Research Article

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CXCL12/CXCR4 as a potential axis in diagnosis and predicting disease severity in COVID-19 patients: a new perspective

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) exhibits variations in terms of patients' clinical symptoms and levels of routinely employed biochemical markers. The aim of the current study was to determine the correlation between serum levels of the C-X-C chemokine ligand type 12 (CXCL12) and C-X-C chemokine receptor type 4 (CXCR4), one of its specific receptors, and disease severity in COVID-19 patients.
Methods: Sixty-nine patients were diagnosed with COVID-19 from February to July 2021, and a healthy control group of 39 individuals were enrolled in the study. Patients were divided into subgroups: mild-moderate and severe. Serum CXCL12 and CXCR4 levels were measured using the enzyme-linked immunosorbent assay method.
Results: CXCL12 and CXCR4 concentrations were both significantly higher in the clinically severe disease group compared to the mild-moderate disease group ($p<0.05$ in both groups). CXCL12 and CXCR4 levels were also significantly higher in the patients with clinically mild-moderate disease compared to the control group ($p<0.001$ and $p<0.05$, respectively). Both CXCL12 and CXCR4 levels were correlated with clinical severity. Serum CXCL12 and CXCR4 levels were significantly positively correlated. Assuming a cut-off value of 1.44 ng/mL, serum CXCL12 levels showed 98 % sensitivity and 84 % specificity to distinguish between COVID-19 patients and healthy individuals (AUC=0.98, $p<0.001$, 95 % CI=0.95–1.0). Serum CXCR4 levels distinguished individuals with COVID-19 from healthy controls with 88 % sensitivity and 72 % specificity at a cut-off value of 69.7 pg/mL (AUC=0.82, $p<0.001$, 95 % CI=0.74–0.9).
Conclusions: Serum CXCL12 and CXCR4 levels may be included among the biomarkers used to differentiate patients with COVID-19 and determine the clinical severity of the disease.

Keywords: COVID-19; biochemical marker; CXCL12 and CXLR4; clinical biochemistry; chemokines

Introduction

The SARS-CoV-2 virus, which emerged in 2019 and resulted in a pandemic, generally manifests with clinical findings including fever, dry cough, shortness of breath, muscle/joint pain, immediate loss of taste or smell, and fatigue that generally appear after 2–14 days. In addition to radiological findings compatible with pneumonia, it also causes changes in several biochemical parameters [1]. Moreover, it constitutes 15–20 % of patients hospitalized due to severe pneumonia or acute respiratory distress syndrome [2]. Respiratory insufficiency is responsible for 70 % of Coronavirus disease 2019 (COVID-19) related deaths [3].

A considerable percentage of individuals experiencing symptoms due to COVID-19 display mild to moderate respiratory tract involvement. Additionally, there are instances of asymptomatic cases. Nevertheless, comprehensive information regarding the clinical severity spectrum and its subcategories, encompassing epidemiological attributes, viral load dynamics, and the immune responses of patients, remains inadequately documented and understood.

Cytokines and their corresponding receptors play a substantial role in the development and progression of viral

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infections. They are a stimulant for neutrophils, CD4+, and CD8+ T cells. Chemokines constitute a diverse group of cytokines distinguished by their potent chemotactic effects. They play a crucial role in orchestrating the movement of immune cells in response to viral or microbial infections. In the context of coronavirus infections, activation of monocytes, macrophages, and dendritic cells occurs, accompanied by the release of proinflammatory cytokines like TNF-α, IL-1, IL-2, IL-6, and IL-18. These cytokines can induce damage to endothelial cells, disrupt tissue perfusion through increased vascular permeability, and contribute to the formation of microthrombi.

The virus enters the cell by targeting type-1 alveolar epithelial cells via angiotensin converting enzyme-2, the host receptor, and replicates rapidly. Virus-laden pneumocytes then initiate the inflammatory process by releasing interleukins (IL-1, IL-6, IL-8, and IL-12) and several different cytokines. It constitutes a chemoattractant for CD4+ and CD8+ T cells, cytokines, and neutrophils. These virus-fighting cells also cause inflammation and lung damage [4]. This 'cytokine storm' can cause viral sepsis, leading to other complications such as pneumonia, acute respiratory distress syndrome, respiratory failure, shock and death [5].

Chemokines are a superfamily of pro-inflammatory polypeptides with low molecular weight involved in immune system cell migration and that are expressed both inducibly and constitutively by various cell types as a reaction to viral infections. They attract leukocytes to the site of infection and are involved in the inflammatory response. One chemokine, C-X-C chemokine ligand type 12 (CXCL12), exhibits several effects on cells, including survival, growth, division, and migration, by interacting with the C-X-C chemokine receptor type 4 (CXCR4) [6, 7].

Chemokine receptors consist of a group of G-protein-coupled receptors with seven transmembrane domains and are preferentially specific for chemokines [8]. Upon ligand binding to CXCR4, the GDP/GTP exchange reaction and G-protein cleavage pathway are initiated. Gαi and Gβγ lead to the activation of various intracellular signaling pathways that initiate chemotaxis, cell growth proliferation, and survival by means of increased intracellular calcium, cellular protein modification, and changes in transcription factor binding and gene expression levels [9]. In contrast to the majority of receptors for inflammatory chemokines, CXCR4's sole ligand is CXCL12. In addition, CXCR4 is expressed in various cell types, including many cell types in bone marrow, lung, and small intestine [10]. The binding of CXCL12, whose heightened levels exhibit a potent chemotactic effect and a notable positive correlation with the severity of COVID-19, to its receptor CXCR4 has several implications. This binding prompts the release of proinflammatory cytokines, including TNF-α, IL-1, IL-2, IL-6, and IL-18. Moreover, it triggers the activation and recruitment of immune cells, such as monocytes, macrophages, dendritic cells, and especially T cells, to the affected site.

Viruses are dependent on their host organisms for replication and propagation in their environment. The CXCR4-CXCL12 axis, commonly exploited by viruses, serves as a focal point for numerous pathogens that employ diverse tactics to manipulate or exploit CXCR4's activity. Although initially identified as a pivotal co-receptor for human immunodeficiency virus type 1 (HIV-1) entry into CD4+ T cells, many other viruses rely on CXCR4 for cellular entry. Moreover, various viruses have been found to modulate CXCR4 expression, directly impacting cell migration, proliferation, and survival [11].

The primary objective of this study was to assess serum concentrations of the important chemokine CXCL12 and its corresponding receptor CXCR4, a previously unexplored feature in hospitalized patients with varying degrees of clinical severity ranging from mild to moderate to severe symptoms. The aim is to shed light on host factors influencing the course of infection in individuals infected with SARS-CoV-2.

Materials and methods

Study description

Sixty-nine patients with COVID-19 diagnosed at the Erzurum Regional Training and Research Hospital between February and July 2021 were enrolled in the study. A control group of thirty-nine asymptomatic and completely healthy adult volunteers was also formed. The Atatürk University Medical Faculty Clinical Research Ethical Committee (B.30.2.ATA.0.01.00/158) has approved the study.

Individuals with cancer, high blood pressure, cardiovascular disease, diabetes mellitus, chronic renal and liver diseases, neurological diseases, using immunosuppressive drugs, and acute or chronic inflammatory diseases were excluded.

Diagnosis and participants

Group 1 consisted of individuals who tested positive for COVID-19 infection via reverse transcription polymerase chain reaction (RT-PCR) analysis using nasopharyngeal swab specimens. Within Group 1, participants were further stratified into two subgroups contingent upon the severity of their pneumonia manifestation: mild-moderate and severe.

Comprehensive clinical assessments were conducted for all members, encompassing thoracic computed tomography (CT) scans and pertinent laboratory analyses.

The subgroup categorized as "mild-moderate pneumonia" encompassed a cohort that presented clinical observations including somatic discomfort, elevated body temperature, non-productive cough accompanied by throat irritation, respiratory rate below 30 breaths per minute upon examination, and peripheral capillary oxygen saturation (SpO2) levels exceeding 90 % under ambient conditions. Additionally, this subgroup exhibited radiological or pulmonary X-ray evidence indicative of mild to moderate pneumonia.

The subset categorized as "severe pneumonia" comprised a cohort that manifested evident clinical indications, such as elevated body temperature, musculoskeletal discomfort, persistent cough accompanied by throat irritation, a respiratory rate equal to or surpassing 30 breaths per minute during the examination, SpO2 registering at or below 90 % in ambient air, and discernible radiographic, X-ray or tomographic evidence confirming the presence of extensive bilateral pneumonia.

Group 2 consisted of asymptomatic adult individuals displaying no discernible physiological anomalies upon comprehensive clinical evaluation. At the time of their enrollment in the study, all constituents of this cohort exhibited negative results for the SARS-CoV-2 virus via RT-PCR analysis.

Analyte analysis techniques

To collect serum samples, blood samples were initially drawn into serum separator tubes (Becton Dickinson (BD), CA, USA), and subsequently, these tubes were centrifuged at 4100 revolutions per minute (rpm) for 10 min. In contrast, to obtain whole blood samples, a tube containing K2 EDTA (BD, CA, USA) was used without undergoing centrifugation. Plasma samples were obtained by drawing blood into a tube containing K2 EDTA (BD, CA, USA), followed by centrifugation at 4,000 rpm for 10 min.

SDF-1/CXCL12 and CXCR4 levels were measured with a Human SDF-1/CXCL12 ELISA kit (Elabscience, Human SDF-1/CXCL12: Cat Log No: E-EL-H0052) and a Human CXCR4 ELISA kit (Elabscience, Human CXCR4: Cat Log No: E-EL-H5490), respectively, using the human serum and the ELISA method. In the manufacturer's instructions, the kit measurement ranges for CXCL12 and CXCR4 were 0.16–10 ng/mL and 78.13–5,000 pg/mL, respectively. Both inter- and intra-assay coefficients of variance given by the manufacturer are <10 % for both CXCL12 and CXCR4. While all of our high patient values were within the reading range, some of the low values of the healthy participants were below the reading range. Still, we were able to measure those values due to the sensitivity of the kit to measure low values.

Total white cell count (WBC) and neutrophil/lymphocyte ratio (NLR) were measured from a whole blood sample using the XN-1000 hematology analyzer (Sysmex, Kobe, Japan). Serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), creatinine, C-reactive protein (CRP), Troponin I and ferritin levels were measured using the Atellica immunoassay and clinical chemistry analyzer and test kits (Siemens Healthineers, Tarrytown, NY, USA). Plasma prothrombin time (PT) and fibrinogen levels were measured using the STA-R MAX coagulometers analyzer (Stago, Paris, France) and Neoptimal 10 assay kits for PT and Owren Koller liquid kits for fibrinogen. D-dimer levels were measured using the CS-2500 Coagulation System analyzer (Sysmex, Kobe, Japan). The ratio of arterial oxygen partial pressure to inspired oxygen fraction (PaO2/FiO2) was calculated using the ABL 800 Flex blood gas analyzer (Radiometer, Copenhagen, Denmark).

Since the controls in our study were selected from completely healthy individuals who met the exclusion criteria, routine laboratory tests were evaluated only in patients.

Statistical analysis

For the sample calculation carried out with the G Power 3.1.9.7 program (Franz Faul, Germany), the effect size d: 0.656 was calculated using the data from the study "Expression levels of CXCR4 and CXCL12 in patients with rheumatoid arthritis and its correlation with disease activity" by Liping Peng et al. In the calculation made with the determined effect size, 80 % power, and 5 % margin of error, it was determined that at least 114 samples should be studied in total, with 38 participants in each group. A total of 108 participants were included in the study: 29 in the mild-moderate group, 40 in the severe group, and 39 in the control group [12].

The collected data were subjected to statistical analysis using the SPSS version 20.0 software program (SPSS Inc., IL, USA) designed for Windows operating systems. Descriptive statistics for the data obtained are presented as numerical counts and corresponding percentages for categorical variables. Descriptive statistics for numerical variables included the standard deviation and mean value (mean ± SD). The normality of distribution was assessed using the

Kolmogorov–Smirnov test. Normally distributed study groups were compared using the statistical method of One-Way Analysis of Variance (ANOVA). Post hoc Tukey test was applied to determine the significance of the differences between the various groups. The distribution of gender between the different groups was evaluated using the chi-square test (χ^2) because the data did not fit a normal distribution. In the context of two-way group comparisons, a Student's *t*-test was used. In addition, correlations between variables were determined using Pearson correlation analysis. Receiver Operating Characteristic (ROC) curve methodology, which indicates predictive ability, was used to calculate specificity, sensitivity, the area under the curve (AUC), and corresponding cut-off values for serum CXCL12 and CXCR4. Significance was attributed to p-values less than 0.05.

Results

Mean ages were 65.9 ± 13.1 years among the COVID-19 patients (n=69) and 65 ± 11.9 in the control group (n=39) and were not significantly different (p<0.05). The COVID-19 patient group consisted of 44 men and 25 women. 18 (62 %) of the 29 patients with mild-moderate COVID-19 and 26 (65 %) of the 40 patients with severe COVID-19 were men. No gender difference was determined between the mild-moderate and severe COVID-19 groups (p<0.05).

Table 1 presents the laboratory values of the patients. In patients with severe COVID-19, lymphocyte count and PaO2/FiO2 values significantly decreased compared to those with mild-moderate COVID-19. Conversely, the NLR, LDH, GGT, PT, CRP, troponin I, D-dimer, ferritin, and fibrinogen values demonstrated significant elevation in the severe COVID-19 group.

CXCL12 and CXCR4 levels in the control and patient groups are shown in Table 2.

Upon stratifying the patients according to clinical severity, it was observed that CXCL12 and CXCR4 levels were notably elevated in individuals with severe disease in comparison to those in the mild-moderate group. Furthermore, patients with mild-moderate disease displayed significantly higher CXCL12 and CXCR4 levels than the control group. Notably, there were correlations between CXCL12 and CXCR4 levels, as illustrated in Figure 1.

The correlation between the laboratory tests employed for COVID-19 diagnosis and serum CXCL12 and CXCR4 levels was examined when both patient groups were considered together. This correlation is presented in Table 3. Notably, strong correlations were observed with tests indicative of inflammation. Furthermore, serum CXCL12 and CXCR4 levels exhibited a robust positive correlation.

In the differentiation of COVID-19 cases from healthy individuals, serum CXCL12 levels demonstrated a sensitivity

Table 1: A comparison of age and laboratory data in patients with mild-moderate and severe COVID-19 at the time of presentation.

	Mild-moderate disease (mean ± SD) (n=29)	Severe disease (mean ± SD) (n=40)	p-Values
Age, years	65.9 ± 14.7	65.9 ± 11.5	>0.05
WBC, 10^9/L	10.1 ± 1.8	14.2 ± 3.2	**<0.001**
Lymphocytes, 10^9/L	1 ± 0.17	0.73 ± 0.19	**<0.001**
Neutrophils, 10^9/L	7.3 ± 2	9.7 ± 2.3	**<0.001**
NLR	7.5 ± 2.6	14.6 ± 6.6	**<0.001**
AST, U/L	56.7 ± 22.8	54.8 ± 18.2	>0.05
ALT, U/L	78.2 ± 29.6	71.8 ± 36.7	>0.05
LDH, U/L	433.1 ± 80.8	633.9 ± 125.3	**<0.001**
GGT, U/L	101.4 ± 175.2	223.4 ± 77.8	**<0.001**
ALP, U/L	85.1 ± 27.2	91.3 ± 31.4	>0.05
Creatinine, mg/dL	0.9 ± 0.3	0.9 ± 0.4	>0.05
PT, s	13.1 ± 0.8	14.7 ± 2.5	<0.05
CRP, mg/L	59.7 ± 32.7	174 ± 75.8	**<0.001**
Troponin-I, ng/L	39.6 ± 20.5	53.1 ± 13.4	<0.05
PaO2/FiO2	273.4 ± 45.8	176.7 ± 14.5	**<0.001**
D-dimer, µg/L	12.7 ± 6.8	45.9 ± 18	**<0.001**
Ferritin, µg/L	5.9 ± 2.4	14.7 ± 1.7	**<0.001**
Fibrinogen, µg/L	3.7 ± 0.7	5.1 ± 0.8	**<0.001**

WBC, white cell count; NLR, neutrophil/lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; PT, prothrombin time; CRP, C-reactive protein; PaO_2/FiO_2, ratio of arterial oxygen partial pressure to the fractional inspired oxygen; SD, standard deviation. The p-values in bold are statistically significant at <0.05.

Table 2: Changes in serum CXCL12 and CXCR4 levels depending on the severity of the disease.

	COVID-19 clinical severity			p-Values
	Mild-moderate (mean ± SD) (n=29)	Severe (mean ± SD) (n=40)	Controls (mean ± SD) (n=39)	
CXCL-12, ng/mL	4.9 ± 2.4	6.4 ± 2.8	0.9 ± 0.8	<0.05[a] <0.001[b,c]
CXCR-4, pg/mL	110.3 ± 42.2	156.4 ± 81.2	71.9 ± 31.7	<0.05[d] <0.05[e] <0.001[f]

[a]p-Value for CXCL12 between mild-to-moderate and severe COVID-19, patients; [b]p-value for CXCL12 between mild-to-moderate COVID-19, patients and control group; [c]p-value for CXCL12 between the severe COVID-19, patients and the control group; [d]p-value for CXCR4 between mild-to-moderate and severe COVID-19, patients; [e]p-value for CXCR4 between mild-to-moderate COVID-19, patients and control group; [f]p-value for CXCR4 between the severe COVID-19, patients and the control group.

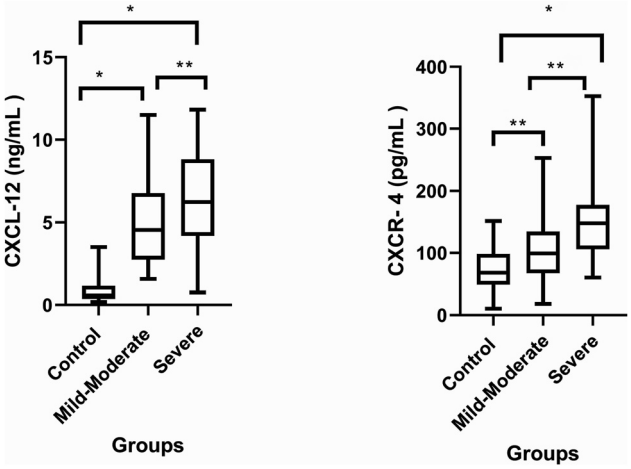

Figure 1: Box-plot chart showing serum CXCL12 and CXCR4 levels in the different COVID-19 disease severity groups (*p<0.001, **p<0.05).

Table 3: Correlation between serum CXCL12 and CXCR4 levels and laboratory tests.

	CXCL12, ng/mL		CXCR4, pg/mL	
	Correlation coefficient (r)	p-Values	Correlation coefficient (r)	p-Values
LDH, U/L	0.576	<0.001	0.675	<0.001
Troponin, ng/L	0.382	>0.05	0.345	<0.001
CRP, mg/L	0.894	<0.001	0.834	<0.001
Ferritin, µg/L	0.451	<0.001	0.380	<0.001
D-dimer, µg/L	0.382	<0.001	0.460	<0.001
Lymphocyte, 10^9/L	−0.752	<0.001	−0.820	<0.001
Neutrophil, 10^9/L	0.851	<0.001	0.730	<0.001

of 98 % and specificity of 84 % at a cut-off value of 1.44 ng/mL. The corresponding AUC was 0.98 (p<0.001, 95 % CI=0.95–1.0), as illustrated in Figure 2.

Serum CXCR4 levels, using a cut-off value of 69.7 pg/mL, exhibited an 88 % sensitivity and 72 % specificity in distinguishing COVID-19 cases from healthy individuals. The AUC for CXCR4 was 0.82 (p<0.001, 95 % CI=0.74–0.9), as depicted in Figure 2.

Discussion

Our study found that both CXCL12 and its receptor CXCR4 were found to be present at elevated levels within the COVID-19 patient group in comparison to the healthy control group. Additionally, these two markers exhibited a substantial degree of correlation with each other. It suggests that the CXCL12/CXCR4 axis may contribute to the phenomenon of cytokine storms that are the hallmark of severe COVID-19 cases. This research contributes to a better understanding of how CXCL12 and CXCR4 might be implicated in the immune response during SARS-CoV-2 infection, potentially playing a role in the clinical course and outcomes of individuals with the disease.

Many viruses have evolved to produce molecules that mimic chemokines, allowing them to interfere with the CXCR4/CXCL12 chemokine pathway. Indeed, CXCR4 is a chemokine receptor that serves as a co-receptor for HIV-1. This co-receptor, along with C-C chemokine receptor type 5,

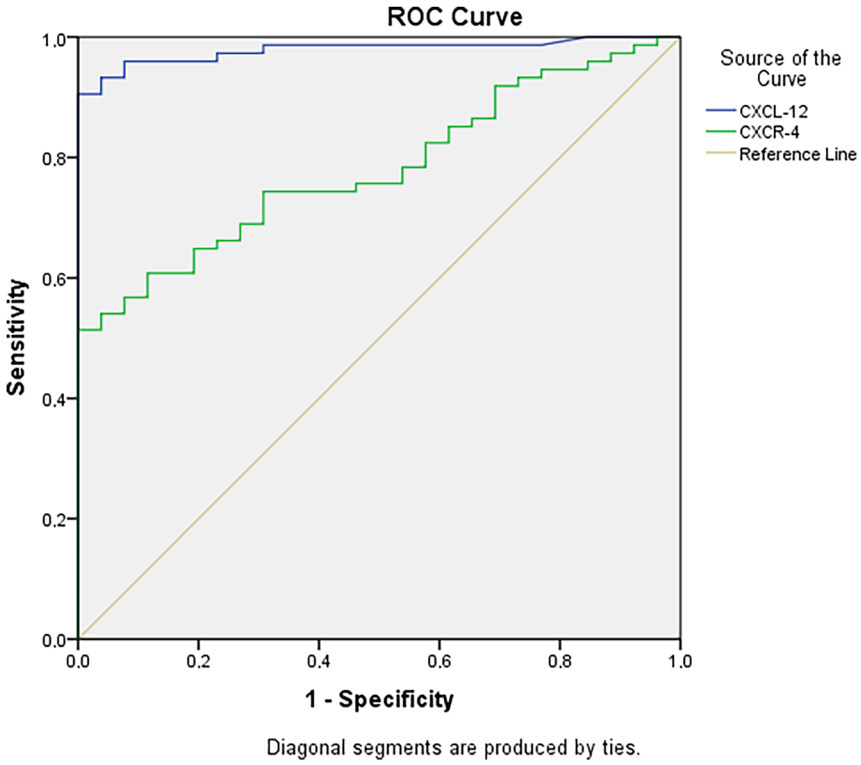

Figure 2: ROC curve analysis of the diagnostic sensitivity and specificity of serum CXCL12 and CXCR4 levels in COVİD-19 patients. ROC, receiver operating characteristic curve.

is vital for the entry of the HIV-1 virus into target cells. Blocking or inhibiting CXCR4 can be a potential strategy for the development of antiviral agents aimed at impeding HIV-1 entry and, in turn, mitigating the progression of HIV infection [13]. This interaction is crucial for the virus's ability to enter cells and replicate. Research has shown that 120 kDa glycoprotein (gp120)-induced CXCR4 binding can lead to the detachment of T cells in a concentration-dependent manner. This suggests that CXCR4's engagement with gp120 might contribute to HIV-1's evasion of the immune system [14]. Given that CXCR4 is targeted by a wide range of viral pathogens, the alteration of host CXCR4 signaling activity is recognized as a significant factor in the progression of viral infections [11].

Reports indicate that individuals with severe COVID-19 exhibit elevated levels of proinflammatory cytokines, including TNF-α, IL-1, and IL-6, in contrast to those with milder disease [15]. Thus, increased vascular permeability manifests clinically as acute respiratory failure, stemming from the accumulation of fluid in lung tissues and interstitial spaces [4]. The occurrence of mild to severe cytokine storms in severe cases underscores the significance of cytokine storm treatment as a critical component in rescuing patients with severe COVID-19.

In another study that compared a group of individuals with severe COVID-19 disease to a group with non-severe disease, significant distinctions were observed between these two groups concerning various parameters. These included WBC count, NLR, CRP, and D-dimer levels [16]. Similar to the present study, we found that WBC count, NLR, LDH, GGT, CRP, D-dimer, ferritin, and fibrinogen levels all showed an increase associated with clinical severity of the disease.

Specific chemokines have been identified to contribute to the cytokine storm triggered by coronavirus infections [17]. Notably, the C-X-C chemokine ligand type 10 (CXCL10) plays a pivotal role in the antiviral response, particularly within the context of airway infections. Research has demonstrated a correlation between CXCL10 levels and the severity and duration of acute airway infections caused by viral pathogens. This correlation has been assessed through various means, such as measuring CXCL10 levels in serum, bronchial-alveolar washes, or nasal secretions [18].

Furthermore, a study focused on biomarkers associated with COVID-19 infection revealed heightened levels of CXCL10 and specific proinflammatory cytokines in individuals exhibiting mild symptomatic manifestations compared to a control group. This highlights the intricate interplay between chemokines like CXCL10 and the immune response during COVID-19 infections [19].

In this study, a range of laboratory parameters, including the NLR, LDH, CRP, D-dimer, fibrinogen, and ferritin, which have been extensively explored in prior research on COVID-19 and linked to higher morbidity and mortality rates, were observed to be elevated in the group of patients with severe disease in contrast to those with mild-moderate disease. Given these findings in the context of existing studies, we deduced that these specific parameters might indeed be correlated with the severity of the disease. This further underscores their potential as valuable indicators for assessing the progression and clinical outlook of COVID-19 cases.

Furthermore, the observation of reduced PaO2/FiO2 values in individuals with severe disease compared to those with mild-moderate manifestations signifies heightened oxygen impairment and potentially more pronounced cytokine release. The robust correlation observed between serum levels of CXCL12, CXCR4, and CRP, an inflammatory marker and a standard diagnostic test for COVID-19, aligns with prior research in the field. These findings collectively point to the complex interaction between chemokine responses, inflammation, and disease severity in COVID-19.

Recent research has uncovered the presence of CXCL12 in the lungs and circulation of individuals afflicted with COVID-19. However, an additional study sought to investigate whether the identified CXCL12 is bioactive, examining its susceptibility to inactivation through NH2- and COOH-terminal post-translational proteolysis. The study revealed that CXCL12 was subject to rapid processing and degradation by proteolysis in patient samples. Consequently, it was suggested that the use of protease inhibitors could extend the half-life and functionality of CXCL12. In light of the elevated levels of CXCL12 and CXCR4 detected in serum in our study, further research is warranted to ascertain their biological activity [20].

Recognizing the pivotal involvement of chemokines in the pathogenesis of COVID-19 symptoms, a study was undertaken to elucidate the immunological mechanisms contributing to the severity and mortality of COVID-19 by examining gene polymorphisms of specific chemokines, including CXCL12 and CXCR4. However, the investigation did not reveal any significant association between the severity of COVID-19 and polymorphisms of CXCL12 and CXCR4 [21]. In contrast, our own study has demonstrated a positive correlation between elevated serum levels of these molecules and disease severity, independent of genetic polymorphism.

In a distinct research study, it was documented that the entry of HIV-1 into target cells involves interactions not only with CXCR4 but also with CD26/DPPIV and its associated receptor agonist, CXCL12. This investigation has revealed that CD26/DPPIV plays a pivotal role in the degradation of

CXCL12, resulting in the localized reduction of CXCL12 concentration, which, in turn, safeguards host cells against viral infection. Concurrently, it was noted that a gp120 on the surface of HIV-1 viruses disrupts the interaction between CD26 and its substrate, the enzyme adenosine deaminase. This disruption leads to an increase in CXCL12 concentration, thereby compromising the protection of host cells against the virus [22, 23].

The hypothesis posited draws parallels between the mechanisms involved in HIV-1 and SARS-CoV-2 infections and provides a plausible rationale for the observed elevation in serum levels of the molecules scrutinized in our study. Importantly, this elevation is directly proportional to the severity of COVID-19.

Some limitations are present in this study. Our sample size is small to confirm the role of CXCL12/CXCR4 in identifying COVID-19 patients; it would be possible to overcome this limitation by working with larger groups. Another limitation of this study was that reference range values were used for routine laboratory tests of the control group.

To summarize, it is evident that anti-inflammatory therapies have demonstrated beneficial outcomes and improved survival rates for COVID-19. Considering these findings, CXCR4 might hold potential as a therapeutic target for certain viral diseases. Targeting CXCR4 could potentially interfere with the viral strategies that hijack the CXCR4/CXCL12 pathway for their benefit, which could have implications for the development of antiviral treatments. Furthermore, the identification of elevated levels of CXCL12 and CXCR4 in the initial stages of the disease might facilitate a more objective forecast of disease severity. Such insights could guide proactive and precise therapeutic strategies, ultimately contributing to better management and improved outcomes in individuals with COVID-19.

Research ethics: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (B.30.2.ATA.0.01.00/158).

Informed consent: Informed consent was obtained from all individuals included in this study or their legal guardians or conservators.

Author contributions: The authors accept responsibility for the entire content of this article and have approved its submission.

Competing interests: The authors declare that there is no conflict of interest.

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Data availability: Not applicable.

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