Orijinal Araştırma / Original Investigation
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The Relationship Between Immune Inflammation Index and Major Cardiovascular Adverse Events in Patients with Heart Failure with Reduced Ejection Fraction

Azalmış Ejeksiyon fraksiyonlu Konjestif Kalp Yetersizliği Hastalarında İmmun İnflamasyon İndeksi ile Major Kardiyovasküler Olay Sıklığı Arasındaki İlişki

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ÖZET

AMAÇ: Sistemik immün inflamasyon indeksi (SII)'nin, düşük ejeksiyon fraksiyonuna sahip Kalp yetmezliği (HFrEF) hastalarında, exitus, stroke ve hospitalizasyon gibi majör kardiyovasküler olayları öngörmede, prognozu belirlemede prediktif değeri olup olmadığını araştırmayı amaçladık.

GEREÇ VE YÖNTEM: Çalışmaya Ocak 2019- Ocak 2022 arası kardiyoloji ve acil polikliniğine başvuran 18 yaş üstü, HFrEF'li (Ejeksiyon Fraksiyonu <% 40) tanısı olan hastalar retrospektif olarak tarandı. Güvenilir klinik verileri olan 597 hasta analiz edilmek üzere çalışmaya grubu olarak kabul edildi. Hastaların ilk başvuru sırasındaki sosyodemografik özellikleri, kronik hastalıkları, sigara kullanımı ve hemogram, biyokimya parametreleri, sol ventrikül ejeksiyon fraksiyonları kullandığı ilaçlar kaydedildi. Tam kan sayımları ve biyokimyasal parametreleri incelendi. Sistemik immün inflamasyon indeksi hesaplandı. Major kardiyak olaylar ile SII arasındaki ilişki değerlendirildi. Major kardiyak olaylar olarak exitus, inme ve hospitalize olma durumu olarak kabul edildi.

BULGULAR: HFrEF'li hastalarda, SII indeksi açısından gruplar karşılaştırıldığında exitus olan grupta (1504,34±1722,74) exitus olmayan gruba göre (893,94±972,13) anlamlı olarak daha yüksek bulundu (p=0,014). Stroke olan ve olmayan, hastaneye yatış olan ve olmayan gruplar SII indeksi açısından karşılaştırıldığında anlamlı bir fark bulunamadı (tablo 2). Exitus varlığı, stroke varlığı ve hastaneye yatış varlığı ile SII indeksi arasında korelasyona bakıldığında exitus varlığı ile SII indeksi arasında anlamlı pozitif korelasyon bulundu (r=0.165 p<0,001) . SII indeksi 697,29 değeri kalp yetmezliği hastalarında Exitusu %604 sensivit, %607 spesivite ile pretikte ettirdiği saptandı (AUC: 0.621, 95%CI 0.539-0.704, p=0.04).

SONUÇ: HFrEF'lı hastalarda, kolayca bakılan bir tam kan sayımındaki lenfosit, trombosit ve nötrofil sayısından kolayca hesaplanabilen, SII indexinin mortaliteyi, predikte ettirdiğinin saptanmasıdır. Bu indexin HFrEF hastalarında prognostik önemi olduğu, özellikle yaşlı ve ISS indexi yüksek hastaların daha yakın izlenmesinin faydalı olabileceğini düşündürmektedir.

Anahtar Kelimeler: immün inflamasyon indeks, kalp yetmezliği

ABSTRACT

OBJECTIVE: We aimed to investigate whether systemic immune inflammation index (SII) has a predictive value in predicting prognosis and major adverse cardiovascular events such as exitus, stroke and hospitalization in heart failure patients with reduced ejection fraction (HFrEF).

MATERIALS AND METHODS: Patients over the age of 18 who applied to the cardiology and emergency outpatient clinics between January 2019 and January 2022 and diagnosed with HFrEF (Ejection Fraction <40%) were retrospectively screened. A total of 597 patients with reliable clinical data were included in the study.The relationship between major adverse cardiovascular events and SII was evaluated. Exitus, stroke and hospitalization were accepted as major adverse cardiovascular events.

RESULTS: In patients with HFrEF, SII index was found to be significantly higher in the Exitus (+) group (1504.34±1722.74) when compared with the Exitus (-) group (893.94±972.13) (p=0.014). On the other hand, SII index was not found to be different between the patients with or without stroke and between those with or without hospitalization. When the correlation between the SII index and presence of exitus, stroke, and hospitalization was evaluated, a significant positive correlation was found between the presence of exitus and SII index (r=0.165 p<0.001). A SII index value of 697.29 was found to predict exitus with 604% sensitivity and 607% specificity in heart failure patients (AUC: 0.621,95%CI 0.539-0.704, p=0.04).

CONCLUSION: SII index, which can be calculated easily from lymphocyte, platelet and neutrophil counts, predicts mortality in patients with HFrEF. This index has prognostic significance in patients with HFrEF, suggesting that closer monitoring of elderly patients with a high SII index may be beneficial.

Keywords: immune inflammation index, heart failure

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INTRODUCTION

Heart failure (HF) is a complex clinical syndrome, characterized by ventricular systolic or diastolic dysfunction and is the leading cause of mortality and morbidity worldwide(1). HF is a major public health problem and the incidence of HF increases with increasing age. Despite advanced modern treatment approaches, mortality rates are still high. Moreover, since HF is a chronic disorder with acute exacerbations, hospitalizations and medications for HF take place near the top in the health spendings.

Recently, a new classification of HF defined by the European Society of Cardiology (ESC) based on left ventricular ejection fraction (LVEF), clinical manifestations, and myocardial changes has received increasing attention. (2) . This classification includes HF with preserved ejection fraction (HEpEF, LVEF>50%), HF with mildly reduced ejection fraction (HFmrEF, LVEF 41-49%), and HF with reduced ejection fraction (HFrEF, LEVF < 40%)(2) .

Remarkably, HFrEF is responsible for almost half of all heart failure cases(3). The main pathological mechanisms causing HFrEF include incompatibility of the neurohormonal system and hyperactivation of the renin-angiotensin aldosterone system (4). In addition, some systemic inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) levels were found to be high in HFrEF patients (5). This inflammatory process can induce myocardial damage, resulting in progression and exacerbation of HFrEF.

The systemic immune inflammation index (SII) is a new inflammatory parameter that includes neutrophil (N), platelet (P) and lymphocyte (L) counts. SII has been previously studied in cancer patients, and it has been found that patients with high SII have a higher risk of death in long-term follow-up (6). In addition, the predictive value of this index was evaluated in predicting mortality in patients with coronary artery disease and acute coronary syndrome (7,8). . In this study, we aimed to investigate whether SII plays a role in predicting prognosis and major adverse cardiovascular events such as death, stroke and hospitalization in patients with HFrEF.

MATERIAL & METHODS

Patients over the age of 18 and diagnosed with HFrEF (Ejection Fraction <40%) in the cardiology and emergency outpatient clinic between January 2018 and January 2021 were retrospectively screened. Initially, a total of 616 patients were included in the study. The data at the first admission including sociodemographic characteristics, haematological and biochemical parameters, medical history, smoking status and echocardiographic parameters were recorded. Fourteen patients were excluded from the study because reliable clinical data were not available. In addition, 5 patients with concurrent active infection were excluded from the study. Finally, analysis was performed in the remaining 597 patients.

Complete blood counts and biochemical parameters were examined in the venous blood samples taken from the antecubital vein. The systemic immune inflammation index was calculated using the neutrophil X platelet / lymphocyte formula.(9).

All patients included in the study undervent 2D transthoracic echocardiographic (TTE) evaluation performed by an experienced cardiologist. (Philips, iE33, the Netherlands). Echocardiographic evaluation was performed in accordance with the recommendations of the American Society of Echocardiography. Left ventricular (LV) end-diastolic and end-systolic diameters, interventricular septum and posterior wall thickness were measured using M-mode in the parasternal long axis view. LVEF was calculated using the modified Simpson's method on apical two-chamber and four-chamber views.

Exitus, stroke and hospitalization were taken as major adverse cardiovascular events. Stroke and hospitalization within 1 year were recorded from the file records. The National Death Notification System was used to evaluate survival status of each case. The study protocol was evaluated and approved by the local ethics committee.

Statistical analysis

Data were tested for normality with the Kolmogorov-Smirnov test and for homogeneity of variance with the Levene test. Groups were compared with Welch's t-test, Mann-Whitney U test and student-t test. The numeric variables were expressed as mean ± SD and median [min-max] while the categorical variables were expressed as percentage. Point biserial correlation test was used to evaluate the correlation between presence of exitus and SII index. Binary logistic regression analysis was used to find parameters that predict exitus. Roc curve analysis was performed to calculate the SII index cut-off value. All statistical analyzes were performed using SPSS v25 (IBM Inc., Chicago, IL, USA) statistical software. The results were

evaluated at the 95% confidence interval and the significance level was p<0.05.

RESULTS

The average age of the patients included in the study was 65.83±11.45 years. 37 % of patients were females and 63 % were males. In the study population, diabetes was detected in 31.5% and hypertension in 52.6%. Sociodemographic characteristics and laboratory parameters of the patients are given in Table 1. The mean LVEF in the study group was 28.5±6.5 %. Baseline echocardiography parameters are shown in Table 1.

SII index was found to be significantly higher in the Exitus (+) group (1504.34±1722.74) when compared to Exitus (-) group (893.94±972.13, p=0.014). On the other hand, SII index was not found to be different between the patients with or without stroke and between those with or without hospitalization (Table 2). When the correlation between the SII index and presence of exitus, stroke, and hospitalization was evaluated, a significant positive correlation was found between the presence of exitus and SII index (r=0.165 p<0.001) (Table 3).

Age and white blood cell count were found to be higher and platellet count was found to be lower in the Exitus (+) group when compared to Exitus (-) group (p=0.001, p<0.001, p=0.042, respectively). Urea, creatinine and AST values were also significantly higher (p<0.001, p<0.001, p<0.001, respectively). The total cholesterol levels were higher in the Exitus (+) group (p=0.014) while TG levels were lower (p=0.015). BNP and Troponin levels were also higher in the Exitus (+) group (p=0.021, p=0.037, respectively, Table 4)

Binary logistic regression analysis revealed that age (Beta: 0.036 95%CI 1.009-1.065 p=0.009) and SII index (beta 0.000 95%1,000-1,000 p=0.003) can predict exitus in heart failure patients (Table 5).

SII index value of 697.29 was found to predict exitus with 604% sensitivity and 607% specificity in heart failure patients (AUC: 0.621, 95%CI 0.539-0.704, p=0.04) (Figure 1).

Table 1. *Sociodemographical characteristics, laboratory and echocardiographic findings*

Variables		Variables	
Age (year)	65,83±11,45	**HDL (mg/dL)**	40.11±11.78
Gender		**LDL (mg/dL)**	129.14±133.56
Female, n(%)	221 (%37)	**TG(mg/dL)**	146.13±95.93
Male, n(%)	376 (%63)	**BNP (pg/mL)**	3122.99±3272.34
Diabetes Mellitus, n(%)	188 (%31.5)	**Troponin (ng/mL)**	0.176±1.707
Hypertension, n(%)	314 (%52.6)	**Exitus**	53 (%8.9)
Hyperlipidemia, n(%)	111 (%18.6)	**Stroke**	60(%10.1)
Chronic kidney disease, n (%)	33(5.52)	**Hospitalization**	108 (%18.1)
Sigara	133 (%22.3)	**SII**	950.76±1077.07
Rhythm		**Duration of heart failure (month)**	23 (9-35)
Sinus Rhythm (%)	311(52.1)	**Medications (%)**	
Atrial fibrillation, n(%)	292 (48.9)	**ACEI**	
Hgb (g/dL)	13.86±6.12	**ARB**	35
WBC (10^3/µL)	8.57±4.41	**Beta blocker**	25
Plt (10^3/µL)	230.16±84.62	**Digoxin**	75
Neutrophil	5.73±4.95	**ASA**	73.2
Lymphocyte	1.65±0.97	**MRA**	75.5
Fasting glucose (mg/dL)	116.73±50.15	**Anticoagulants**	52
Urea, (mg/dL)	41.85±29.76	**Furosemid**	45
Creatinine (g/dL)	1.24±1.66	**NYHA Class(%)**	40
CRP (mg/l)	8.45±9.77	**I**	
AST,(U/L)	32.14±50.20	**II**	30.5
ALT, (U/L)	29.59±39.92	**III**	35
T. Cholesterol (mg/dL)	187.41±45.64	**IV**	32
Left atrium(mm)	42.5±3.1	**RVDD(mm)**	2.5
Septum(mm)	10.9±2.1	**TAPSE**	29.5±3.5
LVDD(mm)	59.1±8.4	**E wave m/sec**	17.2±3.0
LVSD(mm)	42.3±10.2	**A wave m/sec**	1.5 (0.8-1.9)
Ejection fraction %	28.5±6.5	**E/A**	1.1 (0.9-2.5)
			1.36 (0.9-1.2)

SII: Immune Inflammation Index; ACEI - angiotensin-converting enzyme inhibitor; ASA - acetylsalicylic acid; AST - aspartate aminotransferase; ALT - alanine aminotransferase; A wave- A wave velocity; BNP - brain natriuretic peptide;CRP- C reactive protein; E wave- E wave velocity; LDL - low-density lipoprotein; TG -

triglycerides; LVDD - left ventricular diastolic diameter; LVSD - left ventricular systolic diameter; HDL - high-density lipoprotein; Hgb- hemoglobin; Plt- platelet; MRA - mineralocorticoid receptor antagonist; NYHA- New York Heart Association; RVDD – Right ventricular diastolic diameter; ;T. Cholesterol-Total Cholesterol; TAPSE - tricuspid annular plane systolic excursion; WBC- White blood cell.

Table 2. *Comparision of the groups in terms of SII index*

	Exitus (+)(n=53)	**Exitus (-)(n=544)**	**p**
SII index	1504.34±1722.74 (min 81.53 max 8059.42)	893.94±972.13 (min13.73 max 9601.70)	**0.014***
	Stroke (+)(n=60)	**Stroke (-)(n=537)**	
SII index	805.69 (min 139.054 max 4816.0)	591.58 (min 13.371-9601.706)	0.103**
	Hospitalization (+) (n=108)	**Hospitalization (-) (n=489)**	
SII index	608.46 (min 66.14 max 4251.07)	593.54 (min13.731 max 9601.706)	0.573**

**: Welch's t-test **: Mann- Whitney U test SII- Immune Inflammation Index*

Table 3. Point Biserial Correlation test

	SII index	**p**
Exitus (+)	r=0.165	**<0.001**
Hospitalization (+)	r=0.017	0.687
Stroke (+)	r=0.070	0.096

Table 4. Comparision of Exitus (+) and Exitus (-) groups in terms of age and laboratory parameters

	Exitus (+)	**Exitus (-)**	**P value**
Age, year	70.66±12.02	65.34±11.29	***0.001****
Hemoglobin, g/dl	12.85±2.58	13.96±6.34	0.231*
White blood cell10^3/UL	12.55±9.50	8.17±3.28	***<0.001****
Platelet, 10^3/UL	207.42±80.72	232.38±84.74	***0.042****
C-reactive protein, mg/L	5.10 (0.60-72)	5(0.06-73)	0.776**
Fasting glucose (mg/dL)	115.73±49,29	126.98±57.78	0.123
Urea, mg/dl	48(16-208)	36(6-236)	***<0.001***
Creatinine (g/dL	1.2 (0.6-6.5)	0.93 (0.60-11.2)	***<0.001***
AST,U/L	26 (6-756)	22(3-414)	***<0.001***
ALT, U/L	21 (5-146)	20 (5-453)	0.149
T. Cholesterol (mg/dL)	172.74±33,66	188.84±46,42	***0.014***
HDL(mg/dL)	38.31±15,55	40.28±11.36	0.255
LDL (mg/dL)	115.20(11-892)	116(11-892)	0.914
Triglyceride(mg/dL)	114.64±58.09	149.12±98.28	***0.015***
BNP(pg/mL)	3321(48-21400)	2146(25800)	***0.021***
Troponin(ng/mL)	0.027(0.008-0.67)	0.013(0.001-12)	***0.037***

**: Student T testi **: Mann- Whitney U test AST - aspartate aminotransferase; ALT - alanine aminotransferase; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TG - triglycerides; BNP - brain natriuretic peptide*

Table 5. *Independent predictors of Exitus in heart failure patients in binary logistic regression analysis.*

	Beta	**Exp(Beta)**	**95% confidence interval**	**p**
Age	0.036	1.036	1.009-1.065	***0.009***
BNP	0,000	1.0	1.000-1.000	***0.063***
Troponin	-0.186	0.83	0.376-1.834	0.645
SII index	0,000	1.0	1.000-1.000	***0.003***

BNP:Brain natriuretic peptide, SII: Immune Inflammation Index

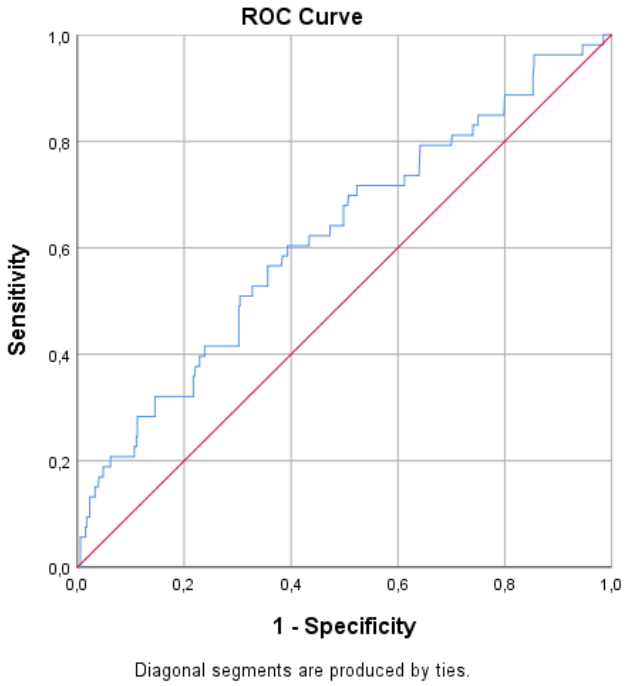

Figure 1. Roc curve analysis; SII index value of 697.29 was found to predict exitus with 604% sensitivity and 607% specificity in heart failure patients (AUC: 0.621, 95%CI 0.539-0.704, p=0.04)

DISCUSSION

The most remarkable outcome of our study is that the SII index, which can be easily calculated from the lymphocyte, platelet and neutrophil counts, can predict mortality in patients with HFrEF. This index has prognostic significance in patients with HFrEF, suggesting that closer monitoring of elderly patients with a high SII index may be beneficial.

It is well known that inflammation has an important role in the pathogenesis of atherosclerosis and cardiovascular diseases (10). The role of inflammation in heart failure has been demonstrated in many previous studies. The heart failure syndrome is mainly due to the imbalance between inflammatory and anti-inflammatory processes (11).

Systemic inflammatory indices which are calculated by platelets, inflammatory activators (neutrophils/monocytes) and inflammatory regulators (lymphocytes), are considered as effective indicators of systemic inflammation and immune balance, and play an important role in the prognostic and therapeutic evaluation of various diseases.

SII is an index calculated using platelet, lymphocyte and neutrophil counts. SII can be considered as a modified and reliable version of the previously described platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte-ratio (NLR). NLR has prognostic value in HF patients with reduced or preserved ejection fraction (12,13). Similarly, recent studies have confirmed the prognostic value of PLR in different cohorts of HF patients (14,15).

Elevated inflammatory marker levels are associated with poor outcome in heart failure, as in many chronic diseases. Increased inflammatory stimulus causes secretion of many inflammatory cytokines such as TNF-alpha, IL-6 and CRP. These inflammatory cytokines cause detrimental effects on the myocardium, leading to decreased left ventricular function and heart failure (10,11). In a study, it was found

that patients with decompensated heart failure had higher NLR and PLR values. Moreover, these parameters were found to have an impotant role in predicting heart failure decompensation (16). These findings about the association between HF and inflammation are also consistent with the results of our study.

In a recent study, SII was found to be an independent predictor for both long-term mortality and requirement of ICD therapy in patients with HFrEF(17). In our study, the fact that SII was associated with mortality but not with hospitalization may suggest that this robust association between SII and mortality results from arrhythmic events.

There is a 2 to 5-fold increased risk of stroke in patients with heart failure(18). A higher incidence of ischemic stroke is observed in patients with chronic HF when compared to general population (8-11% vs. 1%) (19). There was no significant difference in the incidence of stroke between HFrEF, HFmrEF and HFpEF subgroups. On the other hand, stroke risk was found to be higher in the elderly patients and those with atrial fibrillation(20,21).

It is well known that patients with HFrEF have a prothrombotic state due to platelet hyperactivity, increased thrombin production and impaired fibrinolysis (22). The presence of hypercoagulation has also been reported in patients with HFpEF (23). As a result, the presence of HF carries a risk of stroke regardless of its subgroup.

Endothelial dysfunction observed in patients with chronic heart failure leads to decreased endothelial-derived nitric oxide formation and myocardial microvascular activity leading to sub endocardial damage, which ultimately leads to the development of thromboembolic complications.(24,25). The main pathophysiological mechanisms causing progression of HFrEF such as activation of sympathetic and renin-angiotensin-aldosterone systems and systemic inflammation, further increase the risk of stroke in these patients. In our study, lack of a correlation between SII and stroke was an unexpected finding. Although the frequency of stroke was high, a clear relationship between SII and stroke could not be determined. This may be secondary to intensive use of antiaggregant or anticoagulant therapy in patients with HFrEF.

CONCLUSION

SII index, which can be calculated easily from lymphocyte, platelet and neutrophil counts, predicts mortality in patients with HFrEF. This index has prognostic significance in patients with HFrEF, suggesting that closer monitoring of elderly patients with a high SII index may be beneficial.

Study limitations

Limited number of patients and single-center and retrospective design can be considered as the limitations of our study. On the other hand, all consecutive patients with sufficient data were included in the study. Since the exact cause of mortality in our study population is unclear, it was also not possible to distinguish between cardiac and non-cardiac mortality.

Etik: Bu çalışmanın etik kurulu alınmıştır.

Ethics committee approval had been taken.

Yazar katkı durumu; Çalışmanın konsepti; OB, FA, dizaynı; OB, FA, Literatür taraması; OB, FA, verilerin toplanması ve işlenmesi; OB, FA, istatistik; OB, FA, yazım aşaması; OB, FA.

Author contribution status; The concept of the study; OB, FA, design; OB, FA, literature review; OB, FA, collecting and processing data; OB, FA, statistics; OB, FA, writing phase; OB, FA.

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REFERENCES

1. Ardahanli I, Celik M. Serum Uric Acid Levels among Patients who Died in Recent Year due to Heart Failure with Reduced Ejection Fraction. J Coll Physicians Surg Pak. 2020 Aug;30(8):780-7doi: 10.29271/jcpsp.2020.08.7PMID: 32893785.

2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. EurHeartJ. 2021;42(36):3599-37doi: 10.1093/eurheartj/ehab3

3. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev.2017;3(1):7-doi: 10.15420/cfr.2016:25:2

4. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017;14(1):30doi: 10.1038/nrcardio.2016.163.

5. Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. Nat Rev

Cardiol. 2020;17(5):2692doi: 10.1038/s41569-019-0315-x.

6. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer:ameta-analysis. J Cancer. 2018;9(18):3295-3302 doi: 10.7150/jca.25691.

7. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease.Eur J Clin Invest.2020;50(5):e132doi: 10.1111/eci.13230.

8. Su G, Zhang Y, Xiao R, Zhang T, Gong B. Systemic immune inflammation index as a promising predictor of mortality in patients with acute coronary syndrome: a real-world study. J Int Med Res. 2021;49(5):30006052110162doi: 10.1177/03000605211016274

9. Yurdam FS, Kış M. The Predictive Role of Systemic Immune Inflammation Index to the Aortic Valve Calcification in the Elderly Population with Chronic Renal Failure. E J Cardiovasc Med 2023;11:11-16

10. Güzel T, Kış M. Correlation Between Coronary Lesion Severity Detected in Fractional Flow Reserve with Systemic Immune Inflammation Index and Atherogenic Plasma Index 10.4274/BMB.galenos.2022.2022-04-036.

11. Oikonomou E, Tousoulis D, Siasos G, Zaromitidou M, Papavassiliou AG, Stefanadis C. The role of inflammation in heart failure: new therapeutic approaches. Hellenic J Cardiol 2011; 52: 30-PMID: 21292605.

12. Uthamalingam S, Patvardhan EA, Subramanian S, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol. 2011;107(3):4334doi: 10.1016/j.amjcard.2010.09.039.

13. Curran FM, Bhalraam U, Mohan M, et al. Neutrophil-to-lymphocyte ratio and outcomes in patients with new-onset or worsening heart failure with reduced and preserved ejection fraction. ESC Heart Fail. 2021;8(4):3168-31doi: 10.1002/ehf2.13424.

14. Demir M, Duyuler PT, Guray U, Celik MC. Platelet to lymphocyte ratio on admission and prognosis in patients with acute cardiogenic pulmonary edema.JEmergMed.2018;55(4):465-4doi: 10.1016/j.jemermed.2018.06.021

15. Heidarpour M, Bashiri S, Vakhshoori M, et al. The association between platelet-to-lymphocyte ratio with mortality among patients suffering from acute decompensated heart failure. BMC Cardiovasc Disord. 2021;21(1):454 doi: 10.1186/s12872-021-02260-7.

16. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophilto-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol 2015; 105: 606-13 doi: 10.5935/abc.20150126.

17. Hayıroglu M˙I, ÇınarT, Çinier G, et al. Evaluating systemic immune-inflammation index in patients with ICD for heart failure with reduced ejection fraction. Pacing Clin Electrophysiol.2022;45:188–1https://doi.org/10.1111/pace.14436

18. Adelborg, K.; Szépligeti, S.; Sundbøll, J.; et al. Risk of Stroke in Patients With Heart Failure: A Population-Based 30-Year Cohort Study. Stroke 2017, 48, 1161–11doi: 10.1161/STROKEAHA.116.016022.

19. Pullicino, P.M.; Halperin, J.L.; Thompson, J.L. Stroke in patients with heart failure and reduced left ventricular ejection fraction. Neurology 2000, 54, 288–2doi: 10.1212/wnl.54.2.288.

20. Sartipy, U.; Dahlström, U.; Fu, M.; Lund, L.H. Atrial Fibrillation in Heart Failure with Preserved, Mid-Range, and Reduced Ejection Fraction. JACC Heart Fail. 2017, 5, 565–574 doi: 10.1016/j.jchf.2017.05.001.

21. Pullicino, P.M.; Halperin, J.L.; Thompson, J.L. Stroke in patients with heart failure and reduced left ventricular ejection fraction. Neurology 2000, 54, 288–2doi: 10.1212/wnl.54.2.288.

22. Paolillo, S.; Ruocco, G.; Filardi, P.P.; et al. "Right and Left Heart Failure Study Group" of the Italian Society of Cardiology. Direct oral anticoagulants across the heart failure spectrum: The precision medicine era. Heart Fail. Rev. 2020, doi:10.1007/s10741-020-09994-0.

23. Jug, B.; Vene, N.; Salobir, B.G.; Sebestjen, M.; Sabovic, M.; Keber, I. Procoagulant state in heart failure with preserved left ventricular ejection fraction. Int. Heart. J. 2009, 50, 591–6doi: 10.1536/ihj.50.591.

24. Jekell, A.; Kalani, M.; Kahan, T. The interrelation of endothelial function and microvascular reactivity in different vascular beds, and risk assessment in hypertension: Results from the Doxazosin-ramipril study. Heart Vessels. 2019, 34, 484–4doi: 10.1007/s00380-018-1265-7.

25. Scherbakov, N.; Sandek, A.; Martens-Lobenhoffer, J.; et al. Endothelial dysfunction of the peripheral vascular bed in the acute phase after ischemic stroke. Cereb. Dis. 2012, 33, 37–doi: 10.1159/000332809.