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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Laboratory Parameters Predicting Mortality in Heart Failure Patients treated with Implantable Cardioverter Defibrillator: Single Centre, Long-term Results

Takılabilir Kardiyoverter Defibrilatör ile Tedavi Edilen Kalp Yetersizliği Hastalarında Mortaliteyi Belirleyen Laboratuvar Paramaterleri: Tek Merkezli, Uzun Dönemli Sonuçlar

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Abstract

Objectives: Neutrophil/lymphocyte (NLR), Monocyte/HDL (MHR), lymphocyte/monocyte (LMR) and platelet/lymphocyte ratios (PLR) are inflammation markers with proven prognostic values in various cardiovascular diseases. However, a clinical study demonstrating the prognostic value of these markers in heart failure (HF) patients treated with an implantable cardioverter-defibrillator (ICD) is not yet available. It is aimed to demonstrate the relationship between NLR, MHR, LMR, PLR and mortality development in patients with HF with ICD.

Materials and Methods: One hundred and ninety-four patients who underwent ICD implantation due to systolic HF between January 2015 and December 2019 were included in the study.

Results: The mean age was 59.84±13.26 years. The female gender ratio was 25.3%. Death developed in 16 patients (8%) after a median follow-up of 27 months. While basal urea, uric acid, gamma-glutamyl transferase, C-reactive protein and neutrophil levels were found to be high, hemoglobin and lymphocyte levels were found to be low in the exitus developing group. While the rates of NLR, MHR and PLR were statistically significantly higher in the group with death during follow-up (p=0.001, p=0.049, p=0.020, respectively), LMR was significantly lower (p<0.001). In ROC analyses, mortality was predicted with 81% sensitivity and 61% specificity (p=0.001 AUC=0.76) of values of NLR and above 3.06; 86% sensitivity and 61% specificity [p=0.046 Area under curve (AUC)=0.723] of values of MHR and above 0,0196; 81% sensitivity and 55% specificity (p<0.001 AUC=0.784) of values of LMR 3.22 and 113.59 and above of PLR with 75% sensitivity and 51% specificity (p=0.020 AUC=0.68). Multiple logistic regression analysis showed LMR was an independent factor for mortality (p=0.027).

Conclusion: In our study, it has been shown that NLR, MHR, PLR and LMR, which are inflammation markers, can predict mortality in patients with ICD implanted HF. In the multivariate analysis, LMR value has been found to be significant. This is the first study demonstrating the predictive power of these parameters in this patient group.

Key Words: Heart Failure, Neutrophil Lymphocyte Ratio, Monocyte HDL Ratio, Platelet Lymphocyte Ratio, Lymphocyte Monocyte Ratio

Öz

Amaç: Nötrofil/lenfosit oranı (NLR), Monosit/HDL oranı (MHR), lenfosit/monosit oranı (LMR) ve platelet/lenfosit oranı (PLR) kardiyovasküler hastalıklarda prognostik değerleri kanıtlanmış olan enflamasyon belirteçleridir. Fakat bu belirteçlerin takılabilir kardiyoverter defibrillator (ICD) ile tedavi edilen kalp yetersizliği hastalarında prognostik değerini gösteren klinik çalışma henüz mevcut değildir. Bu çalışmada NLR, MHR, LMR, PLR oranları ile ICD'si olan kalp yetersizliği hastalarında mortalite gelişimi arasındaki ilişkinin gösterilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya, Ocak 2015-Aralık 2019 tarihleri arasında sistolik kalp yetersizliği nedeniyle ICD implantasyonu yapılmış 194 hasta dahil edildi.

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Bulgular: Hastaların ortalama yaşı 59,84±13,26 idi. Kadın cinsiyet oranı %25,3 idi. Medyan 27 aylık izlem sonrasında 16 hastada ölüm gelişti (%8). Exitus gelişen grupta bazal üre, ürik asit, gama-glutamil transferaz, C-reaktif protein, nötrofil düzeyleri yüksek saptanırken; hemoglobin ve lenfosit düzeyleri ise düşük saptandı. Takiplerde ölüm gelişen grupta NLR, MHR ve PLR oranları istatistiksel olarak anlamlı şekilde yüksek saptanırken (p=0,001, p=0,049, p=0,020, sırasıyla) LMR belirgin derecede düşük saptanmıştır (p<0,001). Yapılan ROC analizlerinde mortaliteyi NLR'nin 3,06 ve üzerindeki değerlerinin %81 sensitive ve % 61 spesifite [p=0,001 Eğri altında kalan alan (AUC)=0,76]; MHR'nin 0,0196 ve üzerindeki değerlerinin %86 sensitive ve %61 spesifite (p=0,046 AUC=0,723); LMR'nin 3,22 ve altındaki değerlerinin %81 sensitive ve %55 spesifite (p<0,001 AUC=0,784); PLR'nin 113,59 ve üzerindeki değerlerinin %75 sensitive ve %51 spesifite (p=0,020 AUC=0,68) ile öngördüğü saptandı. Bu oranların dahil edildiği multipl lojistik regresyon analizinde LMR değeri istatistiksel olarak anlamlı saptanmıştır (p=0,027).
Sonuç: Çalışmamızda enflamasyon belirteçleri olan NLR, MHR, PLR ve LMR oranlarının ICD implante edilmiş kalp yetersizliği hastalarında mortaliteyi predikte edebileceği gösterilmiştir. Yapılan çok değişkenli analizde LMR değeri anlamlı bulunmuştur. Bu çalışma bu hasta grubunda bu parametrelerin prediktör gücünü gösteren ilk çalışmadır.
Anahtar Kelimeler: Kalp Yetersizliği, Nötrofil Lenfosit Oranı, Monosit HDL Oranı, Trombosit Lenfosit Oranı, Lensofit Monosit Oranı

Introduction

Heart failure is a clinical depiction with symptoms such as dyspnea, orthopnea, weakness in patients as a result of decreased cardiac output or increased intracardiac pressures due to structural or functional disorders developing in the cardiac muscle (1). Moreover; heart failure is defined as a clinical syndrome with inflammation at its center rather than being a disease above this classical definition (2). Even with the most recent treatments in this clinical syndrome, mortality is as high as 17% and many parameters are used to predict it (3-5).

Implantable cardioverter-defibrillator (ICD) is recommended in current guidelines for primary and secondary protection in patients with heart failure (6). Even in patients with heart failure who underwent ICD implantation, the mortality rate is around 22% (7). Despite all current medications and drugs, such a high mortality ratio in patients with heart failure can be explained by the presence of inflammation in the center (2). Neutrophil lymphocyte ratio (NLR), monocyte HDL ratio (MHR), lymphocyte monocyte ratio (LMR), platelet lymphocyte ratio (PLR) are markers of the systemic inflammatory response and have prognostic values in many cardiovascular diseases (8-11). However, no study on the prognostic values of ICD implanted patients is yet available.

The aim of this study is to investigate and compare the predictive values of NLR, MHL, LMR, PLR ratios with proven prognostic values in many cardiovascular diseases due to all causes in patients with ICD implanted heart failure.

Materials and Methods

Patient Group

Patients with systolic heart failure (included ischemic and non-ischemic) and treated with maximal medical treatment and ICD implantation due to primary prevention were included this trail. Systolic heart failure and ICD indication for primary prevention defined as the patients with the left ventricular ejection fraction less than 30% with New York Heart Association (NYHA) 1 or the left ventricular ejection fraction less than 35% with NYHA 2 and 3. Maximal medical treatment defined as beta-blocker (aimed heart rate with 55-65 beat per minute), ACEI/ARB (controlled blood pressure) and spironolactone usage if creatinine and potassium levels were normal.

Exclusion criteria from the study are: 1) Performing ICD implantation for reasons other than systolic heart failure, 2) patient groups who could not receive maximal medical treatment before ICD implantation, 3) being under 18 years of age, 4) ischemic cardiomyopathy with residual ischemia 5) ICD indication other than systolic heart failure (hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia), 6) patient with active infection, hepatic or romatological diseases. The study protocol has been approved by the local ethics committee.

Information of the patients, hospitalized in Gaziantep Dr. Ersin Arslan Training and Research Hospital, has been accessed from the archive. Totally, 194 patients, that signed informed consent, between January 2015 and December 2019 have been included in the study.

Endpoint

The primary endpoint of the study was defined as all-cause mortality.

Laboratory Analysis

In the study, routine biochemistry and whole blood parameters taken from the patients before the procedure have been used. Urea, creatinine, gamma-glutamyl transferase (GGT), uric acid, cholesterol panel, C-reactive protein (CRP) levels from biochemical tests have been included in the study. Leukocyte, haemoglobin, platelet, neutrophil, monocyte, lymphocyte levels and mean platelet volume and red cell distribution width have been included in the study. NLR has been calculated by dividing neutrophil count into lymphocyte number, MHR by dividing monocyte number into HDL cholesterol level, LMR by dividing lymphocyte number into monocyte number and PLR by dividing platelet number into lymphocyte number.

Statistical Analysis

All statistical analyses have been performed using the SPSS program (Version 20.0 for Windows, SPSS Inc. Chicago, IL). The groups have been compared in terms of the obtained data. It has been predicted that the data of continuous variables matching the normal distribution should be given with mean ± standard deviation and the comparison should be made with the Student's t-test. The comparison of continuous variables that do not conform to the normal distribution should be given with the median and 25th and 75th percentile (25%-75%) and the comparison should be made with the Mann-Whitney U test. The data of the categorical variables have been given as a percentage and compared with the chi-squared test. The value of $p<0.05$ has been considered statistically significant.

ROC curves have been drawn to demonstrate the sensitivity and specificity of NLR, MHL, LMR, PLR ratios in predicting mortality. Multiple logistic regression analysis has been performed to compare the effects of these parameters on showing death due to all causes.

Results

The mean age of the patients included in the study was 59.84±13.26. The female gender ratio was 25.3%. Seventy-six patients underwent single-chamber ICD (39.2%), 57 patients underwent double chamber ICD (29.4%) and 61 patients underwent biventricular ICD (31.4%) implantation. The patients were followed for a median of 27 months. Death developed in 16 patients (8%) after this follow-up. Age, female gender ratio, ejection fraction, basal creatinine, high-density lipoprotein, low-density lipoprotein and total cholesterol values have been found to be similar when the group with and without death has been compared (Table 1). Basal blood urea level, uric acid,

Table 1: Comparison of basal demographic and biochemical parameters between survivors and exitus groups

	Survivors (n=178)	Exitus (n=16)	p
Age Median (25%-75%)	61.00 (51.00-68.00)	65.50 (55.00-75.00)	0.111
Female sex N (%)	46 (%25.8)	3 (%15.8)	0.53
Atrial fibrillation N (%)	10 (%6)	1 (%6)	0.83
Ejection fraction % Median (25%-75%)	29.3 (27.9-31.90)	30.1 (28.1-32.10)	0.78
Ischemic cardiomyopathy N (%)	139 (%78)	12 (%75)	0.88
ICD therapies (%) VVI-ICD DDD-ICD CRT-D	 %38.8 %30.9 %30.3	 %43.8 %12.5 %43.8	NS
NYHA class Class 1 Class 2 Class 3	 %14 %51 %35	 %13 %50 %37	NS
Blood urea nitrogen Median (25%-75%)	39.00 (30.00-52.45)	51.25 (39.55-66.20)	**0.029**
Creatinine Median (25%-75%)	1.01 (0.83-1.21)	1.00 (0.93-1.51)	0.334
HDL-C Median (25%-75%)	36.00 (29.85-42.15)	34.20 (26.40-41.30)	0.573
LDL-C Mean ± SD	100.58±39.44	92.77±34.05	0.865
Total cholesterol level Mean ± SD	172.59±43.31	148.49±39.63	0.628
Uric acid level Median (25%-75%)	6.70 (5.40-8.00)	9.50 (7.50-10.80)	0.026
GGT Median (25%-75%)	38.00 (20.00-59.00)	73.00 (43.00-116.00)	**0.020**
CRP Median (25%-75%)	0.69 (0.28-1.73)	4.13 (2.64-5.05)	**0.05**

ICD: Implantable cardioverter defibrillator devices, CRT-D: Cardiac resynchronization therapy defibrillator, CRP: C-reactive protein, GGT: Gama glutamyl transferase, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, NS: Non-significant, SD: Standard deviation, NYHA: New York Heart Association, VVI-ICD: single-chamber implantable cardioverter defibrillators, DDD-ICD: dual-chamber implantable cardioverter defibrillators

GGT and CRT values of the developing death group have been found to be high. While the neutrophil count has been found to be high in the group developing death from complete blood parameters, haemoglobin and lymphocyte levels have been found to be low (Table 2).

NLR has been significantly higher in the group with death [2.6524 (1.80-3.83) vs. 6.18 (3.23-10.64), p<0.001] (Table 3). The NLR value above 3.06 in the drawn ROC curve predicted mortality with 81% sensitivity and 61% specificity (p=0.001 AUC: 0.76) in long-term follow-ups (Figure 1).

MHR has been significantly higher in the group developing death [0.0168 (0.012-0.026) vs. 0.0291 (0.024-0.033), p=0.049] (Table 3). The MHR value above 0.0196 in the drawn ROC curve predicted mortality with 86% sensitivity and 61% specificity (p: 0.046 AUC: 0.723) in long-term follow-ups (Figure 1).

LMR has been significantly lower in the group developing death [3.36 (2.41-4.38) vs. 1.80 (1.30-2.70) p=<0.001] (Table 3). The LMR value of 3.22 and below in the drawn ROC curve predicted mortality with 81% sensitivity and 55% specificity (p<0.001 AUC: 0.784) in long-term follow-ups (Figure 1).

The PLR has been significantly higher in the group developing death [113.04 (77,03-150,64) vs. 180.97 (112,78-245,84) p=0, 0.020] (Table 3). LMR value above 113.59 in the drawn ROC curve predicted mortality with 75% sensitivity and 51% specificity (p=0.020 AUC: 0.68) in long-term follow-ups (Figure 1). In the multivariate logistic regression analysis in which NLR, MHR, LMR, and PLR have been incorporated, the LMR value has been statistically significant (p=0.027) (Table 3).

Discussion

In this study, the predictive power of NLR, MHR, PLR, LMR ratios, which have been shown to play a role in predicting cardiovascular events in many previous studies, due to all causes in patients with ICD implanted heart failure has been

Table 2: Comparison of hemogram parameters between survivors and exitus groups

	Survivors (n=178)	Exitus (n=16)	p
WBC Median (25%-75%)	8.38 (6.84-9.81)	9.73 (7.21-11.85)	0.104
Hmg Mean ± SD	13.71±1.95	12.23±1.63	**0.004**
Platelet Median (25%-75%)	247.00 (183.00-293.00)	220.00 (196.00-343.00)	0.740
RDW Median (25%-75%)	14.60 (13.20-21.10)	16.04 (14.55-21.85)	0.097
MPV Median (25%-75%)	10.50 (9.50-11.30)	10.70 (9.75-11.55)	0.671
Neutrophil Median (25%-75%)	5.25 (4.04-6.77)	7.19 (4.69-8.90)	**0.043**
Lymphocyte Median (25%-75%)	2.11 (1.54-2.81)	1.33 (1.10-1.77)	**0.006**
Monocyte Median (25%-75%)	0.62 (0.50-0.88)	0.7850 (0.58-0.87)	0.192

Hmg: Hemoglobin level, MPV: Mean platelet volume, RDW: Red distribution width, WBC: White blood cell, SD: Standard deviation

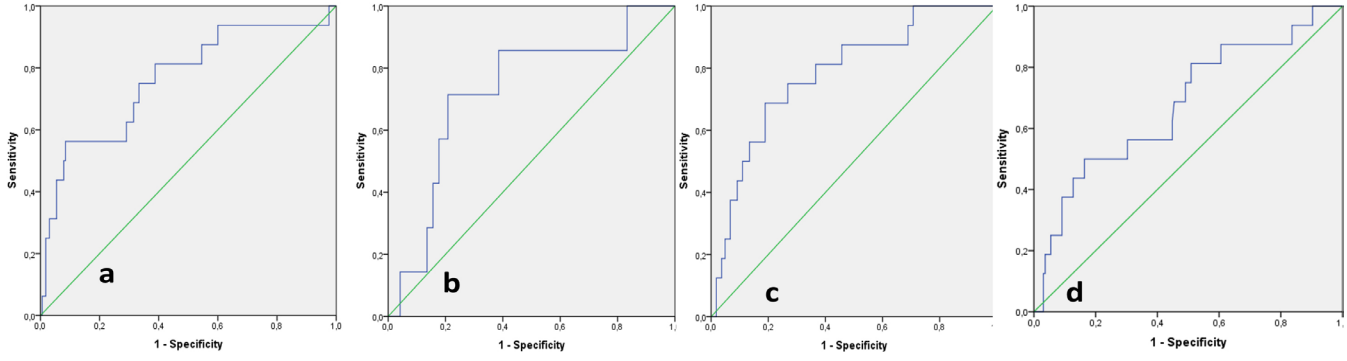

Figure 1: ROC curves showing the sensitivity and specificity of ratios in predicting mortality a) Neutrophil to lynphocyte ratio, b) Monocyte to HDL ratio, c) Lynphocyte to monocyte ratio, d) Plathelet to lynphocte ratio

Table 3: Comparison of neutrophil to lymphocyte, monocyte to HDL, lymphocyte to monocyte and platelet to lymphocyte ratios between survivors and exitus groups

	Univarite analysis			Multivarite analysis		
	Survivors (n=178)	Exitus (n=16)	p	Beta	Wald	p
Neutrophil to lymphocyte ratio Median (25%-75%)	2.6524 (1.80-3.83)	6.18 (3.23-10.64)	**0.001**	0.096	2.486	0.115
Monocyte to HDL ratio Median (25%-75%)	0.0168 (0.012-0.026)	0.0291 (0.024-0.033)	**0.049**	-8.183	0.463	0.496
Lymphocyte to monocyte ratio Median (25%-75%)	3.36 (2.41-4.38)	1.80 (1.30-2.70)	**<0.001**	-0.844	5.376	**0.020**
Platelet to lymphocyte Median (25%-75%)	113.04 (77.03-150.64)	180.97 (112.78-245.84)	**0.020**	0.000	0.018	0.893

HDL: High density lipoprotein

investigated, and when the groups with and without death are compared, these four ratios have been found statistically significant. Death due to all causes has been predicted with 81% sensitivity and 61% specificity (p=0.001 AUC: 0.76) of values of NLR and above; 86% sensitivity and 61% specificity (p=0.046 AUC: 0.723) of values of MHR and above; 81% sensitivity and 55% specificity (p<0.001 AUC: 0.784) of values of PLR and above with 75% sensitivity and 51% specificity (p=0.020 AUC: 0.68). In the multiple logistic regression analysis in which these rates have been incorporated, the LMR value has been statistically significant (p=0.027). To the best of our knowledge for the first time in the literature, we investigated the predictive value of NLR, MHR, PLR, LMR ratios for the development of mortality after ICD implantation in patients with heart failure.

Heart failure progresses with high mortality and morbidity despite all improved drug and device treatments (1). The mortality ratio has been around 17% even with the angiotensin receptor blocker and neprilysin inhibitor that is the newest treatment option recommended in the guidelines and the mortality ratio in previous ICD studies not involving this treatment option has been around 22% (3,7). In this syndrome where mortality ratios are so high, predicting mortality can bring great benefit to the doctor and health system in terms of availability and timing of treatment (1). There are many markers and models that predict death in patients with heart failure (12,13). In addition to the markers predicting mortality such as low sodium, high BNP levels, markers showing systemic inflammatory response are also mentioned in the guidelines (1). NLR, MHL, LMR, PLR (8-11) have been shown to have prognostic values in many cardiovascular diseases as systemic inflammatory responses in previous studies.

Beyond several mechanical or functional disorders that exist in the definition of heart failure, it is now seen as a clinical syndrome with underlying inflammation. As with all other inflammations, white blood cells are known to play a role in this syndrome (2). Due to inflammation in heart failure, many inflammatory cytokine releases such as tumour necrosis factor alpha, interleukin-6 and C-reactive protein from white blood cells are increased (14). Ventricular dysfunction progresses with the direct effect of these cytokines on the myocardium (15). Hence, increased leukocyte levels have been found to be associated with long-term death and increased hospitalization in patients with heart failure (16,17).

In addition to the cumulative effect, neutrophil, monocyte, lymphocyte, and platelets, whose main function is haemostasis, play separate roles in inflammation cascade and should be investigated. Cytokines that cause tissue destruction such as myeloperoxidase, acid phosphatase, and elastase are released from neutrophils activated by inflammation on the basis of heart failure (18-20). Myeloperoxidase levels have been found to be high, especially in patients with heart failure and it is thought to be at the center of the inflammation seen in these patients (21). Myeloperoxidase released from neutrophils may lead to progression of heart failure by increasing myocyte destruction and fibrosis (21). Monocytes are other white blood cells that play a role in the inflammatory response (22) and the first step of atherosclerosis response (23,24). In addition to being the main source of circulating tumour necrosis alpha and interleukin-6, procoagulant effect by tissue factor release and pro-oxidant effects by oxidation of LDL are also present. HDL cholesterol has been shown to reduce these effects of monocytes (25). Lymphocyte' apoptosis and low lymphocyte levels are observed due to increased neurohumoral activation in patients with heart failure (26,27). In systemic inflammatory conditions such as heart failure, platelets act as an inflammatory cell due to their interaction with leukocytes and endothelial cells and start producing cytokines and lead to adhesion and transmigration of monocytes. Platelets act as bridges between inflammation and coagulation in this respect (28,29).

Increased neutrophil, monocyte, platelet and decreased lymphocyte and HDL levels with these basic inflammatory

mechanisms and their effectiveness in showing prognosis in cardiac events have been investigated in many clinical studies. Uthamalingam et al. (8) found that increased neutrophil/lymphocyte ratio (NLR) was associated with long-term mortality in patients with acute heart failure. Yucel et al. (30) found that increased NLR levels in patients with heart failure who underwent ICD implantation were associated with appropriate shock. In our study, we demonstrated that increased NLR levels were associated with death in a similar patient group.

Prevention of procoagulant and proinflammatory effects caused by monocytes by HDL cholesterol suggested that increased MHR rate may predict poor prognosis in cardiovascular diseases (31). This assumption has been proven by many clinical trials. Increased MHR has been shown to be associated with high MACE rates in patients with the acute coronary syndrome, no-reflow and death in ST-elevation myocardial infarction patients and stent restenosis (32-35). However, there is no study showing that increased MHR can predict death in patients with heart failure. In this study, we have shown that increased MHR levels are associated with increased mortality ratios in patients with ICD implanted heart failure.

Low lymphocyte and high monocyte levels have also been believed to be associated with poor prognosis in cardiovascular diseases. The LMR ratio formed by the ratio of these two values is accepted as a marker of poor prognosis in many non-cardiac chronic diseases (36). In cardiac diseases, LMR has been found to be associated with the degree of rheumatic mitral stenosis, short-term mortality in acute pulmonary embolism and acute heart failure (9,11,37). In this study, it has been shown that low LMR levels are associated with increased mortality ratios in patients with ICD implanted heart failure, and multivariate analysis has shown that it is the strongest predictor independently of other ratios.

High PLR levels as a result of increased inflation, coagulation and neurohumoral activity have been found to be associated with the severity and complexity of stenosis in acute coronary syndromes and increased cardiovascular poor outcome in peripheral artery patients and short-term mortality in patients with acute heart failure (38-40). In our study, long-term mortality has also been demonstrated in patients with chronic heart failure implanted with ICD.

Conclusion

High NLR, MHR, PLR and low LMR ratios have been found to be associated with increased mortality in patients with heart failure in which inflammation plays a role and prognoses in its course, despite all medical treatment options including ICD. The use of cytokines such as myeloperoxidase, TNF alpha, which is a direct indicator of inflammation in this patient group, may be both costly and impossible due to the insufficiency of local facilities. However, as shown in our study, these parameters, which can only be obtained with a complete blood count, can predict death with high sensitivity and specificity in this patient group.

Restrictions

There are some limitations to our study. Firstly, in this study investigating the indirect relationship between inflammation and heart failure, markers such as myeloperoxidase and TNF that can directly demonstrate systemic inflammation could not be used. The fact that the study is a retrospective registry study is the second restriction. Finally, the fact that echocardiographic examinations are not elaborated and do not include mortality related conditions such as TAPSE, right ventricilitis parameters can be shown as a restriction.

Compliance with Ethical Standards

The study was not funded. Authors declare no conflicts of interest. The present study was approved by the local ethic committee.

Ethics

Ethics Committee Approval: The study protocol has been approved by the local ethics committee.

Informed Consent: Totally, 194 patients, that signed informed consent, between January 2015 and December 2019 have been included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S., F.P., M.C.G., Concept: V.Ö.B., Design: V.Ö.B., Data Collection or Processing: V.Ö.B., Analysis or Interpretation: V.Ö.B., Literature Search: V.Ö.B., Writing: V.Ö.B., A.B.

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

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References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-2200.
2. Aukrust P, Ueland T, Lien E, et al. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1999;83:376-382.
3. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004.

4. Ganjali S, Gotto AM Jr, Ruscica M, et al. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. J Cell Physiol. 2018;233:9237-9246.
5. Abdul-Rahim AH, Perez AC, Fulton RL, et al. Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation: Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. Circulation. 2015;131:1486-1494.
6. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36:2793-2867.
7. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225-237.
8. 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;107:433-438.
9. Ertem AG, Yayla C, Acar B, et al. Relation between lymphocyte to monocyte ratio and short-term mortality in patients with acute pulmonary embolism. Clin Respir J. 2018;12:580-586.
10. Villanueva DLE, Tiongson MD, Ramos JD, et al. Monocyte to High-Density Lipoprotein Ratio (MHR) as a predictor of mortality and Major Adverse Cardiovascular Events (MACE) among ST Elevation Myocardial Infarction (STEMI) patients undergoing primary percutaneous coronary intervention: a meta-analysis. Lipids Health Dis. 2020;19:55.
11. Demir V, Samet Y, Akboga MK. Association of lymphocyte-monocyte ratio and monocyte-to-high-density lipoprotein ratio with the presence and severity of rheumatic mitral valve stenosis. Biomark Med. 2017;11:657-663.
12. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34:1404-1413.
13. Rahimi K, Bennett D, Conrad N, et al. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail. 2014;2:440-446.
14. Mann DL, Young JB. Basic mechanisms in congestive heart failure. Recognizing the role of proinflammatory cytokines. Chest. 1994;105:897-904.
15. Torre-Amione G, Kapadia S, Benedict C, et al. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol. 1996;27:1201-1206.
16. Engström G, Melander O, Hedblad B. Leukocyte count and incidence of hospitalizations due to heart failure. Circ Heart Fail. 2009;2:217-222.
17. Cooper HA, Exner DV, Waclawiw MA, et al. White blood cell count and mortality in patients with ischemic and nonischemic left ventricular systolic dysfunction (an analysis of the Studies Of Left Ventricular Dysfunction [SOLVD]). Am J Cardiol. 1999;84:252-257.
18. Baldus S, Heeschen C, Meinertz T, et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. Circulation. 2003;108:1440-1445.
19. Mehta J, Dinerman J, Mehta P, et al. Neutrophil function in ischemic heart disease. Circulation. 1989;79:549-556.
20. Tousoulis D, Antoniades C, Koumallos N, et al. Pro-inflammatory cytokines in acute coronary syndromes: from bench to bedside. Cytokine Growth Factor Rev. 2006;17:225-233.
21. Reichlin T, Socrates T, Egli P, et al. Use of myeloperoxidase for risk stratification in acute heart failure. Clin Chem. 2010;56:944-951.
22. Curi R, de Siqueira Mendes R, de Campos Crispin LA, et al. A past and present overview of macrophage metabolism and functional outcomes. Clin Sci (Lond). 2017;131:1329-1342.
23. Açıkgöz SK, Açıkgöz E, Şensoy B, et al. Monocyte to high-density lipoprotein cholesterol ratio is predictive of in-hospital and five-year mortality in ST-segment elevation myocardial infarction. Cardiol J. 2016;23:505-512.
24. Ammirati E, Moroni F, Magnoni M, et al. Circulating CD14+ and CD14highCD16- classical monocytes are reduced in patients with signs of plaque neovascularization in the carotid artery. Atherosclerosis. 2016;255:171-178.
25. Ossoli A, Remaley AT, Vaisman B, et al. Plasma-derived and synthetic high-density lipoprotein inhibit tissue factor in endothelial cells and monocytes. Biochem J. 2016;473:211-219.
26. Swedberg K, Eneroth P, Kjekshus J, et al. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation. 1990;82:1730-1736.
27. Sciarretta S, Ferrucci A, Ciavarella GM, et al. Markers of inflammation and fibrosis are related to cardiovascular damage in hypertensive patients with metabolic syndrome. Am J Hypertens. 2007;20:784-791.
28. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. J Clin Invest. 2005;115:3378-3384.
29. Ginsberg MH, Kozin F, O'Malley M, et al. Release of platelet constituents by monosodium urate crystals. J Clin Invest. 1977;60:999-1007.
30. Yucel H, Zorlu A, Kaya H, et al. Elevated Neutrophil/Lymphocyte Ratio is Associated with Appropriate Shock After ICD Implantation. J Clin Anal Med. 2016;7:772-776.
31. Gratchev A, Sobenin I, Orekhov A, et al. Monocytes as a diagnostic marker of cardiovascular diseases. Immunobiology. 2012;217:476-482.
32. Cetin MS, Ozcan Cetin EH, Kalender E, et al. Monocyte to HDL Cholesterol Ratio Predicts Coronary Artery Disease Severity and Future Major Cardiovascular Adverse Events in Acute Coronary Syndrome. Heart Lung Circ. 2016;25:1077-1086.
33. Balta S, Celik T, Ozturk C, et al. The relation between monocyte to HDL ratio and no-reflow phenomenon in the patients with acute ST-segment elevation myocardial infarction. Am J Emerg Med. 2016;34:1542-1547.
34. Çiçek G, Kundi H, Bozbay M, et al. The relationship between admission monocyte HDL-C ratio with short-term and long-term mortality among STEMI patients treated with successful primary PCI. Coron Artery Dis. 2016;27:176-184.
35. Ucar FM. A potential marker of bare metal stent restenosis: monocyte count - to- HDL cholesterol ratio. BMC Cardiovasc Disord. 2016;16:186.
36. Balta S, Demırer Z, Aparci M, et al. The lymphocyte-monocyte ratio in clinical practice. J Clin Pathol. 2016;69:88-89.
37. Silva N, Bettencourt P, Guimarães JT. The lymphocyte-to-monocyte ratio: an added value for death prediction in heart failure. Nutr Metab Cardiovasc Dis. 2015;25:1033-1040.
38. Kurtul A, Murat SN, Yarlioglues M, 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;114:972-978.
39. Gary T, Pichler M, Belaj K, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One. 2013;8:67688.
40. Ye GL, Chen Q, Chen X, et al. The prognostic role of platelet-to-lymphocyte ratio in patients with acute heart failure: A cohort study. Sci Rep. 2019;9:10639.