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Original Article

Monocyte/high-density lipoprotein cholesterol ratio is superior to neutrophil/lymphocyte ratio in the prediction of 3-month overall death in patients with acute ST-elevation myocardial infarction treated with percutaneous coronary intervention

Monosit/Yüksek-yoğunluklu lipoprotein kolesterol oranının, perkütan koroner girişim uygulanan akut st-elevasyonlu miyokard enfarktüsü hastalarında 3-aylık mortaliteyi öngördürmede nötrofil/lenfosit oranına üstünlüğü

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Abstract

Aim: Although 30-day mortality rates were improved in the setting of acute ST-elevation myocardial infarction (STMI), the same does not hold true for longer-term mortality rates. The ratios of monocyte to high-density lipoprotein cholesterol (MHR) and neutrophil to lymphocyte (NLR) are novel markers with diagnostic and prognostic significance in various disease conditions. Our aim was to evaluate the predictive role of MHR and NLR in in-hospital and 3-month overall death in STMI patients treated with percutaneous coronary intervention (PCI).

Material and Methods: A total of 184 consecutive STMI patients undergoing PCI were included. NLR, MHR, clinical and demographic characteristics, and syntax scores were recorded. The patients were divided into two groups according to the median MHR (group 1, n=92; group 2, n=92). In-hospital and 3-month overall death were noted as the primary outcome.

Results: Median MHR was 19.31. In-hospital mortality and 3-month mortality occurred in 14 (15.2%) and 21 (22.8%) patients, respectively. NLR and number of the patients with cardiogenic shock on admission were greater in group 2. No mortality occurred in group 1. In multivariate logistic regression analysis, higher low-density lipoprotein cholesterol level, higher syntax score and MHR, but not NLR, were independently associated both with in-hospital and 3-month overall death. In ROC analysis, MHR >36.6 and MHR >46.81 emerged as cut-off values for in-hospital and 3-month mortality, respectively.

Conclusion: MHR but not NLR may be utilized in the prediction of in-hospital and 3-month overall death in acute STMI patients treated with primary PCI.

Keywords: monocyte to HDL ratio; neutropil to lymphocyte ratio; mortality; acute myocardial infarction

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Öz

Amaç: Akut ST-elevasyonlu miyokard enfarktüsünde (STME) 30-günlük mortalite oranlarında iyileştirme sağlanabilmiş olmasına rağmen, aynı durum daha uzun sureli mortalite oranlarında sağlanamamıştır. Monosit/yüksek yoğunluklu lipoprotein kolesterol (MHO) ve nötrofil/lenfosit (NLO) oranları, çeşitli hastalık durumlarında prognostik ve tanısal öneme sahip yeni belirteçler arasındadır. Bu çalışmadaki amacımız, MHO ve NLO'nun perkütan koroner girişim (PKG) uygulanmış akut STME hastalarında hastane içi ve 3 aylık mortaliteyi öngördürücü rolünü değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya PKG uygulanmış toplam 184 STME hastası dahil edildi. Hastalara ait NLO, MHO, klinik ve demografik özellikler ile Syntax skorları kaydedilmiş olup hastalar medyan MHO değerlerinde göre iki gruba ayrıldı (grup 1: 92 hasta; grup 2: 92 hasta). Hastane içi ve 3 aylık mortalite oranları birincil sonlanım noktası olarak kaydedildi.

Bulgular: Medyan MHO 19,31 olarak hesaplandı. Hastane içi ve 3 aylık mortalite sırasıyla 14 (%15,2) ve 21 (%22,8) hastada gerçekleşti. NLO ve kardiyojenik şok ile başvuru, grup 2'de anlamlı olarak daha yüksek bulundu. Grup 1'de hiçbir hastada mortalite gelişmedi. Çok değişkenli lojistik regresyon analizinde yüksek düşük-yoğunluklu lipoprotein kolesterol düzeyinin, yüksek Syntax skorunun ve yüksek MHO'nun, hastane içi ve 3 aylık mortalite ile bağımsız ilişkiye sahip olduğu tespit edildi. Fakat aynı ilişki NLO ile gösterilemedi. ROC analizine göre hastane içi ve 3 aylık mortaliteyi öngördüren MHO kestirim değerleri sırasıyla >36,6 ve >46,81 bulundu.

Sonuç: PKG uygulanmış akut STME hastalarında MHO, hastane içi ve 3 aylık mortaliteyi öngördürmede fayda sağlayabilmekte iken aynı fayda NLO ile sağlanamamaktadır.

Anahtar Kelimeler: monosit/HDL oranı; nötrofil/lenfosit oranı; mortalite; akut miyokard enfarktüsü

Introduction

Although a dramatic improvement in 30-day mortality rates has been achieved in acute coronary syndromes (ACS), not a dramatic improvement was achieved in longer-term mortality rates in the preceding 20 years [1]. Acute ST-elevation myocardial infarction (STMI) belongs to the entities comprising the term ''ACS'', and constitutes nearly one third of the patient population worldwide who were admitted to the hospital with an ACS [2]. In this regard, new measures and predictors are warranted in order for the physicians to anticipate better not only the in-hospital mortality but also the longer-term and shorter-term mortality rates among STMI survivors, and provide a closer-follow up for them.

A close relationship has been well recognized between generalized vascular inflammation and atherosclerosis-related plaque formation as well as plaque ruptures. Circulating levels of leukocytes, especially the neutrophil differential, had already been documented to recognize ACS patients at higher risk of major adverse cardiovascular events (MACE) [3]. However, the ratio of neutrophil to leukocyte (NLR) was proposed as a more accurate prognostic indicator compared with either sole neutrophil or lymphocyte counts in a setting of stable coronary artery disease (CAD) or ACS [3-5].

Monocytes constitute a subgroup of leukocytes and their high level, especially the subgroup featuring CD14++, was proposed to relate with future coronary diseases [6, 7]. High-density lipoprotein cholesterol (HDL-C) plays pivotal role in the protection against the generation of atherosclerotic plaques, mainly by refraining the macrophage migration and lipid accumulation under vascular intima [7]. In recent years, the ratio of monocyte count to HDL-C (MHR) appealed to the physicians owing to its potential role in the anticipation of the balance between the pro- and anti-atherogenic status, and hence cardiovascular (CV) events and prognosis [6, 8-13]. Although MHR was demonstrated to have associated with in-hospital MACE in STMI patients, there is no study to date evaluating the relationship of admission MHR in the prediction of 3-month all-cause mortality in acute STMI patients treated with primary percutaneous coronary intervention (PCI).

When it comes to the comparison of these two parameters of prognostic significance in ACS settings, namely MHR and NLR, there is no study comparing the superiority, if any, of these 2 parameters in acute STMI patients. Hence, we sought in the present study to investigate which of these parameters on admission predicts better the 3-month overall death in STMI patients undergoing a successful PCI.

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Material and Methods

Study population

In this single center study, a total of 184 consecutive patients presenting with STMI (46 females and138 males) to our tertiary center and treated with PCI between July 2017 and September 2018 were retrospectively included. The relevant baseline data to the clinical and demographical characteristics together with the physical examination, echocardiographic and coronary angiographic findings of the patients were retrieved through archive search of the patients' medical records. Moreover, information with regard to in-hospital and/or 3-month mortality status of the patients included was obtained either by medical archive search or through phone contact to the patients or their relatives in case of inability to reach their prospective medical records.

Diagnosis of an acute STMI was ascertained based on the presence of following criteria: detection of an increase/decrease in cardiac troponins accompanied by at least one of the such following features as symptoms conducive to ischemia; new / presumed new ST segment elevation in ≥ 2 contiguous leads with or new left bundle branch block; appearance of pathological Q waves in the electrocardiogram; new loss of viable myocardium or new regional wall motion abnormality as evident through imaging modalities; and angiographic demonstration of thrombus in the coronary arteries [14].

The exclusion criteria were defined as follows: history of a recent myocardial infarction; active infection or chronic inflammatory disease thrombolytic agent administration before PCI; severe hepatic, renal, hematological disease; and, history of neoplastic or rheumatologic disease. Our study followed the standards set by the Declaration of Helsinki and received approval from the institutional committee for ethics.

Cardiogenic shock was defined as systolic blood pressure (SBP) < 90 mmHg for longer than 30 min or need for pharmacologic or mechanic support to maintain SBP > 90 mmHg, together with such findings regarding end-organ hypoperfusion as urine output < 30 mL/h, cold extremities, altered mental status, and elevated lactate level [15].

Transthoracic echocardiographic evalation of the enrolled patients were performed using a standard device (Vivid S5, GE Vingmed Ultrasound AS, Horten, Norway). Calculation of left ventricular ejection fraction was through modified Simpson's rule. Echocardiographic evaluation was performed as per the standards of American Society of Echocardiography [16].

Coronary Angiography, the Syntax Score and Percutaneous Coronary Intervention

All patients were treated by complying with the recommendations of the STMI guideline [17]. Once the written informed consent for cardiac catheterization was obtained, an emergency coronary angiography was performed in all subjects on the basis of standard techniques. Cineangiographic views were evaluated in Axiom workstation (Siemens Medical Solution, Erlangen, Germany) by two experienced cardiologist blinded to the study data. Pertinent scores were given to the lesions with a ≥ 50% diameter stenosis in a coronary artery with ≥1.5 mm diameter by use of the SYNTAX score calculator (http://www.syntaxscore.com). If the cardiologists conflict about the lesions, the ultimate score was decided by averaging the scores calculated by each cardiologist.

Glycoprotein IIb/IIIa inhibitor (tirofiban) was administered to the patients in the catheterization laboratory at the operator's discretion. All PCIs performed in eligible patients were performed using the standard clinical practice and choice between the alternatives of drug-eluting stent or bare metal stent was at the operator's discretion. Successful stent implantation in infarct-related artery was fulfilled in all patients.

Laboratory Measurement

Blood samples were obtained on admission to the emergency department and immediately transferred to the laboratory. Measurement of serum biochemical parameters was fulfilled with the help of a clinical chemistry analyzer (Roche Hitachi Cobas c8000 autoanalyzer, Roche Diagnostic Corp., Mannheim, Germany). Hematological parameters were determined by using an automated blood cell counter (Sysmex XN-1000, Sysmex Corporation, Kobe, Japan). Monocyte count was divided by HDL-C to end up with the baseline MHR.

Statistical analysis

Statistical analysis of the study variables was carried out by way of SPSS (SPSS for Windows, Version 21.0. Armonk, NY: IBM Corp., USA). Distribution pattern of the quantitative variables were evaluated Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistic for the study variables were expressed as median (25th – 75th IQR), and numbers (%). Univariate analysis of the study variables were performed using Chi-square test, Fisher's Exact test, Mann-Whitney U test and independent t-test, where appropriate. The study population was divided for the comparison of the demographic and clinical features in two subgroups on the basis of median MHR as the group with MHR<19.31 (group 1) and the group with MHR ≥19.31 (group 2). Bivariate logistic regression analysis was carried out on each study variable in order to examine their effect on 3-month and in-hospital overall death. Furthermore, the variables that

were detected to possess significant effect on the mortality in bivariate logistic regression model underwent a multivariate logistic regression analysis. Backward elimination method was used in order to obtain the best predictive model in the multivariate logistic regression analysis. A further receiver-operating curve (ROC) analysis was performed in an attempt to specify any probable diagnostic cut-off value of the variables that contributes the best to the logistic regression model. Two-sided P <0.05 was regarded significant.

Results

Table 1 represents the demographic and clinical features of the study patients, as categorized into 2 subgroups on the basis of MHR. Compared to the group 1, group 2 had more male patients (p=0.017), less patients with hypertension (p=0.001), less patients with diabetes mellitus (p=0.007), more patients with smoking habit (p=0.008). Moreover, HDL-C was lower (p<0.001), while white blood cell count (p<0.001), hemoglobin level (p=0.003), neutrophil count (p<0.001), lymphocyte count (p=0.003), monocyte count (p<0.001), NLR (p<0.001), cardiac troponin I level (p=0.003) and Creatinin kinase-MB level (p<0.001) were higher in group 2 than those in group 1. Out of 92 patients in group 2, carcinogenic shock was observed on admission in 12. However, there was no shock on admission in groups 1. Furthermore, in-hospital mortality occurred in 14 patients (15.2%), while 3-month mortality occurred in 21 patients (22.8%) in group 2. On the other hand, there was no mortality observed in group 1. Other demographic and clinical characteristics and findings were not significantly different between the groups.

When it comes to the reason for mortality in group 2, it was multiorgan system failure including acute renal insufficiency in 10 patients (10.8% in group 2; 5.4% in all study population), sudden cardiac death in 5 patients (5.4% in group 2; 2.7% in all study population), and cardiogenic shock in 6 patients (13% in group 2; 6.5% in all study population). In-hospital mortality occurred in 14 patients (15.2% in group 2; 7.6% in all study population), while post-discharge mortality occurred in 7 patients (7.6% in group 2; 3.8% in all study population).

In multivariate logistic regression analysis, higher LDL-C level, higher syntax score and MHR were independently associated with both of in-hospital and 3-month overall mortality. However, NLR failed to show such a significant association with mortality (p>0.05).

ROC analysis yielded a cut-off value of > 36.6, which predicted in-hospital mortality with 85.7% sensitivity and 88.8% specificity (AUC:0.939, 95%CI: 0.885-0.993, p<0.01). With regard to 3-month all cause mortality, a cut-off value of >46.81 emerged with 85.7% sensitivity and 97.8% specificity (AUC:0.973, 95%CI: 0.939-0.989, p<0.01). AUC for NLR, syntax score and LDL-C were not statistically significant (p>0.05).

Discussion

Main finding in our study is that acute STMI patients with higher MHR on admission is associated with more cardiogenic shock on admission and have higher rates of in-hospital and 3-month overall mortality on follow-up. Additionally, MHR, LDL-C and syntax score, but not NLR, were independently associated with both in-hospital (Table 2, figure 1) and 3-month (Table 3 , figure 2) mortality in the same patient population. As a readily available and cheap blood parameter, MHR is very likely to provide a more crucial insight into the overall in-hospital and short-term death in the setting of STMI than NLR itself.

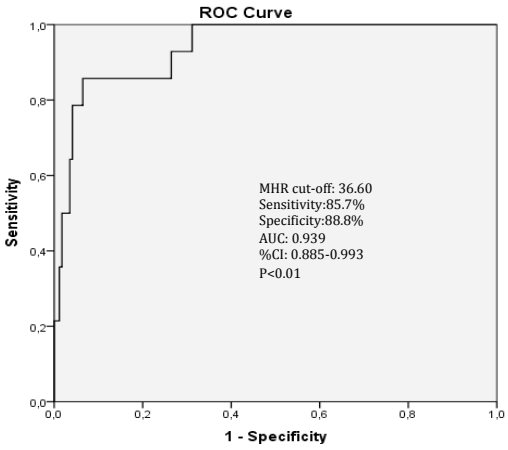

Figure 1. ROC curve for in-hospital mortality

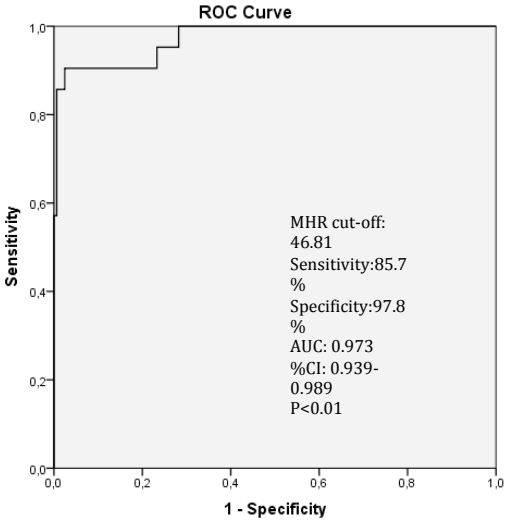

Figure 2. ROC curve for 3-month mortality.

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Table 1: Demographic and clinical characteristics of the study population according to the median MHR ratio of < 19.31 and ≥19.31 (n = 184)

Characteristics		MHR	
< 19.31 (n=92) (Group 1)		≥19.31 (n=92) (Group 2)	P
Gender, female, n (%)	30 (32.6%)	16 (17.3%)	0.017
Age (years)	62(54 69)	62(47.50 65.50)	0.069
DM, n (%)	38 (41.3%)	21 (22.8%)	0.007
CAD, n (%)	16 (17.3%)	8 (8.6%)	0.080
HT, n (%)	54 (58.6%)	32 (34.7%)	0.001
HL, n (%)	22 (23.9%)	26 (28.2%)	0.502
Smoking, n (%)	42 (45.6%)	60 (65.2%)	0.008
MI localization			0.004
Anterior	40 (43.4%)	60 (65.2%)	
Inferior	42 (45.6%)	32 (34.7%)	
Lateral	2 (2.1%)	0 (0%)	
Anterolateral	2 (2.1%)	0 (0%)	
Inferoposterior	6 (6.5%)	0 (0%)	
Shock on admission, n (%)	0 (0%)	12 (13%)	<0.001
In-hospital mortality, n (%)	0 (0%)	14 (15.2%)	<0.001
3-month mortality, n (%)	0 (0%)	21 (22.8%)	<0.001
Glucose, mg/dL	105.5(91.0 157.0)	100.0(88.0 161.0)	0.561
GFR, mL/min/1,73 m2	76.5(60.0 94.0)	85.0(72.0 98.0)	0.154
Triglyceride, mg/dL	139.5(105.0 188.0)	152.0(113.0 228.0)	0.211
Total-C, mg/dL	156 (141.0 187.0)	174 (146.0 195.0)	0.151
LDL-C, mg/dL	79 (64.0 118.0)	93 (66.0 120.0)	0.246
HDL-C, mg/dL	41.5 (37.0 52.0)	35 (30.0 40.0)	<0.001
Calcium, mg/dL	9.3 (9.0 9.5)	9.2 (8.9 9.6)	0.843
Albumin, gr/dL	4 (3.8	4 (3.7 4.3)	0.318
WBC, (x109/L)	7.49 (6.7 9.0)	12.4 (9.0 13.7)	<0.001
Hb, g/dL	13.25 (12.0 14.1)	14.1 (13.4 15.1)	0.003
Plt, (x109/L)	243.5 (215.0 264.0)	251 (228.5 295.0)	0.554
Neutrophil, (x109/L)	4.58 (3.73 5.6)	7.7 (5.0 10.1)	<0.001
Lymphocyte, (x109/L)	1.99 (1.55 2.7)	2.14 (1.55 3.3)	<0.001
Monocyte, (x109/L)	0.59 (0.48 0.65)	0.99 (0.83 1.36)	<0.001
MPV (fL)	10.3 (9.9 11.0)	10.8 (9.9 11.1)	0.674
PDW(fL)	11.55 (11.0 13.1)	12.5 (11.5 13.7)	0.608
C-RP (mg/dL)	0.46 (0.21 1.0)	0.45 (0.23 1.57)	0.446
NLR	2.30 (2.02	3.59 (3.12)	<0.001
Hs- troponin, pg/mL	982.5(111.0 2300.0)	1630 (176.0 5812.0)	<0.001
CK-MB, ng/mL	19.02 (2.6 31.2)	51.2 (7.8 99.51)	<0.001
LV EF (%)	44.2 (30 51)	42.1 (28 47)	0.104
Syntax score 21.75	(14.0 28.5)	22.5 (9.5 26.5)	0.692
Data are in median	(IQR:25%-75%)	or n (%).	

Data are in median (IQR:25%-75%) or n (%).
MHR; monocyte/high-density lipoprotein cholesterol ratio; DM, diabetes mellitus; CAD, coronary artery disease; HT, hypertension; HL, hyperlipidemia; GFR, glomerular filtration rate; Total-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; MPV, mean platelet volume; PDW, platelet distribution width; C-RP, C-reactive protein; NLR, neutropil to lymphocyte ratio; CK-MB; creatin kinase MB fraction; LV EF, left ventricular ejection fraction.

Table 2. Multivariate logistic regression analysis for in-hospital mortality.

						95% CI for Exp (B)	
Variables	B	SE	Wald	P	Exp(B)	Lower	Upper
MHR	0.099	0.023	19.010	<0.001	1.104	1.056	1.153
NLR	-0.017	0.048	0.126	0.722	0.983	0.896	1.079
Syntax score	0.135	0.053	6.460	0.011	1.145	1.031	1.271
LDL-C	0.017	0.009	4.022	0.045	1.017	1.000	1.035

MHR, monocyte to high-density lipoprotein cholesterol ratio; NLR, neutropil to lymphocyte ratio: LDL-C, low-density lipoprotein cholesterol.

Table 3. Multivariate logistic regression analysis for 3-month mortality.

						95% CI for Exp (B)	
Variables	B	SE	Wald	P	Exp(B)	Lower	Upper
MHR	0.390	0.160	5.946	0.015	1.477	1.080	2.021
NLR	0.113	0.116	0.952	0.329	1.120	0.892	1.405
Syntax score	0.320	0.148	4.700	0.030	1.377	1.031	1.839
LDL-C	0.047	0.022	4.715	0.030	1.048	1.005	1.093

MHR, monocyte to high-density lipoprotein cholesterol ratio; NLR, neutropil to lymphocyte ratio: LDL-C, low-density lipoprotein cholesterol.

Inflammation underlies the plaque rupture in a case of an acute STMI, and is associated with adverse cardiac events [13]. More specifically, monocytes make a pivotal contribution to the generation and deterioration of atherosclerosis, mainly through production of inflammatory cytokines [18]. Endothelial dysfunction initiates monocyte attachment onto the endothelium and then their migration into the subendothelial area where they transform into oxidized-LDL scavengers. It is well known from the previous studies that HDL-C assumes anti-inflammatory role and acts by reversing the cholesterol transport from wall of the arteries. Besides, HDL-C helps preventing monocyte migration though the endothelium by refraining the dysfunctional endothelial cells from expression of relevant adhesion molecules to the monocytes [19, 20]. Therefore, it is prudent to assume that MHR reflects a balance of bodily pro- and anti-inflammatory status. Moreover, there is robust evidence that LDL-C leads to the development of atherosclerosis and atherosclerotic plaque vulnerability [21, 22]. In our study, the findings that higher incidence of in-hospital and 3-month overall death, and cardiogenic shock in group 2 characterized with higher LDL-C level and MHR is compatible with the previous evidence. Previous studies suggested an independent association between neutrophil count and long-term death following ACS [23]. Data regarding lymphocyte number in the setting of ACS is conflicting. Dragu et al. [24] reported in their study that lower lymphocyte but higher neutrophil and monocyte counts were independently associated with long-term death in ACS patients, whereas Çiçek et al. [6] suggested greater lymphocyte, neutrophil and monocyte counts in the ACS patient group with worse short- and long-term MACE. Our findings are more compatible with the findings of Çiçek et al.

As a relatively novel anti-inflammatory marker, MHR has been proposed to associate with CV outcomes in a number of studies. Canpolat et al.[25] reported that increased MHR was associated with recurrent atrial fibrillation following atrial fibrillation ablation. Yayla et al. [9] suggested a higher MHR in hypertensive patients with more deteriorated parameters of aortic elasticity. Kanbay et al. [8] reported higher prevalence of adverse CV events in patients with chronic kidney insufficiency. Ulus et al.[26] showed in their study that MHR was a significant predictor of contrast-induced nephropathy following PCI in STMI patients. You et al. [11] suggested a positive association between MHR and death at 3 month after cerebral hemorrhage. In another study by Balta et al.[12], higher MHR was found to correlate significantly with no-reflow phenomenon in STMI patients treated with PCI. Zhang et al.[27] demonstrated a significant association between MHR and MACE over a median 2 year in stable CAD patients; however, neither MHR nor monocyte count was superior to each other in the prediction of MACE in their study. In contrast, although both MHR and monocyte count were greater in group 2 in our study, only MHR but not monocyte count showed independent association with mortality. This might be attributed to the fact that we only included the patients with unstable coronary disease and we sought to correlate the hematological variables with sole overall in-hospital and 3-month mortality. Studies conducted on the predictive role of MHR on the prognosis of acute STMI patient are very limited. Çiçek at al. [6] indicated that MHR predicted well the

in-hospital and 30-month MACE in STMI patients. Our findings are consistent with the findings of the study by Çiçek at al. in regard of greater neutrophil and lymphocyte counts in their patient quartiles with greater MHR. However, they did not include NLR to their model and did not seek to correlate NLR with short- and long-term MACE. Contrary to their study, we compared the prognostic significance of both MHR and NLR in the anticipation of overall death during a shorter follow-up period. Moreover, Karakaş et al. [13] demonstrated in their study conducted on STMI patients that MHR was associated with in-hospital death and MACE. However, they did not follow-up the patients for longer periods in order to seek to correlate MHR with long-term MACE. Contrary to our study, they also did not include NLR to their model.

In their study, Çağdaş et al. [10] proposed MHR as a more precise predictor for syntax 1 and syntax 2 scores than NLR in acute STMI patients. In our study, despite significantly greater MHR and NLR in groups 2, only MHR but not NLR was found to be associated with in-hospital and 3-month overall death. Duffy et al.[28] demonstrated that NLR but not leukocyte count predicted 32-month mortality in STMI patients. Similarly, arbel et al.[4] suggested that NLR >3 could be an indicator of CAD severity and 3-year MACE in patients undergoing coronary angiography for CAD and ACS. However, they did not include MHR in their model, and they also did not correlate NLR with in-hospital or short-term death. In contrast to their study, we did not follow up the patient for such a long time period, which may in part explain the non-predictive role of NLR in our study, or another speculation could be the possibility that NLR might have predicted only the long-term but not the short-term overall death.

Our study had better be evaluated with a number of limitations. This is a single-center study with relatively small patient population. We did not seek to correlate MHR and NLR with longer-term overall mortality. Instead of MACE, in-hospital and 3-month overall mortality was the primary target in our study, and the results could be different upon taking MACE as the primary study target. Syntax 2 score could have been included in the study model.

Conclusion

In conclusion, MHR but not NLR may predict in-hospital and 3-month overall death in acute STMI patients treated with primary PCI. However, further studies with larger cohorts are warranted to assess combined use of MHR and NLR in the prediction of mortality in STMI populations.

Declaration of conflict of interest

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