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Original Article

The role of plateletcrit and neutrophil lymphocyte ratio in showing the clinical severity of the disease in patients with chronic venous insufficiency

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Abstract

Aim: Chronic venous insufficiency (CVI) is a common disease and affects approximately 40% of the population. In this study, we aimed to investigate the relationship of neutrophil to lymphocyte ratio (NLR) and plateletcrit (PCT) values with the clinical severity of the disease in patients diagnosed with CVI.

Material and Methods: The patients hospitalized to our clinic for treatment with the diagnosis of chronic venous insufficiency between August 2014 and August 2019 were included in the study retrospectively. Patients were divided into two groups as Group 1 including patients with stage C1, C2, C3 disease and Group 2 including patients with stage C4, C5, C6 disease according to the clinical evaluation in CEAP staging.

Results: There were 119 patients in Group 1 and their median age was 35 (18- 66) years. There were 55 patients in Group 2 and their median age was 44 (19- 65) years. In multivariate logistic regression analysis, the presence of concomitant perforator vein incompetence (Odds ratio(OR): 1.527, CI 95%: 1.481-2.846 p = 0.019), presence of concomitant deep venous insufficiency (OR: 1.978 CI 95%: 1.250-2.979 p = 0.020), NLR (OR: 3.244, CI 95%: 1.384-4.825 p<0.001) and PCT (OR: 5.354 CI 95%: 2.935-8.586, p = 0.001) values were found to be independent predictors in showing the clinical severity of venous disease.

Conclusions: We determined that the severity of the clinical condition could be predicted by NLR and PCT values in patients with superficial venous insufficiency, the most common insufficiency in the population.

Keywords: Chronic venous insufficiency; inflammation; neutrophil to lymphocyte ratio; plateletcrit; platelets

INTRODUCTION

Chronic venous insufficiency (CVI) is a common disease and affects approximately 40% of the population. Although the superficial venous system is mostly affected, deep veins and perforating veins can also be affected (1). The most commonly used classification in the CVI is the CEAP (Clinical Etiology Anatomy Pathophysiology) classification. According to this classification, clinical evaluation is made as C0: no clinical findings, C1: telangiectatic veins, C2: varicose veins, C3: edema, C4: skin alterations, C5: healed ulcer, C6: active ulcer (2).

The clinical severity of venous insufficiency is important due to the workforce losses it may cause. The disease can lead to significant sociological problems in individuals after it reaches advanced stages and especially after the occurrence of edema (3). In the literature, the relationship between various blood parameters and the clinical severity of venous insufficiency has been demonstrated by various studies. In one study, the relationship between mean platelet volume (MPV) and CVI was investigated and it was found that MPV values were higher than normal in patients with venous insufficiency (4). In another study, it was found that neutrophil lymphocyte ratio (NLR) could show the clinical severity of the disease in CVI patients (5). At the same time, NLR values have been shown to have an effect on perioperative outcomes after endovenous ablation treatment (6).

Studies have shown that platelets play a role in the pathogenesis of CVI. This pathogenesis is a result of multicellular stimulation including platelets, leukocytes, and endothelial cells. Activated platelets take part in margination, rolling, adhesion, and leukocyte stimulation

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(7). Plateletcrit (PCT) is a parameter that shows total platelet mass in blood and it has been shown in several studies that it may be effective in the pathogenesis of vascular diseases (8,9).

In this study, we aimed to investigate the relationship of NLR and PCT values with the clinical severity of the disease in patients diagnosed with CVI.

MATERIAL and METHODS

The patients hospitalized to our clinic for treatment with the diagnosis of chronic venous insufficiency between August 2014 and August 2019 were included in the study retrospectively. The study was approved by the local ethics committee. All patients had saphenous vein (parva and / or magna) insufficiency. The data of the patients were obtained from the hospital registry system and patient files. Patients with known systemic inflammatory disease, patients with diabetes mellitus, patients with chronic renal failure, patients with congenital venous disease, patients with history of deep vein thrombosis, patients with thrombophlebitis, patients diagnosed with lymphedema, patients using anti-inflammatory drugs, patients with known blood disease, patients with atherosclerotic cardiovascular disease and receiving antiplatelet therapy for this disease, patients who had used antibiotics or steroids in the last 2 weeks, reoperations and patients who had received veno-protective drugs in the last one months were excluded from the study. As a result of exclusion criteria, 174 patients were included in the study. Patients were divided into two groups as Group 1 including patients with stage C1, C2, C3 disease and Group 2 including patients with stage C4, C5, C6 disease according to the clinical evaluation in CEAP staging. In the patients with bilateral CVI, the extremity with more advanced disease was included in the clinical staging.

CVI diagnoses of the patients were made by doppler ultrasonography (DUSG). DUSG evaluations for venous system were performed by standing position and augmentation. All patients included in the study had superficial venous system leakage of 1 min or above. The presence of at least 1 min leakage in the deep venous system was considered as deep venous insufficiency (DVI), and the presence of a diameter of 3.5 mm and above in perforating veins was considered as perforating venous insufficiency (PVI). (10) The presence of insufficiency in at least one venous system in the opposite extremity was considered as bilateral disease. Treatment options for these patients include endovenous ablation, stripping, mini-phlebectomy and perforating vein ligation or ablation. (11) Blood measurements of the patients were taken from peripheral venous structures when hospitalized for treatment. Hemogram and biochemical parameters were measured by automatic analyzers. Plateletcrit calculation was made according to the following formula:

PCT: Platelet count (10^3/μL) x(MPV/10.000)

Statistical Analysis

Statistical analysis was performed by using the SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program. Numerical values were expressed as mean ± standard deviation, and Student's t-test was used for values conforming to normal distribution and Mann-Whitney U test was used for values not conforming to normal distribution in the comparison of two independent groups. Chi-square test was used to compare categorical variables. Statistical significance was accepted as $p < 0.05$. Multivariate logistic regression analysis was performed for appropriate variables to show the severity of chronic venous insufficiency. Receiver Operating Characteristic (ROC) analysis was performed for NLR and PCT ratio in order to show the severity of venous disease and the areas under the curve were calculated.

RESULTS

Demographic data of 174 patients included in the study are shown in Table 1. There were 119 patients in Group 1 and their median age was 35 (18- 66) years.

Table 1. Demographic features of the patients

Characteristics	Group 1 N=119	Group 2 N=55	P value
Age(years), median(min-max)	35 (18- 66)	44 (19- 65)	**0.039**[#]
Male gender, n (%)	39 (32.8)	27 (49.1)	**0.040**[a]
Smoking, n (%)	34 (28.5)	21 (38.1)	0.188[a]
BMI(kg/m^2), mean±sd	28.7±5.3	29.8±6.8	0.254[*]
Family history of CVI, n(%)	34 (28.5)	20 (36.3)	0.217[a]
PVI, n (%)	49 (41.1)	35 (63.6)	**0.006**[a]
DVI, n (%)	13 (10.9)	16 (29)	**0.004**[a]
Bilateral disease, n (%)	20 (16.8)	11 (20)	0.410[a]

BMI: Body Mass Index, PVI: Perforator Vein Incompetence, DVI: Deep Venous Insufficiency, [a] Pearson Chi- Suquare, [#] Mann-Whitney U test, [*]Student's-t test

There were 55 patients in Group 2 and their median age was 44 (19- 65) years. There was no statistically significant difference between the groups in terms of smoking, body mass index (BMI), family history, and the presence of bilateral disease. Age, male sex ratio, concomitance rates of PVI and DVI were significantly higher in Group 2 (p values; p = 0.039, p = 0.040, p = 0.006, p = 0.004, respectively).

Laboratory parameters data of the patients are shown in Table 2. There was no difference between the groups in terms of hematocrit, white blood cells, lymphocyte, platelet, albumin and C-reactive protein parameters. Mean platelet volume (MPV), neutrophil, NLR and PCT values were significantly higher in Group 2 (p values; p = 0.001, p = 0.034, p <0.001, p <0.001, respectively).

Table 2. Laboratory variables of the patients

Variables	Group 1 N=119	Group 2 N=55	P value
Hematocrit (%)	39.8±3.6	41.1±4.3	0.194*
WBC (10^3/µL)	7.2±2.6	8.1±2.9	0.072*
Neutrophil (10^3/µL)	2.5 (2-6.7)	3.2 (3- 7.2)	**0.034#**
Lymphocyte (10^3/µL))	1.8 (1.2- 3.5)	1.6 (1.1- 3.2)	0.063#
Monocyte (10^3/µL)	0.33 (0.28- 0.75)	0.35 (0.22- 0.8)	0.422#
Platelet (10^3/µL)	255.6±67.9	271.5±79.5	0.175*
MPV(fL)	7.9±1.3	8.8±1.4	**0.001***
CRP (mg/dL)	3 (1- 18)	5 (3- 25)	0.148#
Albumin (g /dL)	3.8±0.7	3.5±0.4	0.227*
NLR	2.2 (1.5- 4)	2.6 (1.3- 4.1)	**<0.001#**
PCT	0.187 (0.105- 0.390)	0.214 (0.109- 0.410)	**<0.001#**

WBC: White Blood Cell, MPV: Mean Platelet Volume, CRP: C Reactive Protein, NLR: Neutrophil to lymphocyte Ratio, PCT: Plateletcrit, # Mann-Whitney U test (data is axpressed as median (interquartile range)), * Student's-t test (data is axpressed as mean±sd)

Multivariate logistic regression analysis was performed to determine the clinical severity of the disease in patients with venous insufficiency (Table 3). In the evaluation, the presence of concomitant PVI (OR: 1.527, CI 95%: 1.481-2.846 p = 0.019), presence of concomitant DVI (OR: 1.978 CI 95%: 1.250-2.979 p = 0.020), NLR (OR: 3.244, CI 95%: 1.384-4.825 p<0.001) and PCT (OR: 5.354 CI 95%: 2.935-8.586, p = 0.001) values were found to be independent predictors in showing the clinical severity of venous disease.

In the ROC analysis, the cut-off value for NLR was found as 2.75 (AUC = 0.760, p <0.001, 75.2% sensitivity, 69.4% specificity), the cut-off value for PCT was found as 0.195 (AUC = 0.728, p <0.001, 78.8% sensitivity, 64.6% specificity) (Figure 1).

Table 3. Multivariate logistic regression analysis to identify predictors of venous disease severity

Variables	P value	Exp(B) Odds Ratio	95% C.I. Lower- Upper
Age	0.472	1.020	1.007- 1.075
Gender	0.292	0.493	0.132- 1.837
PVI	**0.019**	1.527	1.481- 2.846
DVI	**0.020**	1.978	1.250- 2.979
NLR	**<0.001**	3.244	1.384- 4.825
PCT	**0.001**	5.354	2.935- 8.586

PVI: Perforator Vein Incompetence, DVI: Deep Venous Insufficiency, NLR: Neutrophil to Lymphocyte Ratio, PCT: Plateletcrit

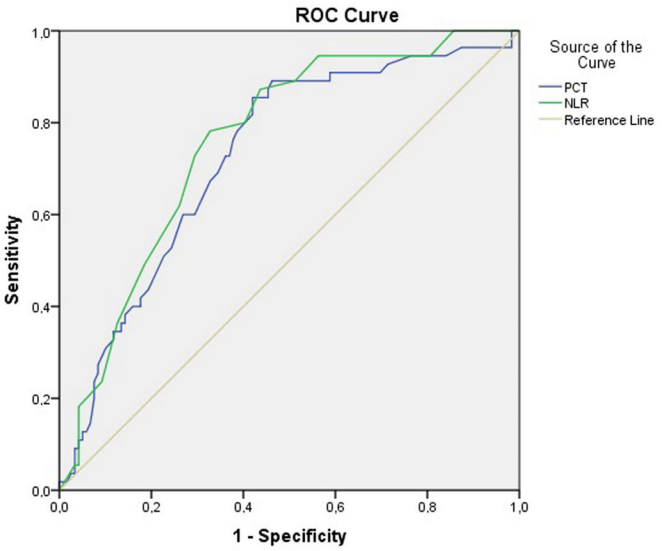

Figure 1. ROC (Receiver operation characteristic) curve and AUC(Area under the curve) for NLR and PCT for predicting venous disease severity. (NLR: AUC: 0.760, p < 0.001, 75.2% sensitivity and 69.4% specificity, cut-off: 2.75) (PCT: AUC: 0.728, p < 0.001, 78.8% sensitivity and 64.6% specificity, cut-off: 0.195)

DISCUSSION

In this study, we investigated the factors that may be effective in clinical progression in CVI patients. We determined NLR value, which can be easily calculated from blood parameters, and PCT value for the first time in the literature as independent predictors of clinical progression of the disease. In addition, the presence of concomitant PVI and DVI were independent predictors in showing advanced clinical stages.

Chronic venous insufficiency (CVI) is a disease caused by disruption of the return of blood from the extremity to the heart as a result of various pathological changes in the lower extremity venous structures and accumulation of blood in the lower extremities. These pathologies are caused by valve insufficiency, venous obstruction, or pressure increases due to insufficient functioning of the muscle pump (12). Due to this increase in pressure, clinical findings such as telangiectasia, skin alterations and venous ulcers may occur in the lower extremities. Chronic venous diseases lead to great socioeconomic effects due to their high prevalence. Moderate venous diseases such as telangiectasia and reticular veins are present in 80-85% of the general population. Varicose veins are seen in 40% of men and 60% of women while ankle edema is seen in 16% of women and 7% of men (13). As risk factors for this disorder, various risk factors have been identified, including age, gender, obesity, and family history (14).

It is important to clarify the mechanisms of clinical progression in patients with CVI. In the Edinburgh Vein Study, patients were followed up for an average of 13.4 years, and 4% of the patients were found to progress to more advanced CEAP stage annually in this process. This progression could not be prevented despite interventional treatments and compression therapies (15). Approximately 70% of CVI patients in the United States have mild levels of the disease (14). Therefore, understanding the pathophysiology of the disease is very important for the measures to be taken in this progression.

The effects of inflammatory processes on CVI formation and progression are known. Due to increased venous pressure, damages occur in the walls of the venous structures, cell infiltration such as neutrophils and monocytes develops in these damaged areas and the pathological process begins (16). According to the leukocyte trapping theory proposed by Smith et al., circulating neutrophils accumulate in venous microcirculation when venous hypertension develops. Thus, capillary circulation is disrupted, and neutrophil activation occurs. Skin alterations and venous ulcers may occur due to toxic materials developing in this process (17). Here, endothelial cells and activated platelets also contribute to the process together with neutrophils (18). As a result, both NLR may increase due to venous inflammation and the increase in the severity of the disease may increase the NLR.

In a study conducted by Mosmiller et al., patients were divided into two groups as C1-2-3 (mild CVI) and C4-5-6 (severe CVI) similar to our study, and the place of inflammatory markers in showing the clinical severity of the disease was investigated. As a result of the study, the severity of the disease was found to be related to neutrophil count, lymphocyte count and NLR. The cut-off value for NLR was found as 2.91 (AUC: 0.778, with 74% sensitivity and 71% specificity) according to ROC analysis in this study. At the end of this study, it was emphasized that the pathways in CVI progression could be demonstrated and measures could be taken in disease progression (5). In our study, the cut-off value for NLR was found as 2.75 with higher sensitivity and specificity. Unlike this study, venous structures causing CVI were more clearly expressed in our study. The study of Mosmiller et al (5). was also retrospective and the patients with CVI were reached through ICD codes and no details were given about the veins with insufficiency. In contrast, the venous structures of the patients causing CVI were reported in our present study.

In the study conducted by Karahan et al., the place of routine blood parameters in determining the severity of CVI was investigated. In this study, the venous clinical severity score (VCSS) and CEAP classification were used for grouping the patients. In the results of the study, WBC, fibrinogen, elevated fibrinogen albumin ratio and low albumin were found to be related to disease severity according to the severity assessment based on the VCSS (19). Unlike our study, the relationship of neutrophil, lymphocyte and NLR with the severity of the disease was not established in this study.

According to the results of the study in which blood homocysteine values in showing the severity of CVI were investigated by Smith et al., age, presence of recurrent varices and homocysteine values were found

as independent predictors in showing the severity of the disease. Similar to our study, venous vessels causing CVI were presented and 90% of the patients had saphenous and / or parva vein insufficiency in this study. In addition, in parallel with our study, deep and perforating vein insufficiency rates have been shown to increase with increased clinical stage (20). Similar to this study, age was significantly higher in the severe venous disease group in our study. Elevated homocysteine values increase the interaction of neutrophils with endothelium and this is important in the pathogenesis of CVI (21). In our study, a significant relationship was found between neutrophil values and the severity of CVI. In addition, MPV and PCT values were found to be related to severe venous disease in our study.

While the role of leukocytes in the pathogenesis of CVI is known, platelet and platelet-derived microparticles may also contribute to the adhesion of leukocytes to the vessel wall (22). The effect of platelet counts and mean platelet volume has been shown in venous thrombosis (23). In addition, it has been suggested that increased platelet reactivity may be effective in the pathogenesis of CVI (7). In our study, we calculated PCT values due to the possible effects of platelet functions and determined it as an independent predictor in showing advanced stage disease.

In many studies carried out in patients with venous ulcers, perforating venous insufficiency was observed at a rate of approximately 60%. Insufficiency of perforating veins is a more serious cause of ambulatory venous hypertension (24). In our study, we demonstrated the presence of concomitant PVI as an independent predictor in showing the clinical severity of the disease.

LIMITATIONS

The most important limitation of our study is that it is based on retrospective database. In addition, the VCSS scoring system is a valuable scoring system in the venous clinical severity assessment. This scoring assessment could not be carried out because our study was retrospective. Also, due to the retrospective nature of our study, we could not evaluate valuable blood parameters in the pathogenesis of CVI such as homocysteine, vascular endothelial growth factor and fibrinogen.

CONCLUSION

Chronic venous insufficiency is an important disease that can lead to significant job losses and psychological problems in the population. Its widespread presence in the population increases its importance even more. We determined that the severity of the clinical condition could be predicted by NLR and PCT values in patients with superficial venous insufficiency, the most common insufficiency in the population. These parameters can be calculated in early-stage patients and more precise information can be obtained to show the progression of the disease with multicenter prospective clinical studies to be performed after this clinical determination result.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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