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Evaluation of CXCL 10 and IL-10 in COVID-19 pneumonia

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Abstract

English:

Background: *Dysregulation the immune system is characteristic of the severe stages of COVID-19 disease; therefore, the study aimed to highlight the defective immune regulation patients with COVID-19 pneumonia without chronic diseases.*
Methods: *The study included 180 individuals, 60 as a control group, and 120 patients with COVID-19, including 67 males and 53 females, whose ages ranged from 27 to 70 years, at Imam Al-Hussein Teaching Hospital in Thi-Qar Province, South of Iraq. The CXCL 10 and IL-10 were evaluated by enzyme-linked immunosorbent assay (ELISA).*
Results: *The current study recorded that CXCL 10 was significantly increased < 0.001 in patients compared to controls, while the IL-10 was decreased significantly in patients, within disease severity the CXCL 10 increased with progress of disease, and IL-10 increased in sever patients, according to BMI the CXCL 10 decrease in obese patients than over and normal weight, while IL-10 increased in normal weight patients.*
Conclusion: *This study investigated the CXCL 10 was highly elevated in COVID-19 patients than control group, also noted the CXCL 10 increased with disease progress, therefor consider a good marker for poor outcome, furthermore the obese patients are more likely to have severe outcomes than others, so BMI is considered a risk factor for patients.*

Keywords

CXCL 10 • IL-10 • COVID-19 • Severity of Disease • Cytokine Storm

Evaluarea CXCL 10 și IL-10 în pneumonia COVID-19

Rezumat

Romanian:

Context: *Dereglarea sistemului imunitar este caracteristică stadiilor severe ale bolii COVID-19; prin urmare, studiul și-a propus să evidențieze pacienții cu reglare imunitară defectuoasă cu pneumonie COVID-19 fără boli cronice.*
Metode: *Studiul a inclus 180 de indivizi, 60 ca grup de control și 120 de pacienți cu COVID-19, respectiv 67 de bărbați și 53 de femei, ale căror vârste variau între 27 și 70 de ani, la Spitalul didactic Imam Al-Hussein din provincia Thi-Qar., la sud de Irak. CXCL 10 și IL-10 au fost evaluate prin test imunosorbent legat de enzime (ELISA).*
Rezultate: *Studiul actual a înregistrat cresterea semnificativa a CXCL 10 < 0,001 la pacienți în comparație cu martori, în timp ce IL-10 a fost scăzut semnificativ la pacienti. In severitatea bolii, în severitatea bolii, CXCL 10 a crescut odată cu progresia bolii, iar IL-10 a crescut IL-10 a crescut la pacientii severi. Conform IMC, CXCL 10 scade la pacienții obezi decât peste și greutatea normală, în timp ce IL-10 a crescut la pacienții cu greutate normală.*
Concluzie: *Acest studiu a investigat CXCL 10 a fost foarte crescut la pacienții cu COVID-19 comparativ cu grupul de contro de control, si a remarcat, de asemenea, că CXCL 10 care a fost foarte crescut odată cu progresul bolii, de aceea poate fi luat in considerare ca un marker bun pentru evolutia nefavorabila, In plus, pacienții obezi sunt mai susceptibili de a avea evolutii severe. comparativ cu altii, astfel încât IMC este considerat un factor de risc pentru pacienți.*

Cuvinte-cheie

CXCL 10 • IL-10 • COVID-19 • severitatea bolii • furtuna de citokine

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Introduction

COVID-19 pneumonia is distinct from pneumonia of other origins due to the sudden deterioration 7-9 days after the commencement of symptoms, the severity of hypoxemia that contrasts with the relatively well-preserved lung mechanics, and the prolonged nature of acute respiratory distress syndrome [1]. ARDS. Several studies have shown that COVID-19 have elevated levels of circulating proinflammatory cytokines [2, 3]. During the rapid progression of COVID-19, a cytokine storm can occur, modifying the immune system by lowering lymphocyte and T-cell counts [4]. Immune dysregulation is a characteristic of the more severe stages of SARS-CoV-2 infection; therefore, understanding the processes by which the immune system contributes to the severity of COVID-19 may lead to the development of new treatment options. Cytokine release syndrome (CRS), also called a cytokine storm, is a life-threatening systemic inflammatory syndrome. It is marked by high amounts of cytokines in the blood, especially IL-1, IL-1, IL-6, TNF-, IL-17, and Chemokines like CXCL 8 and CXCL 10, as well as overactive immune cells. Different pathogens, autoimmune diseases, cancers and T-cell-based treatments can cause it [5], in COVID-19 the inflammatory mediators are not as highly expressed as in some of these other diseases. The most important indicator of severe disease and poor outcome in COVID-19 is an immune response that is disordered and not markedly enhanced [6]. Inflammatory cells are attracted to the site of inflammation by chemoattractant cytokines called chemokines, which travel from the intravascular space via the endothelium and epithelium [7]. Covid-19's role in the dysregulation of chemokines is not well established. Some proinflammatory chemokines, including CXCL10, CXCL8, and CCL2, have been found in the plasma of Covid-19 patients at significantly greater concentrations than in the plasma of healthy controls. individuals requiring critical care unit admission had substantially greater circulation concentrations of CXCL10 and CCL2 compared to individuals with a milder clinical history [8, 9]. Transcriptome sequencing of bronchoalveolar lavage fluid (BALF) revealed that neutrophils, monocytes, and T lymphocytes were recruited to the lungs due to an abundance of these two chemokines [10]. Pulmonary inflammation and involvement in SARS patients were associated with elevated circulating levels of CXCL10 and CCL2 [9, 11]. When compared to type 1 response, type II immunity is anti-inflammatory and repairs tissue, which is a stark difference. In the case of an illness, both type 1 and type 17 reactions work to stop the infection. However, they often have dangerous side effects because antibiotic agents like reactive oxygen and nitrogen species damage tissue [12]. Interleukin 10 is an important antipyretic and immunosuppressant. It acts as a neutrophil inhibitor and a macrophage deactivation agent. In fact, several pathogens decrease host immune responses by inducing IL-10 production or encoding their own IL-10 homologs [13].

Materials and Methods

Ethical Approval

The thesis project has been approved according to the decision of the Research Committee in the Thi-Qar Health Directorate (issue No. 208/2022 on 15/8/2022) and facilitation task issued by the Thi-Qar Health Directorate, Department of Training and Development (issue No. 617 on 17/8/2022), which are attached to the document of University of Thi-Qar /College of Science (issue No. 3/11/982 on 17/7/2022), where the patient's consent is taken verbally when reviewing hospitals designated for Covid-19.

Sample Collection

A total of 180 blood samples were collected for this investigation, arterial blood samples were taken from COVID-19 patients while control group venous samples were drawn as follows. About five ml were collected from each sample and placed in a gel tube and left at room temperature for about 30 minutes. The gel tubes containing samples were centrifuge at 4000 RPM for 5 minutes and the serum sample was divided into three replicates in Eppendorf tubes, each part contains approximately 500 µl and stored in a deep freeze at -20 C°. The serum samples were used for evaluation CXCL 10 and IL-10 by Enzyme-Linked-Immuno-Sorbent-Assay Technique (ELISA).

Inclusion and Exclusion Criteria

The current study included patients with Covid-19 hospitalized in Thi-Qar Health Directorate of both sexes up to the age of 70 years, with the exception of patients with chronic diseases and pregnant women, as well as those over 70 years old.

Statistical Analysis

The data of this study were statistically analysis by using the statistical package for social sciences version 26 SPSS, based on the use of an independent sample t-test to compare rates between patients and the control group, and ANOVA was used for mean comparison according to disease severity and body mass index. Also, person correlation was used to determine the relationship between CXCL 10 and CRP, as well as the ROC test to provide predictive values for the level

of proinflammatory mediators according to body mass and disease severity.

Results

Levels of CXCL 10, IL-10 and CRP in COVID-19 Patients and Control

The Table 1 showed the COVID-19 patients had a high level of CXCL 10 than control group, while the IL-10 decreased significantly in patients than control group at *p*. value < 0.05.

Levels of CXCL 10 and IL-10 in COVID-19 According to Severity of Disease

The Table 2 showed the critical COVID-19 patients had a high level of CXCL 10 than other severity of disease categories, the study also noted the IL-10 was increased sever COVID-19 patients at *p*. value <0.05.

Levels of CXCL 10 and IL-10 in COVID-19 According to BMI

The Table 3 showed the obese COVID-19 patients had a lowest level of CXCL 10, while both normal weight and overweight patients scored high level of CXCL 10 with non-significant difference between them. In contrast the IL-10 was increased normal weight of patients at *p*. value < 0.05.

Table 1. Levels of CXCL 10 and IL-10 in COVID-19 patients and control group

	Patients No. 120	Control No. 60	*p*. value
	Mean ± SD		
CXCL10 ng/l	888.4 ± 286.8	366.9 ± 108.3	<0.01**
IL-10 ng/l	3.38 ± 1.36	5.46 ± 1.49	<0.01**

** significant.

Discussion

The level of CXCL-10 increases significantly in patients than control group, while the IL-10 decreased significantly in patients, within disease severity CXCL 10 increased with progress of disease, according to BMI the CXCL 10 decrease in obese patients than over and normal weight, while IL-10 increase in sever and critical than moderate patients, and scored high level in normal weight patients than other BMI categories. CXC chemokine ligand 10 CXCL10, is a type of protein that can be induced by interferon to chemoattract lymphocytes. It has been confirmed that CXCL10 has many biological functions, such as chemotaxis monocytes, activated T cells and NK cells for expansion [14]. The study of Zhang *et al*. [10], agreed with this study was showed the COVID-19 patients had a high CXCL 10 gene expression, also showed the expression increased as increased expression of IL-1β, IFN-γ, IFN-γ inducible protein 10 (IP10) and MCP-1. The positive correlation between CXCL-10 and pro-inflammatory cytokines and some pro-inflammatory immune factors are the basis for inducing the immune storm. Also, the study of Blot *et al*. [15], recorded the CXCL 10 level increased significantly in COVID-19 patients with SADS than COVID-19 patients without SADS, and the latter was significantly increased compared to the control group, their study also indicated that its level was positively associated with strength and duration of mechanical ventilation. This investigation was the same as that of the current study, where patients with a critical status of the disease recorded

Table 2. Levels of CXCL 10 and CRP in COVID-19 according to severity of disease

	Moderate No. 62	Severe No. 24	Critical No. 34	*p*. value
		Mean ± SD		
CXCL10	873.0 ± 263.0[b]	770.5 ± 236.7[b]	999.7 ± 326.1[a]	0.128[1,2], 0.034[1,3], <0.01[2,3]
IL-10	2.80 ± 0.85[c]	4.27 ± 1.22[a]	3.80 ± 1.16[b]	<0.01[1-2], <0.01[1-3], 0.012[2-3]

[a] significant at <0.001.
[b] significant at <0.01.
[c] significant at <0.05.
[1, 2, 3] groups (moderate, severe, critical).

Table 3. Levels of CXCL 10 and IL-10 in COVID-19 according to BMI

	Normal No. 50	Overweight No. 31	Obesity No. 39	*p*. value and LSD
		Mean ± SD		
CXCL10	992.7 ± 295.1[a]	964.9 ± 265.1[a]	693.8 ± 178.6[b]	0.128[1,2] < 0.01[1,3] < 0.01[2,3]
IL-10	4.12 ± 1.60[a]	2.37 ± 0.59[c]	3.23 ± 0.80[b]	< 0.01 for all

[a] significant at <0.001.
[b] significant at <0.01.
[c] significant at <0.05.
[1, 2, 3] groups (normal, over weight, obesity).

the highest concentration than others. Also, the study of Coperchin *et al*., [16], found that CXCL10 was the most likely to account for the protracted nature of COVID-19 ARDS in both the systemic and the alveolar compartments. CXCL10 (or INF-γ-induced protein (IP-10) is secreted upon INF-γ stimulation by various cell types such as endothelial cells, fibroblasts, monocytes/macrophages, and T lymphocytes and then promotes chemoattraction for activated T lymphocytes, natural killer cells, and monocytes through CXCR3, also, showed the gene expression in female was lower than male. This difference may be related to the different immune response to SARS-CoV-2 between the sexes [17]. While the study of Wang *et al*. [18], showed the CXCL 10 and other cytokines such as IL-17 and IL-12 were elevated in mild cases than sever cases of patients, and their study suggested that these cytokines may be an indicator of further deterioration in the severe condition of the COVID-19 patient. CXCL10 is responsible for inter stimulation of monocytes or NK cells, migration of T lymphocytes, or modulation of the expression of adhesion molecules [19]. Several studies were showed the CXCL10 had positive associated with CRP and both stimulated monocytes produce. Positive correlations between levels of CXCL10 and CRP, and between CXCL10 have been revealed. Moreover, the levels of CXCL10 were increased in patients with severe course and mild–moderate COVID-19 in comparison to healthy volunteers. Also, the study of Kochumon *et al*.[20], showed a significant correlation between CXCL 10 and proinflammatory cytokines, also, noted the gene expression was significantly increase in obese than normal and underweight individuals with metabolic inflammation and insulin resistance. Several studies such as study of Da Porto *et al*. [21], and Omit *et al*. [22], showed that CXCL 10 and other inflammatory cytokines were the main cause of the deterioration of the health status of COVID-19 patients, as it found an increase in gene expression in organs such as pancreas, lung, heart and kidney, these findings may explain why most patients who have recovered from COVID-19 develop high blood pressure, diabetes, and other chronic diseases. The study of Blot *et al*. [23], was noted a positive correlation between CXCL 10 with both IL-4 and IL-10, proinflammatory cytokines and CRP. The positive association between CXCL 10 and anti-inflammatory cytokines may be attributed to the prolonged duration of mechanical ventilation, which is a stimulating factor for CXCL 10 production, while damage to lung and other tissues is a stimulating factor for IL-4 and IL-10 production.

The present study agreed with study of Zhao *et al*.[24], was noted a non-significant between mild patients and control in level during the first week of infection, but increasing with progress of disease, also noted the mild and moderate had high level than sever patients. Also, the study of Qi *et al*.[25], showed the IL-10 increased significantly in control group than patients and in female patients than male. While study of Lu *et al*.[26], those who disagree with the results of the current study point out that there was a greater increase in males compared to females, that IL-4 levels at four to six weeks were higher than at two weeks, and that ICU patients had higher plasma cytokine levels than non-ICU patients. There might be a discrepancy in the readings because of the interval between samples. We hypothesize that the low IL-10 levels at the end of the disease are due to the immune cells producing high levels of IL-10 to induce excessive apoptosis at the end of the disease to prevent destructive their normal tissues in the late phase of inflammation, since cytokine levels may be correlated with disease severity [27, 28]. Rahmati and Moosavi [29], noted the IL-10 was decreased significantly during the beginning of disease, while increasing with disease severity. This result was inconsistent with the current result. The differences may be due to the physiology of the disease itself, as it is not well understood yet, and the patients participating in this study did not have chronic diseases before the infection occurred, in contrast to the comparative studies that included patients with chronic diseases.

The study of Ahmed and Salih, [30], showed the IL-10 increased significantly after vaccination in female more than male. This may be the women exhibition a greater immune response to vaccine and facilities their activity, they also experience more frequency and severity than men. The study of Chang *et al*.[31], was agreed with this study was noted a positive correlation between IL-4 and IL-10 in late stage of disease progress. Also, the study of Queiroz *et al*. [32], showed the level increased non-significantly in female than male, and increase in sever than moderate and mild patients. It is likely that IL10 is regulated to counter overwhelming during COVID-19 infection, but it may involve in infiltration of inflammatory cell and pulmonary fibrosis. IL-10 blocking alone or with programmed cell death protein 1 (PD-1), is hopeful for depleted T cells reactivation and may control COVID-19 disease pathogenesis [33, 34]. In contrast, Dimeglio *et al*.[35], research compared individuals with post-COVID-19 syndrome (long COVID-19) to patients with the disease at its active stage and discovered a statistically significant upregulation of anti-inflammatory IL-4 and IL-10 and a downregulation of pro-inflammatory IL-6, IL12, and IL17. The increased production of IL-4 and IL-10, two anti-inflammatory cytokines, may be the result of organ damage, persistent inflammation, the non-specific consequences of long-term hospitalization or mechanical ventilation, or even underlying health problems. Apoptosis and the healing of infected tissues are hastened by the increased production of anti-inflammatory cytokines.

Conclusion

This study investigated the CXCL 10 was highly elevated in COVID-19 patients than control group, also noted the CXCL 10 increased with disease progress, therefor consider a good marker for poor outcome, furthermore the obese patients are more likely to have severe outcomes than others, so BMI is considered a risk factor for patients.

Funding

None.

Institutional Review Board Statement

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Informed Consent Statement

The informed consent was obtained.

Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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