

## Coronavirus Pandemic

# Does Macrophage Migration Inhibitory Factor predict the prognosis of COVID-19 disease?

Hamad Dheir<sup>1</sup>, Selcuk Yaylaci<sup>2</sup>, Savas Sipahi<sup>1</sup>, Ahmed Cihad Genc<sup>2</sup>, Deniz Cekic<sup>2</sup>, Fatma Betul Tuncer<sup>3</sup>, Erdem Cokluk<sup>3</sup>, Havva Kocayigit<sup>4</sup>, Ahmed Bilal Genc<sup>2</sup>, Salih Salihi<sup>5</sup>, Ceyhun Varim<sup>2</sup>, Oguz Karabay<sup>6</sup>

<sup>1</sup> Division of Nephrology, Sakarya University Faculty of Medicine, Sakarya, Turkey

<sup>2</sup> Department of Internal Medicine, Sakarya University Faculty of Medicine, Sakarya, Turkey

<sup>3</sup> Department of Biochemistry, Sakarya University Faculty of Medicine, Sakarya, Turkey

<sup>4</sup> Department of Anesthesiology and Reanimation, Sakarya University Faculty of Medicine, Sakarya, Turkey

<sup>5</sup> Department of Cardiovascular Surgery, Sakarya University Faculty of Medicine, Sakarya, Turkey

<sup>6</sup> Department of Infectious Diseases and Microbiology, Sakarya University Faculty of Medicine, Sakarya, Turkey

### Abstract

**Introduction:** The aim of this study is to investigate whether macrophage migration inhibitory factor (MIF) predicts the prognosis of COVID-19 disease.

**Methodology:** This descriptive and cross-sectional study was conducted on 87 confirmed COVID-19 patients. The patients were separated into two groups according to the admission in the ICU or in the ward. MIF was determined batchwise in plasma obtained as soon as the patients were admitted. Both groups were compared with respect to demographic characteristics, biochemical parameters and prediction of requirement to ICU admission.

**Results:** Forty seven patients in ICU, and 40 patients in ward were included. With respect to MIF levels and biochemical biomarkers, there was a statistically significant difference between the ICU and ward patients ( $p < 0.024$ ). In terms of ICU requirement, the cut-off value of MIF was detected as 4.705 (AUC:0.633, 95%CI:0.561-0.79,  $p = 0.037$ ), D-dimer was 789 (AUC:0.779, 95%CI: 0.681-0.877,  $p = 0.000$ ), troponin was 8.15 (AUC: 0.820, 95%CI:0.729-0.911,  $p = 0.000$ ), ferritin was 375 (AUC: 0.774, 95%CI:0.671-0.876,  $p = 0.000$ ), and lactate dehydrogenase (LDH) was 359.5 (AUC:0.843, 95%CI: 0.753-0.933,  $p = 0.000$ ). According to the logistic regression analysis; when MIF level  $> 4.705$ , the patient's requirement to ICU risk was increased to 8.33 (95%CI: 1.73-44.26,  $p = 0.009$ ) fold. Similarly, elevation of troponin, ferritin and, LDH was shown to predict disease prognosis ( $p < 0.05$ ).

**Conclusions:** Our study showed that MIF may play a role in inflammatory responses to COVID-19 through induction of pulmonary inflammatory cytokines, suggesting that pharmacotherapeutic approaches targeting MIF may hold promise for the treatment of COVID-19 pneumonia.

**Key words:** COVID-19; SARS-Cov-2; Macrophage migration inhibitory factor; Inflammation.

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### Introduction

The new type of Coronavirus (COVID-19) continues to have important health and economic consequences all over the world. The vast majority of patients with the COVID-19 disease have had a good prognosis, but there were still some critical patients and even deaths [1,2]. In a study including 20,133 patients with COVID-19 reported that 17.1% were admitted to high-dependency or intensive care units (ICU) [1]. A meta-analysis of 1994 hospitalized individuals with COVID-19 showed that the discharge rate of COVID-19 patients was 52%, and the fatality rate was 5% [2]. The clinical manifestations of COVID-19 disease have typically been fever, cough, respiratory distress,

myalgia, lymphopenia, increased acute phase reactants and coagulation indices before progressing to primary viral pneumonia complicated by acute respiratory distress syndrome (ARDS) [3]. An emerging evidence of vaccine efficacy has been demonstrated against COVID-19 [4–6]. While the effect of corticosteroids on COVID-19 associated mortality has been proven, the effect of drugs such as Tozilisumab and remdesivir on mortality is controversial [7-10]. A rapid and well-coordinated innate immune response is the first line of defense against virus damage. However, dysregulation of immune responses may facilitate progression to severe and lethal disease [11]. In general, high levels of expression of cytokines have been detected in patients

with ARDS. Inflammasome activation in macrophages and epithelial cells releases proinflammatory cytokines, which contribute to the pathogenic inflammation responsible for the severity of symptoms of COVID-19, and have positive correlation with mortality rates [12–15]. Many proinflammatory cytokines such as IL-1, IL2R, IL4, IL6, IL18, TNF $\alpha$  and macrophage inflammatory protein-1A are very high in COVID-19 patients, especially in intensive care patients, and have been shown to be associated with disease severity [3,16-18].

It is known that macrophage migration inhibitory factor (MIF), a proinflammatory cytokine and an important regulator of innate immunity, plays a critical role in the host control of the inflammatory response of the lung. This factor was originally described as a T lymphocyte protein that inhibited the random migration of macrophages. It has been suggested that the level of MIF expression can be regarded as a sensitive and effective biochemical indicator in the early diagnosis of ARDS [19]. Also, MIF has been identified in some viral infections like influenza, Human Immunodeficiency Virus (HIV), H5N1 virus and dengue virus infections [20–23].

To our knowledge, there is no information about the relation between MIF levels and COVID-19 disease. In view of the regulatory importance of MIF in the inflammatory and immune response, we aimed to explore whether MIF value is associated with COVID-19 disease and whether it could predict the requirement for intensive care.

## Methodology

### *Patients*

This descriptive and cross-sectional study was conducted on 87 COVID-19 patients who received inpatient treatment for the first time between 20 June 2020 and 30 July 2020, prior to receiving any antiviral and antibacterial treatments that they might receive later on. The study was conducted in accordance with the Declaration of Helsinki, and after approval of the ethics committee of our university faculty of medicine (No:71522473/050.01.04/459). Patients with symptoms of pneumonia and confirmed COVID-19 on reverse transcription-polymerase chain reaction (RT-PCR) nasopharyngeal (NP) swabs were consecutively enrolled. The exclusion criteria were; 1) patients who did not have pneumonia, 2) NP RT-PCR negative, 3) routine biochemical parameters not obtainable, 4) a history of malignancy, and 5) the presence of confirmed bacterial infection at admission. Considering the inclusion and exclusion criteria, we identified 87

patients as the study population from a total of 324 patients hospitalized in our University hospital within the specified period of the study. Within the specified study period the patients were divided into two groups (ICU, Group-1) and ward (Group-2). All ICU patients were intubated and had a diagnosis of ARDS. The International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO 4C mortality score was used to determine disease severity in all patients [24]. Both groups were compared according to demographic characteristics and measurement of the biochemical parameters of the patients. Sera were obtained from all patients at the first 1-2 hours of admission and stored at - 80 degrees.

### *Macrophage migration inhibitory factor measurement*

After the coagulation process of the venous blood samples taken from the patients with tubes without anticoagulants, they were centrifuged and separated into serums. Samples were portioned and stored at -80 degrees. Human Macrophage Migration Inhibitory Factor (HMMIF) levels were studied with the Bioassay Technology Laboratory (Shanghai / Chine BT Laboratory Co., Ltd.) branded human ELISA kit and sandwich model double antibody enzyme-linked immunosorbent method. In the precision study conducted by the manufacturer, the within-run and between-run CV% of the kits was given as <10 %, and the measurement range was specified as 0.1-40 ng/ml.

### *Statistical analysis*

Descriptive analyses were performed to provide information on general characteristics of the study population. Visual (probability plots, histograms) and analytical methods (Kolmogorov-Simironov/Shapiro-Wilk's test) were used to determine whether or not they are normally distributed. Descriptive analyses were presented using medians and interquartile range (IR) for the non-normally distributed variables. The Mann-Whitney U test was used for nonparametric tests to compare these parameters. Pearson Chi-square or Fisher's exact tests used to compare the categorical variables between two groups. The categorical variables were presented as the frequency (%). For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the logistic regression analysis to determine independent predictors of patient outcomes. The goodness of fit was determined by using the Nagelkerke R<sup>2</sup> and Hosmer-Lemeshow goodness of-fit test. We based on the values of biomarkers, which has the highest and closest sensitivity and specificity. A *p*-value < 0.05 was

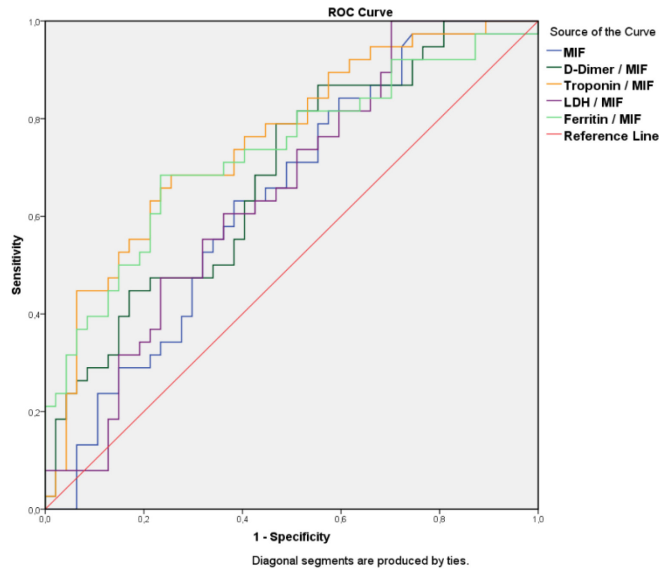
considered significant. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 22.0. Armonk, NY: IBM Corp.)

**Results**

Forty seven patients were in the ICU group (Group 1), and forty patients in the ward group (Group-2). Mean ages were 71 ± 12 and 61 ± 17 years, respectively (p =0.003). There were 22 males (55.2%) in group 1, and 22 (46.8%) in group 2 (p > 0.05). The two groups were similar with respect to the comorbid status. Comorbidities in group 1 and 2 were hypertension in 51.1% vs 50% of the patients, diabetes in 20% vs 34%, heart disease in 25% vs 19.6%, chronic obstructive pulmonary disease (COPD) in 12.5% vs 6.4%, respectively (p > 0.05) (Table 1). The ISARIC WHO 4C mortality scores of group 1 were significantly higher than those of group 2 (p < 0.05). Twenty five (62.5%) of the ICU patients were died due to ARDS. The timeframe for mortal patients was 14 days, and 9 days for survival patients. To address the role of MIF in COVID-19, serum MIF values associated with mortality predictors such as white blood cells (WBC), lymphocyte, neutrophil/lymphocyte ratio, C-reactive protein (CRP), D-Dimer, troponin, ferritin and lactate dehydrogenase (LDH) were evaluated during the first

admission. The serum MIF levels which obtained from both groups are shown in Figure 1. With respect to all these predictors, there was a statistically significant

**Figure 1.** ROC curves of MIF and combined blood biomarkers on differentiating intensive care unit patients from ward patients with COVID-19.



ROC: Receiver operating characteristic curve, MIF: macrophage inhibition factor, LDH: lactate dehydrogenase.

**Table 1.** Comparison of clinical features and blood biomarkers between patients with COVID-19.

	All patients N = 87	ICU patients N = 40	Ward patients N = 47	P
Age, years (mean ± SD)	65 ± 15	71 ± 12	61 ± 17	0.,003*
Gender, Woman, N (%)	43 (49.4)	18 (45.0)	25 (53.2)	0.446***
Time from symptoms onset to admission, means, (days)	4 (3-7)	7 (5-8)	3 (2-4)	0.000**
Hospitalization, mean (days)	10 (6-16)	13 (8-24)	9 (5-13)	0.025**
Diabetes mellitus, N (%)	24 (27.6)	8 (20.0)	16 (34.0)	0.144***
Hypertension, n (%)	44 (50.6)	20 (50.0)	24 (51.1)	0.921***
Coronary artery disease, n (%)	19 (22.1)	10 (25.0)	9 (19.6)	0.560***
White blood cells, median (IR), K/uL	6.4 (5-9.1)	7.1 (5.3-11.3)	5.8 (5-8.01)	0.150**
Neutrophil, median (IR), K/uL	4.57 (2.9-6.5)	4.,9 (3.76-8.5)	3,6 (2.6-5.7)	0.,004**
Neutrophil/lymphocyte ratio	3.78 (4.79)	5.97 (7.06)	2.27 (2.1)	0.000**
D-dimer, median (IR), ugFEU/L	754 (397-1460)	1130 (696.7-1865)	501 (243-868)	0.000**
Troponin, median (IR), ng/L	8.15 (3.1-20)	15.4 (8.3-43.3)	5 (2.2-9.3)	0.000**
Ferritin, median (IR), ug/L	297 (137.6-854)	698 (320.5-1592)	227 (69-336)	0.000**
LDH, median (IR), mmol/L	359.5 (233-447.2)	446 (368-586)	266 (190-370)	0.000**
CRP, median (IR) mg/dL	66 (19-165)	131.5 (52.7-180.5)	22.4 (7.8-87.2)	0.001**
MIF, median (IR), ng/mL	4.72 (3.2-6.8)	5,3 (4.1-7.4)	4.3 (2.78-6.3)	0.024**
<b>ISARIC 4C mortality Score</b>				
Low (0-3), N, (%)	4 (5)	0 (0)	4 (9)	
Intermediate (4-8) N (%)	19 (22)	0 (0)	19 (40)#	
High (9-14) N (%)	36 (41)	13 (33)	23 (49)	0.000***
Very high (≥ 15) N (%)	28 (32)	27 (68)	1 (2)#	
Mortality, N (%)	25 (28.7)	25 (62.5)	0 (0)	0.000**

ICU: Intensive care unit; SD: Standard Deviation; IR: Interquartile Range (25-75 percentiles); \*: One Sample T Test; \*\*: Mann-Whitney U Test; \*\*\*: Pearson Chi-Square Test; \*\*\*\*: Fisher's Exact Test; MIF: Macrophage migration inhibitory factor. LDH: Lactate dehydrogenase; CRP: C-reactive protein; #: p < 0.008.

difference between the ICU and ward patient groups ( $p < 0.05$ ) (Table 1). To predict the ICU requirement of patients with COVID-19, the performance of MIF, D-dimer, Troponin, LDH, Ferritin were assessed using receiver operating characteristic (ROC) curve analysis and by calculating the area under the curve (AUC) of the ROC curves. When a significant cut-off value was observed, the sensitivity, specificity values were presented. In terms of patients needed ICU; the cut-off value of MIF was detected as 4.705 (AUC: 0.633 95%CI: 0.561-0.79, sensitivity: 65, specificity: 62,  $p = 0.037$ ), D-dimer was 789 (AUC: 0.779 95%CI: 0.681-0.877, sensitivity: 71, specificity: 70,  $p = 0.000$ ), troponin was 8,15 (AUC: 0.820, 95%CI : 0.729-0.911, sensitivity: 79, specificity: 72,  $p = 0,000$ , Ferritin was 375 (AUC: 0.774 95%CI: 0.671-0.876, sensitivity: 74, specificity: 81,  $p = 0.000$ , and LDH was 359,5 (AUC: 0.843, 95%CI: 0.753-0.933, sensitivity: 82 specificity: 74,  $p = 0.000$ ) (Table 2). Furthermore, a multivariate logistic regression analysis, using all considered variables, confirmed the independent prognostic value of MIF with an OR= 8.8 (95%CI: 1.73-44.26,  $p = 0.009$ ), troponin (OR = 10.6 (95%CI: 2.26-49.2,  $p= 0.003$ ), ferritin (OR = 8.33 (95%CI: 1.27-31.44,  $p = 0.024$ ) and, LDH (OR = 8.55,95%CI: 1.84-39.62,  $p = 0.006$ ) were similarly found to have significant independent predictant roles, but D-Dimer has not (OR = 3.1, 95%CI: 0.70-13,3,  $p = 0.138$ ) (Table 2).

**Discussion**

In this descriptive comparative cross-sectional study, we evaluated MIF with/without some elevated blood biomarkers such as D-Dimer, troponin, ferritin and LDH as they are potential effective predictors of severity of COVID-19 disease [24–27]. As it is known that COVID-19 disease mainly affects the respiratory and immune system, alveolar epithelial and endothelial damage, thrombotic complications and coagulopathies frequently occur in COVID-19. These pathological conditions can be demonstrated by increased proinflammatory cytokines, LDH, D-Dimer, ferritin, troponin, and minimal abnormalities in prothrombin

time and platelet count [24–28]. We revealed that elevated values of MIF, D-Dimer, troponin, ferritin and LDH were distinctive predictors of ICU admission requirements for COVID-19 patients from ward patients. According to the logistic regression analysis; when MIF level  $> 4.705$ , the patient’s requirement to ICU risk was increased to 8.33 (95%CI: 1.73-44.26,  $p = 0.009$ ) fold. The positive predictive value PPV) was 59%, indicating that 59% of those classified as positive in our model are true COVID-19 patients.

The critical role of macrophage migration inhibitory factor (MIF) in mediating inflammatory lung injury in ARDS has been described. It has demonstrated enhanced MIF protein expression in the endothelium of alveolar capillary and playing a crucial pathological role leading to alveolar inflammation and infiltrating macrophages in non-COVID-19 ARDS patients [29]. The present study has shown enhanced MIF levels in ICU COVID-19 patients with ARDS than ward patients ( $p = 0.024$ ). Also, elevated MIF levels increase the risk of patient’s requirement to ICU by 8,8 fold in COVID-19 patients. In postmortem study, MIF expression was markedly increased in alveolar capillary endothelium of ARDS patients [30]. These outcomes emphasize that the pathophysiologic process of alveolar damage in ARDS is due to enhanced microvascular permeability following the up-regulation of cytokine networks triggered by the released MIF. In one study showed that anti-MIF or dexamethasone treatment can reduce the synthesis of MIF protein by 30% and 85%, respectively [30]. Recently, dexamethasone treatment had been shown to be effective in COVID-19 patients who were receiving either invasive mechanical ventilation or oxygen [7]. In line with these findings, it can be speculated that Anti-MIF and glucocorticoid therapy may represent a novel therapeutic approach for reducing alveolar inflammation in ARDS due to COVID-19 pneumonia.

Nonetheless, this study is limited by relatively small sample size and high mortality rate which observed in ICU patients. In fact, with the treatment experiences gained so far, the mortality in patients with severe

**Table 2.** Diagnostic performance of MIF and blood biomarkers on differentiating patients with ICU patients from wards patients.

Variables	Diagnostoc receiver operating characteristic (ROC) curve analysis						Multivariate model		
	Cut-off Point	AUC	95% CI	Sensitivity %	Specificity %	P value	Cutt-off point	Odds Ratio (95% CI)	P value
MIF	4.705	0.633	(0,515-0,752)	65	62	0.037	MIF $> 4.705$	8.8 (1.73-44.26)	<b>0.009</b>
D-Dimer	789	0.779	(0.681-0.,877)	71	70	0.,000	D-Dimer $> 789$	3.1 (0.70-13.3)	0.138
Troponin	8.15	0.820	(0.729-0.,911)	79	72	0.000	Troponin $> 8.15$	10.6 (2.26-49.2)	<b>0.003</b>
Ferritin	375	0.774	(0.671-0.,876)	74	81	0.000	Ferritin $> 375$	6.33 (1.27-31.44)	<b>0.024</b>
LDH	359.5	0.,843	(0.753-0,933)	82	74	0.000	LDH $> 359.5$	8.55 (1.84-39.62)	<b>0.006</b>

AUC: Area Under the Curve; CI 95%: Confidence Interval; MIF: macrophage migration inhibitory factor; LDH: lactate dehydrogenase.



covid-19 dramatically decreases. Therefore, the actual mortality rate in severe covid-19 patients still needs more research on large studies.

In conclusion the use of MIF as a proinflammatory biomarker has been investigated promising support for diseases with an inflammatory aspect such as systemic viral infections, sepsis, ARDS and autoimmune diseases. Our study showed that MIF may play a role in inflammatory responses to COVID-19 disease through induction of pulmonary inflammatory cytokines and chemokines, suggesting that pharmacotherapeutic approaches targeting MIF may hold promise for the treatment of COVID-19 pneumonia.

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### Author contributions

HD is the guarantor of the integrity and accuracy of the data and the data analysis. OK and HD designed the study. ACG performed the statistical analysis. HD, SY, SS, DC, FBT, EC, HC, ABG, SS and CV contributed substantially to the collection of the data, data analysis, interpretation, and to the writing of the manuscript. All authors read and approved the final manuscript.

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### Corresponding author

Hamad DHEIR, MD  
 Division of Nephrology, Sakarya University Faculty of Medicine  
 Adnan Menderes Cad. Sağlık Street. No. 1, 54100, Sakarya,  
 Turkey.  
 Tel: +905325293390  
 E-mail: hamaddheir@sakarya.edu.tr

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