Sex-based Variations in Clinical Manifestations, Co-morbidities, and Outcome of COVID-19 Patients in Baghdad, Iraq, 2020

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Abstract: *Background:* Although it was reported that a higher percentage of the confirmed COVID-19 cases were males. the differences between males and females in clinical manifestations, comorbidities, severity, and outcome remain an area of active investigation.

Objective: To compare the clinical features, comorbidities, severity, and outcome between male and female COVID-19 patients, Baghdad, Iraq, 2020.

Methods: A records-based cross-sectional study was conducted by extracting sociodemographic, clinical manifestations, severity, and outcome data from the records of COVID- 19 patients admitted to two COVID-19 hospitals in Baghdad, Iraq during June through August 2020.

Results: The total number of patients was 2111; males were 1175 (55.7%). The mean patients' age was 49.6 (±16.4) years with no significant difference between males and females (P=0.240). Respiratory symptoms, sore throat and gastrointestinal manifestations were significantly more common among females (90.5%; P= .034), (14.0%; P=.022), and (11.5%; P=.002), respectively. Males had significantly higher "other" manifestations (5.6%; P=0.024). No significant difference was noted for fever, nasal congestion, conjunctival congestion, headache, and musculoskeletal manifestations (P>0.05). Generally, female patients had a significantly higher proportion of comorbidities compared to males (42.7% vs 36.0%; P=0.002). The proportion of severe cases among males was 28.7% compared to 27.8% among females (P>0.05). Also, the critical cases were seen in 22.3% of males compared to 20.9% of females (P>0.05). The mean time from diagnosis to the outcome was 11.4±6.9 days; it was significantly longer in females (P=.034) while the meantime taken for hospital stay was 7.0±5.1days with no significant difference between males and females (P=0.476). The overall case fatality ratio was 14.8% (313/2111); it was higher in males (16.1%) than females (13.2%) (P= .202).

Conclusion: Gender affects the clinical course and outcome of COVID-19 patients. Male patients may need more attention considering the higher case fatality ratio.

Keywords: COVID-19, Iraq, Gender, Case fatality ratio, Comorbidity.

INTRODUCTION

The novel coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The first reported cases of COVID-19 were in Wuhan, China, and reported to the World Health Organization (WHO) on December 31^{st,} 2019. The disease has continued to spread internationally and was classified by WHO as a pandemic in March 2020 [1]. Coronaviruses belong to a family of single-stranded RNA viruses, which cause different diseases that can affect respiratory, gastrointestinal, hepatic, and neurologic systems [1, 2]. It is similar to the viruses causing Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), and it is the seventh coronavirus known to infect humans [3, 4]. Patients infected with COVID- 19 have an incubation period of 2–14 days with a mean period of 5 days and the clinical presentation may range from asymptomatic condition to acute respiratory failure [5].

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As the COVID-19 pandemic continues, differences between male and female mortality and infectivity remain an area of active investigation. Literature suggested that men tend to have a higher risk of severe infection and mortality related to COVID-19 [6-8], while fewer studies showed the opposite [9].

Sex is among many variables that affect the immune response. It is a biological variable that affects immune responses to both self and foreign antigens (for example, those from fungi, viruses, bacteria, parasites, and allergens) [10].

Possible causes that might explain the sex-based differences may include the differences in inflammatory processes and Angiotensin-Converting Enzyme-2 (ACE2) differences in men and women [11].

The sex difference in the response to the COVID-19 pandemic raises some questions about the differences in vulnerability, susceptibility, the proportion of hospitalization, the similarity in symptoms, and response to treatment [12]. However, different clinical studies have given conflicting reports on the male or

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female predominance of COVID-19 infections. This discrepancy is likely due to the lack of large-scale epidemiological studies, socioeconomic disparities, or other confounders on the prevalence of pre-existing conditions in different countries [13-15].

In Iraq, it was reported that a higher percentage of the confirmed COVID-19 cases were males [16]. Other sex-based variations between males and females associated with COVID- 19 patients in Iraq were not adequately explored.

OBJECTIVES

To determine and compare the variations between male and female COVID- 19 patients in their clinical manifestations, co-morbid illnesses, severity, and outcome, in Baghdad, Iraq, 2020.

METHODS

Study Design

This is a record-based, cross-sectional study.

Settings

The study was conducted in AlKarkh and AlFurat General Hospitals that were selected for the management of COVID-19 patients in the western part of the capital Baghdad (AlKarkh), since the inception of the pandemic in Iraq. Although isolation wards dedicated to COVID-19 were added in other hospitals following the increase in the number of reported COVID-19 cases, these two hospitals remain the main hospitals for treating COVID- 19 patients. AlKarkh General Hospital has a total of 235 beds, including 8 RCU beds, while AlFurat General Hospital has a total of 90 beds including 5 RCU beds [17].

The total population of the capital Baghdad is more than 8.3 million people; the population of AlKarkh side is more than 3.6 million people [18]. From the healthcare perspective, AlKarkh side of Baghdad has 13 general and specialized hospitals, 10 primary health care districts (PHC districts) with 131 Primary Healthcare Centers (PHCs) [18].

Study Population and Sampling

This included all the records of the admitted patients to the assigned two hospitals who tested positive for SARS-CoV-2 using the RT-PCR test from June 1st, 2020 through August 31st, 2020.

Data Collection Tool

A data collection form was developed using the kobo toolbox to gather information from patients' records. The list of information that was comprised was divided into sections. The first section is about the demographics and baseline characteristics like record number; hospital name; date of onset of symptoms; date of hospital admission; gender; age; occupation (classified as HCW or not HCW); and smoking history (classified as current smoker, current non-smoker). The second section was about signs and symptoms like fever; cough; sore throat; nasal congestion; conjunctival congestion; myalgia or arthralgia; backache; nausea and vomiting; diarrhea; fatigue; loss of taste or smell; headache; shortness of breath; hemoptysis; sputum production; chest pain; and other symptoms (to be mentioned) [15], comorbid illnesses like hypertension (HT); type 2 diabetes mellitus (DM); coronary heart diseases; chronic obstructive airways disease (COPD); tuberculosis (TB); Asthma; any other respiratory diseases; renal disease; liver disease; cerebrovascular disease; malignancy (to be specified); obesity; others (to be mentioned), and the degree of severity as mild (upper respiratory disease); moderate (pneumonia but no need for oxygen); severe (pneumonia and needs oxygen); or critical (the patient needs admission to RCU) [15].

The third section is the investigations like COVID-19 test used; white blood cells count; lymphocyte count; platelet count; ESR; CRP; D-dimer; hemoglobin; and creatinine tests. The fourth section is the outcome section which was classified as recovered; death; and others (discharged on own responsibility or referral to other hospitals), also it included the place of death of the patient whether in the general ward or the RCU, the total number of days from diagnosis till outcome, and the total number of days of hospital stay.

Pilot Study

The questionnaire was tested on 15 patients' records before starting the formal data collection process to test the feasibility of the data collection form and to estimate the time needed to complete the record review and fill the form.

Statistical Analysis

Microsoft Excel 2019 was used for data entry and analysis. All results were presented in the form of tables and graphs. Continuous variables were presented as mean ± SD. Categorical variables were presented as counts and percentages. Differences between males and females in continuous variables were tested with Student's *t*-test, and associations between categorical variables were assessed using the chi-square test. Z test for difference between two proportions was also used. *P* values less than .05 were considered statistically significant.

Ethical Considerations

Ethical approval was granted from the Ethical and scientific committee in the Directorate of Public Health, Iraq Ministry of Health. The confidentiality of the patients' information was considered. All the data were saved in a password-secured computer.

RESULTS

The total number of the studied patients was 2111, the demographic characteristics are shown in Table **1**.

There is no significant difference (P= .240) in the mean age between the males and the female patients (49.7± 15.7) and (49.5± 17.2), respectively. Males have higher proportion of healthcare workers 5.6% (n= 65) than females (3.2%, n= 29) and the difference was statistically significant (P= .008). Males have higher percentage of smokers with 28.9% (n= 208) than females (7.9%, n= 48), and the difference is statistically significant (P= .0001) (Table **2**).

For the signs and symptoms, the highest proportion was for the respiratory symptoms, which were seen in 88.9% of the studied patients, and they were higher in males (n=1029, 90.5%) than in females (n= 847, 87.6%) and the difference was statistically significant (P= .034). The sore throat was reported by 12.2% of the studied patients and it was significantly higher in females (n=1310; 14%) than in males (n=126, 10.7%) (P=.022). Also, GIT symptoms were reported by 9.4% of the patients and they were significantly higher in

Table 1: Basic Demographics of the Study Population

		Total (2111)	
		No	%
Sex	Male	1175	55.7
	Female	936	44.3
Age (years)	<40 years	572	27.1
	40-59	879	41.6
	≥60 years	660	31.3
	Mean±SD (Range)	49.6±16.4 (1-93)	
Health care worker	Health care worker	94	4.5
	Not	1977	95.5
Smoking history	Current smoker	256	19.3
	Not smoker	1073	80.7

Table 2: Distribution of the Study Group by Gender and the Basic Demographics

		Male (1175)		Female (936)		Total (2111)		P-value
		No	%	No	%	No	%	
Age (years)	Mean± SD (Range)	49.7±15.7 (3-93)		49.5±17.2 (1-93)		49.6±16.4 (1-93)		P=0.240
Health care worker	Health care worker	65	5.6	29	3.2	94	4.5	0.008
	Not	1094	94.4	883	96.8	1977	95.5	
Smoking history	Current smoker	208	28.9	48	7.9	256	19.3	0.001
	Non- smoker	511	71.1	562	92.1	1073	80.7	

females (n=108, 11.5%) than in males (n= 90, 7.7%) (P= .002). Other symptoms were seen in 4.7% of the patients and they were significantly higher in males (n = 66, 5.6%) than in females (n= 33, 3.5%) (P=.024) (Table **3**).

Co-morbid illnesses were reported among 39% (n= 823) of the patients and they were significantly higher in females (42.7%) than in males (36%) (P= .002). The most prevalent co-morbid illnesses were hypertension and diabetes, which comprised half of the patients with co-morbid illnesses and both are significantly higher among females 29.2% (n= 273) and 27.4% (n= 256) than in males 21.7 (n=255) and 23.1% (n= 271) (P= .0001) and (P= .024), respectively. (Table **4**).

Around 50% (n=1052) of the patients needed oxygen by mask, and although the proportion was higher for the males (50.8%, n= 597) than the females (48.6%, n= 455), but the difference was not statistically significant (P= .316). Around 20% (n= 411) of the patients needed noninvasive ventilation (CPAP) and the proportion was slightly higher in males (19.7%, n= 231) than females (19.2%, n= 180), but the difference was not statistically significant (P=.805).

Generally, the proportion of mild cases among admitted cases was the least 5.5% (n=116) while the proportion of the moderate cases was the highest (44.5%, n= 940). The proportion of the severe cases was 28.3% (n=597) and the critical cases were 21.7% (n= 458). Female patients had higher proportion of mild and moderate cases 5.7% (n= 53) and 45.6% (n=427), respectively, while males have the higher proportion of the severe and the critical cases 28.7% (n= 337) and 22.3% (n= 262), respectively. The difference was not statistically significant (P= .770). (Table **5**)

Table 3: Distribution of the Study Groups by Gender and the Presenting Symptoms

Presenting Signs and Symptoms	Male (1175)		Female (936)		Total (2111)		P-value
	No	%	No	%	No	%	
Fever	858	73.0	693	74.0	1551	73.5	0.599
Sore throat	126	10.7	131	14.0	257	12.2	0.022
Nasal congestion	17	1.4	14	1.5	31	1.5	0.926
Conjunctival congestion	8	0.7	6	0.6	14	0.7	0.911
Headache	91	7.7	74	7.9	165	7.8	0.891
Muscular symptoms	256	21.8	193	20.6	449	21.3	0.515
GIT symptoms	90	7.7	108	11.5	198	9.4	0.002
Respiratory symptoms	1029	87.6	847	90.5	1876	88.9	0.034
Others	66	5.6	33	3.5	99	4.7	0.024

Table 4: Distribution of the Study group by Gender and the Co-morbid Illnesses

	Male (1175)		Female (936)		Total (2111)		P-value
	No	%	No	%	No	%	
Co-morbid Illnesses	423	36.0	400	42.7	823	39.0	0.002
Hypertension	255	21.7	273	29.2	528	25.0	0.0001
Diabetes mellitus	271	23.1	256	27.4	527	25.0	0.024
Heart diseases	45	3.8	47	5.0	92	4.4	0.183
Chronic Respiratory Diseases (COPD, TB, Other resp)	9	0.8	7	0.7	16	0.8	0.962
Asthma	8	0.7	14	1.5	22	1.0	0.067
Other illnesses (Renal, liver, CVA, immune-comp, malignancies, others)	41	3.5	31	3.3	72	3.4	0.823

Table 5: Distribution of the Study Group by Gender and the Severity Classifications

Severity Classification	Male (1175)		Female (936)		Total (2111)		P-value
	No	%	No	%	No	%	
Mild	63	5.4	53	5.7	116	5.5	0.770
Moderate	513	43.7	427	45.6	940	44.5	
Severe	337	28.7	260	27.8	597	28.3	
Critical	262	22.3	196	20.9	458	21.7	

The case fatality rate among the study group was 14.8%. It was higher in males 16.1% than females (13.2%) but the difference was not statistically significant (P= .202).

The mean duration of the disease from diagnosis till outcome was 11.4±6.9 (range: 1-60) days and it was significantly longer in females (11.8±6.8, range: 1-60 days) than males (11.1±7.0, range: 1-60), (P= .034). The mean time for the hospital stay was 7.0±5.1 (range:0-47) days with no significant difference between males (6.9±5.1, range: 0-43)) and females (7.1±5.2, range: 0-47) patients, (P=0.476).

DISCUSSION

The differences in clinical features, the severity of the disease, and outcomes between male and female patients with COVID-19 were addressed in this study. In terms of clinical presentation, more male patients suffered from more severe manifestations and needed ICU admission, and noninvasive ventilation therapy while females had a lower case fatality rate than males. Although sex differences seem to affect the prognosis of COVID-19, the exact mechanism of different outcomes between women and men is still unclear. Some studies may provide some insight into the underlying reasons, estrogen may protect females from poor outcomes during coronavirus infection and women’s immune systems are stronger to fight against SARS CoV-2 [19-22].

Similar coronaviruses, like the Middle East respiratory syndrome coronavirus (MERS) and the severe acute respiratory syndrome-coronavirus (SARS-CoV), were also found to affect more males than females [23]. Many publications from China also revealed the sex differences in the detected cases and the case fatality rate of COVID-19 [24-230]. Only one study of 140 patients with COVID-19 in China found an equal distribution by sex, and approximately 1:1 ratio of male (50.7%) and female (49.3%) COVID-19 patients, and the majority (70%) were more than 50 years old with an overall median age of 57.0 years [31].

In the present study, most of the presenting manifestations were more common among males except for the GIT symptoms and the sore throat that were more common in females, and this is in concordance with the findings in some studies [32, 33].

Females with COVID- 19 demonstrated a higher proportion of co-morbid illnesses, namely, hypertension, other cardiac diseases, diabetes, and asthma. In the study conducted by Grasselli in Lombardy (Northern Italy) [34] hypertension was the most common comorbidity (49%), followed by cardiovascular disease (21%), hypercholesterolemia (18%), and diabetes (17%). Those data were similar to two Chinese studies [35,36]. A review conducted by Cheng [37] underlined that the poor prognosis of patients with COVID-19 was related to factors such as male sex, age >60 years, underlying diseases (hypertension, diabetes, and cardiovascular disease), and complicating secondary acute respiratory distress syndrome (ARDS).

The need for oxygen and CPAP goes with the severity of cases and it is higher in males than in females, and this can be explained by a relatively high number of angiotensin-converting enzyme 2 (ACE2) receptors in males. The ACE2 receptor is the receptor used by coronavirus to infect humans [33] or maybe because males have lower endurance levels than females. The sex-related difference in the immune system, sex hormone milieu, and other unknown causes may be contributing factors for the high mortality of males in stressful conditions including COVID-19 [38].

In concordance with the findings of this study of higher case fatality rate in males than females, other studies revealed a similar finding [39, 40]. On the other hand, in the prospective study conducted on COVID-19 pneumonia by Du *et al.* that included 179 patients the mortality in male patients was 47.6% and in female patients was 52.4% [41].

It is important to consider how sex intersects with gender when determining the differences in occurrence and case fatality between males and females [42]. There is evidence suggesting that the COVID-19 pandemic has primary and secondary effects related to sex and gender. Primary effects include differences between males and females in the incidence and case fatality, while secondary effects include the differences in socioeconomic impacts as a result of the pandemic, including the risk of domestic violence [43], economic and job instability, and increased domestic workload [44]. Gender differences in risk behaviors, such as smoking and drinking, may be contributing to the gender gaps in mortality [45]. Other gendered behaviors and norms which may be contributing to a higher incidence of COVID- 19 among men include lower rates of hand washing, which is a well-known preventative measure and delayed seeking of medical intervention [16]. Rejection of social isolation, social responsibilities, psychological stress, low quality of life, and low socioeconomic status among COVID-19 are all often considered to put females and males at differential risk of infection or mortality [45]. Additionally, women are more likely to look after other sick family members [44].

LIMITATIONS

The missing data from COVID-19 patients' records is the major limitation of this study, especially the laboratory tests which were not available in almost all the records. Also, this study was limited to the capital Baghdad and did not involve other cities in the country.

CONCLUSIONS

The higher COVID-19 case fatality rate and increased severity of disease in males compared with females is likely due to a combination of behavioral/lifestyle risk factors, the disproportional prevalence of co-morbidities may likely contribute to worse COVID-19 outcomes among male patients.

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