Original Article

Role of some interleukins in SARS-CoV-2 severity

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Abstract

This study was established to detect some of the immune parameters changes that accompany Patients with SARS-CoV-2 who have varying degrees of illness severity, by targeting three groups of mild, moderate and severe cases of patients, while the fourth group was healthy volunteers as well as unvaccinated and it represents the group we took 20 samples from each of these four groups, and we performed the following tests for them: IL-1β, IL-17A and IL-18.

In mild case: According to the study's findings, there has been a considerable rise, ($p \leq 0.01$) in the levels of IL1β, IL-17A and IL-18 in SARS-CoV-2 patients group when compared with healthy group.

In moderate case: The results of this study found a high significant increase ($p \leq 0.01$) in levels of IL1β, IL-17A and IL-18 in SARS-CoV-2 patients group when compared with healthy group, healthy group, but IL-17A level lower than in moderate case compared with mild case.

In severe case: The results of this study found a high significant increase ($p \leq 0.01$) levels of IL1β, IL-17A and IL-18 in SARS-CoV-2 patients group when compared with healthy group, but IL-17A level lower than in moderate case compared with mild case and moderate case.

Keywords: Interleukin 1β, Interleukin 17, Interleukin 18 and SARS-CoV-2 disease.

INTRODUCTION

It is a single-stranded (ss) RNA virus with positive sense that shares genetic traits with other coronaviruses in the betacoronavirus 2B lineage. SARS-CoV-2, or respiratory distress syndrome one of its other names is coronavirus 2, viral infection is the root cause of this disease, which manifests clinically as severe acute respiratory syndrome (SARS) [1] As is the case with other coronaviruses, SARS-CoV-2 invades host cells by way of the spike glycoprotein (S protein), an essential target for antiviral drugs and antibodies, the S protein has the RBD that binds receptors for angiotensin-converting enzyme-2 (ACE2), as a result, the S protein is an important antiviral target. The severe respiratory illness associated with coronavirus type 2 is brought on by the virus SARS-CoV-2 (SARS-CoV-2). On the other hand, the nucleocapsid protein, sometimes referred to as N, together with other the immune response may potentially be boosted by structural or non-structural SARS-CoV-2 proteins of the host [2,3].

The clinical picture of SARS-COV-2 may be traced back to the virus' attachment to endothelial cells, which induces endothelium dysfunction and, later on, microvascular thrombotic and inflammatory events [4] Although there is a wide variety of cell types that are susceptible to infection by SARS-CoV-2 due to the presence of ACE2 receptors (endothelial cells, oropharyngeal mucosal cells, pneumocytes, the gastrointestinal tract, and others), there is only one cell type that can become infected with the virus [5].

The attachment of the SARS-CoV-2 virus to the ACE2 receptors that are located on the surface of cells is the initial stage in the progression of the disease caused by this virus, the next phase is the hyperactivation of immune cells, such as NK cells, macrophages, and other immune cells, which causes these cells to produce chemokines and cytokines [6,7].

This step is followed by the hyperactivation of immune cells, SARS-CoV-2 is capable of causing damage to a wide range of organs, and one of the most successful ways for avoiding or treating this damage is to prevent or cure the uncontrolled infiltration of cytokines [8], SARS-CoV-2 may cause harm to a wide number of organs. It is probable that elevated levels of cytokines are the major source of the harm that has been done to several organs as a result of this dysregulated and hyperinflammatory response, the SARS-CoV-2 virus has the potential to harm a wide array of organs [9].

Interleukins are a type of cytokine that are expressed and secreted by leukocytes as well as some other types of cells in the body, the human genome encodes for more than fifty different interleukins and related proteins, Leukocytes are responsible for the expression and release of interleukins [10].

Even though the complications that are associated with Although it is simple to discover uncontrolled and elevated amounts It might be difficult to tell the difference between a healthy and unhealthy response to cytokines and chemokines. Because certain cytokines are required to provide an efficient immune response in order to clear intracellular illnesses like viral infection, it may be challenging to discern between a normal and dysfunctional cytokine response, this is because certain cytokines are necessary to eradicate intracellular illnesses like viral infections [11].

The purpose of this study is to identify the values of specific parameters within the severity of SARS-CoV-2, evaluate some interleukins in the blood severity of SARS-COV-2 patients, and investigate the function that these interleukins play in the immune response.

Materials and working methods

Participants in the study had to have a positive RT-PCR result for SARS-CoV-2 and were either hospitalized or treated as outpatients. Their ages ranged from 25 to 87 years, and they were categorized into mild, moderate, and severe categories according to the severity of their symptoms and their Spo2 levels. In addition, the study contained 20 control volunteers who seemed to be healthy and were justified as persons who did not have any chronic disorders, the following examinations were carried out on each of the groups: IL-1, IL-17A, and IL-18, as well as an evaluation of one's immune system and overall health, these assay the quantitative sandwich enzyme immunoassay technique by Human ELISA device, Cusabio Kit made in USA.

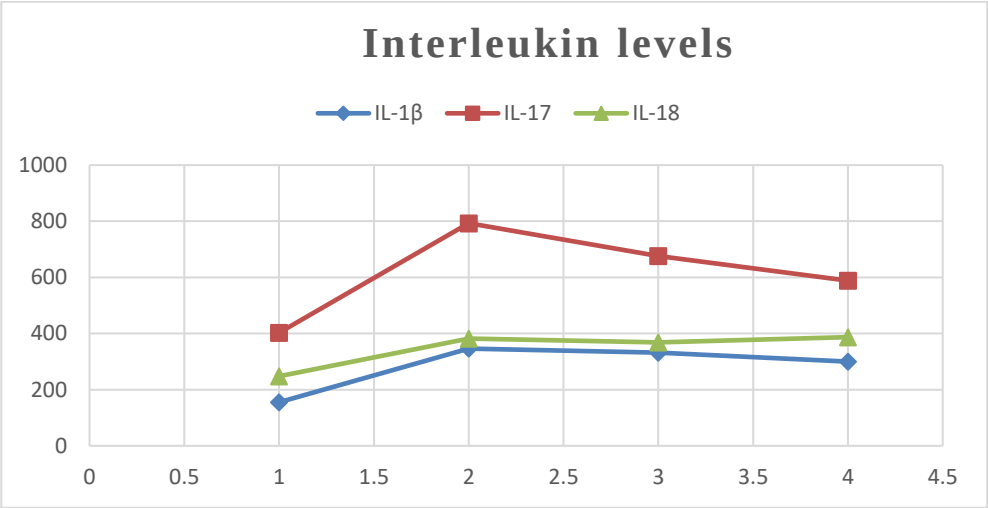
Results:

Different results were obtained among the three groups that we took (mild, moderate and severe) and according to what is mentioned in the working methods, the concentrations of these interleukins were as shown in Table 1 and Figure 1.

Table: 1: General result of interleukins patients and control group

	Control group and Severity SARS-COV-2 Patients				
Parameters levels	**Control**	**Mild**	**Modreat**	**Sever**	***P*-value**
	Mean ± SD				
IL-1β pg/ml	**155.400±35.870**	**346.500±27.120**	**332.350±19.746**	**300.150±28.303**	**≤ 0.01**
IL-17A pg/ml	**403.00±113.061**	**793.150±103.883**	**676.750±103.883**	**588.150±58.591**	
IL-18 pg/ml	**248.00±69.923**	**382.550±51.910**	**368.350±20.825**	**387.350±32.496**	

IL-: Interlukin



1: control, 2: mild, 3: moderate, 4: severe

Figure 1. Interleukins levels patients and control group

Discussion:

1. Role of IL-1β in Severity SARS-CoV-2:

The results shown in Table 1. and Figure 1. indicated a significant difference in describe the levels of IL-1β from increase among the all severity groups, ((mild, moderate, and severe) in contrast to the control group at the probability level P≤ 0.01.

Inflammation of the lungs and tissues, fever, and fibrosis are all caused by stimulated IL-1, which is caused by viral infections [12] because macrophages undertake phagocytic activity on the debris of dead cells and tissues, macrophages stimulated by SARS-CoV-2 are essential for the pathogenesis of fibrosis, this is because macrophages release inflammatory chemicals throughout the process [13], Activation of TLR2, TLR3, or TLR4 by COV-19 results in the production of inflammatory cytokines like IL-1, and these responses can be linked to Danger-associated molecular patterns (DAMPs) that include receptors called "pattern recognition receptors" (PRRs), which also include toll-like receptors (TLRs) [14]., Proinflammatory cytokines are crucial mediators in both local and systemic inflammation, In particular, IL-1 is the most important proinflammatory cytokine, macrophages are necessary for the pathogenesis of fibrosis due to the fact that they phagocytose dead cells and tissues, SARS-CoV-2 stimulation of macrophages is responsible for this [15], after SARS-COV-2 binds to the TLR, a complex forms and releases the pro-inflammatory cytokine IL-1 , IL-1 is then released outside of the macrophage and causes fever, fibrosis, and swelling in the lungs, as well as severe respiratory difficulties [16].

Serum levels of IL-1β were shown to be considerably higher in the mild, moderate, and severe cases, and likely play a proinflammatory in the spread of SARS-CoV-2 and a cytokine storm, as previously established by other investigations [17,18,19], but the level of IL-1β does not reflect the severity of the disease through our study, because there was no significant difference among the study groups of mild, moderate and severe, although it was much higher than the control group.

2. Role of IL-17A in Severity SARS-CoV-2:

According to the findings presented in Table 1. and Figure 1., statistically speaking, the difference between the levels of IL-17A from a gradual increase among the different severity groups, (mild, moderate, and severe), in comparison to the control group at the probability level of P≤ 0.01, but the mild group had levels that were higher than moderate group, and mild and moderate groups had levels that were higher than the severe group.

The results are a significant difference in the levels of IL-17A from a gradual decrease among the different groups, a greater priority than the moderate and severe groups group, and moderate group higher than severe group, this is confirmed by Ghazavi et al., (2021), there are studies that indicated an increase in IL-17A in patients with SARS-CoV-2 [20], but they did not indicate the type of severity such as: [21,22,23].

They help to keep the immune system in balance by dampening overactive immune responses, and abnormalities in their regulation have been linked to a wide range of human conditions, such as autoimmune illnesses, allergies, and cancer, T-regulatory cells play a significant they play also make a contribution to the homeostasis of the immune system, in addition to their involvement in the control of the immunological response [24].

Although conventional T-regulatory when exposed to an inflammatory environment, there is mounting evidence that Treg. cells will produce cytokines that promote inflammation, cells exercise their suppressive impact through through producing anti-inflammatory cytokines including IL-10 and transforming growth factor, in particular, cell-cell contact-dependent and contact-independent mechanisms, these cytokines are responsible for the suppression of inflammation TGF and IL-17A [25]. This is despite the fact that traditional T-regulatory cells use both contact-dependent and contact-independent methods to exert their suppressive impact, this is true even when typical T-regulatory cells decrease immune responses via both contact-dependent and contact-independent routes, this is true despite the fact that both contact-dependent and contact-independent routes are used by classical T-regulatory cells to carry out their suppressive function.

Because it is involved in the inflammation that takes place in the airways, the potent pro-inflammatory cytokine known as IL-17A is a crucial factor in the overactivation and the overwhelming inflammatory reaction of the body's defensive system [26]. This is because it plays a role in the inflammation that takes place in the airways, According to Zhou et al., which investigations in particular shown that IL-17A has a driving role in the development include pulmonary hypertension, lung fibrosis, emphysema, acute lung injury, patients diagnosed with ARDS had elevated levels of IL-17A in their serum [27,28].

The moderate patients had a significantly higher mean level of IL-17A when weighed against both the severe , as well as the control group. This variation was statistically noteworthy, the production of IL-8, which is a powerful neutrophil chemoattractant, is stimulated thanks to IL-17A, which is responsible for this stimulation. As a direct result of this, IL-17A is responsible for a substantial part of the control of neutrophil responses. Most notably, neutrophils have been found to play a function in a number of disorders that affect the immune system, one of which is acute lung injury. In addition, neutrophils have been shown to play a role in a number of conditions that affect the skin [29].

According to the findings of study, delay in clearing up and remaining in the host is caused in part by viruses' capacity to activate and stimulate T-reg cell growth [30,31], TGF- is used by the SARS-CoV-2 as a method for inhibiting the immune response, taking into account the fact that the virus may continue to replicate. Some studies show that TGF- may inhibit the production of Th17 cells. T-reg cells modify the extent of immunity and the result of viral infections [32].

TGF- is a pleiotropic cytokine that has powerful regulatory and inflammatory action [33], this is One of the factors contributing to the decline of patients who recover from their infections this is one of the factors that may have contributed to the decline in patient numbers. who recover from their infection [34].

During the course of our investigation, we came to the conclusion that the concentration of this interleukin gradually drops from mild to moderate to severe cases. This finding suggests that the immune regulation is less robust in severe cases when compared to moderate instances, and when moderate cases are included, when compared to mild cases.

3. Role of IL-18 in Severity SARS-CoV-2:

The findings there was a statistically significant difference in the levels of IL-18 by rise across the severity groups (mild, moderate, and severe), as shown in Table 1 and Figure 1,) compared to the control group at the probability level of P 0.01,

There is a kind of cytokine known as IL-18, a component of the cytokine family known as IL-1, these cytokines have essential roles in the innate and adaptive immune responses, as well as in fibrosis and hematopoiesis, IL-18 is largely generated by monocytes, whereas IL-12 is produced by both monocytes and lymphocytes [35] after the innate immune responses are launched by macrophages in response to damaging stimuli like viruses, the adaptive immune system is then activated., which is brought on by an increase in IL-18 levels [36].

A higher amount of IL-18, which results in a greater activation of the virus's Toll-like receptor [37], effect of IL-18 is a potent inducer of the pro-inflammatory Activation of Th1, NK cells, and the cytokine known as IFN- and macrophages [38].

Increased vascular permeability is what causes increased levels of IL-18, which in turn leads to decreased tissue perfusion, in addition to endothelial degradation and the creation of microthrombus [39], suppressing IL-18 has been shown to be therapeutically efficient in the treatment of certain inflammatory diseases, including SARS-CoV-2, which causes fluid to build up in the interstitial spaces and lung tissue and causes abrupt respiratory failure in patients [40].

It is very difficult to compare the levels of IL-18 with SARS-CoV-2 severity because to a lack of international and domestic research, which is only limited to severe cases. Nevertheless, our study is consistent with the high level of IL-18 in severe cases only, which is the only population that our research focused on, This is referred to research such as [40,41, 42].

There is only one research that indicates the severity of IL-18 for SARS-CoV-2, but our results differed with them from this research [36].

Conclusion

The severity of the illness, which is connected to the high release of cytokines, is what causes the hyper-inflammatory response that results in pneumonia, lung failure, and harm to many different organs in SARS-CoV-2-infected individuals, increase of IL-1β and IL-18 levels in all severity group compared with healthy group, IL-17A increase levels mild group more than moderate and severe group, and in moderate group more than severe group.

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