



## RESEARCH ARTICLE

# Does Gender Influence Differences in Mortality and Length of Stay in Hospitalized Patients Admitted with COVID-19

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## ABSTRACT

**Background:** Gender disparities have previously been reported to influence outcomes of various illnesses, including viral illness such as respiratory syncytial virus and COVID-19 virus. Males have previously been found to be more susceptible to infection and complications of such diseases.

**Objective:** The idea that there are differential impacts by gender on morbidity and mortality of COVID-19 patients admitted to the hospital as well as identifying any confounding factors that might contribute to such disparities were investigated.

**Design:** Retrospective study of patients 65 years and older admitted with COVID-19 infection between February 2020 and February 2022 were included.

**Setting:** Community teaching hospital in Michigan.

**Participants:** All consecutive patients , age 18 years and older, all gender and race with a positive diagnosis for COVID-19 were included in the study.

**Measurements:** Incidence of complications and mortality were measured in both males and females and differences calculated.

**Results:** The 963 patients were divided into two groups: males (n= 483), and females (n=480). The mortality rate for males (n=341, 70.6%), and females (n=345, 71.9%) were similar. However, there were more females with less than 4 associated comorbid conditions compared to males (80.8% vs 70.0%, p=0.0001) and the females had a higher mortality rate (71.9% vs. 70.6%, p=0.66). There were more males with 4 or more associated comorbid conditions and this was significantly higher than in the female group (30.0% vs 19.2%, p=0.0001).

**Limitations:** There was no data collected following discharge from the hospital in regard to late complications.

**Conclusions:** Kidney disease is a significant predictor of mortality of our COVID-19 patients admitted to our hospital, additionally COPD had a similar impact on mortality but only in the female patients.

**Primary funding source:** None

**Keywords:** COVID-19, gender differences, length of stay, mortality

## Introduction

As the year 2019 coming to an end, Wehan city-Hubei province in China experienced an outbreak of upper respiratory illnesses caused by a specific coronavirus called SARS-COV-2 (severe Acute Respiratory Syndrome Coronavirus 2), later renamed Coronavirus disease 2019 (COVID-19)<sup>(1,2)</sup>. Not long after that initial encounter with the highly infectious RNA virus in China, the world came face to face with the reality of dealing with COVID-19 and its disastrous aftermath, with ever increasing morbidity and mortality. Intra cellular replication of the RNA virus, stimulates Humoral and Cellular Immune cascades, and in severe cases lead to highly strong inflammation and hyper immune cytokines response which cause a massive viral pneumonia, acute respiratory distress syndrome, cardiac and kidney injury, hypercoagulability, stroke, hepatic and pancreatic injuries which lead eventually to multi organ failure<sup>(3)</sup>. The spectrum of symptoms of COVID-19 spanning from being asymptomatic, to having a mild upper respiratory tract infection or diarrhea to severe illness<sup>(4)</sup>. A high percentage of severely ill patients have one to several pre existing comorbidities including advanced age, hypertension, type 2 Diabetes, obesity, dyslipidemia, renal and cardio-vascular disease<sup>(4)</sup>.

There is a wide plethora of literature written about the gender differences in response to illnesses<sup>(5-7)</sup>. Recently, studies on viral infection, and in particular rhinoviruses, indicated that outcome (mortality and morbidity) varied significantly between males and females<sup>(8)</sup>. Therefore, gender is a factor to consider when looking at morbidity and mortality in COVID-19. According to Ambrosino et. al. (2020)<sup>(9)</sup>, men in China and Italy were more likely to be infected with COVID-19 than women. It was explained that this could be due to the higher presence of chronic conditions such as obesity, hypertension, diabetes, and cardiovascular disease in men as compared to women. The increased morbidity and mortality from COVID-19 in men can possibly also be explained by the difference in the immune landscape response of men and women to the

virus<sup>(10)</sup>. A study by Takehiro et al. (2020) found that poor T cell response correlates with age and worse outcome in males, but not the female patients. Additionally, mental illnesses in patients with COVID-19 have become more prevalent<sup>(7)</sup>. Those with existing mental illnesses have seen an increase in the severity<sup>(11)</sup> and those without an existing mental illness have seen an increase in new onset mental illness.<sup>(12)</sup> In these patients, there may be a possibility that mental health conditions contribute to the wide spectrum of gender differences previously noted<sup>(11,13)</sup>.

It is important to understand and report data on gender separately as this may help to identify and customize treatment which in turn has the potential to reduce admission (hospital and intensive care unit) as well as mortality. We aimed to further investigate the idea that there are differential impacts by gender on morbidity and mortality of COVID-19 patients admitted to the hospital and identify any confounding factors that might contribute to such disparity.

## Methods

Between February 2020 and February 2022, a retrospective analysis of 1,000 consecutive patients admitted to our community teaching hospital and confirmed to have a positive COVID-19 test was conducted. Patients included were 65 years or older with an active COVID-19 infection and were admitted to either the general medical unit or the intensive care unit. The data collected included age, sex, race, comorbid conditions such as diabetes mellitus (DM) chronic obstructive pulmonary disease (COPD), kidney diseases (KD), hypertension (HTN), coronary artery disease (CAD), obesity, length of stay (LOS), and mortality. These data were retrieved from the electronic medical record and kept secure in REDCap. The patients were divided into two groups according to gender, males and females.

Statistical analysis included descriptive statistics with continuous variables being reported as means (SD) and dichotomous variables were reported as frequencies (percentages). Comparisons were

made between gender using student's t-test for continuous variables and chi-squared test for dichotomous and categorical variables. A significant p-value was set at  $p < 0.05$ . Binary logistic regression analysis was used to identify the likelihood of mortality for each gender while controlling for several comorbid conditions.

Institutional review board approval was obtained prior to the study.

## Results

Retrospective analysis of 1000 consecutive patients with COVID-19 were conducted. Missing data on

37 patients resulted in 963 patients in the final analysis. The mean age of the patients was  $76.9 \pm 7.9$  years. Age was equally distributed between males (76.7, SD: 7.8) and females (77.0, SD: 8.1). The majority of patients were white ( $n=871$ , 90.4%). There were 185 (19.2%) patients admitted to the ICU. The overall length of stay was 8.2 (SD: 8.4) days. The total mortality rate was 71.2% ( $n=686$ ). There were 726 (75.4%) patients who had less than 4 total comorbid conditions and 237 (24.6%) patients who had 4 or more total comorbid conditions. There were 483 patients in the male group and 480 patients in the female group. See table 1 for full demographic data by gender.

Table 1: Variables for Group 1 Males and Group 2 Females

	Males n = 483	Females n = 480	<u>p-value</u>
Age (mean $\pm$ SD) years	76.7 $\pm$ 7.78	77.0 $\pm$ 8.10	0.56
Race (n, %)			
White	437 (90.5)	434 (90.4)	0.79
Black/ African American	33 (6.8)	37 (7.7)	
Asian	3 (0.6)	2 (0.4)	
Native Hawaiian/ Pacific Islander	1 (0.2)	0 (0)	
Unknown	9 (1.9)	7 (1.5)	
Length of Stay (mean $\pm$ SD) days	9.2 $\pm$ 7.99	9.2 $\pm$ 8.87	0.99
ICU Stay (n, %)	101 (20.9)	84 (17.5)	0.18
Yes			
Mortality (n, %)	341 (70.6)	345 (71.9)	0.66
Comorbid Conditions (n, %)			
Hypertension	360 (74.5)	366 (76.3)	0.50
COPD	87 (18.0)	104 (21.7)	0.15
Kidney disease	204 (42.2)	179 (37.3)	0.12
Diabetes	140 (29.0)	137 (28.5)	0.90
4 or more comorbidities (n, %)	145 (30)	92 (19.2)	<0.0001
Less than 4 comorbidities (n, %)	338 (70)	388 (80.8)	<0.0001

There were no statistically significant differences in demographics between genders including the mortality rate (70.6% for males and 71.9% for females,  $p = 0.66$ ). However, patients with less than

4 comorbid conditions were significantly higher in the female group than the male group (80.8% vs 70.0%,  $p = 0.0001$ ), while those with 4 or more comorbid conditions was significantly higher in

males than females (30.0% vs 19.2%  $p=0.0001$ ). Mortality rates were significantly higher in the female patients with COVID-19 when they had less than 4 comorbid conditions ( $p<0.0001$ ), while

males had a significantly higher mortality rate when they had 4 or more comorbid conditions ( $p<0.0001$ ) (table 2).

**Table 2: Mortality Demographics Split by Gender**

	Males n = 341	Females n = 345	p-value
Age (mean $\pm$ SD) years	75.9 $\pm$ 7.7	76.8 $\pm$ 8.0	0.10
Race (n, %)			
White	309 (90.6)	314 (91.0)	0.30
Black/ African American	21 (6.2)	26 (7.5)	
Asian	3 (0.9)	0 (0)	
Native Hawaiian/Pacific Islander	1 (0.3)	0 (0)	
Unknown	7 (2.1)	5 (1.4)	
Length of Stay (mean $\pm$ SD) days	7.3 $\pm$ 6.5	7.0 $\pm$ 6.74	0.49
ICU Stay (n, %)			
Yes	10 (2.9)	5 (1.4)	0.18
Comorbid Conditions (n, %)			
Hypertension	255 (74.8)	269 (78.0)	0.29
COPD	64 (18.8)	63 (18.3)	0.89
Kidney disease	123 (36.1)	106 (30.7)	0.15
Diabetes	100 (29.3)	99 (28.7)	0.89
Mortality with less than 4 comorbid conditions (n, %)	254 (74.5)	294 (85.2)	<0.0001
Mortality with 4 or more comorbid conditions (n, %)	87 (25.5)	51 (14.8)	<0.0001

A binary logistic regression analysis was performed looking at the likelihood of mortality among all patients while controlling for HTN, KD, DM, and COPD. Kidney disease was a significant predictor of mortality in our patients ( $p<0.0001$ , OR = 0.40, 95%CI [0.30,0.53]). Male patients exhibited the same findings with kidney disease being a significant predictor of mortality ( $p<0.0001$ , OR=0.43, 95% CI [0.29,0.64]). When looking at female patients the analysis showed different findings. Hypertension ( $p=0.33$ , OR=1.3, 95% CI

[0.79, 2.04]) and diabetes ( $p=0.5$ , OR = 1.15, 95% CI [0.72, 1.83]) were not significant predictors of mortality among females. On the other hand, COPD ( $p=0.01$ , OR=0.54, 95% CI [0.33, 0.86]) and kidney disease ( $p<0.0001$ , OR=0.37, 95% CI [0.24, 0.56]) were significant predictors of mortality among females.

## Discussion

COVID-19 has killed more than 2 million people since 2019 when it started in China<sup>(14)</sup>. The mortality

rate varies between countries worldwide that range between 12% in developing countries and 2% in developed countries<sup>(15)</sup>. The developed countries specific comorbid conditions associated with poor COVID-19 outcomes include COPD, diabetes, obesity, hypertension, and renal disease<sup>(16-20)</sup>.

Differences between genders as well as type of countries have been observed. Data has shown male mortality was around two and a half times that of the females<sup>(21)</sup>. While gender has played a significant role in the outcome of various illnesses<sup>(6,7,13)</sup>, it is still unsettled whether these gender differences can be generalized in all diseases. This remains an area of interest to investigators to study certain illnesses such as infectious diseases, chronic illnesses, and some acute respiratory diseases, which are found to show significantly different outcomes between males and females<sup>(14,21,22)</sup>. The differences based on gender may be related to differences in the immunological response of the host in these diseases<sup>(13,23)</sup>, and thus reflected in different morbidity and mortality rates as well as lengths of stay.

Gender and sex differences in the incidence and outcome of diseases such as respiratory syncytial viral infections, and COVID-19, are multifactorial<sup>(8-10)</sup>, and include the hormonal differences and its relationship with the immune response of the host, as well as comorbid conditions such as diabetes mellitus, hypertension, cardiovascular diseases, kidney disease, and COPD<sup>(9)</sup>. Some prior studies<sup>(14,23,24)</sup> raised the prospect of therapeutic modulation to alter the outcome of the disease in the male gender. Worldwide data indicate male mortalities from COVID-19 are 2.5 times more than females<sup>(14)</sup>.

Comorbid conditions in patients infected with COVID-19 played a major role in their outcomes in both the male and female groups, especially in patients with diabetes, chronic obstructive pulmonary disease, hypertension, and kidney disease. The influence of these comorbid conditions was more pronounced in females than

males; specifically, when the number of comorbid conditions was less than four. The mortality rates were higher in females with less than four comorbid conditions. On the other hand, there was a significantly higher number of male patients with four or more comorbid conditions, and this group had a higher mortality rate compared to females. Whether the immunoregulatory system's response to COVID-19 infection influenced these changes needs to be further evaluated.

The respiratory and immune system are major targets of the COVID-19 virus and there is growing evidence of renal manifestation and diseases in patients with COVID-19<sup>(15,25,26)</sup>. However the extent of the renal damage remains unknown. Multiple mechanisms for renal involvement include direct viral invasion, hypoxic injury, cytokine storm, thrombotic injury, micro coagulopathy, and rhabdomyolysis. Studies have shown that the incidence of AKI was higher in patients with established chronic kidney disease<sup>(27)</sup>. Increased severity and mortality in CKD patients diagnosed with COVID-19 has been reported in some meta analysis<sup>(28,29)</sup>. Chronic kidney disease has been associated with inflammatory and dysregulation of the immune system<sup>(30)</sup>. The immune system damage may increase susceptibility to bacterial and viral infections and might explain the high mortality due to increased risk of pulmonary infection. It is probable that the pathophysiology of COVID-19 associated AKI is more multi-factor than AKI observed with other causes of critical illness<sup>(31,32)</sup>.

Chronic obstructive pulmonary disorder is a major health problem () and is the third largest cause of death worldwide<sup>(33,34)</sup>. It is a progressive bronchial disease with symptoms of dyspnea and productive cough which is debilitating and difficult to manage considering this, 50% of the patients with COPD had 1-2 comorbid conditions such as hypertension, diabetes mellitus, and cardiovascular disease<sup>(34)</sup>, and 23% have 3 or more comorbid conditions.<sup>30</sup> This association is possibly due to smoke related respiratory and systemic inflammation and



microvascular changes<sup>(34)</sup>, and furthermore COPD is a high risk for any infection, including rhinoviral infections. There is evidence that presence of NK cells will stimulate the production of cytotoxic cells and the hormonal immune system which is required to fight an infection such as COVID-19<sup>(35-36)</sup>. Therefore a high response level of these cells in COPD patients with COVID-19 will be severely diminished since the NK cell level is in exhausted status and they are no longer stimulating the immune response.

In the regression analysis, controlling for comorbid conditions, acute kidney failure was a significant predictor of mortality in both male and female COVID-19 patients. Although the respiratory and immune systems are the target of the COVID-19 virus, there is increasing data to support renal manifestation of COVID-19 illness<sup>(25)</sup>. Acute kidney injury has previously been reported in patients with coronavirus<sup>(16,25,26,37)</sup>. Though the nature of this involvement remains unclear; direct viral renal invasion<sup>(19)</sup>, hypoxic damage to the renal structures<sup>(38)</sup> immune mediated involvement<sup>(28,29)</sup>, cytokine storm<sup>(25)</sup>, thrombotic microangiopathy<sup>(25)</sup>, and rhabdomyolysis<sup>(31,32)</sup>, with the resulting myoglobinemia and myoglobinuria<sup>(25-27)</sup> were considered as potential factors. The incidence of acute kidney injury was high in patients with established chronic kidney disease<sup>(27)</sup>, and has been reported in multiple meta-analyses<sup>(28,29)</sup> as chronic kidney disease has been associated with inflammation and dysregulation of the immune system<sup>(30)</sup>. This immune system damage may enhance the susceptibility to viral infections and might explain the high mortality rate of patients with COVID-19 pulmonary involvement.

COVID-19 virus mainly targeted the immune and respiratory systems, however, there's ample evidence that the renal system is among the major targeted organs, at the same time the extent of that damage remained unclear<sup>(25-27)</sup>. This may explain the higher mortality rate in those with pulmonary infection<sup>(15)</sup>. It is possible that the pathophysiology of acute kidney injury (AKI) associated with COVID-19 infection is multifactorial

and more complicated than AKI associated with other critical illnesses such as circulatory shock<sup>(31,32)</sup>. Our study was limited by the fact that it was a retrospective study. Furthermore, no follow up was made to see if any patient were subsequently admitted and died, including those patients admitted to another hospital.

## Conclusion

Gender differences in regard to mortality were influenced by the patients' pre-existing comorbid conditions, more so in female patients.

Male patients had a significantly higher mortality rate than female patients when they had four or more comorbid conditions, and kidney disease was a significant predictor of mortality in both genders. Additionally, COPD in female patients was also a significant predictor of mortality.

## Conflict of Interest:

None

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None.

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None.

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