The Relation of Inflammatory Markers to Idiopathic Pericardial Effusion

Cemil Zencir[1], Mahmut Akpek[1], Mithat Selvi[1], Sevil Önay[1], Hilal Bektaş[2], Mustafa Yılmaz[3], Mustafa Çetin[4], Kayıhan Kahraman[5], Çağdaş Akgüllü[1], Hüseyin Elbi[6], Hasan Güngör[1]

[1] Adnan Menderes University Faculty of Medicine, Department of Cardiology, Aydın, Turkey
[2] Adnan Menderes University Faculty of Medicine, Department of Internal Medicine, Aydın, Turkey
[3] Adnan Menderes University Faculty of Medicine, Department of Biochemistry, Aydın, Turkey
[4] Adıyaman University Faculty of Medicine, Department of Cardiology, Adıyaman, Turkey
[5] Gaziosmanpaşa University Faculty of Medicine, Department of Cardiology, Tokat, Turkey
[6] Celal Bayar University Faculty of Medicine, Department of Family Medicine, Manisa, Turkey

ABSTRACT

Introduction: With the growing evidence about the role of inflammation on cardiovascular disorders, studies have been focused on inflammatory markers for risk evaluation and disease activity monitoring. The aim of this study was to investigate whether inflammation has a role in idiopathic pericardial effusion (PE) and to reveal its correlation with the disease activity.

Patients and Methods: The study population consisted of 107 patients with PE and 35 age-matched and sex-matched healthy volunteers. Each patient underwent a comprehensive clinical evaluation to identify the probable underlying systemic diseases or other potential causes for PE.

Results: High-sensitivity C-reactive protein levels (hs-CRP), neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) ($p< 0.001$ for each) were significantly higher in the PE group than in healthy volunteers. The patients with PE were divided into three subgroups according to the amount of PE. hs-CRP, NLR and PLR significantly correlated with the amount of PE. In the multivariate logistic regression model NLR (OR 1.363, 95% CI 1.026-1.809; $p= 0.033$) and hs-CRP (OR 1.090, 95% CI 1.030-1.152; $p= 0.003$) remained as independent predictors of severe PE in patients who have PE.

Conclusion: hs-CRP, NLR and PLR may be used for disease activity monitoring, treatment response evaluation and risk stratification of patients with PE.

Key Words: High-sensitivity C-reactive protein; neutrophil/lymphocyte ratio; pericardial effusion; platelet/lymphocyte ratio

İdiyopatik Perikardiyal Efüzyon ile İnflamatuvar Belirteçler Arasındaki İlişki

ÖZET

Giriş: İnflamasyonun kardiyovasküler hastalıklardaki rolü hakkındaki kanıtların gittikçe artmasıyla, çalışmalar inflamatuvar markerların hastalık aktivitesi ve risk değerlendirmesindeki rolüne odaklanmıştır. Bu çalışmanın amacı inflamatuvar belirteçlerin idiyopatik perikardiyal efüzyonla ile ilişkisini ve hastalık aktivitesi ile olan korelasyonu olup olmadığının incelenmesidir.

Hastalar ve Yöntem: Çalışma popülasyonu perikardiyal efüzyonu olan 107 hasta ile yaş ve cinsiyet olarak benzer 35 sağlıklı gönüllülerden oluşmaktadır. Tüm hastalar perikardiyal efüzyonun etyolojisine yönelik kapsamlı bir klinik değerlendirmeye tabi tutulmuştur.

Bulgular: Plevral efüzyonu grubunda, yüksek sensitif C-reaktif protein (Hs-CRP), nötrofil/lenfosit oranı (NLR) ve platelet/lenfosit oranı (PLR) (herbiri için $p< 0.001$), sağlıklı gönüllülerin grubuna göre anlamlı olarak daha yüksekti. Perikardiyal efüzyonu olan hastalar efüzyon miktarına göre 3 gruba bölündü. Hs-CRP, NLR ve PLR perikardiyal efüzyon miktarıyla korele bir şekilde artmaktadır. Çoklu analizde, NLR (OR 1.363, 95% CI 1.026-1.809; $p= 0.033$) ve Hs-CRP (OR 1.090, %95 CI 1.030-1.152; $p= 0.003$), perikardiyal efüzyonu olan hastalarda ciddi perikardiyal efüzyonun bağımsız bir prediktörleridir.

Sonuç: Hs-CRP, NLR ve PLR perikardiyal efüzyonu olan hastalarda, hastalık aktivitesi, tedavi monitörizasyonunda ve risk sınıflamasında kullanılabilir.

Anahtar Kelimeler: Yüksek sensitif C-reaktif protein; nötrofil/lenfosit oranı; perikardiyal efüzyon; platelet/lenfosit oranı

Correspondence

Cemil Zencir

E-mail: drczencir@hotmail.com
Submitted: 18.04.2016
Accepted: 14.06.2016

INTRODUCTION

The space between the parietal and visceral pericardium contains small amount of fluid called pericardial fluid (PF). Pericardial effusion (PE) is a relatively common finding in the daily clinical practice. Several clinical disorders or imbalance between formation and removal of PF can cause its accumulation as PE[1-3]. A large proportion of these cases are defined as idiopathic pericarditis (26.1%). The other following causes for PE are neoplastic diseases (25.6%) and iatrogenic disorders (16.3%)[4].

The total white-blood-cell (WBC) count and its subtypes, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are easily available systemic inflammatory markers. Some recent studies have shown that NLR and PLR have a diagnostic value in certain pathologies characterised by systemic or local inflammatory response, such as diabetes mellitus, coronary artery disease, ulcerative colitis, sarcoidosis, tuberculosis and inflammatory arthritis[5-10].

Accompanied by the growing evidence, recent studies have been focused on high-sensitivity C-reactive protein (hs-CRP) and other inflammatory markers for risk evaluation and disease activity monitoring in various cardiovascular disorders. In the present study, we aimed to investigate whether inflammation has a role in idiopathic PE and to reveal its correlation with the disease activity.

PATIENTS and METHODS

Study Population

This study had a retrospective design. All data were obtained from the database of Adnan Menderes University Hospital. Study protocol was approved by the local Ethics Committee and the institutional review board. A total of 440 consecutive patients with PE between January 2012 and December 2014 were included in the study. Each patient underwent a comprehensive clinical evaluation to identify the probable underlying systemic diseases or other potential causes for PE (myocardial infarction; myocarditis; cardiac disorders; endocarditis; rheumatological disorders; neoplasms; endocrine disorders; chronic renal failure; immunological disorders; trauma; transplantation; viral and/or bacterial infections, including tuberculosis; haematological and gastrointestinal disorders). Three hundred thirty-three patients were excluded for several reasons as shown in Figure 1. After these exclusions the final study population consisted of 107 patients with PE. In addition, age-matched and sex-matched 35 healthy volunteers were included in the study as the control group.

Blood Samples

The glucose, urea, creatinine, cholesterol, serum triiodothyronine, serum thyroxine, TSH, total protein, albumin, globulin, lactate dehydrogenase (LDH) and hs-CRP levels were measured in blood samples. hs-CRP was measured

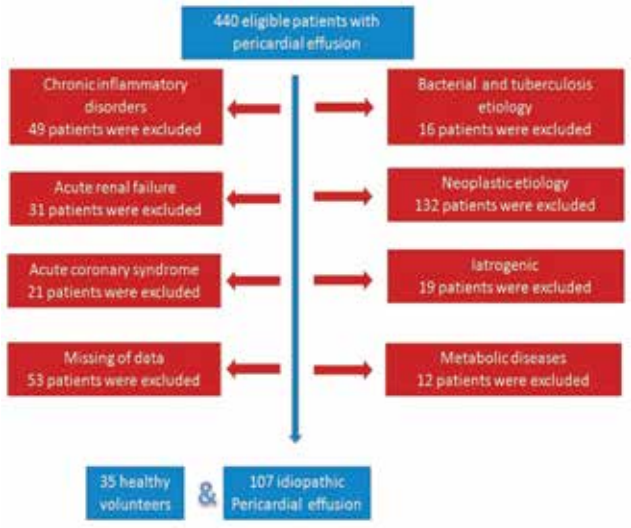

Figure 1. Study Diagram.

using a BN2 model nephelometer (Dade-Behring, Newark, DE, USA) within maximum 5 min after sampling. Complete blood counting (CBC) parameters were measured by a Sysmex K-1000 auto analyser (Block Scientific, Bohemia, NY, USA). WBC differential counts were determined in whole blood by Cell-Dyn Sapphire TM (Abbot Diagnostics). Total leukocyte count and differential counts, including neutrophil, lymphocyte, monocyte and platelet counts, were analysed using by Cell-Dyn SapphireTM (Abbot Diagnostics).

Transthoracic Echocardiography

Echocardiographic examinations were performed on admission before medical and/or interventional management. All measurements were performed using a commercially available machine (Vivid 5s®, GE Vingmed Ultrasound A/S, Horten, Norway) with a 3.5-MHz transducer. The Simpson's method in a two-dimensional echocardiographic apical four-chamber view was used to assess left ventricular ejection fraction, as recommended by the American Society of Echocardiography[11]. The amount of PE was graded as mild (echo-free space in diastole < 10 mm, corresponding to 300 mL); moderate (10-20 mm, corresponding to approximately 500 mL) and large (> 20 mm, > 700 mL)[12].

Statistical Analysis

All data was analysed using the PASW Statistics version 15 software package for Windows software (SPSS, Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. The continuous variables were defined as mean ± standard deviation or median with 95% confidence interval. We compared continuous variables using the Student t-test or Mann-Whitney U test between groups. Categorical variables were defined as percentages and compared with the chi-square test. We used one-way analysis of variance test to compare the variables between more than the two groups. The independent association of variables with severe PE was

calculated with backward elimination multivariate logistic regression analyses. The Receiver Operating Characteristics (ROC) curve was used to determine the sensitivity and specificity of PLR and NLR, and the optimal cut-off value for predicting idiopathic PE in the study group. A two tailed p value of < 0.05 was considered significant.

RESULTS

Baseline characteristics and laboratory parameters are as shown in Table 1. There were 107 patients (mean age 61.0 ± 16.0 years and 45.8% male) in the idiopathic PE group and 35 patients (mean age 57.5 ± 9.9 years and 57.1% male) in the control group. The patients in the idiopathic PE group had significantly higher heart rate (88.8 ± 19.7 vs. 77.2 ± 11.6 beats/min, p= 0.001) and lower LVEF (60.8% ± 6.8% vs. 63.4% ± 4.5%, p= 0.034) than in healthy volunteers.

In laboratory analyses, serum creatinine (0.97 ± 0.43 vs. 0.80 ± 0.13 mg/dL, p= 0.020) and lactate dehydrogenase levels (279.2 ± 132.6 vs. 167.8 ± 59.6 U/l, p < 0.001) were significantly higher in the idiopathic PE group than in the control group, but serum albumin levels (3.46 ± 0.55 vs. 4.03 ± 0.51 g/dL, p= 0.001) were lower. Erythrocyte sedimentation rate [42 (11–94) vs. 21 (15-37) h, p< 0.001] and hs-CRP [17.0 (1.2-67.0) vs. 2.5 (0.4-7.8) mg/L, p< 0.001] were also significantly higher in idiopathic PE than in healthy volunteers.

In CBC analysis, neutrophil counts (5.71 ± 2.14 vs. 4.60 ± 1.39 10^3 μl, p= 0.005), NLR [3.30 (1.28-16.84) vs. 2.09 (0.92–3.39), p < 0.001] and PLR [171.0 (50.4-850.9) vs. 111.81 (50.6-225.4), p< 80.001] were significantly higher in the idiopathic PE group. However, lymphocyte counts (1.62 ± 0.72 vs. 2.36 ± 0.69 10^3 μl, p< 0.001) were significantly lower in the idiopathic PE group. Platelet counts were similar in both groups (p= 0.121).

Table 1. Demographic, clinical characteristic and laboratory parameters pericardial effusion and controls

Variable	Pericardial effusion (n= 107)	Control (n= 35)	p
Age	61.0 ± 16.0	57.5 ± 9.9	0.223
Male, n (%)	49 (45.8%)	20 (57.1%)	0.300
Smoking, n (%)	22 (20.6%)	10 (28.6%)	0.325
Diabetes mellitus, n (%)	33 (30.8%)	7 (20%)	0.216
Hypertension, n (%)	47 (43.9%)	16 (45.7%)	0.853
Pericardiocentesis, n (%)	36 (33.6%)		
Heart rate, (beats/min)	88.8 ± 19.7	77.2 ± 11.6	0.001
Left ventricular ejection fraction (%)	60.8 ± 6.8	63.4 ± 4.5	0.034
Glucose (mg/dL)	111.5 ± 36.1	111.3 ± 44.1	0.982
Urea (md/dL)	42.0 ± 18.7	37.5 ± 13.9	0.187
Creatinine (mg/dL)	0.97 ± 0.43	0.80 ± 0.13	0.020
Thyroid stimulating hormone	1.63 ± 1.54	1.51 ± 1.24	0.765
Total protein (g/dL)	6.78 ± 0.90	6.98 ± 0.59	0.468
Albumin (g/dL)	3.46 ± 0.55	4.03 ± 0.51	0.001
Globulin (g/dL)	3.32 ± 0.48	2.94 ± 0.48	0.075
Lactate dehydrogenase (U/l)	279.2 ± 132.6	167.84 ± 59.63	0.001
Erythrocyte sedimentation rate (h)	42 (11-94)	21 (15-37)	< 0.001
High-sensitivity C-reactive protein (mg/L)	17.0 (1.2-67.0)	2.5 (0.4-7.8)	< 0.001
Common blood counting			
Haemoglobins (g/dL)	11.6 ± 2.1	13.3 ± 1.6	< 0.001
Platelet (10^3 μl)	286 ± 116	255 ± 50	0.121
White blood cell (10^3 μl)	8.22 ± 2.62	7.81 ± 1.92	0.401
Neutrophil (10^3 μl)	5.71 ± 2.14	4.60 ± 1.39	0.005
Lymphocyte (10^3 μl)	1.62 ± 0.72	2.36 ± 0.69	< 0.001
Neutrophil/lymphocyte ratio	3.30 (1.28-16.84)	2.09 (0.92-3.39)	< 0.001
Platelet/lymphocyte ratio	171.0 (50.4-850.9)	111.81 (50.6-225.4)	< 0.001

Data are expressed as mean ± standard deviation for normally distributed data, median (interquartile range) for not normally distributed data and percentage (%) for categorical variables.

The patients with idiopathic PE were divided into three subgroups according to the amount of PE (Table 2). Heart rate was similar between the mild and moderate PE groups (p= 1.000). However, heart rate in the large PE group was significantly higher than that in the mild and moderate groups (p< 0.001 for each). Erythrocyte sedimentation rate was lower in the mild PE group than in the moderate and large PE groups (p= 0.036 and p= 0.008, respectively), but was similar between the moderate and large PE groups (p= 0.986). hs-CRP levels, NLR and PLR significantly increased in correlation with the amount of PE (Figure 2).

The ROC curves of NLR, PLR and hs-CRP for predicting PE are as shown in Figure 3. The NLR values > 2.53 predicted PE with a 74% sensitivity and 83% specificity (AUC: 0.817, 95% CI: 0.744-0.890). PLR values > 135.4 had 70% sensitivity and 74% specificity for the associating PE prediction (AUC: 0.768, 95% CI: 0.680-0.855). In addition, hs-CRP levels > 5.9 predicted PE with 85% sensitivity and 89% specificity (AUC: 0.937, 95% CI: 0.896-0.978).

In patients with PE, we analysed the predictive value of heart rate, erythrocyte sedimentation rate, haemoglobin, NLR, PLR and hs-CRP on severe PE. The independent contributions of heart rate, erythrocyte sedimentation rate, haemoglobin, NLR, PLR and hs-CRP were analysed using a multivariate logistic regression model (Table 3). In the multivariate analysis, NLR (OR 1.363, 95% CI 1.026-1.809; p= 0.033), hs-CRP (OR 1.090, 95% CI 1.030-1.152; p= 0.003) and heart rate (OR 1.072, 95% CI 1.034-1.113; p< 0.001) remained as independent predictors of severe PE (Table 3).

DISCUSSION

Inflammatory disorders, viral and bacterial agents are common causes of PE. However, idiopathic pericardial effusion is an unknown clinical condition in terms of aetiology. With the present study we revealed that inflammation plays an important role in idiopathic PE. In addition, we showed that NLR and PLR, as a sign of inflammatory status of the body, significantly associated with the amount of the PF in patients with idiopathic PE. Furthermore, in patients with PE, heart rate, NLR and hs-CRP levels were independently associated with the presence of severe PE.

Table 2. The distribution of, heart rate, erythrocyte sedimentation rate, high-sensitivity C-reactive protein and hemogram according to the severity pericardial effusion

	Small n= 37	Moderate n= 31	Large n= 39	p (1-2)	p (2-3)	p (2-3)
Heart rate (beats/min)	80.5 ± 14.6	80.8 ± 16.9	103.1 ± 18.0	1.000	< 0.001	< 0.001
Erythrocyte sedimentation rate (h)	34 (11-82)	51 (12-94)	51 (20–88)	0.036	0.008	0.986
High-sensitivity C-reactive protein (mg/L)	7.5 (1.2-28.0)	17.0 (2.3-48.0)	25.0(5.7–67.0)	0.001	< 0.001	0.019
Haemoglobin (g/dL)	12.7 ± 1.8	11.4 ± 2.1	10.8 ± 1.9	0.019	< 0.001	0.639
Platelets (10^3 µL)	282 ± 124	279 ± 101	296 ± 121	1.000	1.000	1.000
White blood cells (10^3 µL)	7.79 ± 2.53	8.37 ± 2.27	8.51 ± 2.94	1.000	0.697	1.000
Neutrophils (10^3 µL)	4.87 ± 1.90	5.91 ± 1.75	6.33 ± 2.41	0.124	0.008	1.000
Lymphocytes (10^3 µL)	2.05 ± 0.63	1.57 ± 0.58	1.26 ± 0.69	0.006	< 0.001	0.144
Neutrophil/lymphocyte ratio	2.06 (1.28-5.59)	3.92 (1.88–7.40)	5.62(1.40-16.84)	< 0.001	< 0.001	0.004
Platelet/lymphocyte ratio	133.3 (50.42-448.5)	171.4 (85.2–548.2)	242.3(53.67-850.9)	0.013	< 0.001	0.012

Data are expressed as mean ± standard deviation for normally distributed data, median (interquartile range) for not normally distributed data. A p< 0.05 was considered to be significant.

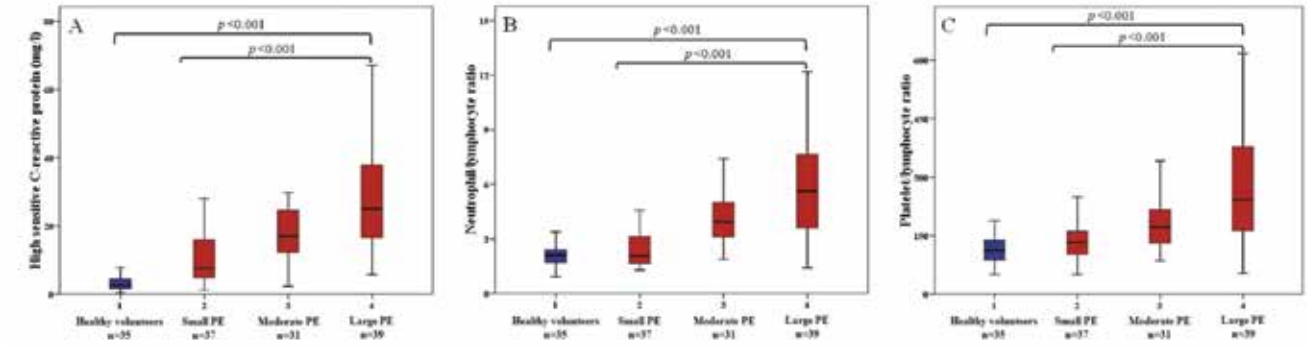

Figure 2. High-sensitivity C-reactive protein **(A)**, neutrophil/lymphocyte ratio **(B)** and platelet/lymphocyte ratio **(C)** in the healthy volunteers and in subgroup of patients with PE.

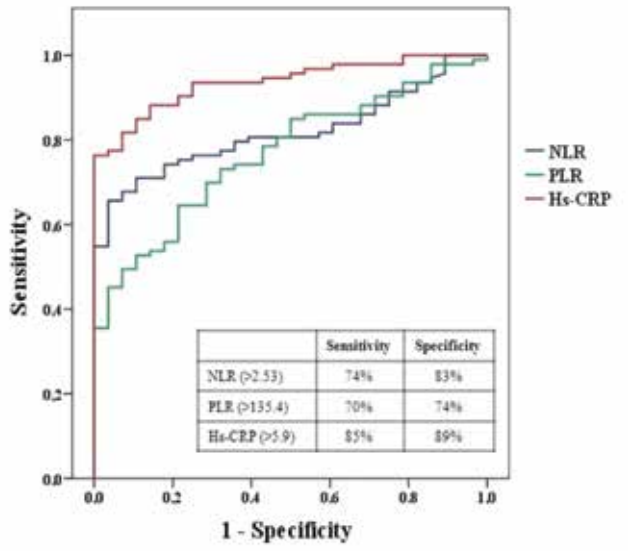

Figure 3. The receiver operating characteristic curve of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and high-sensitivity C-reactive protein for predicting pericardial effusion in the study group.

Table 3. Effects of variables on severe pericardial effusion in multivariate logistic regression analyses in patients who have pericardial effusion

Variables	Adjusted OR	95% CI	p
Neutrophil/lymphocyte ratio	1.363	1.026-1.809	0.033
Platelet/lymphocyte ratio	0.999	0.992-1.006	0.781
High-sensitivity C-reactive protein	1.090	1.030-1.152	0.003
Heart rate	1.072	1.034-1.113	< 0.001
Erythrocyte sedimentation rate	0.987	0.959-1.016	0.379
Haemoglobin	0.932	0.683-1.272	0.656

In general, PE is an incidentally detected clinical condition during echocardiographic examination or another diagnostic imaging studies for a symptomatic patient. There is no sufficient data regarding PE incidence and prevalence. The most common causes of PE are infections (including viral and bacterial infections), cancer, connective tissue diseases, metabolic causes (i.e. hypothyroidism) and aortic diseases. The relative frequency of different causes depends on the local epidemiology. Idiopathic PE is the most common cause in developed countries, whereas tuberculosis is the main cause in developing countries.

Inflammation plays a pivotal role in several cardiovascular disorders. With the growing understanding regarding the role of inflammation in the various cardiovascular diseases, studies have been focused on hs-CRP and other inflammatory markers for risk evaluation and disease activity monitoring[13].

Idiopathic PE still remains as a mystery. Different etiological mechanisms especially inflammation have been found related to idiopathic PE[14]. According to increasing evidences, the usual suspect is the immune mediated pathogenesis. In previous epidemiological studies, the presence of pro-inflammatory cytokines such as interleukin-6, interleukin-8 and interferon-gamma have been demonstrated in the idiopathic PE[15]. Furthermore, anti-nuclear antibodies, anti-heart and anti-intercalated-disk antibodies were detected in the idiopathic PE. Therefore, these evidences were thought to support the inflammatory pathogenesis in idiopathic PE[16,17].

C-reactive protein is one of the acute-phase proteins and rises during nonspecific response to inflammatory processes[18]. The hepatic synthesis of CRP starts immediately after an inflammatory stimulus. The plasma half-life is 19 h, on average and rises to > 5 mg/L by 6 h after onset of stimulus[19]. The total WBC count is an easily available marker for systemic inflammation. The differential analysis of the subtypes of WBC count and platelets, higher levels of neutrophil and platelet count are the sign of subclinical inflammation, whereas the decreased lymphocyte count reflects physiological stress[20]. In the previous epidemiological studies, a positive correlation was found between the acute-phase reactants and pro-inflammatory proteins such as hs-CRP, Tumour necrosis factor alpha, interleukin-1 and interleukin-6 and the elevated platelet count in nonspecific inflammatory conditions[21,22]. In addition, increased platelet counts may reflect the underlying inflammation because several inflammatory mediators stimulate megakaryocytic proliferation and produce relative thrombocytosis. Moreover, lymphocytopenia is a common finding during stress response, secondary to increased corticosteroid levels[23]. Furthermore, lymphocytopenia can be seen in critical inflammatory states because of the increased lymphocyte apoptosis[24]. Therefore, NLR and PLR can provide more information on both the inflammatory status and the stress response of the body. In the recent years, NLR and PLR were widely used as markers of inflammation and were associated with adverse outcomes in various cardiovascular diseases. NLR, as a marker of inflammation, is closely associated with adverse outcomes in all types of acute coronary syndromes and recurrence of arrhythmias after cryoablation[20,25]. It has been also demonstrated that NLR was associated with spontaneous echo contrast in patients with mitral stenosis and increased stroke risk[26]. Although, as an emerging marker of systemic inflammation, NLR and PLR had been studied in several clinical observational studies of cardiovascular diseases, limited data are available about the role of these markers in idiopathic PE and about the association with the effusion amount. In this study, we demonstrated the link between idiopathic PE and inflammation with new cheap and widely available markers, including PLR and NLR. On the other hand, correlation between the PE amount and the levels of inflammatory markers had not been fully elucidated before. For this purpose, we classified the idiopathic PE according to the described criteria above[12]. We showed that hs-CRP, PLR and NLR were positively correlated with the amount of the idiopathic PE. Therefore, more inflammation means more effusion in patients with idiopathic PE.

The possible limitation of our study may be the lack of a mechanistic association between inflammatory markers and idiopathic PE. These biomarkers, including NLR, PLR and hs-CRP, are global measures. If a more specific marker that is directly associated with PE had been used in the present study, we could have talked about a mechanistic relation. Therefore, the relation between NLR, PLR and hs-CRP and idiopathic PE may be an associative rather than a mechanistic one.

In conclusion, idiopathic PE has not been fully explained in terms of aetiology. Therefore, a general anti-inflammatory treatment strategy was preferred rather than targeted therapy in such patients. In the present study, in addition to hs-CRP, we found that NLR and PLR, as a sign of inflammatory status of the body, were significantly higher in patients with PE. Moreover, NLR and PLR levels were positively correlated with the amount of the effusion in idiopathic PE patients. Furthermore, in patients with PE, NLR and hs-CRP levels were independently associated with severe PE. The present study provides a new perspective to better understand the underlying mechanisms of idiopathic PE. In addition to hs-CRP, NLR and PLR are cheap and widely available markers that can be used for disease activity monitoring and treatment response evaluation. In patients with PE, NLR and hs-CRP levels provide additional information about the amount of the PE and may be used for the risk stratification in patients with PE.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: CZ, MA

Analysis/Interpretation: MÇ, HE, MA

Data Acquisition: CZ, MS, SÖ, HE, HB, MY

Writting: CZ, KK, MA

Critical Revision: ÇA, CZ, HG

Final Approval: All of authors

REFERENCES

1. Spodick DH. The pericardium a comprehensive textbook. London: CRC Press, 1996;1-56.
2. Sagristà-Sauleda J, Mercé AS, Soler-Soler J. Diagnosis and management of pericardial effusion. World J Cardiol 2011;26:135-43.
3. Khandaker MH, Espinosa RE, Nishimura RA, Sinak LJ, Hayes SN, Melduni RM, et al. Pericardial disease: diagnosis and management. Mayo Clin Proc 2010;85:572-93.
4. Lorbar M, Spodick DH. 'Idiopathic'pericarditis-the clinician's challenge [nothing is idiopathic]. Int J Clin Pract 2007;61:138-42.
5. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5-14.
6. Celikbilek M, Dogan S, Ozbakır O, Zararsız G, Kücük H, Gürsoy S, et al. Neutrophil-lymphocyte ratio as a predictor of disease severity in ulcerative colitis. J Clin Lab Anal 2013;27:72-6.
7. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012;5:2.
8. Tousoulis D, Antoniades C, Koumallos N, Stefanadis C. Proinflammatory cytokines in acute coronary syndromes: from bench to bedside. Cytokine Growth Factor Rev 2006;17:225-33.
9. Iliaz S, Iliaz R, Ortakoylu G, Bahadir A, Bagci BA, Caglar E. Value of neutrophil/lymphocyte ratio in the differential diagnosis of sarcoidosis and tuberculosis. Ann Thorac Med 2014;9:232-5.
10. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013;8:e67688
11. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-67.
12. Jung HO. Pericardial effusion and pericardiocentesis: role of echocardiography. Korean Circ J 2012;42:725-34.
13. Buyukkaya E, Poyraz F, Karakas MF, Kurt M, Akcay AB, Akpinar I, et al. Usefulness of monocyte chemoattractant protein-1 to predict no-reflow and three-year mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2013;112:187-93.
14. Maestroni S, Di Corato PR, Cumetti D, Chiara DB, Ghidoni S, Prisacaru L, et al. Recurrent pericarditis: autoimmune or autoinflammatory? Autoimmun Rev 2012;12:60-5.
15. Pankuweit S, Wädlich A, Meyer E, Portig I, Hufnagel G, Maisch B. Cytokine activation in pericardial fluids in different forms of pericarditis. Herz 2000;25:748-54
16. Imazio M, Brucato A, Doria A, Brambilla G, Ghirardello A, Romito A, et al. Antinuclear antibodies in recurrent idiopathic pericarditis: prevalence and clinical significance. Int J Cardiol 2009;136:289-93.
17. Caforio AL, Brucato A, Doria A, Brambilla G, Angelini A, Ghirardello A, et al. Anti-heart and anti-intercalated disk autoantibodies: evidence for autoimmunity in idiopathic recurrent acute pericarditis. Heart 2010;96:779-84.
18. Turak O, Ozcan F, Isleyen A, Tok D, Sokmen E, Buyukkaya E, et al. Usefulness of the neutrophil-to-lymphocyte ratio to predict bare-metal stent restenosis. Am J Cardiol 2012;110:1405-10.
19. Akpek M, Kaya MG, Uyarel H, Yarlioglues M, Kalay N, Gunebakmaz O, et al. The association of serum uric acid levels on coronary flow in patients with STEMI undergoing primary PCI. Atherosclerosis 2011;219:334-41.
20. Canpolat U, Aytemir K, Yorgun H, Şahiner L, Kaya EB, Kabakçı G, et al. Role of preablation neutrophil/lymphocyte ratio on outcomes of cryoballoon-based atrial fibrillation ablation. Am J Cardiol 2013;112:513-9.
21. Alexandrakis MG, Passam FH, Moschandrea IA, Christophoridou AV, Pappa CA, Coulocheri SA, et al. Levels of serum cytokines and acute phase proteins in patients with essential and cancer-related thrombocytosis. Am J Clin Oncol 2003;26:135-140.
22. Kurtul A, Murat SN, Yarlioglues M, Duran M, Ergun G, Acikgoz SK, et al. Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. Am J Cardiol 2014;114:972-8.
23. Onsrud M, Thorsby E. Influence of in vivo hydrocortisone on some human blood lymphocyte subpopulations. Scand J Immunol 1981;13:573-9.
24. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:138-50.
25. Akpek M, Kaya MG, Lam YY, Sahin O, Elcik D, Celik T, et al. Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST-elevated myocardial infarction undergoing primary coronary intervention. Am J Cardiol 2012;110:621-7.
26. Kaya MG, Akpek M, Elcik D, Kalay N, Yarlioglues M, Koc F, et al. Relation of left atrial spontaneous echocardiographic contrast in patients with mitral stenosis to inflammatory markers. Am J Cardiol 2012;109:851-5.