RESEARCH ARTICLE

Belgin Coskun[1]
Muge Ayhan[1]
Elif Mukime Saricaoglu[2]
Rahmet Guner[3]
Esragül Akinci[4]
Turan Buzgan[3]
Bircan Kayaaslan[3]
Adalet Altunsoy[4]
Ayse Yasemin Tezer Tekce[4]
Imran Hasanoglu[3]
Ayse Kaya Kalem[3]
Fatma Eser[3]
Yesim Aybar Bilir[1]
Burcu Ozdemir[1]

[1]Ankara City Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye
[2]Ankara University Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye
[3]Yıldırım Beyazıt University, Department of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye
[4]University of Health Sciences Department of Infectious Diseases and Clinical Microbiology, Türkiye

Corresponding Author:
Belgin Coskun
mail: belgintekin@yahoo.com

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konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

The Evaluation of Relationship between Monocyte/High-Density Lipoprotein Ratio (MHR) and COVID-19

ABSTRACT

Objective: Early diagnosis is important for severe diseases in COVID-19. Monocyte/high dansity lipoprotein ratio (MHR) is a new prognostic marker indicating inflammation. We aimed to investigate the relationship between MHR and diseases severity in COVID-19.

Methods: Patients with laboratory confirmed COVID-19, were retrospectively analyzed. Clinical symptoms, signs and laboratory data on the first day of hospitalization were obtained from medical records of hospital. The clinical data of 301 patients were included in study. Cases were diagnosed on the basis of interim guidance of World Health Organization (WHO). Patients were classified into two groups as non-severe COVID-19 and severe COVID-19. MHR were calculated with laboratory data on the first day of hospitalization. The relationship between MHR level and COVID-19 severity was evaluated. Statistical analysis of the data was performed by using SPSS 25 (SPSS Inc., Chicago, IL, USA) package program. Statistical significance level was accepted as $p<0.05$.

Results: One hundred ninety-six patients (65.1 %) had non-severe COVID-19,105 patients (34.9 %) had severe COVID-19. In our study, it was found that the mean age was higher in severe patients and comorbid diseases were more common. Although monocyte count values were not statistically significantly different, MHR was significantly higher in severe COVID-19 than non-severe COVID-19.

Conclusions: Monocytes are very important to cytokine storm in COVID-19. Dyslipidemia can occur in viral infection because of inflammation. MHR can be used as an inflammatory marker in COVID-19.

Keywords: COVID-19, High-Density lipoprotein, Inflammation, Monocyte, Severe Diseases.

Monosit/ Yüksek Dansiteli Lipoprotein (MHR) ve COVİD-19 Arasındaki İlişkinin Değerlendirilmesi

ÖZET

Amaç: COVID-19'da şiddetli hastalığı erken tanımak önemlidir. Monosit / yüksek dansiteli lipoprotein oranı (MHR), inflamasyon seyrini belirlemede kullanılan yeni bir belirteçtir. Bu çalışmada MHR ile COVID-19 seyri arasındaki ilişkiyi incelemek amaçlanmıştır.

Gereç ve Yöntem: Laboratuvar ile konfirme edilmiş COVID-19 hastaları retrospektif olarak analiz edildi. Hastanemize başvuran hastanın ilk günki klinik semptomları, bulguları ve laboratuvar sonuçları hastane bilgi işlem sisteminden taranarak kayıt altına alındı. Çalışmamıza toplam 301 hasta dahil edildi. Hastalar Dünya Sağlık Örgütü (DSÖ) klavuzu dikkate alınarak sınıflandırıldı. MHR hastaların hastaneye kabul edildiği ilk gün bakılan laboratuvar verileri kullanılarak hesaplandı. MHR ile COVID-19 şiddeti arasındaki ilişki değerlendirildi. Hasta verileri SPSS 25 (SPSS Inc., Chicago, IL, USA) kullanılarak analiz edildi. İstatistiksel olarak $P<0.05$ olan farklılıklar anlamlı kabul edildi.

Bulgular: Hastaların 196 (%65,1)'sı hafif ve orta semptomlu COVID-19 iken, 105 (%34,9)'i şiddetli COVID-19 idi. Çalışmamızda şiddetli COVID-19 hastalarında yaş ortalamasının daha yüksek olduğu ve komorbid hastalıkların daha sık görüldüğü bulunmuştur. Çalışmamızda grublar arasında monosit sayısında anlamlı fark izlenmez iken, şiddetli COVID-19 hasta grubunda MHR anlamlı olarak daha yüksek saptanmıştır.

Sonuç: COVID-19'da gerçekleşen sitokin fırtınasında monositler önemli rol üstlenir. Gelişen inflamasyon nedeni ile hastalarda dislipidemi izlenir. MHR COVID-19'da inflamatuar biyobelirteç olarak kullanılabilir.

Anahtar Kelimeler: COVID-19, Yüksek dansiteli lipoprotein, İnflamasyon, Monosit, Şiddetli Hastalık

INTRODUCTION

In December 2019, cases of pneumonia with unknown etiology have been reported in Wuhan, China (1). On February 11 2020, the Word Health Organization (WHO) named the pneumonia with unknown etiology as coronavirus disease 2019 (COVID-19). On March 11 2020, first case of COVID-19 has been reported in Turkey. Clinical features and risk factors are highly variable. For patients with a non-severe diseases of COVID-19, clinical symptoms are fever, cough, fatigue and pneumonia. For patients with severe diseases of COVID-19, acute respiratory distress syndrome (ARDS) and organ failure may develop (2-4). Some patients with pneumonia may progress rapidly and may need mechanical ventilation. Mortality rate for these patients is quite high even reaching a level of 60 % (5). Early diagnosis and early treatment are very important especially for severe disease.

Immune response of severe patients may cause macrophage-activation syndrome (MAS). Low expression of HLA-DR on CD14 monocytes causes immune dysregulation. Immune dysregulation is triggered by monocyte hyperactivation, releases of interleukin-6 (IL-6), and profound lymphopenia. This immune response is different from in either ARDS caused by 2009 H1N1 influenza or bacterial sepsis (6).

Lipids are very important for viral infections such as human immunodeficiency virus (7). High-density lipoprotein cholesterol (HDL-C) has got an immunregulatory effect. It has anti-inflamatory and anti-oxidant effects (8).

Inflammation is very important for the progression of COVID-19. So inflammation biomarkers can be used to determine prognosis of COVID-19 patients (9). The ratio of monocyte count to the HDL-C level (MHR) was used to determine oxidative stress and inflammation (8, 10). MHR is one of the indicators of systematic inflammatory response. Therefore, we aimed to investigate the relationship between MHR and COVID-19 diseases.

MATERIAL AND METHODS

Patients: Patients with laboratory confirmed COVID-19 who were admitted to the hospital, between March 11 2020 and April 30 2020, were retrospectively screened. Patients with COVID-19 were confirmed by a positive result from real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay with nasal and pharyngeal swab specimens for SARS-CoV-2 RNA (Bio-speedy COVID-19 RT-qPCR test kit). The clinical data of 380 patients have been obtained. Patients who were under the age of 18, pregnant, using steroid therapy, who had malignancy, hyperlipidemia and hematological diseases were excluded. A total of 301 patients were included in the final analysis. Cases were diagnosed on the basis of interim guidance of WHO (11). Patients have got positive results of RT-PCR for SARS-CoV-2, were classified into two groups as non-severe disease and severe diseases. A respiratory rate ≥30 and an oxygen saturation (resting state) ≤93 on room air were accepted for severe diseases.

The endpoint of follow up was the admission to the intensive care unit, discharge or cure. This study was approved by Locals Ethics committee (day: 21.05.2020 , number: E1-20-624)

Clinical Characteristics and Laboratory Data: Clinical symptoms, signs and laboratory data were obtained from medical records of hospital. Blood samples were taken from patients on the first day of admission. Laboratory assessments consisted of complete blood count, blood lipid profiles, blood chemistry, coagulation tests (D-dimer, prothrombin time (PT), activated partial prothrombin time (aPTT), international normalized ratio(INR), thrombin time(TT)), C-reaktive protein (CRP) levels, procalcitonin (PCT). MHR was calculated as the ratio of the monocyte count to the level of HDL-C.

Statistical Analysis: Statistical analysis of the data was performed by using SPSS 25 (SPSS Inc., Chicago, IL, USA) package program. The normal distribution of the data was tested with the Shapiro-Wilk test. Descriptive statistics of categorical variables were reported as numbers and percentages (%). Descriptive statistics of continuous variables were presented with mean±standard deviation (SD) and median (min-max) according to data normality distribution. The relationships between severity of COVID-19 and sociodemographic characteristics, comorbidity status, were performed using Chi-square test or Fisher's exact test in accordance with the number of data in crosstab cells. Statistical significance level was accepted as $p<0.05$.

RESULTS

Three hundred and one patients were included in the study. Comparison of demographic, comorbidity status of patients and patient outcome between study groups were presented in table 1. One hundred and twenty one (65.2 %) of patients were women and 105 (34.8 %) were men. There was no statistically difference for gender distribution between study groups ($p = 0.033$, Table 1). The mean age was 42.48 ± 15.24 in non-severe diseases. The mean age was 64.35 ± 13.06 in severe diseases. Ages of patients were statistically different between groups ($p < 0.001$). One hundred ninety six patients (65.1 %) had non-severe disease, 105 patients (34.9 %) had severe diseases.

The mean length of stay at intensive care unit (ICU) in the severe group was 7 (0-41) days. The length of hospital stay of patients with severe diseases was 15 (4-52) days. The length of hospital

stay and length of stay at ICU was significantly different between groups (p <0.001). Comorbidities (Coronary artery disease, hypertension (HT), diabetes mellitus (DM), chronic lung disease, chronic kidney disease) were statistically different between study groups (Table 1).

Table 1. Comparison of demographic, comorbidity status of patients and patient outcome between research groups

		Groups		*P* values
		Non-Severe (n=196)	**Severe (n=105)**	
Gender	Male n (%)	100(51%)	70(63.6%)	0,033
Age Mean (+/- SD)		42.48 +/- 15.24	64.35 +/- 13.06	<0.001
Coronary Artery Disease		8 (4.1%)	18 (17.1%)	<0.001
HT		27 (13.8%)	41 (39.0%)	<0.001
DM		16 (8.2%)	33 (31.4%)	<0.001
Chronic Lung Disease		11 (5.6%)	21 (20.0%)	<0.001
Chronic Kidney Disease		3 (1.5%)	9 (8.6%)	0.005
Intensive Care Unit Status		0 (0%)	32 (30,5%)	<0.001
Mechanical Ventilation		0 (0%)	8 (7.6%)	<0.001
Mortality		0 (0%)	16 (15.2%)	<0.001

In the severe groups, 30.5% of patients were admitted to ICU and 7.6% needed mechanical ventilation.

The comparison of laboratory blood values between research groups is given in Table 2. Although monocyte count values were not statistically significantly different, MHR was significantly different between the groups. MHR level was higher in the severe groups than in the non-severe groups. White blood cell (WBC), neutrophil, lymphocyte, neutropil-to-lymphocyte ratio (NLR), HDL-C, hemoglobin, creatinine, glomerular filtration rate (GFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, CRP, procalcitonin (PCT), troponin, total cholesterol (TC), triglyceride (TG), PT, INR, ferritin, D-dimer and fibrinojen values were significantly different between the study groups (Table 2).

Table 2. Comparison of clinical laboratory values between research groups

	Groups		*P* values
	Non-Severe (n=196)	**Severe (n=105)**	
WBC	4755 (1450-16180)	7320 (3030-19730)	<0.001
Neutrophil	2855 (200-12810)	6110 (2290-18550)	<0.001
Lymphocyte	1270 (186-7360)	640 (260-2190)	<0.001
NLR	2.095 (0-15)	9.600 (1.9-42.2)	<0.001
Monocytes	360 (100-1670)	360 (60-1530)	0.53
HDL	37 (20-98)	28 (11-66)	<0.001
MHR	9.7 (2.4-31.1)	11.3 (1.6-34.8)	<0.015
Hemoglobin	13.8 (9.5-17)	13.1 (7.9-16.8)	<0.001
PLT	215500 (75000-451000)	226000 (31000-591000)	0.044
Creatinine	0.8(0-2)	0.92 (0-5)	<0.001
GFR	103.5(26-148)	78 (9-123)	<0.001
AST	23 (4-166)	41 (15-500)	<0.001
ALT	27 (7-248)	34 (9-634)	<0.001
Total bilirubin	0.5 (0.1-4)	0.5 (0.2-1.9)	0.051
Albumin	45 (36-54)	38 (21-47)	<0.001
CK	100 (12-1186)	123 (15-5395)	0.053
LDH	210.5 (40-551)	372 (45-1000)	<0.001
CRP (g/L)	0.005 (0.001-0.168)	66 (0.001-258)	<0.001
PCT	0.03 (0.01-0.79)	0.11 (0.01-9.7)	<0.001
Troponin	2.5 (0.01-5033)	8 (1-25000)	<0.001
Total Cholesterol	150 (45-318)	140 (61-351)	0.041
LDL	91 (4-270)	83 (26-240)	0.081
TG	99 (10-591)	124 (16-313)	<0.001
PT	12 (10-48)	12.7 (10-44.3)	<0.001
aPTT	24.6 (19.7-95.6)	25 (16.7-49.5)	0.866
INR	1 (0.89-4.40)	1.08 (0.8-4.03)	<0.001
Ferritin	100 (1-1448)	431 (17-2131)	<0.001
D-Dimer	0.32 (0.1-35.2)	0.9 (0.1-35.2)	<0.001
Fibrinogen	2.92 (1.32-7.01)	5.9 (2.2-10.1)	<0.001
Length Of Hospital Stay	10 (2-31)	15 (4-52)	<0.001
Length Of Intensive Stay	0	7 (0-41)	<0.001

DISCUSSION

Most people with COVID-19 develop mild illness. Rate of severe disease development is 14%. And 5% of severe diseases patients require admission to an intensive care unit (ICU) (11). The risk factors associated with disease severity were reported as DM, increased age and organ failure (12-14). Early diagnosis and early treatment is very important for decrease the mortality. It is as important to evaluate laboratory tests as to know the risk groups to know severe patients early. In various studies, some laboratory parameters such as WBC,neutrophil count, lymphocytes count, NLR, creatinine, AST, ALT, CRP, PCT, D-dimer, ferritin were found to be significantly different for severe disease,as in our study (16-18). Could MHR be a new inflammatory marker for COVID-19?

MHR is a new inflammatory marker for several diseases such as cardiovascular diseases.

In this study, count of monocytes was not significantly different between severe and non severe diseases. Some studies showed that, in the severe ICU group, severe non-ICU group and common group were compared. There is not statistically significant difference between the study groups in the number of monocytes (17). Monocytes are cells of the innate immune system are participating in inflammatory response, phagocytosis and antigen presentation. Three types of monocytes are classified according to their CD14 and CD16 expression. These are classical (CD14+, CD16-), intermediate (CD14+, CD16+) and non-classical (CD14dim CD16+) (19). Intermediate monocytes significantly increase in patients with COVID-19. The rate which is 5% of total monocyte in the healthy population increases to over 45% in patients with COVID-19. These monocytes are producing interleukin-6 (IL-6) (20). So that, monocytes are very important to cytokine storm in COVID-19. We couldn't assess monocyte subtypes and IL-6 levels in our study population. This was a limitation of our study.

Dyslipidemia is one of the outcome of inflammation in viral infections (21). SARS-CoV-2 is an enveloped virus surrounded by a lipid bilayer, with a genome of 30.000 nucleotides, encoding four structural proteins. These are nucleocapsid (N) protein, spike (S) protein, nucleocapsid (N) protein, envelope (E) protein and membrane (M) protein (22). Lipids main components of SARS-CoV-2, are involved in fusion of viral membrane to host cell, viral replication, endocytosis and exocytosis. Cholesterol and lipid raft play a key role especially in the early stage of cell infection. Low levels of TC, HDL-C and LDL-C are associated with disease severity and mortality (23). In our study TC, HDL-C, and LDL-C levels decreased, TG levels increases in correlation with disease severity. HDL-C has got protective effects against lipid oxidation. So it is called an anti-inflammatory lipoprotein. HDL-C negatively regulate expression of inflammatory mediators and T-cells activation in dendritic cells and macrophage (15). HDL-C has a protective role in the inflammation effect on the lungs. Described HDL-C level is useful in predicting the severity of COVID-19 disease (24). As the severity of the disease increases, the decrease in the lipid level is exacerbated (25).

In this study, the MHR increased in correlation with disease severity. High MHR may be correlated with a poor prognosis for COVID-19 patients. The further studies with larger patient groups will be beneficial for understanding the relationship between MHR and COVID-19.

Study Limitations: The first limitation of our study is our study sample groups is small. We couldn't assess monocyte subtypes and IL-6 levels in our study population. This was second limitation of our study. The third limitation is the not performing a multivariant analysis. We need advanced studies to determine ıf MHR is an independent risk factor. And we can determine a cut off value of MHR for severe COVID-19 disease.

CONCLUSION

COVID-19 courses are highly variable. So biomarkers are very important to recognize serious disease early. MHR is an important marker for inflammation. MHR can be one of these markers to determine COVID-19 severity. High MHR is correled with the severity of disease ın our study. MHR needs a lot of study with more patients to explore the importance of COVID-19. If researcher can be determine a cut off value of MHR, it can be used as an inflammatory marker in COVID-19 as in cardiovascular diseases.

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