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Interferon-Gamma Inducible Protein-10: Not a Mortality Marker for COVID-19 Disease

İnterferon-gamma ile İndüklenebilir Protein-10: COVID-19 Hastalığı için Bir Ölüm Göstergesi Değildir

[1]Mahmud ISLAM, [1]Hamad DHEIR, [2]Elif OZOZEN SAHIN, [3]Selcuk YAYLACI, [4]Abdulkadir AYDIN, [1]Musa PINAR, [5]Ertugrul GUCLU, [3]Ahmed Cihad GENC, [2]Mehmet KOROGLU, [5]Oguz KARABAY

[1]Division of Nephrology, Medical Faculty of Sakarya University, Sakarya, Türkiye
[2]Department of Microbiology, Medical Faculty of Sakarya University, Sakarya, Türkiye
[3]Department of Internal Medicine, Medical Faculty of Sakarya University, Sakarya, Türkiye
[4]Department of Family Medicine, Medical Faculty of Sakarya University, Sakarya, Türkiye
[5]Sakarya University, Department of Infectious Diseases and Microbiology, Sakarya, Türkiye

Mahmud İslam: https://orcid.org/0000-0003-1284-916X
Hamad Dheir: https://orcid.org/0000-0002-3569-6269
Elif Ozsozen Sahin: https://orcid.org/0000-0002-8873-2884
Selcuk Yaylaci: https://orcid.org/0000-0003-0663-586X
Abdlkadir Aydin: https://orcid.org/0000-0003-0663-586X
Musa Pinar: https://orcid.org/0000-0001-8164-6302
Ertugrul Guclu: https://orcid.org/0000- 0003-2860-2831
Ahmed Cihad Genc: https://orcid.org/0000-0002-7725-707X
Mehmet Koroglu: https://orcid.org/0000-0001-8101-1104
Oguz Karabay: https://orcid.org/0000-0003-1514-1685

ABSTRACT

Objective: Interferon-gamma inducible protein-10 (IP-10) released from macrophages is associated with thrombosis. We aimed to investigate patients' biochemical markers following severe COVID-19, concentrating on the role of IP-10 in mortality.

Materials and Methods: In our study, we retrospectively evaluated data from 88 (females, 44.3%) severe patients followed in our university hospital's intensive care unit (ICU). We obtained demographic and laboratory data from our study population's files and electronic records, including D-dimer, ferritin, uric acid, IP-10 values, and other biochemical markers.

Results: The mean age of all 88 patients with COVID-19 infection followed in the ICU was 70.5 ±10 years. The median for lymphocyte count was 1.3 (1-2.1) vs 0.8 (0.5-1.1) K/uL, ferritin 151 (90.7-255) vs 624 (296-1254) mcg/L, D-dimer 386 (293.5-650) vs 1280 (871-2245) ug/L, LDH 220 (185-286) vs 429.5 (368-560) U/L with a p-value of <0.05 in survivors vs non-survivors respectively. On the other hand, the level of IP-10 was 21.3 (13.2-31.6) vs 26.6 (11.4-43.6) pg/mL with a p-value of 0.04.

Conclusion: In this study, in which non-survivors and survivors were compared in severe COVID-19 patients, it was found that ferritin and D-dimer were good predictors of mortality, while IP-10 could not be a predictor of mortality.

Keywords: Biomarker, COVID-19, IP-10, mortality

ÖZ

Amaç: Makrofajlardan salınan interferon-gama indüklenebilir protein-10 (IP-10) tromboz ile ilişkilidir. Bu çalışma, şiddetli COVID-19 nedeniyle takip edilen hastaların biyokimyasal belirteçlerini ve IP-10'un mortaliteyi göstermedeki rolünü araştırmayı amaçladı.

Materyal ve Metot: Bu çalışmada üniversite hastanesinin yoğun bakım ünitesinde (YBÜ) takip edilen 88 (Kadın % 44,3) ağır hastanın retrospektif verileri değerlendirildi. Demografik ve laboratuvar verileri ile D-dimer, Ferritin, Ürik asit, IP-10 değerleri ve diğer biyokimyasal belirteçlere ilişkin veriler ölen ve yaşayan hastaların dosyalarından elde edildi.

Bulgular: Yoğun bakımda takip edilen COVID-19 enfeksiyonlu 88 hastanın yaş ortalaması 70,5 ±10 idi. Hayatta kalan gurupta, lenfosit sayısı 1,3 (1-2,1) K/uL, ferritin 151 (90,7-255), D-dimer 386 (293,5-650), LDH 220 (185-286) iken, ölen hastalarda ise, lenfosit sayısı 0,8 (0,5-1,1), ferritin 624 (296-1254) mcg/L, D-dimer 1280 (871-2245) ug/L, LDH 429.5 (368-560) U/L saptandı. Bu parametrelerde p değeri <0,05 idi. Buna karşılık, hayatta kalmayanlarda serum IP-10 seviyeleri hayatta kalanlar da 21,3 (1,2-31,6) pg/mL iken ölen hastalarda 26,6 (11,4-43,6) pg/mL, p=0,04.

Sonuç: Şiddetli COVID-19 hastalarında hayatta kalmayanlar ve hayatta kalanların karşılaştırıldığı bu çalışmada, ferritin, ve D-dimerin mortalite için iyi bir tahmin edici potansiyeli olduğu, IP-10'un ise bir belirleyici olamayacağı bulundu.

Anahtar Kelimeler: Biyobelirteç, COVID-19, IP-10, mortalite

Sorumlu Yazar / Corresponding Author:
Mahmud İslam
Adnan Menderes Cad. Sağlık Sok. No. 1, Adapazarı, Post Code: 54100, Sakarya, Türkiye
Tel: +905556551458
E-mail: drisleem@gmail.com

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INTRODUCTION

Early symptoms of patients with the new Coronavirus disease 2019 (COVID-19) are fever, nonproductive cough, and fatigue. Still, it is closely related to multi-organ failure and high cytokine levels in severe patients.[1] Cytokine levels determine the course of symptoms. Cytokine production is related to individual immune function; therefore, some parameters may have a predictive role in estimating the severity of the COVID-19 course. The clinical spectrum of COVID-19 ranges from simple to severe and critical.[2] Criteria and indications for ICU admission, intubation, and therapy changed dynamically with time during the pandemic.

The host immune response against COVID-19 plays a principal role in the pathogenesis and progression.[3] Serum concentrations of proinflammatory cytokines are strongly associated with disease outcomes and are increased in patients with severe disease.[4] In severe cases, stimulated expression of inflammatory cytokines, especially TNF-α and Interleukin 6, is associated with lymphopenia, T-cell depletion, and increased macrophage and neutrophil counts, indicating immune pathways and cell distribution.[5]

In critical OVID-19 patients, inflammatory factors such as interleukins, colony-stimulating factor, interferon, tumour necrosis factor, growth factor, and chemokines usually increase.[6] Most cytokines are produced by T lymphocytes, fibroblasts, and mononuclear macrophages, which are, in turn, affected by them. Cytokines usually mediate inflammation; however, IL-10 has an anti-inflammatory effect. After natural killer cells (NK) and T cells are activated, proinflammatory cytokines and chemokines such as interferon-gamma inducible protein-10 (IP-10) increase. IP-10 is secreted via endothelial cells, monocytes, and adipose tissue. In a recent study, serum levels of interleukins (4, 19, and 1β), MCP-1, and TNF-α were significantly higher in patients with COVID-19 compared to disease free.[7] However, the level of IP-10 levels was significantly lower in COVID patients.[7] IP-10 is associated with thrombosis. [1,8]. Covid-19 was also described as a multiorgan disease with microthrombosis resulting from damage to the microvascular system.[1,8] In our study, we aimed to evaluate the role of several laboratory parameters, including IP-10, to determine whether they have any predictive role regarding the mortality of COVID-19 in patients followed up in our institution.

MATERIALS AND METHODS

Ethical Approval: We obtained ethical committee approval from the Sakarya University Faculty of Medicine Ethical Committee (Date: 28.12.2020, decision no: E-71522473-050.01.04-619); we conducted our study per the Declaration of Helsinki.

Study: Our study is a retrospective, single-center study involving 88 severe (39 female and 49 male) COVID-19 patients recruited from the ICU of our university hospital in Sakarya, western Türkiye. We included adult patients over 18 years who fulfilled COVID-19 disease severity criteria (Those with oxygen saturation less than 90 and or breathing more than 30 breaths per minute despite >5 litre O2 support). We excluded those under 18 years, those with a history of malignancy or evidence of bacterial infection on ICU admission, and those immunocompromised.

Study Group: Our population included surviving and deceased COVID-19 patients admitted to the ICU. Clinical information and laboratory results were collected at the earliest time after hospitalisation. We split our patients into survivors (n=44) and non-survivors (n=44). To study IP-10, serum samples of the patients were drawn on the first day of ICU admission and then stored at -80 degrees. All serum IP-10 levels were measured using an ELISA kit. Clinical symptoms, COVID-19, and laboratory test results were analysed retrospectively.

Follow-up of Patients and Treatment Protocol: The diagnosis was made based on the constantly updated TR Ministry of Health's and COVID-19 diagnosis and treatment guidelines parallel to updated international guidelines.

COVID-19 RNA Detection and Measurement of IP -10: Nasopharyngeal swabs were tested using commercial reagent kits designed detection of SARS-CoV-2 RNA by PCR. Ready-made commercial kits (Bioxcen, Türkiye) were used for the test. Tests of samples were carried out in compliance with the manufacturer's instructions.

Measurement of Human IP-10 (CXCL 10) Levels: Collected samples were sent to our microbiology laboratory in yellow serum separate tubes (SST) biochemistry tube and centrifuged at 4000 rpm for 10 minutes. Collected serum samples were frozen and stored at -80°C until investigated for IP-10 using the micro-ELISA test. Using the ELISA kit, the level of Human IP-10 CXCL10 (Abcam Ltd, Cambridge, UK) was determined in an automatic micro-ELISA device (Grifols, Triturus, Spain). The micro-ELISA test procedure was carried out according to the manufacturer's (Abcam, Cambridge, USA) instructions. The serum levels of IP-10 were measured quantitatively by subtracting the cut-off and calibration curves. The detection range of the kit used is 12.5-800 pg/ml, with an analytical sensitivity of 2.6 pg/mL.

Outcomes and Other Tests: All information regarding patient outcomes and routinely monitored laboratory data were taken from hospital records and the

hospital management system.

Statistical Analyses: A descriptive analysis was performed to provide information on the general characteristics of the study population. We used Visual (probability plots, histograms) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to evaluate the normality of distribution. To compare normally distributed variables, we used mean and standard deviation. For non-normally distributed variables, the descriptive analyses were presented using median and interquartile range (IQR). We used the student's t-test for parametric variables and the Mann-Whitney U test for nonparametric ones. The categorical variables were presented as the frequency (% percentage). Categorical variables between the two groups were evaluated using used Chi -square test. Automated analyses were performed by SPSS statistics software (IBM SPSS Statistics, Version 21.0). P-value <0.05 was considered significant.

RESULTS

This study included 88 patients (44 females & 44 males) confirmed by PCR. The mean age was 70,5 ±10 years. We divided the patients into the Survivor (Group 1) and the non-survivor groups (Group 2). The mean age of group 1 was 69.1 ± 9.5 years, while 72 ± 10.3 years in group 2. The male sex ratio was 50.0% (n=22) and 61.40% (n=17) in group 1 and group 2, respectively. In the non-survivor group, the history of both COPD (n=9; 25%) as well as CKD (n=8; 18,2%) was higher than in the survival group. The non-survivor patients had lower lymphocyte accounts, higher neutrophil accounts, higher uric acid, higher alanine aminotransferase (AST), and lower serum albumin than survived patients. On the other hand, Troponin-I, CRP, and procalcitonin levels were higher than the survivor group. The median of IP-10 serum levels of all patients was 23.1 pg/mL (11.8-35.7). The median IP-10 level of the non-survived group was 26.6 pg/mL (11.4-43.6), whereas 21.3 pg/mL (13.2-31.6) in the survived group. However, this difference was statistically insignificant (Table 1).

As illustrated in Figure 1, the Level of ferritin and D -dimer was prominently higher in the nonsurvivor group (p=0,0). This was minimal concerning IP-10

Table 1. Characteristics and results of Survivor and non-survivor groups.

Characteristics	Survivor Group (n- 44)	Non-survivor Group (n- 44)	All patients (n- 88)	P
Age. Mean ± SD	69.1±9.5	72±10.3	70.5±10	0.177
Sex **Female,** n (%)	22 (50.0)	17 (38.60%)	39 (44.3%)	0.283
Male, n (%)	22 (50.0)	27 (61.40%)	49 (55.7%)	
Fever *	5 (11.4)	11 (25.00%)	16 (18.2%)	0.097
Cough *	12 (27.3)	21 (47.70%)	33 (37.5%)	0.048
COPD *	1 (2.3)	9 (20.50%)	10 (11.4%)	0.007
Chronic kidney disease *	2 (4.5)	8 (18.20%)	10 (11.4%)	0.044
WBC (K/uL) **	5.5 (4.5-7)	8.2 (5.3-10.9)	6.2 (4.9-9)	0.000
Hemoglobin, Mean ± SD, (gr/dl)	12.6±1.8	12.1±1.9	12.3±1.9	0.192
Platelet (K/uL) **	168.2 (134.5-201)	182 (139.5-257)	177(135-223.5)	0.223
Lymphocyte count (K/uL) **	1.3 (1-2.1)	0.8 (0.5-1.1)	1.1 (0.7-1.8)	0.000
Neutrophil, (K/uL) **	3.3 (2.4-4.5)	6.3 (3.9-9.1)	4.3 (2.9-6.7)	0.000
Uric acid, Mean ±SD, (mg/dl)	5.9±1.7	7.2±3.2	6.5±2.6	0.037
AS, median (U/L) **	25.5 (21.9-38.3)	41.5 (25.5-71)	31.5 (22.7-48.5)	0.008
Serum albumin, median (gr/L) **	39.9 (32.6-43)	31.5 (26.9-33.2)	33.1 (30-39.9)	0.000
LDH (U/L) **	220 (185-286)	429.5 (368-560)	310 (214.5-448.5)	0.000
Total cholesterol (mg/dl) **	169 (134-204.5)	136 (121-156)	150 (125-181)	0.008
LDL-cholesterol (mg/dl) **	114 (97.5-139.5)	85 (69-111)	103 (78-128)	0.000
HDL-cholesterol (mg/dl) **	38 (33-46)	35 (26-40)	36 (30-42)	0.037
D-Dimer (ug/L) **	386 (293.5-650)	1280 (871-2245)	774 (377.5-1540)	0.000
Troponin (ug/L) **	4.7 (1.7-9.7)	29.7 (11.7-101)	11.5 (4-40.9)	0.000
Ferritin (mcg/L) **	151 (90.7-255)	624 (296-1254)	296 (135.5-653)	0.000
C-reactive protein (mg/L) **	19.5 (6.2-68.4)	118 (65.3-167.5)	65.3 (16.5-128)	0.000
Procalcitonin (ng/mL)	0.1 (0-0.1)	0.3 (0.2-0.6)	0.1 (0.1-0.3)	0.000
Fibrinogen (mg/dL) **	337 (285-394)	409 (354-462)	376.5 (298-434)	0.003
IP-10 (pg/mL) **	21.3 (13.2-31.6)	26.6 (11.4-43.6)	23.1 (11.8-35.7)	0.406

AST: Alanine aminotransferase; **COPD:** Chronic obstructive pulmonary disease; **CRP:** C-reactive protein**; IP-10:** Interferon-gamma inducible protein-10; **LDH:** Lactate dehydrogenase; **WBC:** White blood cells. IQR: Interquartile range; *: Sshown as n, (%); **: Shown as IQR.

levels (p=0,406). The mean values of D-dimer & Ferritin are dramatically different, while the difference is not prominent for IP-10.

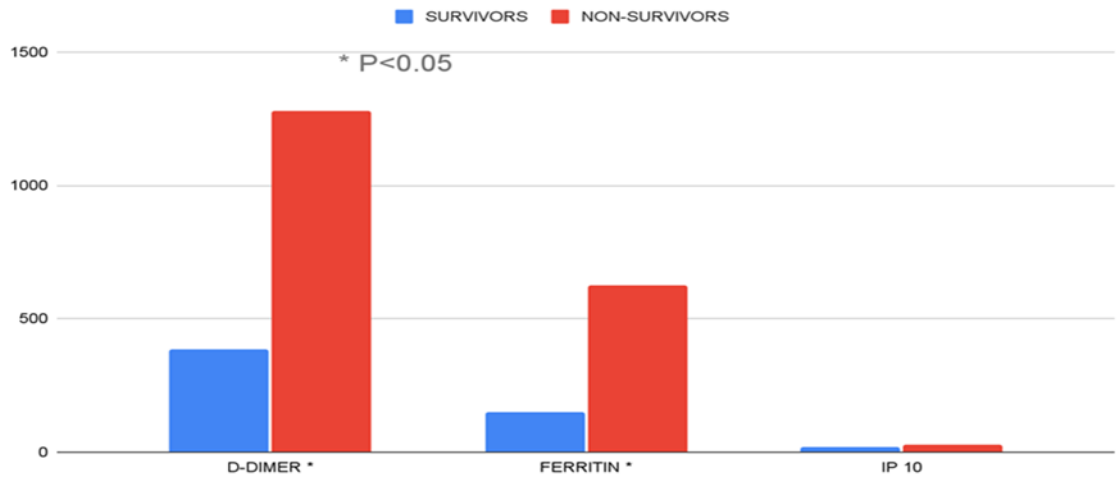

Figure 1. Comparison of survivors and non-survivors according to parameters indicating COVID-19 severity.

response subsides, and the patient recovers.[1] It is a hyperinflammatory condition that may lead to acute lung injury, ARDS, or multiple organ failure, with mortality of up to 15% in such patients. A more hyperinflammatory response is seen in deceased patients.[9] This study aimed to reveal different indicators that determine mortality in the data obtained from 88 patients. Cough, COPD, chronic kidney failure, leukocytosis, lymphopenia, low LDL, high D-dimer, high CRP, and high fibrinogen have been shown as significant predictors of determining mortality in many studies. All these high factors are associated with hyperinflammation.

Patients who died in our study had more cough complaints, more COPD history, and more chronic renal failure history. In addition, lymphopenia, increased uric acid value, low albumin, and high LDH were remarkable in our dying patients. Different researchers in different studies have demonstrated these parameters. Again, high ferritin levels are unprecedented in patients who died in D-dimer tests.[10] According to our findings, ferritin and D-Dimer levels are higher in patients with a mortal course associated with organ damage. Ferritin is an acute-phase protein that can be excreted from destroyed cells. Elevated ferritinemia can result from impaired liver activity or metabolic syndrome. COVID-19 patients with abnormal ferritin levels have a higher risk of liver damage and severe disease, and previous studies have shown liver damage in COVID-19 patients.[11]

DISCUSSION AND CONCLUSION

In most COVID-19-positive patients, a localised, short-lived immune response is sufficient to clear the virus from the lungs, after which the immune

It has been shown that proinflammatory cytokines may affect uric acid excretion or serum uric acid levels.[12] This study found that patients with a mortal course had a significantly higher uric acid level. Uric acid is an important antioxidant that scavenges free radicals and reactive oxygen species. Therefore, more inflammation occurs, producing more oxidants in severe COVID-19 patients. The high uric acid levels may be correlated with the anti-inflammatory effect of protecting the body. IP-10 (CXCL10) is a chemokine with multiple actions. It is important in attracting Th1 lymphocytes, monocytes, and natural killer cells. It is also involved in chemotaxis, apoptosis, and regulation of cell growth. It has a role in the immune system. It was identified as a significant biological marker mediating disease severity.[13] IP-10 is particularly interesting as its expression pattern in COVID-19 patients differs from that observed in traditional viral infections. It has been reported that IP-10 rises rapidly but transiently in viral infections like the common cold, while its concentrations often remain high throughout the COVID-19 course.[12] Different researchers have reported that IP-10 may effectively indicate the severity of COVID-19. Several studies pointed to IP-10 as a marker of COVID-19 progression.[14] For example, a study including 74 COVID-19 patients from China reported IP-10 and MCP-1 as parameters that may indicate mortality.[1] In another study from China evaluating 41 patients,

plasma levels of IL-2, IL-7, IL-10, IP-10, GSCF, MCP-1, TNFα, and MIP-1A were higher in ICU patients.[15] However, this study did not demonstrate any correlation between IP-10 and mortality. Our results showed that the IP-10 levels were 26.6 pg/mL in the non-survivors versus 21.3 pg/mL in the survivors, with no statistical difference between groups. The main reason for the difference between our study's results and other studies seems to be due to the comparison of those admitted to the ICU for more severe diseases and who were already prone to death with those who survived. In Yu Chen et al. study, they compared critically ill patients with severely ill ones in the ICU.[1] On the other hand, other studies compared patients admitted to the ICU with those in the wards or those with different clinical pictures.[16,17]

According to these results, IP-10 may be a good biomarker for predicting the progression of the COVID-19 patient newly admitted to the hospital. Still, it may not be a good biomarker for the COVID patients followed in the ICU.

Our study has some limitations. Being partially retrospective, depending on available health records, we do not have full information about the time lag between the first symptoms and application to the outpatient clinic or admission to ICU. In conclusion, comparing non-survivors and survivors of COVID-19 disease, it was determined that while ferritin, uric acid, and D-dimer were good indicators to show mortality, IP-10 could not be a marker for mortality.

Ethics Committee Approval: Our study was approved by the Sakarya University Faculty of Medicine Ethical Committee (Date: 28.12.2020, decision no: E-71522473-050.01.04-619). All procedures have been carried out in accordance with the Helsinki Declaration.

Conflict of Interest: No conflict of interest was declared by the authors.

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