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Gender differences in disease severity and mortality in COVID-19 patients admitted to a tertiary care hospital of Peshawar, Khyber Pakhtunkhwa, Pakistan

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ABSTRACT

Introduction: Several global studies have identified gender differences in COVID-19 infectivity, clinical features, and outcome, most of which support a poorer male experience. However, studies from Pakistan regarding gender-based analyses are lacking.

Objective: To determine gender as a risk factor for COVID-19 infectivity, severity, and outcomes in adult patients of a tertiary care hospital of Peshawar, Khyber Pakhtunkhwa, Pakistan.

Materials & Methods: A cross-sectional, observational study was conducted at Rehman Medical Institute, Peshawar, Khyber Pakhtunkhwa. Data were obtained from May to August 2020, and covered all adult COVID-19 positive patients admitted to the hospital during that time span. All patient information, including demographics, test results, disease severity, and available outcomes were recorded in a specifically designed Performa. Data were analyzed by SPSS 26 for descriptive statistics.

Results: A total of 84 patients were included in the study. The dominant gender was male with 81% (n= 68) of subjects being males and 19% (n=16) female. 23.8% (n=20) of our study population had mild disease, 29.8% (n=25) had moderate, 22.6% (n=19) had severe and 23.8% (n=20) had critical disease. 60.7% (n=51) were alive, 31.0% (n=26) died and 8.3% (n=7) had unknown outcomes. Comparing disease severity and outcome with gender found that 20.6% (n=14) males had severe and 26.5% (n=18) had critical disease. In females, 31.3% (n=14) had severe disease, and 12.5% (n=2) had critical disease. Mortality for males was 30.9% (n=21) and for females it was 31.3% (n=15). Although males were the dominant gender, a statistically significant link between age, gender, disease severity and adverse outcomes could not be found and similar severity and mortality was noted amongst both sexes.

Conclusion: Though a male dominant prevalence of COVID-19 occurred in adult COVID-19 patients of a tertiary care hospital of Peshawar, Khyber Pakhtunkhwa, disease severity and adverse outcomes in COVID-19 were independent of gender.

Keywords: Male, Female, Coronavirus, Cross-Sectional Studies, Prevalence, Pakistan, COVID-19, Severity of Illness Index, SARS-CoV-2.

The authors declared no conflict of interest. All authors contributed substantially to the planning of research, data collection, data analysis, and write-up of the article, and agreed to be accountable for all aspects of the work.

INTRODUCTION

A devastating outbreak of a mysterious pneumonia with unknown etiology began in Wuhan, China, in December 2019 and quickly spread across the world.[1] A novel coronavirus with a high resemblance to the 2003 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) was discovered after genomic sequencing of infected patients. As a result, the new organism was given the name Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 11, 2020, the World Health Organization (WHO) formally declared COVID-19 a pandemic due to the disease's rapid global spread in such a short period of time.[2]

Approximately 17.2 million Individuals around the world have tested positive for COVID-19 as of August 1, 2020, with 67 thousand deaths. Pakistan is currently experiencing its first wave of cases and Pakistani health officials recorded 278 thousand positive cases country wide, with 5951 confirmed deaths.[3]

COVID-19 is primarily transmitted by droplets and direct touch. According to research symptomatic patients have viral loads similar to asymptomatic patients, thereby having the ability to spread the virus. The first line diagnostic test is a RT-PCR. Imaging namely HRCT (High Resolution Computed Tomography) is also a quick and effective diagnostic tool that can be used to monitor disease progression.[4]

COVID-19 manifests itself in a variety of ways, with the majority of patients suffering from a mild to moderate infection. Some patients, however, develop a more serious or critical illness[1] with deaths linked to acute respiratory distress syndrome (ARDS), septic shock, coagulopathies and metabolic acidosis. The most commonly associated comorbid conditions amongst infected patients are diabetes, cardiovascular disease and chronic lung disease.[5]

Keeping in mind the aggressive spread of the infection and adverse outcomes, it is important to identify risk factors for serious or critical illness so

that patients can be categorized as high-risk early on and handled quickly and efficiently with aggressive medical management and to help in devising new therapies.[1]

Owing to biological and social conditions, several studies have concluded that the pandemic affects men and women differently.[2] Many early reports from China indicated that male patients were more susceptible to COVID-19 and death rates in China were found to be 4.7 percent in men and 2.8 percent in women ,with the bulk of the deceased patients being elderly men.[1] In a similar survey,[6] 16.6% of men and 9.1% of women in Italy were found to be infected; in another, male and female mortality rates were 80 percent and 20 percent, respectively.[7] This begs the question, whether gender is a risk factor for more severe disease and worse outcomes. Female COVID-19 infection rates in Pakistan are substantially lower than male infection rates, being two-thirds of the male rate, according to the Pakistani government's Ministry of National Health Services, Regulation, and Coordination. Male and female ratios are 6.7 and 3.6 percent, respectively.[8]

A variety of cultural, social, and biological factors favor increased infections in Pakistani males. Khyber Pakhtunkhwa is dominated by an ultraconservative Pashtun culture, in which men are in control of all worldly activities. Women are encouraged to remain within the house and observe purdah due to religious and social norms. They are discouraged from participation in the workforce and are mainly home makers. This limits female access to populated areas and thus likely exposure to COVID-19.[4] In addition to this men are also at a biological disadvantage.[2] The virus uses the ACE2 receptor to invade cells which is central to its pathogenicity.[1] Men have more ACE2 than women and increased expression of ACE2 results in disease severity and progression.[9] Another explanation for the differences in results may be attributable to the overproduction of pro-inflammatory cytokines, or the notorious "cytokine storm," which can lead to multi-organ failure and death in the most severe cases and manifests more commonly in males.[2] The value of sex hormones cannot be underestimated either as they influence immune responses.[9]

The present study was conducted to analyze clinical data of 84 adult patients who presented to a major tertiary care hospital in Khyber Pakhtunkhwa, Pakistan; the analysis involved investigating into a possible connection between gender and COVID-19 intensity and negative outcomes. Recognizing a gender predisposition to more serious disease and adverse outcomes will be invaluable in tailoring an aggressive emergent early response at both a personal and community level, as well as explore more structured and targeted novel treatments.[2]

MATERIALS & METHODS

The Rehman Medical Institute in Khyber Pakhtunkhwa, Pakistan, was where this cross-sectional observational research was conducted, from May 2020 to August 2020. The patient's or a surrogate's informed consent was obtained in writing. COVID-19 positive patients who had been admitted to the hospital made up the study's population. An RT-PCR on nasopharyngeal secretions[10] was used as the testing tool. In the event of a negative RT-PCR but high clinical suspicion, an HRCT were performed and classic findings in compliance with the American Radiological Association's guidelines[11] were taken as proof of the disease. The study population was then separated into two groups based on gender i.e. male and female. According to the guidelines released by the National Institute of Health, Islamabad, Pakistan, the patient's disease was then evaluated and subdivided into four severity groups: mild, moderate, severe and critical. Their outcomes were classified as Alive, Dead, or Unknown in case of patients that left against medical advice and their outcomes could not be determined. The disease severity and outcomes were then compared between the two genders to look for a correlation. All patient data, including demographics, disease severity, laboratory results, and clinical outcomes, were recorded first in a pre-designed Performa. SPSS version 26 was used to examine the results. For quantitative variables such as age, mean ± standard deviation was calculated and for qualitative variables such as gender, disease severity, and outcomes, percentage and frequency were calculated. The Chi Square test and T-test were used where appropriate. A $p \leq 0.05$ was considered statistically significant.

RESULTS

A total of 84 patients were enrolled in the study. The median ages of the genders were closely similar, being 57.23 years for males and 56.63 years for females.

Table 1 shows that the dominant gender at 81% (n= 68) was male and 19% (n=16) were female. Disease severity analysis showed that 23.8% (n=20) of patients had Mild disease, 29.8% (n=25) had Moderate disease, 22.6% (n=19) had Severe disease and 23.8% (n=20) were in Critical stage. Analysis of outcomes revealed that 60.7% (n=51) were Alive, 31.0% (n=26) Died and 8.3% (n=7) had Unknown outcomes.

Table 1: Demographic and clinical data of patients (n=84).

Variables	Frequency	Percent
Gender		
Male	68	81.0
Female	16	19.0
Clinical Classification		
Mild	20	23.8
Moderate	25	29.8
Severe	19	22.6
Critical	20	23.8
Outcome		
Alive	51	60.7
Death	26	31.0
Unknown	07	08.3

The disease severity and outcome groups were then compared for gender (Table 2).

Among males, 23.5% (n=16) had mild disease, 29.4% (n=20) had moderate, 20.6% (n=14) had severe, and 26.5% (n=18) had critical disease, compared to females where 25% (n=4) had mild disease, 31.3% (n=5) had moderate, 31.3% (n=14) had severe and 12.5% (n=2) had critical disease. This distribution of disease severity between males and females was not significant (p=0.63).

Regarding outcomes (Table 2), among males, 30.9% (n=21) died, 60.3% (n=41) lived and 8.8% (n=6) had unknown outcomes; 31.3% (n=5) of the females died, 62.5% (n=10) were alive and 6.2% (n=1) had unknown outcome. This distribution of outcomes between males and females was not significant (p=0.94).

Table 2: Disease severity and outcome in patients based on gender (n=84).

Variables	Gender		p value
	Male f (%)	Female f (%)	
Clinical Classification			
Mild	16 (23.5)	04 (25.0)	
Moderate	20 (29.4)	05 (31.3)	0.63
Severe	14 (20.6)	05 (31.3)	
Critical	18 (26.5)	02 (12.5)	
Outcome			
Alive	41 (60.3)	10 (62.5)	0.94
Death	21 (30.9)	05 (31.3)	
Unknown	06 (08.8)	01 (06.2)	

Age was found to be equal between men and women in our data set. There was no statistically significant correlation between age, gender, disease severity, and negative outcomes, with both sexes having similar severity and mortality.

DISCUSSION

Coronaviruses are responsible for a variety of illnesses, from the common cold to extreme pneumonias like Severe Acute Respiratory Syndrome (SARS)[1] and the Middle East Respiratory Syndrome (MERS).[4] The Chinese Center for Disease Control and Prevention (CDC) described SARS-CoV-2 as a novel corona virus. COVID-19 patients' characteristics have been published, but data on COVID-19 prognostic factors is still evolving.[1] The present study endeavors to see if gender is a risk factor for COVID-19.

Age has been linked to a higher risk of negative health outcomes in COVID-19.[5] A Chinese study discovered that the average ages of COVID-19 patients were equal between males and females, but that deceased patients were substantially older than survivors.[1] Our dataset had median ages of 57.23 years and 56.63 years for males and females respectively. Two studies reported similar results, one from Shanghai[12] with a mean age of 50.1 years and another from Wuhan[13] with 221 subjects with a median age of 55.0 years, echoed our observations. Contrary to this two other China based researches, one from Hubei[14] and the other from Chongqing[15] found that the average age of their patients was 46 and 45 years, respectively. In a survey of 393 patients performed in New York[16] the median age of the participants was significantly older than ours i.e. 62.2 years. Another American study[17] of 43 patients showed that the average age of the participants was 48 years. An Indian study[18] of 147 patients, with 70.7 percent being male, reported an average age of 40.9 years. Similarly a second Indian study[19] reported the average age of their participants as 40.3 years, significantly lower than our subjects.

Males were shown to be more vulnerable to COVID-19 infection in early studies, but more recent epidemiological research has shown no sex or gender differences in COVID-19 susceptibility.[5] Contrary to this our study found a male dominance. Global evidence indicates that SARS-CoV-2 has no male tendency. The gender distribution in most countries was quite similar. However, some countries found men to be affected in greater numbers but most importantly the study found a difference in disease severity and mortality rates between the two sexes.[6] Unlike our findings, data from a public data collection of 1,019 COVID-19 survivors (50 percent males) and 43 hospitalized patients (51.2 percent males) revealed that males and females were equally susceptible to SARS-CoV-2 infection.[1]Another Chinese study of 425 COVID-19 positive patients looked into the role of gender in COVID-19-related morbidity and mortality, and found that males made up 56% of the dataset. In a related way, a Chinese study of 140 patients found that 50.7% of their subjects were males. Another Chinese study of 425 patients discovered that 56 percent of the participants were male.[1] According to a survey of 44,672 confirmed COVID-19 cases taken from China's Infectious Disease Information System, 51.4 percent of patients were men.[5] This differed from preliminary studies out of China and Europe which showed that COVID-19 infects nearly equal numbers of males and females.[20] Italy, France, Spain, Germany, China and Switzerland also reported that there were no significant gender discrepancies in the number of COVID-19 cases.[5] Similar reports came from New York and seven other US states, which found an equal number of males and females affected, while the remaining 16 states, including Washington, reported a male superiority similar to our findings (i.e. a male to female ratio of 1 to 0.9/0.8). However interestingly enough a long-term care facility in Washington demonstrated a female dominance, with 68% of the female inhabitants and 76% of the healthcare workers being infected.[16] Similarly, the Maine Center for Disease Control and Prevention (CDC), USA, enrolled 1,622 contacts of COVID-19 patients as part of a contract-tracing initiative; 190 patients developed COVID-19, with 52.1 percent of them being female and 47.9 percent being male. In yet another study from the United States with 1,320,488 subjects, interestingly, a higher percentage of female than male cases were seen.[5] Male sex was found to be a risk factor for mortality, lower recovery rates, and more serious disease in one meta-analysis.[2] There was no discernible difference in vulnerability between the genders in terms of one gender being more susceptible than the other. Though not a significant difference, the study found the male-to-female ratio to be 1:0.9, suggesting that males might be more vulnerable to COVID-19 infections.[2] Another study on 487 cases in Wuhan, China, reported males were more susceptible (73.3%) in comparison to female (26.5%).[21]

The cause for the gender disparity seen in some countries may be due to the fact that women tend to generate fewer pro-inflammatory cytokines, indicating that the infamous cytokine storm is less frequently activated in women. Gender-based differences in innate immunity, steroid hormones, and factors associated with sex chromosomes may explain why males are more susceptible to COVID-19.[2] SARS-CoV-2 attacks cells through the ACE2 receptor.[1] Therefore its increased expression makes the infection worse, though its exact function in SARS-

COV2 pathogenesis is unknown. On the other hand, it is a critical enzyme that protects the lungs from injury. According to one study, men have more ACE2 on the endothelium of their pulmonary vessels than women.[9] Since the lung is the primary site of COVID-19 pathogenesis, increased expression of ACE2 in this tissue may result in disease progression. ACE2 has two biological forms, a soluble form and a membrane bound form. The membrane bound form functions as a receptor for viral attachment, worsening infection outcomes, while the soluble form prevents the viral attachment to cells and plays a defensive role. ACE2 levels in the blood (soluble form) tend to be higher in women than in men, suggesting that it may play a protective role in these individuals by inhibiting viral entry into target cells. The amount of ACE2 in the blood will help determine the seriousness of a disease.[9] Another reason for the disparities between outcomes maybe due to overproduction of pro-inflammatory cytokines or the infamous "cytokine storm" in the most serious cases, potentially leading to multi-organ failure and death.[2] The male immune system functions differently than female, who tend to have a more potent immune response and virus clearance. Antibodies are generated in greater quantities by women than by men, and they last longer in women. A cytokine storm caused by immune deregulation is less common in women than it is in men. Men have higher levels of interleukin 6 (IL-6) than women, a crucial component of the cytokine storm and its driving force. Low levels of interleukin 6 have been related to poor performance in men. The production of antibodies, especially IgG antibodies, in the preliminary stages of COVID19 infection has been found to be more common in women, suggesting that early development of IgG antibodies, may protect women from severe progressive infection. The value of sex hormones cannot be underestimated either as they influence immune responses.[9] The X chromosome is home to a variety of essential immune regulatory genes. Women have two copies of the gene, which contributes to higher expression of the toll-like receptor-7 (TLR7), which is essential in viral pathogen defense. In addition, females have higher levels of CD4+ lymphocytes, which aid virus clearance.[2] According to new research, estrogen therapy plays a significant role in the development of COVID-protective immune responses. Since sex hormones decrease in the elderly, these hormones may be a therapeutic option in older patients with COVID-19.[9]

Chinese men have been generally observed to have a shorter life span as compared to females. This may ring true for the rest of the world as well & could also be a contributing factor to a generally higher incidence of most diseases, with COVID-19 being no exception.[1] Another explanation can be social and cultural influences. A recent study from Punjab, Pakistan found males to be more susceptible to COVID-19 (76%) than females (24%). The study concluded that the high male susceptibility in Pakistan is owing to higher male exposure due to a lower female participation in the workforce due to cultural, social, and religious barriers, thus limiting female access to populated areas. Women are also encouraged to remain at home and this aspect alone has reduced the likelihood of females being exposed to COVID-19.[4]

Our study found disease severity to be independent of gender. These findings are different from a number of studies conducted worldwide. Some literature reports that gender appears to be a risk factor for more serious disease and a higher overall mortality in COVID-19 patients, regardless of a patient's age and susceptibility.[1] A Chinese meta-analysis found that men were almost twice as likely as women to experience more serious disease and die. Genetic, hormonal, and other biological influences, as well as cultural and social factors, can all be involved in the mechanisms at play.[2] According to the clinical severity classification, men have a higher risk of developing serious disease. The majority of deceased COVID-19 patients were older (65 years) than survivors (83.8% in 37 deceased patients vs. 13.2 percent in 1,019 patients) in a Chinese public data set of COVID-19 patients.[1] Similarly another study concluded that male COVID-19 patients had a higher risk of death and more severe disease.[2] Data from 41 COVID-19 patients found a greater number of male admissions to the Intensive Care Unit (ICU). In Lombardy, Italy, a retrospective study of 1591 ICU patients showed 82% being male and 18% female. In Germany, male patients represent a greater proportion of deceased patients, though males make up 49% of total cases, they make up 55% of the total deaths related to COVID-19.[5]

Our study found similar mortality rates between both genders and no statistically important correlation indicating that one gender supported worse outcomes. Older men with chronic conditions had the highest mortality rate, as found in one study.[4] Another research showed that men with COVID-19 had worse outcomes as compared to women.[9] However, contrary to our results, there are several studies that have validated previous findings that male cases of COVID-19 are more extreme and potentially fatal. In a recent study of COVID-19-related deaths, male mortality was 1.77 times greater than female mortality. Male patients also had a higher rate of hospitalization and ICU admission as well as a higher rate of fatality.[5] One Chinese study found that men who tested positive for COVID-19, regardless of age, had a higher chance of dying, so men were more likely to die than women, despite the fact that their susceptibility was equal.[1] The elderly with cardiovascular disease had the worst result, with a 10.5% case fatality rate.[5] Males had a higher mortality rate (4.7%) than females, according to another study in China (2.8%) and in an Italian study men outnumbered women by 16.6 to 9.1%. The Global Health 50/50 reported death rates for 33 countries and showed the death rate was between 2.8 for males and 1.4 for females.[6] COVID-19 results were found to be more serious in men than in women in similar age groups, according to one study.[9] A previous scoping research on the clinical characteristics of SARS-CoV2 infection showed that males had a higher case fatality rate. One random-effects meta-analysis compared male and female mortality, recovery rates, and disease severity and the male sex was found to have a strong link to mortality and a lower risk of recovery. Male patients had a greater risk of a more severe form of COVID-19.[2] Data on COVID-19-related hospitalization in Switzerland and France show that male patients are 50% more likely to be admitted. In Switzerland, male patients are 1.5 times more likely to be admitted to

hospital and case fatality rates for males are consistently higher according to COVID-19 data from Italy, Switzerland, Germany and Spain.[5] Another study also found that men had a higher COVID-19 related mortality. Men were also more likely than women to present with serious disease and be admitted to the intensive care units.[22] Among deceased patients, there are 2.4 times more men than women. Men were more likely to die than women, despite having the same vulnerability.[1] The CDC conducted a study on 10,647 deceased patients and found males with a median age of 75 years, accounted for a higher proportion of the study's deceased patients.[5]

A gender dependent dimorphism appears to exist with females having a lower severity and fatality rate.[23] Further studies are required to fully understand and likely therapeutically target all the biological mechanisms that lead to this susceptibility.[2]

CONCLUSION

A statistically significant correlation between gender, severe/critical illness, and negative outcomes was not found in the current study. Instead, COVID-19 severity and outcomes were unaffected by gender. Men were found to be significantly more susceptible to SARS-CoV2 infection, but this is possibly due to social and religious constraints imposed on women, which limit their exposure to the outside world and thus the virus.

RECOMMENDATION

The present study was not exhaustive and further research with a larger sample size is needed to better understand the sex-specific differences and establish successful, cost-effective COVID-19 management protocols in Khyber Pakhtunkhwa.

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