Original Article

Gender Disparity In COVID-19: Clinicopathological Outcomes Among a Subset Of Karachi Population

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Abstract

Objective: In COVID-19, sex differences are increasing globally, and gender-specific mortality risk for men compared to women has been observed by researchers. This study aimed to explore clinic-pathological characteristics and the sex-related factors that might be the cause of gender disparity in COVID-19 cases.

Methods: A retrospective, observational cohort study was conducted at Ziauddin Hospital, Clifton, Karachi, from April to July 2020. Data were collected from the medical records of the admitted patients aged 18 and above, who tested positive for COVID-19 through the laboratory and had confirmed signs of pneumonia.

Results: Patients (244) were selected, including 167 (68.4%) males (mean ages 56.72±13.31) and 77 (31.6%) females (mean ages 56.36±17.15). The majority of the patients (87, 35.7%) had significant COVID-19 symptoms between 5 and 10 days. Only 4.4% of pregnant females had COVID-19 symptoms. Comorbidities included hypertension [44(18%)], diabetes mellitus [27(11.1%)], both HTN and DM60 [(24.6%)], whereas, 67(27.5%) patients had no known co-morbid. Complications were significantly more pronounced in males (p<0.001). Combined hypertension and diabetes observed a two-fold increase [36(14.8%)] in males than females [24(9.8%)]. Among these severely ill patients, 49 (20%) expired, which included 36 (14.3%) males and 13(5.2%) females, with statistically significant (p<0.05) results.

Conclusion: Our study found that men remained symptomatic for a longer duration (10-14 days) than women. Similarly, the severity of the disease, the complications, and the death rates were much higher in comorbid men than women. Females are genetically different and less exposed to environmental insults therefore we recommend that sex and gender-sensitive medicine (SGSM) may be added as a part of medical education.

Keywords: Coronavirus; Gender; Covid-19; Mortality; Pandemics; Gender Equity.

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SB, A.K, NJ - Conception, Design
HA - Acquisition, Analysis, Interpretation
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Introduction

Worldwide, the SARS outbreak in 2003 and COVID-19, the first and second SARS-CoV, have been observed to cause higher severity and mortality infections among males compared to females across all age groups less than 90 years.[1,2] This outcome advocates an underlying predisposition which is sex-dependent. Many hypotheses regarding social and cultural differences, sex-specific immune defence factors, etc., have been made,[3] but the sex-related clinic-pathological outcomes and relationships of genetic factors have not been explored, which might be the cause of gender disparity by the COVID-19 virus.

Women have a different anatomy, genetics and hormonal disposition, besides biological, behavioural, social and systemic factors. Research has shown that sex hormones influence the angiotensin-converting enzyme 2 (ACE2), the prime receptor for SARS-CoV-1 and 2.[4.] Also, the virus has a sex predisposition, which was observed through an experiment in female mice that, after either administering estrogen-receptor antagonists or performing ovariectomy, showed increased deaths by SARS-CoV-1 infection.[5] Moreover, systemic analysis and cohort studies on COVID-19 infection showed that hospital mortality rates with complications were found more in males compared to females.[6,7] Previous studies on gender differences in hepatic viruses such as HBV and HCV have shown that estrogen has a hepato-protective role. Hence, women in their reproductive years are comparatively safe.[8] Estrogen is said to have a partial role in controlling the immune response by the immune-related cells, including natural killer cells, T cells and antigen-presenting cells. These cells are richly supplied by the receptors called estrogen receptors (ER-alpha and ER-beta), which, upon estrogen binding, regulate immune response.[9]

COVID-19 infection, progression and clinical outcome among men and women with their comorbid are still unclear. However, in Pakistan, not a single study has been found to determine which gender is most likely to have increased mortality from COVID-19. This study aimed to find out the gender differences in terms of clinical features during hospitalisation, analysing the primary endpoint of severity and deaths, happening either after discharge or throughout in-hospital stay. The study also aimed to study COVID-19 patients' complications with and without any co-morbidity associated with mortality.

Materials And Methods

A retrospective, observational cohort study was conducted from April to July 2020 at Dr Ziauddin Hospital, Clifton, Karachi. The study was approved by the Ziauddin Hospital Ethics Review Committee (ERC).

Data on the people included in the study were collected through the laboratory from the medical records of all the admitted patients aged 18 and above, who tested positive for COVID-19 and had confirmed signs of pneumonia. Patients whose data were incomplete and who were less than 18 years of age were excluded from the study. Throughout the study, patient confidentiality was maintained. The patient's diagnosis was made according to the updated WHO guidelines at that time. The patient's data included the medical history, demographic history, exposure to the virus, and clinical signs and symptoms with underlying co-morbidities. The routine laboratory tests, such as blood, urine, tracheal, and radiological tests, performed during the hospital stay were recorded based on clinical needs. Patients having pulmonary and extra-pulmonary complications (pulmonary embolism, ARDS, pneumo-mediastinum, pneumothorax, stroke, cardiomyopathy, myocardial infarction, shock, arrhythmias, acute liver injury and acute kidney injury) were defined as the primary outcome measures. On the other hand, patients' secondary outcome measures were defined based on their length of hospitalisation, ventilator support and mortality.

All the paediatric patients in the pediatric age group, or less than 18 years of age.

The gold standard test, real-time reverse transcriptase-polymerase chain reaction (rt-PCR), was used for diagnosing COVID-19 infection. CT-scan chest showing ground-glass opacities in the peripheral regions of the lower zones of both lungs, respectively. Besides this, the presence of the highest broncho-vascular thickening, traction bronchiectasis and crazy paving appearance was also suggestive of COVID-19 infection.

The sample size of 244 patients was calculated using an open-epi calculator with an incidence of 20% and a confidence interval of 95%. SPSS version 20 was used for data entry. Age was expressed as mean and standard deviation and analysed by an independent T-test. Gender, clinical presentations, complications, length of stay at the hospital, laboratory investigations and treatment were discussed as frequency and percentages. A Chi-square test was used to find an association between qualitative variables. An association of comorbidities with COVID-19 complications was measured using the Chi-square test. P-value <0.05 was considered statistically significant.

Results

The demographic and clinical presentation of 244 adult patients was tabulated in **Table 1,** who were admitted to Ziauddin Hospital.

Table 1: Demographic Data

VARIABLES N (%)	TOTAL N= 244		P value	PCR		P value
	Male = 167 (68.4 %)	Female= 77(31.6 %)		+ve 199(81.6)	-ve 45(18.4)	
Age(years) mean ±SD	56.72±13.31	56.36±17.15	0.024			
Symptoms Yes (217(86.5)	155(63.5)	62(25.4)	0.004*	174 (69.3%)	43(17.1)	<0.001*
Duration of symptoms						
<5 days 52(21.3)	33(13.5)	19(7.8)	0.009*	38(15.6)	14(5.7)	0.153
5-10 days 87(35.7)	59(24.2)	28(11.5)		74(30.3)	13(5.3)	
10- 14 days 65(26.6)	52(21.3)	13(5.3)		53(21.7)	12(4.9)	
>14 days 13(5.3)	11(4.5)	02(0.8)		9(3.7)	4(1.6)	
Comorbidities						
DM 27(11.1)	23(9.4)	4(1.6)	0.089			
Hypothyroidism 1(0.4)	1(0.4)	0()				
Hyperthyroidism 1(0.4)		1(0.4)				
CKD 1(0.4)		1(0.4)				
COPD 1(0.4)	1(0.4)					
Asthma 3(1.2)	2(0.8)	1(0.4)				
Malignancy 5(2)	3(1.2)	2(0.8)				
NKCM 67(27.5)	47(19.3)	20(8.3)				
HTN 44(18)	26(10.7)	18(7.4)				
IHD 8(3.3)	8(3.3)	-				
HTN+DM 60(24.6)	36(14.8)	24(9.8)				
HTN+DM+IHD 21(8.6)	17(7)	4(1.6)				
CVA 1(0.4)		1(0.4)				
CLD 4(1.6)	3(1.2)	1(0.4)				
Outcome						
DC 170(67.6)	118(47)	52(20.7)	<0.001*			
Death 49(19.5)	36(14.3)	13(5.2)				

Independent Sample T-test (for comparing age and gender) with p-value <0.05 is statistically significant. Chi-square test with p-value < 0.05 is statistically significant.

DM: Diabetes mellitus; CKD: Chronic kidney disease; COPD: chronic obstructive pulmonary disease; HTN: Hypertension; NKCM: no known co-morbid; IHD: ischaemic heart disease; CVA: coronary vascular atherosclerosis; CLD: chronic liver disease; DC: discharge; PCR: polymerase chain reaction

Out of 244, males were 167 (68.4%) and females 77 (31.6%). The mean ages of males were 56.72±13.31and females were 56.36±17.15 years, with a non-significant difference. Mostly, patients (87, 35.7%) had significant COVID-19 symptoms between 5 to 10 days. Only 4.4 % of pregnant females had covid 19 symptoms. Among these severely ill patients, 49 (19.5%)

expired, which included 15(5.2%) females and 36 (14.3%) males, which was statistically significant (p< 0.05). Most of the females had HTN and DM, while the majority of the males had NKCM. All the results were statistically significant.
The blood, urine and radiological parameters of patients are shown in Table 2.

Table 2: Investigations: Blood samples, Urine samples and Radiology

Variables	Total N= 244		P-value
N (%)	Male =167 (68.4)	Female= 77(31.6)	
Diagnosis			
PCR 201(82.4)	137(56.1)	64(26.2)	0.837
Radiology 43(17.6)	30(12.3)	13(5.3)	
PCR			
Positive 199(81.6)	135(55.3)	64(26.2)	0.670
CXR			
B/L Infiltrates 226(92.6)	160(65.6)	66(27)	0.004
HRCT			
B/L GGO + Consolidation 89(36.5)	67(27.5)	22(9)	0.082
CMP			
Yes 20(8.2)	13(5.3)	7(2.9)	0.584
Thrombocytopenia			
On Admission 47(18.7)	32()	15()	<0.001*
During a stay at hospital 28(11.2)	22()	6()	
WBC			
<4 9(3.7)	8(3.3)	1(0.4)	0.366
4-10 153(62.7)	102(41.8)	51(20.9)	
>10 82(33.6)	57(23.4)	25(10.2)	
Lymphocytes			
Yes 117(48)	85(34.8)	32(13.1)	0.175
Vitamin D			
Sufficient 33(13.5)	23(9.4)	10(4.1)	0.741
Insufficient 53(21.7)	33(13.5)	20(8.2)	
Deficient 22(9)	15(6.1)	5(2.9)	
Blood C/S			
Positive 6(2.4)	5(2.0)	1(0.4)	0.092
Urine C/S			
Positive 17(7)	10(4.1)	7(2.9)	0.177
Tracheal C/S			
Positive 25(10.2)	17(7)	8(3.3)	0.854

Chi-square; p-value <0.05 statistically significant
PCR: Polymerase chain reaction; CXR: chest x-ray; B/L: bilateral; HRCT: high resolution computed tomography; B/L GGO: bilateral ground glass opacities; CMP: comprehensive metabolic panel; WBC: white blood cells; C/S: culture and sensitivity

The diagnosis of COVID-19 infection was made by PCR. Out of 244 patients, 199 were PCR positive, amongst them 135 patients were male and only 64 patients were female. Most of the patients had bilateral infiltrates on CXR with statistically significant results. WBC counts were observed to be between 4-10×10^9 IU/L. Males had raised lymphocytes compared to females. Insufficient Vitamin D levels were found in 53 patients. Positive tracheal cultures were found in 25 patients. All the results were statistically significant.
The association of treatment and diagnostic tools with gender is shown in Table 3. A steroid drug was given to 163 patients to treat COVID-19 infection. Tocilizumab was given to only 73 patients. Some patients (47) also required BIPAP/CPAP ventilator support. Among the complications in patients (Table 3), the most commonly observed was acute lung injury (ALI), but Pneumomediastinum and pneumothorax showed significant results. Most of the patients had complications with no known comorbid. Acute respiratory disease (ARD) complication was found in patients having HTN and DM.
Acute lung injury (ALI) was present in patients having HTN, IHD & HTN, and DM comorbid shown in Table 4. All the results were significant (p<0.05). Out of a total of 244 patients, 44 (17%) had hypertension (HTN), 27(10.8) had diabetes mellitus (DM), and 60(23.9) had HTN with DM. The patients who were reported with no known co-morbid conditions (NKCM) were 67(26.7%). Despite enough evidence that the coronavirus disease 2019 (COVID-19) pandemic exhibits male bias towards disease severity and mortality between sexes,[10,] the research data is scant and underappreciated.

Table 3: Treatment & Complications

Variables N (%)	Total N= 244		P-value
	Male =167	Female= 77	
Intravenous Immunoglobulin			
Yes 2(0.8)	2(0.8)	-	0.335
Plasma			
Yes 14(5.7)	10(4.1)	4(1.6)	0.804
Steroids			
Yes 163(66.8)	123(50.4)	40(16.4)	0.001
Remdesvir			
Yes 10(4.1)	7(2.9)	3(1.2)	0.914
Tocilizumab			
Yes 73(29.9)	53(21.7)	20(8.2)	0.361
Ventilator Support			
***BIPAP/CPAP* 47(19.3)**	28(11.5)	19(7.8)	0.330
***HFNC* 4(1.6)**	3(1.2)	1(0.4)	
***Invasive mechanical ventilator* 33(13.5)**	26(10.7)	7(2.9)	
ARDS			
***Mild* 40(16.4)**	27(11.1)	13(5.3)	0.214
***Moderate* 48(19.7)**	34(13.9)	14(5.7)	
***Severe* 38(15.6)**	31(12.7)	7(2.9)	
PE			
***Yes* 11(4.5)**	8(3.3)	3(1.2)	0.274
Pneumothorax			
***Yes* 4(1.6)**	4(1.6)	0	0.001*
Arrhythmias			
***A-FIB* 5(2.0)**	5(2.0)	0	0.242
***SVT* 1(0.4)**	1(0.4)	0	
Stroke			
***Yes* 5(2.0)**	5(2)	0	0.157
Pneumo-mediastinum			
***Yes* 6(2.5)**	4(1.6)	2(0.8)	0.001*
Shock			
***Yes* 26(10.7)**	19(7.8)	7(2.9)	0.591
AKI			
***Yes* 57(23.4)**	42(17.2)	15(6.1)	0.009
ALI			
***Yes* 119(48.8)**	87(35.7)	32(13.1)	0.310

Chi-square test with p-value < 0.05 is statistically significant.

BIPAP/CPAP: Bilevel Positive Airway Pressure/ Continuous positive airway pressure; HFNC: High-flow nasal cannula; ARDS: acute respiratory distress syndrome; PE: Pulmonary embolism; A-FIB: atrial fibrillation; SVT: supraventricular tachycardia; AKI: acute kidney injury; ALI: acute lung injury

This study, however, to an extent, helped us understand the increased chances of deaths in males compared to females ascribable to the COVID-19 association of gender-related disease severity, increased infection or co-morbidities in males, and high risk of mortality. This study also highlighted the gender-related differences in COVID-19 infection in hospitalised patients, evaluating the details of demographics, co-morbidities, and complications between them [Table 1]. Among the 244 Covid 19 positive patients in our study, 167 were predominantly males with a mean age of 56.72±13.31. A previous study by Adams RB found that in Pakistan, 72% of males were affected by COVID-19 infection.[11] The biological differences between Males and females are the minor variation that differentiates them on a genetic level, which give rise to all the biological differences that affect virtually every aspect of medicine and biomedical research. Studies on infectious diseases have shown that males and females respond differently to infectious challenges because of the difference in their immune systems. The majority of studies show that males are more susceptible to infections. Females, on the other hand, show a better response to vaccination and produce greater amounts of antibodies. [12]

Table 4: Comorbid association with complications.

Complications	DM 27(10.8)	Asthma 3(1.2)	Malignancy 5(2)	NKCM 67(26.7)	HTN 44(17.5)	IHD 8(3.2)	HTN+DM 60(23.9)	HTN+DM +IHD 21(8.4)	CLD 4(1.6)
ARDS									
Mild	5(2)		1(0.4)	7(2.8)	14(5.6)	0	11(4.4)	2(0.8)	
Moderate	2(0.8)		1(0.4)	9(3.6)	6(2.4)	2(0.8)	17(6.8)	9(3.6)	2(0.8)
Severe	5(2)	1(0.4)	2(0.8)	11(4.4)	7(2.8)	1(0.4)	7(2.8)	2(0.8)	
p-value <0.001*									
PE									
Yes				3(1.2)	3(1.2)		3(1.2)	1(0.4)	
p-value <0.001*									
PNEUMOTHORAX									
Yes				3(1.2)	1(0.4)				
p-value <0.001*									
ARRHYTHMIAS									
A-FIB	1(0.4)		**0**			1(0.4)	2(0.8)	1(0.4)	
SVT	**0**		1(0.4)			**0**	**0**	**0**	
p-value <0.001*									
STROKE									
Yes				2(0.8)		1(0.4)		1(0.4)	1(0.4)
p-value <0.001*									
SHOCK									
Yes	5(2)		1(0.4)	6(2.4)	2(0.8)		9(3.6)	1(0.4)	1(0.4)
p-value <0.001*									
AKI									
Yes	7(2.8)	1(0.4)	1(0.4)	10(4)	10(4)	2(0.8)	15(6)	9(3.6)	1(0.4)
p-value <0.001*									
ALI									
Yes	14(5.6)	1(0.4)	4(1.6)	27(10.8)	21(8.4)	5(2)	32(12.7)	11(4.4)	2(0.8)
p-value <0.001*									

Chi-square test with p-value < 0.05 is statistically significant.

ARDS: acute respiratory distress syndrome; PE: Pulmonary embolism; A-FIB: atrial fibrillation; SVT: supraventricular tachycardia; AKI: acute kidney injury; ALI: acute lung injury; DM: Diabetes mellitus; CKD: Chronic kidney disease; COPD: chronic obstructive pulmonary disease; HTN: Hypertension; NKCM: no known co-morbid; IHD: ischaemic heart disease; CVA: coronary vascular atherosclerosis; CLD: chronic liver disease.

Discussion

Looking at the genetic makeup, the variations in the sex chromosomes are also one of the reasons known for discrepancies between sexes in COVID-19 related to the severity of the disease and death.[13] Previously, it was revealed that the X chromosome carries an increased number of immune-related genes; therefore, females having XX chromosomes have dual copies of genes related to immunity compared to males with a single copy of a gene having one X chromosome. This might boost the innate and adaptive immunity in women, making them more equipped to confront and be more responsive to COVID-19 infection.[14] Secondly, estrogen in females activates the immune responses while testosterone in males suppresses the immune system. Estrogen causes an increase in pro-inflammatory mediators, for example, TNFα, which improves the immune system. On the contrary, testosterone in males upregulates the mediators such as interleukin 10, which suppresses the immune system.[15] Furthermore, innate immunity, a first-line defence mechanism,[16] is initiated at Toll-like receptors (TLRs) [17,] which are the pattern recognition receptors (PRRs), specific for viruses and act by triggering a sequence of reactions producing pro-inflammatory cytokines such as interleukins, TNF-α, and Interferon (IFN).[17] Main PPRs for RNA viruses are TLR 3, 7 and 8.[16] TLR7 in response to "pathogen-associated molecular patterns" PAMPs, activates a signalling cascade to produce interferon I and II.[18] The X chromosome (Xp22.3-p22.2) has gene for TLR7. The X-chromosomes also contain several immunity genes. In females, during fertilisation, one X chromosome (XCI) is inactivated to avoid duplication compared to males. However, many X-linked immunity-related genes, including toll-like receptor (TLR)7, TLR8 and Bruton's tyrosine kinase (BTK), escape XCI, resulting in a biallelic expression with pathophysiological implications.[19]

In COVID-19 patients, the inadequacy of TLR7 causes diminished clearance of the virus and increases the viral load. This, in turn, causes the direct cytopathic effect following a hyper-inflammatory response, creating the well-known cytokine storm. Males have only one X chromosome, and if they inherit it with abnormal genes related to immunity, the expression of the defective genes may cause immune responses with distinct consequences.

However, females are at minimal risk of expressing defective genes related to immunity on X chromosomes. This is because they inherit a copy of the X chromosome from each parent, causing X-linked mosaicism. Even if one X chromosome is inactivated, the gene expression on the active X chromosome is upregulated, which possibly benefits females in various infections, including COVID-19.[20] A study done in China found that 50.7% were males from 140 patients. [21] Therefore, in COVID-19 infection, gender is one of the important risk factors that determine the severity and mortality of the disease, independent of susceptibility and age. Men are consuming more alcohol than women and are involved in other risky behaviours, working outside their homes, being involved in different occupations and interacting with other people, have increases levels of their exposure and puts them at higher risk of getting infected by COVID-19. Moreover, symptomatic illness was found to be more common in men, and during earlier epidemics of coronavirus, they had severe disease outcomes and high mortality.[14] Our study also found more symptomatic men (21.3%) whose symptom duration was 10-14 days.

Some studies suggested that the risk factor for developing severe COVID-19 infection is diabetes. This may be due to the low pulmonary function of diabetic patients, [14,] which is probably inclined to accompany viral and bacterial infection. In this study among diabetic COVID-19-positive patients, males were 23(9.4%) and females 4(1.6%). However, Yongli Yan and his group reported that a total of 193 patients were admitted to the ICU and had severe COVID-19 infection, 68% were male, and among them, 48 (24.9%) were diabetic, and all were older and had higher mortality rates.[22] Our observations are consistent with the earlier findings that the prevalence of diabetes in severe COVID-19 patients is 27 (10.8%).

Comorbidity hypertension showed a 17.5% frequency, including 10.7% males compared to 7.4% women. Combined hypertension and diabetes were observed to have a twofold increase of 36(14.8%) in males and 24(9.8%) in females. In a previous study, COVID-19 and its mortality rate were found to be high only in hypertensive individuals.[23, 24] It was postulated that SARS-CoV-2 interacts with the renin-angiotensin-aldosterone system (RAAS) because it enters the cell through ACE2 receptors.[25] Therefore, high blood pressure and diabetes most likely increase the risk of mortality in COVID-19 by impairing oxygen delivery and affecting lung function. Moreover, we haven't found significant numbers of ischemic heart disease (IHD), but 21(8.4%) IHD individuals were observed with diabetes and hypertension. However, the current study found 67(26.7%) patients with non-known commodities (NKCM) from a total of 244 covid patients males were 47(19.3%) and 20(8.2%) were females.

The gene for ACE2 is also located on X chromosomes, as well as that of inhibitors of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) kinases (IKKs) and receptor-associated kinases of IL-1 (IRAKs). Therefore, females with two X chromosomes have a greater chance of having fewer COVID-19-related clinical complications.[26]

The study sample size is small and single-centred. The history of the disease before the onset of symptoms and its severity was not reported. Control groups were not there in our study.

Conclusions

Symptomatic COVID-19 infection is more prevalent in men with hypertension and diabetes compared to women. Furthermore, women have less chance of severe symptoms and are likely to survive more from COVID-19 infection. Sex and gender-sensitive medicine (SGSM) should be incorporated into medical education. Despite the indication of these potentially comprehensive data, theoretical frameworks are currently absent. Due to the scarcity of research focused on SGSM implementation is lacking within medical curricula. We recommend that sex and gender-sensitive medicine (SGSM) as a part of medical education will significantly improve the quality of healthcare for individuals across all gender identities.[27]

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