



# Lymphocyte, IL-10, IL-6, and IFN- $\gamma$ Cytokines Modulation in SARS-CoV-2 Patients

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## Abstract

**Background:** The outbreak of Coronavirus Disease 2019 (COVID-19) shows significant challenges globally since its emergence in late 2019. This study aimed to investigate the severity of COVID-19 infection among patients admitted to Baquba Teaching Hospital, Diyala Province, Iraq, focusing on gender disparities and their correlation with laboratory results, including serum levels of Interleukin-10 (IL-10), Interleukin-6 (IL-6), and Interferon- $\gamma$  (IFN- $\gamma$ ). **Methods:** A cross-sectional study was conducted between September and December 2020, involving the collection of 172 human serum samples. These samples were divided into four groups: moderate, severe, critical, and control, with each group comprising forty-three samples. **Results:** Statistical analysis revealed a higher infection rate among males (65.9%) compared to females (34.1%). Lymphocyte levels exhibited a significant decrease in the male group ( $9.66 \pm 0.57\%$ ) compared to the female group ( $11.55 \pm 1.05\%$ ), with a p-value of 0.020. The level of IFN- $\gamma$  showed a significant increase in the female group ( $160.81 \pm 16.19$  pg/lm) compared to the male group ( $136.73 \pm 14.93$  pg/ml), with a p-value of 0.022. Furthermore, the levels of IL-10 and IL-6 significantly increased in the male group ( $247.70 \pm 23.93$  pg/ml and  $39.24 \pm 6.55$  pg/ml, respectively) compared to the female

group ( $174.75 \pm 18.63$  pg/ml and  $18.55 \pm 3.31$  pg/ml, respectively), with p-values of 0.009 and 0.008, respectively. **Conclusions:** The study concluded that the rate of COVID-19 infection is higher in men than in women. Additionally, lymphocyte count decreased in all COVID-19 patients, particularly significantly in the male group compared to the female group.

**Keywords:** IL-10, IL-6, IFN- $\gamma$ , COVID-19 severity, Gender differences, Cytokine levels, Lymphocyte count, Iraqi patients

## Introduction

The emergence of Coronavirus Disease 2019 (COVID-19) in Iraq marked a pivotal moment on February 24, 2020, when the country reported its first confirmed case. Since then, the global community has grappled with understanding the intricacies of this novel respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The primary modes of transmission identified early on included respiratory droplets and direct contact, highlighting the contagious nature of the virus (Jadoo et al., 2020; Ambrosino et al., 2020).

COVID-19 manifests with a spectrum of symptoms ranging from mild to severe, with common manifestations including cough, fever, dyspnea, myalgia, joint pain, gastrointestinal disturbances, and anosmia (Docherty et al., 2020). However, certain demographic and health factors have been identified as predisposing individuals to more severe outcomes. Advanced age, male gender, and underlying comorbidities such as cardiovascular diseases and diabetes have consistently emerged as significant risk factors

**Significance** | The study showed gender disparities in COVID-19 severity, revealing elevated cytokine levels of IL-10, IL-6, and IFN- $\gamma$  in males, as a potential immune response variation.

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associated with severe COVID-19 illness (Visuddho et al., 2021; Zuin et al., 2020; Chen et al., 2020; Henry & Lippi, 2020).

In severe cases, uncontrolled infection with SARS-CoV-2 can trigger a cytokine storm, characterized by an excessive release of pro-inflammatory cytokines and chemokines. This cytokine dysregulation leads to widespread tissue damage and multi-organ dysfunction (Williamson et al., 2020, Aishath et al. 2021, Esra et al. 2024). Among the prominent cytokines implicated in COVID-19 severity is interleukin-6 (IL-6), which is notably elevated in patients with severe disease and has emerged as a crucial prognostic marker (Tay et al., 2020).

Conversely, interleukin-10 (IL-10), an anti-inflammatory cytokine, plays a dual role in the immune response to COVID-19. Initially acting to mitigate excessive inflammation, IL-10's prolonged elevation during disease progression can paradoxically contribute to the cytokine storm, exacerbating tissue damage (Potere et al., 2021; Qin et al., 2020).

Interferons (IFNs), particularly IFN- $\gamma$ , are pivotal in antiviral defense mechanisms. Studies have shown that lower levels of IFN- $\gamma$  correlate with disease severity in COVID-19 patients, suggesting a potential role for early IFN- $\gamma$  intervention to mitigate viral replication and subsequent fibrosis (Hu et al., 2020; Lee et al., 2018). Lymphocytes, essential in orchestrating immune responses, have also emerged as critical players in COVID-19 pathogenesis. Lymphopenia, characterized by reduced lymphocyte counts, has been identified as a prognostic marker associated with disease progression and severity (Liu et al., 2020).

Gender disparities in immune responses have been observed in COVID-19, with males generally exhibiting higher susceptibility to severe illness and increased mortality rates compared to females (Yuan et al., 2020; Klein and Flanagan, 2016). To delve deeper into these gender-related differences, this study aims to investigate variations in COVID-19 severity between male and female patients, focusing on key immunological markers such as IL-10, IL-6, and IFN- $\gamma$ . By analyzing these cytokine profiles, researchers seek to uncover potential mechanisms underlying gender-specific variations in disease outcomes.

Understanding the interplay between gender and immune response in COVID-19 could offer crucial insights into tailoring therapeutic approaches and vaccination strategies. Clinicians may enhance personalized treatment strategies and prognostic assessments by identifying specific cytokine signatures associated with disease severity in males versus females.

In conclusion, lymphocytes play a pivotal role in immune homeostasis and serve as important prognostic indicators in COVID-19 patients. Gender disparities in immune responses contribute significantly to variations in disease severity, with males exhibiting heightened vulnerability to severe illness. This study endeavors to unravel the immunological mechanisms driving these

differences, with a particular focus on cytokine profiles as potential biomarkers of disease severity.

## Materials and Methods

### Study Design

This cross-sectional study evaluated the severity of COVID-19 infection among patients admitted to Baquba Teaching Hospital in Diyala Province, Iraq, from September 1st, 2020, to December 1st, 2020. A total of 165 patients were included based on a calculated sample size aimed at achieving a 95% confidence level with a margin of error between 7% to 8%. A 10% non-response correction was applied to the initial estimate.

Participants were categorized into four groups based on disease severity: moderate, severe, critical COVID-19 cases, and a control group comprising healthy individuals. The age range of participants was 18 to 88 years, with 85 males and 44 females included in the patient groups (moderate, severe, critical). All patients in these groups were CT-positive, with 102 PCR-positive and 27 PCR-negative cases. The control group consisted of 43 healthy individuals.

Blood samples were collected under strict aseptic conditions. Venous blood was drawn, with 2 ml collected into EDTA tubes for Complete Blood Count (CBC) and 3 ml into gel tubes for serum isolation. Samples were transported to the laboratory in a thermos wagon, where gel tubes were centrifuged to obtain serum. Serum samples were then transferred to Eppendorf tubes and stored at -80°C until further testing.

### Inclusion and Exclusion Criteria

Serum samples were collected from adult patients meeting specific criteria: (1) Confirmation of COVID-19 diagnosis via nasopharyngeal swab specimens preserved in viral transport medium and subjected to real-time polymerase chain reaction (PCR) testing, following WHO interim guidance. (2) Patients who underwent chest computerized tomography (CT) scans along with a comprehensive panel of routine laboratory tests, including complete blood count and blood biochemistry. Exclusions included children, pregnant women, and individuals unwilling to participate.

### Laboratory Analysis

Various laboratory kits were utilized for analysis: virellaSARS-CoV-2 sec real-time RT-PCR Kit (Gerbion, Germany) for PCR testing, RNA extraction Kit (Biocomma, China), C-Reactive Protein Kit (SPINREACT, Spain), Complete Blood Count Solution (Sysmex Corporation, Japan), Human Interleukin 10 (IL-10) ELISA Kit (abba, England), Human Interleukin 6 (IL-6) ELISA Kit (abbexa, England), and Human Interferon Gamma (IFN- $\gamma$ ) ELISA Kit (abbexa, England). All analyses were performed according to the manufacturers' instructions.

### Statistical Analysis

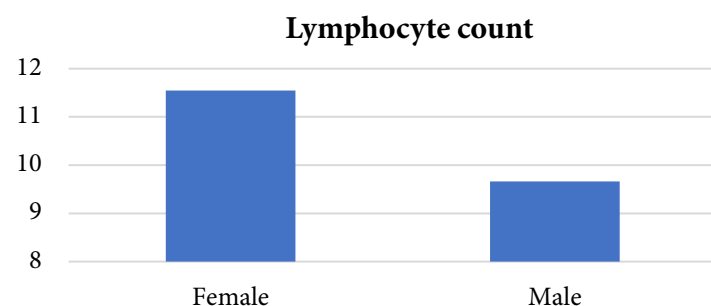
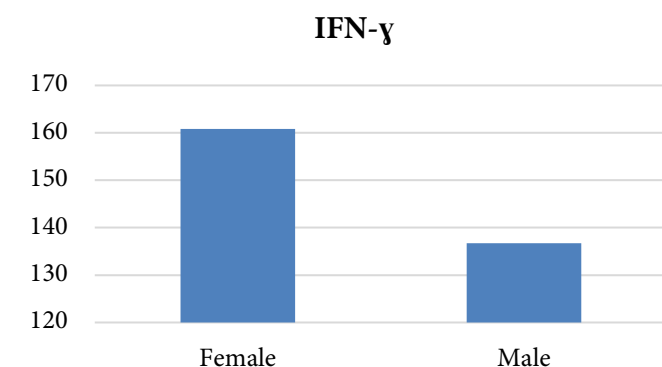
**Table 1.** Characterization of COVID-19 patients (N = 129)

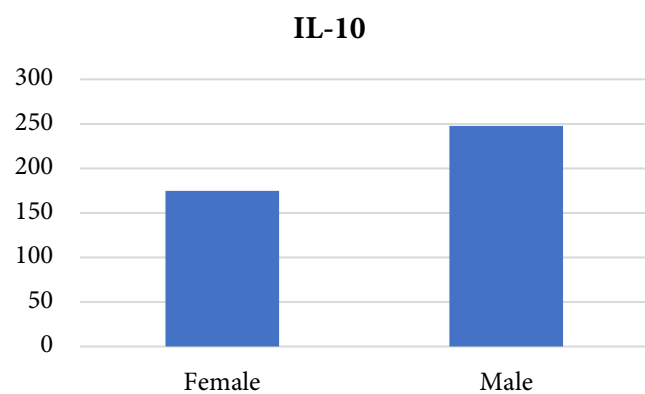
Characters of patients	Categories				
Age (year)	Range (16-88) Mean $\pm$ SD (43.83 $\pm$ 14.34)			Males	Females
Gender	Males	N= 85	(65.9 %)		
	Females	N= 44	(34.1 %)		
Tests	C.T scan	N= 132	(100 %)		
	CRP	N= 132	(100 %)		
	PCR +ve	N= 102	(79 %)	(53.48 %)	(26.35 %)
	PCR-ve	N= 27	(20.9 %)	(12.40 %)	(7.75 %)
Comorbidities	DM	N= 60	(46.5 %)	(25.75 %)	(20.15 %)
	HT	N= 57	(44.1 %)	(23.25 %)	(20.15 %)
	CVD	N= 13	(10 %)	(8.33 %)	(2.27 %)
Severity of disease	Moderate	N= 43	(33.3 %)	(22.0 %)	(11.36%)
	Sever	N= 43	(33.3 %)	(18.18 %)	(14.72 %)
	Critical	N= 43	(33.3%)	(24.80 %)	(7.75 %)

DM: Diabetic. HT: Hypertension. CVD: Cardiovascular disease

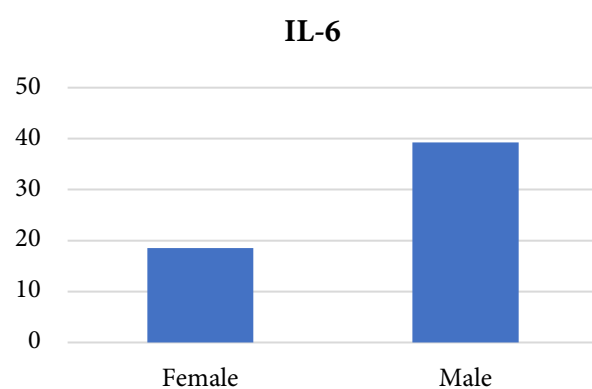
**Table 2.** Lymphocytes count and cytokine concentration in COVID-19 patients (n=129)

Parameters	Group	Mean $\pm$ Std. Error Mean	t-test, p-value
Lymph	Female	11.55 $\pm$ 1.05	0.020
	Male	9.66 $\pm$ 0.57	
IFN	Female	160.81 $\pm$ 16.19	0.022
	Male	136.73 $\pm$ 14.93	
IL-10	Female	174.75 $\pm$ 18.63	0.009
	Male	247.70 $\pm$ 23.93	
IL-6	Female	18.55 $\pm$ 3.31	0.008
	Male	39.24 $\pm$ 6.55	


**Figure 1.** Lymphocyte count in COVID-19 patients males and females.

**Figure 2.** The concentration of IFN- $\gamma$  in COVID-19 patients males and females.



**Figure 3.** The concentration of IL-10 in COVID-19 patients males and females.



**Figure 4.** The concentration of IL-6 in COVID-19 patients males and females

Data were analyzed using SPSS-20 software. Descriptive statistics such as simple frequencies and percentages were used for data presentation. Mean differences in quantitative data were evaluated using Student's t-test for independent means comparison, with statistical significance set at  $p \leq 0.05$ .

## Results

This study involved the analysis of 172 human serum samples, focusing on 129 patients diagnosed with COVID-19. The cohort had a mean age of 43.83 years ( $\pm 14.34$ ), with 65.9% males and 34.1% females. Notably, all patients tested positive for both C.T. scan and CRP, indicating the presence of lung abnormalities and systemic inflammation across the cohort. PCR testing confirmed COVID-19 infection in 79.0% of patients, despite 20.9% presenting negative PCR results alongside clinical symptoms suggestive of the disease.

The patient group exhibited a spectrum of comorbidities, with diabetes mellitus affecting 46.5%, hypertension 44.1%, and cardiovascular disease 10.0% of individuals. Disease severity was evenly distributed among moderate (33.3%), severe (33.3%), and critical (33.3%) classifications, ensuring a balanced representation of COVID-19 stages.

Analysis of immune markers highlighted significant gender disparities. Males showed significantly lower lymphocyte levels ( $9.66\% \pm 0.57$ ) compared to females ( $11.55\% \pm 1.05$ ), with a  $p$ -value of 0.020, suggesting differing immune responses between genders. Conversely, IFN- $\gamma$  levels were notably higher in females ( $160.81 \text{ pg/ml} \pm 16.19$ ) than in males ( $136.73 \text{ pg/ml} \pm 14.93$ ), with a significant  $p$ -value of 0.022, indicating a potentially more robust antiviral response in females.

Further investigation into cytokine profiles revealed significant differences: IL-10 and IL-6 levels were significantly elevated in males ( $247.70 \text{ pg/ml} \pm 23.93$  and  $39.24 \text{ pg/ml} \pm 6.55$ , respectively) compared to females ( $174.75 \text{ pg/ml} \pm 18.63$  and  $18.55 \text{ pg/ml} \pm 3.31$ , respectively). The observed  $p$ -values of 0.009 and 0.008 underscored substantial variations in inflammatory responses between male and female COVID-19 patients.

Comprehensive numerical data and visual representations can be found in Table 2 and Figures 1–4, providing a detailed overview of these gender-specific immune response patterns. These findings contribute valuable insights into the intricate interplay of COVID-19 infection, gender differences in immune function, and their potential implications for tailored therapeutic approaches and clinical management strategies.

## Discussion

In December 2019, COVID-19, caused by a novel  $\beta$ -coronavirus, sparked a global health crisis in Wuhan City, China (Gebhard et al., 2020). Early investigations from China indicated distinct gender-

based disparities in both the incidence and severity of COVID-19 cases.

Recent research underscores that while both men and women are equally susceptible to contracting COVID-19 (Guan et al., 2021), men generally exhibit more severe outcomes and higher case fatality rates than women (Wan et al., 2020). This phenomenon is multifaceted, involving biological sex differences and sex-specific behavioral risk factors such as smoking and alcohol consumption (Forsblom et al., 2021). Notably, women tend to seek medical assistance more promptly than men, potentially influencing differential health outcomes where delayed diagnosis and treatment among men may contribute to poorer prognoses (Wenham et al., 2020; Klein and Flanagan, 2016).

Fundamental disparities between males and females in their immune responses to viral infections have been observed. Females generally exhibit heightened innate immune responses, characterized by increased activity of immune cells like monocytes, macrophages, and dendritic cells, as well as enhanced inflammatory responses compared to males (Thompson et al., 2024). This heightened immune activity in females is partially attributed to higher expression levels of Toll-like receptor 7 (TLR7), a gene located on the X chromosome, which plays a crucial role in recognizing single-stranded RNA viruses like coronaviruses (Melgert et al., 2010).

In adaptive immune responses, females also demonstrate stronger humoral and cell-mediated immune reactions, evidenced by higher levels of immunoglobulins, antibodies, and cytotoxic T-cell activity, which are influenced by estrogen levels (Souyris et al., 2018; Cook, 2008; Markle, 2008). Estrogen, along with other sex steroids, influences immune cell function by binding to receptors on lymphoid tissue cells, circulating lymphocytes, macrophages, and dendritic cells, thereby modulating immune responses at a molecular level (Markle et al., 2013; Kovats et al., 2009).

Moreover, the expression and function of key viral entry proteins such as angiotensin I converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) vary between sexes. ACE2, crucial for SARS-CoV-2 entry into host cells, is located on the X chromosome, while TMPRSS2 expression is regulated by sex hormones like androgens and estrogens (Lazar, 2021). These differences may contribute to varying susceptibility and outcomes in COVID-19 cases between males and females (Baena, 2013; Patel et al., 2013).

Epidemiological studies consistently indicate that males have a higher case fatality risk from COVID-19 compared to females (Asselta et al., 2021). This disparity is influenced by intricate biological mechanisms, including genetic and hormonal factors that shape immune responses and disease progression differently in men and women (Forsblom et al., 2021; Rozenberg et al., 2020).

Recent clinical studies have highlighted distinct cytokine profiles in males versus females during COVID-19 infection. Males tend to exhibit higher levels of pro-inflammatory cytokines such as IL-6, which is associated with more severe disease outcomes, including acute respiratory distress syndrome (ARDS) and organ failure (Moulton, 2018; Torcia et al., 2012). Conversely, females often show lower levels of inflammatory cytokines like IL-6 but higher levels of anti-inflammatory cytokines such as IL-10, which may contribute to their better prognosis in viral infections (Jung et al., 2015).

In conclusion, understanding the complex interplay of biological sex differences, hormonal influences on immune responses, and genetic factors is crucial for elucidating why males tend to experience more severe COVID-19 outcomes compared to females. This knowledge underscores the importance of tailored therapeutic strategies and public health interventions that consider sex-specific vulnerabilities and immune responses in combating COVID-19 and other infectious diseases effectively.

## Conclusion

The disparity in COVID-19 infection rates between males and females highlights significant differences in disease outcomes based on gender. Notably, males generally exhibit a higher susceptibility to severe COVID-19 symptoms compared to females. This discrepancy is underscored by observations of reduced lymphocyte counts in COVID-19 patients, with males experiencing a more pronounced decrease relative to females. Furthermore, cytokine profiles play a crucial role in disease severity, with elevated levels of IL-10, IL-6, and IFN- $\gamma$  commonly observed in COVID-19 patients. Specifically, within these cytokines, the male cohort consistently displays significantly higher levels of IL-10 and IL-6, which are associated with heightened inflammatory responses and potentially more severe disease progression. In contrast, females tend to exhibit significantly elevated levels of IFN- $\gamma$ , indicative of a robust antiviral response that may contribute to better disease control compared to males.

These findings underscore the complex interplay between biological sex differences, immune responses, and cytokine dynamics in shaping COVID-19 outcomes. Understanding these nuances is crucial for developing targeted therapeutic strategies and public health interventions that account for sex-specific vulnerabilities and potentially improve clinical outcomes in COVID-19 and other infectious diseases.

## Author contributions

I.A.A. served as the principal investigator and was responsible for the conceptualization and data analysis of the project. I.I.L. contributed by developing the methodology, collecting samples, and conducting the statistical analysis. N.F.G. focused on writing the introduction and discussion sections. S.A.A.J. handled the

laboratory analysis, interpreted the results, and wrote the results section.

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## Competing financial interests

The authors have no conflict of interest.

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