

Sex difference in hospitalized patients with COVID-19 infection

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Abstract

The pandemic of COVID-19 infection is rapidly progressing to one of the most severe threats to human health. The different responses of the immune system in females and males to a range of infectious and inflammatory stimuli were investigated. We aimed to explore the association of sex with the course of infection among the hospitalized COVID-19 patients. This Comparative cross-sectional study was conducted on RT-PCR positive COVID-19 patients. Severe and critical patients who required hospital or ICU admission were included in the study. The total number of patients was 150 (75 males and 75 females) with mean age of $57Y \pm 14.7$. There was a statistical significance in age between both groups [mean \pm SD: males 60.5 (12.2), females 54 (15.3) ($p=0.007$)]. The prevalence of diabetes mellitus, hypertension, chronic kidney disease and ischemic heart disease was higher among males but without statistical significance. Consolidation was significantly more prevalent in female group (85.3% vs 61.3% in male group). The need of mechanical ventilation was higher in men, but with no statistical significance (44% Vs 32%, $p=0.302$). Also, mortality rate was higher (48%) in males than in females (37.3%), but with no statistical significance ($p=0.262$). During the COVID-19 infection, the risk factors of severe disease and progression to the need of mechanical ventilation support in addition to mortality rate are more prevalent among males. However, radiological patterns apart from consolidation, distribution of radiological abnormalities and CT severity score in both groups did not show significant sex difference.

Introduction

The pandemic of the novel coronavirus (COVID-19) evolved after identifying a cluster of pneumonia cases in Wuhan, a city in China, in December 2019. Since then, it becomes an extraordinary international health crisis in over 188 countries in the world.¹ The COVID-19 infection has various clinical manifestations. The clinical spectrum ranged from mild, uncomplicated illness (about 81% of the patients), severe illness that required oxygen supplementation (about 14% of the patients), and acute infection that required ICU admission (about 5% of the patients).^{2,3} The critical COVID-19 infection is still fulfilling the Berlin criteria to define the ARDS.⁴

The influence of sex in the different responses of the immune system to variable infectious and inflammatory diseases such as TB, malaria, hepatitis, HIV, flu, measles, adenovirus, etc. was investigated.⁵ It was found that women are less susceptible to viral infections in comparison to men.⁵

This may be explained by steroid hormone production by the gonads, factors related to sex chromosomes, and the different innate and adaptive immunity. Sex hormones modulate the innate immune responses to various infectious diseases including viral infections.⁵ The X chromosome acts on various elements of the immune system such as FOXP3, TLR7, TLR8, CD40L, and CXCR3, which can be over-expressed in women and influence the response to viral infections and vaccinations.⁶ Pandemics and outbreaks have differential impacts on women and men. Global and national strategic plans for COVID-19 preparedness and response must be grounded in solid gender analysis and must ensure meaningful participation of affected groups.⁵

This study aimed to characterize the cohort of the hospitalized COVID-19 patients based on their gender.

Materials and Methods

This Comparative cross-sectional study was conducted on RT-PCR positive COVID-19 patients. This study was conducted within the required ethics guidelines of the Mansoura institutional research board ethics committee (code number: R.20.06.860).

The study aimed to determine the sex differences in the clinical profile, course, and prognosis of the disease among the hospitalized COVID-19 patients.

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Patients

Severe and critical - according to the WHO definition³- confirmed patients with RT-PCR positive COVID-19 necessitating hospital admission were included in the study.

The severe COVID-19 infection is defined by the presence of oxygen saturation $< 90\%$ on room air or respiratory rate > 30 breaths per minute in adults or signs of severe respiratory distress, *i.e.*, accessory muscle use, inability to complete whole sentences. While acute COVID-19 infection is defined by the presence of the ARDS, sepsis, septic shock, the need for vasopres-

or therapy, or the need for non-invasive or invasive mechanical ventilation.³

Patients below 18 years old were excluded. The sample size was calculated for the comparative cross-sectional study by using EPI INFO version 7.2.2.16.

The following data was collected: i) Medical history: age, sex, occupation, comorbidities, previous treatment; ii) Radiological data from chest CT: a) Radiological pattern: Radiological terms (ground-glass opacity (GGO), crazy paving pattern, pulmonary consolidation) were defined according to the standard glossary for thoracic imaging reported by the Fleischner Society.⁷ Other features such as fibrosis, subpleural lines, "halo sign," were also described; b) Distribution of lung abnormalities: predominately peripheral, central, or both peripheral and central; c) A semi-quantitative CT severity scoring proposed by Pan *et al.*⁸ was calculated per each of the five lobes considering the extent of anatomic involvement, as follows: 0: no involvement; 1: < 5% involvement; 2: 5–25% involvement; 3: 26–50% involvement; 4: 51–75% involvement; 5: > 75% involvement. The summation of each lobar score resulted in a global CT score (0 to 25); iii) Laboratory data: D-dimer, CRP, CBC; iv) Outcome assessment, including need of oxygen, need of mechanical ventilatio, improvement in clinical data, and mortality.

Statistical analysis of the data

The collected data was prepared, tabulated, and statistically analyzed using the Statistical Package for Social Science (SPSS) version 26. Frequencies and proportions were used to present categorical variables. In contrast, means (SD) or Median (min-max) were used to present continuous data according to the Shapiro-Wilk testing of normality of variables. Significance testing was being done using the Chi-Square test, or Fisher's exact test for categorical variables. Independent t-test and Mann-Whitney U test were used for testing significance among continuous variables, wherever appropriate. The level of significance will be set at $p < 0.05\%$.

Results

In our study, 150 confirmed COVID-19 patients (severe and critical patients) were included. Regarding sex, the study included 75 males and 75 females, with a mean age of $57Y \pm 14.7$. Nearly one-third of participants had Diabetes mellitus, 37.3% had hypertension, 12.7% had ischemic heart disease, 6.7% had chronic kidney disease, 5.3% had chronic liver disease. About 62%

of studied patients were classified as severe COVID (Table 1 and Figure 1).

The results of this study showed that there was a statistically significant difference in age between both groups [mean \pm SD: males 60.5 (12.2), females 54 (15.3) ($p=0:0.007$)]. Also, a history of previous ischemic cerebral stroke was more prevalent among males (10.7%) than females

(1.3%) with statistical significance ($p=0.034$). The prevalence of diabetes mellitus, hypertension, chronic kidney disease, and ischemic heart disease was higher among males than females but without statistical significance. In addition, bronchial asthma was more prevalent among females than males, without statistically significant difference (Table 2).

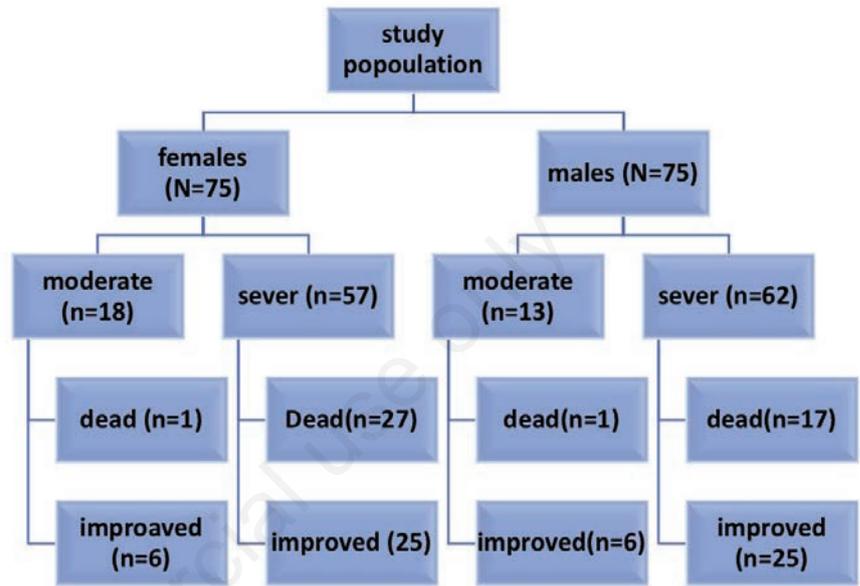


Figure 1. Flowchart of the studied population.

Table 1. Characteristics of the patients studied (N=150).

Parameter	N	%
Age mean (SD)	57 (14.7)	
Sex		
Male	75	50
Female	75	50
Comorbidity		
Diabetes mellitus	49	32.7
Hypertension	56	37.3
Cardiac	5	3.3
Ischemic heart disease	19	12.7
Chronic kidney disease	10	6.7
Chronic liver disease	8	5.3
Autoimmune disease	6	4
Bronchial asthma	3	2
Cerebral Stroke	9	6
Malignancy	3	2
COVID-19 clinical classification		
Severe	93	62
Critical	57	38
GIT symptoms		
No	116	77.3
Yes	34	22.7
Outcome		
Improved	64	42.6
Dead	86	57.4

As regards radiological data, consolidation was significantly more prevalent in the female group (85.3% vs 61.3% in the male group, $p=0.035$). However, Other radiological patterns, distribution of radiological abnormalities, and CT severity score in both groups did not show statistically significant differences (Table 3).

The proportion of studied males who needed mechanical ventilation was higher than that in females, but with no statistical significance (44% vs 32%, $p=0.302$). Also, the mortality rate was higher (48%) in males than in females (37.3%) but with no statistical significance ($p=0.262$). In addition, the presence of gastrointestinal symptoms also was not different between both groups (Table 4).

Discussion

Until now, many aspects of the COVID-19 infection are still not apparent, and a clear picture of the epidemiology of this COVID-19 is not yet well understood. The knowledge about the immune response to the COVID-19 infection is still evolving.⁹ Our study aimed to determine the sex characteristics among the hospitalized patients with severe and critical illness SARS-COV-2 infection who were admitted to Mansoura university quarantine, Egypt.

The difference of immune response to infectious agents according to gender was observed with higher susceptibility to infection and development of the resistance in male patients. Mostly it is related to androgens which affect the host immunity and disease-resistant genes.¹⁰

The mean age of all included patient was 57 years old. The older age was investigated in many studies as a risk factor for worse outcomes of COVID-19 infection. However, we observed a statistical difference in the age between studied males and females with the tendency of older age in males (60.5 years old). Older age was observed as a risk factor for COVID-19 infection without difference between ICU and non-ICU patients.¹¹ The results of this study showed a statistically significant difference in age between both groups (mean age in males was 60 and was 54 in females). These results are compatible with Goujon *et al.*,¹² which illustrated that more cases were notified among men aged from 55 to 80 years old than women. In comparison, higher numbers of mild cases are reported among women aged from 15 to 55 years.

Hypertension (37.3%) then DM (32.7%) were the most common observed comorbidities in the study. Pre-existing cardiovascular conditions, especially hypertension, are now recognized as one of the

demographic risk factors that are associated with a worse outcome in COVID-19 infection.^{13,14} Similarly, type II DM was observed in 30.1 % in the infected patients. They were reported by Istituto Superiore di Sanita (Italy).¹⁵ This could be explained by endothelial dysfunction as common findings in cardiovascular and DM patients, especially within elderly patients.^{16,17} Additionally, it suggested that cardiovascular patients were more vulnerable to COVID-19 infection due to higher ACE2 expression in vascular and heart tissues.¹⁸ Tissues rich with ACE2 are the primary binding site for virus entry in the cells.¹⁹ Moreover, cardiac injury is reported in COVID-19 infection and independently related to increased mortality in COVID-19 patients.²⁰ This may be caused by endothelial damage by the massive inflammatory changes complicating severe COVID-19 infection.²⁰ Consolidation was prevalent in the studied female (85.3% vs 61.3% in

males, $p=0.035$). However, other radiological patterns and distribution of radiological abnormalities in males and females did not show significant differences. Similarly, Moradi *et al.*²¹ found no significant differences in chest CT involvement patterns between men and women.

Also, CT severity scores in both studied groups did not show significant differences in our study. In contrast to Dangis *et al.*,²² who found a more excellent CT severity score in men (9.25 versus 7.04.8, $p:0.001$) with a trend toward more bilateral lung involvement (89.3% versus 78.8%, $p:0.06$). However, the study was limited by a lack of information on whether this more extensive lung involvement on chest CT correlated with a more adverse clinical outcome in men during follow-up.²² Nevertheless, women younger than 60 years had a higher CT score that indicated an unfavorable prognosis like ICU admission or death.²¹

Table 2. Gender difference in age and comorbidities among studied patients.

Parameter	Males N=75 N (%)	Females N=75 N (%)	Significance
Age mean (SD)	60.5 (12.2)	54 (15.3)	$t=2.75, 0:0.007^a$
Diabetes mellitus			$\chi^2: 3.6, p= 0.055$
No	46 (60)	56 (74.7)	
Yes	30 (40)	19 (25.3)	
Hypertension			$\chi^2:0.11, p:0.736$
No	46 (61.3)	48 (64)	
Yes	29 (38.7)	27 (36)	
Cardiac			$p:0.367^a$
No	71 (94.7)	74 (98.7)	
Yes	4 (5.3)	1 (1.3)	
Chronic kidney disease			$\chi^2:0.43, p:0.513$
No	69 (92)	71 (94.7)	
Yes	6 (8)	4 (5.3)	
Chronic liver disease			$p:1^a$
No	71 (94.7)	71 (94.7)	
Yes	4 (5.3)	4 (5.3)	
Ischemic heart disease			$\chi^2:0.06, p:0.806$
No	65 (86.7)	66 (88)	
Yes	10 (13.3)	9 (12)	
Autoimmune			$p:0.209^a$
No	74 (98.7)	70 (93.3)	
Yes	1 (1.3)	5 (6.7)	
Bronchial asthma			$p:0.245^a$
No	75 (100)	72 (96)	
Yes	0	3 (4)	
Cerebral stroke			$p:0.034^* a$
No	67 (89.3)	74 (98.7)	
Yes	8 (10.7)	1 (1.3)	
Malignancy			$p:0.1^a$
No	74 (98.7)	73 (97.3)	
Yes	1 (1.3)	2 (2.7)	

^aIndependent t-test, b: Fisher's exact test

The need for mechanical ventilation support and mortality rate in this study was higher in males than in females, but with no statistical significance. The higher incidence of comorbidities may explain those findings, *e.g.*, IHD, hypertension, and especially DM in male patients compared to the studied females as explained above.

Our findings could be explained on behave the known effect of the sex hormone on the innate and adaptive immune response.²³ The higher morbidity and mortality among the male patients may be explained by the stimulatory effect of testosterone hormone of both Angiotensin-Converting Enzyme (ACE 2) and Transmembrane Protease Serine-Type 2

(TMPRSS2), leading to increase viral load and delay the virus clearance. On the other hand, in female patients, the interaction of the renin-angiotensin-aldosterone system as well as the immune stimulatory genes which present on X Chromosome.^{23,24}

A study conducted by Cagnacci and Xholli²⁵ and data from the World Health Organization (WHO) and China²⁶ showed significantly higher mortality rates in male patients with COVID-19. Also, critically ill men patients who needed admission to the ICU were twice that of women.²⁷ Additionally, the age-independent disease severity and mortality were higher in men.²⁸ Many factors (*e.g.*, social, genetic, and immunological) may contribute to males'

overall higher morbidity and mortality rate. There is a high rate of smoking among males compared to females in Egypt,²⁹ and therefore, smoking is associated with higher ACE2 receptors expression, which enhanced the virus entry.³⁰ Furthermore, the ACE2 gene is located on the X chromosome, and higher circulating ACE2 levels are observed in men.²⁸ The absence of significant differences between both sexes in our study may refer to our study's nature, which included only moderate and severe cases. Meanwhile, other studies and data reported mortality and severity rates among the cohort of infected patients. This allows for consideration of severity as a predictor of the outcome. It was reported that the severity among males was higher than females.

Table 3. Sex-specific analysis of differences in the radiological parameters of studied patients.

Parameter	Males N=75 N (%)	Females N=75 N (%)	Significance
Severity score median (min-max)	13 (5-25)	12 (7-22)	Z: 0.04, P: 0.962
Crazy paving			
No	44 (58.7)	39 (52)	X ² :0.37, p: 0.543
Yes	31 (41.3)	36 (48)	
Consolidation			
No	29 (38.7)	11 (14.7)	X ² :4.4, p: 0.035*
Yes	46 (61.3)	64 (85.3)	
Vascular dilatation			
No	12 (16)	14 (18.7)	P:1
Yes	63 (84)	61 (81.3)	
Subpleural band			
No	60 (80)	62 (82.6)	X ² :0.01, p:1
Yes	15 (20)	13 (17.3)	
Distribution of lung abnormalities			
Peripheral	39 (52)	31 (41.3)	X ² :0.45, p:0.501
Peripheral and central	36 (48)	44 (58.7)	
Halo sign			
No	49 (65.3)	47 (62.7)	X ² :0.05, p:0.832
Yes	26 (34.7)	28 (37.3)	
GGO			
No	17 (22.7)	16 (21.3)	X ² : 0.001, p:0.974
Yes	58 (77.3)	59 (78.7)	

Table 4. Sex-specific analysis of differences in the clinical parameters of studied patients.

Parameter	Males N=75 N (%)	Females N=75 N (%)	Significance
GI/T symptoms			
No	60 (80)	56 (74.7)	X ² :0.4, p: 0.526
Yes	15 (20)	19 (25.3)	
Respiratory support			
O ₂ (severe)	42 (56)	51 (68)	X ² :2.3, p:0.302
Mechanical ventilation (critical)	33 (44)	24 (32)	
Outcome			
Dead	36 (48)	28 (37.3)	X ² :1.2, p:0.262
Improved	39 (52)	47 (62.7)	

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