Original Article

Iranian Journal of Immunology

September 2024; 21(3):

The Protective Role of IL-17 and IL-22 in COVID-19 Infection

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ABSTRACT

Background: The development of a cytokine storm in Coronavirus Disease 2019 (COVID-19) infection can make the disease fatal. We hypothesize that this excessive cytokine production impairs mucosal healing. IL-17 and IL-22 are cytokines that play a key role in protecting and regenerating mucosal tissues. IL-17 and IL-22 support each other, and the imbalance between them plays a role in the pathogenesis of many rheumatologic diseases.

Objective: To investigate whether COVID-19 severity is related to IL17, IL-22, and the IL-17/IL-22 ratio.

Methods: The study was planned prospectively and included 69 patients with active COVID-19 infection. Three groups were created: patients with upper respiratory tract infection, pneumonia, and cytokine storm. Blood samples were taken from the patients upon their first admission and serum levels of IL-17 and IL-22 were measured using the enzyme-linked immunosorbent assay (ELISA). We assessed the relationship between IL17, IL22, IL17/IL22 ratio, clinical and lung involvement by comparing them with the healthy group.

Results: The levels of IL-17 were significantly higher in COVID-19 patients with upper respiratory tract infection compared to the control group (p=0.027). IL17/IL-22 ratio significantly increased in patients with cytokine storm compared to the healthy controls (p=0.027). Serum levels of IL-22 were negatively correlated with the CO-RADS score (r=-0.31, p=0.004), while IL-17/IL-22 ratio was positively correlated with the CO-RADS score (r=0.29, p=0.008).

Conclusion: Levels of IL-17, IL-22, and IL-17/IL-22 may provide valuable insights into the progression of COVID-19.

Keywords: COVID-19, Interleukin-17, Interleukin-22, IL-17/IL-22 ratio, Th17

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Cite this article as:
Aksakal S, Gorgun S. The Protective Role of IL-17 and IL-22 in COVID-19 Infection. *Iran J Immunol.*
doi: 10.22034/iji.2024.100909.2721.

Received: 2023-11-27
Revised: 2024-03-15
Accepted: 2024-03-30

INTRODUCTION

The pandemic of the new millennium, Coronavirus disease 2019 (COVID-19) infection usually starts with flu like symptoms (1), and can be asymptomatic or may have a mild to severe course. Our study is founded on the premise that the disease induces more severe lung infections in specific patients (2). The basis of our study is that the disease causes more severe infection in the lungs of certain patients. During the process of COVID-19 infection, initially, it was believed that organ damage was caused by the recruitment and activation of CD4, CD8 and natural killer (NK) cells, particularly in the lung tissue (3). Later, it was thought that hyperinflammation caused by the COVID-19 infection was the main factor contributing to severe lung infection in certain patients (4). More recently, it is believed that inflammation with a neutrophil dominance is responsible for organ damage during COVID-19 infections (5). Lymphocytosis is more common in viral infections (6). However, many studies have shown that neutrophilia and lymphopenia develop in COVID infection (7, 8). The cause of neutrophilia in this viral infection is not yet clear.

IL-17 and IL-22 are the major cytokines released from T helper (Th) 17 cells. They have a synergistic or additive effect in combating mucocutaneous infections, ensuring mucocutaneous stability (9, 10). Depending on the presence of the transcription factor aryl hydrocarbon receptor (AHR) and tetrachlorodibenzo-p-dioxin (TCDD) as well as certain endogenous ligands, the secretion of IL-22 and IL-17 by Th17 cells changes (11). Although IL-17 and IL-22 have complementary roles in mucocutaneous infections, there are instances where their interaction is different. IL-17 plays a pro-inflammatory role in fighting infections, by causing the secretion of antimicrobial proteins in the epithelium, stimulating granulopoiesis, and promoting the accumulation of neutrophils in the epithelium (12). IL-22, on the other hand, is a cytokine that protects the homeostasis, and has pro-inflammatory functions in cases of inflammation. In addition to being released by Th17 cells, IL-17 is also released from natural killer T cells (NKT), innate lymphoid cells (ILC), γδ-T cells (13). It is also released from mast cells and neutrophils during infection (14). IL-22, is also released from $CD4^+$ T cell, $CD8^+$ T cell, γδ-T cell, natural killer cell and ILCs. IL-22 is associated with Th17 differentiation. Th17 cells, co-secrete IL-22 and IL-17 (15). T-helper 22 also releases IL-22 along with tumor necrosis factor-α (TNF-α) (16).

IL-17 and IL-22 work together in harmony and are the most crucial cytokines for maintaining mucocutaneous homeostasis. The balance between these two cytokines is disrupted in certain diseases. For instance, deficiencies or dysfunctions in IL-22 and IL-17 may increase susceptibility to mucocutaneous infections. A similar condition is also observed in inflammatory bowel diseases. While IL-22 plays a dominant role, elevated levels of IL-17 can lead to chronic inflammation, resulting in conditions like arthritis and psoriasis (12, 17-21). In Fig. 1, the balance of IL-17 and IL-22 and the diseases associated with the imbalance between these two cytokines are presented (12).

The definitive diagnosis of COVID-19 is typically made using reverse transcription-polymerase chain reaction (RT-PCR) testing. However, there have been instances where the PCR test initially yielded a negative result followed by a positive result (22). Therefore, imaging has emerged as an alternative method for diagnosis. During the pandemic, tomography findings have been analyzed leading to the establishment of the COVID-19 Reporting and Data System (CO-RADS) to standardize COVID-19 lung findings. This classification is outlined in Table 1 (23).

We included PCR SARS-CoV-2 positive cases in our study at the institution where we worked. We planned this study to investigate the role of IL-17 and IL-22, which maintain and repair mucocutaneous stability, in the severe course of COVID-19 infection.

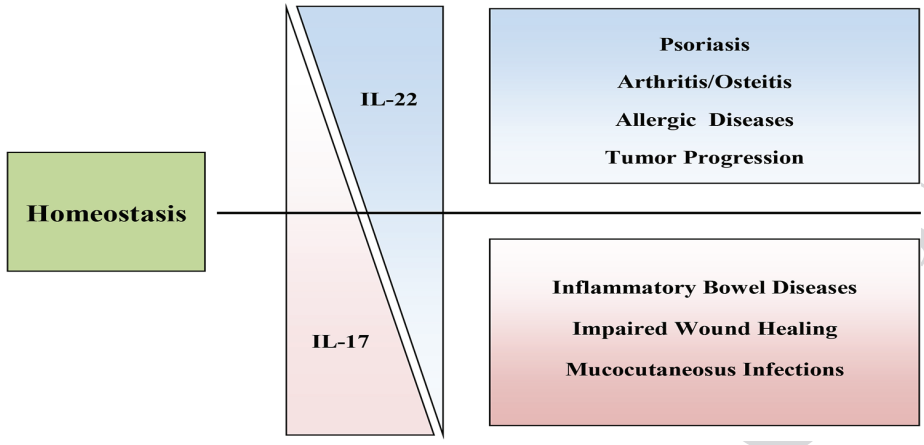

Fig. 1. IL-17 and IL-22 imbalance contributes to the pathogenesis of various disorders

Table 1. COVID-19 Reporting and Data system Category (23).

Co-RADS Category	Level of suspicion for pulmonary involvement in COVID-19	Summary
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very low	Normal or not infected
2	Low	Typical for other infections but not for COVID-19
3	Equivocal/unsure	Features compatible with COVID-19 but also other diseases
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

RT-PCR: reverse transcription-polymerase chain reaction, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

MATERIALS AND METHODS

Patients diagnosed with COVID-19 infection and receiving treatment in the institutional ward were included in the study following approval of the study protocol by the non-interventional clinical research ethics committee of the University of Health Sciences (approval date: 07/07/2021 approval number: GOKA/2021/14/1). Healthy volunteers were enrolled as the control group.

Patients with active infections unrelated to COVID-19, as well as those with cancer, acute kidney or liver conditions, and inflammatory diseases, were excluded from the study. Pregnant women were also not included in the research cohort.

Age, sex, comorbidities, the presence of upper respiratory tract symptoms and the presence of cytokine storm were all noted. Chest tomography of the patients at the time of blood collection was also recorded.

Serum IL-17 and IL-22 levels were measured using an enzyme-linked immunosorbent assay (ELISA) in peripheral venous blood. Venous blood samples were taken from all the participants, centrifuged and serum samples were stored at -80°C until needed for analysis. The levels of serum IL-17 and IL-22 were measured using a human ELISA kit (Bioassay Technology Laboratory, Shanghai, China). The analysis was performed according to the instructions provided in the kit's package insert.

Hemogram and serum C-reactive protein (CRP), were also measured and recorded. The proportion of IL-17/IL-22 and neutrophil–to-lymphocyte ratio (NLR) were calculated. According to the clinical course, patients were classified into three groups: those with only upper respiratory tract infection (URTI), patients with lower respiratory tract infection (pneumonia), and those with severe vital signs-cytokine storm.

The data of the COVID-19 patients and the control subjects were then compared. Additionally, we compared the data of women and men with COVID-19.

Statistics

Commercial statistical software (SPSS 20.0 for Windows, IBM Co. Armonk, NY, USA) was used to conduct the statistical analyses. The Kolmogorov-Smirnov test was used to determine whether continuous variables fit a normal distribution among both COVID-19 and control subjects. Comparisons of the homogeneous and non-homogeneous data were conducted using the student t test and the Mann-Whitney U test, respectively. Data that fit into a normal distribution were presented as means and standard deviations whereas data that did not fit into a normal distribution were presented as medians and interquartile ranges (IQR). Categorical variables were compared using the Chi-square test and expressed as numbers and percentages. The correlation between study parameters was analyzed using Pearson's correlation analysis test. ROC curve analysis was conducted to determine the sensitivity and specificity of the study variables in predicting COVID-19 infection. Results were considered statistically significant when the *p*-value was less than 5%.

RESULTS

There were 69 patients in the COVID-19 group and 16 subjects in the control group. The mean age of the COVID-19 group was 62±20 years while the control groups had a mean age of 41±13 years ($p<0.001$). In the COVID-19 group, there were 35 (51%) women compared to 10 (62.5%) women in the control group ($p=0.4$). Among patients, 26 had upper respiratory tract infections, 36 had pneumonia, and seven patients experienced cytokine storm. Table 2 summarizes general characteristics and laboratory values of the study groups.

Three groups were created: one with upper respiratory tract infection (UTRI), another with pneumonia and a third with cytokine storm clinics. Comparisons were made

Table 2. Characteristics and data of the COVID-19 and the control subjects

Variable		COVID-19 group	Control group	*p*
		n (%)		
Gender	Men	34 (49)	6 (37.5)	0.4
	Women	35 (51)	10 (62.5)	
		Mean±SD		
Age (years)		62±20	41±13	<0.001
Hemoglobin (g/dL)		12±2.2	14.2±1.4	<0.001
Lymphocytes (k/mm^3)		1.24±0.7	2.01±0.5	<0.001
		Median (IQR)		
White blood cells (k/mm^3)		7.9 (5.6)	6.1 (1.9)	0.03
Neutrophils (k/mm^3)		4.9 (5.6)	3.7 (1)	0.004
Plathelets (k/mm^3)		234 (78)	252 (12)	0.24
NLR (%)		5.3 (4)	1.9 (0.5)	<0.001
CRP (mg/L)		42 (112)	1.4 (1.4)	<0.001
CO-RADS score		2 (3)	1 (1)	<0.001
IL-17 ng/L		114 (76)	107 (35)	0.38
IL-22 ng/L		91 (629)	104 (288)	0.85
IL-17/IL-22 ratio (%)		0.99 (1.45)	0.97 (1)	0.54

The variables with homogeneous distribution have been presented with mean±SD, and student samples't-test was used for comparisons regarding them. The variables with non-homogeneous distribution have been presented with median (IQR), and Mann Whitney U test was used for comparisons regarding them. COVID-19: Coronavirus disease 2019, SD: Standard deviation, IQR: Inter-quartile range.

separately with the control group, and the results are presented in Table 3. The median IL-17 levels of the URTI-COVID-19 and the control groups were 228 ng/L and 108ng/L, respectively, showing a statistically significant difference (p=0.027). However, there was no significant statistical difference detected in IL-17 levels between pneumonia and cytokine storm groups, respectively (p=0.529, p=0.198). IL-22 levels showed no statistically significant difference among all three groups. However, a statistically significant increase in the IL17/IL-22 ratio was detected in the patients with cytokine storm (p=0.027). The median IL17/IL-22 ratio in the patients with cytokine storm and the control groups was 1.5 and 0.9, respectively.

The median IL-17 levels of the COVID-19 and control groups were 114 (76) ng/L and 107 (35) ng/L, respectively (p=0.38). In addition, the median IL-22 levels of the COVID-19 and control groups were 91 (62) ng/L and 104 (29) ng/L, respectively (p=0.85). Similarly, there was no statistical difference between the COVID-19 and control groups in terms of the IL-17/IL-22 ratio (p=0.54).

The median NLR of the COVID-19 patients (5.3 (interquartile range (IQR): 4)) was significantly higher than that of the control subjects (1.9 (IQR: 0.5), p<0.001).

Comorbidities (p<0.001), and upper respiratory tract symptoms (p=0.002) were more prevalent in the COVID-19 group compared with the control group but the rate of cytokine storm (p=0.18) in those groups was similar (Table 4).

The serum IL-22 level correlated inversely with CO-RADS score (r=-0.31, p=0.004). The IL-17/IL-22 ratio also showed a positive correlation with CO-RADS score (r=0.29, p=0.008). The NLR level correlated directly with CRP (r=0.4, p<0.001), and the CO-RADS score (r=0.34, p=0.002).

The sensitivity and specificity of NLR in predicting COVID-19 infection, when higher than 2.1%, were 83% and 81%, respectively (AUC: 0.86, p<0.001, 95%CI: 0.79-0.94). The sensitivity and specificity of NLR in predicting COVID-19 were higher than those of IL-17, IL-22, and the IL-17/IL-22 ratio. In the ROC analysis, it was determined that the sensitivity and specificity values for the optimum threshold determined at the levels of the cytokines included in the study varied between 38% and 50% for sensitivity and 60% and 80% for specificity. For example, the specificity value for IL-22 was 80%, while the sensitivity was 38% (Fig. 2).

Table 3. IL-17, IL-22, IL-17/IL-22 levels in COVID-19 infection

	IL-17			IL-22			IL-17/IL-22		
	Mean	SS	*p*	Mean	SS	*p*	Mean	SS	*p*
Control	108,4	27,1	0,027	251,5	295,2	0,083	0,9	0,6	0,511
URTS	228,3	196,5		570,3	464,4		0,8	0,7	
Control	108,4	27,1	0,529	251,5	295,2	0,174	0,9	0,6	0,365
Pneumonia	132,1	132,0		228,6	286,4		1,2	0,9	
Control	108,4	27,1	0,198	251,5	295,2	0,222	0,9	0,6	0,027
Cytokine storm	196,3	198,4		246,4	461,3		1,5	0,6	

Table 4. Comorbidities and presentation of the study cohort

Variable	COVID-19 group	Control group	*p*-value
	n (%)		
Comorbidities present	35 (51)	0 (0)	<0.001
Upper respiratory tract symptoms present	27 (39)	0 (0)	0.002
Cytokine storm present	7 (10)	0 (0)	0.18

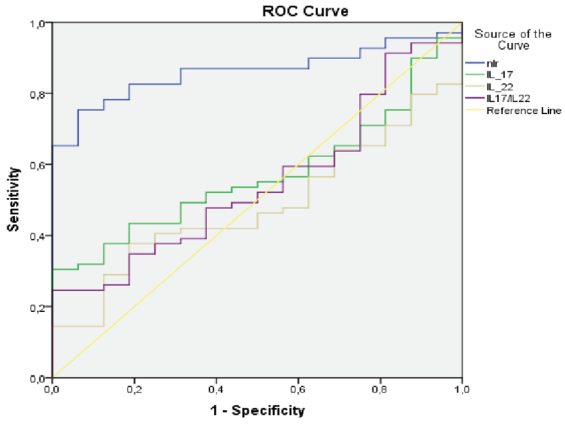

Fig. 2. The sensitivity and specificity of the NLR, IL17,IL-22, IL17/IL-22 in predicting Covid-19

In the subgroup analysis, none of the characteristics or laboratory data of the men and women with COVID-19 infection were statistically different. This includes CRP, NLR, IL-17, IL-22, and the IL-17/IL-22 ratio (p>0.05 for all).

DISCUSSION

The current study revealed significant results that can be summarized as follows: (i) IL-17 significantly increased in COVID-19 patients with upper respiratory tract infection compared to healthy individuals, but there was no significant difference in IL17 levels between the pneumonia patients and those experiencing cytokine storm with the control group. IL-22 levels were not significantly different among all the groups of COVID-19 patients compared to healthy subjects. A statistically significant increase in the IL17/IL-22 ratio was observed in the patients with cytokine storm. However, no significant statistical difference was found between the two groups. (ii) NLR significantly increased in COVID-19 patients compared to healthy individuals, (iii) additionally, NLR correlated with CRP and CO-RADS score, while IL-22 (inversely) and the IL-17/IL-22 ratio (positively) only correlated with CO-RADS score, and (iv) NLR demonstrated high sensitivity and specificity in predicting COVID-19 infection, which was higher than that of IL-17, IL-22, and the IL-17/IL-22 ratio.

Th17 plays a role in autoimmune diseases and tumor progression (24). Its involvement in infections has been demonstrated in the defense against extracellular bacteria (25). Virus infections do not interact directly with Th17 cell. Furthermore, studies have showin that Th17 is associated with the pathogenesis of infections such as Hepatitis-B (HCV), Herpes simplex virus (HSV), Human papilloma virus (HPV), and Respiratory Syncytial Virus (RSV) (26, 27). The role of Th17 varies depending on the virulence and the infectivity of the viruses (25, 27). In COVID infections, studies have shown an increase in IL-17 levels in cases of severe infections (28, 29). However, it is important to note that IL-17 is not only released from Th17 cells but also from NKT cells, ILC, γδ-T cells, mast cells and neutrophils during an infection (14). IL-17 also attracts neutrophils and monocytes to infected tissues promoting the release of cytokines such as G-CSF and IL-6. It induces the production of chemokines such as (CXCL) 1, CXCL2 and CXCL10, facilitating the recruitment of myeloid cells to the site of infection (30). We found that patients presenting with upper respiratory tract infection had higher serum levels of IL-17 compared to the controls. However, we were unable to establish a statistical significance in the group of patients who developed pneumonia and cytokine storm. We also observed an increase in the IL-17/IL-22 ratio in the group experiencing cytokine storm. These results suggest that there is an inflammation with IL-17 dominance in the initial stages of COVID infection. As the viral infection progresses, the increase of IL-17 is regulated by compensation mechanisms. The patient will either improve or deteriorate depending on this mechanism, ultimately determining the clinical outcome. We believe that IL-17 dominance emerges as the disease progresses, leading to neutrophil-dominant inflammation that hinders the repair of infection-related damage. However, the

current study was hindered by a low number of control subjects, primarily due to subject attrition throughout the study, including instances of participants discontinuing participation and loss of contact. This could potentially impact the validity of our study findings. Additionally, there was a smaller number of patients with severe clinical symptoms, which may have influenced the outcome.

The number of patients with pulmonary involvement scores of 4 and 5, according to the CORADS, was 18 (23). The CO-RADS score significantly correlated with the IL-17/IL-22 ratio (positive correlation) and IL-22 levels (inverse correlation). Indeed, the CO-RADS score was reported to be correlated with pulmonary involvement in subjects with COVID-19 infection (23). IL-22 plays a role in protecting the epithelial barrier, promoting epithelial homeostasis and healing. When deficient, organ damage healing prolong and deteriorate (31, 32). In our study, it was shown that the levels of IL-22 decreased as the severity of COVID-19 infection increased. Additionally, an increase in the IL-17/IL-22 ratio was observed as the disease progressed. As the infection persists and progresses, a decrease in the level of IL-22 will lead to deficiencies in the repairing damage to the lung epithelium worsening the disease. Conversely, cases of good clinical response to COVID-19 pneumonia and cytokine storm with IL-17 inhibitor Secukinumab have been reported (33, 34). Our conclusion is that IL-17 dominance resulting from a decrease in IL-22 disrupts the balance of mucosal stability and impairs repair function. Therefore, the IL-17/IL-22 ratio may have a predictive value in the progression of the disease. We consider Secukinumab to be a suitable treatment option for severe COVID-19 infection. However, if the pneumonia phase of the disease continues to progress despite viral infection and supportive treatment, Secukinumab may be one of the treatment options. Nevertheless, further research is necessary to confirm this issue.

Although lymphocyte levels often increase in viral infections, it is unexpected that lymphocyte levels decrease in most patients with COVID-19 (34, 35). It has been reported that lymphopenia develops in a significant proportion of patients. Accordingly, average NLR levels may increase in COVID-19 patients (36, 37). In our study, the average NLR level in COVID-19 patients was found to be significantly higher than in the control group. We attribute this to the dominance of Th17 inflammation and high levels of IL-17.

Our study has several limitations. Firstly, the limited size of our study population, especially in relation to control subjects, undermines the reliability of our findings. Secondly, the single-center design of our study may impede the generalizability of our results. Additionally, we did not conduct a thorough analysis before collecting data. The disparity between the groups also posed a limitation to the study. However, to the best of our knowledge, this is the first study in the literature that reported a significant correlation between the IL-17/IL-22 ratio and CO-RADS score as well as clinical findings in COVID-19 subjects.

The findings from our study show that IL-17 increased during the initial period of COVID-19 infection. In addition, IL-22 levels and the IL17/IL-22 ratio were found to be associated with Co-RADS scores which indicate the level of lung involvement in COVID-19. Therefore, these results suggest that IL-17, IL-22, and the IL-17/IL-22 levels could provide valuable information for diagnosing and tracking the progression of COVID-19.

ACKNOWLEDGMENTS

The IL-17 and IL-22 serum kit was provided by Samsun Education Research Training Board. No other financial support was received.

AUTHORS' CONTRIBUTION

SA conducted all work related to the current

study. SG performed IL-17 and IL-22 laboratory analysis.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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