When groups were checked against according to biochemical parameters; urea, creatinine, aspartate aminotransferase (AST), white blood cell (WBC), monocytes, troponin, pro–B-type natriuretic peptide (proBNP) were higher in the non-survivors group (respectively p= 0.003, p= 0.002, p= 0.001 p= 0.038, p=0.003, p=0.053, p=0.014). TC, TG, HDL-C and LVEF were lower in the non-survivors group (respectively p= 0.052 p= 0.007 p= 0.023 p= 0.001) (Table 2). We found the MHR and other inflamatuary biomarkers NLR, PLR were significantly higher in the non-survivors group (p=0.001 for all) (Table 2) (Figure 1).

**Table II:** Comparison of Blood Parameters And Ejection Fractions of Study Groups

| Variables | Survivors N: 507 | Non-survivors N:45 | P value |
|---|---|---|---|
| Glucose (mg/dl) | 100(64-536) | 202.5 (72-425) | 0.123 |
| Urea (mg/dl) | 37 (6-236) | 44 (16-208) | *0.003* |
| Creatinine (mg/dl) | 0.91 (0.4-11.2) | 1.2(0.6-6) | *0.002* |
| AST (U/L) | 22(3-414) | 26 (12-756) | *0.001* |
| ALT (U/L) | 19 (5-453) | 19.50 (5-146) | 0.115 |
| Total cholesterol (mg/dl) | 178 (42-407) | 172 (106-287) | *0.052* |
| Triglycerides (mg/dl) | 128.5 (17-1181) | 108.50 (59-294) | *0.007* |
| LDL-C (mg/dl) | 114 (11-2584) | 114.10(11-164) | 0.884 |
| HDL-C (mg/dl) | 39 (16-74) | 32(23-79) | *0.023* |
| CRP (mg/L) | 5.1 (0.06-73) | 5.1(0.6-72) | 0.949 |
| Hemoglobin (g/dl) | 14 (8.38-19.10) | 13.05(7.4-18) | 0.124 |
| WBC (X10 $^{6}$ U/L) | 7.700 (1.900-30.900) | 8.100 (4.100-46.400) | *0.038* |
| Platelets (x10 $^{6}$ µl) | 218.000 (10.400-781.000) | 202500 (72000-425000) | 0.197 |
| Lymphocytes(x10 $^{6}$ µl) | 1.500 (0.00-9.220) | 1.400 (400-2.600) | 0.109 |
| Monocytes (x10 $^{6}$ µl) | 600 (0.00-2800) | 700 (300-2800) | *0.003* |
| Troponin (µg/L) | 0.012(0.001-38.7) | 0.053(0.014-42.0) | *0.053* |
| proBNP (pg/ml) | 2441(32.26-25800) | 3321(48-21400) | *0.014* |
| MHR | 13.95(0.00-83.87) | 20.68 (6.33-40.58) | *0.001* |
| NLR | 2.3 (1.5-2.7) | 3.6 (3.1-4.9) | *0.001* |
| PLR | 114 (87-144) | 147 (128-201) | *0.001* |
| LVEF (%) | 30(15-45) | 25(15-40) | *0.001* |

*Categorical variables were demonsrated as numbers and percentage, numerical variables were demonsrated as mean±SD or median (min-max)AST: aspartate aminotransferase; ALT: alanine aminotransferase; HDL-C: High density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; CRP:C-reactive protein; WBC: White blood cell; BNP: pro–B-type natriuretic peptide; MHR: Monocyte to high-density lipoprotein cholesterol ratio; NLR: Neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LVEF: Left ventricular ejection fraction;*

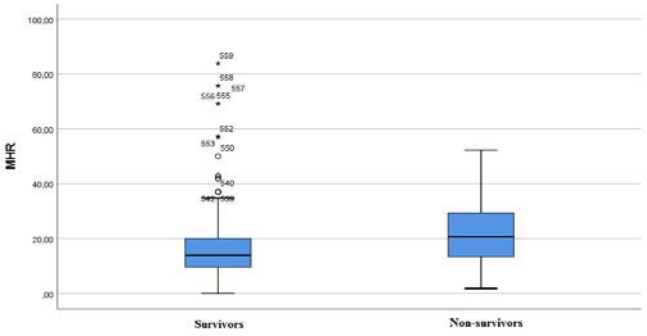


**Figure 1.** Comparison of Monocyte to high-density lipoprotein cholesterol ratio (MHR) between two groups

**Table III:** Correlation Between MHR and Clinical Characteristics of Population

| | *r* | *P* |
|---|---|---|
| Age | 0.156 | < 0.001 |
| Male | 0.185 | < 0.001 |
| Smoking | 0.055 | 0.043 |
| Diabetes mellitus | 0.084 | 0.002 |
| Chronic kidney disease | 0.190 | < 0.001 |
| proBNP | 0.274 | < 0.001 |
| Albumin | -0.202 | < 0.001 |
| Creatinine | 0.193 | < 0.001 |
| Cholesterol | -0.090 | 0.001 |
| C-reactive protein | 0.108 | 0.004 |
| White blood cell | 0.312 | < 0.001 |
| Left ventricular ejection fraction | -0.071 | 0.009 |
| Sacubitril/valsartan | -0.142 | < 0.001 |
| NLR | 0.146 | < 0.001 |
| PLR | 0.095 | < 0.001 |
| Statins | -0.083 | 0.002 |
| NYHA class | 0.190 | < 0.001 |

*MHR: Monocyte to high-density lipoprotein cholesterol ratio; BNP: pro–B-type natriuretic peptide; NLR: Neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; NHYA: New York Heart Association;*

The results of the correlation analyse were shown in Table 3. Overall, the MHR was positively correlated with age, gender of male, smoking, a history of diabetes mellitus or chronic kidney disease, proBNP, creatinine, C-reactive protein, white blood cell, NLR, PLR, NYHA class. The MHR also was negatively correlated with the albumin, cholesterol, hemoglobin, LVEF, a usage of sacubitril/valsartan or statins.

A multivariate Cox regression analysis with a stepwise retrospective model was applied to establish independent predictors of mortality at 1-year follow-up in patients with HFrEF, using variables that showed significant association with mortality in univariate analyzes. These variables are shown in Table 4. NLR, PLR, and MHR were found to be significant predictors of mortality as a result of multivariate analysis.

**Table IV:** Univariate analysis and independent predictors of mortality in multiple logistic regression analysis.

| | **Unadjusted OR** | **P** | **Adjusted OR** | **P** |
|---|---|---|---|---|
| Age | 1.168(1.038–1.236) | 0.335 | 1.049(1.011–1.116) | 0.092 |
| Male gender | 0.854 (0.259–2.699) | 0.632 | | |
| DM | 1.591(1.347–1.815) | 0.006 | 1.355(1.218–1.703) | 0.025 |
| NYHA class | 0.764(0.269–0.926) | 0.492 | 0.889(0.642-0.971) | 0.056 |
| LVEF | 0.574(0.446-0.942) | 0.012 | 0.761(0.359-0.932) | 0.008 |
| PLR | 1.106(1.016-1.242) | 0.001 | 1.063(1.006-1.135) | 0.001 |
| NLR | 1.041 (1.019-1.090) | 0.003 | 1.027(1.003–1.062) | 0.001 |
| MHR | 3.255 (1.832–5.192) | 0.001 | 2.471 (1.729–4.092) | 0.005 |

*OR: Odds ratio; DM: Diabetes mellitus; NHYA: New York Heart Association; NLR: Neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; MHR: Monocyte to high-density lipoprotein cholesterol ratio; LVEF: Left ventricular ejection fraction;*

The ROC curves of MHR, NLR and PLR for predicting mortality in HFrEF at 1 year follow-up are shown in Figure 2. We found that the AUC of MHR (0.831, %95 CI: 0.799-0.869, p=0.001) was significantly higher than both AUCs of NLR (0.649. %95 CI: 0.573-0.721, p=0.001) and PLR (0.702. %95 CI: 0.661-0.758,

p=0.001) The cut-off value of 6,39 can be used to predict the mortality with 83% sensitivity and 91% specificity.

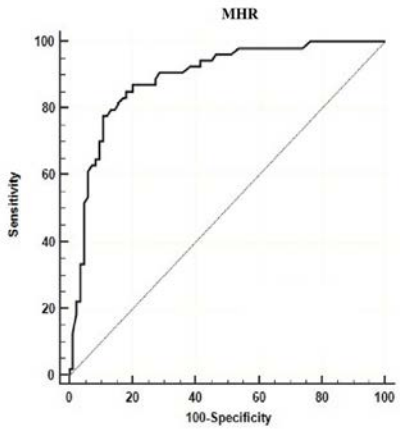


**Figure 2.** Roc Curve Analysis of MHR, NLR and PLR for predicting the mortality at 12 month follow-up

## DISCUSSION

Our study is the first that demonstrate the relationship between MHR and mortality in patients with HFrEF. We also demonstrated the association between MHR and mortality. MHR might be accepted as an independent predictor of mortality in patients with HFrEF. In the complex management of patients with HFrEF, MHR can be used to predict mortality.

Inflammation is an extremely important factor in both the onset and progression of atherosclerotic cardiovascular disease[2,3]. However, the levels of different blood lipid components have critical importance in the atherosclerotic process. Inflammation has also been shown to be common in HF and different studies have indicated that it may be associated with adverse cardiovascular events[12]. Many inflammatory cytokines, as well as some proteolytic enzymes, which are increased as a result of the inflammatory stimulus, cause myocardial remodeling with a destructive effect on the myocardium and result in a reduction in left ventricular functions[2,13].

HF is a disease with the high mortality rate despite all treatment methods. The estimated motility rate for one year is over 20%[14]. However mortality in HF studies are few in Turkey, and the mortality rate in Yılmaz and colleagues study was higher than the rate we found in our study[13]. If we want to explain this difference, firstly, it is acceptable for our study that the higher number of patients under sacubiril/valsartan treatment, which has a significant effect on mortality. Another important reason is the high rate of implanted defibrillator devices in the study patients. Many clinical scores and biomarkers have been identified for adverse outcome in patient with cardiovascular disease. The most important of these are advanced age, lower LVEF, proBNP level, etc.[15,16]. Several laboratory parameters correlated with inflammation were examined and represented to be the predictors of in-hospital or long-term mortality in HFrEF[17,18].

Recently, MHR has become a useful marker of poor prognosis in a varius cardiovascular diseases[19-21]. Higher levels of monocytes secreting proinflammatory and prooxidant cytokines and lower HDL-C, which has an antiinflammatory and antioxidant effect, after all MHR indicates inflammation and oxidation in the body[22,23]. HDL-C, which prevents the migration of macrophages into the vascular wall, neutralizes prooxidant and proinflammatory cytokines released from monocytes. In addition, it suppresses the activation, proliferation and differentiation of monocytes. Increasing monocytes converting to macrophage in the vascular wall and lower HDL-C levels contribute progressively to the atherosclerotic process[24,25]. Ganjali et al stated as a result of their study that MHR can be a parameter that shows the development and progression of atherosclerosis[26]. Bolayir et al, one of the studies on the correlation of MHR

with adverse cardiovascular events, found that higher MHR predicts short-tem mortality in patients with stroke[27]. Wu et al. stated that it predicted major adverse cardiovascular outcomes and mortality in patients with ischemic heart disease treated by percutaneous coronary intervention (PCI)[28]. Similarly, Karataş et al. showed in their study that MHR correlated with major in-hospital cardiac events after primary PCI. In another study it was shown that MHR may be a strong predictor of future cardiovascular events in acute coronary syndrome patients[29,30]. However, there has been no available data about the MHR and mortality in HF patients until now. In this study, we showed that the MHR levels of non-survivor group were significantly elevated than the survivors group. In our study, we showed that MHR as a strong parameter can predict of mortality in HFrEF patients. In addition, the AUC of MHR was the highest AUC among all inflammatory parameters NLR, PLR for predicting mortality. It is thought that the the cut-off value of 6,39 for MHR can be used to predict the mortality in HFrEF.

### Study limitations

This study contains few limited situations. Initially the design small. Second, we used a single MHR value instead of a timed trend for our analysis. Another, other common used inflammatory markers such as sedimentation were not analyzed and compared with the MHR.

## CONCLUSIONS

The findings of our study showed a significant association between higher MHR and the risk of mortality in HFrEF patients. MHR was found to be superior to NLR and PLR for mortality at 1-year follow-up. Based on the current findings, it can be considered that MHR might be used as an inexpensive and practical parameter to predict mortality in HFrEF patients in Daily practice.

**Ethics Committee Approval:** The study was confirmed by the Ordu University Clinical Research Ethics Committee (12/03/2020-06-45). Inscriptive aware consent was acquired obtained from all patients.

**Declaration of Conflicting Interests:** The authors declare that they have no conflict of interest.

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