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The association between monocyte/HDL-C ratio and heart failure

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ABSTRACT: The monocyte/HDL-cholesterol ratio (MHR) was shown to be a marker of inflammation. This study investigated the utilization of this ratio as a measure of severity for heart failure which is a condition associated with inflammation. The MHR was calculated for 323 ambulatory patients with chronic heart failure and compared to other variables associated with the severity of the condition. Additionally, the impact of MHR on the Seattle Heart Failure Model (SHFM) score was investigated. MHR correlated positively with C-reactive protein (r: 0.312, p<0.001) and neutrophil-to-lymphocyte ratio (r: 0.242, p<0.001), but not with platelet-to-lymphocyte ratio. In addition, a correlation was found between the SHFM score and MHR (r:-0.267, p<0.001). The SHFM score exhibited a significant result for proB-type natriuretic peptide (pro-BNP) (p<0.001), neutrophil (p<0.001), hematocrit (p=0.001), and serum creatinine (p=0.001) in the ordinal logistic regression analysis, but not for MHR. MHR showed a negative correlation with left ventricular ejection fraction (r: -0.151, p: 0.007), exhibited a positive association with pro-BNP (r: 0.184, p<0.001), and no correlation with New York Heart Association classes. There is a significant correlation between the MHR value and the factors associated with the severity of heart failure. The prognosis and management of this condition may be assessed by utilizing the MHR value in conjunction with existing biomarkers.

KEYWORDS: HDL-cholesterol; heart failure; ınflammation; MHR; monocyte

1. INTRODUCTION

Heart failure (HF) is defined as "a complex clinical syndrome characterized by symptoms and signs arising from any anatomical or functional impairment of ventricular filling or ejection of blood" [1]. It has a growing prevalence and is a rapidly growing entity in developed Western countries. Despite medical breakthroughs in the prevention and treatment of this condition, most hospitalized patients have a poor prognosis. After the initial diagnosis, HF patients are hospitalized once every year on average. A 67% mortality rate within 5 years following diagnosis was reported [2].

In the last decade, the importance of inflammation in heart failure prognosis has drawn more attention for both heart failure with preserved and reduced ejection fractions. C-reactive protein (CRP), tumor necrosis factor-α, and interleukin-6 serum concentrations are revealed to be elevated in congestive heart failure [3]. The level of elevation of these proinflammatory cytokines in chronic heart failure is considerably lower than in autoimmune diseases or acute infections. This information suggests that a low level of chronic inflammation may have a significant effect on the improvement or worsening of heart failure [4].

Leukocyte count and subtypes are immune markers in cardiovascular diseases [5]. The neutrophil-to-lymphocyte ratio (NLR) was evaluated as a marker after physiological stress-induced neutrophilia and lymphocytopenia were observed in inflammatory diseases and heart failure [6]. The platelet count is also elevated in HF, the pathogenesis of which includes oxidative stress [7]. From this point of view, some studies have shown that platelet-to-lymphocyte ratio (PLR) and NLR values are useful in determining the severity of heart failure and predicting mortality [8–10].

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The understanding of the established role of monocytes and macrophages as well as the suppressive impact of high-density lipoprotein cholesterol on inflammation [11, 12] has prompted the suggestion that the monocyte/HDL-C ratio (MHR) might serve as a predictive marker for inflammatory diseases. The hypothesis was confirmed by studies about renal failure [13] and several cardiovascular diseases [14–17]. The most recent studies showed a relationship between MHR and more severe states of pulmonary embolism, psoriasis and obstructive sleep apnea syndrome [18–20].

As for mortality, MHR is related not only to individuals with coronary artery disease but also to the general population [21]. Although numerous studies have been conducted on a variety of inflammatory markers in heart failure [22–24], there is no study examining their relationship with MHR. One of the major problems with HF is the repetitive need for hospitalization which is uncomfortable for the patients and expensive. Therefore, an early powerful predictor of clinical worsening of heart failure could be helpful for preventing hospitalization. The objective of this research was to elucidate the potential role of MHR for the assessment of heart failure severity in comparison to other common parameters.

2. RESULTS

Our study included 323 patients with reduced ejection fraction heart failure who had all the necessary demographic and laboratory data. The median MHR value was 14.7 (IQR 11-20.5). Patients had a median left ventricular ejection fraction (LVEF) value of 25% (20-35%) and it showed a significant difference between MHR quartile groups (Table 1).

Of all patients, there were 75 (23%) females and 248 (77%) males. No statistically significant differences were observed between genders regarding LVEF, New York Heart Association (NYHA) classes, or proB-type natriuretic peptide (pro-BNP) values. There was no significant distinction between genders in the levels of the inflammatory marker CRP. However, MHR was 15.55 (IQR 12.4-21.5) for males and 11.4 (IQR 8.1-15.2) for females ($p<0.001$).

The patients' age range was 23 to 85. The median age was calculated as 52 (IQR 45-57) and didn't show a significant difference for MHR quartile groups. In our study, 319 patients' weight and height information were present. Among these patients, 55 had (17%) a normal body mass index (BMI), 113 (35%) were overweight, 104 (33%) were obese, and 47 (15%) were morbidly obese. BMI groups have shown significant differences between MHR quartile groups as shown in Table 1.

The majority of our patients were in the NYHA class of I (52%) and had a Seattle Heart Failure Model (SHFM) score of -1 (58%). Both the classification and score have shown a significant correlation with MHR quartile groups. Demographic variables, laboratory tests, medical history and other information about the study population are presented in detail in Table 1.

Comparisons between MHR quartile groups showed significant differences in; Pro-BNP, CRP, and other laboratory parameters ($p<0.05$). SBP and smoking status did not show statistical significance between MHR quartile groups. It was determined that among MHR quartile groups, the NLR median value differed only between MHR1 (<11) and MHR4 (>20.5), while the PLR median value did not differ between the MHR quartile groups (Table 1).

Analysis revealed that pro-BNP, MHR and NLR were significantly lower in patients with non-ischemic HF, whereas LVEF, NYHA classes, and CRP have shown no significant difference between ischemic and non-ischemic HF. The median values of the variables and significance levels are shown in Table 2.

MHR value had a significant positive correlation with age, BMI, pro-BNP, CRP, white blood cell (WBC), and a negative correlation with LVEF, eGFR, total cholesterol (T. Chol), and albumin. MHR doesn't have a correlation with the NYHA classes or low-density lipoprotein cholesterol (LDL-C).

Pro-BNP, CRP, and NLR exhibited a modest positive correlation with MHR (r: 0.184, r: 0.312, r: 0.242, $p<0.001$), respectively. The findings of correlations between MHR and the laboratory and demographic parameters of the patients are displayed in Table 3.

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Table 1. The data and statistical difference of the study population's demographic and clinical objectives according to MHR quartile groups

	Total	MHR				p-value
	(n=323)	MHR1 <11 (n=80)	MHR2 11-14.7 (n=81)	MHR3 14.7-20.5 (n=82)	MHR4 >20.5 (n=80)	
Age (year; median), (IQR)	52 (45-57)	47 (42-56)	52 (45,5-57)	53 (47-58)	52 (46-58)	0.060
Male, n (%)	248 (77%)	43 (54%)	64 (79%)	69 (84%)	72 (90%)	<0.001*
Diabetes mellitus, n (%)	111 (34%)	21 (26%)	21 (26%)	26 (32%)	43 (54%)	<0.001*
BMI (kg/m²; median), (IQR)	29 (26-33)	27 (24-31)	29 (26-32)	29 (25-32)	31 (27-36)	0.001*
Ischemic HF, n (%)	163 (50%)	26 (32%)	38 (47%)	45 (55%)	54 (67%)	<0.001*
LVEF (%, median),(IQR)	25 (20-35)	30 (25-35)	30 (20-35)	25 (20-30)	25 (20-30)	0.018*
Pro-BNP (pg/mL, median) (IQR)	179 (73-512)	110.7 (41-301)	161.8 (75-528)	166.2 (69-436)	283.2 (117-806)	0.004*
SHFM score, n (%)						<0.001*
-1	186 (58%)	57 (71%)	50 (62%)	50 (61%)	29 (36%)	
0	97 (30%)	17 (21%)	25 (31%)	26 (32%)	29 (36%)	
1	34 (10%)	6 (8%)	5 (6%)	4 (5%)	19 (2%4)	
NYHA classes, n(%)						0.027*
I	168 (52%)	39 (49%)	45 (56%)	43 (53%)	41 (51%)	
II	109 (34%)	33 (41%)	25 (31%)	32 (39%)	19 (24%)	
III	40 (12%)	6 (7.5%)	11 (14%)	5 (6%)	18 (22%)	
IV	6 (2%)	2 (2.5%)	0 (0%)	2 (2%)	2 (2.5%)	
CRP (mg/dL; median) (IQR)	2 (1-7)	1 (1-3)	2 (1-5)	2 (1-7)	4 (1-13)	<0.001*
WBC (10³/µl; median) (IQR)	7.8 (6.6-9.3)	6.5 (5.5-7.5)	7.4 (6.4-9)	8.0 (7.4-9.7)	9.5 (8.2-11.2)	<0.001*
Total cholesterol (mg/dL, median) (IQR)	185 (154-219)	194 (162-224)	187 (161-222)	187,5 (162-219)	168,5 (141-211)	0.035*
LDL-C (mg/dL; median) (IQR)	115 (85-138)	122 (87-141)	115,5 (91-141)	118 (96-142)	99 (71-127)	0.009*
Triglyseride (mg/dL, median) (IQR)	147 (98-225)	114 (80-162)	149 (107-216)	142,5 (100-223)	197,5 (117-274)	<0.001*
Serum creatinin (mg/dL, median) (IQR)	0.94 (0.8-1,1)	0.84 (0.8-1.0)	0.96 (0.8-1.2)	0.92 (0.8-1.1)	1.07 (0.9-1.3)	<0.001*
eGFR (MDRD; median), (IQR)	83.7 (71-96)	88.7 (77-102)	83.7 (66-94)	86.8 (75-98)	75.2 (59-92)	0.001*
Albumin (g/dL; median), (IQR)	4.4 (4.1-4.6)	4.4 (4.2-4.6)	4.4 (4.1-4.6)	4.4 (4.2-4.5)	4.3 (4.0-4.5)	0.014*
Hematocrit (%, median) (IQR)	42.5 (39-45)	41.4 (38-44)	42.6 (40-45)	43.2 (39-46)	42.6 (39-45)	0.282
Neutrophil-to-Lymphocyte Ratio	2.13 (1.63-3.0)	1,8 (1,4-2,6)	2,1 (1,7-3,0)	2,1 (1,7-2,9)	2,6 (1,8-3,7)	<0,001*
Platelet-to-Lymphocyte Ratio	109.1 (88.4-140.7)	117,9 (95-156)	108,2 (84-135)	103,9 (90-132)	108,4 (81-146)	0,214

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; ARNI: Angiotensin receptor–neprilysin inhibitor; BMI: body mass index; CRP: C-reactive protein; e-GFR: estimated glomerular filtration rate; HF: heart failure; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; Pro-BNP: pro-B natriuretic peptide; SBP: systolic blood pressure; WBC: White blood cell; The statistical analysis Chi-square test was used for categorical parameters, and Kruskal-Wallis H test was used for continuous parameters; * p<0,05 is statistically significant.

Table 2. The difference in some parameters between patients with ischemic and non-ischemic etiology

	Ischemic (n=163)	Non-ischemic (n=160)	p-value
LVEF (%)	25 (20-30)	30 (20-35)	0.285
NYHA classes	1 (1-2)	1 (1-2)	0.792
Pro-BNP (pg/mL)	206 (97-512)	143 (46-501)	0.008*
CRP (mg/L)	2 (1-7,5)	2 (1-6)	0.393
MHR	16.5 (12.6-22.6)	13.65 (9-18)	<0.001*
NLR	2,3 (1,7-3,2)	2 (1,5-2,7)	0,024*
PLR	108 (85-145)	110 (92-135)	0,719

CRP: C-reactive protein; LVEF: left ventricular ejection fraction; MHR: Monocyte/HDL-cholesterol ratio; NLR: neutrophil-to-lymphocyte ratio; NYHA: New York Heart Association; PLR: platelet-to-lymphocyte ratio; Pro-BNP: pro-B natriuretic peptide.* p<0.05 is statistically significant

Table 3. The correlation between MHR value and the patient's laboratory and demographic characteristics

	MHR r value	p-value
Age	0.127	0.022*
BMI	0.207	<0.001*
NYHA	0.037	0.512
LVEF	-0.151	0.007*
Pro-BNP	0.184	0.001*
e-GFR	-0.174	0.002*
T. chol	-0.161	0.002*
LDL-C	-0.011	0.843
TG	0.248	<0.001*
Albumin	-0.196	<0.001*
SHFM score	-0.267	<0.001*
NYHA	0.037	0.512
LVEF	-0.151	0.007*
CRP	0.312	<0.001*
NLR	0.242	<0.001*
PLR	0.073	0.190

BMI: body mass index; CRP: C-reactive protein; e-GFR: estimated glomerular filration rate; LDL-C: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MHR: Monocyte/HDL-cholesterol ratio; NLR: neutrophil-to-lymphocyte ratio; NYHA: New York Heart Association; PLR: platelet-to-lymphocyte ratio; Pro-BNP: pro-B natriuretic peptide; SHFM: Seattle heart failure model; T.chol: total cholesterol; TG: triglyceride * p<0.05 is statistically significant.

The SHFM score of all 323 patients was calculated. The SHFM score was -1, 0, 1, 2, and 3 in 186, 97, 34, 4 and 2 respectively. Patients with scores two and three were not analysed due to insufficient patient numbers. The median MHR levels have shown significant differences between SHFM scores. Pro-BNP, CRP, serum creatinine and albumin are parameters that aren't included in the calculation of the SHFM score and their median values have also shown significant differences between SHFM scores (Table 4).

The ordinal logistic regression analysis revealed that Pro-BNP, serum creatinine, neutrophil count, and hematocrit were shown to be significant predictors of the SHFM score (p<0.01). The variables CRP and MHR did not have a statistically significant impact (p>0.05) on the prediction of the score.

Table 4. The SHFM scores exhibit variations across the parameters of the patients.

	SHFM score -1 (n=186)	SHFM score 0 (n=97)	SHFM score 1 (n=34)	p-value
eGFR (MDRD; median), (IQR)	88.15 (75.45-99.02)	80.70 (63.7-93.4)	72.30 (57.9-88.8)	<0.001*
CRP (mg/dL; median) (IQR)	1.5 (1-4)	3 (1-9)	4 (1-13)	<0.001*
Pro-BNP (pg/mL, median) (IQR)	113.1 (43-237)	312.5 (103-699)	766.0 (346-1487)	<0.001*
Monocyte/HDL-cholesterol Ratio (median) (IQR)	13.7 (10-18)	15.40 (12-22)	23.8 (14-27)	<0.001*
Neutrophil-to-Lymphocyte Ratio (median) (IQR)	1,85 (1,4-2,4)	2,6 (1,85-3,5)	2,9 (1,9-3,7)	<0,001*
Platelet-to-Lymphocyte Ratio (median) (IQR)	103,7 (84-128)	111,7 (93-149)	124 (90-193)	0,006*

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; ARNI: Angiotensin receptor–neprilysin inhibitor; BMI: body mass index; CRP: C-reactive protein; e-GFR: estimated glomerular filration rate; HF: heart failure; LDL-C: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; Pro-BNP: pro-B natriuretic peptide; SBP: sistolic blood pressure; WBC: White blood cell; * p<0.05 is statistically significant.

3. DISCUSSION

The objective of this study was to examine the probable relationship between MHR and heart failure severity measures, as well as the SHFM score, which is a heart failure mortality risk score. The main finding is that MHR has a positive correlation with pro-BNP and SHFM, a negative correlation with LVEF, and no correlation with NYHA classification. We found that MHR did not predict the SHFM score, but it significantly increased in patients with higher SHFM scores. CRP has the strongest correlation with MHR of any other inflammatory markers and parameters investigated in this study.

The fact that the MHR value is an indicator of inflammation suggested that patients with more severe heart failure in the patient population of our study would have a higher MHR value. Parameters that are associated with more severe heart failure and also increase the risk of heart failure mortality include being male, older age, relatively lower body weight, ischemic etiology, higher BNP level, higher NYHA class, lower EF [1, 2, 25].

GuJiang et al. have shown that there are more men in the highest MHR tertile in the general population [21]. In our study, MHR value was significantly higher (p<0.001) in male patients regardless of their CRP values. Moreover, numerous studies indicate that the mortality risk is elevated in male heart failure patients [25–27].

Our study observed no link between age and MHR values, which may be due to our study population's relatively young median age. Age, however, is related to elevated B-type natriuretic peptide (BNP) levels [28] and inflammation [29, 30], regardless of the presence of heart failure.

This study reported a positive correlation between BMI with CRP and MHR. This finding can be explained by the relation between obesity and inflammation [30, 31]. Jiang et al. have shown that BMI is higher in the highest MHR tertile of the general population [21]. In our study population, BMI has a negative correlation with pro-BNP (p<0.001) and no correlation with NYHA classes or LVEF values (p>0.05). Studies have shown similar results that patients with a higher BMI value have lower BNP levels [32–34].

There are heart failure studies that show the effect of ischemic etiology on the risk of mortality [25, 35]. In our study, age, pro-BNP, and MHR were found to be higher in ischemic HF patients. Although LVEF and CRP showed no difference, pro-BNP showed the risk of ischemic etiology in terms of heart failure severity and MHR in terms of inflammation. A study found that there is a relationship between CRP and mortality in ischemic HF, but not in non-ischemic HF [36]. However, most studies point out that CRP value

and therefore inflammation are elevated in heart failure patients, independent of the disease etiology [37–39].

Like other heart failure studies [40–42], our study demonstrated a substantial association between BNP, NYHA classes, and LVEF. Although there was no significant correlation between MHR and NYHA classes, there was a positive correlation between MHR and pro-BNP, and a lesser correlation between MHR and LVEF. BNP shows a link with CRP. Significant variations were seen only for MHR1 and MHR4 in terms of pro-BNP and LVEF between quartile groups.

BNP level is associated with elevated end-diastolic pressure, left ventricular wall tension, LVEF, and heart failure functional groups [41]. While the hemodynamic, symptomatic, and neurohumoral effects of HF can be evaluated through BNP as well as LVEF and NYHA; the inflammatory progression of this syndrome should be evaluated independently. MHR, which is considered an inflammatory marker to assess the severity of HF; is not an alternative to BNP, SVEF, or NYHA but can be used as an additional parameter. In our study, CRP and MHR were found to be correlated. Additionally, a significant relationship was found between both values and pro-BNP. In research that examined the correlation between heart failure severity and CRP; CRP or high sensitive CRP (hs-CRP) values were found to be associated with BNP or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) values, supporting our results. Studies have demonstrated an increase in BNP levels in tandem with CRP levels [38, 43–45].

Studies about cardiovascular diseases other than heart failure have shown that CRP and MHR values are correlated and support each other's results [15, 16]. On the other hand, Canpolat et al. have shown no relation between CRP and MHR in their study [14]. It is observed that CRP and MHR can not reach the sensitivity and specificity of BNP, but can provide additional information about HF by taking into account its inflammatory pathway. However, more studies are required to find a superiority between CRP and MHR.

The ordinal logistic regression analysis results showed that pro-BNP, serum creatinine, neutrophil count, and hematocrit ($p<0.01$) can predict SHFM score and thus may predict mortality risk. On the contrary, CRP, albumin, platelet, MHR, and smoking status did not predict the SHFM score. Similarly, Wedel et al. reported NT-pro-BNP as a strong predictor of all-cause death, but not hs-CRP [24]. In another study, the addition of different markers to the BNP-added SHFM was analyzed and pre-albumin was found to have the strongest impact, while hs-CRP did not contribute to the model [22].

Ky et al. designed a multimarker score model in their study including; BNP, hs-CRP, serum creatinine, and uric acid [23]. This model showed stronger accuracy and significance when compared with SHFM and when added to SHFM. This study demonstrated that CRP value contributes to determining the risks of death.

NLR is another inflammation-related ratio, and Benites-Zapata et al reported that NLR is correlated with BNP, but not LVEF [8]. However, Durmuş et al. found a correlation between LVEF and NLR, but not PLR [9].

4. CONCLUSION

MHR value can be a significant indicator of heart failure severity. Though it cannot be used in place of other parameters, it can be used in conjunction to predict patient prognosis. A prospective study may give better insight into the role of MHR in patients with heart failure.

5. MATERIALS AND METHODS

Study Population

This study was carried out as a single-centred, cross-sectional retrospective study in a heart failure clinic, and the study was approved by the Ethics Committee of Medipol University (Nr:2017-509). All adult consecutive patients who visited the heart failure clinic between December 2017 and January 2020 have been evaluated. Patients who were at least 18 years old, had reduced ejection fraction heart failure, and had complete patient files were included in the study. Patients with incomplete patient files, those with signs of acute infection, autoimmune disease, severe renal disease (serum creatinine >2.0 mg/dL, estimated glomerular filtration rate >30 mL/min/1.73 m^2), severe hepatic disease, and suspected malignancy were excluded. All demographic information of the study population including age, gender, smoking status, medical history were recorded.

Study Design

Demographic information and routine laboratory values of patients were recorded from the hospital's electronic information system. All laboratory data pertaining to heart failure encompassed serum levels of sodium, uric acid, pro-BNP, creatinine, CRP, and albumin, in addition to lipid profile, liver function tests, and the total blood count was evaluated. Additional characteristics taken into account were, New York Heart Association (NYHA) classes, systolic blood pressure, pulse, LVEF, etiology of heart failure, presence of the pacemaker and BMI.

Monocyte-to-HDL-C ratio was calculated for all patients. Glomerular filtration rate estimates were derived using the Modification of Diet in Renal Disease (MDRD) formula. The neutrophil to lymphocyte ratio along with the platelet to lymphocyte ratio were computed for each individual patient. Estimated survival percentages of all patients were calculated with the SHFM online calculator (https://depts.washington.edu/shfm/index.php?width=1366&height=768). SHFM score was calculated using the related formula [SHFMScore=Ln (Ln (SHFM estimated 1-year survival)/Ln (0.9604))]. Patients taking angiotensin receptor–neprilysin inhibitor (ARNI) medication were marked as angiotensin receptor blockers (ARB) users in the risk calculator since SHFM doesn't include this drug category.

Statistical Analysis

The Kolmogorov-Smirnov test was used for the assessment of normality. The participants in the study were divided into quartile groups according to their monocyte/HDL-C ratio values. The researchers computed and compared the median and percentage values of the demographic and clinical data of the patients across these groups. The relationship between the MHR value and the parameters indicating the severity of heart failure, as well as other continuous parameters was evaluated by Spearman's rank correlation. The patients were categorized into two groups based on the ischemic nature of their heart failure cause. The differences of the continuous variables between these groups are analyzed by Kruskal-Wallis H or Mann-Whitney U tests. The chi-square test was used for categorical variables. Ordinal logistic regression was performed to analyze if MHR could be an additional predictor for the SHFM score.

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