Assessment of Interleukin-10, 20, and Matrix Metalloproteinase-7 in Iraqi Patients Infected with COVID-19

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ABSTRACT

Background & Objective: COVID-19, caused by SARS-CoV-2, can lead to a wide range of clinical severities in infected individuals. Among the observed manifestations, pulmonary fibrosis stands out, characterized by chronic inflammation and collagen buildup in the interalveolar space. Numerous studies have indicated that proinflammatory cytokines may contribute to this condition. The cytokine storm, a critical phase in the deterioration of COVID-19 patients, plays a significant role in this process. The main objective of this study was to determine the levels of IL-10, IL-20, and MMP7 in COVID-19-infected people.

Materials & Methods: During the period between November-2022 to March-2023, a case-control study with 200 participants was carried out at Al-Ramadi Hospitals in Anbar province, Iraq. A total of 100 individuals diagnosed with COVID-19 and 100 healthy controls (HCs) took part in the study. Serum concentrations of interleukins, including IL-10, IL-20, and MMP7, were assessed using enzyme-linked immunosorbent assays (ELISA).

Results: The current study revealed significant differences in IL-10 and IL-20 concentrations among the groups being compared with a P-value of <0.01. Notably, the COVID-19 group had significantly more MMP7 than the control group or the group of individuals who had recovered from the disease. This outcome raises the possibility that MMP7 could act as an independent indicator of COVID-19 infection.

Conclusion: Patients with COVID-19 disease had IL-10, IL-20, and MMP-7 levels that were noticeably higher than those found in healthy controls.

Keywords: COVID-19, Cytokines, IL-10, IL-20, MMP7

Introduction

The novel coronavirus pandemic has been characterized by a rapid spread of a recently discovered virus that causes systemic along with localized pneumonia complications all over the world. The virus was later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), observed first in China with an unknown etiology (1-3). Numerous studies have provided evidence that the genetic composition of this coronavirus is nearly identical to the SARS-CoV virus that emerged in 2003. Additionally, the coronavirus and SARS-CoV utilize ACE2 as a cellular receptor for infection (4, 5). The innate immune response serves as the initial line of defense against viral infections. Within the host's dendritic cells, pattern recognition receptors detect the presence of viral genomic DNA or RNA, triggering the production of cytokines and chemokines (6). Depending on the source and target cells of these signaling molecules, immune cells like macrophages,

neutrophils, and T-cells are then attracted to the infection site. Pro-inflammatory cytokines, including interleukins (IL-1, IL-6) and Tumor Necrosis Factor-α (TNF-α), play a significant role in the early immune response. On the other hand, during prolonged infections, anti-inflammatory molecules like Interleukin-10 (IL-10) are produced to regulate inflammation and maintain immune homeostasis (7). As previously mentioned, individuals with severe or critically ill COVID-19 display a notable increase in IL-10 levels in their blood, and this elevation is directly associated with the severity of the disease. Recent research findings also indicate immune activation and inflammation in COVID-19 patients, providing further support for the hypothesis that IL-10 might contribute to the pathogenesis of COVID-19 by exerting a proinflammatory and immune-activating role (8). Interleukin-20 (IL-20) is a cytokine that belongs to the IL-10 family. This family of cytokines shares some

similarities in their amino acid sequences but have different biological functions. IL-20 is a hematopoietic growth factor that can stimulate the growth of CD34+ multipotential progenitors but no other progenitor cells. It signals through a receptor system composed of type I IL-20Rα and type II IL-20Rβ. Overexpression of IL-20 in keratinocytes that express both receptor subunits have been linked to developing inflammatory skin diseases **(9)**.

Matrix Metalloproteinase-7 **(**MMP-7), also known as matrix metalloproteinase 7, indicates inflammation in viral infections. It functions as a protease responsible for breaking down the extracellular matrix, a network of proteins that supports tissues. In the lungs, the extracellular matrix helps keep the airways open and prevents fluid from leaking into the lungs. When the extracellular matrix is broken down, it can lead to inflammation and lung injury **(10)**. This suggests that MMP-7 could be used to predict which patients are at risk of developing ARDS and to track the progress of the disease **(11)**. The current study focuses on estimating the proinflammatory cytokines IL-10, IL-20, and MMP-7 in individuals diagnosed with COVID-19 in Anbar, Iraq.

Materials and Methods

Study Design:

During the period between November-2022 to March-2023, a total of 200 participants from Iraq were enrolled in this case-control study. With an age range of 18 to 72, 100 of them (patients' group) were found to have COVID-19 infection. The other 100 individuals were in good health and acted as the control group; their ages were similar to those of the patients. Each patient's data was obtained using a specialized questionnaire form.

Exclusion and Inclusion Criteria:

This section encompasses both the criteria for inclusion and exclusion. The inclusion criteria involved personal details like gender, marital status, and treatment status. The exclusion criteria encompass factors such as alcohol consumption, the number of children, smoking habits, use of heart medication, presence of Diabetes mellitus, and utilization of blood pressure medication. Each of these variables was meticulously taken into account. The demographic attributes of patients afflicted with COVID-19 comprised gender, age over 40, absence of medication for chronic ailments, along with a high severity level of COVID-19. Additionally, radiographic observations indicating abnormalities on chest computed tomography (CT) scans were made based on physician recommendations.

Identification of COVID-19 Infection:

These individuals sought diagnosis and treatment at Al-Ramadi Hospitals in Anbar province, with confirmation of clinical identification provided by the hospital's consultant medical staff. Molecular methods such as real-time PCR and the BIOZEK COVID-19 rapid test were used to confirm the presence of the virus in the samples.

ELISA Technique:

The measurement of interleukins IL10, IL20, and MMP7 was conducted using a human interleukin ELISA kit supplied by SUNLONG Biotech Co., LTD (China). The assay procedure was performed following the instructions provided by the company SUNLONG Biotech.

Research Ethics and Approval:

Prior to the study, all participants voluntarily agreed to give blood samples. Each participant provided informed consent, which was approved by the ethical approval committee at Ramadi General Teaching Hospital in Al-Anbar Province, Iraq. A structured questionnaire was utilized to gather information about the patients and controls, ensuring that data collection followed the guidelines outlined in the informed consent process.

The Statistical Analysis:

The statistical analysis of the serum levels of the parameters was performed using the ANOVA test via GraphPad Prism® Version 8.0 computer software. The data were presented as mean ± standard deviation (SD) or as a percentage (%). Student's t-test was utilized to calculate the comparisons between different groups as appropriate. A significance level of P-value$\leq$ 0.05 or P-value$\leq$ 0.01 was considered statistically significant.

Results

Figure 1 shows the baseline demographic characteristics of the 200 participants in the study. According to the data, males made up the majority of participants, accounting for 60% of patients and 54% of controls. The remaining participants were female, with 40% of patients and 46% of controls being female.
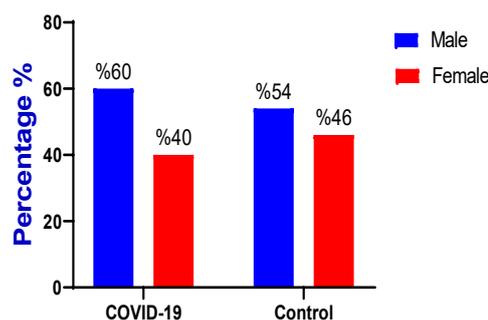

Figure 1. Displaying the distribution of the **study population based on gender.**

The mean serum concentration of cytokines (IL-10, and IL-20) in patients with COVID-19 and healthy individuals were presented in Table 1. The concentration of MMP-7 in the serum of patients with COVID-19 and healthy individuals was presented in Table 1. In the present study, the serum level of MMP-7 was significantly increased in patients with COVID-19

compared to controls (4.8±0.5 versus 1.46±0.13ng/mL, $P<0.0001$).

Table 1. The serum levels of IL-10, IL-20, and MMP7 in patients with COVID-19 and controls

Parameters	Normal range	Patients (n=100)	Controls (n=100)	P
IL-10 Conc.(pg/mL)	82-135 pg/ml	224.3+17.1	97.9+11.18	0.00004
IL-20 Conc. (ng/L)	85-276 ng/l	479.2+59.4	215.8+23.17	0.00002
MMP-7 Conc. (ng/mL)	1.28-1.78 ng/ml	4.8±0.5	1.46±0.13	0.0001

Discussion

COVID-19 infection can cause severe lung disease, including pneumonia and acute respiratory distress syndrome (ARDS). ARDS is a life-threatening condition that occurs when the lungs become inflamed and filled with fluid. This can make it difficult to breathe, and patients may require mechanical ventilation to help them breathe [12]. The cytokine storm involves the rapid release of inflammatory cytokines and chemokines, highlighting the dysregulated immune response observed in severe cases of COVID-19 [12].

According to the present study, there was a higher prevalence of infection in males, accounting for 60% of the cases, compared to females, who accounted for 40% of the cases. These findings are consistent with the outcomes of several other studies conducted in other countries. For example, Al Omari et al. (2020) conducted four studies in Saudi Arabia and reported that 80% of confirmed cases were males [13]. Alsofayan et al. (2020), also in Saudi Arabia, found that among 1519 confirmed SARS-CoV-2 cases, the infection rate in males was 54.4% [14]. Mohammed et al. (2021, Anbar of Iraq) observed that 66.3% of SARS-CoV-2 infections were males [15]. Alamri et al. (2021, Saudi Arabia) found that among all confirmed cases, the infection rate in females was 51.1% [16]. According to Shahriarirad et al. (2020), 62.8% of infections in Iran occurred among males, a percentage that was considerably greater compared to the prevalence in females [17].

Various results were supported by several studies, including [18], which indicated that the significant and rapid rise in IL-10 levels during the initial phases of severe COVID-19 cases is a noteworthy and seemingly contradictory finding given IL-10's traditional role as an anti-inflammatory cytokine [19]. Also, the same finding was observed by [20], among MERS-CoV patients, was found higher levels of IL-2R, IL-6, IL-10, and TNF-α. Other studies [21-23] found significantly higher levels of IL-10 in COVID-19 patients compared to the healthy control group. In COVID-19 patients, the levels of IL-10 in the peripheral blood were found to be significantly elevated in those admitted to the intensive care unit (ICU) when compared to patients who were not admitted to the ICU [24, 25].

Conversely, Cytokine is considered to be a response to the rapid accumulation of proinflammatory cytokines, acting as a negative feedback loop and serving as a potential biomarker in the disease [26, 27]. IL-10 plays a crucial role during infections by primarily inhibiting the host's immune response to pathogens and microbiota, which helps to mitigate tissue damage and immunopathology. Its main mechanisms involve the suppression of pro-inflammatory cytokine production and antigen presentation in activated monocytes/macrophages and dendritic cells. Additionally, IL-10 helps to regulate T cell activation and proliferation, preventing excessive immune responses [18, 28, 29]. IL-10's anti-inflammatory effects are primarily mediated by binding to the IL-10 receptor, which is mainly expressed in monocytes/macrophages. This interaction activates the JAK1-TYK2-STAT3 signaling pathway, leading to the transcription of genes mediated by STAT3. These genes help to restrict the inflammatory response [30], and the anti-inflammatory effects of IL-10 may specifically be mediated by its ability to induce SHIP1-STAT3 complex formation thereby differentiating IL-10 signaling from other cytokines that activate STAT3 [31]. In the present study, it was observed that the serum levels of IL-20 were significantly higher in COVID-19 patients compared to the control group (479.2+59.4 vs. 215.8+23.17 pg/mL, $P<0.001$). These results are in line with the findings of a research study by Saheb Sharif-Askari et al. (2022) that found elevated levels of IL-20 in COVID-19 patients' lungs, especially among those with severe disease. These results suggest that IL-20 may play a role in the development of severe COVID-19 by promoting inflammation and tissue damage in the lungs and other organs [32].

MMP7 is expressed by a variety of cell types, including epithelial cells, fibroblasts, and macrophages. It is involved in several biological processes, including 1- cell migration, 2-tissue repair, 3-inflammation, and 4-cancer [33]. These results are in agreement with the studies by Siouda et al. and Chavez-Galan et al. [28, 34], which indicated that MMP-7 levels were significantly increased in the serum of COVID-19 patients compared to healthy controls.

MMP-7, a versatile matrix metalloprotease, is closely linked to inflammatory lung injury observed in acute respiratory distress syndrome (ARDS). It exhibits overexpression in the lung microenvironment and elevated levels in the serum of patients diagnosed with various interstitial lung diseases, including idiopathic pulmonary fibrosis, which can potentially progress to fibrosis **(29, 35, 36)**. Overall, these findings suggest that MMP-7 may play a role in the development and progression of COVID-19, particularly about lung injury. However, more research is needed to understand the mechanisms underlying this association fully and to determine whether targeting MMP-7 could be a viable therapeutic strategy for the treatment of COVID-19 **(37)**.

In viral infections, higher matrix metalloproteinase-7 (MMP-7) levels have been determined as an inflammatory marker **(33)**. MMP-7 is an enzyme that breaks down the extracellular matrix present in the lungs after injury **(38, 39)**.

Conclusion

The presence of proinflammatory cytokines in COVID-19 patients can serve as a predictive factor for clinical severity, lung fibrosis, and mortality. The unregulated release of cytokines, commonly referred to as the cytokine storm, is associated with increased morbidity and mortality rates in these patients. However, certain cytokines exhibit protective effects, and elevated levels of these cytokines enhance the chances of survival. MMP7 and COVID-19 research are still in their early stages. More research is needed to confirm the relationship between MMP7 and COVID-19 and to determine the clinical significance of this relationship. Further investigations in Iraq on IL-10, IL-20, and MMP7 may shed light on the immunological and molecular aspects of COVID-19, possibly paving the way for the creation of specialized treatments or other interventions to enhance patient outcomes.

Ethical Approval

The current study is derived from the thesis of a medical student and approved by the Ethical Approval Committee of the University of Anbar, Anbar, Iraq (IRAQ.Anbar.07809839542).

Authors' Contribution

All authors contributed to the conception and design of the study, analysis of data, statistical analysis, preparation, editing, and reviewing of the article.

Conflict of Interest

The authors declared no conflict of interest.

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