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Deciphering gender disparities in laboratory biomarkers among deceased COVID-19 patients in Erbil city-Iraq: A retrospective study

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Abstract

Introduction: SARS-CoV-2 was a new strain of the Coronaviridae family. It caused the coronavirus disease in December 2019 that first arose in Wuhan, China, and it developed into a worldwide health issue. COVID-19 gives rise to a wide range of symptoms which can range from having no symptoms to having extensive fatal pneumonia.
Objectives: The purpose of the study was to figure out how infecting the virus could influence and impact the various laboratory biomarkers among dead male and female patients.
Patients and Methods: The data and statistics were obtained from the dead patients of West Emergency Hospital and the data was investigated directly. The investigation was conducted from June 1st to November 1st, 2020. Epidemiological, clinical as well as lab data of approximately 659 dead cases of SARS-CoV-2 infected individuals were examined in that period. A real-time polymerase chain reaction (RT-PCR) technique was applied to confirm infecting of SARS-CoV-2. The deceased cases were categorized into 2 fractions, which were a male and female group. The male group had 407 individuals and the female group had 252 individuals.
Results: This study revealed that the male cases had lower lymphocyte and platelet counts than females but substantially higher levels of urea and creatinine, also the male cases were older compared to the female cases. However, D-dimer and C-reactive protein (CRP) levels did not indicate any notable differences between the two groups.
Conclusion: The study showed a gender-situated differences in the laboratory biomarkers of dead COVID-19 cases.

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Introduction

Many unexplained cases of pneumonia have been reported since December 2019 and most cases have no specific or explained cause (1,2). Subsequently, it was revealed that SARS-CoV-2 was the causative agent, and the disease was named and indicated as COVID-19 (3). Coronavirus can induce various systemic infections, including Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (4-6). COVID-19 cases generally have mild signs and symptoms in the beginning but then due to viral replication and cytokine storm it progresses and develops into acute respiratory distress syndrome (ARDS) along with severe complications affecting different organs (7).

Acute lung inflammation is a pathophysiological mechanism that requires cytokines and chemokines, which are inflammatory mediators. Cytokines, as inflammatory mediators, stimulate alveolar macrophages, disrupting and activating the immune system (8). The seriousness and severity of COVID-19 disease is speculated to be caused by a cytokine storm, which is an inflammatory immune response that causes organ deterioration and damage (9,10). Similarly, elevated levels of interleukin-6 (IL-6) have been associated with severe cases of COVID-19 and cytokine storms (11). This results in liver producing C-reactive protein

Key point

The study investigates the impact of SARS-CoV-2 infection on laboratory biomarkers among deceased male and female patients. This study conducted between June 1st and November 1st, 2020, at West Emergency Hospital. This study examined epidemiological, clinical, and lab data from 659 deceased cases of COVID-19. Real-time polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection. Results showed that male cases exhibited lower lymphocyte and platelet counts, however they had higher urea and creatinine levels compared to females. Male patients were also older. Conversely, D-dimer and C-reactive protein (CRP) levels showed no significant gender-based differences. The findings suggest gender-related disparities in laboratory biomarkers among deceased COVID-19 patients.

(CRP) that also leads to inflammatory responses noticed in these conditions (12).

Retrospective studies identified that levels of inflammatory proteins like IL-6, CRP, D-dimer, ESR, ferritin and LDH were much greater in the cases that died than those who lived through (13,14). It had been made clear that reduced platelets and lymphocytes also related to SARS-CoV-2 infection severity (15). There were many treatments applied for COVID-19 and it turned out that immunomodulatory treatment options are of great significance and they decrease the mortality of COVID-19 and it indicated the importance of having a strong immunity in such circumstances (16). There was an increase of kidney problems and complications in patients with severe COVID-19 infections. This raised the awareness that the respiratory organs are not the only affected organs in the body. Hence, it is important to check for urea and creatinine to evaluate kidney function (17).

These results indicated that hyperimmune occurs mainly because of increased inflammatory biomarkers. After all, the hematological, immunological, and kidney biomarkers may change between dead male and female cases of COVID-19.

Objectives

The purpose of this study is to identify the gender-based differences between laboratory biomarkers of dead COVID-19 patients in Erbil.

Patients and Methods

Study design

For this study, 659 dead patients were examined (407 males and 252 females) for five months (starting from the 1st of June to the 1st of November 2020). The patients were chosen on the basis of their medical records, mainly because they met the approved lab results and also the criteria for the known clinical symptoms. The patients were previously diagnosed by RT-PCR technique. All the data of the dead patients were collected in the government and private hospitals including, epidemiological, clinical, and laboratory data from patients' medical records. In cases where patients were unable to provide their signature due to life-threatening emergencies, consent was obtained from their relatives, who served as substitute decision-makers, legal guardians, or held power of attorney for the patient.

Statistical analysis

The software used to graph the data was GraphPad prism 9. Different tests like the Mann-Whitney U test and the Spearman's test were conducted for seeing the difference in data and in between the two genders variables. The data is also nonparametric according to standards; therefore, they did not pass the normality test of (De-Agostino, Shapiro, and Kolmogorov). The test is non-parametric, showing median interquartile range (IQR). For the *P* value, if it was less than 0.05, it is considered statistically significant. *$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ and **** $P < 0.0001$.

Results

In this study, of 659 dead cases, 407 (61.76%) were dead male patients since 252 (38.24%) were dead females. The majority of patients were males with a median age of 67.00 (60.00-78.00) years, however the median age of dead female patients was 65.00 (53.00-75.00) years. There was a significant difference between their ages ($P = 0.004$; Table 1 and Figure 1a). Our study showed an association between comorbidities and gender ($P = 0.002$).

To figure out the laboratory biomarkers in COVID-19 based on gender we compared coagulation, inflammatory, hematological and kidney function biomarkers. We found no statistically significant difference among the participants' CRP and D-dimer based on gender as their *P* values were 0.731, and 0.318, respectively (Table 1 and Figures 1b and 1c).

In correspondence to our study's results, the median values of lymphocyte 0.700 (0.500-1.000) 10^9 cells/liter versus 0.800 (0.500-1.200) 10^9 cells/liter, platelet 191.0 (132.0-248.5) versus 228.0 (164.5-295.3) 10^9 cells/liter, presents considerable and significant difference among the two groups, as their *P* values were 0.047, and 0.002, respectively (Table 1, Figures 1d and 1e).

The dead male patients had significantly higher kidney biomarkers like creatinine ($P = 0.002$) and serum urea ($P < 0.0001$) as compared to female patients (Table 1 and Figures 1f and 2).

The correlation between variables

The Spearman's correlation was performed between variables (age, D-dimer, CRP, lymphocyte, platelet, blood urea, and serum creatinine). The significant correlation coefficients (r) were found between D-dimer and blood urea ($r = 0.207$, $P < 0.009$), and CRP and D-dimer ($r = 0.192$, $P = 0.012$. The detailed correlations can be seen in Table 2.

Discussion

Normally, the human's immune system maintains

Table 1. Demographics and other laboratory biomarkers

Parameters	Male Median (IQR)	Female Median (IQR)	*P* value
Number	407 (61.76)	252 (38.24%)	
Comorbidities (Yes)	264	193	0.002
Comorbidities (No)	143	59	
Age (y)	67.00 (60.00-78.00)	65.00 (53.00-75.00)	0.004
CRP (mg/L)	61.18 (42.00-127.0)	62.26 (43.45-110.3)	0.731
Lymphocyte ($\times 10^9$/L)	0.700 (0.500-1.000)	0.800 (0.500-1.200)	0.047
Platelets ($\times 10^9$/L)	191.0 (132.0-248.5)	228.0 (164.5-295.3)	0.002
D-dimer (ng/mL)	1390 (382.3-3353)	1029 (370.6-2883)	0.318
Urea (mg/dL)	70.85 (47.00-101.8)	48.40 (31.25-71.00)	< 0.0001
Creatinine (mg/dL)	1.130 (0.860-1.580)	0.920 (0.700-1.330)	0.002

CRP, C-reactive protein.

body health by creating specific reactions to certain encountered pathogens (17). Following creating a cascade of events that end up in the production of cytokines which if not controlled well, can cause more harm than benefits like organ failure (9). The SARS and MERS like to stay confined in the chest where they have been proven to produce a huge level of pro-inflammatory cytokines. This condition results in a severe pneumonia that is manifested by a huge build-up of immune cells and an increase in pro-inflammatory cytokines (4,18).

In this study, the male patients were seen more prone to the effects of the viruses compared to females. The X chromosome and the different sex hormones in females have been proven to be the attributes for the increased protection that the females had (19). There also was a notable difference in the female's IgG serum levels that some think also must have helped in the protection that females had (20,21). Even with the different serum IgG levels, it is not considered as a very big reason for the different mortality rates in the genders, as demonstrated in the study conducted by Ishaq et al (22) in Erbil-Iraq. For example, the general male lifestyle and the androgens along with its receptors are bigger contributors to the mortality differences. The lifestyle of male is different from

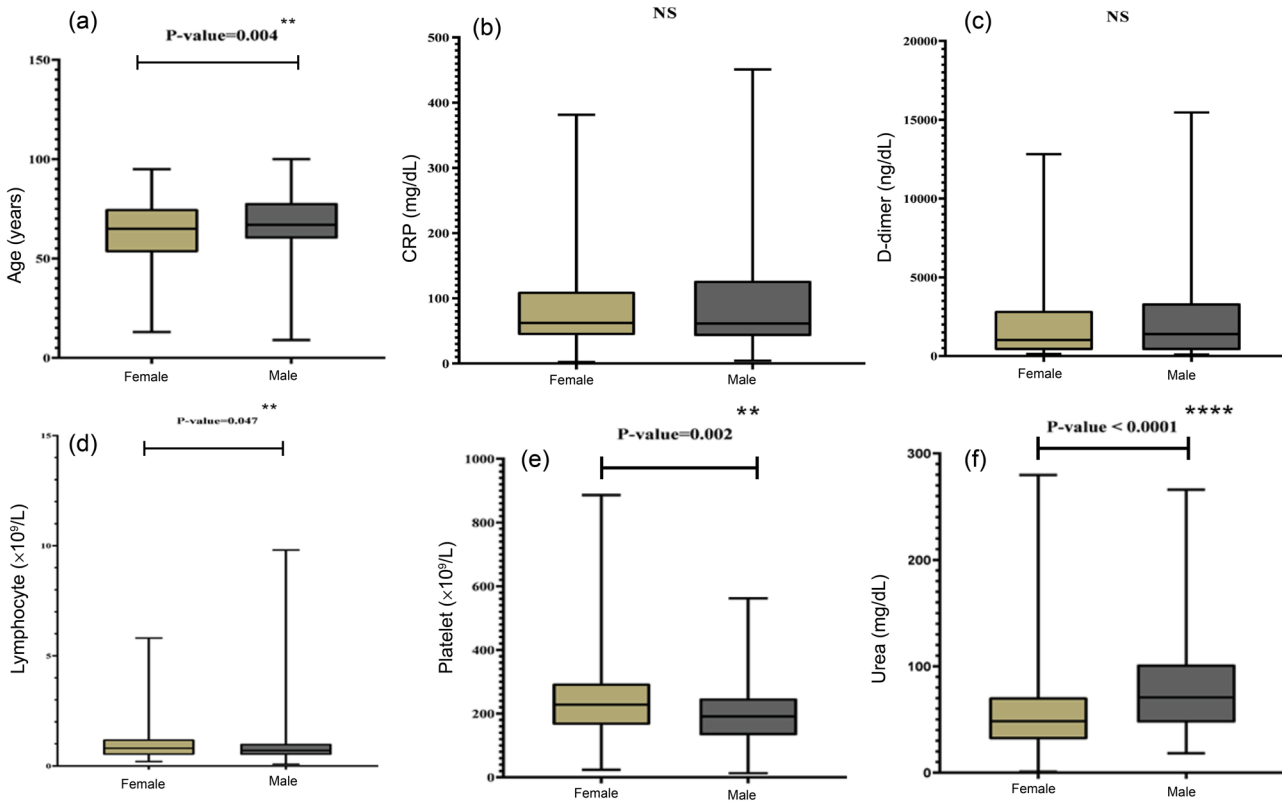

Figure 1. Comparison (a) age, (b) CRP, (c) D-dimer, (d) lymphocyte, (e) platelet, and urea (f) between the dead female and male COVID-19 patients. Mann-Whitney U test was conducted for the comparison.

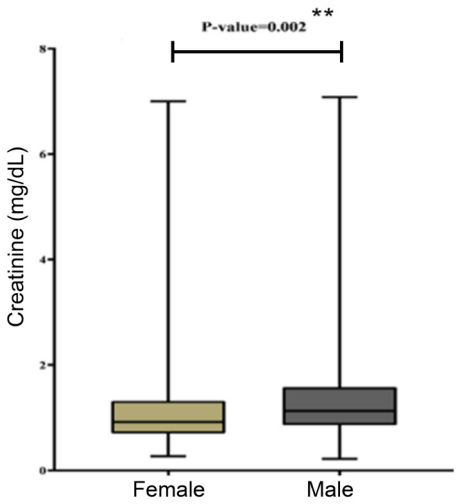

Figure 2. Comparison creatinine between the dead female and male COVID-19 patients. Mann-Whitney U test was conducted for the comparison.

woman because they consume more alcohol and smoke, this results in less susceptibility of females (23). Males also have an increased expression of TMPRSS2, which along with their increased androgens, have given them more susceptibility to the SARS-CoV-2 strain. The study also examined the comparison of inflammatory markers between genders. For example, males have an increased level of CRP, ferritin and IL-6 compared to females. In contrast, the increased survival of female was due to the defensive effects of estrogen hormone (24).

The inflammatory parameters between the two genders were compared to figure out the different immune responses (21). discovered differences between the genders in contrary to our findings. For example, inflammatory markers such as IL-2, CRP, IL-6 and ferritin were increased compared to females. Further investigation and studies should be authorized to clarify the specific mechanisms.

In our study with 659 patients, lymphopenia was detected in males which seems to be a huge mortality inducer. Lymphopenia is seen generally in COVID-19 patients especially in the critical patients which has a significant influence on the survival rates (20). Another interesting observation was that patients also had thrombocytopenia. That factor is what contributes to the thrombus formations in the course of the disease. Their increased activation and use up of the amount available forms clots. The presence of lymphopenia and thrombocytopenia leads to bad prognosis. This is associated with mortality of dead male COVID-19 cases. The presence of platelets in thrombotic and endothelial variations of SARS-CoV-2 was extensively established. Due to the increased activation of platelets, they are consumed and decreased (25,26).

In the investigation the relationship between SARS-CoV-2 infection and kidney function tests measuring serum urea and creatinine, male cases exhibited higher results. This was also justified by the study by Cheng et al (27), which showed a large group of cases with pneumonia

Table 2. Correlation among various variables

Independent variable	Dependent variable	*r*	*P* value
D-dimer	Urea	0.207	0.009
D-dimer	Creatinine	0.0008	0.991
CRP	Age	0.005	0.9421
CRP	D-dimer	0.192	0.012
Platelet	D-dimer	-0.077	0.276
Lymphocyte	CRP	-0.041	0.556

that had renal disease signs like increased urea and creatinine. These results concluded that COVID-19 gets into bloodstream and lodge in the kidney tissues because of the ACE2 expression in the kidney cells.

Conclusion

The data from this study provided an initial assessment of the immunological response in deceased COVID-19 patients in Erbil, Iraq. Our findings revealed significant differences in immune responses, including inflammation, coagulation, hematological, and kidney function biomarkers, between deceased male and female patients infected with COVID-19.

Limitations to the study

There were some limitations to our study. The markers like IL-6 and ferritin had not been measured, since only CRP was measured as inflammatory marker. Likewise, in other studies measurement of lymphocyte to neutrophil ration suggests. We also suggest larger studies on this aspect of COVID-19.

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Conflicts of interest

The authors do not have any conflict of interest.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of Salahaddin University-Erbil (SUE) in (approval number: R22-025; 104 approved on April 19, 2020). Prior to any

intervention, all participants provided written informed consent. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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