



# Evaluating serum levels of interleukin-8 and interleukin-17 in patients with COVID-19 and their correlation with disease severity

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## Abstract

**Introduction:** In COVID-19 patients, those with underlying disease are relatively more susceptible to respiratory viral infections and are more likely to develop severe symptoms compared to people without underlying disease.

**Objectives:** This study aimed to evaluate the serum levels of interleukin (IL)-8 and IL-17 in patients infected with severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) and patients with underlying disease.

**Patients and Methods:** Serum samples were collected before administration of any antiviral and/or immunosuppressive drug. Around 64 adult patients with COVID-19 and 12 adult patients with underlying disease were compared with 16 healthy subjects as controls. The cytokine levels were assessed by ELISA (enzyme-linked immunosorbent assay) method and the statistical analysis was carried out using the one-way analysis of variance (ANOVA).

**Results:** The average levels of these cytokines in the severe group were significantly higher than those in the mild and control group ( $r=0.48$ ,  $P<0.016$ ); it is worth noting that patients with underlying disease also displayed a higher level of these cytokines than those with mild and control groups ( $r = 0.283$ ,  $P<0.049$ ). No significant differences were observed between severe and other patients with underlying disease and also between mild and control groups.

**Conclusion:** Our data indicate that IL-17 and IL-8 are involved in inducing and mediating proinflammatory responses and that the elevated level of these inflammatory cytokines could be the effective ground in the severity of COVID-19 and being susceptible in people with underlying disease. Thus, providing a platform of inflammatory signature cytokines in COVID-19 patients with underlying co-morbidities or without as well as in non-COVID-19 patients with underlying diseases might provide a promising solution to COVID-19 disease.

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## Introduction

A coronavirus leading to multiple respiratory infections has overwhelmed the world in a pandemic and has become a life-threatening disease.

Patients with different risk factors are generally more susceptible to respiratory viral infections; thus the mortality rate in COVID-19 patients with underlying diseases, older age, or a compromised immune system is higher than those with normal bodies. In these patients- those with COVID-19 and elderly people with risk factors- the disease is more severe and also the disability and multiple organs failure are more evident (1).

A recent study demonstrates that neutrophilic inflammation, as a contributory factor, plays a crucial role in severity and tightens the rate of mortality in COVID-19 patients with comorbidities of diseases such as

## Key point

Interleukin-8 and interleukin-17 are involved in inducing and mediating proinflammatory responses in patients infected SARS-CoV-2 with underlying comorbidities.

cardiovascular and diabetes (2).

Studies have also demonstrated the putative role of severe inflammation in the death of COVID-19 patients and also there are reports indicating that the level of inflammatory cytokines, such as interleukin-1 (IL-1), IL-17, IL-6, IL-8 in COVID-19 pathogenesis significantly is on the increase. It is worth noting that the role of pro-inflammatory cytokines in pathogens in many viral respiratory infections via triggering inflammatory mechanisms can lead to cytokine storm and tissue damage in



multiple organs (3).

Other studies demonstrate, a poor initial response from interferon (IFN), which allows viral replication and high activity of proinflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ), IL-1, IL-6, interferon-gamma-induced protein (IP-10) and monocyte chemoattractant protein (MCP-1), which is the result of a late immune response to virus, could have deleterious effects on COVID-19 patients. In addition, macrophages, neutrophils, B and T lymphocytes activation results from inflammatory responses to virus, thereby triggering inflammatory process and aggressive immune response (4).

The evidence indicates that the count of activated inflammatory macrophages in lungs of patients with acute respiratory distress syndrome (ARDS) and acute lung injury significantly increase; in addition, the level of inflammatory chemokines (IL-8) in these patients is remarkably higher than normal individuals. Furthermore, the evidence shows that patients with severe asthma are more susceptible to respiratory viral infections such as coronavirus than healthy people due to abnormal airway epithelium and impaired innate immune system responses (5).

Interleukin-8 is a chemotactic factor for neutrophils, T lymphocytes and basophils which are induction into releasing lysosomal enzymes and oxidative bursts. Additionally, there is evidence indicating that the level of IL-8 significantly increases in inflammatory human diseases, including diabetes, rheumatoid arthritis, gouty arthritis, psoriatic scale and adult respiratory distress syndrome (6).

It has been reported that the level of IL-17 is significantly higher in viral infections such as human immunodeficiency virus (HIV), herpes simplex virus and respiratory syncytial virus infection in rodents. Moreover, IL-17 overexpression into the lung could lead to upregulation of chemokines, such as IL-8, which recruit inflammatory cells to the airway and tissue damage. The imbalance between subsets of T-helper-cell (TH) such as TH1, TH2, TH17 and regulatory T-cells (Treg) with high levels of TNF- $\alpha$ , IL-1 $\beta$  and IL-8 can contribute to pathogenesis of COVID-19 (7).

## Objectives

Here, we measured the level of IL-17 and IL-8, as a signature marker, in COVID-19 patients and patients with underlying diseases to evaluate the role of these inflammatory cytokines in such patients and to depict why such diseases are more susceptible to respiratory viral infection.

## Patients and Methods

### Study design

In this study, patients have been in three groups: mild, mild and severe by a hospital infectious disease specialist. We placed patients who were admitted on an outpatient basis

in the mild group, patients who were admitted in the mild group, and patients in severe group who were admitted to the intensive care unit (ICU).

In this study, 64 patients with COVID-19 (41 women and 23 men) and 16 healthy control (eight women and eight men) and 12 patients with underlying disease participated. All patients have been COVID-19 positive based on reverse transcription-polymerase chain reaction (RT-PCR) test. Patients were hospitalized at Taleghani hospital of Abadan medical sciences university, south west of Iran, between November 2020 to April 2021. All samples were collected in December 2020.

### Blood samples

The blood samples were collected from Taleghani hospital in Abadan in southwest of Iran. Five milligram of blood was taken between 7 AM and 13 PM. All serum samples were aliquoted into 500- $\mu$ L volumes and stored at -70°C refrigerating conditions until needed. All blood samples were taken before administration of any antiviral and/or immunosuppressive drug.

### IL-8 assay

The concentration of IL-8 was determined by IL-8 ELISA kit (ZellBio GmbH, Germany) and all the processes were undertaken at 37°C. Briefly, the serum samples and biotinylated anti IL-8/CXCL8 antibodies were added to the wells for one hour, which were pre-coated with anti-IL-8/CXCL8 monoclonal antibody. After incubation and washing, followed by streptavidin-peroxidase for 10 minutes, the blue solution turned yellow with the effect of acid. The absorbance was measured at 450 nm. The concentration values (pg/mL) of IL-8 were obtained by interpolating the absorbance values on the respective calibration curve.

### IL-17 assay

The IL-17 concentration was determined by IL-17 ELISA kit (ZellBio GmbH, Germany) in the same way described above.

### Statistical analysis

Data was analyzed by SPSS (Statistical Package for the Social Sciences) (version26 ) and represented as mean  $\pm$  standard error of the mean (SEM). Differences in inflammatory cytokines between groups were evaluated by ANOVA (one-way analysis of variance) test. Differences between each of the groups and controls were evaluated employing the Tukey test. To indicate optimal cut-off values of cytokines levels, receiver operating characteristic (ROC) curve analysis was applied. The evaluation of correlation was conducted by Pearson's correlation coefficients. Graphs were drawn using GraphPad Prism 8 software. A *P* value of 0.05 or less was considered to be statistically significant.

**Results**

All the 92 subjects were enrolled in the present study (64 patients with COVID-19, 12 patients with inflammatory diseases [or underlying diseases], 16 cases as control), and the plasma level of IL-8 and IL-17 were determined by ELISA. Patients with COVID-19 were consisted of 20 cases in mild group and 44 cases in severe group. Elevated concentrations of inflammatory cytokines, IL 8 and IL-17 have been reported in patients with COVID-19 and those with risk factors.

In serum samples, inflammatory cytokine levels including IL-8 and IL-17 were assayed. According to our data, the average levels of IL-8 and IL-17 were significantly higher in the severe group than the mild and control group. It is worth mentioning that patients with inflammatory disease also displayed a higher level of these cytokines than those in the mild and control group. No significant differences were observed between severe and other patients with risk factor and also between mild and control group (Table 1, Figures 1a and 1b).

In addition, increased serum IL-17 levels correlated with higher IL-8 in severe group in COVID-19 ( $r = 0.48, P < 0.016$ ) and in patients with underlying disease ( $r = 0.283, P < 0.049$ ), respectively. Receiver operator characteristic (ROC) curve analysis of cytokines were different in mild and severe COVID-19 group and are shown in Table 2, Figures 2a and 2b.

**Discussion**

The severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) is positively correlated with inflammatory

cytokines involvement. This study depicts the significant role of IL-17 and IL-8, notably IL-17, in the severity of COVID-19.

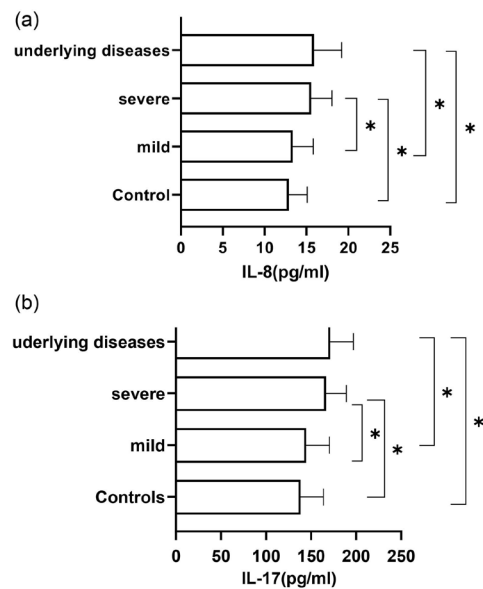
Th17 cells and Th17-derived cytokines play a central role in neutrophilic inflammation and tissue damage. Studies have shown, Th17 cells neutralize the inhibitory properties of Treg cells and this imbalance between Treg and Th17 cells appears to be implicated in the development and the pathogenesis of autoimmune and inflammatory diseases such as severe asthma, ARDS, atherosclerosis, psoriasis, cardiovascular, type 2 diabetes and diabetes retinopathy (8). Elevated IL-17 level expression has been reported in the sputum, lung and sera in patients with asthma, demonstrating the severity of acute hypertension respiratory in these patients, which is inextricably bound up with IL-17 expression levels. A similar study depicted that the number of Th17 cells were increased in lung tissue of patients with severe asthma compared to other groups of asthma patients. The level of IL-17 protein in patients with asthma is on the increase, thereby indicating the high level of IL-17 protein in their airways that can induce neutrophil infiltration, chemokine IL-8 production and the degree of airway hyperresponsiveness (9). Mikacenic et al showed that circulating and alveolar levels of IL-17 were significantly higher in human with ARDS (10).

Studies provide evidence that the presence of IL-17A directly increases the permeability of human alveolar epithelial cells and thus extends the role of IL-17A in the neutrophil inflammation observed in ARDS, suggesting a possible mechanism for the effects of IL-17 in ARDS of any cause (10).

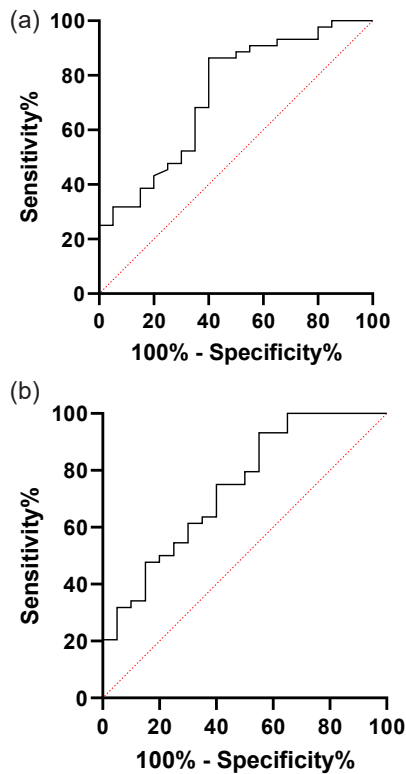
Accumulating evidence shows that IL-17A and IL-17F

**Table 1.** Average levels of IL-8 and IL-17 in different groups

Groups	Case number	IL-8 (pg/mL)	IL-17 (pg/mL)
Mild	20	13.371 ± 2.45	144.626 ± 25.76
Severe	44	15.578 ± 2.48	166.755 ± 22.27
<i>P</i> value		0.010	0.005
Mild	20	13.371 ± 2.45	144.626 ± 25.76
Underlying disease	12	15.902 ± 3.30	171.382 ± 25.56
<i>P</i> value		0.038	0.016
Mild	20	13.371 ± 2.45	144.626 ± 25.76
Control	16	12.904 ± 2.17	138.376 ± 25.33
<i>P</i> value		0.947	0.865
Severe	44	15.578 ± 2.48	166.755 ± 22.27
Underlying disease	12	15.902 ± 3.30	171.382 ± 25.56
<i>P</i> value		0.979	0.934
Severe	44	15.578 ± 2.48	166.755 ± 22.27
Control	16	12.904 ± 2.17	138.376 ± 25.33
<i>P</i> value		0.003	0.001
Underlying disease	12	15.902 ± 3.30	171.382 ± 25.56
Control	16	12.904 ± 2.17	138.376 ± 25.33
<i>P</i> value		0.014	0.003



**Figure 1.** (a) Mean IL-8 level change in serum of different groups. The data are given as mean (standard error of mean) \* $P < 0.05$ . (b) Mean IL-17 level change in serum of different groups. The data are given as mean (standard error of mean) \* $P < 0.05$



**Figure 2.** (a) ROC curve of IL-8 to predict the severe COVID-19. (b) ROC curve of IL-17 to predict the severe COVID-19.

can induce to secrete proinflammatory cytokines from lung epithelial cells including TNE, IL-1 $\beta$ , granulocyte colony-stimulating factor (G-CSF) and IL-6 and chemokines such as CXCL1/Gro- $\alpha$ , CXCL2 and CXCL8/IL-8 and consequently prompt neutrophil infiltration, which plays a significant role in inflammation and tissue damage. Further, elevated mucin 5A (MUC5A) mRNA expression in endothelial cells results in mucus hypersecretion in asthmatic airways (11).

The propose of the present study in conducting this assay was to compare the levels of inflammatory cytokines including IL-8 and IL-17 in COVID-19 patients in two different stages (mild and severe) and to compare them with different non-COVID-19 patients with underlying disease, including type 2 diabetes, heart disease (atherosclerosis and cardiovascular ) and severe asthma to evaluate the deleterious effects of IL-17 in inflammation and tissue injuring in COVID-19 patients severe group and non-COVID-19 patients with underlying disease to evaluate the importance. What is important in these patients to be susceptible to SARS-CoV-2 is the putative role of these inflammatory cytokines. We found that IL-17 and IL-8 serum level of severe COVID-19 patients and non-COVID-19 patients with underlying disease are

remarkably higher than those of mild and control group (all  $P < 0.05$ ), which was consistent with the previous studies. In addition, in the present study, between each two of these cytokines, there was a positive correlation in the severe group and in the group with underlying disease (all  $P < 0.05$ ).

No significant difference between severe group and non-COVID-19 patients with risk factors implicates the detrimental effect of IL-17 on the pathogenesis of these diseases. This data shows that the group with severe COVID-19, display increased plasma levels of IL-17 and indicate the strong role of IL-17 in increasing IL-8 and neutrophil inflammation which might be the major cause of lung injury in COVID-19. These results are congruent with those obtained in many other studies.

The area under the curve (AUC) of IL-8 and IL-17 were above 0.7, thus indicating their effectiveness in severity and implying their prognostic value in this disease. The positive correlation between levels of IL-8 and IL-17 in the severe group and patients with underlying disease suggests that the IL-8/IL-17 axis is of high importance in COVID-19 patients.

The role of neutrophils in the progression of the SARS-CoV-2 infection has been proved. Recent findings have detected, inducing recruitment of neutrophils by the T helper 17 (Th17) cells and IL-17-related pathways in COVID-19 results in lung injury (12).

Furthermore, nitric oxide synthases in neutrophils can induce a Th17 response in this disease and thus these effector lymphocytes reach the lung tissue and produce IL-17 (13). Other cytokines including IL-21 and IL-22 elevate the level of IL-8 expression, thereby recruiting more neutrophils and tissue injury eventually (13). It should be noted that Th17 differentiates towards producing IL-17A. Interestingly, Janus kinase (JAK), signal transducer of activation (STAT) pathway (JAK/STAT) can induce activation of IL-6 and this function trigger differentiation of TH17 subtype pathway in early stages of inflammation (14,15). Additionally, an excessive level of chemokines in lung trafficking such as IL-8 and IL-17 is probably activated through the Toll like receptor 9 (TLR-9) signaling pathway. As a result, blocking IL-17 itself, the IL-17 receptor or indirectly targeting the IL-17 related pathway could be the potential treatment in COVID-19 patients. For instance, a favorable outcome has been reported in COVID-19 patients treated with secukinumab and guselkumab, monoclonal antibodies against IL-17A, even in the presence of associated risk factors for severe disease (16,17). Further, an ongoing clinical trial on the substantial effects of ixekizumab (an IL-17A inhibitor)

**Table 2.** ROC curve analysis of cytokines to differentiate mild from severe COVID-19

Variables	AUC	Sensitivity (%)	Specificity (%)	95% CI	P value
IL-8 (Cut off:16.97 pg/mL)	0.730	31.82%	95%	0.594-0.866	0.0034
IL-17 (Cut off: 169.2 pg/mL)	0.739	47.73	85%	0.606-0.872	0.0022

as a possible treatment for COVID-19 is currently being conducted (18). Previous investigations demonstrated that administration of medications such as secukinumab and ixekizumab which selectively target IL-17A in psoriasis treatment, an autoimmune disease, are effective (18,19).

With respect to the significant role of retinoid-related orphan receptor gamma t (ROR $\gamma$ t) in exaggerating Th17 response in COVID-19 patients, the administration of drugs that cause a decrease in protein levels of ROR $\gamma$ t, owing to IL-17 level decline, alleviates lung tissue inflammation (20).

The use of anakinra, toclizumab, and ustekinumab are known as inhibitors of IL-1, IL-23 and IL-6 respectively. The key factors in inducing Th17 differentiation could have an effective therapeutic role in the treatment of this disease (21). The impeding effect of JAK2 inhibitors (fedratinib) on the production of several Th17 signature cytokines in a murine model has been demonstrated (22), and thus it alleviates the proinflammatory function of Th17 cells. Therefore, JAK2/STAT3 pathway inhibitors could be the possible useful therapeutic drugs.

Interestingly, some researchers highly recommended the use of colchicine in the COVID-19 conditions. This is because colchicine expedites IFN- $\alpha$  and IFN- $\beta$  expression and regulates anti-oxidative factor production, and thus makes a remarkable effect on viral disease (23).

It is worth noting that all these inhibitors' mechanisms might have significant effects on SARS-CoV-2-related immune response and affect antiviral protective responses negatively; for instance, blocking IL-12 is the result of using ustekinumab, which negatively affects interferon production (23).

### Conclusion

We found, providing a platform of inflammatory signature cytokines in COVID-19 patients with underlying comorbidities, including diabetes, cardiovascular diseases, severe asthma, or without such inflammatory diseases and in non-COVID-19 patients with underlying diseases, could provide a promising solution and make a contribution to improving our understanding of COVID-19 disease.

### Limitations of the study

This study has some limitations. First, the effects of some drugs have not been evaluated due to lack of having access to data related to patients with underlying diseases and insufficient budget for this project. This study could have been more effective if it had been carried out as a cohort study. Moreover, this is a relatively small study, which is related to restraints on access to patients' information.

### Authors' contribution

Conceptualization, FS, SAM, SMBM, NC and ASB. Methodology, SMAM, SMBM, ZK, NC and ASB. Investigation, FS and ASB. Writing-original draft, ZK, NC and FS. Writing- review and editing, FS and ASB. Data analysing; FS. Funding acquisition, ZK. Supervision, ZK.

### Conflicts of interest

The authors declare that there is no conflict of interest.

### Ethical issues

The research conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Abadan University of Medical Sciences (IR. ABADANUMS.REC.1399.016). Written informed consent was obtained from all participants. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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