

# COVID-19 and Sex-/Gender-Specific Differences: Understanding the Discrimination

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Coronavirus disease in 2019 (COVID-19), as caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been associated with significant morbidity and mortality worldwide. Although SARS-CoV-2 primarily targets the respiratory system, it can cause various hematological and hemostatic derangements, most notably coagulopathies in severe cases.<sup>1,4</sup> Thrombocytopenia and elevations in fibrinogen and D-dimer have been reported to be prognostic indicators of COVID-19 severity and/or mortality.<sup>2,4</sup> Changes in hemostatic parameters correlate with parallel rises in inflammatory markers such as cytokines and C-reactive protein (CRP).<sup>4</sup> Key mechanisms for SARS-CoV-2-induced coagulopathy include severe lung injury, alterations in the renin-angiotensin-aldosterone system (RAAS), and overactivation of the immune inflammatory pathways.<sup>3,4</sup>

Of relevance to the current commentary, certain demographic and clinical factors, such as older age and preexisting comorbid conditions, can increase the risk of more severe infections.<sup>5,6</sup> The number of COVID-19 cases is similar among males and females, as evidenced by data from over 700,000 confirmed COVID-19 cases collected by the World Health Organization (WHO).<sup>7</sup> However, a recent meta-analysis suggests that men are more likely to experience severe disease and mortality compared with women.<sup>8</sup> Yet, it is unclear whether the disparities in COVID-19 clinical outcomes are due to underlying sex-based biologic differences or gender-based behavioral differences. Exploration of the sex- and gender-based differences in SARS-CoV-2 infection is vital, as these may carry potential implications for disease progression, outcome severity, vaccine response, therapeutic intervention and effectiveness, recruitment of males and/or

females to clinical research studies, as well as identification of novel therapies for use in both sexes. In this report, we highlight those differences based on available evidence, attempt to explore and discuss possible underlying reasons, and provide our views for future research.

## COVID-19 and Sex Differences

While males and females are both equally susceptible to COVID-19 infection, males are at increased risk for severe disease progression and poor outcomes. The Chinese Center for Disease Control and Prevention (CDC) analyzed 44,672 confirmed cases of COVID-19 and reported that the mortality rate in men (2.8%) was nearly double that of women (1.7%).<sup>9,10</sup> Similar trends of greater COVID-19 severity and mortality in men compared with women were observed in reports from other countries. As of May 20, 2020, in 39 of 41 countries for which sex-disaggregated data are available, males were more likely to die from COVID-19 than females,<sup>11</sup> highlighting a 2:1 male to female death ratio (MFDR) in most.<sup>11,12</sup> In Italy, men comprised approximately 70% of COVID-19 deaths<sup>13</sup> and the MFDR was 3:1 in patients over 70 years of age,<sup>14</sup> while Thailand had a MFDR of 2.8.<sup>11</sup> Similarly, a case series of 5,700 patients hospitalized with COVID-19 in the New York City area found that the mortality rates were consistently higher in males, compared with females, across every age group above 20 years.<sup>15</sup> Italy likewise reported higher mortality rates in men over 40 years of age.<sup>16</sup>

In terms of hospitalizations, reports from the United States (U.S.) CDC and Italy showed that men comprised more than half of COVID-19 hospitalizations.<sup>17,18</sup> All 10 countries that

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currently provide COVID-19 admission rates by sex reported higher hospitalization rates in males than in females,<sup>11</sup> with males comprising at least 61% of all COVID-19-related ICU admissions in these countries.<sup>11</sup> Furthermore, across Europe, men constituted 73% of all COVID-19-related ICU admissions.<sup>16</sup> A meta-analysis of 206,128 reported cases of COVID-19 worldwide found that male patients are at significantly higher risk of ICU admission (odds ratio [OR], 2.5) and death (OR, 1.6) compared with female patients.<sup>8</sup> Other studies likewise consistently showed significant sex-specific differences in clinical characteristics and prognosis, with male sex as a risk factor for severe disease and mortality.<sup>16,19–22</sup>

### Potential Causes of Sex and Gender Differences in COVID-19

This striking support for a male bias toward worse clinical outcomes in the COVID-19 pandemic demonstrated by the global epidemiologic data deserves investigation of the mechanisms underlying these sex- and perhaps gender-based differences. There are multiple plausible explanations, including (1) sex-specific biological differences (differences in the immune or inflammatory response, genetic profile, hormone types and levels, and differential expression of angiotensin-converting enzyme 2 [ACE2], the receptor for SARS CoV-2); (2) gender-specific behavioral or lifestyle differences; and/or (3) differences in underlying comorbid conditions. **Fig. 1** provides a summary of those potential explanations.

#### The Potential Role of the X-Chromosome

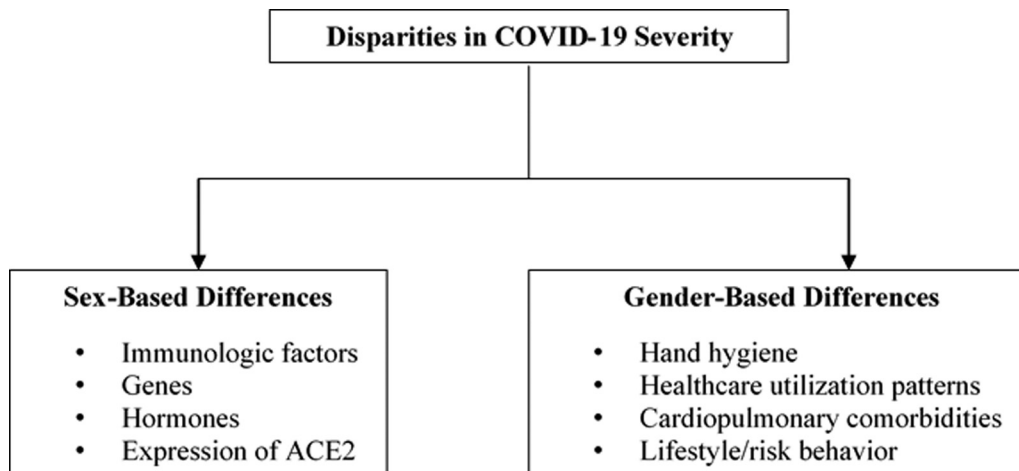
Known to carry the largest number of immune-related genes in the human genome, the X chromosome confers females a significant immunological advantage over males.<sup>23–25</sup> Years of evidence have shown that compared with males, females typically mount stronger antibody and cell-mediated immune responses than males.<sup>26–29</sup> Male susceptibility to poorer health outcomes is evident from the fetal period through adulthood.<sup>23,24,30</sup> X-linked genes, X-linked micro-RNAs, female mosaicism, and heterogeneity or errors in X chromo-

some inactivation may result in sex-specific immunological differences.<sup>23,25,31</sup> Fetal-placental programming, genetic variation, and sex hormones can play a role in shaping the sex-specific innate and adaptive immune inflammatory responses.<sup>23,24,30,32–35</sup> In support of this, a study analyzing serum from 331 hospitalized patients found that most female patients with severe COVID-19 had more than 100 AU/mL of SARS-CoV-2 IgG antibodies, while most male patients had less than 100 AU/mL.<sup>36</sup> Additionally, females generated a stronger IgG production early on in the disease course compared with male patients, which is consistent with preexisting literature.<sup>36</sup>

#### Sex Hormones

The sex-specific differences in COVID-19 severity may, at least in part, be explained by sex hormones and their regulatory effects. Androgens, which are found in higher concentrations in males, upregulate transmembrane serine protease 2 (TMPRSS2), which primes the spike protein of SARS-CoV-2 and facilitates its entry into the host.<sup>37–40</sup> In vitro studies have shown that camostat mesylate, an inhibitor of TMPRSS2, blocks SARS-CoV-2 infection of lung cells, and its potential for viral load reduction in early COVID-19 infection is currently being investigated.<sup>37,41</sup>

In general, estrogens are considered immunostimulatory, and thus may be protective in the context of COVID-19, while androgens and progesterone are relatively immunosuppressive.<sup>34</sup> Previous studies have also demonstrated that sex hormones regulate cytokine levels and the RAAS.<sup>42–47</sup> Yet at the same time, studies have found an association between lower testosterone levels and increased inflammatory cytokines,<sup>46</sup> and postulated that a reduction of testosterone in older men may be responsible for their increased vulnerability to severe disease, as well as to increased risk of both transfer to ICU and mortality.<sup>48</sup> Similarly in females, reduced estrogen levels following menopause may explain the increased infection risk that older women have compared with the risk observed in younger women. In animal studies of SARS-CoV, ovariectomy or blockage of estrogen receptors was associated with increased susceptibility to the infection



**Fig. 1** Possible explanations for sex- and gender-based disparities in COVID-19 severity. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019.

and increased mortality, implying that estrogen signaling may be protective for females.<sup>35,49</sup>

### Susceptibility in Pregnancy and Effects of Hormonal Contraception

In contrast to other viral infections, including Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which were characterized by high rates of severe morbidity and mortality during pregnancy, the COVID-19 infection does not appear to result in disproportional morbidity and/or mortality in pregnant women in comparison to the general population thus far.<sup>5,50</sup>

This may be explained by the fact that a significant proportion of morbidity and mortality in COVID-19 has been ascribed to cytokine storm syndrome, an aberrant immune response to SARS-CoV-2,<sup>51</sup> a response which is immune in origin. The immunomodulatory actions of estrogen and progesterone are well established,<sup>52</sup> and both play an important role in the modulation of the expression of Th1 and Th2 cytokines.<sup>53</sup> These effects may contribute to the relatively mild course of COVID-19 in the majority of pregnant patients, whose estrogen and progesterone levels are elevated, and is supported by a recent report describing that 88% of women testing positive for SARS-CoV-2 on admission for delivery had no symptoms at presentation.<sup>54</sup>

Given the immunostimulatory effects of estrogen, the use of hormonal contraceptive pills may likewise be protective for females. For instance, hormonal contraception has been shown to reduce the susceptibility to HIV in females aged < 25 years.<sup>55</sup> The fact that as many as three quarters of reproductive age women use oral contraceptives at some point in their lives<sup>56</sup> may thus in part explain some of the sex-based differences in COVID-19 severity. Observation of these effects in females has led one author to propose the extension of these potential hormonal modulating effects to males, by prescribing a fixed dose oral contraceptive pill as an adjunct to COVID-19 treatment.<sup>57,58</sup> A clinical trial is currently underway to investigate if an estrogen patch can reduce disease severity in men and older postmenopausal women with COVID-19 infection.<sup>59</sup>

### Variation in ACE2 Expression

It is well known that ACE2, the natural SARS-CoV-2 receptor, is integral to the pathophysiology of COVID-19. ACE2 is found in various organ systems throughout the body, and it has two different functional forms: transmembrane and soluble.<sup>60</sup> SARS-CoV-2 uses the transmembrane form as a receptor for host cell entry.<sup>60</sup> The soluble ACE2 lacks the transmembrane domain, and may act as a competitive interceptor, inhibiting the entry of SARS-CoV-2 and other coronaviruses.<sup>60</sup> A recent in vitro study demonstrated that ACE2 fused to immunoglobulin potentially neutralized SARS-CoV-2.<sup>61</sup>

The gene for ACE2 is located on the X chromosome,<sup>62</sup> which means that the double X chromosome in females may be protective, as heterozygous females can have a mosaic advantage while males are hemizygous.<sup>63</sup> Furthermore, animal studies have revealed sexual dimorphism in ACE2 activity.<sup>64</sup> However, data from human studies on whether higher or lower

levels of ACE2 are more protective are conflicting, and controversy persists regarding expression of ACE2 in different subpopulations. For instance, Swård et al observed that males expressed higher serum levels of soluble ACE2 than females, with differences becoming more pronounced with age, although the sample included only pediatric and adolescent patients up to a mean age of 23.5 years.<sup>65</sup> Contrary to this study, Chen et al found significantly higher ACE2 expression in Asian females, with the highest levels observed in East Asian females, compared with males and other ethnic groups.<sup>66</sup> They also noted that ACE2 expression decreased with increasing age and in the presence of certain inflammatory cytokines, in particular interleukin (IL)-2 and IL-7.<sup>66</sup> Given the findings of higher ACE2 levels in females and younger individuals, it is possible that higher baseline ACE2 levels confer an advantage by counteracting the depletion of ACE2 by SARS-CoV-2, though this hypothesis will need to be tested in future studies.<sup>63,66</sup>

SARS-CoV-2 decreases ACE2 levels, leading to accumulation of angiotensin II, aldosterone, and ACE, shifting the hemostatic balance toward a hypercoagulable and hypofibrinolytic state, further characterized by decreased tissue plasminogen activator (tPA) to plasminogen activator inhibitor-1 (PAI-1) ratio.<sup>3</sup> Angiotensin II directly increases PAI-1 expression from endothelial cells and from adipocytes.<sup>3</sup> Aldosterone increases ACE expression, which increases bradykinin breakdown, inhibiting bradykinin-mediated increase in tPA.<sup>3</sup> Thus, high baseline ACE2 levels could be protective, as they may mitigate the procoagulant effects of angiotensin II, aldosterone, and ACE, and in doing so attenuate the risk of severe COVID-19. This is supported by previous studies which demonstrated that recombinant ACE2 can rapidly decrease angiotensin II and IL-6 levels,<sup>67</sup> and can reduce the viral load of SARS-CoV-2.<sup>68</sup> Interestingly, abundant ACE2 expression has likewise been noted within the human placenta: mainly within the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of the villi.<sup>69</sup> Clarification of the potential links between placental ACE2 expression and SARS-CoV-2 susceptibility, disease severity in pregnancy, vertical transmission, and fetal outcomes require examination in larger studies.

### SARS CoV-2 Viral Tropism

The genetic characteristics of the organisms may play a role in virus tropism and this seems to vary by age and sex. Spanish influenza killed proportionately more young males compared with other influenza viruses.<sup>70</sup> Poliomyelitis and hepatitis C showed higher male mortality in all ages, while smallpox, measles, rubella, hepatitis B, and influenza showed higher female mortality.<sup>71</sup> The mechanisms of varying tropism remain unknown. Studies to uncover the characteristics of viral tropism of SARS CoV-2 are yet to be conducted.

### Gender-Based Behavioral/Lifestyle Differences

Aside from biological factors, gender-based behavioral and lifestyle differences may contribute to the male predisposition for more severe disease. Smoking is a well-known risk factor for cardiopulmonary comorbidities through alteration of the RAAS homeostasis,<sup>72</sup> thereby heightening vulnerability to poor clinical outcomes. Globally, smoking is more common

in men than in women.<sup>73</sup> However, it is difficult to isolate the effect of smoking or any one comorbidity on disease prognosis. A meta-analysis of five studies did not find a statistically significant difference between active smoking and severity of COVID-19.<sup>74</sup> The relationship between smoking and COVID-19 is complex; while smoking upregulates ACE2, it is unclear whether this increases or decreases risk for COVID-19 severity.<sup>75</sup>

Additional gender-based differences include the higher frequency with which females access medical care in comparison to males, and the greater likelihood that females comply with hand-hygiene practices.<sup>76–78</sup> By contrast, males are more likely to engage in risky behavior, including activities that may compromise their health.<sup>76,79</sup>

### Concluding Remarks and Recommendations for Future Studies

Worldwide epidemiological data show that sex and gender can be major drivers of risk for severe disease and mortality. While the prevalence of COVID-19 seems to be similar between the sexes, men appear to be at higher risk for severe infection and mortality. The sex-specific discrepancies seen in COVID-19 outcomes are not unique to this disease, as

similar trends have been observed with many viral respiratory tract infections.<sup>26,35</sup> The epidemics of SARS in 2002–2003 and MERS in 2012 also exhibited a male bias for more severe disease and mortality.<sup>35,73,80,81</sup> Given that sex differences in disease outcomes exist, it is worth exploring the mechanisms mediating these differences. Sex is a biological variable, and consequently, differences in immunologic responses, genes, hormones, and the expression of ACE2 may be driving a male bias toward more severe COVID-19 infection and mortality. It is also important to acknowledge that gender-based differences in behavior and lifestyle habits may also contribute to the disparities seen in disease manifestations.

Identifying and studying the effects of sex and gender differences on COVID-19 susceptibility, disease severity, and mortality will help us evaluate vaccine responses and strategies, therapeutic intervention, recruitment decisions of males and/or females to clinical research studies, and identification of novel therapies for use in both sexes. In ► **Table 1**, we provide suggestions for future studies to better understand the reasons for sex- or gender-based differences in COVID-19 severity and prognosis. For all future studies, sex- and gender-disaggregated data are critical for understanding differences in risk and response to infection, and thereby for

**Table 1** Recommendations for future studies on COVID-19

	Recommendations for future studies
Sex-based differences	
Immunologic factors	– Compare cytokine levels in males versus females with COVID-19 of similar disease severity – Compare immunoglobulin levels by sex and disease outcomes
Genes	– Determine genetic markers that may predict increased susceptibility to severe COVID-19
Hormones	– Determine the effect(s) of hormones and their receptors on ACE2 and TMPRSS2 levels, and in general on SARS-CoV-2 entry, replication, and spread through in vitro studies – Measure hormonal levels by sex and age groups and correlate findings with severity of COVID-19 – Investigate the effect of hormonal contraception on susceptibility to COVID-19
Expression of ACE2	– Analyze variation in ACE2 expression by sex and ethnic groups – Correlate sex-specific variation in ACE2 expression with severity of COVID-19
Pregnancy	– Examine differences in susceptibility to COVID-19 in pregnant vs. nonpregnant individuals – Explore placental expression of ACE2 and its links to SARS-CoV-2 susceptibility, vertical transmission, as well as maternal and fetal outcomes
Gender-based differences	
Handwashing	– Survey relevant groups to assess differences in handwashing practices, patterns, and attitudes
Healthcare utilization patterns	– Assess factors affecting decisions regarding when medical care is accessed based on sex and gender
Lifestyle/risk behavior	– Assess other lifestyle differences, including risk behaviors
Sex- or gender-based differences	
Comorbid conditions	– Record frequency, type, and number of comorbid conditions by sex
Therapy	– Examine the role of RAAS medications in suppressing COVID-19 – Devise clinical trials to evaluate safety and efficacy of camostat mesylate for treatment of COVID-19 – Determine if there are sex-specific differences in response to various therapies for COVID-19

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RAAS, renin-angiotensin-aldosterone system; TMPRSS2, transmembrane serine protease 2.

guiding effective targeted prevention and management of disease.

#### Conflict of Interest

None.

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