DOI: 10.4274/terh.galenos.2021.99710
J Tepecik Educ Res Hosp 2022;32(3):439-47

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Association of Left Ventricular Ejection Fraction with Inflammation Parameters and Indexes

Sol Ventrikül Ejeksiyon Fraksiyonunun Enflamasyon Parametreleri ve İndeksleri ile İlişkisi

Selçuk Öztürk[1], Alisultan Başaran[2], Mehmet Erdoğan[3], Yaşar Turan[1]

[1]Yozgat Bozok University Faculty of Medicine, Department of Cardiology, Yozgat, Turkey
[2]Yozgat Bozok University Faculty of Medicine, Department of Internal Medicine, Yozgat, Turkey
[3]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Cardiology, Ankara, Turkey

Cite as: Öztürk S, Başaran A, Erdoğan M, Turan Y. Association of Left Ventricular Ejection Fraction with Inflammation Parameters and Indexes. J Tepecik Educ Res Hosp 2022;32(3):439-47

Abstract

Objective: Left ventricular ejection fraction (LVEF) measurement through transthoracic echocardiography is the recommended parameter for evaluating LV systolic functions. This retrospective study aimed to evaluate the association of LVEF with inflammatory biomarkers and indexes including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI).

Methods: After the application of exclusion criteria, 854 patients remained for statistical analyses. NLR, PLR, SII and SIRI were calculated from admission complete blood count test. Patients with LVEF ≥50% were defined as preserved LVEF (pLVEF), LVEF 41-49% mildly reduced LVEF (mrLVEF) and LVEF ≤40% reduced LVEF (rLVEF). LVEF <50% was defined as impaired LVEF.

Results: Patients were classified into three groups with respect to their LVEF namely pLVEF (n=784), mrLVEF (n=24) and rLVEF (n=46). PLR and SII levels were comparable between groups. Patients with mrLVEF and rLVEF had higher NLR and SIRI levels compared to pLVEF patients. The area under the curve (AUC) values for NLR, PLR, SII and SIRI to predict impaired LVEF were 0.59, 0.54, 0.55, and 0.63, respectively. The AUC values for NLR, PLR, SII and SIRI for predicting mrLVEF were 0.61, 0.55, 0.55, and 0.65, respectively. The AUC values for NLR, PLR, SII and SIRI to predicting rLVEF were 0.58, 0.53, 0.54, and 0.61, respectively. Multivariate regression analysis revealed age, coronary artery disease (CAD) and SIRI (odds ratio: 1.39, 95% confidence interval (CI): 1.09-1.76, p=0.007) as independent predictors of impaired LVEF. Multinomial logistic regression analysis performed for evaluating predictors of mrLVEF and rLVEF in contrast to pLVEF demonstrated that CAD independently predicts mrLVEF, whereas CAD and SIRI (odds ratio: 1.42, 95% CI: 1.09-1.84, p=0.009) are independent predictors of rLVEF.

Conclusion: SIRI is a novel biomarker that is associated with impaired LVEF and rLVEF but not mrLVEF.

Keywords: Left ventricular ejection fraction, systemic immune-inflammation index, systemic inflammation response index

Address for Correspondence/Yazışma Adresi: Selçuk Öztürk MD, Yozgat Bozok University Faculty of Medicine, Department of Cardiology, Yozgat, Turkey
Phone: +90 553 537 66 13 **E-mail:** selcuk.ozturk@bozok.edu.tr
ORCID ID: orcid.org/0000-0002-3426-1212

Received/Geliş tarihi: 30.09.2021
Accepted/Kabul tarihi: 19.12.2021

Öz

Amaç: Transtorasik ekokardiyografi ile sol ventrikül ejeksiyon fraksiyonu (SVEF) ölçümü, SV sistolik fonksiyonlarını değerlendirmek için önerilen parametredir. Bu retrospektif çalışmada, SVEF ile nötrofil/lenfosit oranı (NLO), trombosit/lenfosit oranı (TLO), sistemik immün-enflamasyon indeksi (SII) ve sistemik enflamasyon yanıt indeksi (SIYI) gibi enflamatuvar biyobelirteçler ve indeksler arasındaki ilişkinin değerlendirilmesi amaçlandı.

Yöntem: Hastalar dışlama kriterlere tabii tutulduktan sonra istatistiksel analizler için 854 hasta kaldı. NLO, TLO, SII ve SIYI değerleri başvuru sırasındaki tam kan sayımı testi aracılığıyla hesaplandı. SVEF ≥%50 olan hastalar korunmuş SVEF (kSVEF), SVEF %41-49 hafif derecede azalmış SVEF (haSVEF) ve SVEF ≤%40 azalmış SVEF (aSVEF) olarak tanımlandı. SVEF <%50 bozulmuş SVEF olarak tanımlandı.

Bulgular: Hastalar SVEF'lerine göre kSVEF (n=784), haSVEF (n=24) ve aSVEF (n=46) olmak üzere üç gruba ayrıldı. TLO ve SII seviyeleri gruplar arasında benzerdi. haSVEF ve aSVEF'li hastalar, kSVEF hastalarına göre daha yüksek NLO ve SIYI seviyelerine sahipti. Bozulmuş SVEF'yi öngörmek için NLO, TLO, SII ve SIYI için eğri altında kalan alan sırasıyla 0,59, 0,54, 0,55 ve 0,63 olarak hesaplandı. haSVEF'yi öngörmek için NLO, TLO, SII ve SIYI için eğri altında kalan alan sırasıyla 0,61, 0,55, 0,55 ve 0,65 olarak hesaplandı. aSVEF'yi öngörmek için NLO, TLO, SII ve SIYI için eğri altında kalan alan sırasıyla 0,58, 0,53, 0,54 ve 0,61 olarak hesaplandı. Çok değişkenli regresyon analizi yaş, koroner arter hastalığı (KAH) ve SIYI (odds oranı: 1,39, %95 güven aralığı: 1,09-1,76, p=0,007) bozulmuş SVEF'nin bağımsız öngörücüleri olarak gösterdi. kSVEF kıyasla haSVEF ve aSVEF öngörücülerini değerlendirmek için gerçekleştirilen multinomial lojistik regresyon analizi, KAH'ın haSVEF'i bağımsız olarak öngördüğünü, buna karşın KAH ve SIYI'nın (odds oranı: 1,42, %95 güven aralığı: 1,09-1,84, p=0,009) aSVEF'nin bağımsız öngörücüleri olduğunu gösterdi.

Sonuç: SIYI, bozulmuş SVEF ve aSVEF ile ilişkili olan ancak haSVEF ile ilişkili olmayan yeni bir biyobelirteçtir.

Anahtar Kelimeler: Sol ventrikül ejeksiyon fraksiyonu, sistemik immün-enflamasyon indeksi, sistemik enflamasyon yanıt indeksi

Introduction

Transthoracic echocardiography (TTE) is a widely used non-invasive imaging method for evaluating cardiac anatomy and functioning. The left ventricular ejection fraction (LVEF), which is the recommended parameter for assessing LV systolic functions, provides substantial diagnostic and prognostic information and guides the clinician for several key therapeutic decisions[1,2]. LV systolic dysfunction (LVSD) occasionally occurs after a myocardial infarction (MI) and increases the risk of heart failure (HF) development and sudden cardiac death[3].

Inflammation is a significant contributor in the pathogenesis of HF and is considered both as a cause and consequence of HF[4]. Because leukocytes white blood cells (WBCs) and their subtypes, neutrophils, lymphocytes and monocytes, and platelets, are directly related to inflammation, several biomarkers have been developed recently by using the count of these cells. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are well-defined predictive and prognostic biomarkers, which reflect systemic inflammatory status in the body[5,6]. Systemic immune-inflammation index (SII) was found to be superior to NLR and PLR in cancer and coronary artery disease (CAD) patients[7,8]. Besides, systemic inflammation response index (SIRI) has recently been developed and found to predict poor survival better than NLR, PLR and SII in cancer patients[9]. Thus, we evaluated the association of LVEF with inflammatory biomarkers and indices, including NLR, PLR, SII and SIRI.

Materials and Methods

Study Design and Patients

We evaluated clinical data and hospital records of 1991 patients who underwent TTE imaging at our center between August 2020 and April 2021 retrospectively. We defined the following conditions as exclusion criteria: Acute MI, unstable angina pectoris, acute decompensated and/or Class IV HF according to the New York Heart Association Classification, aortic dissection, acute pulmonary embolism, acute stroke, severe valvular disease and/or history of valve surgery, acute renal insufficiency, severe chronic renal insufficiency and/or dialysis therapy, active bacterial or viral infection, active malignancy, active hematological disease, rheumatic disease, inflammatory disease, steroid therapy, severe hepatic failure, severe respiratory failure, thyroid dysfunction, severe anemia, life threatening arrhythmia, pregnancy, pericardial tamponade. Additionally, we excluded patients with missing data and poor echocardiographic window and/or suboptimal imaging.

Arterial hypertension (HT) was diagnosed if repeated blood pressure measurements were ≥140/90 mmHg or the previously diagnosed HT with or without the usage of antihypertensive agents. Diabetes mellitus (DM) was diagnosed if the fasting plasma glucose level was ≥126 mg/dL in multiple measurements or glucose level was ≥200 mg/dL at any measurement including non-fasting or treatment with antidiabetic agents. Smoking was defined as

active smoking in the past six months. Hyperlipidemia was diagnosed if a baseline cholesterol level was ≥200 mg/dL and/or low-density lipoprotein cholesterol level of ≥130 mg/dL or previously diagnosed and treated hyperlipidemia by lipid lowering agents. Atrial fibrillation (AF) was diagnosed as irregular ventricular beats lacking p waves and presence of fibrillatory waves on electrocardiography (ECG) at hospital admission, follow-up ECGs, ambulatory ECG recordings, or a previous diagnosis of AF. CAD was defined as a history of MI and/or angiographically documented CAD.

Because the study was designed retrospectively, informed consent from the patients was waived with the approval of the study protocol by the local ethics committee of the hospital (2017-KAEK-189_2021.07.07_07). All study procedures were performed in line with the recommendations of the Good Clinical Practices Guidelines and the Helsinki Declaration.

Blood Sampling and Analysis

Peripheral venous blood sampling was performed from a large antecubital vein in the morning hours after at least an eight hours fasting period. Total complete blood count (CBC) test (Sysmex XN-1000, Kobe, Japan) and biochemical measurements (Roche Diagnostic Modular Systems, COBAS 6000, Tokyo, Japan) including glucose, creatinine, blood urea nitrogen, liver enzymes, electrolytes and lipid profile were performed at the hospital biochemistry laboratory. Blood samples were taken into ethylenediamine tetra-acetic acid containing tubes for CBC test and measurements were performed immediately after the blood sampling.

NLR was computed by dividing the neutrophil count to the lymphocyte count. PLR was calculated by dividing the platelet count to the lymphocyte count. SII was computed as platelet count x neutrophil count/lymphocyte count. SIRI was calculated as monocyte count x neutrophil count/lymphocyte count[9].

Transthoracic Echocardiography

Two-dimensional TTE was performed on each patient on the day of admission using a commercially available machine (Philips Logic Affiniti 50G machine; Philips, Amsterdam, Netherlands) with a broadband transducer. Patients were placed at left lateral decubitus position during TTE. All measurements were carried out conventionally from parasternal long-axis, short-axis, and apical views. LVEF was computed through Simpson's method. All echocardiographic procedures agreed with the American Society of Echocardiography guideline recommendations[10].

LVEF data were obtained from the hospital records of the patients retrospectively. Patients were categorized into three groups with respect to their LVEF: Patients with LVEF ≥50% were defined as preserved LVEF (pLVEF), LVEF 41-49% mildly reduced LVEF (mrLVEF) and LVEF ≤40% reduced LVEF (rLVEF)[2]. However, LVEF <50% was defined as impaired LVEF[11].

Statistical Analysis

Statistical tests were carried out through IBM Statistical Package for the Social Sciences Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, New York, USA). The distribution pattern of continuous variables was evaluated through Shapiro Wilk test. Categorical variables were described as percentages, and comparisons were performed using the chi-square test. Comparison of quantitative variables according to LVEF was performed by Kruskal-Wallis test because of abnormal distributions and the results were given as medians with interquartile ranges (percentiles 25th and 75th). Receiver operating characteristic (ROC) analyzes were conducted to evaluate the ability of the NLR, PLR, SII and SIRI to predict impaired LVEF, mrLVEF and rLVEF and determine the cut-off value of SIRI for impaired LVEF. The area under the ROC curve (AUC) values of NLR, PLR, SII and SIRI to predict impaired LVEF, mrLVEF and rLVEF were given with 95% confidence interval (CI) and with sensitivity and specificity of cut-off value of SIRI to predict impaired LVEF.

Variables associated with impaired LVEF were investigated using univariate and multivariate binary logistic regression analyzes. Variables which could be associated with impaired LVEF, such as age, gender, HT, DM, CAD, AF, creatinine and SIRI, were included in the univariate analysis. The variables with a p-value<0.1 in univariate tests were included in the multivariate regression analysis. Then, multinominal logistic regression analysis was performed as there were three categories of the dependent variable. A two-sided p-value below 0.05 was determined as statistically significant for all tests.

Results

There remained 854 patients for statistical analyses after the exclusion criteria were applied and the study cohort was categorized according to their LVEF and named as pLVEF (n=784), mrLVEF (n=24) and rLVEF (n=46).

Table Baseline clinical characteristics and laboratory parameters are presented in Table 1. Patients with pLVEF were more likely to be younger and female, and had less HT, CAD and AF compared with patients with mrLVEF and

Table 1. Table baseline clinical characteristics and laboratory parameters of the patients				
Variables	**LVEF ≤40% (n=46)**	**LVEF 41-49% (n=24)**	**LVEF ≥50% (n=784)**	**p value**
Demographics				
Age (years)	69 (60-76)	69 (61-76)	57 (45-66)	<0.001
Gender (male)	30 (65%)	17 (71%)	376 (48%)	0.008
Smoking	8 (18%)	2 (9%)	142 (19%)	0.421
Comorbidities				
Hypertension	37 (80%)	17 (71%)	358 (46%)	<0.001
Diabetes mellitus	15 (33%)	9 (37%)	197 (25%)	0.222
Hyperlipidemia	23 (50%)	16 (67%)	314 (40%)	0.186
Coronary artery disease	32 (70%)	20 (83%)	161 (20%)	<0.001
Atrial fibrillation	9 (20%)	2 (8%)	45 (6%)	0.001
Medications				
Antiplatelet agents	31 (67%)	20 (83%)	192 (25%)	<0.001
Anticoagulants	9 (20%)	1 (4%)	42 (5%)	<0.001
Statins	20 (43%)	15 (62%)	120 (15%)	<0.001
Fibrates	0	0	9 (1%)	0.666
ACEi or ARBs	30 (65%)	12 (50%)	260 (33%)	<0.001
Mineralocorticoid receptor antagonists	14 (30%)	3 (12%)	18 (2%)	<0.001
Diuretics	20 (43%)	9 (37%)	76 (10%)	<0.001
Beta blockers	29 (63%)	16 (67%)	213 (27%)	<0.001
Calcium channel blocker	6 (13%)	6 (25%)	85 (11%)	0.092
Oral anti-diabetic agent	8 (17%)	4 (17%)	130 (17%)	0.990
Insulin	1 (2%)	3 (12%)	34 (%4)	0.120
Nitrate	5 (11%)	4 (17%)	13 (1%)	<0.001
Laboratory parameters				
Blood urea nitrogen (mg/dL)	18 (13-25)	16 (11-20)	13 (11-17)	<0.001
Creatinine (mg/dL)	0.97 (0.83-1.17)	0.94 (0.72-1.28)	0.81 (0.68-0.96)	<0.001
Alanine amino transferase (U/L)	14 (12-22)	16 (10-22)	17 (12-25)	0.446
Aspartate amino transferase (U/L)	17 (14-20)	18 (14-23)	17 (14-20)	0.737
Sodium (mEq/L)	140 (139-142)	140 (138-142)	140 (138-141)	0.344
Potassium (mEq/L)	4.53 (4.36-4.81)	4.41 (4.25-4.63)	4.43 (4.20-4.66)	0.079
Total cholesterol (mg/dL)	149 (122-175)	149 (125-180)	183 (157-215)	<0.001
Low-density lipoprotein cholesterol (mg/dL)	71 (57-105)	83 (62-108)	105 (82-133)	<0.001
High-density lipoprotein cholesterol (mg/dL)	40 (32-47)	43 (37-48)	43 (37-52)	0.016
Triglyceride (mg/dL)	114 (85-163)	118 (80-157)	140 (101-201)	0.019
Leukocytes ($x10^9$/L)	7.35 (6.10-8.95)	7.10 (5.90-8.75)	7.40 (6.40-8.70)	0.796
Hemoglobin (g/L)	13.6 (12.0-15.2)	13.9 (12.0-15.1)	14.2 (13.0-15.5)	0.072
Neutrophils ($x10^9$/L)	4.25 (3.40-5.91)	4.00 (3.50-5.60)	4.30 (3.50-5.38)	0.886
Lymphocytes ($x10^9$/L)	2.05 (1.50-2.32)	1.85 (1.42-2.38)	2.20 (1.80-2.70)	0.008
Platelets ($x10^9$/L)	236 (211-273)	240 (192-280)	260 (225-300)	0.033
Monocytes ($x10^9$/L)	0.64 (0.50-0.80)	0.63 (0.50-0.79)	0.54 (0.45-0.67)	0.002
Eosinophil ($x10^9$/L)	0.11 (0.07-0.18)	0.13 (0.07-0.20)	0.13 (0.08-0.21)	0.623

Data are median (IQR) and number (%). A p value less than .05 was considered significant for statistical analyses.

ACEi: Angiotensin-converting enzyme inhibitor, ARBs: Angiotensin receptor blockers, IQR: Interquartile range, LVEF: Left ventricular ejection fraction

rLVEF. Usage of antiplatelet agent, anticoagulant, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, mineralocorticoid receptor antagonist, diuretic, beta blocker and nitrate significantly differed between groups (p<0.001 for all). Biochemical parameters except blood urea nitrogen, creatinine and cholesterol panel, were similar between the groups. Lymphocyte count and platelet count were significantly elevated, whereas monocyte count was significantly decreased in the pLVEF group. WBC count, hemoglobin, neutrophil and eosinophil count were comparable between the groups. Hematological indices of the patients according to LVEF are demonstrated in Table 2. PLR and SII levels were comparable between the groups. Patients with mrLVEF and rLVEF had higher NLR (p=0.02) and SIRI (p=0.001) levels than the pLVEF group patients.

ROC curve analyses for NLR, PLR, SII and SIRI to predict impaired LVEF, mrLVEF and rLVEF are demonstrated in Figure 1. The AUC values for NLR, PLR, SII and SIRI to predicting impaired LVEF were 0.59 (95% CI: 0.52-0.67, p=0.006), 0.54 (95% CI: 0.47-0.61, p=0.22), 0.55 (95% CI: 0.47-0.62, p=0.15) and 0.63 (95% CI: 0.56-0.70, p<0.001), respectively. The cut-off value of SIRI (1.37) was associated with 53.0% sensitivity and 69.0% specificity. The AUC values for NLR, PLR, SII and SIRI to predicting mrLVEF were 0.61 (95% CI: 0.50-0.72, p=0.05), 0.55 (95% CI: 0.46-0.65, p=0.32), 0.55 (95% CI: 0.44-0.67, p=0.35) and 0.65 (95% CI: 0.54-0.76, p=0.009), respectively. The AUC values for NLR, PLR, SII and SIRI to predicting rLVEF were 0.58 (95% CI: 0.49-0.67, p=0.05), 0.53 (95% CI: 0.44-0.62, p=0.44), 0.54 (95% CI: 0.45-0.64, p=0.29) and 0.61 (95% CI: 0.52-0.69, p=0.01), respectively.

Logistic regression analysis performed for evaluating predictors of impaired LVEF is given in Table 3. Univariate analysis rendered age, gender, HT, DM, CAD, AF, creatinine and SIRI as associated parameters with impaired LVEF. In multivariate analysis, age, CAD and SIRI (odds ratio: 1.39, 95% CI: 1.09-1.76, p=0.007) remained independent predictors of impaired LVEF. Multinomial logistic regression analysis performed for evaluating predictors of mrLVEF and rLVEF in contrast to pLVEF is given in Table 4. CAD was found to predict mrLVEF independently, whereas CAD and SIRI (odds ratio: 1.42, 95% CI: 1.09-1.84, p=0.009) were found to be independent predictors of rLVEF.

Discussion

Our study results emphasize that SIRI, which is a novel marker that includes monocyte, neutrophil and lymphocyte counts, is independently associated with impaired LVEF. Moreover, age and CAD are also independently associated with impaired LVEF. Multinominal logistic regression analysis revealed SIRI as an independent predictor of rLVEF but not mrLVEF. To our knowledge, this is the first study to evaluate the association between various inflammation and immune system-related biomarkers and LVEF.

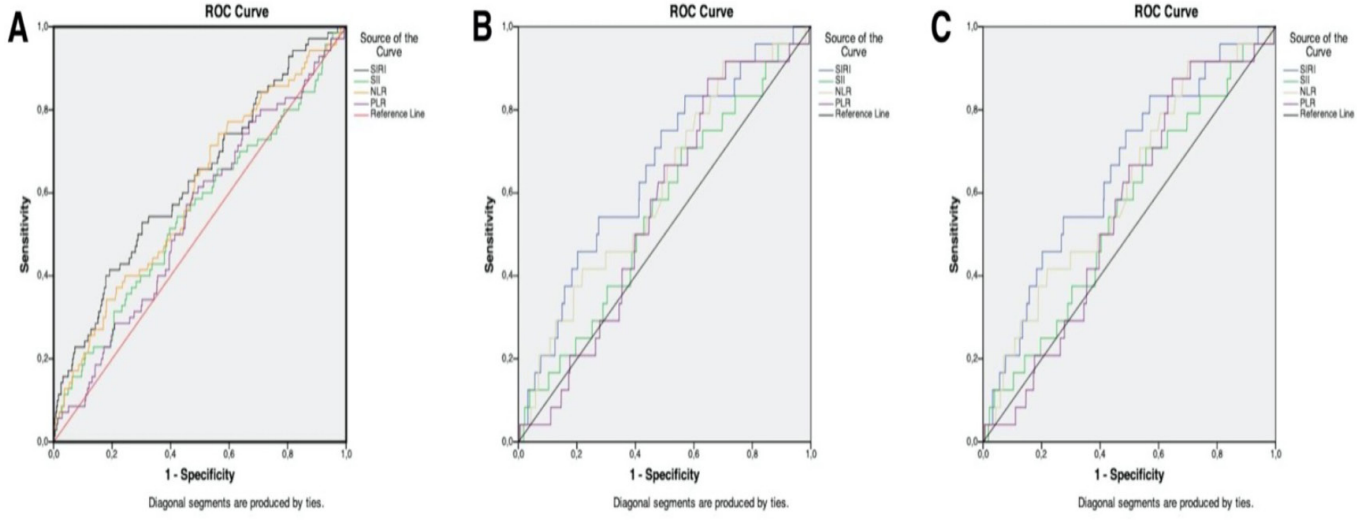

Figure 1. ROC curve analyses for NLR, PLR, SII and SIRI to predict impaired LVEF (LVEF <50%) (A), mildly reduced LVEF (LVEF 41-49%) (B), and reduced LVEF (LVEF ≤40%) (C).

ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, LVEF: Left ventricular ejection fraction

Table 2. Hematological indices of the patients according to LVEF

Variables	LVEF ≤40% (n=46)	LVEF 41-49% (n=24)	LVEF ≥50% (n=784)	p value
Neutrophil to lymphocyte ratio	2.12 (1.70-3.17)	2.15 (1.76-3.42)	1.92 (1.48-2.57)	0.021
Platelet lymphocyte ratio	124 (91-163)	124 (106-146)	116 (93-150)	0.446
Systemic inflammation response indexes	1.39 (0.84-2.27)	1.51 (1.05-2.10)	1.07 (0.75-1.54)	0.001
Systemic immune inflammation index (x10^3)	574 (352-799)	557 (404-744)	495 (370-693)	0.359

Data presented as median (IQR). A p value less than 0.05 was considered significant for statistical analyses.
IQR: Interquartile range, LVEF: Left ventricular ejection fraction

Table 3. Predictors of LVEF <50% by logistic regression analysis

Variables	Univariate		Multivariate*,†	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.06 (1.05-1.09)	<0.001	1.03 (1.01-1.06)	0.015
Gender	2.22 (1.32-3.72)	0.003	1.56 (0.84-2.89)	0.157
Hypertension	4.02 (2.26-7.14)	<0.001	1.48 (0.73-2.99)	0.277
Diabetes mellitus	1.55 (0.92-2.61)	0.096	0.66 (0.35-1.23)	0.191
CAD	11.1 (6.36-19.6)	<0.001	7.15 (3.79-13.5)	<0.001
Atrial fibrillation	3.06 (1.50-6.23)	0.002	1.55 (0.65-3.66)	0.322
Creatinine	4.88 (2.23-10.7)	<0.001	1.44 (0.62-3.31)	0.394
SIRI	1.62 (1.33-1.96)	<0.001	1.39 (1.09-1.76)	0.007

A p value less than .05 was considered significant for statistical analysis.
*Nagelkerke R square: 0.29; -2 log likelihood: 359; p value<0.001
†Hosmer-Lemeshow test's chi-square value: 8.7; p value=0.370
CAD: Coronary artery disease, CI: Confidence interval, LVEF: Left ventricular ejection fraction, OR: Odds ratio, SIRI: Systemic inflammation response index

LVEF is the recommended quantitative parameter to evaluate LV systolic functions and a prognostic parameter including mortality and hospitalizations both in cardiac and non-cardiac situations[1,2,12]. HF is a clinical syndrome that develops after LV systolic and/or diastolic function impairment and TTE is the recommended imaging modality for evaluating suspected HF[2]. Increasing preclinical and clinical data suggest a robust, complex and bidirectional relationship between HF and inflammation, nevertheless the causal relationship is not well-known. This might be due to both inflammation and HF possess diverse clinical phenotypes and pathophysiological mechanisms[4,5]. For example, inflammation is characterized according to cause, duration and intensity, such as sterile inflammation, para-inflammation and chronic inflammation[4]. Besides, HF may occur even in normal LVEF[2]. Recent data also consider a new phenotype defined as HF with supranormal LVEF[13,14]. However, there is a well-defined relationship between increased serum proinflammatory cytokines and adverse clinical outcomes in HF patients[15].

WBC count and its subtypes, specifically neutrophils, monocytes and lymphocytes, and platelet counts have been suggested to be important prognosticators in various cardiovascular diseases (CVDs). This has led to the development of various biomarkers from the counts of these cells[6,8,9,16]. Because they can be calculated from a CBC test, which is relatively inexpensive, and quickly and easily accessible, they have gained a lot of attention in the scientific community. For instance, high WBC counts were associated with increased HF hospitalizations in the long term[17]. NLR and PLR were found to be predictors of mortality at one year follow-up in acute decompensated HF[5]. Durmus et al.[18] demonstrated that NLR, but not PLR, predicted mortality approximately at 1-year follow-up in acute decompensated HF patients. Regarding our study population, we did not investigate the clinical status of patients regarding HF, and we excluded patients with acute conditions such as acute decompensated HF patients and sought to evaluate the relationship between LVEF and the immune system and inflammation-related biomarkers. In our analyses, PLR and SII did not associate with LVEF, whereas SIRI and NLR were

Table 4. Predictors of LVEF† by multinominal logistic regression analysis

LVEF=41-49% vs LVEF ≥50%					
Variables	**Beta**	**SE**	**Odds ratio**	**CI 95%**	**p value**
Age	0.04	0.02	1.04	0.99-1.09	0.073
Gender	0.45	0.50	1.57	0.59-4.22	0.368
Hypertension	-0.18	0.54	0.84	0.29-2.41	0.740
Diabetes mellitus	-0.22	0.49	0.80	0.31-2.09	0.649
CAD	2.51	0.59	12.3	3.84-39.5	<0.001
Atrial fibrillation	-0.31	0.83	0.74	0.14-3.78	0.714
Creatinine	0.44	0.60	1.56	0.48-5.06	0.460
SIRI	0.27	0.18	1.31	0.93-1.86	0.123
LVEF ≤40% vs LVEF ≥50%					
Variables	**Beta**	**SE**	**Odds ratio**	**CI 95%**	**p value**
Age	0.03	0.02	1.03	0.99-1.06	0.072
Gender	0.43	0.37	1.55	0.74-3.20	0.242
Hypertension	0.71	0.44	2.04	0.85-4.89	0.109
Diabetes mellitus	-0.53	0.38	0.59	0.28-1.25	0.170
CAD	1.72	0.37	5.58	2.67-11.63	<0.001
Atrial fibrillation	0.71	0.48	2.02	0.79-5.17	0.140
Creatinine	0.33	0.52	1.39	0.50-3.83	0.522
SIRI	0.35	0.13	1.42	1.09-1.84	0.009

A p value less than .05 was considered significant for statistical analysis.
Nagelkerke R square: 0.27; p value<.001
†Reference category is LVEF ≥50%.
CAD: Coronary artery disease, CI: Confidence interval, LVEF: Left ventricular ejection fraction, SE: Standard error, SIRI: Systemic inflammation response index

significantly elevated in mrLVEF and rLVEF patients compared with patients with pLVEF. Besides, SIRI was independently associated with impaired LVEF in logistic regression analysis and rLVEF in multinominal logistic regression analysis.

The relationship between HF and inflammation is bidirectional and they trigger each other reciprocally. Systemic inflammation induces cardiomyocyte apoptosis, hypertrophy, stiffness, collagen synthesis, endothelial dysfunction and subsequent cardiac remodeling and LV dysfunction. These destructive alterations in the myocardium are partly mediated through proinflammatory cytokines, including tumor necrosis factor-alfa, interleukin-6, interleukin-1ß, proteolytic enzymes secreted by leukocytes and their subtypes[4,19]. For instance, patients with rheumatoid arthritis possess an increased risk of CVDs and poor outcomes[20]. However, HF induces inflammation in the heart itself through cytokines and inflammatory mediators released by stressed, malfunctioning, or dead cells. These cytokines and mediators induce systemic inflammation and affect other organs such as skeletal muscles, bone marrow, spleen, gut, etc.[4,19]. However, the relationship between inflammation and LVEF is not as obvious as in HF. A previous study failed to demonstrate an association between LVEF and high-sensitivity C-reactive protein (hs-CRP) in stabile HF patients[21]. Similarly, there was no relationship among LVEF and hs-CRP in patients with LVSD and HF despite hs-CRP being associated with poorer functional capacity and an independent predictor of mortality[22]. The conflicting results between our study and these studies might originate from the differences in patient characteristics, HF phenotypes and inflammation patterns, as discussed above.

Beside NLR and PLR, SII is a novel biomarker that shows the balance between inflammation and immune system and has recently been described in CVDs[8,23]. SII was found to predict functionally significant CAD better than NLR and PLR in a recent study[8]. However, SIRI is a new marker that is calculated from neutrophil, monocyte and lymphocyte counts. Feng et al.[9] demonstrated that SIRI predicts poor survival better than NLR, PLR and SII in locally advanced nasopharyngeal carcinoma patients. Furthermore, Jin et al.[24]

found that increased SIRI but not SII levels independently predict the risk of MI in patients aged below 60-years-old. Contrary to these reports, our results do not suggest direct evidence to conclude that SIRI is superior to NLR, PLR and SII for predicting impaired LVEF, mrLVEF, or rLVEF. Nevertheless, it should be mentioned that the AUC value of SIRI was numerically higher than the other biomarkers in all three groups.

Diverse cut-off values and terminologies for normal LVEF, abnormal LVEF and HF status have been used for years[2,11,13,14]. Therefore, we chose to define various cutoff values for LVEF, which was recommended for use by the most recent guidelines[2,13]. In this context, we defined LVEF <50% as impaired LVEF and LVEF ≥50% as pLVEF. Furthermore, we categorized impaired LVEF patients into two groups. We defined LVEF 41-49% as mrLVEF and LVEF ≤40% as rLVEF[2,11,13]. Multinominal logistic regression analysis demonstrated that SIRI is an independent predictor of rLVEF but not mrLVEF, when pLVEF was computed as the reference variable. Considering this finding, it might be reasonable to conclude that patterns of inflammatory status vary according to LVEF and that the inflammatory phenotype of patients with mrLVEF might be different from rLVEF patients.

It is reasonable to question why SIRI, but not SII, is associated with impaired LVEF. Both SIRI and SII included the neutrophil count as the nominator and lymphocyte count as the denominator. This is multiplied by the platelet count for calculating SII and monocyte count for calculating SIRI. A previous paper demonstrated that elevation in a subtype of monocytes negatively correlates with LVEF at six months after MI[25]. Besides, HF provokes monocytopoiesis in the bone marrow and spleen that subsequently results in increased monocyte count in peripheral blood[4]. However, decreased platelet levels are related to mortality in patients with HF[26]. This might explain why SIRI, but not SII, was associated with impaired LVEF and rLVEF in our study population. Neutrophils secrete various proteolytic enzymes such as myeloperoxidase (MPO), acid phosphatase and elastase, that induce cardiomyocyte destruction and fibrosis. For instance, increased MPO levels predicted 1-year mortality in acute HF[27]. Lymphocytes reflect immune system activity and undergo apoptosis in stressful situations such as HF due to neurohormonal cascade activation and increased cortisol secretion. This decreases lymphocytes' concentration[28]. A previous study found decreased lymphocyte count as a predictor of survival in advanced HF[29].

Study Limitations

Many significant and inherent limitations need to be underlined while interpreting the results of this study. The retrospective design, a relatively low number of patients with mrLVEF and rLVEF, lack of CRP and natriuretic peptides, lack of clinical data of patients regarding HF status should be kept in mind. Besides, it would be better if we could determine subtypes of cells which possess diverse functions in different pathophysiological conditions[25]. It would also be more appropriate if we to evaluate LV functions by additional measurements such as global longitudinal strain, three-dimensional TTE, or tissue Doppler echocardiography. Besides, it should be acknowledged that cardiac magnetic resonance imaging is the gold standard technique for evaluating LV systolic functions[30]. Further studies should address these limitations.

Conclusion

SIRI is a novel biomarker that is associated with impaired LVEF and rLVEF but not mrLVEF.

Ethics

Ethics Committee Approval: The study were approved by the Yozgat Bozok University Ethics Committee (decision no: 2017-KAEK-189_2021.07.07_07).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ö., A.B., M.E., Y.T., Concept: S.Ö., M.E., Design: S.Ö., M.E., Y.T., Data Collection or Processing: S.Ö., A.B., M.E., Y.T., Analysis or Interpretation: S.Ö., A.B., M.E., Y.T., Literature Search: S.Ö., M.E., Writing: S.Ö., A.B., M.E., Y.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Angaran P, Dorian P, Ha ACT, et al. Association of Left Ventricular Ejection Fraction with Mortality and Hospitalizations. J Am Soc Echocardiogr 2020;33:802-11.e6.
2. McDonagh TA, Metra M, Adamo M, et al. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021;42:4901.

3. Cleland JG, Torabi A, Khan NK. Epidemiology and management of heart failure and left ventricular systolic dysfunction in the aftermath of a myocardial infarction. Heart 2005;91 Suppl 2:ii7-13; discussion ii31, ii43-8.
4. Van Linthout S, Tschöpe C. Inflammation - Cause or Consequence of Heart Failure or Both? Curr Heart Fail Rep 2017;14:251-65.
5. Ashry M, Hafez R, Atef EM. Predictive value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in decompensated heart failure. The Egyptian Journal of Internal Medicine 2019;31:353-9.
6. Cankurt T, Celik İE, Ozturk S, Maden O. Inflammatory Conditions in Acute Coronary Syndrome Patients Treated with Percutaneous Coronary Intervention of Saphenous Vein Graft. Int J Angiol 2020;29:237-44.
7. Gao Y, Guo W, Cai S, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected esophageal squamous cell carcinoma. J Cancer 2019;10:3188-96.
8. Erdoğan M, Erdöl MA, Öztürk S, Durmaz T. Systemic immune-inflammation index is a novel marker to predict functionally significant coronary artery stenosis. Biomark Med 2020;14:1553-61.
9. Feng Y, Zhang N, Wang S, et al. Systemic Inflammation Response Index Is a Predictor of Poor Survival in Locally Advanced Nasopharyngeal Carcinoma: A Propensity Score Matching Study. Front Oncol 2020;10:575417.
10. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
11. Tribouilloy C, Rusinaru D, Mahjoub H, et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J 2008;29:339-47.
12. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005;112:3738-44.
13. Hudson S, Pettit S. What is 'normal' left ventricular ejection fraction? Heart 2020;106:1445-6.
14. Wehner GJ, Jing L, Haggerty CM, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? Eur Heart J 2020;41:1249-57.
15. Edelmann F, Holzendorf V, Wachter R, et al. Galectin-3 in patients with heart failure with preserved ejection fraction: results from the Aldo-DHF trial. Eur J Heart Fail 2015;17:214-23.
16. Oksuz F, Elcik D, Yarlioglues M, et al. The relationship between lymphocyte-to-monocyte ratio and saphenous vein graft patency in patients with coronary artery bypass graft. Biomark Med 2017;11:867-76.
17. Engström G, Melander O, Hedblad B. Leukocyte count and incidence of hospitalizations due to heart failure. Circ Heart Fail 2009;2:217-22.
18. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol 2015;105:606-13.
19. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:1324-40.
20. Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. Eur Heart J 2015;36:482-9c.
21. Thierer J, Acosta A, Vainstein N, et al. Relation of left ventricular ejection fraction and functional capacity with metabolism and inflammation in chronic heart failure with reduced ejection fraction (from the MIMICA Study). Am J Cardiol 2010;105:977-83.
22. Windram JD, Loh PH, Rigby AS, Hanning I, Clark AL, Cleland JG. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. Am Heart J 2007;153:1048-55.
23. Erdoğan M, Öztürk S, Kardeşler B, et al. The relationship between calcific severe aortic stenosis and systemic immune-inflammation index. Echocardiography 2021;38:737-44.
24. Jin Z, Wu Q, Chen S, et al. The Associations of Two Novel Inflammation Indexes, SII and SIRI with the Risks for Cardiovascular Diseases and All-Cause Mortality: A Ten-Year Follow-Up Study in 85,154 Individuals. J Inflamm Res 2021;14:131-40.
25. Tsujioka H, Imanishi T, Ikejima H, et al. Impact of heterogeneity of human peripheral blood monocyte subsets on myocardial salvage in patients with primary acute myocardial infarction. J Am Coll Cardiol 2009;54:130-8.
26. Mojadidi MK, Galeas JN, Goodman-Meza D, et al. Thrombocytopaenia as a Prognostic Indicator in Heart Failure with Reduced Ejection Fraction. Heart Lung Circ 2016;25:568-75.
27. Reichlin T, Socrates T, Egli P, et al. Use of myeloperoxidase for risk stratification in acute heart failure. Clin Chem 2010;56:944-51.
28. Núñez J, Miñana G, Bodí V, Núñez E, Sanchis J, Husser O, Llàcer A. Low lymphocyte count and cardiovascular diseases. Curr Med Chem 2011;18:3226-33.
29. Ommen SR, Hodge DO, Rodeheffer RJ, McGregor CG, Thomson SP, Gibbons RJ. Predictive power of the relative lymphocyte concentration in patients with advanced heart failure. Circulation 1998;97:19-22.
30. Wood PW, Choy JB, Nanda NC, Becher H. Left ventricular ejection fraction and volumes: it depends on the imaging method. Echocardiography 2014;31:87-100.