

## Coronavirus Pandemic

# Identification of CXCL9 chemokine as a potential biomarker for assessing clinical severity in COVID-19 patients

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### Abstract

**Introduction:** The severity and clinical outcome of COVID-19 depend on virus-specific factors and the host's inflammatory response. Identifying biomarkers of severe COVID-19 is a crucial condition and predicts disease severity.

**Methodology:** This study enrolled a total of 167 patients with COVID-19. These patients were categorized into three groups based on the severity of the disease: moderate course - 78 individuals, severe course - 52 individuals, and extremely severe course - 37 individuals. We analyzed chemokines (IP-10, CXCL9, CCL17) and cytokine IL28B levels using the enzyme immunoassay (EIA) method.

**Results:** CXCL9 levels were increased in severe and extremely severe cases compared to moderate ones. The CCL17 chemokine demonstrated significant elevation in severe cases. However, there was no significant difference in the level of IP-10, and IL28B in the compared groups.

**Conclusions:** Our findings suggest that CXCL9 and CCL17 chemokines could be used as biomarkers to assess the clinical status of patients with COVID-19 and can relate to disease severity. These biomarkers could aid in identifying patients at high risk for severe disease and help guide clinical decision-making for the effective management of COVID-19.

**Key words:** COVID-19; IP-10; CXCL9; CCL17; IL28B.

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### Introduction

The emergence of the disease caused by the novel coronavirus SARS-CoV-2 in late December 2019 has already entered into history as a global pandemic of the 21st century. Globally, as of 2 August 2023, there have been 768,983,095 confirmed cases of COVID-19, including 6,953,743 related deaths, reported to WHO [1]. Currently, COVID-19 does not have a high mortality rate due to large-scale vaccination programs in the population. However, despite an active worldwide vaccination campaign against COVID-19 to prevent the spread of the infection, cases of severe disease and death persist among vulnerable populations, especially among unvaccinated individuals. The emergence of new variants and mutations of SARS-CoV-2 that reduce the efficacy of existing COVID-19 vaccines may lead to the re-infection of vaccinated individuals and convalescents. The newly emerged SARS-CoV-2 variants like Omicron lead to vaccine breakthroughs in individuals who have been vaccinated against COVID-19 or have previously recovered from the disease. The severity of

COVID-19 can vary from mild to critical depending on the extent of clinical symptoms [2]. Several risk factors associated with poor clinical outcomes of COVID-19 include male gender, advanced age (> 75 years), and comorbidities such as lung disease, cardiovascular disease, diabetes mellitus, obesity [3-5] and cancer (either solid and hematological) [6,7].

The clinical course of the disease and prognosis are associated with a systemic inflammatory response called cytokine release syndrome (CRS), characterized by increased levels of proinflammatory cytokines [8]. Presently, researchers are increasingly interested in studying various chemokines and cytokines such as Chemokine (C-X-C motif) ligand 9/Monokine induced by gamma interferon (CXCL9/MIG), C-X-C motif chemokine ligand 10/Interferon gamma-induced protein 10 (CXCL10/IP-10), Thymus and activation regulated chemokine/C-C motif chemokine ligand 17 (TARC/CCL17), Interferon-gamma (IFN- $\gamma$ ) to investigate their potential link to COVID-19 clinical progression [9-13] suggesting that these biomarkers can correlate with disease severity.

Monitoring patients with COVID-19, identifying key indicators of clinical status, and studying sensitive indicators reflecting disease severity are relevant tasks for early assessment of disease progression and selection of appropriate treatment strategies. Identifying biomarkers indicating the severity of COVID-19 remains an urgent challenge and, in this regard, this study aimed to investigate certain chemokines and cytokine and their association with the severity of COVID-19.

## Methodology

### *Study group*

Our study was conducted among COVID-19 patients who were admitted to the Research Institute of Virology in Tashkent, Uzbekistan, between June 09 and August 22, 2021. Throughout the survey period, the dominating variant in the local region was the Delta variant (clade 21A) of the SARS-CoV-2. During this period, 1660 patients with confirmed COVID-19 were hospitalized. The confirmation of COVID-19 was based on the detection of SARS-CoV-2 RNA in nasopharyngeal swabs by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) using ROSSAmed COVID-19 RT-PCR kit (ROSSA, Uzbekistan) during their hospitalization. The study used systematic random sampling to select participants regardless of their gender or COVID-19 severity. Every tenth patient out of 1660 patients was selected. As a result, a total of 167 patients were included in the study, with varying degrees of COVID-19 severity. The study group consisted of 65 (38.9%) men and 102 (61.1%) women, with 78 (46.7%) patients having a moderate course of the disease, 52 (31.1%) a severe course, and 37 (22.2%) an extremely severe course. Patients were divided into moderate, severe, and critical groups according to the “Interim recommendations for the treatment of patients with COVID-19 coronavirus infection” of the Ministry of the Health of Uzbekistan (Version 8, 2021).

### *Disease severity stratification*

1. Moderate course: difficulty in breathing and shortness of breath during normal (domestic) exertion, unproductive cough, chest pain, symptoms of intoxication (fever or chills, headache, fatigue, cough, nausea or vomiting, etc.),  $t > 38.5^{\circ}\text{C}$  more than 4–5 days, respiratory rate  $\geq 22$  breaths per minute, heart rate 91–100 beats per minute, oxygen saturation  $\text{SpO}_2 \leq 93\%$ .

2. Severe course: unproductive cough, difficulty breathing and shortness with little exertion or at rest,

symptoms of intoxication (fever or chills, headache, fatigue, cough, nausea or vomiting, etc.), decreased level of consciousness and agitation, fever (often febrile), respiratory rate  $\geq 24$  breaths per minute, heart rate  $< 120$  beats per minute, arrhythmia, oxygen saturation  $\text{SpO}_2 \leq 92\%$ .

3. Extremely severe course: acute respiratory distress syndrome, acute respiratory failure with the need for respiratory support (invasive ventilation), septic shock, multiple organ failure, persistent fever, respiratory rate  $\geq 30$  breaths per minute, heart rate  $> 120$  beats per minute, arrhythmia, oxygen saturation  $\text{SpO}_2 \leq 80\%$ .

During hospitalization on the ward, as part of routine practice, the patient’s oxygen saturation ( $\text{SpO}_2$ ) was measured using a pulse oximeter. To assess the severity of the disease,  $\text{SpO}_2$  measurement was conducted without administering oxygen support. Among the hospitalized 78 patients with moderate COVID-19, only 2 (2.6%) individuals had received COVID-19 vaccines. However, none of the patients categorized as severe or extremely severe had been vaccinated against COVID-19.

### *Sample collection and laboratory procedures*

Blood plasma samples from patients with COVID-19 were obtained from patients during the first three days of hospitalization. The levels of IP-10, CXCL9, CCL17 chemokines, and IL28B were measured by EIA using Human Interferon-Inducible Protein 10 (IP-10) kit, Human monocyte interferon-gamma-inducing factor (MIG) kit, Human thymus activation-regulated chemokine (TARC) kit, and Human Interleukin 28B (IL28B) kit manufactured by Cusabio (China), respectively, according to the manufacturer’s instructions.

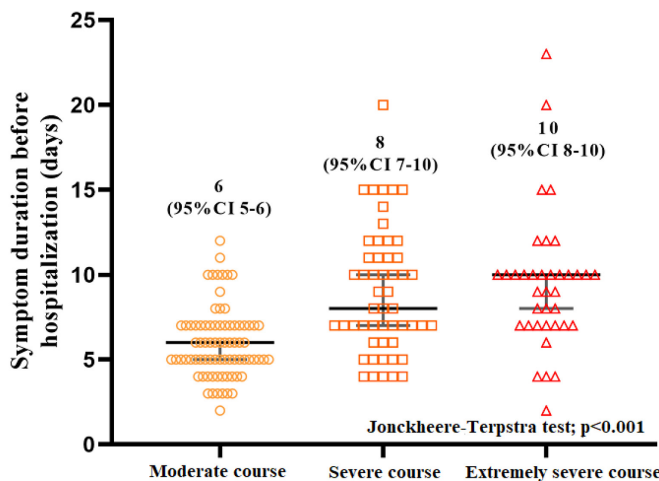
### *Ethics statement*

All studies were carried out following the relevant recommendations and regulations and conducted according to the guidelines of the Declaration of Helsinki. Ethical approval statements for the study were approved by the Ethical Committee of the Ministry of Health of the Republic of Uzbekistan under protocol number 6/13-1456/30/10/2020. Informed consent was obtained from all patients.

### *Statistical analysis*

In our study, we conducted data analysis using descriptive statistics to summarize categorical and numeric variables. Frequencies and relative frequencies for categorical variables and mean with standard

**Figure 1.** The duration of the symptomatic period prior to hospital admission.

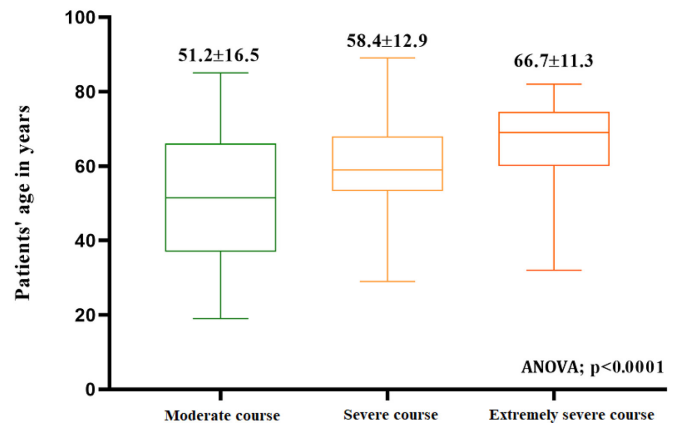


deviation (SD) for normally distributed numeric variables. For non-normally distributed numeric variables, we used a median with a 95% confidence interval. We categorized the COVID-19 patients into three groups: moderate, severe, and extremely severe. To compare these severity groups, we used either a one-way ANOVA or Kruskal-Wallis’s test for numeric variables and Chi-squared tests for categorical variables. We considered a *p* value less than 0.05 as statistically significant. For our data analysis, we utilized IBM SPSS statistics version 26 software. Diagrams were created using GraphPad Prism version 8.0.1 software.

**Results**

This study enrolled a total of 167 patients diagnosed with COVID-19, comprising 65 (38.9%) male and 102 (61.1%) female individuals. The mean age of the patients was 56.8 years. The study found no statistically

**Figure 2.** Age characteristics of patients depending on the severity of the disease.



significant difference in disease severity based on the gender of the patients (*p* > 0.05). Similarly, there were no significant variations in age or comorbidities between the male and female patients. The findings indicate that delayed hospitalization may have an impact on the severity of the disease (Figure 1). Moreover, the analysis of variance demonstrated that patients with severe and extremely severe disease courses were notably older compared to those with a moderate course of the disease (Figure 2). The oxygen saturation (SpO<sub>2</sub>) levels among the patients were categorized as follows: SpO<sub>2</sub> ≤ 96% in the moderate group, SpO<sub>2</sub> ≤ 86% in the severe group, and SpO<sub>2</sub> ≤ 81% in the extremely severe group. The application of Dunn's multiple comparison test with adjusted *p* values demonstrated a significant difference in SpO<sub>2</sub> levels between the moderate group and both the severe and extremely severe groups (*p* < 0.001). However, no statistically significant differences were observed in SpO<sub>2</sub> levels between the severe and extremely severe groups.

**Table 1.** Data on comorbidities and complications in patients with COVID-19.

Characteristic	Moderate course (n = 78)	Severe course (n = 52)	Extremely severe course (n = 37)	<i>p</i> value
Age, mean ± SD	51.2 ± 16.5	58.4 ± 12.9	66.7 ± 11.3	< 0.0001
Male, n (%)	27 (34.6%)	19 (36.5%)	19 (51.4%)	> 0.05
Female, n (%)	51 (65.4%)	33 (63.5%)	18 (48.6%)	> 0.05
<b>Comorbidities</b>				
Hypertension, n (%)	48 (61.5%)	41 (78.8%)	32 (86.5%)	< 0.01
Ischemic heart disease, n (%)	15 (19.2%)	30 (57.7%)	28 (75.7%)	< 0.01
Diabetes mellitus, n (%)	12 (15.4%)	19 (36.5%)	15 (40.5%)	< 0.01
Obesity, n (%)	4 (5.1%)	7 (13.5%)	5 (13.5%)	> 0.05
Diseases of the pulmonary system, n (%)	16 (20.5%)	5 (9.6%)	2 (5.4%)	> 0.05
<b>Complications</b>				
Pneumonia, n (%)	72 (92.3%)	52 (100%)	37 (100%)	< 0.05
Chronic heart failure, n (%)	7 (9.0%)	18 (34.6%)	31 (83.8%)	< 0.01
Acute respiratory failure, n (%)	3 (3.8%)	23 (44.2%)	33 (89.2%)	< 0.01
Acute respiratory distress syndrome, n (%)	0	8 (15.4%)	26 (70.3%)	< 0.01
Encephalopathy, n (%)	0	5 (9.6%)	13 (35.1%)	< 0.01

The frequency of comorbidities was also assessed throughout the study. It was found that the prevalence of hypertension, ischemic heart disease, and diabetes mellitus significantly increased with disease severity, with hypertension being most prevalent in extremely severe patients (86.5%), ischemic heart disease in extremely severe patients (75.7%) and severe patients (57.7%), and diabetes mellitus in extremely severe patients (40.5%) and severe patients (36.5%) compared to moderate patients ( $p < 0.01$  for all). In patients with extremely severe COVID-19, complications such as pneumonia (100%), chronic heart failure (83.8%), acute respiratory failure (89.2%), acute respiratory distress syndrome (70.3%), and encephalopathy (35.1%) were observed much more frequently compared to those with severe and moderate disease courses (Table 1).

*Chemokines and cytokine levels in patients*

Based on the study's findings, there was a consistent increase in the expression of CXCL9 with the severity of the disease ( $p < 0.01$ ). The expression levels of CCL17 were found higher in patients with severe COVID-19 ( $p < 0.05$ ) compared to those with moderate severity. IP-10 and IL-28B expression levels were almost same in all severity groups. The study's findings regarding the levels of chemokines (IP-10, CXCL9, CCL17) and cytokine IL-28B are illustrated in Figure 3.

**Discussion**

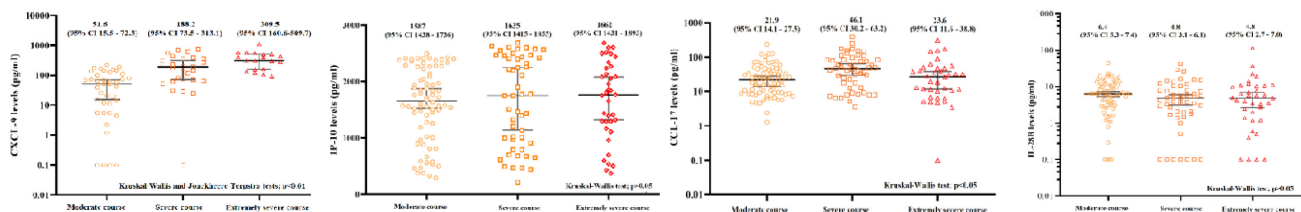
COVID-19 has a wide spectrum of clinical manifestations, ranging from a mild course of the disease to the progression of severe pneumonia leading to multi-organ failure and death. COVID-19 in people with comorbidities has an increasingly rapid and severe progression, often leading to death. Especially elderly patients aged 65 and over with comorbidities have an increased admission rate into the intensive care unit (ICU) and mortality from COVID-19 [14,15]. Male gender has an increased risk for infectivity with SARS-CoV-2 and intensive care unit admission and worse overall outcomes compared with females [16]. In our study, there was no statistically significant association

of disease frequency between males and females ( $p > 0.05$ ). Severe and extremely severe COVID-19 were significantly associated with late hospitalization (8 and 10 days of illness, respectively), older age (58.4 and 66.7 years, respectively), and the presence of comorbidities such as hypertension, ischemic heart disease, diabetes mellitus, and complications (pneumonia, chronic heart failure, acute respiratory failure, acute respiratory distress syndrome, and encephalopathy) which were also more common with increasing severity of the disease. In addition to the above-mentioned confounders that influenced the infection with SARS-CoV-2 and the severity of the disease, it was noted that all severe, extremely severe and 97.4% moderate patients were not vaccinated against COVID-19, which is important for susceptibility to infection.

COVID-19 is known to induce a cytokine storm [17]. Increased cytokine levels can play a vital role in the immunopathogenesis of the infection and are associated with the disease severity and outcome [18-20]. Studies suggest that high levels of cytokines and chemokines may cause cell and tissue damage, also triggering a more potent inflammatory cascade, which can be destructive in viral infections, including COVID-19 [21,22]. This can be considered a «sepsis-like presentation» and could be associated with disease severity and outcomes.

Circulating CXCL10 levels were positively correlated with COVID-19 severity, as evidenced by measurements at various time points during the disease course [23]. These findings suggest that CXCL9/MIG and CXCL10/IP-10 may be important indicators of COVID-19 severity and highlight their potential as biomarkers for disease monitoring and predicting disease progression. Nevertheless, there have been reports of an increase in the level of pro-inflammatory cytokines and chemokines not only in severe and extremely severe cases, but also in the moderate course, at an early stage of the disease, and in the recovery phase. For instance, Chi *et al.* found increased levels of cytokines and chemokines including Interferon gamma-induced protein 10 (IP-10), Monokine induced by

**Figure 3.** Change in the level of chemokines and cytokine depending on the severity of the course of COVID-19.



gamma interferon (MIG) in both symptomatic and asymptomatic individuals with COVID-19, which normalized after recovery. However, higher levels of these biomarkers were associated with disease severity and were more pronounced in male patients [9]. Wang *et al.* [24] reported that IP-10 was augmented markedly in the serum of patients at an early stage of the disease but remained at a high level during the convalescent stage in severe and moderate patients. Increased levels of CXCL9/MIG and CXCL10/IP-10 were observed in the blood plasma of patients with COVID-19 during the acute phase of the disease, but there was no difference in CXCL10/IP-10 concentration depending on the severity of the disease, as reported by Arsentieva *et al.* [25].

In our study, the levels of CXCL9/MIG were significantly higher in severe and extremely severely ill COVID-19 patients, implying an association between this chemokine and disease progression. Our findings align with the results of Arsentieva *et al.* [25] where there was no disparity in the concentration of CXCL10/IP-10 depending on the disease severity. We observed a non-significant increase in the level of pro-inflammatory chemokine CXCL10/IP-10 in all three groups of patients (moderate, severe, and extremely severe) and it could be attributed to the presence of pneumonia in 92.3%, 100%, and 100% of cases respectively in the compared groups (Table 1).

According to Sugiyama *et al.* [26], patients with severe/critical COVID-19 exhibit lower levels of CCL17 than those with mild/moderate disease. The strong statistical association between CCL17 and the development of COVID-19-associated pneumonia suggests that this chemokine may serve as a primary marker for the disease [26]. Plenty of conflicting results have been reported in several studies, where a minor increase in the level of CCL17 was observed in severe COVID-19 cases. The level of CCL17 was slightly higher in patients with severe disease than in those with moderate disease, but the difference was not statistically significant [27]. Similarly, Tufa *et al.* found that the levels of this chemokine did not significantly differ ( $p = 0.3889$ ) between patients with severe and moderate disease, with values of 71.94 ng/L and 68.64 ng/L, respectively [28]. Upon hospital admission, the expression profile of IL-33, IP-10, and CCL17 showed no significant increase in levels between moderate and severe COVID-19 patients and, they are not suitable as predictors of disease severity and progression, as suggested by Moustafa *et al.* [29]. In contrast, Suzuki *et al.* [30] reported that the performance of CCL17 in predicting high-flow nasal cannula (HFNC) oxygen

therapy or higher severity was poor. Considering that the results were opposite on days 0-4 (388.7 pg/mL) and 5-7 (47.7 pg/mL), CCL17 may fluctuate dynamically in the early phase of COVID-19. Nevertheless, the authors consider that CCL17 may be a helpful marker if the timing of sample collection is optimized. Our study findings revealed a significant increase in CCL17/TARC levels in severe cases compared to moderate and extremely severe cases.

The clinical outcome of patients with COVID-19 is associated with IFN responses, which are modulated by both viral and host factors. IFN- $\lambda$ 3 levels were found to be significantly higher in the severe group than in the mild group, indicating that IFN- $\lambda$ 3 may be a biomarker for predicting the severity of COVID-19 pneumonia [31], while some studies have shown a decrease in serum IFN- $\lambda$  expression in patients with severe COVID-19 compared with patients with mild COVID-19 [32]. The results of the study align with those of other authors, demonstrating an insignificant decrease in IL28B in severe and extremely severe cases compared to moderate ones. Therefore, the severe course of COVID-19 is associated with the compromised functioning of the innate immune system and the activation of interferon-stimulated genes.

The application of prognostic biomarkers in patient monitoring may be useful for early detection of disease severity and may help in the proper stratification of COVID-19 patients, ultimately leading to earlier intervention and desired clinical outcomes.

## Limitations

There are several limitations to the study that need to be acknowledged. Firstly, the study was conducted at a single medical center, which may limit the generalization of the findings to other populations. Secondly, the sample size was relatively small, which may limit the statistical power of the study to detect small but clinically significant differences in the levels of chemokines and cytokines between the groups. Thirdly, there was an unequal distribution of sex among the study participants, which could potentially affect the results and limit the findings. Fourthly, there was a lack of P/F ratios for the definition of COVID-19 severity and patients' description. Lastly, the study was cross-sectional in design, which means that causality cannot be inferred. These limitations should be taken into account when interpreting the results of the study and when planning future research in this area.

## Conclusions

Our research revealed that severe and extremely severe COVID-19 and its associated complications such as pneumonia, chronic heart failure, acute respiratory failure, acute respiratory distress syndrome, and encephalopathy have been associated with late hospitalization, older age, decreased SpO<sub>2</sub> levels, and comorbidities like hypertension, coronary heart disease, and diabetes mellitus. Notably, CXCL9 levels were significantly elevated in severe and extremely severe cases compared to moderate ones, while CCL17 chemokine demonstrated significant elevation in severe cases. As a result, the chemokines CXCL9 and CCL17 hold potential as biomarkers for assessing the clinical status of COVID-19 patients and could serve as indicators of disease severity. These biomarkers along with other clinical data may prove useful in stratifying and managing patients, optimizing the allocation of healthcare resources, and mitigating the occurrence of severe COVID-19 complications. Furthermore, ongoing research on biomarkers for predicting COVID-19 severity will undoubtedly contribute to enhancing patient care and preventing adverse outcomes related to the disease.

## Authors' contributions

NI conceived the study and conceptualization, developed the study design, interpreted the results, and wrote the manuscript. AKh was responsible for data analysis. UM conducted the statistical analysis, interpreted the data, and revised the draft paper. NK conducted EIA. MB was responsible for the critical revision of the manuscript. EM was supervisor of the study, and was responsible for critical revision of the manuscript.

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