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RESEARCH ARTICLE

Gender-based differences of inflammatory, coagulation, and cardiac markers in COVID-19 patients in Erbil city

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ABSTRACT

In December 2019, a new coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan city and quickly became a global health issue. COVID-19 causes various symptoms ranging from no symptoms to potentially deadly pneumonia. The study aimed to understand the effects of SARS-CoV-2 infection on immune response and the differences in inflammatory, coagulation, and cardiac biomarkers between male and female patients. Between June 1st and November 1st, 2020, 95 cases of SARS-CoV-2 infected individuals were studied at Zanko Hospital. SARS-CoV-2 infection was confirmed using the real-time RT-PCR technique. All cases were analyzed for clinical, epidemiological, and laboratory data. On average, the patients were 50.64 (SEM= 2.359) years old, with 61 males and 34 females. The patients had elevated C-reactive protein (CRP), which was 43.96 (SEM= 6.154), while the erythrocyte sedimentation rate (ESR) was 50.50 (SEM= 5.498). The mean of D-Dimer, ferritin and lactate dehydrogenase (LDH) were 1.204 (SEM= 0.164), 534.7 (SEM= 61.48), and 366.6 (SEM= 36.81), respectively. There were no significant differences in the study's data mentioned above between male and female patients. In conclusion, inflammation is the most prominent symptom in COVID-19 patients, and males and females are nearly equally affected.

Keywords: COVID-19, D-dimer, inflammatory markers, LDH, sex difference

INTRODUCTION

Since December 2019, many cases of pneumonia with an unidentified cause have been recorded in Wuhan city of China (Guan *et al.*, 2020; Wu and McGoogan, 2020). Later it was confirmed that SARS COV-2 is the causative agent, and the disease was nominated as COVID-19 (WHO, 2020b). Coronaviruses can cause a variety of systemic infections, including respiratory tract infections, such as severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) (Peiris *et al.*, 2003a; Zaki *et al.*, 2012; Yin and Wunderink, 2018).

Early signs and symptoms of COVID-19 patients are typically relatively mild, and the infection may even be asymptomatic.

However, the disease can quickly progress into acute respiratory distress syndrome (ARDS) and serious multi-organ issues because of rapid viral replication and cytokine storms (Chen *et al.*, 2020).

Acute lung inflammation is a complicated pathophysiological process that involves inflammatory mediators, such as cytokines and chemokines, which induce macrophages in the alveoli and disrupt the immune system (Nicholls *et al.*, 2003). Cytokine storm, an inflammatory immune response that leads to organ failure, is thought to be the cause of the severity of COVID-19 disease (Wang and Ma, 2008; Ciceri *et al.*, 2020). Severe cases of COVID-19 disease and cytokine storm have been associated with a high concentration of interleukin-6 (IL-6) (Hu *et al.*, 2021), which induces the liver to release CRP (Sproston and Ashworth, 2018).

Retrospective studies revealed that the levels of the inflammatory proteins CRP, IL-6, ESR, D-dimer, ferritin, and LDH were higher in patients who passed away than in survivors (Ruan *et al.*, 2020; Huang *et al.*, 2020). The fact that immunomodulatory treatments are the only ones that have been shown to reduce mortality in severe COVID-19 emphasizes the significance of a robust immune response in this condition (Group, 2020).

These findings suggested that an overactive immunity, expressed primarily as increased inflammatory biomarkers, is likely to be associated with the intensity and outcomes of the COVID-19 disease. However, the inflammatory, coagulation and cardiac biomarkers are expected to change SARS-CoV-2 infections between men and women. The current study aims to determine the sex-based difference in inflammatory, coagulation, and cardiac biomarkers in COVID-19-positive patients in Erbil city.

MATERIALS AND METHODS

Study design and data collection

We examined 95 patients for this retrospective, single-centre study (61 males and 34 females) from June 1st to November 1st 2020. This study enrolled all patients diagnosed with SARS-CoV-2 at the hospital based on WHO interim guidance. COVID-19 patients had symptoms of COVID-19 and visited Zanko hospital. They were involved because they were confirmed clinically (symptoms), and laboratory (RT-PCR). They met the requirements for the new coronavirus pneumonia prevention and control program and were identified by RT-PCR (Liang, 2020). The COVID-19 patients were excluded if they suffered from other inflammatory conditions that may interfere with increased inflammatory markers.

All the data of the involved cases have been gathered in the laboratory. We gathered clinical, epidemiological, and laboratory data from patients' medical records. The ethics committee at Zanko Hospital gave their approval to the study. ESR was measured by the Westergren method. Serum CRP, LDH and D Dimer determination were performed using a Cobas Integra 400 analyzer (Roche Diagnostics System, Mannheim, Germany). At the same time, serum Ferritin measuring was achieved by COBAS INTEGRA® 400 plus analyzer (Diagnostics Roche System, Germany). All the procedures from RNA extraction, cDNA synthesis, and virus detection in the swab were done by Bio-Rad Reliance SARS-CoV-2 RT-PCR Assay Kit (Bio-Rad, USA).

Statistical analysis

GraphPad Prism 6.0 was used for doing statistics and making graphs. The data were parametric since they obey the criteria of parametric data (they pass the normality test of De-Agostino, Shapiro, and Kolmogorov). The comparison of parameters between the male and female groups was done by independent t-test. The data are parametric, representing the mean and standard error of the mean (SEM). A p-value of less than 0.05 is regarded as statistically significant.

RESULTS

The present study involved 95 COVID-19 patients. In the analysis, there were 61 (64.2%) male patients and 34 (35.8%) female patients. The patients were mostly men, with a mean age of (50.64 ± 2.359). In order to determine the immune response to COVID-19, patients' serum levels of common inflammatory parameters and other biomarkers, including CRP, ESR, D-Dimer, Ferritin and LDH, were assessed. CRP (43.96 ± 6.154), ESR (50.50 ± 5.498), D-Dimer (1.204 ± 0.164), ferritin (534.7 ± 61.48), and LDH (366.6 ± 36.81) were all elevated in the patients (Table1).

Table 1. Inflammatory, coagulation, and cardiac biomarkers in COVID-19 patients

Parameters	*Mean ± SEM*	*Normal range*
CRP (mg/L)	43.96 ± 6.15	< 10 mg/L
ESR (mm/hr)	50.50 ± 5.498	Male: 1-13 mm/hr, Female: 1-20 mm/hr
D-dimer (µg/ml)	1.204 ± 0.164	< 0.5 µg/ml
Ferritin (ng/ml)	534.7 ± 61.48	Male: 12-300 ng/mL, Female: 12-150 ng/mL
LDH (U/L)	366.6 ± 36.81	Adults: 140- 280 U/L

*The data are shown as mean ± SEM. CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, D-Dimer: fibrin degradation product, LDH: Lactate dehydrogenase.

To determine the immune response in COVID-19 regarding gender and variations, we compared inflammatory, coagulation, and cardiac biomarkers between males and females. We discovered no statistically significant variation in participants' ages based on gender (47.80 ± 2.739 vs 56.33 ± 4.233) (Table 2).

According to the results of this study, the mean values of CRP (45.61 ± 8.026 vs 40.59 ± 9.237), ESR (47.83 ± 7.490 vs 56.50 ± 6.071), D-Dimer (1.039 ± 0.214 vs 1.484 ± 0.2520), ferritin (612.2 ± 78.58 vs 379.9 ± 88.35), and LDH (333.5 ± 23.82 vs 438.8 ± 105.1) showed no significant differences between the male and female groups (Table 2).

Table 2. Inflammatory parameters and other biomarkers difference between male and female COVID-19 patients

Parameters	*Male*	*Female*	*P-Value*
Age (Years)	47.80 ± 2.739	56.33 ± 4.233	0.081
CRP (mg/L)	45.61 ± 8.026	40.59 ± 9.237	0.695
ESR (mm/1hr)	47.83 ± 7.490	56.50 ± 6.071	0.433
D-Dimer (µg/ ml)	1.039 ± 0.214	1.484 ± 0.252	0.197
Ferritin (ng/ml)	612.2 ± 78.58	379.9 ± 88.35	0.064
LDH (U/L)	333.5 ± 23.82	438.8 ± 105.1	0.215

*The data are shown as mean ± SEM. P value < 0.05 is statistically significant. CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, D-Dimer: fibrin degradation product, LDH: Lactate dehydrogenase

DISCUSSION

The immune system reacts to pathogens in various ways depending on the infectious agent. Several immune mediators are released when a virus interacts with a cell to fight the invading virus (Iwasaki and Pillai, 2014). However, a strong immune system is required to regulate and eradicate the infection, and an overactive or persistent immune reaction is harmful. Overproduction of inflammatory mediators has been related to many immune disorders and the onset of organ failure (Wang and Ma, 2008). SARS and MERS viruses mainly affect the respiratory tract, resulting in serious and often fatal pneumonia marked by a massive accumulation of immune cells and a high level of pro-inflammatory cytokines (Peiris *et al.*, 2003b; Oboho *et al.*, 2015).

In the 95 cases of SARS-CoV-2 infection analyzed in this study, COVID-19 infection was more common in males than females. Previous studies have demonstrated that males are more susceptible to infection with SARS-CoV and MERS-CoV than females (Badawi and Ryoo, 2016; Channappanavar *et al.*, 2017). Jaillon and his colleagues found that females are less susceptible to viral infections, which may be due to X chromosome and sexual hormone defenses, both of which are essential in the innate and adaptive immune system (Jaillon *et al.*, 2019). Our results suggest that men were more likely than women to become infected with SARS-CoV-2, but their immune response was nearly similar to that of females. More importantly, IgG level in infected women is higher than in men, pretending why the survival rate and better patient's prognosis are higher in females (Zeng et al., 2020; Xiang et al., 2020). However, there were no significant differences in IgG levels in both genders in the study done by Ishaq *et al.* (2021) in Erbil-Iraq.

Furthermore, according to one of the studies performed by Sarhan et al. (2020) in Iraq, in which antibody level production was in males close to the females, the survival rate in men is lower than in females (Sarhan *et al.*, 2020). However, antibody production level may not be the only reason men have a higher death rate than women. Still, it might be due to men having a worse lifestyle than women, such as smoking and alcohol consumption (Griswold *et al.*, 2018). The presence of androgens, androgen receptors, and higher expression of TMPRSS2 may be responsible for a higher death rate in a male. TMPRSS2 is participating in SARS-CoV-2 infection combined with immunosuppressive effects of Androgens, and comorbidities might have a role in the severity of the disease. On the other hand, a higher survival rate in women may be due to estrogens' protective function, which has a more robust innate immune response necessary for faster clearance of virus loads in females (Chakravarty *et al.*, 2020).

This study evaluated the serum concentrations of inflammatory, coagulation, and cardiac biomarkers such as CRP, ESR, D-dimer, ferritin and LDH in COVID-19 patients. All of these markers were found to be significantly elevated, and these results are similar to what have been reported by other studies (Chen *et al.*, 2019; Ali *et al.*, 2020).

We compared inflammatory parameters between male and female patients to see whether there was a difference in immune response between the two genders. All laboratory data were found to be non-significant in both male and female participants. In contrast to our findings, Zeng and his colleagues found many inflammatory markers, such as the soluble form of the IL-2 receptor, IL-6, ferritin, procalcitonin, and CRP were significantly higher in male patients compared with female patients (Zeng *et al.*, 2020). Overproduction of the inflammatory parameter in male patients may be related to a hormonal difference between the sexes, and the exact processes should be researched further.

There are a few limitations to our study. The study comprised a limited number of individuals with COVID-19 since we excluded other COVID-19 patients who lack RT-PCR or one of the studied parameters. Having as many patients as possible in

Erbil and other Iraq places would be ideal for learning more about the SARS-CoV-2 infection. We, unfortunately, did not involve the control since it was challenging to find someone who had never been infected with COVID-19 at the time of the study. Additionally, at the time of the study, more thorough patient data such as lymphocyte to neutrophil ratio, particularly about the results of clinical studies, was not accessible. However, the information from this study enables an early evaluation of the immunological response in COVID-19 patients in Erbil, Iraq.

CONCLUSION

Our findings revealed no apparent variations in the immune responses regarding inflammatory, coagulation, and cardiac biomarkers between male and female COVID-19 infected individuals in Erbil, Iraq.

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CONFLICT OF INTERESTS

The authors mention no conflicting interests.

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