

Investigation of the Predictive Values of Triglyceride/HDL Cholesterol Ratio and Whole Blood Viscosity with Regard to Severe Peripheral or Carotid Artery Disease in Patients Scheduled for Coronary Bypass

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ABSTRACT

Background: The incidence of atherosclerotic cardiovascular diseases, which constitute an important disease group, is expected to rise with increasing life expectancy. The aim of this study was to investigate the predictive values of triglyceride/HDL cholesterol (TG/HDL-C) ratio and whole blood viscosity on possible severe carotid or peripheral arterial disease in patients who were admitted to our clinic and scheduled for coronary artery bypass graft (CABG) surgery.

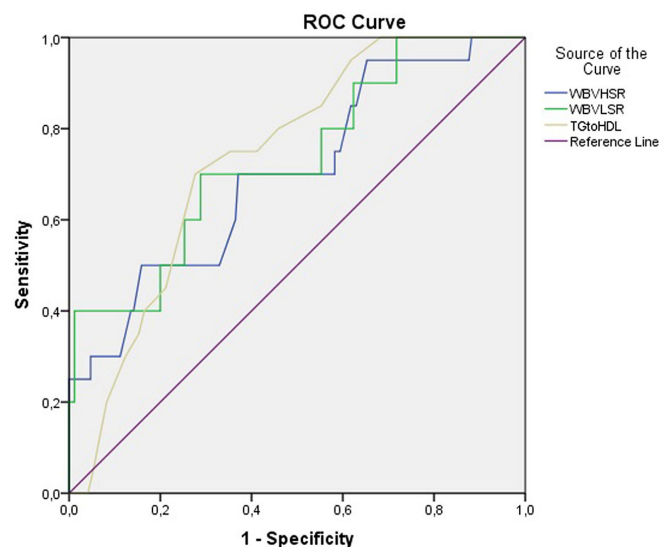
Methods: This study retrospectively examined 299 patients who were admitted to our clinic and scheduled for CABG between August 1, 2015, and August 1, 2019. Patients with severe carotid or peripheral arterial disease were included in group 2; those in whom peripheral arterial disease and stenosis were not detected were included in group 1.

Results: Group 1 consisted of 255 patients, mean (\pm standard deviation) age 58.1 ± 8.9 years; the 44 patients in group 2 had a mean age of 64.1 ± 10.6 years ($P = .018$). The incidence of diabetes mellitus and tobacco use were significantly higher in group 2 ($P < .001$ and $P = .034$, respectively). Triglyceride values, TG/HDL-C, and whole blood viscosity at high and low shear rates were significantly higher in group 2 ($P = .017$, $P < .001$, $P < .001$, and $P < .001$, respectively). Receiver operator characteristic analysis revealed that the cutoff value of TG/HDL-C was 3.2 with 77% sensitivity and 72% specificity; that of high-shear-rate viscosity was 16.1 with 73% sensitivity and 69% specificity; and that of low-shear-rate viscosity was 59.2 with 70% sensitivity and 63% specificity.

Conclusion: It is possible to predict severe additional arterial diseases in patients scheduled for CABG with whole blood viscosity and TG/HDL-C ratios, both of which can be obtained with simple blood tests.

INTRODUCTION

The incidence of atherosclerotic cardiovascular diseases, which constitute an important disease group, is expected to rise with increasing life expectancy. Among these, coronary artery disease is the most commonly seen. Despite widespread usage of endovascular methods, coronary artery bypass graft (CABG) surgery is the gold standard treatment method in various cases of vascular and main coronary diseases [Hillis 2011; Teker Açık 2019]. A thorough examination and preparation of patients is essential before CABG. The preoperative diagnosis of possible comorbidities, such as severe carotid or peripheral artery disease, which may affect surgical strategy, is of foremost importance. For example, the team may preoperatively determine the possible intra-aortic balloon pump (IABP) placement method in a patient with low ejection fraction and bilaterally occluded iliac arteries. Also, a case with severe carotid artery stenosis (CAS) may necessitate a revision in surgical strategy.



ROC curve and AUC for TG/HDL-C, WBVLSR, and WBVHSR for predicting concomitant severe carotid artery disease or PAD in patients scheduled to undergo CABG. TG/HDL-C cutoff 3.2, 77% sensitivity, 72% specificity; WBVHSR cutoff 16.1, 73% sensitivity, 69% specificity; WBVLSR cutoff 59.2, 70% sensitivity, 63% specificity.

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Table 1. Demographic Data of the Patients*

Variable	Group 1 (n = 255)	Group 2 (n = 44)	P
Age (y)	58.1 ± 8.9	64.1 ± 10.6	.018†
Ejection fraction (%)	50.4 ± 6.9	48.6 ± 7.1	.214
Body mass index (kg/m ²)	29.3 ± 3.9	28.9 ± 4.1	.356
Male sex	162 (63.5)	32 (72.7)	.686
Previous PCI	82 (32.1)	18 (40.9)	.499
COPD	55 (21.5)	11 (25)	.866
Hypertension	163 (63.9)	27(61.3)	.827
Diabetes mellitus	71 (27.8)	29 (65)	<.001†
Tobacco use	90 (35.3)	26 (59)	.034†
ASA use	87 (34.1)	19 (43.1)	.481
ACEI/ARB use	76 (29.8)	14 (31.8)	.969
Statin use	69 (27)	10 (23)	.480
Beta-blocker use	66 (25.8)	12 (27.2)	.623

*Data are mean ± SD or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.

†Statistically significant at $P < .05$.

Easily obtainable from routine blood tests of the patients, the ratio of triglycerides to high-density-lipoprotein cholesterol (TG/HDL-C) ratio, also known as the atherogenic index, is reportedly related to mortality in cardiovascular diseases [Chang 2017; Frohlich 2003]. In addition, it has been shown to correlate with disease severity in patients who underwent coronary angiography. Whole blood viscosity (WBV) is the main determinant factor of endothelial shear stress (ESS) and is considered a predictor of many cardiovascular diseases, such as hypertension and hyperlipidemia [Cecchi 2011; Ozcan Cetin 2015].

The aim of this study was to investigate the predictive values of the TG/HDL-C ratio and whole blood viscosity on possible severe carotid or peripheral arterial disease in patients who were admitted to our clinic and scheduled for CABG.

METHODS

This study retrospectively examined 299 patients who were admitted to Mehmet Akif İnan Training and Research Hospital, Department of Cardiovascular Surgery, and scheduled for CABG between August 1, 2015, and August 1, 2019. The study was approved by the institutional review board. The patients were divided into 2 groups after preoperative evaluations: group 1 consisted of patients with coronary artery disease only, and group 2 included those with stage C/D (according to Trans Atlantic

Inter-Society Consensus-II [TASC-II] classification) aortoiliac or femoropopliteal diseases or severe carotid artery diseases. Emergency operations, reoperations, patients who required additional cardiac surgery, patients with chronic renal failure or any known systemic inflammatory or rheumatic diseases were excluded from the study. Patient data were gathered from the hospital registry and patient files. All patients' demographic characteristics, hemograms, biochemical parameters, and preoperative examinations regarding peripheral artery or carotid artery systems were recorded.

Measurement of Blood Parameters

The blood samples of all patients who admitted to our clinic with planned surgeries were obtained from peripheral veins, and EDTA-coated test tubes were used for analysis. Automatic and molecular analyzers were used for the measurement of hematologic and biochemical parameters, respectively. TG/HDL-C ratio and whole blood viscosity were calculated from the results of these analyses.

Calculation of Whole Blood Viscosity

Two values of whole blood viscosity were calculated at high shear rate (WBVHSR) and at low shear rate (WBVLSR). Total protein (TP) and hematocrit (HCT) parameters were used for the following formulas [Nwose 2010]:

$$\text{WBVHSR (208 s}^{-1}\text{)} = (0.12 \text{ HCT}[\%]) + 0.17 (\text{TP [g/L]} - 2.07);$$

$$\text{WBVLSR (0.5 s}^{-1}\text{)} = (1.89 \text{ HCT}[\%]) + 3.76 (\text{TP [g/L]} - 78.42).$$

Diagnosis of Severe Carotid or Peripheral Artery Disease

During preoperative preparation, all patients underwent carotid artery Doppler ultrasonography (DUSG). All patients with internal carotid artery peak systolic flow velocity (PSV) >125 cm/s (>50% stenosis) or ICA PSV/common carotid artery PSV >2 were evaluated by computed tomographic angiography or conventional angiography. Carotid artery stenosis levels were determined according to the North American Symptomatic Carotid Endarterectomy ratings, and accordingly, 1-sided ≥70% stenosis was considered serious carotid artery disease (22 patients). Before the operation, detailed examinations of the patients whose coronary bypass was planned for the diagnosis of peripheral artery disease were performed. Doppler ultrasonography was performed in all patients with pathological findings in peripheral pulses and in those with ankle brachial index <0.9. Patients with ≥50% stenosis findings in the peripheral arteries were evaluated by computed tomographic angiography or conventional angiography. Based on this examination, TASC classification [Norgren 2007] was made, and those with stage C/D disease were evaluated as patients with serious peripheral artery disease (14 patients). Eight patients had both severe carotid and peripheral arterial diseases.

Statistical Analysis

SPSS 21.0 (IBM, version 21.0, Chicago, IL) was used for data analysis. Continuous and ordinal data were presented as mean and standard deviation. Kolmogorov-Smirnov and Shapiro-Wilk tests were used the evaluation of normality of

Table 2. Laboratory Variables of the Patients*

Variables	Group 1 (n = 255)	Group 2 (n = 44)	P
White blood cells (10 ³ /μL)	9.7 ± 3.9	10.9 ± 4.1	.131
Hematocrit (%)	40.1 ± 4.9	39.3 ± 5.2	.414
Platelets (10 ³ /μL)	270.3 ± 71.4	291.7 ± 62.8	.216
Neutrophils (10 ³ /μL)	6.2 ± 1.3	6.6 ± 1.2	.615
Lymphocytes (10 ³ /μL)	2.7 ± 1.3	2.3 ± 1.1	.314
Total protein (g/dL)	6.9 ± 0.4	7.2 ± 0.3	.060
Albumin (mg/dL)	4.2 ± 0.3	4.3 ± 0.4	.393
Urea (mg/dL)	31.4 ± 8.1	33.1 ± 7.9	.224
Creatinine (mg/dL)	0.97 ± 0.23	0.99 ± 0.3	.182
C-reactive protein (mg/dL)	8.8 ± 9.7	9.1 ± 10.7	.096
Total cholesterol (mg/dL)	189.4 ± 66.9	195.8 ± 57.8	.260
LDL cholesterol (mg/dL)	124.7 ± 41.9	126.9 ± 37.6	.456
HDL cholesterol (mg/dL)	42.2 ± 7.3	39.8 ± 8.7	.074
Triglycerides (mg/dL)	181.9 ± 86.7	193.9 ± 74.7	.017†
TG/HDL-C	2.5 ± 0.9	3.7 ± 0.5	<.001†
WBVHSR	15.46 ± 1.50	16.84 ± 1.62	<.001†
WBVLSR	51.96 ± 16.08	66.29 ± 17.41	<.001†

*Data are mean ± SD.

†Statistically significant at $P < .05$.

distribution. Student's t test and Mann-Whitney U test were used for normally and non-normally distributed data, respectively. Frequency and percentage analysis were performed for nominal variables, which were compared with χ^2 test. Multivariate binary logistic regression analysis was used to analyze the predictors of peripheral and carotid artery stenosis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive values of whole blood viscosity and TG/HDL-C ratio in comorbid additional severe arterial diseases, and the area under the curve (AUC) was calculated.

RESULTS

The demographic data of 299 patients are presented in Table 1. Group 1 consisted of 255 patients, mean age 58.1 ± 8.9 years. The 44 patients in group 2 had a mean age of 64.1 ± 10.6 years ($P = .018$). The 2 groups were similar in terms of sex, body mass index, hypertension, chronic obstructive pulmonary disease (COPD), and current medication (eg, statin and beta blocker use). The incidence of diabetes mellitus (DM) and tobacco use were significantly higher in group 2 ($P < .001$ and $P = .034$, respectively).

The laboratory parameter data of the patients are presented in Table 2. There was no significant difference between

Table 3. Multivariate Logistic Regression Analysis to Predict Severe Peripheral or Carotid Arterial Disease in Patients Scheduled to Undergo CABG

Variable	Adjusted OR	95% CI	P
Model 1			
Age	1.085	1.014 to 1.160	.038†
Triglycerides	1.017	0.999 to 1.034	.065
Tobacco use	0.455	0.156 to 1.021	.114
DM	2.651	1.006 to 2.998	.009†
TG/HDL-C	3.426	1.316 to 8.921	.012†
WBVHSR	2.161	1.382 to 3.378	.001†
Model 2			
Age	1.070	1.010 to 1.158	.047†
Triglycerides	1.013	0.996 to 1.030	.128
DM	2.415	1.001 to 2.644	.011†
Tobacco use	0.354	0.120 to 1.047	.061
TG/HDL-C	3.886	1.458 to 10.353	.007†
WBVLSR	1.063	1.023 to 1.105	.002†

†Statistically significant at $P < .05$.

the 2 groups in terms of hemogram parameters, total protein, albumin, urea, creatinine, C-reactive protein, total cholesterol, HDL cholesterol, and LDL cholesterol (LDL-C). Triglyceride values, TG/HDL-C, WBVHSR, and WBVLSR were significantly higher in group 2 ($P = .017$, $P < .001$, $P < .001$, and $P < .001$, respectively).

In patients scheduled for CABG, multivariate logistic regression analysis was performed in 2 different models with respect to WBVHSR and WBVLSR values to evaluate additional severe PAD or CAS (Table 3). Age, DM, TG/HDL-C ratio (odds ratio [OR] 3.426, 95% confidence interval [CI] 1.316 to 8.921, $P = .012$) and WBVHSR (OR 2.161, 95% CI 1.382 to 3.378, $P = .001$) were identified as the independent predictors of comorbid serious arterial disease in model 1. Age, DM, TG/HDL-C ratio (OR 3.886, 95% CI 1.458 to 10.353, $P = .007$) and WBVLSR (OR 1.063, 95% CI 1.023 to 1.105, $P = .002$) were the independent predictors in model 2.

ROC curve analysis revealed that the cutoff value of TG/HDL-C was 3.2 with 77% sensitivity and 72% specificity; that of WBVHSR was 16.1 with 73% sensitivity and 69% specificity; and that of WBVLSR was 59.2 with 70% sensitivity and 63% specificity (Figure).

DISCUSSION

Coronary artery bypass operations are major surgeries. One of the principal factors affecting the success of the operation is the preoperative preparation of the patients, which includes their systematic evaluation. Physicians must beware

of carotid and peripheral artery disease in patients scheduled for CABG, because they may cause serious morbidity and mortality. With our current study, we detected, for the first time in the literature, that WBV and TH/HDL-C ratio, which are easily obtainable from routine blood parameters, may predict serious additional arterial diseases in patients scheduled for CABG.

Atherosclerosis is the basis of cardiovascular diseases, and various inflammatory mechanisms play a role in its pathophysiology [Xing 2019]. Epidemiological research has shown that increased blood lipid values are a risk factor for atherosclerotic heart diseases [Di Angelantonio 2009; Sarwar 2007]. Further studies report that TG/HDL-C ratio has a higher predictive value than a single blood lipid parameter [Asia Pacific Cohort Studies Collaboration 2005]. HDL cholesterol has protective effects against atherosclerosis, the most commonly known being the transportation of cholesterol from macrophages on vessel walls to the liver [Cuchel 2006]. Additionally, it induces vasorelaxation and contributes to protecting the hemostasis of endothelial cells by inhibiting cellular adhesion, thereby preventing the migration of proinflammatory cytokines to vascular endothelia [Calabresi 2003]. In contrast, increased TG values are a risk factor for atherosclerosis. Puri et al [2016] detected a direct correlation between increased TG values and atherosclerosis. In light of this data, it is safe to predict that a rise in TG/HDL-C ratio poses an important risk factor for atherosclerosis.

In the prospective cohort study of Chen et al [2020] on 96,542 volunteers, the association of TG/HDL-C with cardiovascular events was investigated over a 9-year follow-up period, during which 5422 cardiovascular events occurred in patients whose TG/HDL-C ratios were significantly increased. Chi et al [2018] conducted a study in 1599 individuals >65 years of age, examining the efficiency of lipid parameters in reflecting target organ damage, specified as progression in peripheral arterial disease, aortic thickening, or renal damage occurring due to atherosclerosis. The results of the study showed that TG/HDL-C and non-HDL-C values were more effective in reflecting target organ damage compared with other lipid parameters [Chi 2018]. In light of these data, we determined that increased TG/HDL ratio could predict severe comorbid carotid and peripheral artery disease in patients scheduled for CABG in our clinic and calculated the cutoff value as 3.2 with 77% sensitivity and 72% specificity based on ROC curve analysis.

The pathophysiology of atherosclerosis is complex and is yet to be understood. Hyperlipidemia, DM, and smoking are known risk factors. However, half of the patients with myocardial infarct do not have hyperlipidemia, and traditional risk factors cannot be identified in 20%. Therefore, other mechanisms are suspected to underlie this condition, which is how whole blood viscosity came to be researched. Whole blood viscosity is a marker of ESS and is closely related to cardiovascular diseases. Hyperviscosity is pathophysiologically similar to the traditional risk factors such as hypertension, smoking, DM, male sex, and hyperlipidemia [Sloop 2015].

As one of the important determinants of ESS, WBV plays a critical role in maintaining normal endothelial

function. Increased ESS may disrupt microvascular circulation owing to thrombogenic events that occur with atherosclerotic plaque rupture and may cause major events in cerebral, cardiac, and peripheral circulation [Cecchi 2011; Kim 2013]. In the normally functioning vascular endothelia, mild increases in viscosity induce the release of nitric oxide (NO), thereby ensuring circulation continuity. However, in cases of endothelial dysfunction due to atherosclerotic changes, NO release is disrupted, resulting in circulatory disorders resulting from increased viscosity [Salazar Vázquez 2010]. Infiltration of lipid particles and fibrinogen to vascular endothelia by the cause of increased WBV is another mechanism leading to this pathophysiology [Marossy 2009].

In the Edinburgh Artery study, along with risk factors such as hypertension and hyperlipidemia, WBV was found to correlate with cardiovascular events and stroke [Lowe 1997]. In patients who developed ST-elevated myocardial infarct, Cetin et al [2016a] investigated the prognostic importance of WBV during a mean follow-up time of 34.6 months and found that increased WBV values were related to short- and long-term major adverse events. The West of Scotland Coronary Prevention Study detected a direct correlation between increased WBV and coronary artery risk factors as well as peripheral and coronary atherosclerosis [Lowe 2000]. In another study, the relationship between WBV and coronary collateral circulation was investigated. Coronary artery disease patients with total occlusion were divided into 2 groups based on collateral circulation, and the risk factors for insufficient collateral circulation were researched. Multivariate logistic analysis revealed that both WBVHSR and WBVLSR were independent predictors for insufficient development of collateral circulation. The cutoff values for WBVLSR and WBVHSR were 67.1 (sensitivity 73%, specificity 67.1%) and 16.8 (sensitivity 70%, specificity 70.5%), respectively [Cetin 2016b]. Similarly, we detected a correlation between WBV and severe additional arterial disease in our group of coronary artery disease patients.

Possible severe CAS may increase the cerebrovascular event risk. Even if no intervention is planned for the carotid artery, being aware of it preoperatively may allow the team to take precautions such as maintaining a high perfusion pressure during surgery. Peripheral artery disease may also pose risks during CABG operations and should be diagnosed preoperatively. Ignorance of possible severe aortoiliac diseases may cause difficulty in the placement of mechanical support systems (IABP, etc) after the operation. In addition, distal perfusion may be impaired during coronary bypass in patients with severe femoropopliteal lesions [Te Kolste 2015]. We showed that WBV and TG/HDL-C ratio, both of which can be obtained with simple blood tests, may predict possible severe additional arterial diseases in patients scheduled for CABG.

The retrospective nature of this study is its most prominent limitation. In addition, although routine carotid DUSG is preoperatively performed to all patients in our clinic, peripheral artery DUSG is not a routine practice. Also, because physical examination is subjective, the diagnosis of PAD may have been omitted in a small number of patients.

In conclusion, it is possible to predict severe additional arterial diseases in patients scheduled for CABG with WBV and TG/HDL-C ratio, both of which can be obtained with simple blood tests.

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