



Существует ли связь между средним уровнем MIDKINE и прогнозом заболевания COVID-19?

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РЕЗЮМЕ

Цель. Исследование направлено на измерение уровня Midkine (МК)* в плазме крови у пациентов с COVID-19 и оценку его клинической значимости.

Материалы и методы. В исследование включены 88 пациентов, наблюдавшихся в клинике с диагнозом COVID-19. Изучены демографические характеристики пациентов, клинические и лабораторные данные, а также исследована взаимосвязь между уровнями МК, прогнозом и другими параметрами.

Результаты. Из 88 пациентов, включенных в исследование, 43 (48,9%) были женщинами и 45 (51,1%) – мужчинами. 24 (27%) пациента умерли. Средний возраст невыживших составил $70 \pm 12,3$ года, а выживших – $61,9 \pm 18,2$ года. Предикторы смертности, такие как D-димер, ферритин, тропонин, ЛДГ, СРБ и прокальцитонин, были значительно выше у умерших, чем у выживших ($p < 0,05$). Медиана уровня МК (IR) составила $152,5 \pm 125$ пг/мл у всех пациентов, 143 ± 149 пг/мл у выживших и $165,5 \pm 76$ пг/мл у умерших ($p = 0,546$). Разница между этими 2 группами была незначима. Было обнаружено, что площадь под кривой ROC составляет 0,542 (95% ДИ 0,423–0,661, $p = 0,546$).

Вывод. МК не является биомаркером, который может заменить или усилить известные предикторы смертности у пациентов с COVID-19.

Ключевые слова: средние уровни, COVID-19, смертность, прогнозирование, биомаркер

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Is there an association between MIDKINE levels and the prognosis of COVID-19 disease?

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ABSTRACT

The objective was aimed to measure plasma midkine (MK)* levels in patients with COVID-19 and assess its clinical significance.

Materials and Methods. 88 patients observed in our hospital with a diagnosis of COVID-19 were included in the study. The patients' demographic characteristics, clinical, and laboratory data were studied, and the relationship between MK levels, prognosis, and other parameters was investigated.

Results. Of the 88 patients included in the study, 43 (48.9%) were female and 45 (51.1%) were male. 24 (27%) patients died. The mean age of non-survivors was 70 ± 12.3 years and the survivors were 61.9 ± 18.2 years. Mortality predictors such as D-dimer, ferritin, troponin, LDH, CRP, and procalcitonin were significantly higher in non-survivors than in survivors ($p < 0.05$). The median MK level (IR) was 152.5 ± 125 pg/ml in all patients, 143 ± 149 pg/ml in survivors, and 165.5 ± 76 pg/ml in non-survivors ($p = 0.546$). The difference between these two groups was not statistically significant. The area under the ROC curve was found to be 0.542 (95% CI 0.423–0.661, $p = 0.546$).

Conclusion. MK is not a biomarker that can replace or reinforce known predictors of mortality in COVID-19 patients.

Key words: midkine levels, COVID-19, mortality, prediction, biomarker

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Introduction

The new coronavirus (SARS-COV-2) that causes COVID-19 disease was first detected in Wuhan, China in December 2019 and rapidly spread to more than 200 countries [4]. Severe COVID-19 disease is an uncon-

trolled response of the immune system to the infection, in which high levels of circulating cytokines lead to a generalized inflammatory response with failure of at least one organ function and high mortality rates [9, 23]. Many COVID-19-related prognostic biomarkers such as D-dimer, C-reactive protein (CRP), ferritin,

* Midkine (МК) – гепарин-связывающий фактор роста, участвующий в различных физиологических процессах (размножении и восстановлении клеток). Представляет собой растворимый секретируемый белок, уровень которого повышается при различных заболеваниях, особенно при раке, и поэтому рассматривается как ценный биомаркер заболевания. / Midkine (МК) is a heparin-binding growth factor involved in various physiological processes (cell reproduction and repair). It is a soluble secreted protein, the level of which increases in various diseases, especially cancer, and therefore, it is considered as a valuable biomarker of the disease.

pentraxin-3, and other proinflammatory cytokines have been demonstrated so far [1, 10, 12, 15, 18, 21, 23]. However, the search for different disease-specific biomarkers continues.

Midkine (MK) is a multifunctional cytokine, expressed primarily in midgestation. It is a heparin-binding growth factor sensitive to retinoic acid released from various cell types during embryogenesis. It promotes angiogenesis, cell growth, and cell migration. Midkine is also expressed in various malignancies, suggesting that it may play a role in tumorigenesis, perhaps through its effects on angiogenesis. Cytokines and growth factors are classified into structurally related protein families such as the fibroblast growth factor family [14]. In addition, MK organizes the proliferation, differentiation, survival, adhesion, migration, and gene expression of immune cells. At the same time, MK is a mitogenic, antiapoptotic, migrating, chemotactic, angiogenic, and fibrinolytic molecule that plays a role in controlling the inflammatory response [25]. MK can alleviate hypoperfusion and myocardial cell damage due to hypoxia, as well as promote angiogenesis in myocardial infarction [6]. However, it may accelerate tubular necrosis in drug or autoimmune kidney damage and pulmonary fibrosis due to acute respiratory distress syndrome (ARDS) [2, 14, 26]. The interesting issue about MK is that it has bactericidal, antifungal, and antiviral effects in some viruses such as herpes simplex and human immunodeficiency virus (HIV) [7, 16, 17].

COVID-19 is a new disease and many proinflammatory cytokines and other acute phase protein levels have been found to correlate with poor prognosis in the literature. However, there are no specific biomarkers in the prognosis and surveillance of COVID-19 [24]. The aim of our study was to investigate MK levels in COVID-19 infection and to explore whether there is a relationship between the prognosis of patients and midkine levels.

Materials and Methods

This study was conducted on 88 confirmed COVID-19 patients who were hospitalized due to symptomatic pneumonia between April 15, 2020, and August 15, 2020. The study population was determined as patients hospitalized in the Training and Research Hospital within the specified period. Patients whose serum could be separated for MK at admission to hospitalization were included in the study. Also, patients with symptomatic pneumonia had an indication for hospitalization and had confirmation of COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal (NP) swabs. The patients who did not have radiologic signs of pneumonia, had a NP RT-PCR negative test result, had a malignancy, and had a confirmed bacterial infection at admission were excluded. The patients were divided into two groups according to surviving (group 1 = survivor group and group 2 = non-survivor group). Both groups were compared according to demographic features, comorbid diseases, and laboratory findings of

patients. Before receiving any antimicrobial or anti-inflammatory drug, the serum MK was obtained from all patients at the first admission to the ward or intensive care unit (ICU).

Statistical analysis. Descriptive analyses were performed to provide information on the general characteristics of the study population. Visual (probability plots, histograms) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) were used to determine whether they were normally distributed or not. 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, Independent Sample T Test was used for parametric tests to compare these parameters. The chi-squared test was used to compare the categorical variables between the two groups. The categorical variables were presented as the frequency (% percentage). The performance of MK was assessed using receiver operating characteristic (ROC) curve analysis and by calculating the area under the curve (AUC) of the ROC curves. 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

The demographics of the 88 patients are provided in Table 1. The cohort had a median age of 64.1 ± 18.2 years. There were 45 (51.1%) men and 43 (48.9%) women. The patients were divided into two groups according to their mortality as the survivor group (group 1) and the non-survivor group (group 2). Of the 88 patients included in the study, 24 (27%) patients died. Ten of the female patients (41.7%) and 14 of the male patients (58.3%) resulted in death, and there was no significant difference in mortality between men and women ($p = 0.408$). The group 2 was older than the group 1 (70 ± 12.3 years vs 61.9 ± 18.2 years, respectively; $p = 0.020$). Concerning diabetes mellitus, hypertension, heart disease, chronic obstructive pulmonary disease, chronic renal failure, and other accompanying morbid diseases, there was no significant difference between the two groups ($p > 0.05$). 27 (42.2%) patients from the group 1 had a fever, while it was present in only 4 (16.7%) patients from the group 2 ($p = 0.026$). In addition, 23 (35.9%) of the group 1 and 16 (66.7%) of the group 2 had shortness of breath and this difference was significant ($p = 0.001$). Other symptoms were not significantly different between the groups ($p > 0.05$) (Figure 1). Mortality predictors of COVID-19 in the group 2 were significantly higher than those in the group 1 ($p < 0.05$) (Table 2).

The median (IR) value of the MK level was 152.5 pg/ml (125) in all patients, 143 pg/ml (149) in survivors, and 165.5 pg/ml (76) in non-survivors. However, this difference concerning mortality was not statistically significant ($p = 0.546$) (Table 1). ROC analysis was performed to determine whether there was a cut-off

Table 1. Demographic characteristics of patients with COVID-19

Indicators	Survivors, n = 64	Non-Survivors, n = 24	All patients n = 88	p
Age, year, mean (±SD)	61.9 (18.2)	70 (12.3)	64.1 (17.1)	0.020*
Sex Female, n (%)	33 (51.6%)	10 (41.7%)	43 (48.9%)	0.408***
Diabetes Mellitus, n (%)	17 (26.6%)	7 (29.2%)	24 (27.3%)	0.807***
Hypertension, n (%)	35 (54.7%)	13 (54.2%)	48 (54.5%)	0.965***
Heart Disease, n (%)	13 (20.3%)	7 (29.2%)	20 (22.7%)	0.377***
COPD, n (%)	6 (9.40%)	3 (12.5%)	9 (10.2%)	0.700***
CKD, n (%)	5 (7.80%)	3 (12.5%)	8 (9.10%)	0.496***
Cerebrovascular disease, n (%)	3 (4.70%)	4 (17.4%)	7 (8.00%)	0.076***
Unit Ward, n (%)	47 (73.4%)	0 (0.00%)	47 (53.4%)	0.0001***
ICU, n (%)	17 (26.6%)	24 (100.%)	41 (46.6%)	

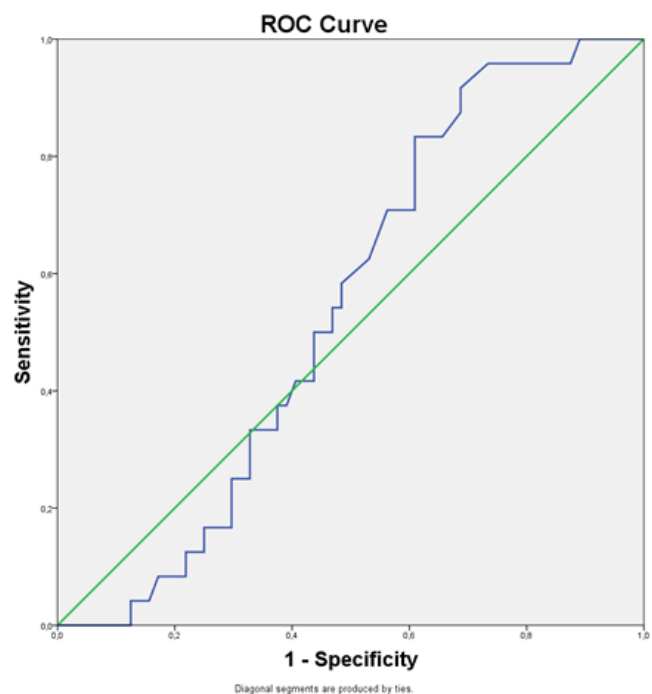
Table 2. Comparison of laboratory findings between the groups

Indicators	Survivors, n = 64	Non-Survivors n = 24	All patients, n = 88	p
WBC (K/uL), median (IR)	7 (9.1)	8.1 (5.4)	7.1 (6.2)	0.974**
Lymphocyte (K/uL), median (IR)	1.3 (1.8)	0.6 (0.4)	1.1 (1.0)	0.000**
Neutrophil (K/uL), median (IR)	5 (8.1)	6.0 (4.9)	5.1 (6.3)	0.739**
Platelet (K/uL), median (IR)	190.9 (59.6)	219.9 (154.3)	198.8 (95.1)	0.862**
Prothrombin time (sec), median (IR)	12.8 (2.6)	14.0 (2.0)	13.1 (2.5)	0.001**
D-DIMER (ugFEU/L), median (IR)	1030.6 (1287.2)	3461.8 (7462.5)	1693.7 (4136.2)	0.001**
Troponin (ng/L), median (IR)	28.8 (75.0)	2272.8 (10406.8)	622.0 (5357.2)	0.000**
Ferritin (µg/L), median (IR)	561.9 (1003.7)	1195.1 (1770.8)	736.6 (1282.9)	0.004**
Serum albumin (g/dL), mean (±SD)	3.4 (0.5)	3.0 (0.4)	3.3 (0.5)	0.000*
LDH (U/L), median (IR)	331.4 (155.4)	499.3 (182.8)	375.8 (178.3)	0.000**
CRP (mg/L), median (IR)	33.5 (131.0)	161.5 (41.0)	72.0 (153.5)	0.001**
Procalcitonin (ng/ml), median (IR)	0.1 (0.2)	0.3 (0.6)	0.1 (0.3)	0.000**
Fibrinogen (g/dl), median (IR)	377.8 (105.0)	395.8 (87.5)	383.1 (99.9)	0.06**
Lactate (mmol/L), median (IR)	1.6 (0.7)	2.1 (0.7)	1.7 (0.9)	0.001**
Midkine, median (ng/L) (IR)	143 (149.0)	165.5 (76.0)	152.5 (125.0)	

value that could be considered significant in predicting mortality in patients with Covid-19. The area under the ROC curve was found to be 0.542 (95% Confidence Interval 0.423–0.661, $p = 0.546$). Therefore, a suitable cut-off value was not found for statistical significance (Figure).

Discussion

In the present study, for the first time in the literature, MK levels were measured in COVID-19 patients. There was no significant difference between non-survivor and survivor groups concerning serum MK levels. At the same time, it was determined that serum MK levels did not have significant importance in predicting mortality due to COVID-19 disease. Since COVID-19 disease mainly affects the respiratory and immune systems, respiratory epithelial cells and immune T lymphocytes appear to be clear targets for COVID-19 disease [7, 11, 16, 17, 22, 24]. MK is produced in varying concentrations in the skin and major respiratory tract against potential pathogens, which the body encounters for the first time. This protein is a growth factor, the function of which has been investigated in many healthy volunteers, in the



ROC curves of Midkine in predicting mortality in patients with COVID-19. ROC: Receiver operating characteristic curve

setting of some bacterial or viral infections and serious conditions such as sepsis [4, 8, 16, 17]. The serum MK levels in healthy individuals ranged from 302 to 1068 pg/mL [8]. In vitro studies reveal that MK had a strong bactericidal activity against the respiratory pathogen *Streptococcus pneumoniae* and *Escherichia coli* but no activity against *Staphylococcus aureus* [13, 19]. Also, it's a cytokine that inhibits HIV infection in an autocrine and paracrine manner by preventing the adherence of HIV particles when added to CD4 cells before the infection occurs, however, it has no significant effect when added after virus entry to the T lymphocyte [7]. In our study population, we measured MK levels within normal limits in non-survivor and survivor patients. A significant sensitivity and specificity could not be reached as a result of the ROC analysis performed to establish a certain cut-off value.

Recent studies showed that MK has a new role in acute and chronic inflammatory diseases including colitis, atherosclerosis, multiple sclerosis, nephritis, and rheumatoid arthritis. These diseases are alleviated in the presence of MK in animal models [22]. These chronic inflammatory diseases critically affect patients' quality of life. For instance: in cases of atherosclerosis, when endothelial dysfunction develops, MK excessively expresses and causes leukocyte infiltration in the damaged area. In an animal study, it has been shown that leukocyte infiltration could not occur in MK-deficient mice [5]. It has been shown to cause fatal thrombotic microangiopathies as a result of hyperinflammation occurring secondary to COVID-19. A SARS-CoV-2 virus invading the endothelium with its ACE2 receptor may cause severe endothelial damage and degradation in endothelial cell membranes [3, 9, 20, 27]. Despite this, although our study population accompanied

chronic diseases such as diabetes mellitus and hypertension, we did not find any significant relationship between MK levels and mortality. Perhaps, MK may have a more meaningful function in the chronic inflammation process rather than in acute inflammation. Also, this result might be caused by the collection of the samples for MK as soon as the patients were hospitalized. Maybe if we had taken several MK measurements at different stages of the disease during hospitalization, we could have reached a more accurate result.

Many acute-phase reactants and proinflammatory cytokines have been identified as determining factors in mortality from COVID-19 disease [24]. In our study, we think that the increased serum values of these indicators of mortality in COVID-19 patients were in accordance with the literature supporting the reliability of the patient population and the results of the study for MK.

The small number of patients and the shorter observation period are among the limitations of our study. In addition, plasma MK levels were measured only once at admission and were not continuously monitored as we mentioned above; therefore, trends in plasma MK levels in survivors and non-survivors are unknown. We think that MK should be studied in subgroups such as patients with bacterial superinfection.

In conclusion, MK is not a biomarker that can latch onto the known predictors of mortality in COVID-19 patients and can provide better predictions of mortality. Nevertheless, COVID-19 is a self-limited infection, in which the strength of the host's immune system plays a crucial role against it. It can be speculated that the MK can help this self-limited infection due to its antiviral feature. This assumption should be confirmed by in vitro and in vivo studies with larger sample sizes.

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Ethical approval. The study was conducted in accordance with the Declaration of Helsinki, and after approval of the Ethics Committee of our University of the Faculty of Medicine (No:71522473/050.01.04/461).

Информированное согласие. Для такого типа исследования не требовалось письменного информированного согласия.

Informed consent. No written informed consent was necessary for this type of study.

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Conflict of Interests. The authors state that they have no conflict of interests.

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