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Prognostic Value of Monocyte-to-High-Density Lipoprotein Cholesterol Ratio in COVID-19 Patients

COVID-19 Hastalarında Monosit-Yüksek Yoğunluklu Lipoprotein Kolesterol Oranının Prognostik Değeri

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Abstract

Aim: A significant portion of individuals infected with COVID-19 experience severe illness and require intensive care. Especially in these cases, the disease may ultimately be fatal. Monocyte-to-high-density lipoprotein cholesterol ratio (MHR) has been reported to be a novel marker for major adverse outcomes in many diseases. In this study, we aimed to reveal the relationship of MHR with the prognostic markers of COVID-19 and its role in predicting the severity of disease and in-hospital mortality in COVID-19.

Material and Method: This single-center, retrospective, and cross-sectional study included 195 hospitalized patients diagnosed with COVID-19. The patients who were discharged from the hospital constituted the survivor group, while those who died constituted the non-survivor group. Clinical, laboratory and radiologic data of patients were retrospectively reviewed from medical records.

Results: The age of the patients ranged from 19 to 92 years and the mean age was 57.0±16.3 years. Ninety-eight (50.3%) of the patients were female. Forty-one of the patients died during hospitalization due to COVID-19 and related complications. MHR was significantly higher in the non-survivor group than in the survivor group. MHR was significantly correlated with age, ferritin, uric acid, urea, and creatinine levels. No difference was found between the MHR values of patients according to their disease severity at the time of admission (p=0.600). Univariate logistic regression analysis demonstrated no significant association between MHR and in-hospital mortality (p=0.132).

Conclusion: MHR is increased in COVID-19 survivors compared to non-survivors and correlates with age, ferritin, uric acid, urea, and creatinine levels. However, MHR cannot be used as a prognostic marker to predict the severity of the disease and in-hospital mortality in COVID-19 patients.

Keywords: COVID-19 virus disease, in-hospital mortality, monocyte, HDL cholesterol, prognostic factor

Öz

Amaç: COVID-19'a yakalanan bireylerin önemli bir kısmı ağır hastalık geçirmekte ve yoğun bakıma ihtiyaç duymaktadır. Özellikle bu vakalarda hastalık nihayetinde ölümcül olabilir. Monosit-yüksek yoğunluklu lipoprotein kolesterol oranının (MHR) birçok hastalıkta önemli olumsuz sonuçlar için yeni bir belirteç olduğu bildirilmiştir. Bu çalışmada, MHR'nin COVID-19'un prognostik belirteçleriyle ilişkisini ve COVID-19'da hastalığın şiddetini ve hastane içi mortaliteyi tahmin etmedeki rolünü ortaya koymayı amaçladık.

Gereç ve Yöntem: Tek merkezli, retrospektif ve kesitsel çalışmaya COVID-19 tanısı almış ve hastaneye yatırılmış 195 hasta dahil edildi. Hastaneden taburcu edilen hastalar sağ kalan grubu oluştururken, hayatını kaybedenler ise sağ kalamayan grup olarak kategorize edildi. Hastaların klinik, laboratuvar ve radyolojik verileri tıbbi kayıtlardan retrospektif olarak incelendi.

Bulgular: Hastaların yaşları 19 ile 92 arasında değişiyordu ve ortalama yaş 57,0±16,3 yıldı. Hastaların 98'i (%50,3) kadındı. Hastaların 41'i COVID-19 ve ilgili komplikasyonlar nedeniyle hastanede yatarken öldü. MHR, hayatta kalmayan grupta hayatta kalan gruba göre anlamlı şekilde daha yüksekti. MHR, yaş, ferritin, ürik asit, üre ve kreatinin seviyeleriyle anlamlı şekilde ilişkiliydi. Hastaların başvuru sırasındaki hastalık şiddetlerine göre MHR değerleri arasında fark bulunmadı (p=0.600). Tek değişkenli lojistik regresyon analizi, MHR ile hastane içi mortalite arasında anlamlı bir ilişki olmadığını gösterdi (p=0,132).

Sonuç: MHR, COVID-19'dan sağ kurtulanlarda hayatta kalmayanlara göre artmıştır ve yaş, ferritin, ürik asit, üre ve kreatinin seviyeleriyle ilişkilidir. Ancak MHR, COVID-19 hastalarında hastalığın şiddetini ve hastane içi mortaliteyi tahmin etmek için prognostik bir belirteç olarak kullanılamaz.

Anahtar Kelimeler: COVID-19 virüs hastalığı, hastane içi mortalite, monosit, HDL kolesterol, prognostik faktör

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that emerged in China, in December 2019, has caused a coronavirus disease 2019 (COVID-19) pandemic and led to significant loss of life all over the world.[1] Apart from causing pneumonia, SARS-CoV-2 can also damage various organs and systems, such as the heart, liver, and kidneys.[2] COVID-19 has been associated with ischemic complications such as myocardial infarction and stroke, especially in older individuals.[3] SARS-CoV-2 binds to cells expressing appropriate viral receptors, particularly angiotensin-converting enzyme 2 (ACE-2).[2] ACE-2 is also expressed in the heart, providing a link between SARS-CoV-2 and the cardiovascular system. SARS-Co-V-2 can down-regulate myocardial and pulmonary ACE-2 pathways, thereby mediating myocardial inflammation, lung edema, and acute respiratory failure.[4] Pro-inflammatory cytokines are up-regulated in the lungs and other organs of patients, and the systemic inflammatory response syndrome provides a possible mechanism for multi-organ failure (usually involving the heart) in severe cases. Complications may also develop from COVID-19 due to the formation of endothelial dysfunction.[5] One of the mechanisms for the development of endothelial dysfunction is oxidative stress, which develops during infection with the SARS-CoV-2.[6] The increase in levels of reactive oxygen species during a COVID-19 infection is well-established.[7] In COVID-19 patients, inflammation and oxidative stress markers guide the prognosis and treatment strategies of the disease.[8]

The clinical course of COVID-19 may range from asymptomatic cases to severe disease. Studies report the mortality rate of COVID-19 to be below 5%. However, 15-18% of patients are diagnosed with severe or critical disease and need treatment in the intensive care unit. The mortality rate is 49% in patients diagnosed with critical disease.[9] Anticipating poor outcomes early in COVID-19 patients could help decrease the demand for intensive care treatment and reduce mortality rates. Therefore, early identification of critically ill patients is important.

Monocytes are involved in the synthesis and release of proinflammatory and prooxidant cytokines and contribute to the development of atherosclerosis. These cells play a particular role in vascular endothelial damage, which is the most important stage in the pathogenesis of atherosclerosis.[10] High-density lipoprotein (HDL) cholesterol has been shown to protect the endothelium from the harmful effects of low-density lipoprotein (LDL) cholesterol and inhibit the oxidation of LDL cholesterol.[11] In this way, HDL cholesterol acts as an anti-inflammatory and antioxidant substance. The effects of HDL particles on monocytes include mediating the cholesterol influx from macrophages and protecting endothelial cells from oxidation and inflammation.[12]

Research indicates that the monocyte-to-HDL cholesterol ratio (MHR) could serve as a novel indicator of systemic inflammation and oxidative stress. Moreover, MHR is closely linked to the occurrence and prognosis of specific cardiovascular conditions.[13,14] MHR can serve as a predictive marker for atherosclerosis development and an estimate of cardiovascular events.[15-17] The role of MHR in determining systemic inflammation and oxidative stress, which are important mechanisms of systemic effects of COVID-19, has raised the possibility of its use as a prognostic marker in COVID-19. The few studies investigating the predictive value of MHR in COVID-19 have conflicting results.[18,19] In this study, we aimed to investigate the predictive value of MHR on in-hospital mortality and its relationship with prognostic markers in COVID-19.

MATERIAL AND METHOD

A total of 195 patients, hospitalized with the diagnosis of COVID-19 between March 2020 and July 2020, were included in our single-center, retrospective, and cross-sectional study. Patients who died during hospitalization due to COVID-19 and related complications constituted the non-survivor group, and those who recovered and were discharged constituted the survivor group. COVID-19 diagnosis was confirmed through the polymerase chain reaction test (Rotor-Gene Q, Qiagen, Hilden, Germany). Patients using medications that may affect complete blood count and lipid metabolism including antiviral agents, those with hematological or liver disease, and patients with malignancy were excluded from the study. Demographic characteristics and laboratory test results of the patients were obtained from medical records. Laboratory results including complete blood count, renal and liver function, lipid profiles, and inflammation markers were recorded within 2 days of admission and before initiation of any treatment for COVID-19 including antiviral therapy. Monocyte counts and HDL cholesterol levels were calculated from blood samples taken simultaneously. MHR was calculated by division of monocyte count (cells/μL) to HDL cholesterol level (mg/dL). The severity of COVID-19 disease was classified according to symptoms of patients at hospital admission, vital signs, laboratory test results, findings in chest computed tomography (CT), levels of respiratory distress, and need for respiratory support. Upper respiratory tract infection (URTI) was defined as an upper respiratory tract disease in which no radiographic evidence of COVID-19 pneumonia was detected in the review of radiology reports. Mild-to-moderate COVID-19 was defined as fever, cough, and other symptoms with pneumonia on chest CT. Severe COVID-19 was defined as pneumonia on chest CT with at least one of the following conditions met 1) Respiratory distress with respiratory rate ≥30/minute. 2)

Oxygen saturation on room air at rest ≤93%. 3) The ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen ≤300 mmHg. Acute respiratory distress syndrome (ARDS) was defined as pneumonia on chest CT with at least one of the following conditions met. 1) Respiratory failure occurs and mechanical ventilation is required. 2) Shock occurs. 3) Other organ dysfunction is present, requiring intensive care unit monitoring and treatment.

This retrospective study involving human participants was carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out with the permission of Kütahya Health Sciences University, Clinical Research Ethics Committee (Date: 17 September 2020, Decision No: 2020/14-18).

Statistical Analysis

We conducted statistical analyses using SPSS for Windows version 22.0 (SPSS, Chicago, IL, USA). We assessed the normal distribution of continuous variables using the Kolmogorov-Smirnov and Shapiro-Wilk tests. To compare continuous variables between the two groups, we used the student's t-test for normally distributed data and the Mann-Whitney U test for non-parametric data. We compare categorical parameters using the Chi-square test and Fisher's Exact test. Spearman's rank correlation was used to measure the level of association between two variables. Univariate logistic regression analysis was used to assess the predictive value of clinical and laboratory parameters for in-hospital mortality. To assess the discrimination ability of MHR to survive, the receiver-operating characteristic (ROC) curve was calculated, and the optimal cutoff value was determined by maximizing the Youden index. Time to a composite endpoint was investigated using survival analysis by a Kaplan–Meier plot and compared using the log-rank test. P <0.05 was considered statistically significant for all tests.

RESULTS

The age of the patients ranged from 19 to 92 years and the mean age was 57.0 ± 16.3 years. Ninety-eight of the patients (50.3%) were women. Forty-one of the patients (21%) died during hospitalization due to COVID-19 and related complications. The clinical presentations of COVID-19 at admission according to the clinical outcome of the patients are shown in **Figure 1**. The most common clinical presentations of COVID-19 at admission were severe COVID-19 (n=31, 75.6%) and ARDS (n=7, 17.1%) in the non-survivor group and mild-to-moderate COVID-19 (n=88, 57.1%) and URTI (n=30, 19.5%) in the survivor group. There were no admissions with URTI in the non-survivor group.

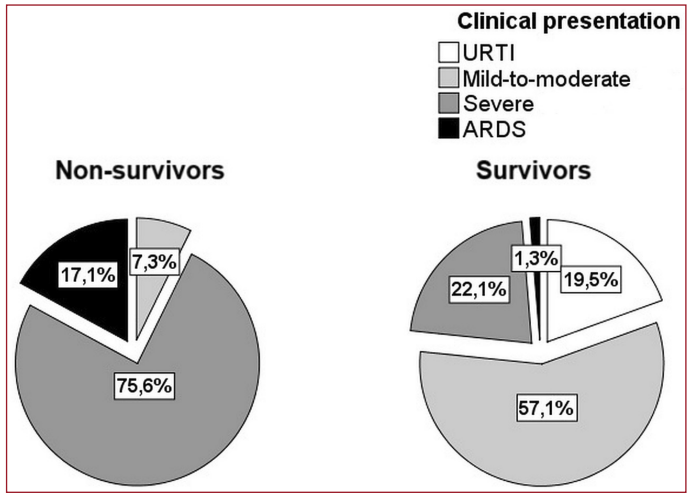

Figure 1. Clinical presentations of COVID-19 patients at admission (URTI, Upper respiratory tract infection; ARDS, Acute respiratory distress syndrome).

Comparison of clinical characteristics and laboratory parameters according to the outcome of patients are presented in **Table 1**. The age of the non-survivor group was significantly higher (p<0.001) but there was no significant difference in terms of gender distribution (p=0.205). The prevalence of cardiovascular disease and chronic kidney disease was significantly higher in the non-survivor group. The monocyte count was similar between the groups (p=0.333). HDL cholesterol level was significantly lower and MHR was significantly higher in the non-survivor group (p=0.031 and p=0.046, respectively).

HDL cholesterol level was significantly lower, and monocyte count and MHR ratio were significantly higher in men than in women (p=0.028, p=0.005, p=0.001, respectively) (**Table 2**). There was a weak negative correlation between HDL cholesterol level and age (correlation coefficient -0.23, p=0.001). Although monocyte count was not correlated with age, a weak but significant correlation was observed between MHR and age (correlation coefficient 0.13, p=0.075, correlation coefficient 0.19, p=0.008). HDL cholesterol levels were significantly lower in smokers than in nonsmokers [31 (26-37) mg/dL vs 33 (29-41) mg/dL, p=0.034].

Table 2. Comparison of monocyte counts, HDL cholesterol levels, and MHR values according to gender.

Parameters	Women (n=98)	Men (n=97)	p value
Monocyte count, cells/μL	340 (240-510)	440 (320-575)	0.005
HDL-C, mg/dL	33 (28-42)	31 (27-37)	0.028
MHR, ratio	10.00 (6.56-15.40)	12.94 (9.62-19.51)	0.001

Data are presented as median with interquartile ranges (25th-75th percentiles). Abbreviations: HDL-C, high-density lipoprotein cholesterol; MHR, monocyte-to-high-density lipoprotein cholesterol ratio.

No difference was found between the MHR values of COVID-19 patients according to their disease severity at the time of admission (**Figure 2**). There was a weak positive correlation between MHR and age, ferritin, uric acid, urea, and creatinine (**Table 3**).

Table 1. Comparison of clinical characteristics and laboratory parameters of the patients.

Parameters	Non-survivor (n=41)	Survivor (n=154)	p value
Clinical Parameters			
Women, n (%)	17 (41.5%)	81 (53%)	0.205
Age, years	73 (66-82)	54 (43-63)	<0.001
Hospital stay, days	9 (6-17)	10 (6-14)	0.826
Smoking, n (%)	12 (29%)	69 (45%)	0.116
Hypertension, n (%)	19 (46%)	49 (32%)	0.083
Diabetes mellitus, n (%)	18 (44%)	64 (42%)	0.787
COPD, n (%)	9 (22%)	26 (17%)	0.452
Cardiovascular disease, n (%)	13 (32%)	9 (6%)	<0.001
Chronic kidney disease, n (%)	13 (20%)	3 (2%)	<0.001
Laboratory Parameters			
C-reactive protein, mg/L	90.2 (47.9-228.5)	12.9 (4.7-31.1)	<0.001
Procalcitonin, ng/ml	0.32 (0.19-1.10)	0.12 (0.07-0.24)	<0.001
Ferritin, ug/L	354 (166-976)	96 (44-192)	<0.001
D-dimer, ng/mL	1718 (691-3284)	518 (300-768)	<0.001
Lactate, mmol/L	2.2 (1. 5-3.4)	1.7 (1.3-2.4)	0.033
Lactate dehydrogenase, U/L	411 (253-502)	247 (195-336)	<0.001
Fibrinogen, mg/dL	512 (377-639)	435 (352-529)	0.022
Troponin-I, ng/L	26.3 (10.5-56.4)	3.2 (2.0-6.4)	<0.001
Total cholesterol, mg/dL	129 (107-168)	146 (125-173)	0.168
HDL-C, mg/dL	29 (24-37)	33 (28-39)	0.031
LDL-C, mg/dL	74 (49-104)	88 (65-108)	0.061
Triglycerides, mg/dL	141 (114-185)	121 (90-165)	0.024
Uric acid, mg/dL	6.9 ± 2.7	4.8 ± 1.7	<0.001
Urea, mg/dL	64 (45-96)	30 (23-39)	<0.001
Creatinine, mg/dL	1.35 (1.00-2.01)	0.91 (0.80-1.05)	<0.001
Aspartate transaminase, U/L	32.0 (22.5-52.5)	25.5 (19.0-36.3)	0.010
Alanine transaminase, U/L	17.0 (11.0-27.5)	20.5 (14.8-31.0)	0.086
Leukocyte count, ×1000/µL	7.52 (5.29-11.92)	5.02 (3.95-6.63)	<0.001
Neutrophil count, ×1000/µL	5.88 (3.75-9.62)	2.94 (2.23-4.30)	<0.001
Lymphocyte count, ×1000/µL	0.93 (0.57-1.21)	1.43 (1.10-1.85)	<0.001
Neutrophil-to-lymphocyte ratio	7.12 (4.03-13.48)	2.12 (1.48-3.17)	<0.001
Platelet count, x1000/µL	155 (133-230)	198 (159-239)	0.075
Platelet-to-lymphocyte ratio	155 (121-329)	136 (106-181)	0.040
Monocyte count, cells/µL	460 (250-610)	380 (270-550)	0.333
Lymphocyte-to-monocyte-ratio	2.50 (1.24-3.55)	3.79 (2.80-5.29)	<0.001
MHR, ratio	13.16 (9.29-21.40)	11.67 (8.24-16.76)	0.046
Hemoglobin, g/dL	12.6 ± 2.7	13.1 ± 1.8	0.268
Mean corpuscular volume, fL	90 (87-95)	88 (85-91)	0.001
Red blood cell count, x106/µL	4.380 ± 0.842	4.536 ± 0.563	0.267
Mean platelet volume, fL	10.5 (9.4-11.6)	9.7 (8.9-10.5)	0.002
RDW, %	14.5 (13.6-15.7)	13.4 (12.7-14.0)	<0.001

Normally distributed data are presented as mean ± standard deviation and non-normally distributed data are presented as median with interquartile ranges (25th-75th percentiles). Abbreviations: COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol, MHR, monocyte-to-high-density lipoprotein cholesterol ratio; RDW, red blood cell distribution width.

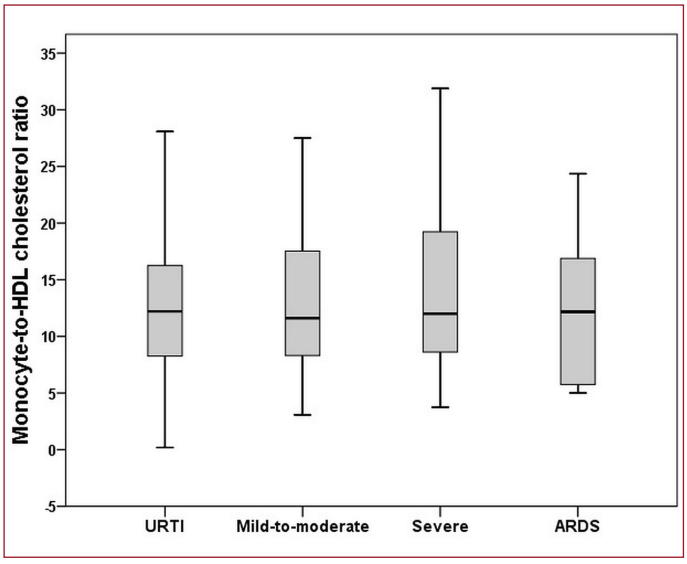

Figure 2. Comparison of monocyte-to-high-density lipoprotein cholesterol ratio according to the clinical presentation of COVID-19 patients at admission to the hospital (URTI, Upper respiratory tract infection; ARDS, Acute respiratory distress syndrome).

Table 3. The correlation of monocyte-to-high-density lipoprotein cholesterol ratio with clinical and laboratory parameters.

Parameters	Spearman's Rank Correlation Coefficient	p-value
Age	0.18	0.010
Ferritin	0.16	0.033
Uric acid	0.22	0.003
Urea	0.19	0.009
Creatinine	0.18	0.011

In the univariate regression analysis, the MHR was found not to predict survival (OR 1.013, 95% CI 0.996-1.030, p=0.132). According to the regression analysis model, age, cardiovascular disease, chronic kidney disease, C-reactive protein, D-dimer, lactate dehydrogenase, troponin-I, uric acid, urea, leukocyte count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte-ratio, mean corpuscular volume and red blood cell distribution width were the most significant factors in predicting survival (p<0.001). Univariate logistic regression analyses for the determinants of in-hospital mortality are shown in **Table 4**.

ROC analysis revealed that MHR showed a weak prediction of mortality (AUC, 0.602; 95% CI 0.500-0.703, p=0.046). At a threshold of 16.83 determined by maximizing the Youden index, MHR predicts mortality with 46% sensitivity and 76% specificity (**Figure 3**). The Kaplan-Meier survival curves and log-rank tests showed that patients with higher MHR (>16.83) had the same survival rate as patients with lower MHR (<16.83) (divided according to the best threshold) (p=0.054) (**Figure 4**).

Table 4. Univariate logistic regression analyses for the determinants of mortality.

Parameters	Odds Ratio	95% CI	p value
Clinical Parameters			
Female gender	0.638	0.318-1.282	0.207
Age	1.107	1.069-1.146	<0.001
Hospital stay	1.048	1.007-1.091	0.021
Smoking	0.508	0.216-1.193	0.120
Hypertension	1.851	0.918-3.731	0.085
Diabetes mellitus	1.101	0.549-2.205	0.787
Chronic obstructive pulmonary disease	1.385	0.591-3.244	0.454
Cardiovascular disease	7.480	2.918-19.174	<0.001
Chronic kidney disease	23.369	6.252-87.355	<0.001
Laboratory Parameters			
C-reactive protein	1.017	1.011-1.023	<0.001
Procalcitonin	20.179	2.735-148.885	0.003
Ferritin	1.003	1.002-1.004	<0.001
D-dimer	1.001	1.001-1.002	<0.001
Lactate	1.602	1.108-2.315	0.012
Lactate dehydrogenase	1.007	1.004-1.010	<0.001
Fibrinogen	1.003	1.001-1.006	0.006
Troponin-I	1.040	1.019-1.062	<0.001
Total cholesterol	0.998	0.990-1.006	0.630
High-density lipoprotein cholesterol	0.959	0.920-0.999	0.043
Low-density lipoprotein cholesterol	0.994	0.984-1.004	0.239
Triglycerides	1.003	0.999-1.007	0.116
Uric acid	1.591	1.311-1.929	<0.001
Urea	1.038	1.024-1.053	<0.001
Creatinine	1.674	1.238-2.264	0.001
Aspartate transaminase	1.018	1.003-1.033	0.016
Alanine transaminase	0.992	0.971-1.014	0.471
Leukocyte count	1.000	1.000-1.000	<0.001
Neutrophil count	1.000	1.000-1.001	<0.001
Lymphocyte count	0.998	0.998-0.999	<0.001
Neutrophil-to-lymphocyte ratio	1.390	1.231-1.570	<0.001
Platelet count	0.996	0.990-1.001	0.135
Platelet-to-lymphocyte ratio	1.005	1.001-1.008	0.007
Monocyte count	1.000	1.000-1.001	0.160
Lymphocyte-to-monocyte-ratio	0.567	0.439-0.733	<0.001
MHR	1.013	0.996-1.030	0.132
Hemoglobin	0.887	0.750-1.049	0.161
Mean corpuscular volume	1.141	1.060-1.228	<0.001
Red blood cell count	0.670	0.382-1.174	0.161
Mean platelet volume	1.620	1.203-2.181	0.001
Red blood cell distribution width	1.591	1.277-1.982	<0.001

Abbreviations: CI, confidence interval; MHR, monocyte-to-high-density lipoprotein cholesterol ratio.

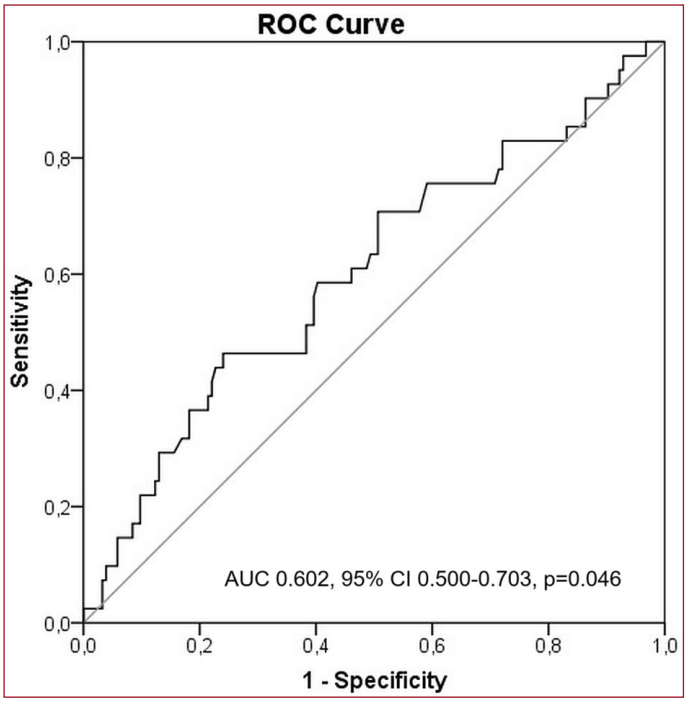

Figure 3. Receiver-operating characteristic (ROC) curve analysis of monocyte-to-high-density lipoprotein cholesterol ratio for predicting mortality. Receiver-operating characteristic (ROC) curve for the predictive ability of monocyte-to-high-density lipoprotein cholesterol ratio for in-hospital death of patients with COVID-19.

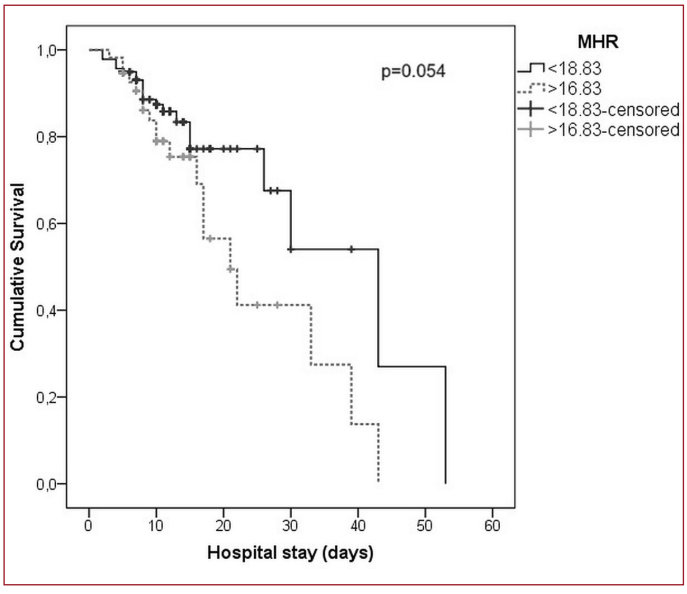

Figure 4. Kaplan-Meier survival curves according to MHR optimal cutoff value. A log-rank test was used to evaluate the difference between groups (MHR, monocyte-to-high-density lipoprotein cholesterol ratio).

DISCUSSION

The present study has revealed the relationship between MHR and prognostic markers, as well as the value of MHR in predicting in-hospital mortality in patients hospitalized with a diagnosis of COVID-19. While MHR shows a weak correlation with some of the prognostic biomarkers in COVID-19, it appears to be not useful in predicting in-hospital mortality in COVID-19 patients. The results of previous studies on the prognostic value of MHR in COVID-19 are contradictory. Gunay-Polatkan et al. showed that MHR does not predict in-hospital mortality in COVID-19.[18] In another study, Argun et al. showed that MHR predicts the severity of COVID-19 disease and patient outcomes.[19] However, as we found in our study, MHR was found to be high in the non-survival group in these studies.[18,19]

In SARS-COV-2 infection, an immune response develops through the immune system and various cytokines, mainly interferons, are released to control the infection.[20] In some cases, uncontrolled immune response and excessive release of cytokines trigger a cytokine storm, leading to the development of multiple organ damage, especially in the respiratory system, and consequently, death.[20] Therefore, evaluation of certain clinical features and laboratory findings has come to the fore so that clinicians may be able to predict the clinical severity and prognosis of COVID-19. Several lab parameters have been evaluated to determine the severity of COVID-19 in studies conducted to date.[21]

MHR has been investigated in several conditions such as cardiovascular disease, polycystic ovary syndrome, chronic obstructive pulmonary disease, psoriasis, pulmonary thromboembolism, and aggressive periodontitis.[22-25] MHR represents a new marker indicating inflammation and oxidative stress, and it is closely linked to the occurrence and prognosis of specific cardiovascular conditions.[14,26,27] Efe et al. demonstrated that the MHR independently predicted mortality in patients with acute pulmonary embolism.[26] Oylumlu et al. demonstrated that increased MHR was a significant and independent predictor of in-hospital and long-term mortality in patients with acute coronary syndrome.[27]

Monocytes are immune system cells that play a role in the inflammatory response, phagocytosis, antigen presentation, and various immune functions.[28] In COVID-19, SARS-CoV-2 infects the pulmonary epithelium and capillary endothelial cells, stimulates the inflammatory response, and triggers a monocyte and neutrophil influx.[20] Tumor necrosis factor-alpha and interleukin 1 and 6, released from monocytes and other macrophages, enhance the inflammatory response. There are conflicting results concerning monocyte count in COVID-19. While some studies have reported an increased monocyte count, others showed no significant changes and a few reported a decrease in the number of monocytes.[29] In our study, although the monocyte count increased in the non-survivor group compared to the survivor group, it did not reach statistical significance. In studies conducted on patients with COVID-19, monocyte count was not found to be valuable in distinguishing patients who test positive and those who test negative for COVID-19.[30] Furthermore, it has been shown that monocyte count does not provide valuable data for predicting the prognosis of COVID-19 at the time of admission or hospitalization.[29] This controversy shows that

alteration in monocytes is still open to debate and this issue remains to be extensively discovered.

It is widely recognized that viral infections lead to alterations in plasma lipid levels.[31] Infections typically lead to decreased levels of total cholesterol, LDL cholesterol, and HDL cholesterol, along with either elevated or normal triglyceride levels. Generally, the changes in blood lipid levels correlate with the severity of the underlying infection.[32] That is to say, the more severe the infection, the more severe the changes in lipid and lipoprotein levels.[31-33] Numerous studies have been conducted to investigate cholesterol levels in COVID-19 patients. A decrease has been observed in total cholesterol, triglyceride, LDL cholesterol, and HDL cholesterol levels in patients with COVID-19 compared to healthy individuals.[34,35] HDL cholesterol concentration was found to be negatively correlated with C-reactive protein and positively correlated with lymphocytes.[35] Decreased serum apolipoprotein A-1 and HDL cholesterol levels are predictors for severe disease and in-hospital mortality in COVID-19 patients.[33-35] In our study, total cholesterol and HDL-cholesterol levels were lower and triglyceride levels were higher in patients with a fatal outcome compared to survivors, and a relationship between HDL-cholesterol and in-hospital mortality has been demonstrated. The decrease in the immunomodulatory, antithrombotic, and antioxidant effects of HDL cholesterol due to low HDL cholesterol levels may contribute to the poor prognosis observed in COVID-19.

Age, current smoking, body mass index, alcohol intake, triglyceride, and LDL cholesterol level have significant impacts on HDL cholesterol level.[36] Women have higher levels of HDL cholesterol than men.[37] In our study, we found that HDL cholesterol levels were lower, and monocyte counts and MHR levels were higher in men than in women. In COVID-19, factors associated with in-hospital mortality are increasing age, male sex, and major comorbidities.[38] Older age, smoking, and overweight or obesity are associated with lower HDL-C levels.[36] We found a weak negative correlation between HDL cholesterol and age in our study. This negative correlation between HDL cholesterol and age is reflected as a positive correlation between MHR and age. Age was also found to be one of the predictors of mortality in our study but a similar result was not found in gender. HDL cholesterol levels were significantly lower in smokers than in nonsmokers. However, smoking was not one of the predictors of mortality in our study. There are contradictory reports about the effect of smoking on COVID-19 infections. A large meta-analysis of over 17,278,392 COVID-19-infected adults showed a lower incidence of infection in smokers.[39] However, several studies showed adverse effects of smoking on COVID-19 outcomes.[40] We speculate that the complex effect of smoking on COVID-19 disease may account for our result.

Older age, presence of chronic kidney disease, and increased ferritin levels are poor prognostic markers in COVID-19 patients.[41] In a retrospective study by Zheng et al., uric acid levels were found to be high in COVID-19 non-survivors, and serum uric acid level was positively correlated with inflammatory markers.[42] The researchers proposed that uric acid released from damaged cells might act as a danger signal, intensifying the hyperinflammatory response in severe COVID-19 cases, and that lowering uric acid levels through therapy could be beneficial for these patients.[42] In our study, patients with a fatal outcome were older than survivors, and similar to previous study results, the rate of chronic kidney disease was higher, and higher ferritin and uric acid levels were observed in non-survivors compared to survivors. We found weak but significant and positive correlations between MHR and age, ferritin, uric acid, urea, and creatinine.

Our study has several limitations. The main limitation is the small study population, which may have limited our ability to detect the predictive value of MHR for disease severity and in-hospital mortality in COVID-19. Furthermore, due to the small study population, we were unable to divide the patients into subgroups and further investigate potential confounding factors influencing our results such as age, cardiovascular disease, and chronic kidney disease. Another limitation is the study's retrospective design. As a result, we were unable to obtain parameters that could affect study results, such as the heights and weights of patients.

CONCLUSION

Although MHR is higher in in-patient COVID-19 cases with a fatal outcome compared to survivors, it does not predict the severity of disease or in-hospital mortality. However, MHR shows a positive correlation with age, ferritin, uric acid, urea, and creatinine levels, which have been previously reported to be prognostic indicators in COVID-19 patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kütahya Health Sciences University, Clinical Research Ethics Committee (Date: 17 September 2020, Decision No: 2020/14-18).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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