Angiology
2017, Vol. 68(2) 151-158

DOI: 10.1177/0003319716641827
journals.sagepub.com/home/ang
SAGE

Determinants of Chronic Total Occlusion in Patients With Peripheral Arterial Occlusive Disease

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Abstract

Chronic total occlusion (CTO) is a common finding in 40% of the patients with peripheral arterial disease (PAD). The aim of this study was to investigate the determinants of CTO in patients with PAD. The study included a total of 211 nonanemic patients with PAD. All patients were categorized according to the Fontaine classification. In lower extremity angiography cohorts, CTO^- patients were designated as group 1 and CTO^+ patients were designated as group 2. Patients with CTO had significantly higher red cell distribution width (RDW), neutrophil–lymphocyte ratio, uric acid, and high-sensitivity C-reactive protein compared to patients without CTO ($P \leq .001$, $P = .036$, $P \leq .001$, and $P = .015$, respectively). Albumin, total bilirubin, and direct bilirubin were significantly lower in the patients with CTO compared to patients without CTO ($P = .023$, $P \leq .001$, and $P = .049$, respectively). Multivariate logistic regression analysis showed that RDW, uric acid, and total bilirubin were independent predictors of CTO in patients with PAD. We demonstrated that increased RDW and uric acid levels and lower total bilirubin values were independently associated with CTO in patients with PAD.

Keywords

peripheral arterial disease, chronic total occlusion, red cell distribution width, uric acid, bilirubin

Introduction

Atherosclerosis in peripheral arteries is a chronic condition that causes narrowing of the arteries. Symptoms may appear with different intensities depending on the level of narrowing in each vascular region. In current epidemiology studies, it has been determined that the prevalence of this disease was 18% in the population aged between 60 and 90 years and that the intermittent claudication was 7%.[1] Peripheral arterial disease (PAD) is seen more frequently in males and the elderly individuals and is associated with increased mortality and morbidity.[2]

If PAD is not diagnosed early, the disease may advance to critical limb ischemia (CLI). Critical limb ischemia results in death in 25% of patients within 1 year; the 1-year mortality rate in patients who underwent amputation due to PAD has been reported to be as high as 45%.[3] Symptoms worsen in 25% of the patients with claudication, and 8% progress to CLI within the year following diagnosis.[4] The purpose of treatment in patients with PAD is to reduce cardiovascular mortality and morbidity, increase the quality of life by reducing symptoms of claudication, eliminate pain during resting, and preserve leg viability. Lifestyle changes, including risk factor modifications, and pharmacological treatments can be considered for the reduction of adverse cardiovascular events. Optimal treatment of CLI consists of endovascular intervention or surgical reconstruction.

In the last decade, endovascular revascularization for patients with PAD has developed rapidly. Currently, due to low morbidity and mortality as compared with vascular surgery, an increasing number of clinical centers prefer endovascular approaches for the treatment of lifestyle-limiting claudication and CLI; however, they retain the option of surgery in case of failure. Chronic total occlusion (CTO) is a common finding in

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patients with PAD, occurring in up to 40%.[5,6] Peripheral arterial disease ranges in severity from simple narrowing of vessels to CTO. Additionally, endovascular treatment is preferred by many patients because of its reduced costs, shorter hospitalization stay, and reduced procedural morbidity.

Determination of CTO predictors in patients with PAD may provide progress in the management of this disease. Therefore, the aim of this study was to investigate the determinants of CTO in patients with PAD who underwent lower limb angiography.

Materials and Methods

Study Design and Patient Selection

The study included a total of 211 nonanemic patients with PAD who were admitted to the Erzincan Mengücek Gazi Training and Research Hospital and Gaziantep Dr Ersin Uysal State Hospital who underwent lower limb peripheral angiography between January 2014 and October 2015. Narrowing of >50% in the symptomatic lower limb shown by lower extremity peripheral angiography performed according to clinical evaluations and current protocols was defined as PAD. All patients were categorized according to the Fontaine classification.[7] Patients in stages II to IV according to the Fontaine classification were defined as having symptomatic PAD. Symptom time interval (months) was defined as the time period from the onset of the ischemic symptoms to a diagnosis of lower extremity peripheral angiography. Chronic total occlusion was defined as the angiographic determination of 100% occlusion in any segment along the lower extremity trace. In lower extremity peripheral angiography cohorts, CTO^- patients were designated as group 1 and CTO^+ patients were designated as group 2. Patients with a lower extremity amputation history, surgical and endovascular revascularization of the leg, acute-phase lower extremity ischemia history in the last 3 months (acute embolism or thrombus), history of autoimmune disease, acute infections unrelated to PAD, recent (<3 months) acute coronary syndrome or stroke, decompensated heart failure, malignancy, hepatic or renal disease, hepatobiliary disease, chronic inflammatory disease, gut disease, leukocyte count above reference limits, and those with baseline anemia (hemoglobin <13 g/dL for males, <12 g/dL for females) and a history of blood transfusion in the last 3 months were excluded from the study. The protocol was approved by the local ethics committee and complied with the Declaration of Helsinki.

A detailed medical history of each patient was obtained, and a full physical examination was performed. Age, sex, diabetes mellitus (DM), hypertension (HT), smoking, coronary artery disease history, the family history of coronary artery disease (CAD), dyslipidemia, body mass index (weight [kg] / height squared [m^2]), and medications were recorded. The glomerular filtration rate (GFR), biochemical parameters, and hematological indices of all patients were measured upon admission to the hospital. The GFR was calculated from serum creatinine using the Cockcroft-Gault equation: (140−age) × (weight in kg) × (0.85 if female) / (72 × creatinine).

Laboratory Analysis

After a fasting period of 12 hours, blood samples were drawn from an antecubital vein before lower limb angiography. Fasting glucose, serum creatinine, albumin, uric acid, total bilirubin, direct bilirubin, aspartate amino transferase, alanine amino transferase, high-sensitivity C-reactive protein (hsCRP), and lipid profile were recorded. These parameters were analyzed using an auto-analyzer (AU 2700 plus analyzer, Beckman-Coulter, Tokyo, Japan).

Hematological parameters, including white blood cell count, hemoglobin, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, and mean platelet volume (MPV) were measured as part of the automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Inc, Miami, Florida). The neutrophil–lymphocyte ratio (NLR) was obtained by dividing the total count of neutrophils by the lymphocyte count.

The normal range for RDW value is 10% to 16%. Blood samples for hematological parameters were collected into EDTA-containing tubes and measured within 30 minutes approximately.

Clinical Definitions

A baseline hemoglobin concentration of <13 mg/dL in men and <12 mg/dL in women at the time of admission was accepted as anemia according to the World Health Organization criteria. Diabetes mellitus was defined if the plasma fasting glucose was >126 mg/dL or if the patient used hypoglycemic agents. If the systolic pressure exceeded 140 mm Hg and/or the diastolic pressure exceeded 90 mm Hg at least twice or if the patient was on an antihypertensive medication, the participant was considered to have HT. A fasting total serum cholesterol >200 mg/dL or any previous history of statin use was defined as hyperlipidemia. Both current and former smokers were regarded as smokers. Patients with a positive family history of CAD were regarded as having premature CAD in a close relative (men <55 and women <65 years). Pain emerging with exercise and reduced pain in rest was defined as intermittent claudication (Fontaine stage II). Patients with PAD having ischemic rest pain and/or skin ulceration/gangrene, according to current guidelines that reflect the patients with Fontaine stages III and IV, were regarded as CLI.[7]

Angiography Procedure

Lower extremity peripheral angiography was performed by a cardiologist by entering from the femoral artery with a 6F sheath. Screening was conducted by introducing a radiopaque (Iopromide; Ultravist-370 Schering AG, Berlin, Germany) agent from the distal abdominal aorta using a pigtail catheter or from right or left main iliac artery using diagnostic catheters.

Table 1. Baseline Demographic and Clinical Characteristics of Study Groups.

Variables	CTO^-, n = 120	CTO^+, n = 91	*P* Value
Age, years	63 (44-79)	67 (41-81)	.046
Sex, male, n (%)	98 (81.7)	76 (83.5)	.726
Diabetes mellitus, n (%)	44 (36.7)	45 (49.5)	.063
Hypertension, n (%)	62 (51.7)	54 (59.3)	.267
Smoking, n (%)	50 (41.7)	48 (52.7)	.11
Dyslipidemia, n (%)	54 (45.0)	47 (51.6)	.338
Previous history of CAD, n (%)	44 (36.7)	43 (47.3)	.122
Family history of CAD, n (%)	32 (26.7)	28 (30.8)	.513
Symptom time interval, months	28 (4-48)	32 (4-60)	.042
BMI, kg/m^2	25.8 (20.3-27.9)	26.1 (20.1-28.8)	.815
Fontaine classification, n (%)			
II	89 (74.2)	54 (59.3)	
III	26 (21.7)	30 (33)	.071
IV	5 (4.2)	7 (7.7)	
Previous medications, (%)			
Aspirin, n (%)	73 (60.8)	63 (69.2)	.207
Clopidogrel, n (%)	42 (35.0)	29 (31.9)	.633
Cilostazol, n (%)	36 (30.0)	32 (35.2)	.427
Statin, n (%)	49 (40.8)	31 (34.1)	.316

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CTO, chronic total occlusion.

The right and left common iliac artery, iliac externa, interna, main femoral, superficial femoral, deep femoral artery, popliteal, tibioperoneal trunk, anterior tibial artery, posterior tibial artery, and the parts up to peroneal artery distal were examined. Lower extremity peripheral angiography was reviewed by an interventional cardiologist who was not aware of the hematological and biochemical parameters of the patients.

Statistical Analysis

Continuous variables were calculated as mean ± standard deviation; categorical variables were calculated as percentages. The one-sample Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was normal. Student *t* test or the Mann-Whitney *U* test was used to compare the continuous variables between the 2 groups. The χ^2 or Fisher exact test was used for the comparison of categorical variables. For the determination of the independent predictors of CTO, significant parameters ($P < .05$) in the univariate analysis were included in multivariate logistic regression analyses. Ninety-five percent confidence interval (CI) and odds ratios (ORs) were provided. Receiver–operating characteristics (ROC) curve analysis was performed for the prediction of cutoff values for total bilirubin, RDW, and uric acid. MedCalc statistic software (version 13.2.0, Mariakerke, Belgium) was utilized for the analysis. Two-tailed values ($P < .05$) were considered significant. SPSS version 17 (SPSS Inc, Chicago, Illinois) was used to analyze the data.

Results

The study population consisted of 211 patients with PAD (mean age 63.9 ± 8.6 years and 82.5% male). Baseline demographic and clinical characteristics of the patients of the study groups are presented in Table 1.

The CTO^+ group was older than the CTO^- group (median age: 63 [44-79] years vs median age: 67 [41-81] years, $P = .042$). Body mass index values and presence of DM, HT, smoking, dyslipidemia, previous history of CAD, medication history, and family history of CAD were not significantly different between the groups ($P > .05$). The symptom time interval was significantly higher in the CTO^+ group compared to the CTO^- group ($P = .046$). There were no significant differences between the groups according to Fontaine staging ($P = .071$). Although CLI was higher in CTO^+ group compared to the CTO^- group, this difference was not statistically significant (n = 25, 27.5% vs n = 28, 23.3%, $P = .49$).

The baseline laboratory characteristics of the study groups are presented in Table 2. The white blood cell count, hemoglobin, MCV, MCH, MCHC, platelet count, and MPV were not significantly different between the groups ($P > .05$). Patients with CTO had significantly higher RDW (median 17.0 [13.9-18.4] vs 15.7 [12.9-19.0], $P < .001$) and NLR (median 3.43 [1.95-4.68] vs 3.39 [1.76-4.46], $P = .036$) compared to patients without CTO.

The GFR, fasting glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, total cholesterol, aspartate amino transferase, and alanine amino transferase were not significantly different between the groups ($P > .05$). Albumin (median 3.9 [2.9-4.9] vs 3.7 [2.9-4.7] mg/dL, $P = .023$), total bilirubin (median 9.0 [0.94-18.94] vs 4.49 [0.96-16.80] μmol/L, $P < .001$), and direct bilirubin (median 2.27 [0.32-4.40] vs 1.93 [0.37-4.97] μmol/L, $P = .049$) were significantly lower in the patients with CTO compared to patients without CTO. Uric acid (median 7.3 [5.4-10.7] vs 6.7 [3.6-9.8] mg/dL, $P < .001$) and hsCRP (median 3.7 [1.4-17.2] vs 3.2 [1.0-16.1] mg/L, $P = .015$) were significantly higher in the CTO^+ group compared to the CTO^- group. Red cell distribution width, uric acid, and total bilirubin levels between 2 groups are shown in Figures 1, 2, and 3, respectively. The localizations of CTO and interventional procedures of the patients with CTO are shown in Table 3.

Multivariate and ROC Analyses

The independent predictors for CTO in the patients with PAD, including age, symptom time interval, RDW, NLR, albumin, hsCRP, uric acid, total bilirubin, and direct bilirubin were included in the multivariate logistic regression analysis. Red cell distribution width (OR: 1.998, 95% CI: 1.517-2.631; $P < .001$), uric acid (OR: 1.661, 95% CI: 1.260-2.215; $P = .001$), and total bilirubin (OR: 0.823, 95% CI: 0.759-0.894; $P < .001$) were independent predictors of CTO in patients with PAD (Table 4).

The cutoff value of uric acid, total bilirubin, and RDW for CTO were 7.6 mg/dL with a sensitivity of 45.1% and a

Table 2. Baseline Laboratory Characteristics of Study Groups.

Variables	CTO^-, n = 120	CTO^+, n = 91	*P* Value
White blood cell count, $\times 10^9$/L	6.9 (4.1-11.8)	7.7 (4.4-11.6)	.122
Hemoglobin, g/dL	14.3 (13.0-17.5)	14.4 (12.9-17.7)	.588
MCV, fL	92 (77-105)	92 (75-106)	.06
MCH, pg	31.0 (27.0-37.0)	32.0 (28.0-37.0)	.133
MCHC, g/dL	33 (31-36)	33 (32-37)	.387
Red cell distribution width (%)	15.7 (12.9-19.0)	17.0 (13.9-18.4)	<.01
Platelet count, $\times 10^9$/L	211 (152-447)	239 (157-365)	.12
Mean platelet volume, fL	8.7 ± 1.53	9.0 ± 1.28	.175
Neutrophil–lymphocyte ratio	3.39 (1.76-4.46)	3.43 (1.95-4.68)	.036
Fasting glucose, mg/dL	113 (69-277)	117 (75-250)	.06
GFR, mL/min/1.73m^2	88.0 (79.0-109.0)	87.0 (76.0-107.0)	.255
LDL-cholesterol, mg/dL	120.6 (57.0-231.6)	121.0 (61.0-194.0)	.549
HDL-cholesterol, mg/dL	37 (28-51)	36 (28-50)	.081
Triglyceride, mg/dL	151 (59-397)	157 (69-364)	.092
Total cholesterol, mg/dL	191 (140-307)	197 (132-303)	.455
Aspartate amino transferase, u/L	26 (12-36)	27 (13-35)	.281
Alanine amino transferase, u/L	25 (15-34)	26 (18-35)	.136
Albumin, mg/dL	3.9 (2.9-4.9)	3.7 (2.9-4.7)	.024
Total bilirubin, μmol/L	9.0 (0.94-18.94)	4.49 (0.96-16.80)	<.001
Direct bilirubin, μmol/L	2.27 (0.32-4.40)	1.93 (0.37-4.97)	.049
Uric acid, mg/dL	6.7 (3.6-9.8)	7.3 (5.4-10.7)	<.001
hsCRP, mg/L	3.2 (1.0-16.1)	3.7 (1.4-17.2)	.015

Abbreviations: CTO, chronic total occlusion; GFR, glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume.

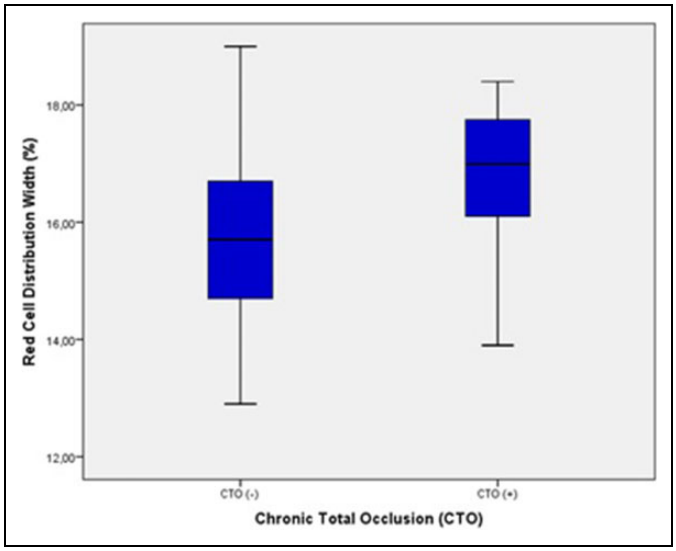

Figure 1. Red cell distribution width values between in patients with and without chronic total occlusion (CTO) groups.

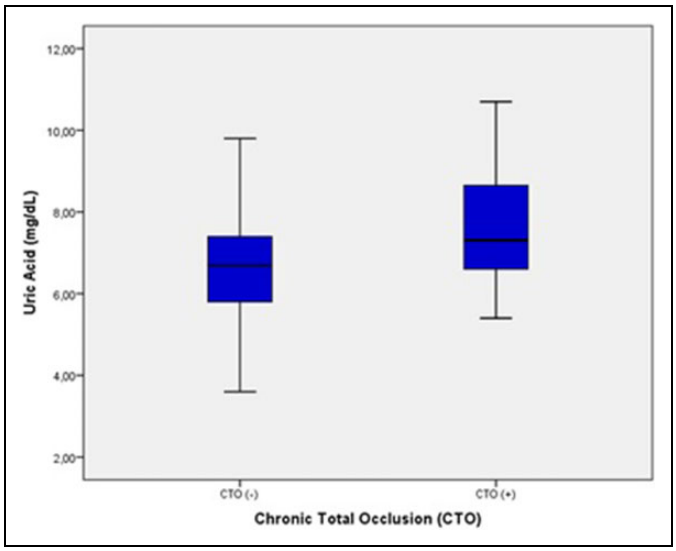

Figure 2. Uric acid values between in patients with and without chronic total occlusion (CTO) groups.

specificity of 80.8% (area under curve [AUC], 0.673; 95% CI, 0.605-0.736; $P < .001$), 8.8 μmol/L with a sensitivity of 81.3% and a specificity of 52.5% (AUC, 0.715; 95% CI, 0.649-0.775; $P < .001$), and 16% with a sensitivity of 80.2% and a specificity of 60.5% (AUC, 0.726; 95% CI, 0.661-0.785; $P < .001$) in the ROC curve analysis, shown in Figure 4 and Table 5, respectively.

Discussion

Our results showed that RDW, uric acid, and total bilirubin levels were independent predictors of CTO in patients with PAD. To the best of our knowledge, this is the first study to demonstrate the determinants of CTO in patients with PAD.

Red cell distribution width is an indicator of the variability in the size of circulating erythrocytes; it is an easily measurable complete blood count parameter.[8] It was considered that inflammation disrupts erythrocyte membrane and causes changes in erythrocyte maturation, resulting in an increase in RDW. Also, a correlation was shown between RDW and inflammatory indicators, including CRP and the erythrocyte sedimentation rate.[9,10] Previous studies have shown that RDW is associated with cardiovascular diseases including acute myocardial infarction, heart failure, and PAD; it has also been reported that RDW is an indicator of morbidity and mortality.[11,12] Ye et al showed that a 1% increment in RDW was associated with a 10% greater risk of all-cause mortality, and they have reported that RDW was an independent prognostic marker in patients with PAD.[13] Zalawadiya et al showed that RDW is a strong predictor of the future cardiovascular events.[14] Similarly, in our study, RDW proved to be an independent predictor, indicating CTO in patients with PAD.

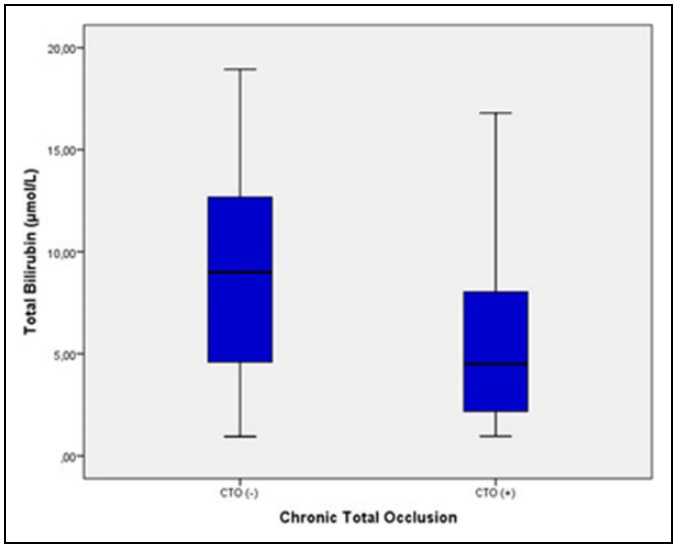

Figure 3. Total bilirubin values between in patients with and without chronic total occlusion (CTO) groups.

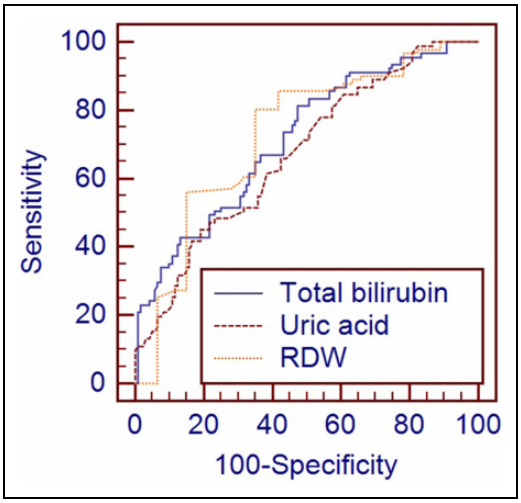

Figure 4. The receiver–operating characteristic (ROC) curves of red cell distribution width, uric acid, and total bilirubin for predicting chronic total occlusion.

Table 3. The Localizations and Interventional Procedures of Chronic Total Occlusion.

Variables	CTO^{+}
The localizations of chronic total occlusion, n (%)	
Iliac stenosis, n (%)	23 (25.3)
SFA stenosis, n (%)	49 (53.8)
Popliteal stenosis, n (%)	11 (12.1)
Infrapopliteal stenosis, n (%)	8 (8.8)
Interventional procedures	
Vascular surgery, n (%)	24 (26.4)
Angioplasty/stenting, n (%)	59 (64.8)
Conservative, n (%)	8 (8.8)

Abbreviations: CTO, chronic total occlusion; SFA, superficial femoral artery.

Table 4. Multiple Logistic Regression Analyses Investigating the Effect of Variables on CTO.

Variables	Multivariate OR (95% CI)	*P* Value
Age, years	0.991 (0.952-1.031)	.658
Symptom time interval, months	1.031 (0.997-1.067)	.076
Red cell distribution width, %	1.998 (1.517-2.631)	<.001
Neutrophil–lymphocyte ratio	0.620 (0.220-1.745)	.365
Albumin, mg/dL	0.785 (0.344-1.791)	.565
hsCRP, mg/L	1.050 (0.950-1.160)	.338
Uric acid, mg/dL	1.661 (1.260-2.215)	.001
Total bilirubin, µmol/L	0.823 (0.759-0.894)	<.001
Direct bilirubin, µmol/L	0.720 (0.513-1.012)	.058

Abbreviations: CI, confidence interval; CTO, chronic total occlusion; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

Table 5. Comparison of ROC Curves of Uric Acid, Total Bilirubin, and RDW in Prediction of CTO.

	AUC	95% CI	Sensitivity, %	Specificity, %
Uric acid (>7.6 mg/dL)	0.673	0.605-0.736	45.1	80.8
Total bilirubin (<8.8 µmol/L)	0.715	0.649-0.775	81.3	52.5
RDW (>16%)	0.726	0.661-0.785	80.2	60.5

Abbreviations: AUC, area under curve; CI, confidence level; CTO, chronic total occlusion; RDW, red cell distribution width; ROC, receiver–operating characteristic.

High serum uric acid levels are frequently seen in patients with cardiovascular disease, and hyperuricemia may be predictive of an adverse outcome. The positive association of hyperuricemia with obesity, impaired glucose tolerance, HT, and history of heart disease was observed on a large Finland cohort population (aged 40-69).[15] Lifestyle and diet play a role in serum uric acid levels. Epidemiological and research studies have supported this evidence. Recently, new research has shown associations between vitamin C, alcohol, coffee, tea, milk, and yogurt with uric acid.[16]

A damaged or dysfunctional endothelium is the triggering factor in the initiation of vascular atherogenesis.[17,18] Endothelial dysfunction impairs the anticoagulant and anti-inflammatory effects of healthy endothelial cells and leads to progression of atherosclerosis. Additionally, it is a predictor of cardiac events in patients with cardiovascular diseases. The increase in serum uric acid levels contributes to oxidative stress, endothelial dysfunction, and smooth muscle cell proliferation; it is also closely associated with unfavorable cardiovascular events and mortality.[19-21] In patients with high serum uric acid levels, markers indicating endothelial dysfunction were also high.[22] Akpek et al determined that high uric acid level measured at the time of admission in patients with acute myocardial infarction who had undergone primary percutaneous coronary intervention was the predictor of reduced coronary flow and in-hospital major adverse cardiac events.[23] Kurtul et al showed that serum uric acid level was an

independent predictor of CTO in the nonculprit artery in patients with acute coronary syndrome.[24] Shankar et al showed that high uric acid levels were associated with PAD.[25] In our study, high uric acid level was an independent predictor for the presence of CTO in patients with PAD.

Oxidative stress and inflammation are present in the pathogenesis of atherosclerosis.[26-28] Bilirubin has antioxidant properties under normal physiological conditions and suppresses inflammation in the blood vessels.[29,30] Bilirubin inhibits lipid peroxidation, which is effective in the onset and progression of atherosclerosis.[31] Additionally, bilirubin has a cytoprotectant functionality.[32] A low bilirubin concentration is a predictor of current or future cardiovascular events.[33-37] It has been shown that a 50% decrease in serum bilirubin concentrations leads to a 47% increased risk of CAD.[38] It has been found that CAD was more serious and extensive in patients with low bilirubin levels.[39] Also, low bilirubin levels are associated with increased cardiovascular risk in patients with familial or nonfamilial hypercholesterolemia.[40,41] Breimer et al reported is a U-shaped relationship between serum bilirubin concentration and ischemic heart disease.[42] Perlstein et al reported a relation between high bilirubin concentration and reduced PAD prevalence.[43] In the observational cohort study by Wang et al, bilirubin levels were lower in patients with Fontaine stage IV.[44] Those researchers concluded that there is a negative correlation between the low serum bilirubin levels and the severity of PAD.[44] Krijgsman et al showed that low serum bilirubin and albumin levels were associated with the presence of vascular disease.[45] In our study, low bilirubin level was an independent predictor that indicated CTO in patients with PAD. Total bilirubin may be used as a cardiac marker for predicting CTO in PAD at a cutoff level of 8.8 μmol/L with 81.3% sensitivity and 52.5% specificity. Despite the favorable data in cross-sectional studies,[33-38,46,47] prospective studies failed to demonstrate a linear association between bilirubin and cardiovascular events.[40,48] Therefore, controversy exists regarding the association between bilirubin and cardiovascular disease. Although our results do not implicate causality due to cross-sectional design, we added additional information to the medical literature.

Neutrophil–lymphocyte ratio is an inexpensive and readily available indicator, which reflects the severity and extension of systemic inflammation and atherosclerosis.[49,50] The relation of elevated NLR with higher mortality and morbidity in patients with severe PAD including CLI has been shown in recent studies.[51] Neutrophil–lymphocyte ratio is a significant novel biomarker, which singles out individuals at risk of future major cardiovascular events.[52,53] Erturk et al demonstrated that an increased NLR was related to higher cardiovascular mortality in patients with PAD who were admitted with CLI or intermittent claudication.[54] In our study, patients with CTO had significantly higher NLR compared to patients without CTO.

An endovascular approach is widely applied in the treatment of CTOs of the lower extremity arteries. In the treatment of CTO lesions, experienced endovascular specialists spend more time and labor for CTO^+ patients compared to CTO^- patients; thus, CTO^+ patients and interventional physicians are exposed to higher levels of radiation. Also, passing the CTO and maintaining distal flow can be more challenging compared to lesions with no total occlusion. Therefore, CTO should be considered in patients with PAD with increased RDW and uric acid levels and reduced total bilirubin levels. The patients with PAD who have higher RDW, uric acid, and lower total bilirubin values may benefit from aggressive antithrombotic therapy, statins, and changes in their lifestyles such as giving up smoking, regular physical activity, and losing weight.

The number of patients is a limitation of the current study. Additionally, as the study was cross-sectional, no analyses related to long-term events were performed. As our study was not prospective controlled, cause and effect relationships could not be based on the findings. The single measurement of the hematological and biochemical parameters is another limitation.

This study determined that increased RDW, uric acid levels, and lower total bilirubin levels were independent predictors of CTO in patients with PAD. These markers are indicative in the pathogenesis of CTO. Determination of the RDW, uric acid, and total bilirubin levels may be helpful for the stratification of risk in patients with PAD.

Authors' Note

H. Hamur, E. M. Bakirci, H. Degirmenci, and O. A. Onk conceived and designed the study. H. Hamur, O. A. Onk, E. M. Bakirci, H. Degirmenci, Z. Kucuksu, and E. Vuruskan were responsible for the data collection. H. Duman, M. Buyuklu, and E. Topal were responsible for data analysis and interpretation. H. Hamur, H. Duman, E. M. Bakirci, and E. Topal were responsible for the statistical analyses. H. Hamur, H. Degirmenci, and E. Vuruskan were responsible for the manuscript writing. All authors approved the final version of the text.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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