	<0.001
apoA-I	3.77	0.50–28.53	0.199
Blood creatinine	0.96	0.93–0.99	0.003
White blood cell count	0.91	0.77–1.07	0.231
SBP on admission	1.00	0.98–1.02	0.744
Type IV circle of Willis	1.00	Reference	Reference
Type III circle of Willis	2.14	0.53–8.68	0.288
Type II circle of Willis	10.50	3.57–30.91	<0.001
Type I circle of Willis	22.63	6.25–81.96	<0.001

$p < 0.05$ indicates that the difference is statistically significant. apoA-I, apolipoprotein A-I; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OR, odds ratio; SBP, systolic blood pressure.

of Willis, were protective factors for good collateral circulation, whereas increased Lp(a) and serum creatinine levels were independent predictors of poor collateral circulation.

The specific mechanism underlying how HDL-C exerts a protective effect on collateral circulation is unclear, but we consider that it may be related to the antiatherosclerotic and vascular protection effects of HDL-C. Numerous epidemiological studies have confirmed that HDL-C and its main apolipoprotein (apoA-I) exert direct antiatherosclerotic effects, and that reduced levels of these two indices are risk factors for atherosclerosis.¹⁸ There are two main mechanisms underlying how HDL-C exerts its antiatherosclerotic effect. The first involves HDL-C playing a role in lipid metabolism by transporting cholesterol and oxidized cholesterol from extrahepatic tissues to the liver tissue for metabolism, thereby reducing the serum cholesterol level and inducing an antiatherosclerotic effect. The reverse transport function of HDL-C to cholesterol makes it imperative to the formation of atherosclerosis and the instability of plaques. The second possible mechanism is via HDL-C playing an anti-inflammatory role. In the early stage of atherosclerosis, leukocytes in the blood adhere and migrate to the vascular intima, where they promote endothelial cells to express vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, and P-selectin, thereby promoting the occurrence and development of atherosclerosis. Numerous studies have confirmed that HDL-C attenuates the expression levels of VCAM-1, ICAM-1, and E-selectin,¹⁹ and reduces the synthesis of interleukin 6.²⁰ One study also found that the plasma HDL-C level was in-

versely proportional to the C-reactive protein level.²¹ HDL-C can increase the vasodilation function of the vascular endothelium by increasing the production of nitric oxide.²² At the same time, HDL-C can inhibit the production of platelet-activating factor in endothelial cells so as to inhibit platelet aggregation and smooth-muscle contraction.²³ It has also been shown that HDL-C can promote the migration of endothelial cells after vascular injury.²³

The concentration of Lp(a) in plasma is mainly determined by variants of *LPA*.²⁴ The Lp(a) concentration differs markedly between individuals, is not affected by environmental factors, and tends to be stable throughout the lifetime. Therefore, we believe that Lp(a) is more suitable than other blood lipid parameters as a predictor of the risk and prognosis of ASCVD. Several decades of research has confirmed that Lp(a) is related to the risk and prognosis of ASCVD.^{12,25,26} These study findings are mainly due to researchers increasingly recognizing the role of Lp(a) in promoting the occurrence and development of atherosclerosis. In the early stage of atherosclerosis, Lp(a) can interact with the β 2-integrin Mac-1 to promote the adhesion and migration of mononuclear macrophages.²⁷ Lp(a) can also induce vascular endothelial cells to produce monocyte chemoattractant protein, thereby promoting the migration of monocytes to endothelial cells that differentiate into macrophages and subsequently absorb lipids to form foam cells.²⁸ Lp(a) can cause blood neutrophil infiltration in atherosclerotic plaques, which decreases plaque stability.²⁹ It has also been shown that Lp(a) can promote endothelial dysfunction, increase phospholipid oxidation, and destroy the anticoagulant function of the vascular endothelium. Moreover, collateral circulation is established via a joint effect of angiogenesis and arterial formation, and the integrity of endothelial cell function is an important factor affecting angiogenesis and arterial formation. Therefore, the effect of Lp(a) on the function of vascular endothelial cells can at least partially explain its association with poor collateral circulation. In experimental animal models of peripheral vascular disease, high serum Lp(a) concentrations inhibited the activation of transforming growth factor β , thereby inhibiting angiogenesis.³⁰ One study also showed that in patients with coronary atherosclerotic heart disease, Lp(a) had a strong negative correlation with vascular endothelial growth factor via inhibition of the formation of collateral circulation by affecting the production and activity of vascular endothelial growth factor.³¹

While the clinical hazards of high LDL-C and TC levels are well recognized, and although statins are widely administered to patients with hyperlipidemia, drugs that can affect blood lipid levels are still not widely used to increase HDL-C or reduce Lp(a). Moreover, meta-analyses^{32,33} found that the use of statins increased the Lp(a) level by 8.5%–19.6% and that ator-

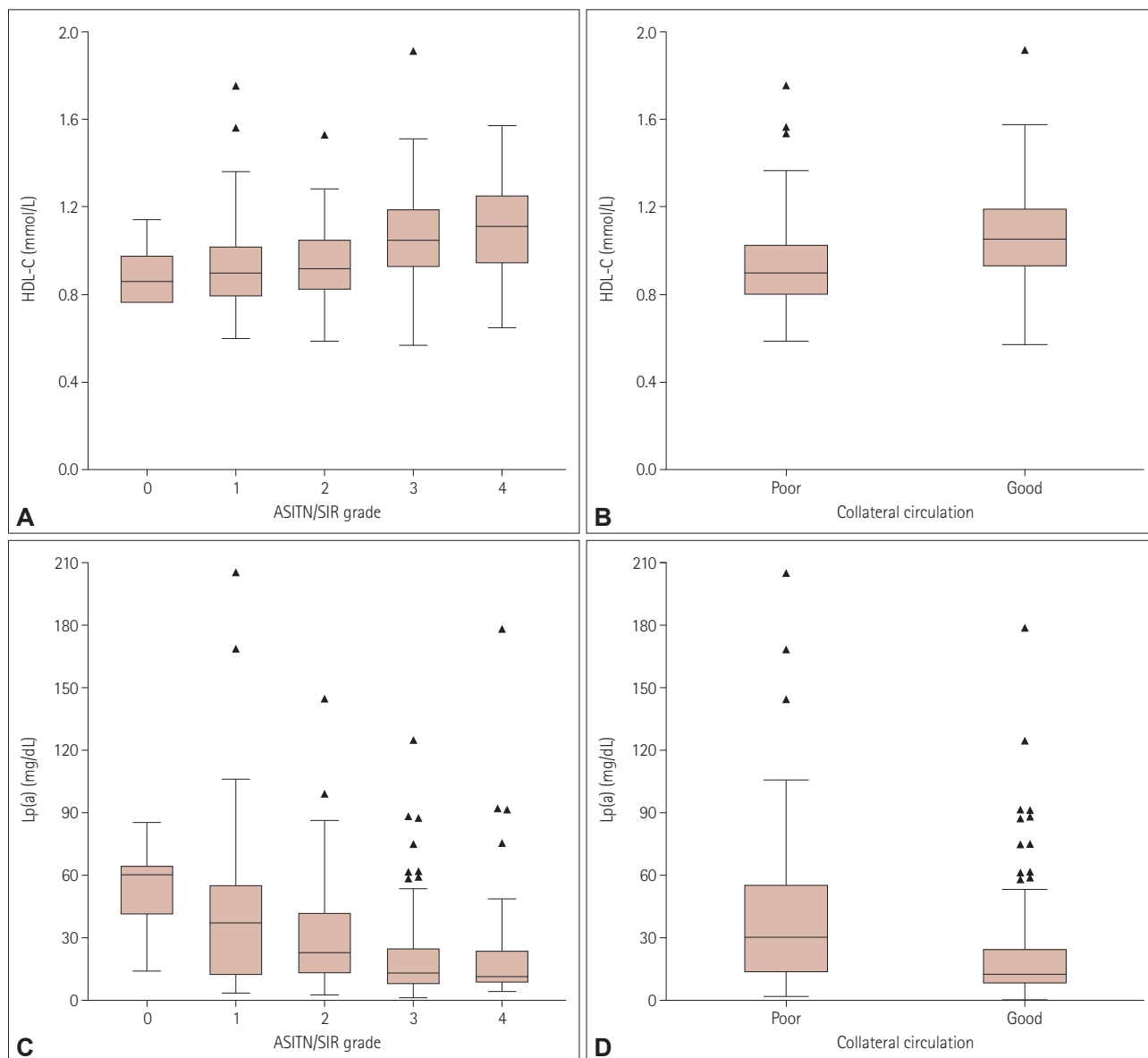


Fig. 2. The distributions of HDL-C and Lp(a) in patients. A: HDL-C distribution according to ASITN/SIR grade. B: HDL-C distributions in groups with good and poor collateral circulation. C: Lp(a) distribution according to ASITN/SIR grade. D: Lp(a) distributions in groups with good and poor collateral circulation. ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/American Society of Interventional Radiology; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

vastatin at 10 mg/day increased the Lp(a) level by 18.7%–24.2%. There has been a lack of independent research on the risk and prognosis of ASCVD in patients with an increased Lp(a) level after the use of statins, but this does not prevent clinicians from carefully choosing statin therapy or replacing lipid-lowering drugs when managing patients with an elevated Lp(a) level in whom the LDL-C or TC level increases. Two proprotein convertase subtilisin/kexin type 9 inhibitors are currently available for clinical use. Alirocumab has been found to significantly reduce the concentration of Lp(a) by 23%–29% regardless of whether or not it is combined with statins.³⁴ Evo-

locumab was reported to decrease the LDL-C level by 60.7% and the Lp(a) level by 13.9%.³⁵ Niacin can also effectively reduce the Lp(a) level. Studies have shown that when used alone or in combination with statins, niacin can reduce the Lp(a) level by 12%–28%. Niacin is also the oldest and most effective drug for increasing the HDL-C level, but it has not been promoted because serious adverse reactions can occur after excessive doses.³⁵ Cholesteryl ester transfer protein (CETP) inhibitors can reduce the transfer of the cholesterol in HDL-C to apoB by inhibiting the activity of CETP, thus reducing LDL-C while increasing HDL-C; CETP inhibitors have also been

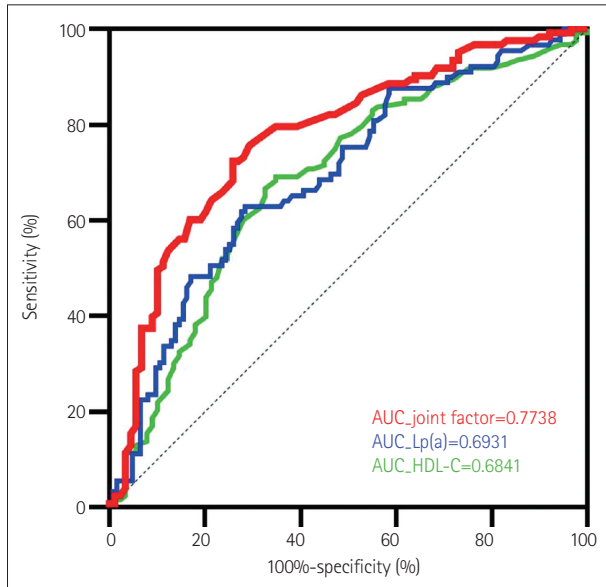


Fig. 3. Receiver operating characteristics curves for HDL-C, Lp(a), and the joint factor in predicting good, poor, and good collateral circulation, respectively. AUC, area under the receiver operating characteristics curve; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

found to reduce the Lp(a) level. Administering evacetrapib alone at 100 mg/day or 500 mg/day reduced the Lp(a) level by 32% and 40%, respectively.³⁶ Evacetrapib has also been found to increase HDL-C in a dose-dependent manner; daily evacetrapib at 100 mg or 500 mg increased HDL-C by 94.6% and 128.8%, respectively.³⁷ Many compounds that inhibit CETP are still in the clinical research stage, but their future appears promising.

In the present study, 30.77%, 36.92%, 9.74%, and 22.56% of patients had a type I, II, III, and IV circle of Willis, respectively. This is roughly equivalent to the distribution of the types of circle of Willis found previously in another study.³⁸ We found that patients with a complete circle of Willis or at least a complete anterior half of the circle of Willis had better compensatory ability than did other patients with severe ICA stenosis or occlusion, which is consistent with previous results.¹⁶ The compensatory ability of the circle of Willis is related to the integrity and variation of the composition of the circle. Previous studies have shown that the ACA is the main compensating vessel when one ICA is stenosed or occluded, and that its compensatory ability exceeds that of the PCA.¹⁷

The present study has also revealed that an increased blood creatinine level is an independent risk factor for good collateral circulation. Another study⁸ also showed that a low serum creatinine level was an independent protective factor for better leptomeningeal collaterals, those authors did not explore the mechanism. Our study did not include patients with severe renal insufficiency, but some patients with mild renal

insufficiency still underwent DSA, and the blood creatinine level may be a sensitive indicator of renal function. No studies have focused on the direct correlation between mild renal insufficiency and collateral circulation, but this did not prevent us from exploring possible mechanisms. First, the accumulation of toxic substances in the blood of patients with renal insufficiency can damage endothelial cells and reduce the production of nitric oxide by inhibiting the function of nitric oxide synthase.³⁹ Second, the renin-angiotensin-aldosterone system is activated in patients with chronic kidney disease, and aldosterone can stimulate the oxidative activity of NADPH so as to damage endothelial cells.⁴⁰ Third, patients with chronic kidney disease often have chronic microinflammatory states manifested by increased levels of interleukin-6, C-reactive protein, and tumor necrosis factor- α ,⁴¹ and these inflammatory reactions can also damage the function of endothelial cells. These changes are not conducive to the formation of collateral circulation.

This study is the first to suggest that Lp(a) can affect the compensatory ability of cerebrovascular collaterals, but it was subject to some limitations. First, it had a single-center retrospective design with strict inclusion and exclusion criteria that resulted in a small sample. Second, we were only able to draw conclusions based on clinical data, and so certain assumptions needed to be made to postulate the specific mechanism underlying how HDL-C, Lp(a), and serum creatinine influence the cerebrovascular collateral circulation. Finally, missing laboratory parameters meant that we could not analyze data on the levels of C-reactive protein, cytokines, and other related inflammatory indicators to further clarify the mechanism underlying how HDL, Lp(a), and blood creatinine affect the compensation of cerebrovascular collaterals.

In conclusion, in patients with severe unilateral ICA stenosis or occlusion, the HDL-C level and a complete anterior half of the circle of Willis were found to be independent protective factors for good collateral circulation, while elevated Lp(a) and serum creatinine levels were independent risk factors for good collateral circulation. Additionally, the combination of HDL-C and Lp(a) can be considered a useful predictor of collateral circulation.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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