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Gender disparities in lymphocyte counts and cytokine expression in COVID-19

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Abstract

Background: This study seeks to assess gender differences in the severity of COVID-19 infection, which have been noted in different regions during the early stages of the pandemic.

Methods: A cross-sectional study conducted at Baquba Teaching Hospital in Diyala, Iraq, from October 1st to December 31st, 2020, included 132 confirmed COVID-19 patients. These patients underwent a comprehensive set of routine laboratory tests, including complete blood count, blood biochemistry, and D-dimer assessment. Statistical analysis was carried out using SPSS-20, with significance set at $p < 0.05$.

Results: The study included patients with a mean age of 45.61 (±11.32) years, predominantly male (63.0%), residing in urban areas (57.6%), and presenting with comorbidities (78.8%). All patients exhibited positive results on CT scans (100%) and CRP tests (100%). However, PCR testing confirmed COVID-19 infection in 87.2% of cases, with 12.8% testing negative. Among males, there was a significant increase in IL-6 and IL-10 levels (42.57 ± 7.64 pg/ml and 255.27 ± 21.03 pg/ml) compared to females (16.43 ± 4.19 pg/ml and 187.48 ± 20.35 pg/ml), with p-values <0.001 and 0.003, respectively. Conversely, there was no significant difference in IFN-ɣ levels between males (165.73 ± 16.54 pg/ml) and females (176.12 ± 17.10 pg/ml), with a p-value of 0.105. However, lymphocyte levels were significantly lower in males (4.79 ± 0.85%) compared to females (14.01 ± 1.36%), with a p-value <0.001.

Conclusion: Overall, COVID-19 affects males more severely than females, with males showing weaker immune responses and higher levels of inflammatory cytokines like IL-6 and IL-10. While IFN-ɣ levels do not differ significantly between genders, males have lower lymphocyte counts compared to females.

Keywords: COVID-19, IL-6, IL-10, IFN-ɣ, PCR test, Lymphocyte, Gender, Iraq

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Background

COVID-19 was officially recorded in Iraq on February 24, 2020, likely with earlier community transmission [1]. The high ability to transmit the infection via respiratory droplets and direct contact with infected individuals caused the outbreak of a global pandemic in short time [1,2]. Increasingly, research suggests that advanced age, being male, and various comorbidities elevate the risk of COVID-19 [3,4,5]. Male and female individuals exhibit diverse immunological reactions to both foreign and self-antigens, displaying discrepancies in innate and adaptive immune responses [6]. These sex-related immunological variations are crucial factors contributing to differences in autoimmune diseases, malignancies, susceptibility to infections, and responses to vaccines among males and females [7]. Overstimulation of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-8, and IL-10, alongside acute inflammatory proteins like hyper-sensitive C-reactive protein (hsCRP), contributed to the development of SARS-related acute respiratory distress syndrome (ARDS) [8-10]. During the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak an excessive innate immune response was reported by overproduction of proinflammatory cytokine IL-6 which significantly led to several organ damage and fatalities [Hong KH, 11]. Furthermore, Zhou et al. [12], and Liu et al. [13], in their studies on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) found that dead patients and those with severe illness did not have enough lymphocytes

(Lymphopenia or lymphocytopenia), however, they presented with increased levels of serum IL-6 (proinflammatory cytokine storm). IL-6 stands out as a key pro-inflammatory cytokine, often elevated in COVID-19 patients, particularly those with severe illness, and is increasingly recognized as a prognostic indicator in the disease [14]. Conversely, IL-10, an anti-inflammatory cytokine, has been found elevated in severe cases of COVID-19 [15]. Initially, during viral infection, IL-10 serves as a counterbalance to pro-inflammatory factors through negative feedback. However, as the disease progresses, endogenous IL-10 levels rise, potentially exacerbating the cytokine storm [16]. Interferons (IFNs) are recognized for their antiviral properties, crucial in curbing viral replication [17]. IFN-γ levels correlate inversely with COVID-19 fibrosis progression at discharge, suggesting its early antiviral action and fibrosis inhibition for enhanced recovery [18,19]. Severe COVID-19 cases exhibit lower IFN-γ levels compared to moderate cases [20]. Lymphocytes are pivotal in regulating immune balance and inflammation throughout the body, with lymphopenia indicating a reduced lymphocyte count [21]. In COVID-19, lymphopenia serves as a prognostic indicator, often declining notably in severe cases [22]. The study aimed to explore the gender differences in COVID-19 severity considering some cytokines and lymphocyte counts.

Methods

Study design and participants

From October 1st to December 31st, 2020, a cross-sectional study took place at Baquba Teaching Hospital in Diyala Province, Iraq. Patients were enlisted from COVID-19 units within the hospital, and all procedures were carried out at the hospital's laboratory.

Sample size

Considering the margin of error between 7%, a confidence level of 90%, and a 50% response distribution the sample size reached 152 (138 +10% drop out) using the following formula: N= [Za2 x P X Q / (M.E.)2]

Inclusion and exclusion criteria

All confirmed cases for COVID-19 by real-time polymerase chain reaction, those who underwent chest computed tomography (CT), both genders and able to sign the consent form were included in the study. Pregnant women, aged less than 18 years, very severe cases, unconscious or unable to give the verbal consent were excluded.

Procedure

All patient underwent to full set of routine laboratory tests, including complete blood count, blood biochemistry, and D-dimer assessment. Venous blood samples were obtained following rigorous aseptic procedures. After disinfecting the skin with 70% alcohol, a 5 ml blood sample was drawn via venipuncture. Of this, 2 ml was transferred to EDTA tubes for Complete Blood Count (CBC), while the remaining 3 ml was placed in gel tubes. Subsequently, the samples were transported to the laboratory using a thermo wagon. Upon arrival, the gel tubes were centrifuged to isolate serum, which was then stored in Eppendorf tubes at -80°C until analysis.

Lymphocyte determination

Lymphocyte counts were automatically determined using the Sysmex XN350 hematological analyzer. The laboratory utilized various kits for this study, including the virellaSARS-CoV-2 seqc real-time RT-PCR Kit by Gerbion (Germany), RNA extraction Kit by Biocomma (China), C-Reactive Protein Kit by SPINREACT (Spain), Complete Blood Count Solution by Sysmex Corporation (Japan), Human Interleukin 10 (IL10) ELISA Kit by abbexa (England), Human Interleukin 6 (IL6) ELISA Kit by abbexa (England), and Human Interferon Gamma (IFN-ɣ) ELISA Kit by abbexa (England). Laboratory analyses adhered to the manufacturers' instructions.

Dependent and independent variables

The dependent variable was the gender, categorized as either "male or female". Independent variables are sociodemographic, laboratory and clinical features

Statistical analysis

The analysis utilized SPSS-20 statistical software (Statistical Packages for Social Sciences, version 20). Data were presented using simple frequency and percentage measurements. The difference in means was assessed using the student's t-test for independent means, with statistical significance determined at $p \leq 0.05$.

Results

Characterization COVID-19 patients

Out of 152 collected samples, 132 were analyzed. The Mean ±SD of age (year) was (45.61. ± 11.32), ranged 27-73 years. Most of them were males (83. 63.0%), urban residents (57.6), presented with comorbidities (78.8%) (Table 1). All patients exhibited positive results on CT scans (100%) and CRP tests (100%). However, the percentage of confirmed COVID-19 infection via PCR testing was 87.2%, with 12.8% testing negative. Patients were further categorized by disease severity: moderate (53.8%), severe (29.5%), and critical (16.7%) as shown in Table 2.

Table1: sociodemographic factor of patients (n=132)

Variables	Categories	N (%)
Age	Mean (SD)	45.61
	Range	27-73
Gender	Male	83 (63.0)
	Female	49 (37.0)
Residence	Rural	56 (42.4)
	Urban	76 (57.6)
Comorbidities	HT	41 (31.1)
	DM	36 (27.3)
	CVD	27 (20.4)
	None	28 (21.2)

Table2: Laboratory and clinical features of patients (n=132)

Variables	Categories	N (%)
Tests	C.T scan	132 (100.0)
	CRP	132 (100.0)
	PCR +ve	115 (87.2)
	PCR-ve	17 (12.8)
Severity of disease	Moderate	71 (53.8)
	Severe	39 (29.5)
	Critical	22 (16.7)

Most of the male patients presented with comorbidities especially HT and DM compared to females. The highest percentage of positive PCR was among males (72, 86.7%) (Table 3).

Table 3: laboratory and clinical findings in gender (n=132)

Variables	Categories	Total N(%)	Male N(%)	Female N(%)
Observation		132 (100.0)	83 (63.0)	49 (37.0)
Comorbidities	HT	41 (31.1)	26 (31.3)	15(30.6)
	DM	36 (27.3)	23(27.7)	13(26.5)
	CVD	27 (20.4)	17(20.5)	10(20.4)
	None	28 (21.2)	17(20.5)	11(22.5)
PCR test	PCR +ve	115 (87.2)	72(86.7)	43(87.8)
	PCR-ve	17 (12.8)	11(13.3)	6(12.2)
Severity of disease	Moderate	71 (53.8)	45(54.2)	26(53.1)
	Severe	39 (29.5)	24(28.9)	15(30.6)
	Critical	22 (16.7)	14(16.9)	8(16.3)

Bivariate analysis on patients' gender

The male group demonstrated a notably higher increase in IL-6 and IL-10 levels (42.57 ± 7.64 pg/ml and 255.27 ± 21.03 pg/ml) compared to the female group (16.43 ± 4.19 pg/ml and 187.48 ± 20.35 pg/ml), with p-values <0.001 and 0.003, respectively. Conversely, there was no significant difference in IFN-ɣ levels between males (165.73 ± 16.54 pg/ml) and females (176.12 ± 17.10 pg/ml), with a p-value of 0.105. However, lymphocyte levels were significantly lower in males (4.79 ± 0.85%) compared to females (14.01 ± 1.36%), with a p-value <0.001 (Table 4).

Table 4: IL-6, IL-10, IFN and lymphocytes concentration in COVID-19 patients (n=132)

Variables	Male Mean ± SD	Female Mean ± SD	t-test	p-value
IL-6	42.57 ± 7.64	16.43 ± 4.19	17.723	0.000
IL-10	255.27 ± 21.03	187.48 ± 20.35	13.541	0.003
IFN	165.73 ± 14.93	176.12 ± 17.10	0.863	0.105
Lymphocytes	4.79 ± 0.85	14.01 ± 1.36	15.332	0.000

Discussion

This research provides insights into the gender disparities among Covid-19 patients in Iraq during 2020, highlighting variations in laboratory results and illness severity. Notably, the study recorded proportions of severe and critical cases at 29.5% and 16.7%, respectively, potentially influenced by data collection during the peak of the disease outbreak in Iraq. In this study, 16.7% of the critical COVID-19 patients were male, accounting for 22 out of 83 cases. Males exhibited a higher rate of positive PCR results compared to females (72, 62.6% vs 43, 37.4%). While both genders displayed similar instances of cardiovascular disease (CVD), males experienced a higher prevalence of hypertension (HT), and diabetes mellitus (DM), rendering them more prone to mortality than their counterparts without such comorbidities. Additionally, the average age of 45.61 years suggests a propensity for COVID-19 to affect older individuals [23]. This trend underscores the vulnerability of the elderly population to the virus, potentially due to age-related physiological changes and underlying health conditions that may exacerbate the severity of the disease [24]. COVID-19 affects males and females alike [25], but males tend to experience more severe cases and higher fatality rates [4]. This outcome in males is likely influenced by biological differences and gender-specific behaviors such as smoking and alcohol consumption [26]. Additionally, research indicates that females tend to seek healthcare services more promptly than men [27], whereas males with fatal outcomes often face delays in diagnosis and admission to healthcare facilities [28].

Previous research on SARS patients highlighted the potential for an abnormal inflammatory response, characterized by elevated levels of various cytokines and inflammatory proteins such as IL-6, IL-8, IL-10, TNF-α, and hsCRP, contributing to lung damage, ARDS, and multiple organ failure. Our study also found a correlation between the severity of COVID-19 and increased expression of these inflammatory markers, suggesting a similar pathogenic mechanism in severe cases of COVID-19 [29]. Additionally, prior studies indicated that males exhibited increased IL-10 production in peripheral blood mononuclear cells (PBMCs) compared to females upon virus stimulation, correlating positively with androgen levels in males. Moreover, males displayed elevated levels of proinflammatory cytokines (e.g., TNF) and chemokines (e.g., CXCL10) following lipopolysaccharide stimulation [10]. Our study highlights a lower lymphocyte count in males than in females, possibly due to greater T cell activation and proliferation in females [6]. Additionally, variations in innate immune cell numbers and functions exist between genders. Males generally have higher natural killer (NK) cell frequencies, while females exhibit increased phagocytic activity in neutrophils and macrophages. Moreover, antigen-presenting cells (APCs) from females demonstrate superior peptide presentation compared to those from males [32]. Our study found a significantly higher level of IL-6 in males compared to females, consistent with previous research indicating lower production of inflammatory IL-6 after viral infection in females. This pattern is often associated with

better longevity in females [33]. Multiple studies have highlighted changes in laboratory parameters during COVID-19, notably the reduction in total lymphocytes, strongly linked to disease severity [34]. Sex-specific clinical outcomes may also be influenced by pre-existing comorbidities like hypertension, cardiovascular disease, and diabetes, which are more prevalent and severe in men with severe and fatal COVID-19 cases [34, 36]. This study has several limitations. Firstly, its cross-sectional design prevents establishing causal relationships. Secondly, being a single-center study conducted solely at Baquba Teaching Hospital, generalizing findings may be limited due to sample size constraints. Lastly, conducting laboratory tests only upon admission restricts understanding the dynamic changes in blood cytokine levels, which could offer valuable insights into COVID-19 pathogenesis and treatment efficacy.

Conclusion

Overall, COVID-19 infection rates are higher in males than females. Male patients exhibit compromised immune responses and heightened production of inflammatory cytokines, particularly IL-6 and IL-10. Levels of IL-6 and IL-10 are notably elevated in males compared to females, while IFN-ɣ shows no significant gender difference. Additionally, lymphocyte counts significantly decreased in COVID-19 male patients compared to females.

Abbreviation

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease; HT: Hypertension; DM: Diabetes mellitus; CVD: Cardiovascular Disease; CBC: Complete Blood Count; CT: Computed Tomography; SD: Standard Deviation; TNF-α: Tumor Necrosis Factor-α; IL-6: Interleukin-6, IL-8: Interleukin-8; IL-10: Interleukin-10; CRP: C-Reactive Protein; ARDS: Acute Respiratory Distress Syndrome. IFN-ɣ: Interferon Alpha; NK: Natural Killer; PBMCs: Peripheral Blood Mononuclear Cells; APCs: Antigen-Presenting Cells

Declaration

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Availability of data and materials

Data will be available by emailing ismail@uodiyala.edu.iq

Authors' contributions

All authors equally conceived and designed the study, analyzed and interpreted the data; drafted the manuscript; and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

We conducted the research following the declaration of Helsinki. The ethical approval [Ref. No. 2020] was obtained from the Ethic Committee of College of Medicine, University of Diyala, Iraq.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interests.

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