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

Inaam Ali Abid [1*], Ismail Ibrahim Latif [2], Namer Fadhil Ghaab [3], Saad Ahmed Ali Jadoo [4]

## 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-ɣ (IFN-ɣ). 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 ± 0.57%) compared to the female group (11.55 ± 1.05%), with a p-value of 0.020. The level of IFN-ɣ showed a significant increase in the female group (160.81 ± 16.19 pg/lm) compared to the male group (136.73 ± 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 ± 23.93 pg/ml and 39.24 ± 6.55 pg/ml, respectively) compared to the female group (174.75 ± 18.63 pg/ml and 18.55 ± 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-ɣ, COVID-19 severity, Gender differences, Cytokine levels, Lymphocyte count, Iraqi patients

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

*Correspondence. Ahmed Jassim Muklive Al-Ogaidi, The University of Technology, Baghdad, Iraq.
E-mail: ahmedmuklive@gmail.com

Editor Fouad Saleih Al-Suede, And accepted by the Editorial Board Apr 06, 2024 (received for review Mar 05, 2024)

## 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

**Author Affiliation.**
[1] Medical Microbiology, College of Medicine, University of Diyala, Diyala, Iraq
[2] Medical Immunology, College of Medicine, University of Diyala, Diyala, Iraq
[3] Department of Anatomy, University of Diyala, College of Medicine, Diyala, Iraq
[4] Department of Family and Community Medicine, University of Diyala, College of Medicine, Diyala, Iraq

**Please cite this article.**
Ahmed Jassim Muklive Al-Ogaidi, Hamssa ahmed easa et al. (2024). Lymphocyte, IL-10, IL-6, and IFN-ɣ Cytokines Modulation in SARS-CoV-2 Patients, Journal of Angiotherapy, 8(4), 1-8, 9584

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). 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-γ, are pivotal in antiviral defense mechanisms. Studies have shown that lower levels of IFN-γ correlate with disease severity in COVID-19 patients, suggesting a potential role for early IFN-γ 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-ɣ. 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-ɣ) 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 ±SD (43.83 ± 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 ± Std. Error Mean** | **t-test, p-value** |
|---|---|---|---|
| Lymph | Female | 11.55 ± 1.05 | 0.020 |
| | Male | 9.66 ± 0.57 | |
| IFN | Female | 160.81 ± 16.19 | 0.022 |
| | Male | 136.73 ± 14.93 | |
| IL-10 | Female | 174.75 ± 18.63 | 0.009 |
| | Male | 247.70 ± 23.93 | |
| IL-6 | Female | 18.55 ± 3.31 | 0.008 |
| | Male | 39.24 ± 6.55 | |

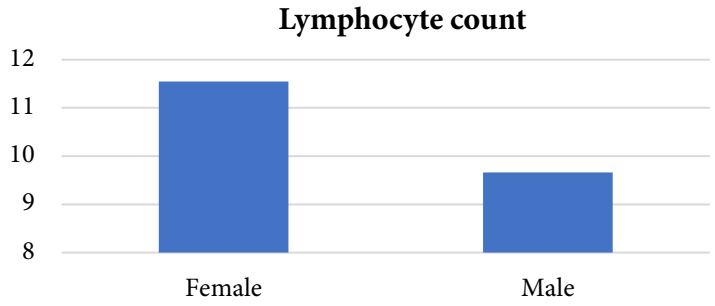


**Figure 1.** Lymphocyte count in COVID-19 patients males and females.

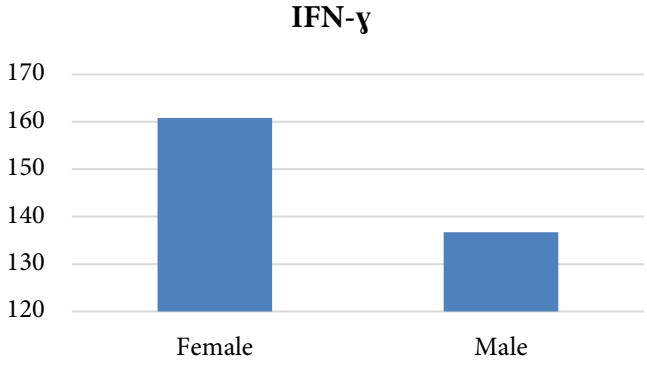


**Figure 2.** The concentration of IFN-ɣ in COVID-19 patients males and females.

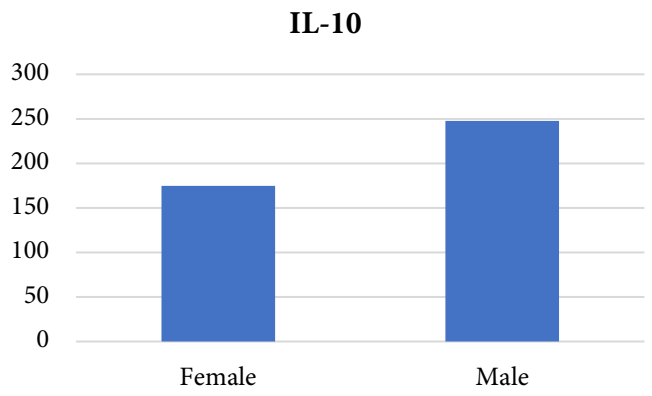


**Figure 3.** The concentration of IL-10 in COVID-19 patients males and females.

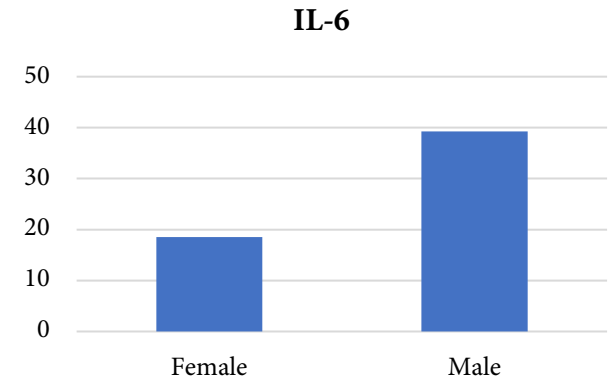


**Figure 4.** The concentration of IL-6 in COVID-19 patients males and females

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 (± 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% ± 0.57) compared to females (11.55% ± 1.05), with a p-value of 0.020, suggesting differing immune responses between genders. Conversely, IFN-ɣ levels were notably higher in females (160.81 pg/ml ± 16.19) than in males (136.73 pg/ml ± 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 pg/ml ± 23.93 and 39.24 pg/ml ± 6.55, respectively) compared to females (174.75 pg/ml ± 18.63 and 18.55 pg/ml ± 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 β-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-ɣ 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-ɣ, 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.

## Acknowledgment

The authors expressed their appreciation to the Diyala Health and Education Directorates for allowing him to undertake this research. The author is grateful for the patient's willingness to participate in the study.

## Competing financial interests

The authors have no conflict of interest.

## References

Abdel-Hamed, E. F., Ibrahim, M. N., Mostafa, N. E., Moawad, H. S., Elgammal, N. E., Darwiesh, E. M., ... Hindawi, S. I. (2021). Role of interferon gamma in SARS-CoV-2-positive patients with parasitic infections. Gut Pathogens, 13(1), 29.

Ambrosino, I., Barbagelata, E., Ortona, E., Ruggieri, A., Massiah, G., Giannico, O. V., ... Moretti, A. M. (2020). Gender differences in patients with COVID-19: A narrative review. Monaldi Archives for Chest Disease, 90(2).

Asselta, R., Paraboschi, E. M., Mantovani, A., & Duga, S. (2020). ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY), 12(11), 10087.

Baena, E., Shao, Z., Linn, D. E., Glass, K., Hamblen, M. J., Fujiwara, Y., ... Li, Z. (2013). ETV1 directs androgen metabolism and confers aggressive prostate cancer in targeted mice and patients. Genes & Development, 27(6), 683-698.

Chen, R., Liang, W., Jiang, M., Guan, W., Zhan, C., Wang, T., ... for COVID, M. T. E. G. (2020). Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest, 158(1), 97-105.

Cook, I. F. (2008). Sexual dimorphism of humoral immunity with human vaccines. Vaccine, 26(29-30), 3551-3555.

De Groot, N. G., & Bontrop, R. E. (2020). COVID-19 pandemic: Is a gender-defined dosage effect responsible for the high mortality rate among males?

Dhar, S. K., Vishnupriyan, K., Damodar, S., Gujar, S., & Das, M. (2021). IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: Results from meta-analysis and regression. Heliyon, 7(2).

di Mauro, G., Scavone, C., Rafaniello, C., Rossi, F., & Capuano, A. (2020). SARS-Cov-2 infection: Response of human immune system and possible implications for the rapid test and treatment. International Immunopharmacology, 84, 106519.

Docherty, A. B., Harrison, E. M., Green, C. A., Hardwick, H. E., Pius, R., Norman, L., ... & Semple, M. G. (2020). Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ, 369.

Forsblom, E., Silen, S., Kortela, E., Ahava, M., Kreivi, H. R., Holmberg, V., ... & Meretoja, A. (2021). Male predominance in disease severity and mortality in a low Covid-19 epidemic and low case-fatality area–a population-based registry study. Infectious Diseases, 53(10), 789-799.

Fox, H. S., Bond, B. L., & Parslow, T. G. (1991). Estrogen regulates the IFN-gamma promoter. Journal of immunology (Baltimore, Md.: 1950), 146(12), 4362-4367.

Gadi, N., Wu, S. C., Spihlman, A. P., & Moulton, V. R. (2020). What's sex got to do with COVID-19? Gender-based differences in the host immune response to coronaviruses. Frontiers in immunology, 11, 562631.

Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H. K., Morgan, R., & Klein, S. L. (2020). Impact of sex and gender on COVID-19 outcomes in Europe. Biology of sex differences, 11, 1-13.

Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... & Zhong, N. S. (2020). Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine, 382(18), 1708-1720.

Henry, B. M., & Lippi, G. (2020). Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. International urology and nephrology, 52, 1193-1194.

Hewagama, A., Patel, D., Yarlagadda, S., Strickland, F. M., & Richardson, B. C. (2009). Stronger inflammatory/cytotoxic T-cell response in women identified by microarray analysis. Genes & Immunity, 10(5), 509-516.

Hirano, T., & Murakami, M. (2020). COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. Immunity, 52(5), 731-733.

Hu, Z. J., Yin, J. M., & Feng, Y. M. (2020). Lower circulating interferon-gamma is a risk factor for lung fibrosis in COVID-19 patients. Frontiers in immunology, 11, 585647.

Jadoo, S. A. A., Alhusseiny, A. H., Yaseen, S. M., Al-Samarrai, M. A. M., Al-Delaimy, A. K., Abed, M. W., & Hassooni, H. R. (2020). Knowledge, attitude, and practice toward COVID-19 among Iraqi people: A web-based cross-sectional study. Journal of Ideas in Health, 3(Special2), 258-265.

Jung, S. Y., Kim, B. G., Kwon, D., Park, J. H., Youn, S. K., Jeon, S., ... & Park, B. J. (2015). An outbreak of joint and cutaneous infections caused by non-tuberculous mycobacteria after corticosteroid injection. International Journal of Infectious Diseases, 36, 62-69.

Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. Nature Reviews Immunology, 16(10), 626-638.

Klein, S. L., Jedlicka, A., & Pekosz, A. (2010). The Xs and Y of immune responses to viral vaccines. The Lancet Infectious Diseases, 10(5), 338-349.

Kovats, S., Carreras, E., & Agrawal, H. (2009). Sex steroid receptors in immune cells. In H. Agrawal (Ed.), Sex hormones and immunity to infection (pp. 53-91). Berlin, Heidelberg: Springer Berlin Heidelberg.

Lazar, A. M. (2021). ACE2 enzymatic role in the SARS-CoV-2 activation: A perspective through the evolutionary promiscuity and substrate diversity of enzymes. Journal of Ideas in Health, 4(4), 581-587.

Lee, A. J., & Ashkar, A. A. (2018). The dual nature of type I and type II interferons. Frontiers in Immunology, 9, 403701.

Li, P. J., Jin, T., Luo, D. H., Shen, T., Mai, D. M., Hu, W. H., & Mo, H. Y. (2015). Effect of prolonged radiotherapy treatment time on survival outcomes after intensity-modulated radiation therapy in nasopharyngeal carcinoma. PloS One, 10(10), e0141332.

Liu, W., Tao, Z. W., Wang, L., Yuan, M. L., Liu, K., Zhou, L., ... & Hu, Y. (2020). Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chinese Medical Journal, 133(09), 1032-1038.

Lu, L., Zhang, H., Dauphars, D. J., & He, Y. W. (2021). A potential role of interleukin 10 in COVID-19 pathogenesis. Trends in Immunology, 42(1), 3-5.

Markle, J. G., Frank, D. N., Mortin-Toth, S., Robertson, C. E., Feazel, L. M., Rolle-Kampczyk, U., ... & Danska, J. S. (2013). Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science, 339(6123), 1084-1088.

Melgert, B. N., Oriss, T. B., Qi, Z., Dixon-McCarthy, B., Geerlings, M., Hylkema, M. N., & Ray, A. (2010). Macrophages: regulators of sex differences in asthma?. American journal of respiratory cell and molecular biology, 42(5), 595-603.

Moulton, V. R. (2018). Sex hormones in acquired immunity and autoimmune disease. Frontiers in immunology, 9, 414334.

OpenSAFELY Collaborative, Williamson, E., Walker, A. J., Bhaskaran, K., Bacon, S., Bates, C., ... & Goldacre, B. (2020). OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. MedRxiv, 2020-05.

Patel, S. K., Velkoska, E., & Burrell, L. M. (2013). Emerging markers in cardiovascular disease: where does angiotensin-converting enzyme 2 fit in?. Clinical and Experimental Pharmacology and Physiology, 40(8), 551-559.

Peretz, J., Pekosz, A., Lane, A. P., & Klein, S. L. (2016). Estrogenic compounds reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors. American Journal of Physiology-Lung Cellular and Molecular Physiology, 310(5), L415-L425.

Potere, N., Batticciotto, A., Vecchié, A., Porreca, E., Cappelli, A., Abbate, A., ... & Bonaventura, A. (2021). The role of IL-6 and IL-6 blockade in COVID-19. Expert review of clinical immunology, 17(6), 601-618.

Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., ... & Tian, D. S. (2020). Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clinical infectious diseases, 71(15), 762-768.

Rettew, J. A., Huet-Hudson, Y. M., & Marriott, I. (2008). Testosterone reduces macrophage expression in the mouse of toll-like receptor 4, a trigger for inflammation and innate immunity. Biology of reproduction, 78(3), 432-437.

Rozenberg, S., Vandromme, J., & Martin, C. (2020). Are we equal in adversity? Does Covid-19 affect women and men differently?. Maturitas, 138, 62-68.

Souyris, M., Cenac, C., Azar, P., Daviaud, D., Canivet, A., Grunenwald, S., ... & Guéry, J. C. (2018). TLR7 escapes X chromosome inactivation in immune cells. Science Immunology, 3(19), eaap8855.

Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. F. (2020). The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews Immunology, 20(6), 363-374.

Thompson, A. E., Anisimowicz, Y., Miedema, B., Hogg, W., Wodchis, W. P., & Aubrey-Bassler, K. (2016). The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Family Practice, 17, 1-7.

Torcia, M. G., Nencioni, L., Clemente, A. M., Civitelli, L., Celestino, I., Limongi, D., ... & Palamara, A. T. (2012). Sex differences in the response to viral infections: TLR8 and TLR9 ligand stimulation induce higher IL10 production in males. PLoS One, 7(6), e39853.

Visuddho, V., Subagjo, A., Setyoningrum, R. A., & Rosyid, A. N. (2021). Predictive accuracy of blood inflammatory markers on COVID-19 mortality. Journal of Ideas in Health, 4(Special4), 623-629.

vom Steeg, L. G., & Klein, S. L. (2016). SeXX matters in infectious disease pathogenesis. PLoS Pathogens, 12(2), e1005374.

Wan, S., Xiang, Y. I., Fang, W., Zheng, Y., Li, B., Hu, Y., ... & Yang, R. (2020). Clinical features and treatment of COVID-19 patients in northeast Chongqing. Journal of Medical Virology, 92(7), 797-806.

Weinstein, Y. A. C. O. B., Ran, S. O. F. I. A., & Segal, S. H. R. A. G. A. (1984). Sex-associated differences in the regulation of immune responses controlled by the MHC of the mouse. Journal of Immunology (Baltimore, Md.: 1950), 132(2), 656-661.

Wenham, C., Smith, J., & Morgan, R. (2020). COVID-19: the gendered impacts of the outbreak. The Lancet, 395(10227), 846-848.

Yuan, X., Huang, W., Ye, B., Chen, C., Huang, R., Wu, F., ... & Hu, J. (2020). Changes of hematological and immunological parameters in COVID-19 patients. International Journal of Hematology, 112, 553-559.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet, 395(10229), 1054-1062.

Zuin, M., Rigatelli, G., Zuliani, G., Rigatelli, A., Mazza, A., & Roncon, L. (2020). Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis. The Journal of Infection, 81(1), e84.