The Relationship between Coronary Collateral Circulation and Neutrophil/Lymphocyte Ratio in Patients with Coronary Chronic Total Occlusion

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Abstract

Objectives: To investigate the relationship between neutrophil/lymphocyte ratio (NLR) and coronary collateral circulation (CCC) in patients with coronary chronic total occlusion. *Subjects and Methods:* Our study population consisted of 275 consecutive patients with chronic total occlusion. One hundred and thirty-eight patients with chronic total occlusion were included in the study. They were classified into 2 groups as follows: impaired CCC (group 1: Rentrop grades 0–1) and good CCC (group 2: Rentrop grades 2–3). The NLR was calculated from the complete blood count. *Results:* The NLR values of the patients with impaired CCC (4.5 ± 0.7) were significantly higher than of those with good CCC (2.7 ± 0.6, p < 0.001). In the multivariate logistic regression test, NLR (OR 33.36, 95% CI 8.189–135.7, p < 0.001), high-sensitivity C-reactive protein (hs-CRP; OR 2.152, 95% CI 1.226–3.777, p = 0.008), estimated glomerular filtration rate (OR 1.167, 95% CI 1.049–1.298, p = 0.004) and systolic blood pressure (OR 1.068, 95% CI 1.009–1.1310, p = 0.025) were independent predictors of impaired CCC. The NLR value >3.55 yielded an area under the curve value of 0.957 (95% CI 0.921–0.992, p < 0.001) and demonstrated a sensitivity of 95% and a specificity of 90% for the prediction of CCC. A moderate correlation between NLR and hs-CRP was observed (r = 0.443; p < 0.001). *Conclusion:* Our findings reveal that NLR correlates with the impaired development of coronary collaterals.

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Introduction

Coronary collateral circulation (CCC) is the adaptation of the heart to ischemia, which develops in order to maintain tissue perfusion [1]. In normal individuals, coronary collaterals exist between the large coronary arteries, but these cannot be visualized on coronary angiography because they carry an insignificant volume of blood [2, 3]. It is generally accepted that their active functioning is directly linked to the occurrence of severe and recurrent ischemia, but some studies indicate that other factors may also influence their development. Impaired development of collaterals resulting from the increase in acute-phase reactants, e.g. C-reactive protein (CRP), indicates the role of inflammation in this process [4].

It is well known that leukocyte activation occurs during an inflammatory reaction. Moreover, leukocytes are in-

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volved in atherogenesis and thrombus formation. Along with a high number of leukocytes, there is a significant relationship between the neutrophil/lymphocyte ratio (NLR) and the severity and prognosis of cardiovascular disease [5]. To date, the relationship between NLR and CCC in patients with chronic total occlusion has not been investigated. Our aim was to investigate this relationship.

Subjects and Methods

Study Population

The study was approved by the Institutional Ethics Committee, and all patients signed an informed consent form. Four hundred and seventy-five patients with stable angina pectoris, with objective signs of ischemia, underwent coronary angiography at the State Hospital in Hatay, Turkey. Patients were excluded who had a coronary angiogram showing a lesion of <100% diameter (n = 266), active and ongoing infection (n = 12), chronic inflammatory disease (n = 4) or a history of percutaneous coronary intervention (n = 37) or coronary artery bypass grafting (n = 18). Hence, 138 patients (78 males and 60 females) were included in the study.

The clinical risk factors of the patients, such as age, gender, hypertension, diabetes, a history of hyperlipidemia, smoking status and family history, were noted. Furthermore, upon admission, each patient was evaluated for blood pressure (BP), heart rate, previously used drugs, the presence of preinfarction angina, high-sensitivity (hs)-CRP, serum creatinine, blood glucose, lipid profile and hematologic indices. Prior to the coronary angiography, each patient underwent transthoracic echocardiography using the biplane Simpson's method, and left ventricular ejection fraction (LVEF) was measured. Hematologic indices, such as levels of hemoglobin, white blood cells, neutrophils and lymphocytes as well as mean platelet volume and platelet counts, were measured as part of the automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Galway, Ireland). Hypertension was defined as a systolic pressure >140 mm Hg and/or a diastolic pressure >90 mm Hg on at least 2 occasions, or if the individual was on antihypertensive medication. The diagnosis of diabetes mellitus was based on a previous history of diabetes treated with or without drug therapies. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Modification of Diet in Renal Disease Study equation.

Coronary Angiography

Quantitative coronary angiography was performed using the standard Judkins technique via the transfemoral route. Coronary chronic total occlusion is characterized by a heavy burden of atherosclerotic plaque, resulting in complete occlusion of the artery for >3 months [6]. CCC was graded according to the Rentrop classification [7] 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. In patients with more than one coronary lesion, when there was more than one coronary collateral, the one with the highest Rentrop grade was used. The patients were classified into 2 groups: those with impaired CCC (group 1: Rentrop

Table 1. Baseline characteristics according to CCC

Variables	Group 1 (n = 66)	Group 2 (n = 72)	p value
Age, years	60±9.2	59.6±7.4	0.760
Male, %	52.6	61.7	0.285
Diabetes, %	35	16.7	0.013
Hypertension	38.3	20.5	0.021
Smoking, %	20.5	18.3	0.749
Family history of CAD, %	21.8	18.3	0.616
Systolic BP, mm Hg	152±19	143±15	0.001
Diastolic BP, mm Hg	84±10	83±14	0.833
LVEF, %	42.6±7	48.1±7.8	<0.001
WBC count, ×10³/μl	9.5±3.7	9±3.1	0.532
Platelet count, ×10³/μl	255±78	270±88	0.339
Mean platelet volume, fl	8.1±1.0	8.0±1.2	0.821
NLR	4.5±0.7	2.7±0.6	<0.001
Blood glucose, mg/dl	145±64	149±69	0.735
eGFR, ml/min/1.73 m²	80.8±6.5	89.9±9.9	<0.001
LDL-cholesterol, mg/dl	123±29	120±34	0.581
HDL-cholesterol, mg/dl	36±9	37±7	0.703
Triglyceride, mg/dl	155±40	150±48	0.123
hs-CRP, mg/l	4±1.9	3±1.3	0.001
Previous medications			
Aspirin	26.9	35	0.307
Statins	23.1	21.7	0.844
ACE inhibitors/ARB	32.1	35	0.716
Beta-blockers	33.3	30	0.677
Calcium-channel blockers	25.6	18.3	0.308
Multivessel disease	50	46.7	0.698

ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; WBC = white blood cell.

grades 0–1; n = 66) or those with good CCC (group 2: Rentrop grades 2–3; n = 72). Multivessel disease was defined as the presence of a lesion in two or more major epicardial arteries.

Statistical Analysis

Continuous variables are expressed as a mean ± standard deviation, whereas categorical variables are expressed as a percentage. Comparisons between the 2 groups were made by using the Student t test, the Mann-Whitney U test or the χ^2 test, as appropriate. Comparisons between Rentrop grades were made using the analysis of variance, and the Tukey HSD test was chosen as a post hoc test. Multiple logistic regression analysis was performed to identify the independent predictors of CCC using variables showing marginal association with it on univariate testing (p < 0.10). Receiver operating characteristic (ROC) analysis was used to detect the cutoff value of NLR in the prediction of CCC. Correlation analysis between variables was performed using the Pearson or the Spearman correlation. A p value of <0.05 was considered significant. All statistical analyses were carried out using SPSS 17.0 for Windows (SPSS Inc., Chicago, Ill., USA).
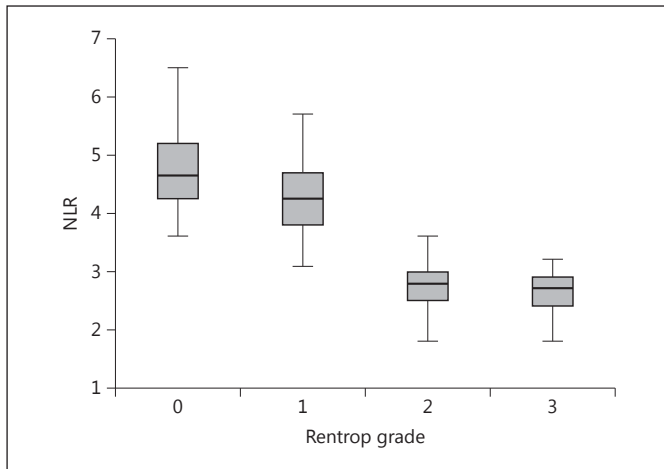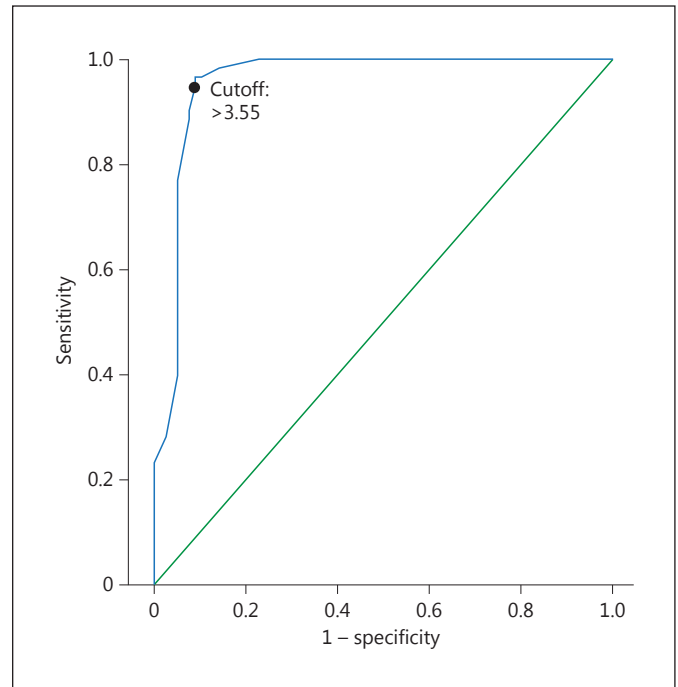
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Fig. 1. NLR values according to Rentrop grades.

Results

The mean age of 138 patients with chronic total occlusion was 59.8 ± 8.4 years (range 38–74). A comparison of group 1 and group 2 relative to baseline characteristics is shown in table 1. Patients with impaired CCC exhibited a higher frequency of diabetes, hypertension, systolic BP, NLR and hs-CRP as well as a lower eGFR and LVEF than patients with good CCC. Fasting blood glucose levels (145 ± 64 vs. 149 ± 69 mg/dl) and mean platelet volumes (8.1 ± 1.0 vs. 8.0 ± 1.2 fl) were comparable between the groups.

The patients with impaired CCC manifested significantly higher NLR values than those with good CCC (4.5 ± 0.7 vs. 2.7 ± 0.6, $p < 0.001$). While these values were lower in Rentrop grade 1 patients than in grade 0 patients (4.3 ± 0.7 vs. 4.7 ± 0.7, $p = 0.019$), there was no difference between Rentrop grade 2 and grade 3 patients (2.7 ± 0.5 vs. 2.8 ± 0.6, $p = 0.901$; fig. 1).

Univariate analysis found the following variables to be significant: age, sex, diabetes, hs-CRP, NLR, eGFR, systolic BP and LVEF. The multivariate logistic regression analysis showed that NLR (OR 33.36, 95% CI 8.189–135.7, $p < 0.001$) and systolic BP (OR 1.068, 95% CI 1.009–1.131, $p = 0.024$) were independent predictors of impaired CCC (table 2). Discriminative accuracy of the analysis without including NLR (–2 log likelihood: 129.2, Cox and Snell R^2: 0.351 and Nagelkerke's R^2: 0.471) was significantly lower when compared to the analysis with incorporation of the NLR (–2 log likelihood: 49.9, Cox and Snell R^2: 0.635 and Nagelkerke's R^2: 0.851). ROC curve analysis was performed to detect the best cutoff value of the NLR in the prediction of impaired CCC. An NLR value of >3.55 yielded an area under the curve value of 0.957 (95% CI 0.921–0.992, $p < 0.001$) and demonstrated a sensitivity of 95% and a specificity of 90% for the prediction of CCC (fig. 2). Correlation analysis revealed a moderate correlation between NLR and hs-CRP ($r = 0.443$; $p < 0.001$).

Discussion

Our findings revealed that a higher NLR was associated with impaired CCC. The small vascular structures between the epicardial coronary arteries in a normal human heart cannot be visualized on normal angiography due to the very small volume of blood flowing inside them [2, 3]. However, the development of a stenosis in the epicardial coronary arteries leading to ischemia causes a pressure gradient within the collaterals which increases the blood flow within the collateral arteries and, consequently, the collaterals may become visible on angiography [8]. The development of CCC occurs as a result of angiogenesis (new vessel formation) and/or arteriogenesis (the growth of preexisting arterioles) [9]. Many factors may affect the development of CCC, such as the severity/ rate of progression of coronary stenosis, diabetes, hyper-

Table 2. Multivariate logistic regression analysis to detect the independent predictors of impaired coronary collateral circulation

Variables	Univariate OR (95% CI)	Univariate p value	Multivariate OR (95% CI)	Multivariate p value
Age	0.994 (0.955–1.034)	0.760	1.083 (0.948–1.237)	0.242
Sex	0.689 (0.374–1.310)	0.285	0.804 (0.146–4.439)	0.803
Diabetes	2.692 (1.213–5.977)	0.013	0.620 (0.072–5.135)	0.662
Hypertension	2.409 (1.130–5.135)	0.021	0.654 (0.089–4.795)	0.676
LVEF	0.906 (0.860–0.954)	<0.001	0.943 (0.823–1.081)	0.401
Systolic BP	1.034 (1.012–1.056)	0.001	1.068 (1.009–1.131)	0.024
NLR	24.19 (8.915–65.65)	<0.001	33.36 (8.189–135.7)	<0.001
eGFR	0.923 (0.880–0.967)	<0.001	0.967 (0.897–1.041)	0.371
hs-CRP	1.795 (1.346–2.393)	0.001	1.946 (0.861–4.397)	0.110

tension, smoking status, endothelial dysfunction, exercise, endogenous mediators, oxidative stress and certain drugs [10]. The development of CCC in acute coronary syndromes has been shown to be associated with a better myocardial perfusion and ventricular function as well as a lower incidence of adverse cardiovascular events in the long term [11–13]. During CCC development, many endogenous mediators such as growth factors, vascular endothelial growth factor, nitric oxide and inflammatory and neurohumoral markers are involved along with endothelial dysfunction. Moreover, proinflammatory enzymes and cytokines secreted from the inflammatory cells are considered to play a role in the development of collaterals. CRP was demonstrated to inhibit the production of nitric oxide and angiogenesis [14].

NLRs calculated from leukocyte subtypes have been accepted as being markers of inflammation in cardiovascular diseases [5]. Neutrophils are the first elements of inflammation in the injured myocardium and they play a major role in thrombotic and inflammatory processes. They are involved in the inflammatory response (when a significant increase in their numbers is observed) while lymphocytes play a role in the specific immune response. A correlation has been shown between the neutrophil count and reduced ejection fraction and infarction expansion [15]. It has been suggested that the decreased lymphocyte count in inflammation might be related to the increased level of steroids (cortisol) in relation to stress and increased apoptosis [16]. A decreased lymphocyte count indicates a poor outcome in acute coronary syndrome [17, 18]. The NLR is considered more effective than the leukocyte count in predicting increased cardiovascular risk [5]. Horne et al. [5] reported that while white blood cell count is an independent predictor of death/

myocardial infarction, NLR has a greater predictive value. Many studies have shown that inflammation plays a major role in both the initial phase and the progression of atherosclerosis [19, 20]. A link between inflammatory cytokines and collateral development has been discovered [9]. Along with endothelial dysfunction, cytokines such as TNF-α and IL-6 have been found to be predictors of poor collateral development. Moreover, many studies show that higher hs-CRP concentrations are associated with insufficient CCC development [21, 22]. Our findings confirm these observations. Whether it is the cause or the effect, NLR is associated with impaired development of CCC in chronic total occlusion patients. This suggests that the determination of NLR might be helpful in the detection of high-risk patients.

The limitations of this study include the relatively small sample size and the lack of data on other plasma markers involved in the pathophysiology of impaired CCC, such as vascular endothelial growth factor, nitric oxide and TNF-α. In addition, this was a cross-sectional study, so no follow-up was conducted.

Conclusion

This study has shown that a high NLR was associated with impaired CCC in patients with coronary chronic total occlusion. Further studies are needed to investigate the cause and effect relationship between NLR and CCC.

Disclosure Statement

The authors have no conflicts of interest to declare.

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