

**Investigating the sex differences in COVID-19: Another step forward, but many unanswered questions.**

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Coronavirus disease 19 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has developed into a worldwide pandemic and a serious global health crisis since December 2019. Even in the midst of a rapidly growing pandemic, the scientific community has still devoted heroic efforts not only to control the spread of SARS-CoV-2, but also to understand the characteristics of COVID-19 and test the efficacy of various treatments. Within a few months of the beginning of the pandemic, several studies from various parts of the world have already reported the characteristics of patients affected by COVID-19<sup>1-3</sup>. While these studies provided valuable information about the risk factors and outcomes from COVID-19, an important issue that has not been addressed in these studies is the sex differences in COVID-19. Other than simply reporting the proportion of male and female patients in their study populations, prior studies have not explored the gender differences in detail. As a result, little is currently known about how men and women may be affected differently by the disease.

There are undoubtedly important differences between men and women with regard to their susceptibility and response to many diseases. The higher female susceptibility to autoimmune diseases is probably a widely known example, but such differences exist in infectious diseases as well. For example, it has been reported that women are more prone to human immunodeficiency virus (HIV) infections, whereas tuberculosis and parasitic infections are more prevalent in men<sup>4</sup>. The reasons for such differences are complex. There may be biologic factors such as chromosomal and hormonal differences between men and women that can impact their susceptibility to infections, immunologic responses to infections, and progression of disease. In addition, there are behavioral, cultural, and socioeconomic factors that cause health disparities between men and women, leading to different risks of exposure and

transmission of infections<sup>4,5</sup>. Despite the knowledge of such differences, there is a scarcity of literature that investigates the sex differences in infectious diseases, and the underlying mechanisms are just starting to be understood.

This is the knowledge gap that motivated Qian and colleagues to explore the sex differences in a large number of patients affected by COVID-19 in mainland China. In this study, the investigators utilized the data from a national registry of over 80,000 reported cases of COVID-19 in mainland China, as of late April 2020. The main finding from the study was that while female patients were more likely to be affected by COVID-19, female patients had a lower proportion of severe or critical cases (PSCC) and a lower case fatality rate (CFR) compared to male patients. The study also showed higher overall attack rates, higher severity of illness, and higher CFR with increasing age, a trend that was consistent with the findings from earlier reports<sup>1,2,6</sup>. Performing subgroup analyses by age groups showed that the attack rate was higher in women 50-69 years of age, but the PSCC and the CFR was lower in women in most of the age groups. It appeared that the sex differences in the attack rate, PSCC, and CFR in Hubei Province, which contained the vast majority of COVID-19 cases in mainland China, likely shaped the overall trends seen nationwide; the trends seen in other regions were more variable. The lower PSCC and CFR for female patients remained significant in multivariate logistic regression analysis after controlling for potential confounders.

This study provides valuable insight into the epidemiology of COVID-19 and adds to the increasing body of knowledge about this new disease. The results of this study are similar to those of a smaller prior study, which also reported more severe illness and higher mortality from COVID-19 in men compared to women<sup>7</sup>. These findings may be one of the potential reasons for the predominance of male patients (82%) in the Italian cohort of COVID-19 patients admitted to

the intensive care units<sup>2</sup>, suggesting that male patients were more likely to suffer severe disease and require higher levels of care. It is also worth noting that a similar coronavirus outbreak, the severe acute respiratory syndrome (SARS) epidemic in 2002-2004, also showed a higher case fatality rate in men compared to women<sup>7,8</sup>. These findings suggest that these viral illnesses can affect men and women differently, and indicate the need for a better understanding of various factors that may be contributing to these differences. The authors of this study propose several potential reasons for the sex differences found in COVID-19. These include biologic factors such as the location of angiotensin converting enzyme-2 (which is involved in SARS-CoV-2 entry into cells) and immune-related genes on the X chromosome, as well as development of higher levels of IgG against SARS-CoV-2 in females. They also suggest social and behavioral differences, such as the fact that women more commonly assume caregiver roles and that men have higher smoking rates. The higher proportion of females among healthcare workers, who tend to have less severe disease from SARS-CoV-2 than the general population<sup>9</sup>, may have contributed as well.

Unfortunately, we are still left with many unanswered questions, some of which arise from the limitations of the study itself. First, the criteria used for diagnosing SARS-CoV-2 infection, classifying the severity of illness, and reporting the cases to the national surveillance database may have been inconsistent, especially early on in the outbreak. The database also did not include detailed information regarding the patients' medical comorbidities or the treatments received. As the authors admit, there was likely a wide variation in how these patients were treated, especially early on in the outbreak when there was no clear guidance on how to best treat COVID-19 and many patients were being given unproven therapies. It is impossible to know whether any of these treatments or the underlying comorbidities of the patients may have

confounded the results of this study in any way. Moreover, the vast majority of patients in this study were from Hubei Province, and the sex differences noted in other regions of China appeared more variable. It is not yet clear whether the findings of this study will be generalizable to other parts of the world. As discussed previously, currently available studies describing the characteristics of COVID-19 patients in other countries do not provide a deep exploration of the sex differences. With the disease still continuing to spread all throughout the world, our understanding of the sex differences in COVID-19 will likely continue to evolve in the coming months.

Overall, this study of a large number of COVID-19 patients in China points out the different impact of COVID-19 based on sex, and pushes us another step forward in understanding this novel disease. It is too early to determine whether sex differences identified in this study would have practical implications for management, especially because the numerous potential reasons for such differences still need to be further elucidated. Nonetheless, the study highlights the importance of recognizing specific populations at increased risk for an infection and better understanding the differences in outcomes. It raises awareness of this important issue and provides a valuable foundation on which to conduct future studies investigating the sex differences in infectious diseases. We hope that understanding the sex differences will someday contribute to formulating individualized treatments and determining better interventions, not only for COVID-19 but also for other infectious diseases.

Neither author has any potential conflicts of interest.

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