INTRODUCTION

The viral pandemic, named as COVID-19 (SARS-CoV-2), has affected the entire world in a short time after the first pneumonia patients with unknown aetiology were reported in December 2019 in Wuhan in the Chinese province of Hubei. SARS-CoV-2 infection is associated with fever, cough, sore throat, shortness of breath, headache, muscle aches, loss of taste and smell, and diarrhoea. The clinical manifestation ranges from asymptomatic infection, to mild upper respiratory system infection, moderate lung infection with radiological abnormalities, severe viral pneumonia with respiratory failure and increased fatal patients. The epidemiological and clinical properties of COVID-19 patients have been reported by health authorities, although the pathogenesis of SARS-CoV-2 infection is not defined clearly. Researchers have identified some common characteristics in critically ill COVID-19 patients. These include: sudden worsening at 7-14 days after the onset of the disease, low levels of lymphocytes (LYs) in the blood, increased C reactive protein (CRP) and pro-inflammatory cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, and IL-17A) and extremely high inflammatory parameters, hypercoagulation and multiple organ damage. Clinical reports showed that pneumonia is the most common complication following SARS-CoV-2 infection with rapid virus replication, resulting in multiple inflammatory cell infiltration and cytokine storm.
acute lung injury followed by acute respiratory distress syndrome (ARDS).4,5

The stimulation of the host’s innate and adaptive immunity including activation of T cells, CD4 and CD8+T cells production of several proinflammatory cytokines are required to control viral replication after viral infections, to limit the spread of the virus and to kill infected cells. However, tissue damage because of the virus may induce the exaggerated production of proinflammatory cytokines, macrophages, granulocytes and other immune cells.6 Several clinical studies have proposed blocking cytokine production or lowering their blood levels as possible solutions.7-9 However, the pandemic period continues, and for possible treatments, more randomised controlled studies are required to understand the pathogenesis of the infection.

Researchers in different centres worldwide have compared patients clinical characteristics by means of molecular, biochemical and radiological assays to determine the course of the disease progression.10,11 However, these investigations were performed on a limited number of patients, and the published data are different from each other. Since IL-6, IL-8 (CXCL 8), and IP-10 (CXCL 10) from the cytokine and chemokine family are known to be significant in SARS and MERS, their significance in SARS-CoV-2 (COVID-19) infection is still the subject of investigation.12,13

This study, we investigated the role of the relationship between IL-6, IL-8, and IP-10 levels, routine biochemical parameters (white blood cell (WBC), neutrophil (NE), LY, haemoglobin (HB), platelets (PLT), BUN, total protein, albumin, d-dimer, sedimentation, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), troponin, C-reactive protein, ferritin, and procalcitonin (PCT)) and IL-6, IL-8, IP-10 levels in the prognosis of COVID-19 in healthy individuals, mild-moderate and in severe COVID-19 patients.

2 | METHODS

2.1 | Identification of groups and treatment

The control groups (n = 30) consisted of healthy volunteers who had not been diagnosed with COVID-19 and with no symptoms or known disease. The mild-moderate group (n = 30) consisted of patients diagnosed with COVID-19, with positive RT-PCR test results, and hospitalised for treatment in the Atatürk University Research Hospital COVID department. Patients with a respiratory rate of <30/min, SpO₂ level >90% in room air, and signs of mild-moderate pneumonia (<50% involvement) by chest radiography or tomography were classified as a mild-moderate clinical condition. The severe group (n = 30) consisted of patients diagnosed with COVID-19, with positive RT-PCR test results, and hospitalised for treatment in the Atatürk University Research Hospital COVID department. Patients with a respiratory rate of ≥30/min, SpO₂ level ≤90% in room air, and signs of bilateral diffuse pneumonia (>50% involvement) by chest radiography or tomography were classified as a severe clinical condition. The study included healthy volunteers and patients over 18 years of age.

The protocol in the COVID-19 Treatment Guide prepared by the Ministry of Health of the Republic of Turkey has been applied to COVID-19 patients treated in the clinic (for mild-moderate and severe patients; Favipiravir, Steroid, Low-molecular-weight Heparin etc).

2.2 | Sampling of blood samples

All patients in the study were informed about the study, and their written and verbal consents were obtained. Blood samples were taken from mild-moderate and severe patients with positive COVID-19 RT-PCR test on the first day. The sitting position after blood from the antecubital area was taken into biochemistry tubes by experienced people using a vacutainer. The samples were centrifuged after coagulation at room temperature for 30 minutes, and serum samples were separated. They were frozen and stored at −80°C until analysis. After the serum samples were dissolved under optimal conditions for analysis, all analyzes were performed in a single session at the Medical Biochemistry Laboratory of the Atatürk University Health Research and Practice Center.

2.3 | Biochemistry analysis

IL-6 levels in serum samples are analysed by commercially purchased Bioassay Technology Laboratory brand (Cat No: E0090Hu), IL-8 levels by Bioassay Technology Laboratory brand (Cat No: E0089Hu), IP-10 levels by Bioassay Technology Laboratory brand (Cat No: E0412Hu) (1008 Junjiang Intel. Bldg) using ELISA kits by ELISA method on a Dynex brand automatic ELISA reader device (Dynex Technologies Headquarters) in line with the standard protocol suggested by the manufacturer. Intra and inter-assay CVs of the kits were <10%. Routine laboratory assays of the patients include whole blood count (WBC, NE, NE%, LY, LY%, HB, PLT), Bun, Total protein, Albumin, d-dimer, Sedimentation, Creatinine, AST, ALT, LDH, CK,
volumes. Mean ± SD. Deviation and P values are presented in Table 1. Also, there was no statistically significant difference in IL-6, IL-8, IP-10 levels among 9 ex and 21 discharged patients in the severe patient group.

We found a statistically significant positive correlation between serum IL-8 and IL-6 levels (P = .001, r = .660; Table 2 and Figure 1). A statistically significant positive correlation was found between serum IP-10 and IL-6 (P = .001, r = .599; Table 2 and Figure 2). A statistically significant positive correlation was found between serum IP-10 and IL-8 (P = .001, r = .729; Table 2 and Figure 2).

Routine blood parameters were evaluated by IL-10. A statistically significant positive correlation was found between IL-8 (pg/mL)/CRP (P = .000, r = 0.468), IL-8 (pg/mL)/Ferritin (P = .002, r = 0.387), IL-8 (pg/mL)/PCT (P = .000, r = 0.518), IL-8 (pg/mL)/o-dimer (P = .017, r = 0.307). A negative significant correlation was found between IL-8 (pg/mL)/o-dimer (P = .012, r = 0.322; Table 3).

Routine blood parameters were evaluated by IL-6. A statistically significant positive correlation was found between IL-6 (pg/mL)/CRP (P = .040, r = 0.265), IL-6 (pg/mL)/PCT (P = .019, r = 0.303). A significant negative correlation was found between IL-6 (pg/mL)/o-dimer (P = .006, r = −0.352). No significant relationship was found between IL-6 (pg/mL)/o-dimer (P = .285, r = 0.140) and IL-6 (pg/mL)/o-dimer (P = .203 r = 0.167; Table 3).

Routine blood parameters followed up in the mild-moderate and severe COVID 19 patient groups were compared. A statistically significant difference was found in WBC, NE%, NE, LY%, LY, HB, BUN, Total protein, Albumin, o-dimer, Sedimentation values between the groups. PLT (P = .094) the value was not statistically significant. LY%, LY, HB, albumin, and total protein values were significantly lower in severe patient groups. NLR rate was higher in the severe patient group. PNI was lower in the severe patient group (Table 4).

When mild-moderate and severe patient groups were compared by routine parameters in the not normally distributed group, LDH, CK, Troponin, ferritin, CRP, PCT parameters were higher in the

### TABLE 1. IL-6, IL-8, and IP 10 blood serum levels of the groups

| ELISA       | Healthy volunteers (n = 30) | Mild-moderate (n = 30) | Severe patients (n = 30) | P    |
|-------------|-----------------------------|------------------------|--------------------------|------|
| IP-10 (pg/mL) | 62.24 ± 24.80               | 246.74 ± 43.39         | 668.93 ± 224.74          | .001 |
| IL-8 (ng/L)  | 22.54 ± 6.49                | 76.79 ± 25.78          | 140.40 ± 65.03           | .001 |
| IL-6 (ng/L)  | 15.55 ± 4.09                | 111.13 ± 30.34         | 166.48 ± 83.11           | .001 |

Note: Statistically significant P values are shown in bold. Abbreviations: n, number; SD, standard deviation.
severe patient group and statistically significant ($P < 0.005$). No significant relationship was found between groups in creatin, AST, ALT parameters ($P > 0.005$; Table 5).

4  |  DISCUSSION

Cytokines are studied as an important marker in the prognosis of COVID 19 infection, and the effects of cytokines vary depending on the targeted cell. Different cytokines may have similar effects or exhibit synergistic effects.$^{14}$ Its role is the regulation of immune response, autoimmune mechanisms and acute phase responses.$^{15}$

In the studies on SARS-CoV-2 infection, almost all researchers reported that IL-6 is associated with cytokine storm, ARDS and poor prognosis with mortality.$^{16-18}$ Studies have reported high IL-8 levels are high in SARS-CoV and SARS-CoV-2 infections, especially in the lungs of patients with ARDS.$^{14}$ While several literature studies have reported that IL-8 levels are not associated with ARDS, many other studies have shown that in severe cases, SARS-CoV-2 infection activates both the innate and adaptive immune system in the alveolar tissue, inducing cytokine release and then cytokine release syndrome, suggesting high levels of proinflammatory cytokines (IL-1, IL-6, IL-8, TNF-α and IFN) as an important cause of mortality.$^{19,20}$

One of the hallmarks of SARS-CoV and SARS-CoV2 infections is an increase in of IL-6, IL-8, IP-10 levels with systemic inflammation and cytokine storm.$^{10,21}$ In their study of a specific COVID-19 hallmark associated with poor prognosis, Laing et al reported increased IL-6, IL-8 and IP-10 levels in both COVID-19 patients and non-COVID-19 patients with lower respiratory infections, and that the, increase in IL-8 and IP-10 is associated with the disease severity. They also reported a persistent increase in IP-10, a chemokine-induced rapidly and temporarily during viral infections, in COVID-19 and that this is associated with severity.$^6$ Valle et al also studied the effects of IL-1β, TNFα, IL-6, and IL-8 on the poor prognosis of COVID-19 and reported that TNF-α and IL-6 has significant prognostic value.$^{16}$ In their research published in the first months of COVID19 infection, Huang et al, investigated plasma cytokine and chemokine (IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17A, eotaxin (CCL 11), FGF2, GCSF, GMCSF, IFN γ, IP-10, MCP-1, MIP-1A, MIP-1B, PDGFB, RANTES (CCL 5), TNF-α, and VEGFA) levels in the patients and reported that IL-1β, IFN-γ, IP-10, and MCP-1 levels elevation in the patients infected with SARS-CoV2.$^{17}$

In this study, IL-6, IL-8, and IP-10 serum levels were higher in the mild-moderate and severe groups compared with the healthy volunteers. Parameter levels were also higher in the severe patient group as compared with the mild-moderate group. These results are in line with most of the literature studies. Besides, IL-6/IL-8; IP-10/IL-6; IP-10/IL-8 levels were compared between the study groups, and a positive correlation was observed. This correlation was considered

| TABLE 2  Correlation between serum IL-8-IL-6, IP-10-IL-6, and IP-10-IL-8 in all groups |
|-----------------|-----------------|------------------|
| IL-8 (pg/mL)/IL-6 (ng/L) | .001 | 0.660 |
| IP-10 (pg/mL)/IL-6 (ng/L) | .001 | 0.599 |
| IP-10 (pg/mL)/IL-8 (ng/L) | .001 | 0.729 |

Note: Statistically significant $P$ and $r$ values.
to be associated with poor prognosis (Figures 1-3). When the effect
on survival was examined, there was no statistically significant dif-
ference in IL-6, IL-8, IP-10 levels among 9 ex and 21 discharged pa-
tients in the severe patient group. It was thought that this situation
might be related to the small number of groups compared and the
advanced age of the patients who died.

In the studies, which were performed to determine the progno-
sis of COVID 19, the evaluation of routine biochemical parameters
varies. Several researchers reported that CRP, ferritin, d-dimer, LDH,
PCT levels may be useful to predict COVID 19 prognosis, however,
other several researchers reported that the parameters vary
related to additional diseases, treatment and sepsis, independently
of COVID 19. The findings of the present study showed that the
laboratory parameters including WBC, Ne, Ne%, NLR, CRP, ferritin,
d-dimer, sedimentation, PCT, Troponin, LDH, CK, and BUN values
increased in the severe patient group, this increased statistically sig-
nificant in the severe patient group (P < .005). Besides LY, LY%, HB,
total protein, albumin, PNI values decreased significantly in the se-
vere patient group (P < .005). The platelet ratio decreased; however,
nevertheless, it was not statistically significant. Sex was similar in all groups in our
study, a statistically significant difference was not observed.

It was observed that all SARS, MERS, and SARS-CoV-2 infections
cause lymphocyte depletion in the infected patients, and it was
reported that this condition may be caused by the direct attack of
coronavirus on lymphocytes or immune-mediated apoptosis of lym-
phocytes. It was reported that the number of leukocytes decreases
in the early stage of the disease, however increases in the later stage.
The inflammatory response may stimulate neutrophile production
and may accelerate apoptosis of lymphocytes. Considering the in-
creased neutrophils and decreased lymphocyte count, NLR was cal-
culated as an inflammation marker. Our study showed that NLR was
high in the severe patient group. The other studies showed that the
higher levels of inflammatory cytokines, chemokine, and NLR in the
SARS-CoV-2 patients may be associated with the disease severity as
compared with the non-severe patients.25
CRP is an acute-phase protein induced by IL-6 in the liver. Most of the literature studies report that CRP values increase with the disease severity.23,26 Also, in our study, CRP was significantly higher in the severe patient group. Liu et al reported that high CRP, ferritin, IL-6, and LDH are associated with the requirement of prolonged treatment period, broader antibiotic treatments, and intensive care support. PCT is the precursor of calcitonin, its serum levels are generally low. PCT levels increase with bacterial infections and relatively low in viral infections. Thus, it may be used to differentiate bacterial and viral infections. Because of decreased immune function in COVID 19 infections, the probability of bacterial secondary infection is higher, this finding explains the increased level of Ne, CRP and PCT in our study.18

TABLE 4 Normally distributed laboratory findings between mild-moderate and severe patient groups

| Parameter       | Mild-moderate (n = 30) | Severe patients (n = 30) | P     |
|-----------------|------------------------|-------------------------|--------|
| WBC (×10⁹/L)    | 5909 ± 1910            | 9205 ± 7678             | 0.026  |
| NE, %           | 60.19 ± 14.87          | 75.42 ± 14.57           | 0.001  |
| NE (×10⁹/L)     | 3659.35 ± 1865.73      | 7119 ± 5882.08          | 0.003  |
| LY, %           | 26.66 ± 12.65          | 14.01 ± 10.53           | 0.001  |
| LY (×10⁹/L)     | 1470 ± 67.9            | 941 ± 487.01            | 0.001  |
| NLR             | 3.16 ± 2.46            | 9.33 ± 7.64             | 0.001  |
| HB              | 14.46 ± 1.86           | 12.18 ± 2.06            | 0.001  |
| PLT (×10⁹/L)    | 229 466 ± 66 435       | 190 733 ± 105 398       | 0.094  |
| BUN             | 12.64 ± 3.46           | 26.22 ± 20.85           | 0.001  |
| Total protein   | 6.80 ± 0.69            | 5.7 ± 0.97              | 0.001  |
| Albumin         | 3.55 ± 0.40            | 2.67 ± 0.68             | 0.001  |
| d-Dimer         | 559.96 ± 213.1         | 8092.66 ± 18 487.28     | 0.030  |
| Sedimentation   | 22.43 ± 16.89          | 63.9 ± 23.78            | 0.001  |
| PNI             | 42.92 ± 5.89           | 32.13 ± 6.38            | 0.001  |

Note: Abbreviations: HB, hemoglobin; LY, lymphocyte; NE, neutrophil; PLT, platelets; WBC, white blood cell.

TABLE 5 Not normally distributed laboratory findings among mild-moderate and severe patient groups

| Parameter       | Mild-moderate (n = 30) | Severe patients (n = 30) | P     | Z     |
|-----------------|------------------------|-------------------------|--------|-------|
| Creatinine (µmol/L) | 0.45-1.41             | 0.30-4.7                | 0.086 | -1.715|
| AST (U/L)       | 15-217                 | 13-800                  | 0.060 | -1.878|
| ALT (U/L)       | 9-181                  | 15-160                  | 0.188 | -1.317|
| LDH             | 190-1180               | 5416-234                | 0.001 | -3.918|
| CK              | 25-224                 | 4845-14                 | 0.016 | -2.403|
| Troponin        | 0.00-2137              | 2414-1.30               | 0.001 | -3.571|
| Ferritin (µg/L) | 6.2-1100               | 21-7500                 | 0.001 | -4.790|
| CRP (mg/L)      | 3-120                  | 20.3-433                | 0.001 | -5.947|
| PCT             | 0.01-0.34              | 0.02-18                 | 0.001 | -5.148|

Note: Statistically significant P and Z values are shown in bold.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin.
We observed that albumin and lymphocyte levels and calculated PNI value were lower in the severe patient group. PNI, a common marker of nutrition and inflammatory condition is prognostically important for malignancies, chronic diseases, viral and bacterial infections, cardiovascular diseases.\(^{23}\) Increased \(d\)-dimer indicates the hypercoagulation condition in COVID 19 patients. Increased pro-inflammatory response and endothelial cell dysfunction cause hyper thrombin formation. In line with the literature, our study showed that \(d\)-dimer level was higher in the severe patient group as compared with the mild-moderate group.\(^{29}\)

When the correlation of IP-10, IL-6, and IL-8 with laboratory parameters are evaluated, PCT and CRP were significant with positive correlation in all groups, but LY was significant with negative correlation. Independently, ferritin and \(d\)-dimer were high in the severe patient group; however, the correlation of ferritin with IL-6 was not statistically significant. However, \(d\)-dimer was not correlated with IL-6 and IP-10. COVID 19 may also increase \(d\)-dimer because of increased pro-inflammatory response as well as stimulate thrombosis by increased blood viscosity because of hypoxia and induced signal pathways. COVID 19 patients may have risk factors for clotting including lung organ dysfunction, underlying conditions, prolonged bed resting, invasive treatments.\(^{29}\) Given that IL-6 and IP-10 are not correlated with \(d\)-dimer, we suggested that they might be associated with these conditions.

This study evaluated some inflammatory and biochemical markers affecting the course of the COVID19 disease. IL-6, IL-8, and IP-10 were suggested as the parameters affecting the course of the COVID19 disease. Because these parameters have increased in mild-moderate and severe COVID 19 patients in a correlated way as compared with healthy volunteers. PCT shows a positive correlation with CRP, IL-6, IL-8 and IP-10, while LY count is significant with a negative correlation. These inflammatory markers were found to be prognostically significant. Unlike many literature studies, \(d\)-dimer was not correlated with IL-6 and IP-10. A difference with positive significant correlation was observed between IL-8 and K-dimer. More evidence should be obtained from wider patient groups at different centres to accept IL-8 and \(d\)-dimer as risk factors.

ACKNOWLEDGMENT
This work was supported by Atatürk University Scientific Research Projects Coordination Unit (Project code: THD-2020-8619). Thank you to Atatürk University for their support.

CONFLICTS OF INTEREST
Fatma Kesmez Can, Zülal Özkurt, Nurinnisa Öztürk and Selma Sezen declare that they have no conflict of interest.

AUTHORS’ CONTRIBUTIONS
Fatma Kesmez Can; Planning the study, collecting blood samples, patient follow-up, statistical analysis and article writing. Zülal Özkurt: Planning the study, patient follow-up and article writing. Nurinnisa Öztürk: Planning the study, biochemical analysis, statistical analysis and article writing. Selma Sezen; Planning the study, statistical analysis and article writing.

ETHICS APPROVAL
This study was designed and then presented to the Republic of Turkey Ministry of Health Covid-19 Scientific Research Assessment Commission and the Atatürk University Faculty of Medicine, Clinical Research Ethics Committee and approved by the commission (NO: B.30.2.ATA.0.01/275).
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How to cite this article: Kesmez Can F, Özkurt Z, Öztürk N, Sezen S. Effect of IL-6, IL-8/CXCL8, IP-10/CXCL10 levels on the severity in COVID 19 infection. Int J Clin Pract. 2021;75:e14970. doi: 10.1111/iap.14970