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Triglyceride to HDL-cholesterol ratio as an independent risk factor for the poor development of coronary collateral circulation in elderly patients with ST-segment elevation myocardial infarction and acute total occlusion

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Abstract

To determine the prognostic role of triglyceride (TG) to high-density lipoprotein cholesterol (HDL) ratio for poorly developed coronary collateral circulation (CCC) in elderly patients with ST-segment elevation myocardial infarction (STEMI) and acute total occlusion (ATO).

As a retrospective case–control study, elderly patients (age ≥60 years) with both STEMI and ATO (n = 346) were classified as having either poorly- or well-developed CCC (Rentrop grades 0–1 and 2–3, respectively). The ratio of TG/HDL was calculated according to the detected levels of TG and HDL. The difference of TG/HDL ratio in those 2 groups was compared by Student *t* test, and multivariate logistic regression analysis indicating occurrence of poorly developed CCC was performed. Receiver operator characteristic curve (ROC) analysis of TG/HDL ratio which determine the optimal cut-off value of TG/HDL ratio was applied.

The TG/HDL ratio was significantly higher in patients with poorly developed CCC than in those with well-developed CCC (2.88 ± 2.52 vs 1.81 ± 1.18, $P < .001$). In multivariate logistic regression analysis, higher TG/HDL ratio (OR 1.789, 95% CI 1 . 346–2.378, $P < .001$) and the presence of left circumflex branch of coronary artery (LCX) occlusion (OR6.235, 95% CI 2.220–17.510, $P = .001$) were emerged as independent positive predictors of poor development of CCC, whereas presence of right coronary artery (RCA) occlusion (OR 0.474, 95% CI 0.265–0.850, $P = .002$) and onset time (OR 0.693, 95% CI 0.620–0.775, $P < .001$) were found as negative indicators. The optimal cut-off value of TG/HDL ratio was found as 1.58 in ROC analysis, which yielded an area under the curve value of 0.716 (95% CI 0.654–0.778, $P < .001$) and demonstrated a sensitivity of 80.9% and a specificity of 59.3% for prediction of poorly developed CCC.

TG/HDL ratio is an independent risk factor for predicting poor development of CCC in elderly patients with STEMI and ATO.

Abbreviations: AMI = acute myocardial infarction, ATO = acute total occlusion, BMI = body mass index, CAG = coronary angiography, CCC = coronary collateral circulation, CRP = C-reactive protein, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, eNOS = endothelial nitric oxide synthase, HDL = high-density lipoprotein cholesterol, LAD = left circumflex branch of coronary artery, LCX = left circumflex branch of coronary artery, LDL = low-density lipoprotein cholesterol, PCAD = premature coronary artery disease, PUFAs = polyunsaturated fatty acids, RCA = right coronary artery, ROC = receiver operator characteristic curve, SBP = systolic blood pressure, STEMI = ST-segment elevation myocardial infarction, TC = total cholesterol, TG = triglyceride, TIMI = thrombolysis in myocardial infarction, VEGF = vascular endothelial growth factor.

Keywords: acute total occlusion, coronary collateral circulation, ST-segment elevation myocardial infarction, TG/HDL ratio

1. Introduction

Acute myocardial infarction (AMI) is a global challenge for health care system, which is a major risk factor for cardiovascular mortality, and the prognosis of AMI is related to coronary collateral circulation (CCC).[1,2] To identify associated risk factors that contribute to the development of CCC is of great importance.

Dyslipidemia is a major factor contributed to vascular endothelial dysfunction.[3] It is necessary for coronary collateral growth of intact vascular endothelium and normal endothelial function. Thus, vascular endothelial dysfunction could lead to poor development of CCC. Previous studies suggested that patients with diseases related to vascular endothelial dysfunction such as diabetes and metabolic syndrome own more impaired CCC.[4–6] Individuals with dysfunction of endothelium have mixed dyslipidemia frequently, and lipid ratios such as triglyceride (TG) to high-density lipoprotein cholesterol (HDL) ratio may reflect correlated lipid problem. Therefore, we hypothesized that TG/HDL ratio is potentially associated with the development of CCC.

It has been found that TG/HDL ratio had a mediating effect on inflammation markers and the metabolic syndrome.[7] Moreover, TG/HDL ratio is also a marker for identifying insulin resistance

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and predicting new-onset chronic kidney disease.[8–11] Although sharing similar risk factors with coronary artery disease (CAD), little is known about the association between TG/HDL ratio and CCC, especially in aged patients with AMI. Hence, this study was aimed to explore the association between TG/HDL ratio and development of CCC in elderly population with ST-segment elevation myocardial infarction (STEMI) and acute total occlusion (ATO).

2. Subjects and methods

2.1. Study population

A total of 451 consecutive elderly patients (age >=60 years old) with both STEMI and ATO was enrolled into this study from September 2014 to March 2017. Especially, these patients all underwent coronary angiography (CAG) and primary percutaneous coronary intervention during the 12-hour time window after symptom onset at our hospital.

A total of 115 patients was excluded from this study for the following conditions: left main coronary occlusion (n=8), combination of occlusion of nonculprit vessel(s) visible by angiography (n=41), a recent history of blood transfusion (n=3), history of myocardial infarction (n=12), history of PCI (n=29), history of coronary artery bypass grafting (n=5), chronic inflammatory or autoimmune disease (n=6), severe hepatic disease (n=2), renal failure (n=5), and active cancer or hematological proliferative disease (n=4).

Finally, a total of 346 elderly patients with both STEMI and ATO was included in this study and classified according to their Rentrop collateral grades as either poorly developed CCC (group 1: Rentrop grades 0–1) or well-developed CCC (Group 2: Rentrop grades 2–3).

This retrospective study was approved by the ethics committee of our institute. All patients have signed the informed consent form.

2.2. Data collection

Trained research assistants retrospectively reviewed all individual's medical records. Demographic characteristics (age, gender) were collected, as well body mass index (BMI), estimated glomerular filtration rate (eGFR), onset time (the time from the onset of symptom to CAG), and preoperative systolic blood pressure (SBP), and diastolic blood pressure (DBP). Also noted were data regarding coronary risk factors (hypertension, diabetes, hyperlipidemia, current smoking status, and family history of premature coronary artery disease) and the following biochemical indicators: plasma glucose, total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL), and HDL. TG/HDL ratio was calculated according to the levels of TG and HDL. Preoperative medication and coronary angiography were obtained from medical records.

2.3. Blood samples and analysis

All blood samples were drawn at the time of preoperation and were processed with half an hour of collection. All biochemical indicators including fasting plasma glucose, TC, HDL, LDL, and TG were detected by the clinical laboratory of hospital with using an automatic biochemical analyzer (Beckman coulter UniCel DxC800 Synchron). TG/HDL ratio was obtained through calculation. All data were collected by reviewing medical records of patients.

2.4. Coronary angiography and assessment of TIMI grade flow and CCC

CAG was performed using standard Judkins' techniques. Two experienced interventional cardiologists who were unaware of the subjects' clinical information performed the angiographic analysis, including the assessment of coronary lesion, thrombolysis in myocardial infarction (TIMI) flow and grade of CCC. ATO was defined as a culprit lesion with TIMI grade 0 flow. The stenosis of entire coronary artery was measured as Gensini scores.

The TIMI flow grade (range, 0–3) reflects the degree of coronary blood flow during coronary angiography, as follows: TIMI 0, no perfusion, or the absence of any antegrade flow beyond a coronary occlusion; TIMI 1, penetration without perfusion, or faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed); TIMI 2, partial reperfusion, or delayed or sluggish antegrade flow with complete filling of the distal territory; and TIMI 3, normal flow, filling the distal coronary bed completely.

CCC grade (range, 0–3) was based on the Rentrop classification as follows: grade 0, no filling; grade 1, filling of side branches via collateral channels without visualization of the epicardial segment; grade 2, partial filling of the epicardial major coronary artery via collateral channels; and grade 3, complete filling of the epicardial major coronary artery. If a patient had more than one collateral vessel, the highest collateral grade was applied.

2.5. Statistical analysis

All statistical analyses were carried out using SPSS 22.0 for Windows (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean ± standard deviation and categorical variables were defined as percentages. For categorical variables, the comparisons between the groups were carried out using the chi-square test. The comparisons of continuous variables between the groups were performed with student t test when the distributions were normal or rank sum test (Mann–Whitney U test) when the distributions were non-normal. Kolmogorov–Smirnov test was applied to test the normality of variables. One-way analysis of variance was used to compare Rentrop grades. Multivariate logistic regression analysis was performed to identify the independent predictors of poorly developed CCC using fixed adjustment variables including variables showing marginal association with it on univariate testing ($P<.10$). A receiver-operating characteristic (ROC) curve was used to determine the optimal cut-off value of TG/HDL ratio in the prediction of poorly developed CCC. A P value $<.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of subjects

The mean age of 346 elderly patients with STEMI and ATO was 67. 8±5.9 (60–85) years and 79.2% of participants were men. There were 238 patients with poorly developed CCC in the study. The baseline of each group including demographic characterization, clinical laboratory, angiographic characteristics, and preoperative medication were compared in Tables 1 and 2. There was no difference in terms of gender, history of angina, SBP, DBP, and BMI between patients with poorly developed CCC and well-developed CCC. Furthermore, both of the groups had no statistic difference in risk factors of cardiovascular disease, including diabetes, hypertension, current smoking,

hyperlipidemia, and family history of premature coronary artery disease (PCAD). Also, there were no significant differences in angiographic features such as coronary advantage type and Gensini scores, but there was a significant difference in the position of acute total occlusion artery between the 2 groups.

3.2. Univariate analysis of parameters in the poorly/well-developed CCC groups

Patients in the poorly developed CCC group were slightly but significantly older than those of the well-developed CCC group ($P=.03$), and their mean HDL concentration was significantly lower ($P=.02$; Table 1). Particularly of note, the TG concentration and TG/HDL ratio of the poorly developed CCC group were higher than that of the well-developed CCC group ($P<.001$, both). Specifically, the mean TG/HDL ratio of patients in the poor-CCC group was 2.88 ± 2.52, compared with 1.81 ± 1.18 of the well-developed CCC group. The TG/HDL ratio negatively correlated with the CCC Rentrop grade (TG/HDL ratio 3.15 ± 2.99, 2.40 ± 1.08, 1.82 ± 1.22, and 1.70 ± 0.82 at Rentrop grades 0, 1, 2, and 3, respectively, $P<.001$; Fig. 1).

In the poorly developed CCC group, 21.8% and 31.1% experienced acute total occlusion in the LCX or RCA, respectively, compared with 5.6% and 53.5% of patients in the well-CCC group ($P<.001$; Table 2).

3.3. Multivariate regression analysis for the detection of an independent predictor of poorly developed CCC

A multivariate regression analysis was conducted to determine an association between possible risk factors and poor coronary collateralization (Table 3). This included age, onset time, TG/HDL ratio, thrombolytic therapy, occlusion of LCX, or occlusion of RCA as covariates, and with or without poor collateralization as the dependent variable. We found that the following were independent positive predictors of poor collateralization: higher TG/HDL ratio (OR 1.789, 95% CI 1.346–2.378, $P<.001$) and LCX occlusion (OR 6.235, 95% CI 2.220–17.510, $P=.001$). Negative predictions of poor collateralization were the presence of an RCA occlusion (OR 0.474, 95% CI 0.265–0.850, $P=.01$), and onset time (OR 0.693, 95% CI 0.620–0.775, $P<.001$).

3.4. ROC analysis of TG/HDL ratio

In the ROC curve analysis, a cut-off of 1.58 was determined as the optimal TG/HDL value for predicting poor collateralization

Table 1

Baseline characteristics of the study participants.

Variables	Group1 (poorly developed CCC, n=238)	Group2 (well developed CCC, n=108)	*P* value
Demographic characteristics			
Age, years	68.22±6.17	66.72±5.06	.03
Male, n, %	186 (78.2)	88 (81.5)	.48
Education			
Primary education or below, n, %	112 (47.1)	50 (46.3)	.89
Secondary education, n, %	102 (42.9)	48 (44.4)	.78
College education or above, n, %	24 (10.1)	10 (9.3)	.81
Occupation (=Farmer/Herder, n, %)	112 (47.1)	51 (51.9)	.41
Clinical characteristics			
Onset time, hours	4.10±2.66	6.73±2.19	<.001
History of angina	106 (44.5)	50 (46.3)	.76
History of diabetes, n, %	34 (14.3)	18 (16.7)	.57
History of hypertention, n, %	80 (33.6)	42 (38.9)	.34
History of hyperlipidemia, n, %	11 (3.2)	2 (1.9)	.34
Current smoking, %	136 (57.1)	62 (57.4)	.96
Family history of PCAD, n, %	6 (2.5)	2 (1.9)	.70
Systolic BP, mm Hg	116.05±23.15	114.02±27.16	.46
Diastolic BP, mm Hg	94.98±16.76	90.29±21.49	.50
BMI, kg/m^2	25.87±6.68	26.07±6.10	.80
eGFR, mL/min 1.73 m^2	103.21±32.03	98.57±32.77	.216
Biochemical indicators			
Plasma glucose, mmol/L	8.95±3.84	8.88±4.14	.87
TC, mmol/L	4.83±1.00	4.76±1.19	.54
LDL, mmol/L	3.19±0.80	3.09±0.95	.33
HDL, mmol/L	1.04±0.23	1.11±0.25	.02
TG, mmol/L	2.74±1.65	1.88±1.09	<.001
TG/HDL ratio	2.88±2.52	1.81±1.18	<.001
Preoperative medication			
Trombolytic therapy, n, %	4 (1.7)	12 (11.1)	<.001
Aspirin, n, %	238 (100)	108 (100)	–
Clopidogrel/Ticagrelor, n, %	238 (100)	108 (100)	–
Statins, n, %	238 (100)	108 (100)	–
ACEI/ARB, n, %	74 (31.1)	43 (39.8)	.11
Beta-blockers, n, %	96 (40.3)	52 (48.1)	.17
Heparin/LMH, n, %	186 (78.2)	82 (75.9)	.65

ACEI=angiotensin converting enzymeinhibitor, ARB=angiotensin receptor blocker, BMI=body mass index, eGFR=estimated glomerular filtration rate, HDL=high-density lipoprotein cholesterol, HR=heart rate, LDL=low-density lipoprotein cholesterol, LMH=low molecular heparin, PCAD=premature coronary artery disease, TC=total cholesterol, TG=triglyceride.

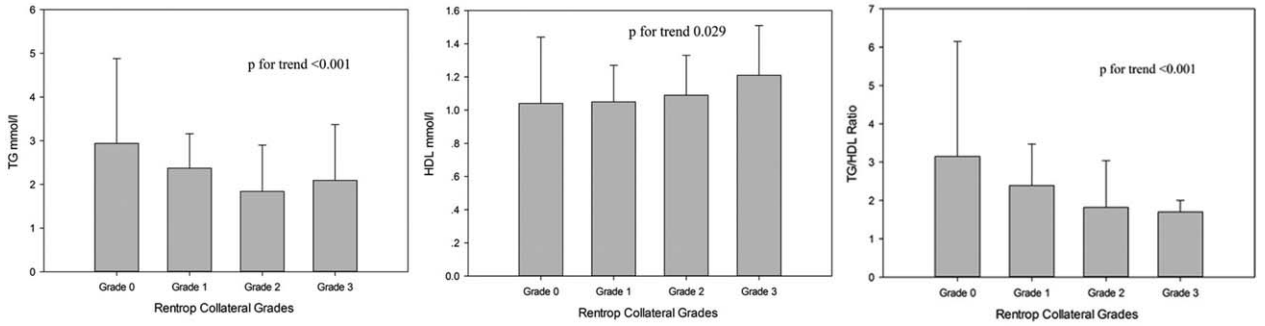

Figure 1. Comparisons of TG, HDL, and TG/HDL ratio according to Rentrop collateral grades in each group divided by Rentrop collateral grades. General differences were found in one-way analysis of variance of TG, HDL, and TG/HDL ratio. HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, TG = triglyceride.

(Fig. 2). The area under the ROC curve was 0.716 (95% CI 0.654–0.778, $P < .001$), with a sensitivity of 80.9% and a specificity of 59.3% for prediction of poor coronary collateralization.

4. Discussion

In this cross-sectional study of a population with STEMI and ATO within 12 hours after the onset of AMI, we found that a higher TG/HDL ratio was significantly associated with poor CCC. This association persisted even after adjusting for demographic and clinical characteristics, including age, onset time, thrombolytic therapy, and the position of acute total occlusion artery.

The degree of coronary stenosis is considered as a strong independent factor for determining the extent of CCC.[12] The patients with ATO of only one culprit vessel were chosen for this study, so that the stenosis of culprit vessels were in the same degree (100%). Also, the Gensini scores between the 2 groups which indicating the severity of entire coronary artery stenosis, were similar in univariate analysis. Consequently, the effect of coronary stenosis on the formation of CCC had no interference with the results of the present study. Nevertheless, the variation of

Table 2

Coronary angiographic features of the divided 2 groups.

Variables	Group 1 (poorly developed CCC, n = 238)	Group 2 (well-developed CCC, n = 108)	*P* value
Coronary advantage type			
Left, n, %	52 (21.8)	26 (24.1)	.65
Right, n, %	160 (67.2)	64 (59.3)	.15
Balanced, n, %	26 (10.9)	18 (16.7)	.14
Position of acute total occlusion atery			
LAD, n, %	112 (47.1)	44 (40.7)	.27
LCX, n, %	52 (21.8)	6 (5.6)	<.001
RCA, n, %	74 (31.1)	58 (53.7)	<.001
Gensini scores	63.26 ± 75.82	57.68 ± 27.56	.46
Grades of CCC			
0	158 (66.4)	—	—
1	80 (33.6)	—	—
2	—	94 (87.0)	—
3	—	14 (13.0)	—

LAD = left anterior descending branch of coronary artery, LCX = left circumflex branch of coronary artery, RCA = right coronary artery.

Table 3

Univariate and multivariate regression analysis for the detection of independent relationship with the occurrence of poorly developed CCC.

	Univariae			Multivariate		
Variables	β	OR (95% CI)	*P*	β	OR (95% CI)	*P*
Age	0.046	1.047 (1.005–1.092)	.03	0.040	1.041 (0.993–1.092)	.10
Onset time	−0.377	0.686 (0.621–0.758)	<.001	−0.367	0.693 (0.620–0.775)	<.001
TG/HDL ratio	0.682	1.977 (1.502–2.602)	<.001	0.582	1.789 (1.346–2.378)	<.001
Thrombolytic therapy	−1.990	0.137 (00.43–0.435)	.001	−1.155	0.315 (0.089–1.113)	.07
Occlusion of LCX	1.559	4.753 (1.974–11.445)	.001	1.830	6.235 (2.220–17.510)	.001
Occlusion of RCA	−0.944	0.389 (0.244–0.621)	<.001	−0.746	0.474 (0.265–0.850)	.01
Constant				−2.115	0.121	.22

HDL = high-density lipoprotein cholesterol, LCX = left circumflex branch of coronary artery, RCA = right coronary artery, TG = triglyceride.

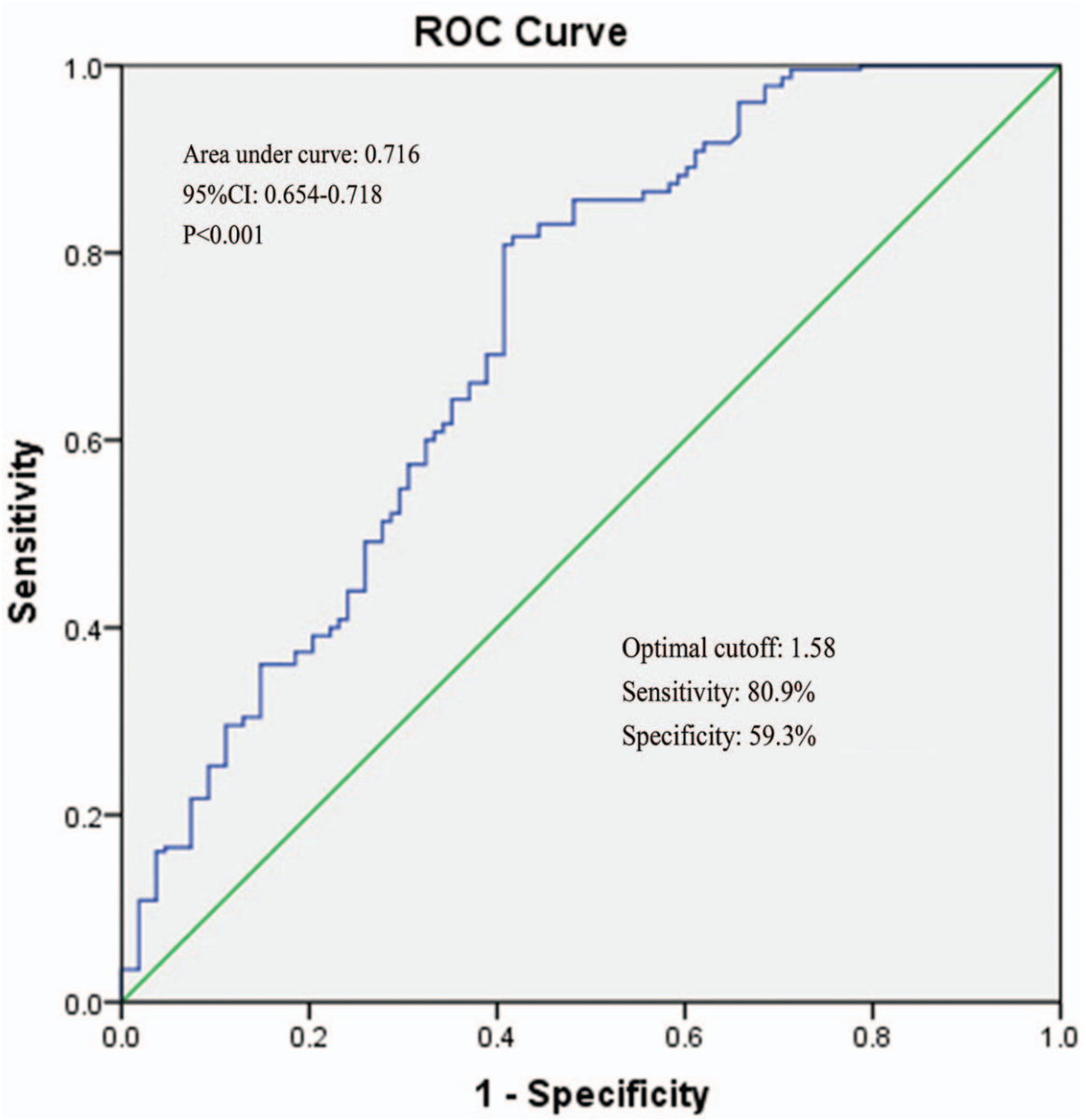

Figure 2. Receiver-operating characteristic (ROC) curves for TG/HDL ratio in predicting for poorly developed CCC with high sensitivity and specificity. ROC analysis demonstrated a medium diagnostic value of TG/HDL ratio. CI: confidence interval. CCC = coronary collateral circulation, HDL = high-density lipoprotein cholesterol, ROC = receiver-operating characteristic, TG = triglyceride.

CCC development varied greatly in patients even with the same severity of coronary stenosis and adjusting for age and gender, which indicating other underlying factors contributed to the formation of CCC. In our present study, univariate analysis demonstrated that a higher TG level and a lower HDL level were significantly associated with poor development of CCC, a higher TG/HDL ratio also played as an indicator for the poor development of CCC.

Previous studies showed that vascular endothelial cells played a key role in the development and progression of CCC.[4,13] The coronary collaterals are activated by mitosis and proliferation of endothelial cells and smooth muscle cells when potential ischemia of the cardiomyocytes occurs on account of coronary stenosis or even totally occlusion.[13] Consequently, keeping the status of intact endothelium and complete endothelial function is indispensable for the adaptation of CCC, and vascular endothelial dysfunction is considered as one of pivotal factors involving in the process of CCC formation.[14] Chronic inflammation is involved in the formation of impaired vascular endothelial function through various ways. One of the most important ways is that inflammation leads to increased production of reactive oxygen species, this oxidative stress finally causes a process of endothelial dysfunction.[15] Oxidative stress can decrease bioavailability of nitric oxide, which is association with vascular endothelial growth factor (VEGF)-signaled endothelial cell proliferation and the development of CCC.[16] A recent research showed that TG/HDL ratio had a significant mediating effect on interleukin 6 in patients with metabolic syndrome.[7] As an important inflammatory marker, interleukin 6 contributes to metabolic regulation of C-reactive protein (CRP),[17] which can be regarded as a marker of the process of endothelial dysfunction.[18] It also participates in down

regulation of endothelial nitric oxide synthase (eNOS) and in transcription of vascular endothelial cells, which leads to degradation of eNOS-RNA.[18] This process causes reduced production of nitric oxide.[17] Interestingly, it has been investigated that oral omega-3 polyunsaturated fatty acids (PUFAs) can reduce the levels of interleukin 6 along with the reduction of TG concentrations.[19] Additionally, some studies found that HDL level was inversely associated with the incidence of endothelial dysfunction, and vice versa.[20,21]

Together, the higher TG/HDL ratio can be considered as an inflammatory marker, which mediates endothelial function and collateral circulation growth by affecting a series of inflammatory reactions.

Moreover, lipid treatment can improve vascular endothelial function and reduce microvascular complications. Tousoulis et al[19] found that supplementation of PUFAs resulted in a significant improvement in flow-mediated dilation of the brachial artery and carotid-femoral pulse wave velocity in patients with metabolic syndrome. In other words, treatment with omega-3 PUFAs can improve endothelial function. Also, previous studies showed that omega-3 PUFAs had a consistent effect of reduction in plasma TG levels.[22–24] The study of Fenofibrate Intervention in Event Lowering in Diabetes (FIELD) demonstrated that fenofibrate therapy was associated with a significant reduction of advanced retinopathy required laser interventions and less albuminuria progression in patients with type 2 diabetes mellitus.[25,26] Other studies also indicated that statin therapy remarkably improved brachial artery endothelial function in metabolic syndrome patients.[27–29] An animal experimental study also indicated that HDL treatment of HAECs prevented 7-KC–induced ROS production and active eNOS dimer disruption in an ABCG1-dependent manner.[30] Nevertheless, a recently study found that the acute impact influence of high-dose lipid-lowering therapy on endothelial progenitor cells is of no avail in stable CAD patients.[31] It seems to be inconsistent with previous studies. The reason may be that the treatment time was too short to show the effect or the number of cases was too small, a total of only 38 cases. So further research is needed to validate this effect.

In our present study, we found that the position of acute total occlusion artery is association with the development of CCC in elderly patients following STEMI and ATO. CCC is better developed in patients with RCA occlusion, while worse development in patients with LCX occlusion. These findings are in line with previous studies,[8,12,32] In these studies, it is exhibited that RCA occlusion develops better collateralization compared with left anterior descending branch of coronary artery (LAD) occlusion. This implies better development of CCC from the left coronary artery (especially the LAD) than those from other vessels, possibly contributed to the difference of pressure gradient at both ends of the CCC. An increased pressure gradient across the pre-existing collateral network resulting from ATO occurs, which triggers the subsequent increase in tangential shear stress and stretching of collateral arteriole and promotes maturity of CCC.[33] According to the above findings, LCX occlusion along with poor collateralization indicated LCX occlusion resulting in smaller pressure gradient, while RCA occlusion causing greater pressure gradient. Additionally, our result of the association of onset time with CCC in STEMI and ATO confirmed the previous research result: the flow of CCC in the infarcted area tends to increase as time goes on.[34]

Our study has several limitations listed as following: First, the sample size is relatively small, one multicenter study wound be designed to make the conclusion more evidence. Second, as a case–control study, the subjects are the inpatients from a single center which may result in unavoidable selective bias. Third, the cross-sectional design of the present study made it difficult to comment on the casual relationship of TG/HDL ratio and poor development of CCC. Fourth, we cannot conclude whether TG/HDL ratio influences the initiation of CCC rather than early progress. Fifth, it provided no other age group for comparison in this study. Sixth, whether the results of our study can be extended to other populations is unknown.

5. Conclusion

In conclusion, in the present population of elderly patients with both STEMI and ATO, the TG/HDL ratio is an independent risk factor for the poor development of CCC. RCA occlusion is an independent predictor for well-developed CCC, but LCX occlusion is an independent predictor for poorly developed CCC. We would suggest that onset time is an independent positive factor for predicting good collateralization. Further study is needed to repeat the findings in other populations and to compare the predictive ability of other lipid parameters and inflammatory factors.

Author contributions

Conceptualization: Zheng Zhang.
Data curation: Guo-Yong Liu, Xiao-Xue Meng.
Formal analysis: Guo-Yong Liu.
Investigation: Zheng Zhang.
Methodology: Guo-Yong Liu.
Writing – original draft: Guo-Yong Liu.
Writing – review & editing: Guo-Yong Liu.

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