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Atherosclerosis

Predictive Value of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio in Patients with Coronary Slow Flow

Mustafa Çetin,[1] Emrullah Kiziltunc,[1] Özgül Uçar Elalmış,[1] Zehra Güven Çetin,[1] Muhammed Bora Demirçelik,[2] Hülya Çiçekçioğlu,[1] Alparslan Kurtul,[3] Selçuk Özkan,[4] Candan Mansuroğlu Avan,[1] Ender Örnek[1] and Feridun Vasfi Ulusoy[1]

Background: Increased microvascular resistance due to chronic inflammation is assumed to be one of the mechanisms associated with coronary slow flow (CSF). Previous studies have shown that the platelet-to-lymphocyte ratio (PLR) and the neutrophil-lymphocyte ratio (NLR) are markers of inflammation for various diseases. In this study we aimed to evaluate the relationship between CSF and PLR-NLR.

Methods: Seventy-eight patients with CSF and 50 patients with normal coronary flow were enrolled into this study. The study subjects underwent medical examination and testing, after which their platelet-to-lymphocyte ratios and NLR values were calculated. An independent observer measured the coronary flow rate by Thrombolysis in Myocardial Infarction Frame Count (TFC) method. The platelet-to-lymphocyte ratio and NLR values were compared between the groups and correlation analysis was performed to explore the relationship between mean TFC with PLR and NLR.

Results: Platelet-to-lymphocyte ratio and NLR values were significantly higher in patients with CSF ($p < 0.001$). There was a positive significant correlation between TFC with NLR and PLR (Spearman's Rho: 0.59, $p < 0.001$ and Spearman's Rho: 0.30, $p = 0.001$, respectively). Multivariate logistic regression analysis revealed that NLR is the one independent predictor for CSF.

Conclusions: This study demonstrated an association between CSF and PLR-NLR. Although the exact mechanism could not be explained, our findings support the possible role of inflammation in CSF physiopathology.

Key Words: Coronary slow flow • Inflammation • Neutrophil lymphocyte ratio • Platelet lymphocyte ratio

INTRODUCTION

Coronary slow flow (CSF) phenomenon is characterized by late opacification of the distal vascular bed during coronary angiography in normal or near normal coronary arteries. Thrombolysis in Myocardial Infarction Frame Count (TFC) can be used to obtain a more objective diagnosis, and a TFC value greater than two standard deviations from the normal published TFC value for a vessel can be defined as CSF.[1] However, a definite and reliable mechanism of CSF is still not known. Small coronary artery disease,[2] increased resting coronary vasomotor tone,[3] endothelial dysfunction,[4,5] platelet function disorder[6] and diffuse atherosclerosis[7] are the proposed mechanisms for CSF phenomenon. Recent studies have shed light to the role of inflammation, and currently CSF is suggested to be the result of coronary

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[1]Department of Cardiology, Ankara Numune Education and Research Hospital; [2]Department of Cardiology, Turgut Özal University School of Medicine; [3]Department of Cardiology, Ankara Education and Research Hospital; [4]Department of Cardiology, Ankara Keçiören Education and Research Hospital.
Address correspondence and reprint requests to: Dr. Mustafa Çetin, Bağcı Caddesi, No. 98, A blok – Daire 35, 06020, Etlik/Ankara/Turkey. Tel: 00905057793535; E-mail: mdmustafacetin@yahoo.com

microvascular changes due to chronic inflammation.

As the span of medical knowledge has increased, it has been understood that chronic inflammation plays a crucial role in many cardiovascular diseases, especially in atherosclerosis. The ratio of peripheral blood cells are affected by inflammatory status. An increased platelet count and PLR, as well as NLR are significant markers of inflammation and PLR is a predictor for mortality in various diseases.[8-12]

As inflammation is thought to be an important underlying mechanism for CSF and PLR-NLR, and can be used as a marker of inflammation for various diseases, we aimed to evaluate the relationship between CSF and PLR-NLR.

MATERIALS AND METHODS

A total of 128 patients who underwent coronary angiography with indications of positive stress tests (exercise electrocardiography or myocardial perfusion scintigraphy), unstable angina pectoris or typical chest pain with 3 or more cardiovascular risk factors were enrolled. Risk factors for coronary artery disease, hemogram parameters, serum biochemistry parameters, lipid parameters, body mass index and past medications were recorded. Thereafter, the platelet-to-lymphocyte ratio and NLR values were calculated. Patients with coronary ectasia, coronary calcification, coronary plaque and significant atherosclerotic lesion were excluded from the study. Patients with heart failure, cardiomyopathy (dilated, hypertrophic or restrictive), significant valvular disease, abnormal hepatic and renal functions, active infection, chronic inflammatory disease, chronic obstructive pulmonary disease and malignancy were also excluded.

Coronary angiography and determination of slow coronary flow

Coronary angiography was performed on all patients utilizing the standard Judkins technique via the femoral approach. Patient coronary arteries were visualized in the right and left oblique planes with cranial and caudal angulations and recorded at a film rate of 30 frames/second. An independent, experienced observer who was blinded to the study reviewed the coronary angiograms and coronary flow rates which had been calculated using the TFC method.[1] In this method, the number of cine frames, recorded at 30 frames/s, required for the contrast to reach standard distal coronary landmarks in the left anterior descending (LAD), left circumflex (LCx) and right coronary arteries (RCA) were measured. Predefined distal landmarks are the distal bifurcation for the LAD, commonly referred to as the 'pitchfork' or 'whale's tail', the distal bifurcation of the segment with the longest total distance for the LCx, and the first branch of the posterolateral artery for the RCA. Normal TFC values are 36.2 ± 2.6 frames for LAD, 22.2 ± 4.1 frames for LCx, and 20.4 ± 3.0 frames for RCA.[1,13] As the LAD is usually longer than the other major coronary arteries, TIMI frame count for this vessel is often higher. Therefore, the TFC for LAD was divided by 1.7 to obtain the corrected TFC (cTFC). The standard cTFC for LAD is 21.1 ± 1.5 frames. Mean value of frame counts of LAD, LCx and RCA was accepted as the mean TFC value. Any TFC value greater than two standard deviations from the normal published value in the literature was accepted as CSF.

Statistical analysis

Statistical analysis were performed using the SPSS software version 17. The univariate analysis to identify variables associated with slow flow was investigated using Chi-square, student's t and Mann-Whitney U tests where appropriate. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the logistic regression analysis to determine independent predictors of slow flow. While investigating the association between non-normally distributed variables, the correlation coefficients and their significance were calculated using the Spearman test. A 5% type-I error level was used to infer statistical significance.

RESULTS

Baseline characteristics of the groups are shown in Table 1. Seventy-eight patients had CSF. The mean TFC value and TFC values for all three coronary arteries were significantly higher in the CSF group than in the normal coronary flow group. Upon univariate analysis, PLR and

Table 1. Baseline characteristics of study population

Variables	Overall (N = 128)	Slow flow (n = 78)	Normal flow (n = 50)	p
Age, years (mean ± SD)	52.2 ± 9.3	52.7 ± 10.0	51.5 ± 8.1	0.49
Hyperlipidemia, n (%)	72 (56.3)	44 (56.4)	28 (56)	0.96
Hypertension, n (%)	62 (48.4)	37 (47.4)	25 (50)	0.77
Gender, male, n (%)	80 (62.5)	49 (62.8)	31 (62)	0.92
Diabetes mellitus, n (%)	16 (12.5)	11 (14.1)	5 (10)	0.49
Smoking, n (%)	80 (62.5)	52 (66.7)	28 (56)	0.22
Positive family history, n (%)	15 (11.7)	10 (12.8)	5 (10)	0.69
Beta blocker, n (%)	31 (24.2)	18 (23.1)	13 (26)	0.70
ACEI, n (%)	38 (29.7)	21 (26.9)	17 (34)	0.39
ARB, n (%)	16 (12.5)	10 (12.8)	6 (12)	0.89
CCB, n (%)	29 (22.7)	18 (23.1)	11 (22)	0.88
Statin, n (%)	37 (28.9)	18 (23.1)	19 (38)	0.06
Waist circumference	100 (94-108)	100 (94-110)	100 (93.7-107.0)	0.38
Systolic blood pressure, mmHg, (median-IQR)	130 (120-137.75)	130 (120-137.25)	128.5 (120.0-140.0)	0.50
Diastolic blood pressure, mmHg, (median-IQR)	80 (70-85)	80 (70-86.25)	77 (70-85)	0.19
Fasting blood glucose, mg/dl(median-IQR)	85 (79.2-97)	85 (78-97)	86 (80-97)	0.51
Total cholesterol, (median-IQR)	183.5 (170-207)	184 (168.5-207.5)	182 (168.5-205)	0.77
LDL-C, mg/dl (median-IQR)	121.5 (102-138)	103.5 (81.2-126.5)	121 (106.5-1136.5)	0.98
HDL-C, mg/dl (median-IQR)	37 (32-40)	36.5 (30.0-42.2)	37 (33-39.2)	0.91
Triglyceride, mg/dl (median-IQR)	135 (111-188)	145.5 (105-202.5)	129.5 (113-176.7)	0.95
Hb, g/dl (mean ± SD)	14.6 ± 1.4	14.7 ± 1.6	14.6 ± 1.0	0.66
Plt, $x10^3/mm^3$ (mean ± SD)	239.7 ± 51.3	241.6 ± 51.3	238.8 ± 51.5	0.60
Htc, %(mean ± SD)	43.0 (40.8-45.8)	43.0 (41.0-46.0)	43 (40.6-45.4)	0.49
Corrected TFC value (LAD)	40 (24-42)	42.0 (40.0-43.0)	23 (22-24)	< 0.001
TFC value (LCx)	38 (21-41)	41 (39-42)	20 (18.7-22.0)	< 0.001
TFC value (RCA)	37 (21-38)	38 (37-38)	21 (19-22)	< 0.001
TFC value(mean)	38.3 (21.6-40.3)	40.3 (38.6-41.0)	21 (20.6-22.6)	< 0.001
Platelet/lymphocyte ratio	111.5 (82.0-145.6)	124.5 (94.2-158.1)	99.2 (74.4-116.6)	< 0.001
Neutrophil/lymphocyte ratio	1.75 (1.40-2.50)	2.19 (1.66-3.08)	1.42 (1.24-1.66)	< 0.001

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Hb, hemoglobin; HDL-C, high density lipoprotein cholesterol; Htc, hematocrit; IQR, interquartile range 25-75; LAD, left anterior descending artery; LCx, left circumflex artery; LDL-C, low density lipoprotein cholesterol; RCA, right coronary artery; SD, standard deviation; TFC, thrombolysis in myocardial infarction frame count.

NLR were significantly higher in the CSF group (Figure 1, p < 0.001). Statin use was higher in normal coronary flow group, but insignificantly so (38% vs 23.1% p = 0.06). Multivariate logistic regression analysis revealed that NLR is an independent predictor of CSF (Table 2).

We made a correlation analysis to exhibit the nature of the relationship between mean TFC value and NLR-PLR. We found a positive correlation between mean TFC value and NLR-PLR (Spearman's Rho: 0.59, p < 0.001 and Spearman's Rho: 0.30, p = 0.001, respectively).

DISCUSSION

The present study demonstrated that patients with CSF have significantly higher PLR and NLR than normal coronary flow patients. We found a positive correlation between mean TFC value and PLR-NLR; however, multiple logistic regression analysis indicated that only NLR is an independent predictor for CSF.

The definite physiopathological changes causing CSF are still not known. However, increased vasomotor tonus and microvascular resistance seem to be located at the center of CSF physiopathology. Mangieri et al. evaluated endomyocardial biopsy specimens of patients with CSF.[14] They observed patchy histopathological changes suggestive of small coronary artery disease, thickening of vessel walls with luminal size reduction, mitochondrial abnormalities, and glycogen content reduction. They also observed relief of CSF with dipyridamole infusion but

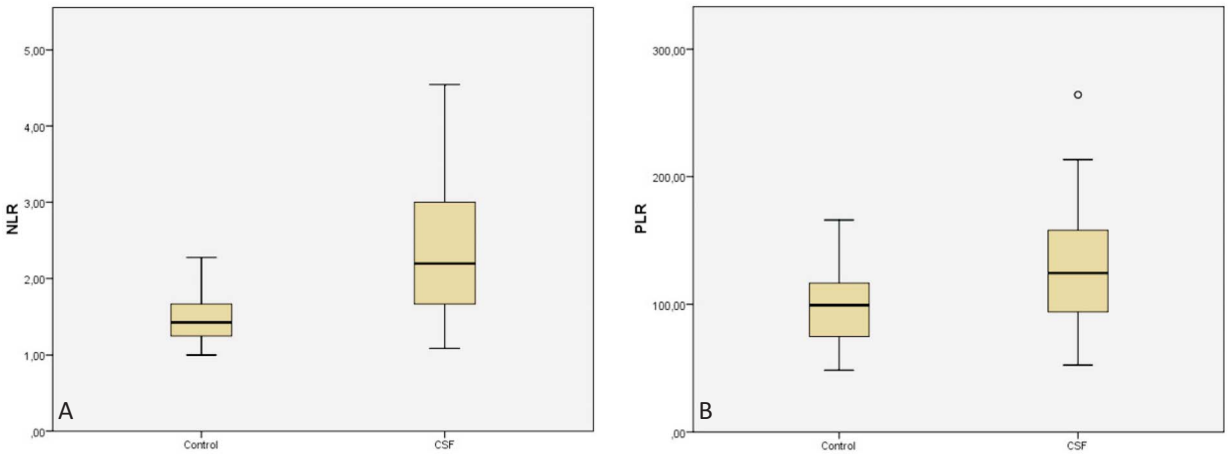

Figure 1. *Neutrophil lymphocyte ratio (A) and platelet lymphocyte ratio (B) in coronary slow flow and normal coronary flow patients.*

Table 2. Logistic regression analysis for coronary slow flow

Risk factor	OR (%95 CI)	p
Platelet/lymphocyte ratio	1.01 (0.99-1.03)	0.22
Neutrophil/lymphocyte ratio	0.03 (0.01-0.15)	< 0.001
Statin use	0.40 (0.15-1.10)	0.07

CI, confidence interval; OR, odds ratio.

not with nitroglycerine, which suggested that < 200 micrometer-sized vessels were associated with CSF. Fineschi et al. demonstrated that resting coronary microvascular resistance was increased in patients with CSF by invasive hemodynamic measurements.[15] They found that microvascular resistance was within normal limits during hyperemia.

Endothelial functions are impaired in many cardiovascular diseases, and similarly true in CSF as well. Deficiency regarding endothelium-dependent vasodilation has been postulated to be the cause of increased microvascular resistance in the CSF phenomenon. Sezgin et al. showed that endothelial function was impaired in people with CSF and TFC correlated well with endothelial dysfunction, which is determined by flow-mediated dilation of the brachial artery.[5] Endothelial dysfunction is the mainstay of atherosclerosis and many studies have exhibited the association between CSF and atherosclerotic risk factors. Camsari et al. showed the association between CSF and increased carotis intima media thickness.[16] In that study, they performed intravascular ultrasound on CSF patients and found that 88% of slow flow patients had extensive coronary calcification. TFC was significantly correlated with intimal thickness of carotid and coronary arteries. The relationship between CSF and novel biomarkers associated with endothelial dysfunction, including adiponectin,[17] homocysteine,[18] and endothelin[19] have been demonstrated in prior studies. In contrast to novel biomarkers, classical risk factors for atherosclerosis were similar between CSF patients and normal coronary flow patients in virtually all of the studies. In fact, only one study demonstrated higher low density lipoprotein, and total cholesterol levels in CSF patients.[20]

The role of chronic inflammation in cardiovascular disease is generally well-recognized. Studies evaluating inflammatory status in CSF have revealed the increased inflammatory status associated with this medical condition. Madak et al. demonstrated the association between high-sensitivity C-reactive protein and CSF.[21] Li et al. showed the positive correlation between interleukin 6 and TFC.[22] Serum soluble adhesion molecule levels were found to be significantly higher in patients with CSF by Turhan et al.[23] Peripheral blood cells are affected by inflammatory status. PLR, NLR, platelet distribution width, red cell distribution width, and mean platelet volume all can be derived from complete blood count easily and inexpensively. These parameters can be used as markers for inflammatory status, given the association between these parameters and various cardiovascular diseases where cardiovascular risk factors have been well-documented by numerous earlier studies. In a previous study, NLR was shown to be an independent predictor of CSF.[24] We found that both NLR and PLR were significantly elevated

in our study. We also found a significant correlation between TFC with NLR and PLR; however, NLR but not PLR is the independent predictor for CSF.

The definite underlying mechanism of CSF has not been fully elucidated. The most reliable hypothesis seems to be that CSF is caused by increased microvascular resistance induced by endothelial dysfunction due to chronic inflammation. Our study, and other available recent evidence in the literature, supports this hypothesis, as we have discussed in detail in these pages. Increased PLR, although not explaining the exact mechanism, provides some supporting evidence to the role of inflammation in the CSF phenomenon.

This study has a number of limitations. First, this was a single center and cross-sectional study in which only admission PLR and NLR values were calculated. Follow-up values of these parameters and their relation to clinical prognosis were not evaluated. Second, other parameters (C-reactive protein, interleukin 6, serum soluble adhesion molecule levels, etc.) as markers for inflammatory status and their association with PLR, NLR values and TFC values were not investigated. Lastly, low patient number was another limitation of our study, which could have an effect on the broader applicability of our conclusions.

CONCLUSIONS

We observed that PLR is significantly higher in patients with CSF, and there is a significant correlation between TFC values and PLR. These findings support evidence showing the role of inflammation in the pathogenesis of the CSF phenomenon. Thus, NLR and PLR assessments which are routinely performed upon admission and universally available may be considered in clinical practice for prediction of CSF phenomenon.

CONFLICT OF INTEREST, FUNDS, SUPPORT

None.

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