Nat. Volatiles & Essent. Oils, 2021; 8(4): 5317-5327

NVEO
Natural Volatiles &
Essential Oils

The Effect Of Aggressive Immune Response Representing by Interleukin 6 (IL-6) In Patients With COVID19

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Abstract

The pathogen that causes coronavirus disease in 2019 is the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) (COVID-19). COVID-19 has claimed the lives of 347,192 people worldwide as of May 25, 2020. According to the latest research, extremely unwell patients have a higher concentration of pro-inflammatory cytokines such as interleukin (IL)-6 than those who are moderately ill. In COVID-19, the high amount of cytokines also suggests a poor prognosis. Increasing evidence suggests that the "cytokine storm" may play a role in COVID-19 mortality. The clinical and pathologic aspects of the cytokine storm in COVID-19 are summarized here. SARS-Cov-2 specifically produces a high level of IL-6 and causes lymphocyte exhaustion, according to our findings. This study aims to show the effect of high immune response In patients of COVID19 that lead to what is called cytokine storm this storm must be prevented by inhibiting IL-6 to be more controlled cases.

Keywords: COVID-19, IL-6,and cytokine storm.

1. Introduction

1.1. Coronavirus (COVID-19)

COVID-19 disease 2019 first appeared in Wuhan, China, in December 2019 and quickly spread around the world due to an increase in cases. The disease is caused by the extremely contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lai et al., 2020). As of June 15, 2020, a total of 7,823,289 cases of SARS-CoV-2 infection had been confirmed worldwide. COVID-19 has been linked to 431,541 fatalities (World Health Organization, 2020)[(1)]. The condition has a wide spectrum of severity. Asymptomatic and moderate flu-like symptoms, such as fever, dry cough, weariness, or muscle soreness, were seen in some persons. Infected people, on the other hand, may become extremely unwell and even die[(2)]. Acute Respiratory Distress Syndrome (ARDS) is a condition (ARDS), Some of the severe clinical indications of COVID-19 progression are pneumonia and various organ dysfunction, according to experts [(3)].

1.2. Interleukin-6

Interleukin-6 is a cytokine that has a diverse set of biological functions. It functions as a mediator for immunoglobulin type substitution and acute phase response regulation. It's also a sign of inflammation in the body[4]. IL-6 can also be used as an investigative marker in the case of bacteremia [5].

IL-6 is an endogenous molecule that plays a function in both B cell growth and the inflammatory response. It can act as a pyrogen, generating fever in cases of infection, non-infection, and autoimmune diseases. Tumors, injuries, burns, and infections can cause chronic or acute inflammation, depending on the situation [6].

In addition, IL-6 is expected to reduce the risk of diabetes and the systemic form of juvenile rheumatoid arthritis, macrophages and monocytes produce IL-6 in response to other inflammatory cytokines such as tumor necrosis factor (TNF)-beta and interleukin-11. IL-6 receptors are present in the resting phase of normal activated B-cells, hepatic and myeloid cell lines, as well as normal T cells. B-cells that have been converted by the Epstein-Barr virus produce IL-6, by activating transcription factors identified in a variety of inflammation pathways, IL-6 causes an inflammatory response. Protein kinase C is the starting point in addition to cAMP/protein kinase A, and calcium release[7,8].

IL-6 on the basis of its manufacturinghas a variety of functions and forms, as well as pleiotropic activity, in the early stages of infectious inflammation, macrophages and monocytes generate IL-6 when Toll-like receptors (TLRs) are stimulated with distinct pathogen-related molecular patterns (PAMPs), when non-infectious inflammation, such as traumatic inflammation, arises,damage-related molecular patterns (DAMPs) from damaged areas activate TLRs, causing them to generate IL-6 [9,10].

1.3. Cytokine storm

The importance of cytokines in the immune response, such as a defense mechanism against viral infection, has long been recognized [11]. However, the SARS-CoV-2 infection has become more severe caused an overabundance of cytokines to be released (cytokine storm), which could lead to pneumonia [12]. The cytokine storm, which has been reported to be present in ARDS and multi-organ functional derangement due to an overactive immunological response, plays an important role in producing ARDS and multi-organ functional derangement as in Figure 1[13]. COVID-19 in severely sick patients [14, 15]. As a result, one of the therapeutic techniques for preventing COVID-19 progression and saving the patient's life is to limit or inhibit the cytokine storm. The current literature on COVID-19 and SARS-CoV-2, its relationship with cytokine storm, and current and stem cell-based therapeutic options are reviewed in this paper. to stop the cytokine storm in COVID-19 patients. This review aimed to give relevant information for the formulation of clinical guidelines for COVID-19 diagnosis and therapy[16, 17].

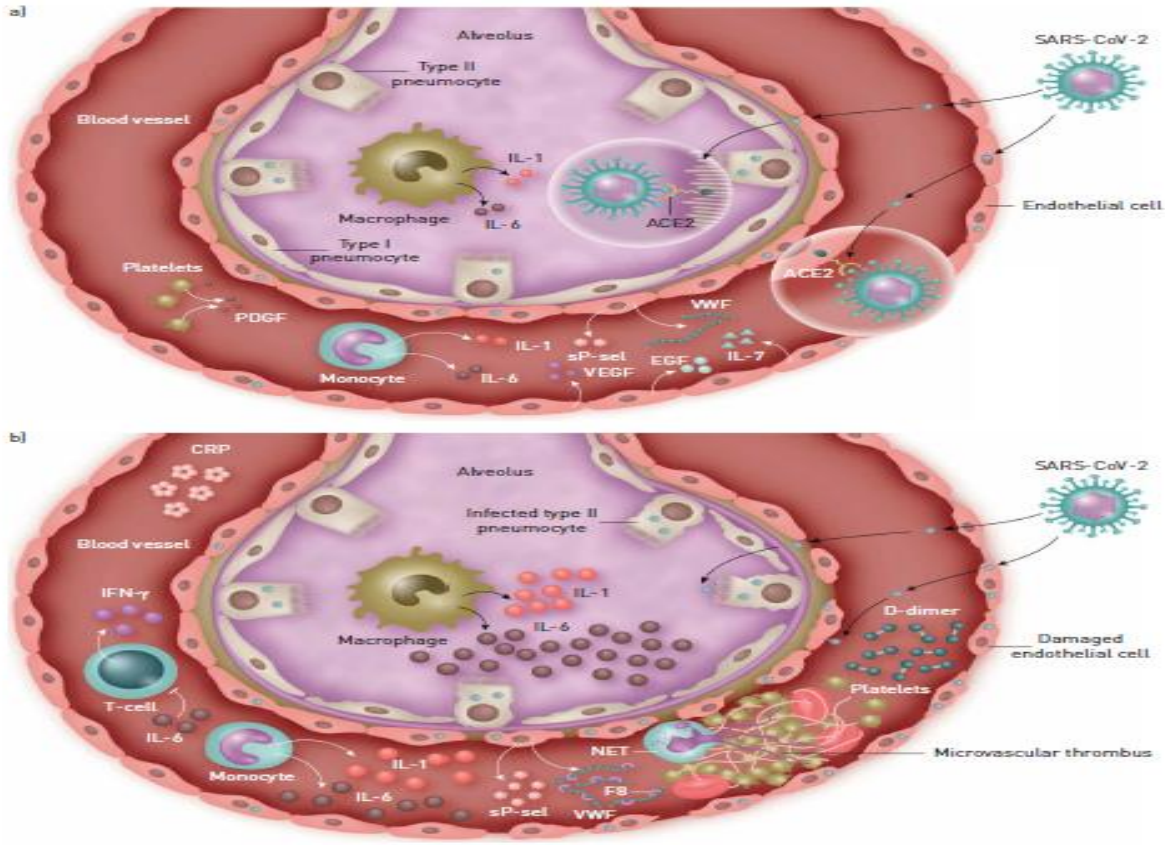

Figure 1: TheRole of IL-6 in COVID19[13]

2. Method

2.1. Study individuals

In this case-control study, 200 individuals have been selected they were divided into twogroups: group (A) contain 100 patients with COVID19 from a private infectious clinic in AlNajaf Al-Ashraf in Iraq,and group (B) contain 100 healthy individuals, group A were also divided according to sex, ages, and duration of disease.

2.1.1. The inclusion and exclusion criteria

All the selected patients were well diagnosed by the physician to have COVID19, without any chronic diseases the age of all 200 individuals was between 15 to 60 years old, other patients with chronic disease were excluded.

2.1.2. Statistical analysis

To analysis, the data between the two groups the student Tand ANOVA tests were used SPSS Inc., Chicago, IL.

3. Result and discussion

3.1 Distribution of the Enrolled Patients

The evaluation of the data indicated that the selected patients were distributed according to different factors.They were distributed according to sex, age,and the duration of the disease.The characteristics of the COVID19 patients are mentioned in Table 3.1 by mean and the standard deviation (Mean ± SD).

Table 3.1 Characteristics of patients included in the study

Factors	Mean ± SD
Sex (m/f)	52/48
Age (years)	36.15 ± 12.35
Duration of disease (days)	18.15 ± 4.23
IL-6 (pg/ml)	21.31 ± 3.5

3.2. Levels of Interleukin-6 (IL-6) in COVID19 Patients and the Control Group

When comparing the amounts of IL-6 in COVID19 patients to those in the control group, there was a substantial increase ($p < 0.001$) (Table 3.2). Increased IL-6 levels in COVED19 patients could be due to persistent infection, impaired cytokine clearance in the kidneys (caused by increased production, decreased removal, or both), accumulation of advanced glycosylation end-products that can trigger the inflammatory response, and reduced plasma antioxidant capacity caused by infection-induced oxidative stress. COVID19 infection can affect renal function, resulting in decreased urinary IL-6 receptor clearance and higher circulating levels of IL-6 soluble receptors than healthy controls [18-20].

The pathophysiology of COVID-19, as well as many infectious diseases, is dominated by cytokine release syndrome. Through the angiotensin-converting enzyme 2 (ACE2) receptor, SARS-CoV-2 infects alveolar epithelial cells mostly alveolar epithelial type 2 (AEC2) cells. The virus is released once epithelial cells are destroyed and cell permeability increases. The innate immune system is activated by SARS-CoV-2, which causes macrophages and other immune cells to release a high number of cytokines and chemokine, including interleukin-6 (IL-6). Antigen-presenting cells can also trigger adaptive immunity. T- and B-cells not only perform an antiviral role, but also increase the release of inflammatory cytokines, either directly or indirectly. Furthermore, when inflammatory stimuli stimulate the alveoli, a high number of inflammatory exudates and erythrocytes enter the alveoli, causing dyspnea and respiratory failure [9,12,21].

Table 3.2 Serum Interleukin-6 (IL-6) levels in COVID19 patients and the control group

Parameter	Subject	NO.	Mean ± SD	Range	P-value
number	Patients	100	**********	**********	> 0.001
	Control	100	**********	**********	
Sex (m/f)	Patients	(52/48)	**********	**********	> 0.001
	Control	(55/45)	**********	**********	
Age (y)	Patients	100	36.15 ± 12.35	12-60	> 0.001
	Control	100	35.12 ± 11.23	13-58	
IL-6 (pg/ml)	Patients	100	8.24 ± 1.01	6.44–10.15	< 0.001
	Control	100	3.53 ± 0.33	2.31 – 4.52	

3.3 The Effect of Sex on Serum Levels of Interleukin-6 in COVID19 Patients:

In this study,according to the statistical analysis,there is no significant difference in the levels of IL-6 between bothsex groups, as in Table 3.3.

The underline cause is due to the effect of sex hormones, such as estrogen and testosterone, that shown to modulatecytokine expression (IL-6) in addition to the acute-phase protein CRP in human macrophage cells, the results seem to be less in male rather than female the cause is the effect of testosterone more than progesterone in immune modulation with no effects according to gender differences. It's likely that there is an identical increase of IL-6[22,23].

Table 3.3 Serum Interleukin-6 (IL-6) levels in COVID19 patients according to sex variation

Parameter	Male	Female	Mean ± SD	Range	P-value
Sex (m/f)	52	48	********** **********	********** **********	> 0.001
IL-6 (pg/ml)	male	52	6.53 ± 1.25	4.25 - 9.12	>0.001
	female	48	7.12 ± 1.55	3.85 - 10.15	

3.4 The Effect of Age on Serum Levels of Interleukin-6 in COVID19 Patients

In this study, the patient's group was divided into five groups according to age each group has a gap of about ten years to show the effect of aging on the deterioration of immune reaction of COVID19 patients.

The result was a significant increase in immune reaction in aged patients rather than those patients with less age that may cause cytokine storm in older patients more than others as in Table 3.4.

Aging is a complex process that includes morphological and metabolic changes in individual cells as well as the entire body [24]. Immunosenescence is the result of ongoing attrition caused by lifelong antigenic load, which is responsible for persistent immune system activation and pro-I inflammatory cytokine hyperproduction [25].

The condition of chronic inflammation that characterizes aging is known as inflame-aging. It is the result of the immune system's ability to combat stressors, and it serves as the foundation for a wide spectrum of age-

related disorders with an inflammatory etiology, aging was linked to an increase in systemic oxidative stress, which is one of the most common causes of elevated inflammatory markers in all patients[26].

So that aging is associated with significant changes in cell surface cytokine receptor expression patterns, implying a possible mechanism that may contribute to senescent changes in cardiac microvasculature activity and may be downregulated in older endothelial cells of cytokine receptors (s)[27].

Table 3.4 Serum Interleukin-6 (IL-6) levels in COVID19 patients according to age groups

Age groups	NO.	IL-6 (pg/ml) Mean ± SD	Range	P-value
15-25 years	15	5.20 ± 0.36	3.84– 5.25	< 0.0001
26-36 years	25	7.05 ± 0.25	6.15 – 7.30	
37-47 years	28	8.23 ± 0.55	7.50– 8.25	< 0.0001
48-60 years	32	10.12 ± 0.33	9.12 – 10.15	

3.5 The Influence of Duration of COVID19 infection on Interleukin-6 (IL-6)

In this study, the patient's group was divided into three groups according to the duration of infection to show the effect of duration time of COVID19 infection on the deterioration of immune reaction.

The result of this study was a significant increase of cytokine storm represented by IL-6 that was increased in patients with a long duration than patients with less duration as in Table 3.5, there are many underlying causes of this phenomenon, firstly, the long duration may cause multi organs dysfunction leading to exacerbation of immune reaction, secondly, other cause in the long duration of COVID19 patient may cause more immune reaction because of the continuous fight between the virus and the immune response[28,29].
This is the first study to develop and use a new score to swiftly identify COVID-19 individuals who are at a hyper-inflammatory stage and treat them quickly to avoid intubation (ventilator invasive support). Cytokines have long been thought to play a crucial role in viral infection immunopathology. The first line of defense against viral infections is a quick and well-coordinated innate immune response. Immune responses that are dysregulated or overactive, on the other hand, inflict harm to the human body [30,31].

Interleukin (IL)-6, IL-10, and TNF-_ are significantly greater in severe COVID-19 infected patients, and proinflammatory cytokines and chemokine are known to contribute to the formation of cytokine storm, most experts believe that COVID-19's "cytokine storm" is to blame for the disease's progression to a more severe state and that controlling it early on is crucial to lowering mortality[32-34].

Table 3.5 Serum Interleukin-6 (IL-6) levels in COVID19 patients according to duration of infection

Duration of infection (days)	**NO.**	**IL-6 (pg/ml) Mean ± SD**	**Range**	**P-value**
Less than 5 days	22	5.15 – 0.63	3.85 – 7.22	< 0.005
5 – 10 days	30	9.35 – 0.25	9.88 – 10.33	

More than 10 days	48	11.22 ± 0.33	10.25 – 12.13	

4. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have, or could be perceived to have, influenced the work reported in this article.

5. Acknowledgments

The author would like to thanks to participants who were willing to give a response to the data of this survey. And I thank all who helps to complete this article especially Ali.

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