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Monocyte-to-Hdl-Cholesterol Ratio as a Prognostic Marker in Covid-19

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Abstract **Background:** There is an urgent need for mortality predictors for COVID-19 so that clinicians can diagnose severe cases and triage them as soon as possible. Many studies have suggested using hematologic markers to predict mortality and severity of COVID-19 disease. This study investigates the use of monocyte-to-high density lipoprotein cholesterol ratio (MHR) as a predictive marker for COVID-19 severity and mortality. **Methods:** This retrospective cross-sectional study was performed on 81 PCR-confirmed COVID-19 patients between 25 March 2020 to 26 June 2020. Patients were classified into two presentation categories: the non-severe group (n=37) and the severe group (n=44). Patients in the severe group were also divided into two subgroups: severe survivors (n=14) and severe non-survivors (n=30). In the receiver operating characteristic (ROC) analysis, optimal cut-off values of the monocyte count, high-density lipoprotein cholesterol (HDL-C), and MHR were calculated for the differentiation of severe and non-severe COVID-19 patients, as well as survivors and non-survivors. **Results:** A total of 81 patients, 29 (35.8%) males and 52 (64.2) females, with a median age of 71 (IQR 63-81) years. Both HDL-C and MHR showed a reasonable ability to distinguish severe disease from non-severe disease, while MHR had a higher area under curve (AUC) than HDL-C (0.799, 95%CI 0.704-0.894, $p<0.001$ vs 0.734, 95% Cl 0.626-0.843, $p<0.001$). Only MHR could distinguish survivors from non-survivors with an ROC AUC of 0.735 (95%Cl 0.619-0.850). The optimal cut-off values of MHR for predicting severe disease were 0.0061 (sensitivity: 66% and specificity: 66%) and 0.0066 (sensitivity: 70% and specificity: 62%) for predicting mortality. The optimal cut-off value of MHR for predicting severe disease was 0.0061 (sensitivity: 66% and specificity: 66%), and it was 0.0066 for predicting mortality among patients with severe disease (sensitivity: 70% and specificity: 62%). **Conclusion:** Our results showed that MHR was observed to be able to distinguish severe COVID-19 patients from non-severe patients as well as survivors from non-survivors.

Key Words Monocyte-to-HDL-cholesterol ratio, COVID-19, severity, mortality

1. Introduction

COVID-19, a member of the Coronaviridae family, originated in Wuhan, China. Transmission of the virus is possible through close contact with an infected person or object and via the release of airborne droplets [1]. The most important symptoms of the disease are fever, cough, shortness of breath, and gastrointestinal disorders [2]–[4]. In severe cases, the disease may cause acute respiratory distress syndrome, which can further lead to intensive care unit (ICU) hospitalization and even death [1]–[4].

The older the patient, the greater the risk of death and complications [3], [4]. Sometimes, a person is asymptomatic but can still be a carrier [5], [6]. Serological tests and measurement of acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can help to diagnose the disease. However, a definitive diagnosis is made with polymerase chain reaction (PCR) [4]. Computed tomography (CT) shows lung involvement in these patients, and the most common radiological finding is ground-glass opacification/opacity in the lower lobe and the subpleural region [6]–[8].

There is an urgent need for mortality predictors for COVID-19 so that clinicians can diagnose severe cases and triage them as soon as possible. Many biochemical markers are used to predict disease exacerbation and mortality. Some

of these markers are leukopenia or leukocytosis [6], lymphopenia, elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) [8], acute phase reactants such as CRP and ferritin [9], anemia, thrombocytopenia, increased blood urea nitrogen (BUN) [10], prolonged prothrombin time (PT), increased d-dimer and prothrombin [11], [12].

Many studies have suggested using hematological markers such as monocyte, lymphocyte, or neutrophil counts to predict mortality and severity of COVID-19 disease [13]–[15]. These studies have reported an increase in monocytes and lymphocytes and a decrease in neutrophil counts in severe COVID-19 patients [11], [12]. Other studies have shown that the number of these white blood cells (WBC) alone can not accurately predict the mortality and severity of COVID-19 disease [16], [17]. Previous studies have shown that the monocyte-to-HDL-cholesterol Ratio (MHR) can predict systemic inflammation [18]–[22]. However, we could not find any previous study that investigated MHR for predicting COVID-19 severity and mortality. Therefore, this study investigated using MHR as a predictive marker for COVID-19 severity and mortality.

2. Materials and Methods

Out of 300 patients diagnosed with COVID-19 admitted to Ayancık State Hospital from 25 March 2020 to 26 June 2020, 81 patients were managed as inpatients and retrospectively included in the study. Detection of COVID-19 was performed according to the World Health Organization (WHO) guidelines and using quantitative polymer chain reaction (qPCR). COVID-19 was considered to be severe according to the following criteria: 1) Oxygen saturation level (SpO2) below 93%; 2) respiratory pressure above 30 breaths per minute; 3) lung involvement of more than 50% on lung imaging. Patients with a previous diagnosis of cancer, endocrine disorder, liver or kidney failure, autoimmune disease, chronic infectious disease, and pediatric patients were excluded from the study. Pregnant and breastfeeding patients and those receiving long-term anti-inflammatory drugs were also excluded from the study. Clinical and laboratory data and medical records of all the study participants were collected from a digital version of their health history at Ayancık State Hospital. All patient records were evaluated until discharge or death. 81 COVID-19 patients were classified into two presentation categories: non-severe group (n=37) and severe group (n=44). Patients in the severe group were also divided into two subgroups: severe survivors (n=14) and severe non-survivors (n=30).

A. Ethical Approval

This study was conducted in accordance with the ethical rules and with the approval of Medicana International Samsun Hospital's clinical research ethics committee (decision no. 7159, date: 09.12.2021).

B. Statistical Analyses

The data analysis was performed with the SPSS version 26 software. The normality of continuous variables was tested using the Shapiro-Wilk test. As variables had non-normal distribution, we used nonparametric methods. Summaries for categorical (qualitative) variables are presented as numbers and percentages (%), while for numerical (quantitative) variables, median and interquartile range values (25%-75% quartiles) were used. The chi-square or Fisher exact test was used to compare the different groups. Mann-Whitney U-test was used to compare two independent groups regarding a quantitative variable. The optimal cut-off values (95% confidence levels) of the monocyte count, HDL-C, and MHR for the differentiation of patients with severe and non-severe disease, as well as survivors and non-survivors patients, were calculated by applying the receiver operating characteristic (ROC) analysis. A $p<0.05$ was considered statistically significant.

3. Results

Of the 81 COVID-19 patients, 29 (35.8%) were males and 52 (64.2) were females, with a median age of 71 (IQR 63-81) years, 58 (71.6%) were $\leq$65 years, and two (2.5%) were smokers. Hypertension was the most common comorbidity (n=43; 53%). The patients mostly presented with complaints of fever, cough and malaise (n=26; 32% for all of them). Table 1 shows the demographic and clinical variables of the non-severe and severe groups.

Compared with the patients in the non-severe group, those in the severe group were older, had significiantly higher monocyte count and MHR, while had significantly lower HDL-C levels (for monocyte count p=0.004, otherwise $p<0.001$) (Table 1 and Figure 1).

As shown in Table 2 and Figure 1, monocyte counts, HDL-C and MHR levels were similar between severe survivors and severe non-survivors (p=0.647, p=0.579 and p=0.480, respectively). However, non-survivors showed significantly higher monocyte counts and MHR levels, whereas showed significantly lower HDL-C levels compared with the survivors (p=0.037, $p<0.001$ and p=0.006, respectively) as shown in Figure 1.

Optimal cut-off values of the monocyte count, HDL-C and MHR to predict disease severity and mortality are shown in Table 3. Both HDL-C and MHR showed a reasonable ability to distinguish severe disease from non-severe disease, while MHR had a higher ROC AUC than HDL-C (0.799, 95%CI 0.704-0.894, $p<0.001$ vs 0.734, 95% Cl 0.626-0.843, $p<0.001$) as shown in Figure 2. To distinguish survivors from non-survivors only MHR showed a reasonable ability with a ROC AUC of 0.735 (95%Cl 0.619-0.850). The optimal cut-off value of MHR for the prediction of severe disease was 0.0061 (sensitivity: 66% and specificity: 66%) and it was 0.0066 for predicting mortality among patients with severe disease (sensitivity: 70% and specificity: 62%). HDL-C: high-density lipoprotein cholesterol, MHR: Monocyte-to-high-density lipoprotein cholesterol ratio.

Variable	Non-severegroup (n=37)	Severe group (n=44)	P value
Age, years	65.0 (56-76)	77.5 (70.5-83.5)	<0.001
Age $\geq$ 65 years	21 (56.8)	37 (84.1)	0.007
Gender, male	8 (21.6)	21 (47.7)	0.015
Smoker	0 (0)	2 (4.5)	0.498
Comorbidity			
HT	18 (48.6)	25 (56.8)	0.463
DM	7 (18.9)	13 (29.5)	0.269
*Hearth diseases	2 (5.4)	15 (34.1)	0.002
**Respiratory disease	2 (5.4)	10 (22.7)	0.029
Other	11 (29.7)	4 (9.1)	0.017
Complaint on admission			
Fever	11 (29.7)	15 (34.1)	0.675
Cough	12 (32.4)	14 (31.8)	0.953
Shortness of breath	8 (21.6)	16 (36.4)	0.148
Myalgia	13 (35.1)	13 (29.5)	0.591
Malaise	14 (37.8)	12 (27.3)	0.310
Other(headache, diarrhea, etc.)	14 (37.8)	19 (43.2)	0.626
Hospital-lenght-of-stay, days	7 (6-9)	6 (4-10)	0.307
Laboratory parameters			
Monocyte count, 103/μL	0.21 (0.20-0.30)	0.30 (0.20-0.40)	0.004
HDL-C, mg/dL	44.7 (40.3-50.1)	36.7 (30.4-43.3)	<0.001
MHR	0.005 (0.003-0.006)	0.007 (0.006-0.011)	<0.001

Table 1: Comparison of demographic and clinical characteristics of the non-severe and severe groups
*Coronary artery disease or heart failure, **COPD/Asthma/Bronchitis. Quantitative data were expressed as median (25%-75% quartiles) and qualitative data were expressed as number and percentage (%). Bold font indicates statististical significant (<0.05 level) P values. HT:hypertension, DM:diabetes mellitus, COPD: chronic obstructive pulmonary disease, HDL-C: high-density lipoprotein cholesterol, MHR: Monocyte-to-high-density lipoprotein cholesterol ratio.

Variable	Severe survivors (n=14)	Severe non-survivors (n=30)	P value
Age, years	70.5 (60-74)	81.5 (76-85)	<0.001
Age$\geq$years	8 (57.1)	29 (96.7)	0.002
Gender, male	4 (28.6)	17 (56.7)	0.082
Smoker	1 (7.1)	1 (3.3)	0.540
Comorbidity			
HT	6 (42.9)	19 (63.3)	0.202
DM	4 (28.6)	9 (30.0)	0.923
*Hearth diseases	5 (35.7)	10 (33.3)	0.877
**Respiratory disease	3 (21.4)	7 (23.3)	0.888
Other	1 (7.1)	3 (10.0)	0.759
Complaint on admission			
Fever	5 (35.7)	10 (33.3)	0.877
Cough	8 (57.1)	6 (20.0)	0.034
Shortness of breath	5 (35.7)	11 (36.7)	0.951
Myalgia	6 (42.9)	7 (23.3)	0.288
Malaise	6 (42.9)	6 (20.0)	0.152
Other (headache, diarrhea, etc.)	6 (42.9)	13 (43.3)	0.976
Hospital-lenght-of-stay, days	9.5 (8-11)	5 (4-8)	0.001
Laboratory parameters			
Monocyte count, 103/μL	0.30 (0.21-0.40)	0.30 (0.20-0.60)	0.647
HDL-C, mg/dL	36.3 (32.6-43.2)	36.7 (28.5-43.8)	0.579
MHR	0.006 (0.006-0.009)	0.007 (0.006-0.013)	0.480

Table 2: Comparison of demographic and clinical characteristics of the severe survivors and severe non-survivors groups
*Coronary artery disease or heart failure, **COPD/Asthma/Bronchitis. Quantitative data were expressed as median (25%-75% quartiles) and qualitative data were expressed as number and percentage (%). Bold font indicates statististical significant (<0.05 level) P values. HT:hypertension, DM:diabetes mellitus, COPD: chronic obstructive pulmonary disease, HDL-C: high-density lipoprotein cholesterol, MHR: Monocyte-to-high-density lipoprotein cholesterol ratio.

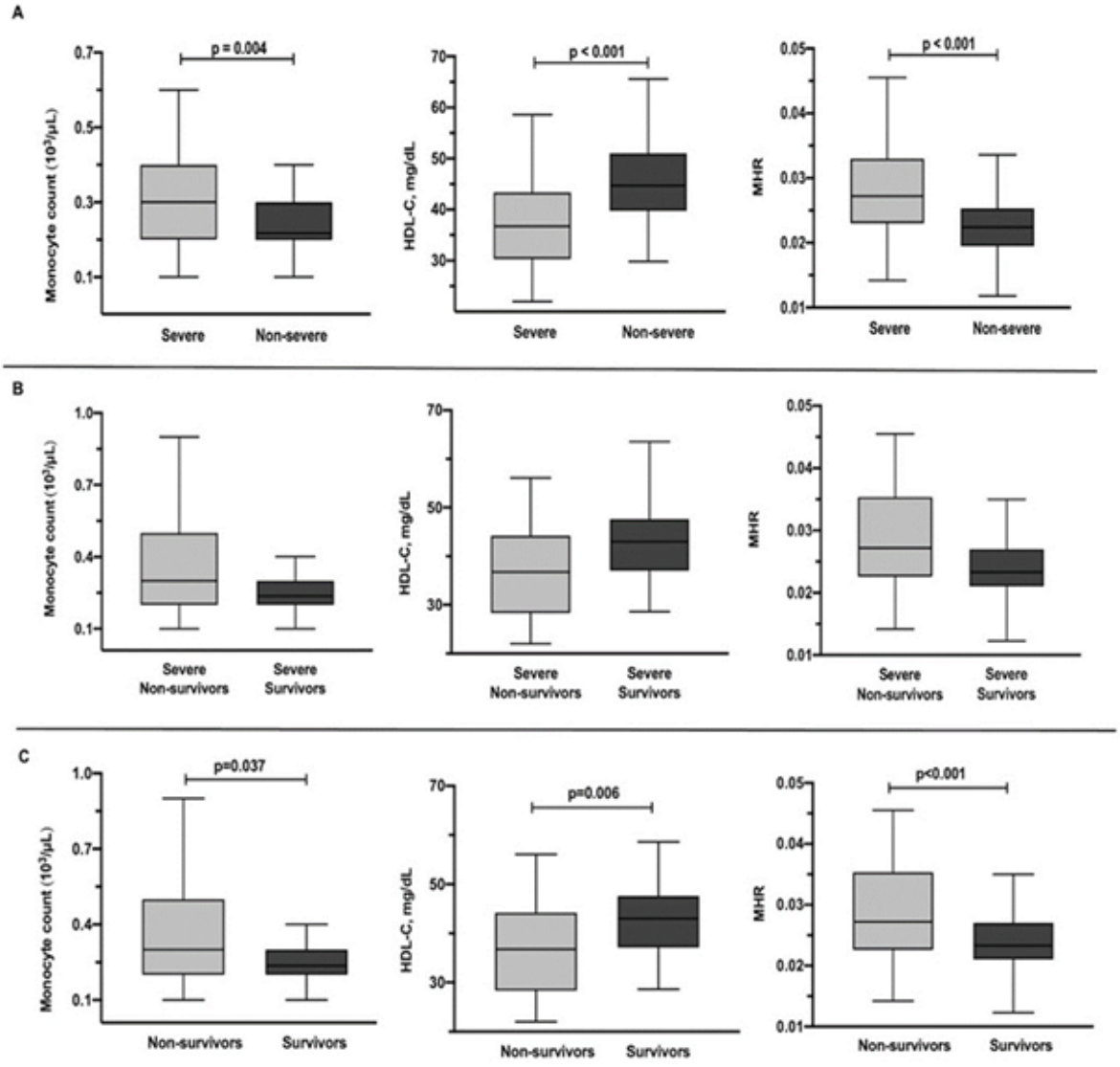

Figure 1: Comparison of monocyte count, high-density lipoprotein cholesterol (HDL-C) and Monocyte-to-HDL-C ratio (MHR) between severe and nonsevere groups (A), severe non-survivors and severe survivors groups (B), survivors and non-survivors (C)

Prediction of the severe disease					
Parameters	AUC (95% Cl)	Cut-off values	Sensitivity	Specificity	P value
Monocyte count, 103/μL	0.681 (0.566-0.796)	0.229	0.63	0.51	0.005
HDL-C, mg/dL	0.734 (0.626-0.843)	42.6	0.72	0.64	<0.001
MHR	0.799 (0.704-0.894)	0.0061	0.66	0.66	<0.001
Prediction of non-survivors					
Method	AUC (95%Cl)	Cut-off levels	Sensitivity	Specificity	P value
Monocyte count, 103/μL	0.637 (0.500-0.774)	0.229	0.66	0.49	0.040
HDL-C, mg/dL	0.684 (0.558-0.809)	41.2	0.66	0.62	0.006
MHR	0.735 (0.619-0.850)	0.0066	0.70	0.62	<0.001

Table 3: Comparison of area under the curves (AUCs) to predict the disease severity and mortality

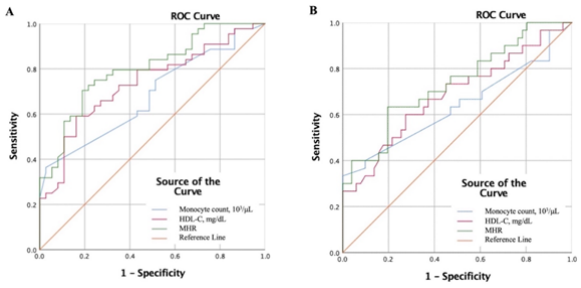

Figure 2: ROC curves for monocyte count, high-density lipoprotein cholesterol (HDL-C) and Monocyte-to-HDL-C ratio (MHR) for predicting severe disease (A) and mortality (B)

4. Discussion

Finding accurate and reliable markers to diagnose the severity and mortality of COVID-19 disease is essential. Many studies have proposed hematological markers such as monocyte, lymphocyte, or neutrophil count to predict the severity and mortality of COVID-19 disease [2]–[4], [10], [21]. This is the first study investigating MHR as a biomarker to predict disease severity and mortality in patients with COVID-19. The study found that the MHR was significantly higher in patients with severe disease and non-survivors than in patients with non-severe disease and survivors. Our results also show that HDL alone is higher in patients with non-severe disease than those with severe disease. Also, the monocytes alone were higher in patients with severe disease and in non-survivors.

The inflammatory effects of COVID-19 disease have been studied in various studies. Dizziness, weakening of taste, nerve pain up to seizures, and strokes are among the neurological symptoms of the SARS-CoV-2 virus, associated with hypoxia and inflammation of the brain. Inflammation of the brain can be indirectly caused by a cytokine storm or directly caused by viral encephalitis [23]. COVID-19 also causes cardiovascular complications by causing thrombosis in the arteries and veins. The thrombosis mechanism in this disease is inflammation, platelet activation, vascular dysfunction, and vascular occlusion [24]. The cardiovascular manifestations of COVID-19 infection, which occur in approximately 8 to 12% of COVID-19 patients, are of considerable concern [24]–[26]. Acute heart damage, defined by a significant rise in cardiac troponin levels in blood tests, has been reported as the most common heart abnormality in COVID-19. Other published reports indicate myocarditis and cardiac arrest [25]. The most common mechanisms responsible for myocardial injury appear to be due to the direct involvement of myocardial cells (cardiomyocytes) with SARS coronavirus [23], and immune-mediated inflammation such as cytokine storm [27].

In patients with the critical form of COVID-19, it may lead to liver failure. Liver damage in patients with COVID-19 may be directly due to viral infection of the liver cells, immune-mediated inflammation such as cytokine storm, and hypoxia due to pneumonia [28], [29]. The virus can also cause a severe inflammatory condition, impair the pancreas' ability to release insulin and reduce the liver's ability to detect hormones [27], [30]. The COVID-19 disease has been reported to be progressively associated with increased hypercoagulation, leading to neurovascular complications [31]. Other mechanisms include viral neurotropism, hypoxia, endothelial dysfunction, and inflammation so that in many patients with COVID-19, elevated inflammatory markers such as d-dimer and interleukin-6 are reported [24], [28], [29], [31], [32].

MHR is mentioned as one of the new biomarkers of oxidative stress and inflammation in the body. In their study, Wu et al. [33] showed that MHR could be used to predict systemic inflammation in patients with infectious endocarditis [33]. Cakir et al. [18] used MHR to predict inflammation in diabetic patients and showed that elevated MHR levels could help predict diabetic retinopathy (DR). Demirbas et al. [34] showed in their study that MHR could be used as a biomarker to diagnose inflammation and oxidative stress in patients with vitiligo, and this marker can be a sign of disease severity. Canpolat et al. [35] conducted a study on patients with Slow Coronary Flow (SCF) and showed that high MHR values have a significant and independent relationship with oxidative stress and inflammation in these patients. They showed that the MHR could be used as a biomarker to detect systemic inflammation. Katipoglu et al. [36] organized a study in patients with keratoconus and showed that MHR could be used as an indicator of systemic inflammation and oxidative stress. Our findings are consistent with these studies.

Previous studies have examined the association between HDL levels and blood monocytes in acute diseases such as ischemic heart disease and renal failure. Their results showed lower HDL levels in people with coronary artery disease [37]–[40]. Consistently, our results showed lower HDL levels in COVID-19 patients with severe disease and mortality. However, previous studies have not considered the association between MHR and COVID-19 disease. The only study similar to ours [41] studied the lipid profile of COVID-19 patients and found that total cholesterol (TC), HDL cholesterol, and LDL cholesterol levels were sharply reduced in COVID-19 patients. MHR, on the other hand, increased significantly in COVID-19 patients compared to the healthy group. These findings are consistent with the findings of the present study. However, this study does not investigate the predictive role of MHR in COVID-19 disease severity and mortality.

Previous studies on MHR have focused more on the predictive role of this biomarker in renal and cardiovascular diseases [12], [14], [25], [36]. Since inflammation is one of the main complications of COVID-19 infection, and according to the results of previous studies on MHR and its predictive role on systemic inflammation [18], [20], [34], [36], the findings of the present study are consistent with previous studies. It can be concluded that MHR can be used as a marker to predict inflammation, thus predicting disease severity and

mortality in patients with COVID-19.

One of the limitations of this study was its small sample size, and it is suggested that these studies be performed on larger sample sizes to confirm the findings of this study and obtain more accurate results. Because our data came only from one clinical center, the demographic characteristics may be biased, so future studies must aggregate the results of several clinical centers. The results of this study can be used as a baseline for more detailed future studies of the role of MHR in diagnosing disease severity and mortality in COVID-19 patients.

5. Conclusion

Examining the predictive role of MHR in disease severity and mortality among COVID-19 patients showed that the amount of MHR had increased significantly in patients with severe disease and death. Further studies are needed to confirm our results so that the MHR can be used as a marker to predict disease severity and mortality in COVID-19.

Conflict of interest

The authors declare no conflict of interest. All authors read and approved the final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

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