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## COVID Review

# Sex- or Gender-specific Differences in the Clinical Presentation, Outcome, and Treatment of SARS-CoV-2



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### ABSTRACT

This review describes the sex and gender differences in COVID-19 presentation, treatment, and outcomes. We discuss the differences between the sexes in susceptibility to infection, the role of sex chromosomes on the body's immunologic response and the influence of hormones on the body's response to the virus. Additionally, the sex differences in clinical and laboratory presentation, complications of infection and outcomes, as well as differences in response to treatment and prevention are reviewed. (*Clin Ther.* 2021;43:557–571) © 2021 Elsevier Inc.

**Key words:** Immunology, long haulers, Sars Cov2, sex-disaggregated analysis, sex and gender based medicine.

### INTRODUCTION

On March 11, 2020, the World Health Organization declared the outbreak of coronavirus disease 2019 (COVID-19) a pandemic.<sup>1,2</sup> Since then, clinicians have learned a great deal about this disease causing single stranded RNA virus severe acute respiratory syndrome—coronavirus 2 (SARS-CoV-2), virus—especially that infection with the virus is

associated with increased morbidity in older individuals with hypertension, diabetes, cardiovascular disease (CVD), and obesity.<sup>3</sup> In addition, even the earliest case reports from Wuhan, China, demonstrated that COVID-19 was associated with disproportionately greater mortality in men than women.<sup>4</sup> Since those early reports, studies, meta-analyses, and global tracking systems have confirmed that men are at greater risk for morbidity and mortality from infection with SARS-CoV-2.<sup>3,5</sup> Global Health 50/50 showed higher death rates among men in 68 of the 84 countries from which sex-disaggregated data were available, with death ratios varying from 0.5 to 3.8 (men vs women).<sup>5</sup> In the United States, tracking by the Centers for Disease Control and Prevention of over 185,000 COVID-19–related deaths revealed that 54% of those deaths occurred in men.<sup>5,6</sup> Although rates of infection seem to be similar, the age at which infection occurs may be related to sex and age: It has been reported that women aged 20–50 years are at increased risk for infection, as are men over the age 50 years (Marina

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S, Piemonti L. Sex and age effects on the rates of infection and deaths in individuals with confirmed SARS-CoV-2 infection in six European countries. <https://doi.org/10.2139/ssrn.3576790>. Submitted.). After infected, men may have a greater likelihood of intensive care unit (ICU) admission and death, suggesting that sex and/or gender (S/G)-related factors affect disease trajectory.<sup>3</sup> There is increasing evidence of important S/G differences in patients infected with SARS-CoV-2, yet many researchers have not evaluated their data for potential S/G influences. In a recent review of data from almost 2500 registered clinical studies in SARS-CoV-2 infection, <5% had planned for sex-disaggregated analysis of the results (Brady E, Nielsen MW, Andersen JP, et al. Lack of consideration of sex and sex in clinical trials for COVID-19. <https://doi.org/10.1101/2020.09.13.20193680>. Submitted.). The purpose of this article was to review state-of-the-art evidence related to S/G-specific differences in the clinical presentation, physiology, and outcomes of SARS-CoV-2 infection and to highlight the critical necessity of inclusion and analysis of these variables in future research.

## MATERIALS AND METHODS

Authors identified key topic areas of interest for this review and each, using their individual styles and experience, developed their own search method to obtain the content specific to the topic area that they respectively authored. The reference lists of identified articles were used by some to find additional papers eligible for inclusion. Generally, data from articles that were not in the English-language were excluded from review. To keep the total number of references within the scope of typical reviews, when creating the document, individual authors were asked to include approximately 15-20 references that they believed best encapsulated the research relevant to their section with particular focus on articles written between March to December 2020.

As the terms *biological sex* and *gender* are often misrepresented in scientific research, to ensure clarity in this review, biological sex is based on an individual's sex chromosomes, hormones, and anatomy, while gender is heavily rooted in sociocultural constructs (see [Supplemental Appendix 1](#) for additional information of their complex interrelationship).

## RESULTS

A total of 136 articles were identified by the authors to include as citations for their cumulative sections. After exclusion of some by peer review, the remaining citations were included in the present review.

A summary of S/G differences in COVID-19 can be found in [Table I](#).

### Susceptibility and Response to Infection

Although individual differences in habits and behaviors can affect virus-exposure rates, to prevent significant illness after infection, 3 things must happen: (1) a rapid innate immune response that alerts the body of viral invasion and attempts to mitigate its impact; (2) the trigger of a secondary adaptive immune response that leads to the production of virus-specific antibodies and T cells to neutralize viral particles, kill viral-laden cells, and stimulate the production of memory lymphocytes to “stand guard” for re-exposure; (3) an effective recovery period when innate immune cells and epithelial regenerative pathways repair and/or remove damaged cells.<sup>10,11</sup> Age and sex can influence each of these steps.<sup>10,11</sup> In COVID-19, women appear to shed the virus for a shorter period of time and it may clear from their bodies more quickly.<sup>12</sup> In addition to SARS-CoV-2 infection, men are also at greater risk for complications from viral infection due to hepatitis B virus, SARS-CoV-1, and Middle East respiratory syndrome—CoV; these biological sex differences (BSDs) in risk are both sex chromosome—based and sex hormone—based.<sup>13</sup>

### Role of Sex Chromosome—Based Differences in Immunologic Response

There are BSDs in immunologic response that begin before puberty and extend into advanced age. In response to these differences, scientists increasingly are focusing on the role that sex chromosomes play in the immune response.<sup>14</sup> In SARS-CoV-2, the gene that encodes angiotensin-converting enzyme (ACE)-2 receptors (the viral binding site on the cell surface membrane), along with many other immune-related genes necessary for combatting infection, are found on the X chromosome.<sup>14</sup> As men have only one X chromosome, and, therefore, one copy of any X-linked genes, if that copy is maladaptive then they may be at a disadvantage compared with women,

Table I. Sex differences in SARS-CoV-2.\*

Parameter	Males	Females
Presentation	Higher risk for infection at age >50 y	Higher risk for infection at age 20–50 y; higher risk for hyposmia, anosmia, gustatory dysfunction, “COVID toes”
Risk factors	Known CVD; smoking	Greater prevalence in health care workers
Immune response	Lower adaptive T-cell response; higher prevalences of complications and severity	Higher and more robust proinflammatory cytokines; virus shedding for shorter duration
Laboratory testing	Higher serum CRP, ESR, ALT, AST, GGT, ferritin, fibrinogen and LDH, aPTT, IL-8; of note, there do not appear to be clear sex differences in D-dimer elevation from COVID-19; however, having an elevated dimer is associated with greater morbidity	Higher serum calcium and sodium levels
Outcomes	Higher rates of hospitalization, admission to ICU; higher mortality	Subclinical disease; greater prevalence of “long haulers”
Cardiac manifestations	Myocarditis, particularly 2 wk after infection; acute coronary syndrome; maladaptive immune response; arrhythmia	Takotsubo; arrhythmia
Lung injury	Testosterone activates the serine protease; TMPRSS-2 on cell membrane increases virus entry into the alveoli; testosterone suppresses inflammatory response by decreasing peripheral mononuclear cells, cytokines	Estrogen increases NO, prostacyclins and reduces platelet aggregation, decreases PMN recruitment and decreases local cytokine release; in mice, estrogen stimulates activation of Ang (1–7) via the Mas receptor, which protects endothelial barrier in acute lung injury; estradiol downregulates expression of ACE-2 in alveolar cells, and has estrogen activates innate, humoral and cellular immunity in a more balanced and adaptive way
VTE	Higher risk in hospitalized patients	—
Obesity	Obese men at higher risk due to dysregulation of ACE-2 in adipose tissue with activation of Ang 1–7 levels	—

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; Ang = angiotensin; aPTT = activated partial thromboplastin time; AST = aspart aminotransferase; CRP = C-reactive protein; CVD = cardiovascular disease; ESR = erythrocyte sedimentation rate; GGT =  $\gamma$ -glutamyl transferase; ICU = intensive care unit; IL = interleukin; LDH = lactate dehydrogenase; NO = nitric oxide; PMN = polymorphonuclear neutrophil; SARS-CoV-2 = severe acute respiratory syndrome–coronavirus 2; TMPRSS = transmembrane protease serine; VTE = venous thromboembolic event.

\* Data from references 7–9; Marina S, Piemonti L. Sex and age effects on the rates of infection and deaths in individuals with confirmed SARS-CoV-2 infection in six European countries. doi: <https://dx.doi.org/10.2139/ssrn.3576790>. Submitted; Ten-Caten F, Gonzalez-Dias P, Castro I, et al. In-depth analysis of laboratory parameters reveals the interplay between sex, age and systemic inflammation in individuals with COVID-19. <https://doi.org/10.1101/2020.08.07.20170043>. Submitted; and Sudre CH, Murray B, Varsavsky T. et al. Attributes and predictors of long-COVID: analysis of COVID cases and their symptoms collected by the COVID Symptoms Study app. <https://doi.org/10.1101/2020.10.19.20214494>. Submitted.

who have access to a second copy from the other X chromosome. In addition, some of the X-linked immune-related genes involved in SARS-CoV-2 avoid “X inactivation,” the typical cellular process that occurs in females that turns off the expression of one copy of the X chromosome to prevent the overexpression of X-linked genes.<sup>15</sup> This creates the possibility that females express a “double dose” of certain immune-related genes that could provide the immune response with a boost after exposure to certain infections. The downside is that it could put females at higher risk for certain types of autoimmune diseases or infection with pathogens known to trigger an exuberant inflammatory response. A COVID-19–related gene that appears to avoid typical X inactivation is the gene that encodes Toll-like receptor (TLR)-7.<sup>16</sup> TLR-7 is an important part of the innate immune response relevant to patients’ response to COVID-19, as it recognizes single-stranded RNA virus invasion and helps to stimulate interferon production.<sup>16</sup> In females, higher amounts of interferon are released after TLR-7 activation, and case reports suggest a risk for more severe illness in SARS-CoV-2–infected males who have a defect in the TLR-7 gene.<sup>17</sup> In addition to containing genes that code for specific immunologic functions, the X chromosome also contains genes that regulate the expression of genes on other chromosomes, underscoring the importance of sex chromosomes in epigenetics and homeostasis.<sup>18</sup>

### Role of Sex Hormone–Based Differences in Disease Severity

Sex hormones likely influence the severity of COVID-19 after SARS-CoV-2 infection (Table II). Both sexes produce estrogen, progesterone, and testosterone, but the amount produced varies as a result of biological sex, age, obesity, stage of the menstrual cycle (in women of child-bearing age), and use of exogenous hormones.<sup>19</sup> Many immune cells, including neutrophils, macrophages, natural killer cells, T cells, and B cells, contain receptors for sex hormones.<sup>19,23</sup> In addition, sex hormones can influence DNA transcription of the genes involved in immune-cell development and signaling.<sup>10,20</sup>

Testosterone and progesterone are immunosuppressant, while the activity of estrogen is more variable and complex.<sup>21</sup> Estrogen can be immune-enhancing or -suppressing, depending on

plasma concentration, the site of interaction along immunomodulating pathways, and the type of estrogen receptor binding the estrogen.<sup>22</sup> At low doses, estrogen can promote pro-inflammatory cytokine release, while at high or sustained doses it can help to shut off pro-inflammatory pathways, decrease leukocyte recruitment, and enhance antibody production.<sup>23,22</sup>

The complicated interaction between coronavirus, hormones, and severity of illness is highlighted in research involving SARS-CoV-1–infected mice. In male mice, viral concentrations and inflammatory changes in the lungs were higher after viral inoculation, but this association was dependent on the age of the mice. In infected middle-aged mice (age 10–14 month), 90% of male mice died compared to 20% of females.<sup>24</sup> This difference disappeared in older mice and in female mice with ovaries removed, suggesting that estrogen may help to limit disease severity.<sup>24</sup> Alternatively, during the influenza A virus subtype H1N1 pandemic, researchers reported increased morbidity in women of child-bearing age, as H1N1 triggered an exuberant immune response that was amplified by the effects of female-ratioed sex hormones.<sup>23</sup> These examples highlight the complex interaction between pathogen and host. Morbidity can be influenced by factors surrounding the infection, the immune response, host factors, or a combination of these.

Clinical studies of the effects of adding and blocking estrogens, particularly estradiol, on the outcomes of patients infected with SARS-CoV-2 are ongoing.<sup>25</sup> Hormone augmentation in other viruses has been studied, with estrogen therapy showing improved cellular immunity in female patients with HIV, and decreased progression to liver fibrosis in patients with chronic hepatitis C.<sup>26,27</sup>

Testosterone may also contribute to sex-based differences in COVID-19–related mortality.<sup>28</sup>

It has been postulated that increased transmembrane protease serine 2 (TMPRSS)-2 levels may enhance infectivity.<sup>28</sup> In a small-scale study of this theory, 79% (122/175) of men admitted for the treatment of COVID-19 symptoms had evidence of male-pattern baldness, suggesting an excess of androgens.<sup>29</sup> Three studies are looking at the impact of testosterone suppression on COVID-19–related mortality.<sup>25,30,31</sup> Conversely, low levels of circulating testosterone have been linked to an increased risk for poor outcomes in

Table II. Sex hormones and immune response.<sup>10,19–22</sup>

Hormone	Immune Response
Estrogen	<ul style="list-style-type: none"> <li>- Effect on immune response is complex and appears to be dependent on circulating levels and site of action along different immune pathways</li> <li>- Low physiologic levels appear to enhance production of certain proinflammatory cytokines (IL-6, -12, -1<math>\beta</math>)</li> <li>- Higher levels suppress many inflammatory cytokines, trigger regulatory cytokine (IL-10), and decrease migration of neutrophils and monocytes to inflamed tissues</li> <li>- Estradiol enhances macrophage activation</li> <li>- Increases TLR-7 (which can promote interferon)</li> <li>- Increases B- and T-helper cell response</li> <li>- In animal models, estrogen down-regulates cardiac ACE-2 receptors</li> <li>- In certain viruses, may decrease replication in mucosal cells</li> <li>- Increases nitrous oxide and prostacyclins and reduces platelet aggregation</li> <li>- Postmenopausal women have increased amounts of inflammatory cytokines: IL-1, IL-6, and TNF-<math>\alpha</math> (which can be attenuated by hormone replacement)</li> <li>- Tips RAAS system toward vasodilation/anti-inflammation</li> </ul>
Progesterone	<ul style="list-style-type: none"> <li>- Progesterone receptors are found in most immune cells</li> <li>- May act on glucocorticoid and mineralocorticoid receptors</li> <li>- Inhibits proinflammatory cytokines IL-1<math>\beta</math> and IL-12</li> </ul>
Testosterone	<ul style="list-style-type: none"> <li>- Immunosuppressant responses</li> <li>- Down-regulates pro-inflammatory cytokines (IL-6, IL-1<math>\beta</math>, and TNF-<math>\alpha</math>) and NK cells, and increases anti-inflammatory cytokine IL-10</li> <li>- Decreases IFN-<math>\gamma</math> response (and more prone to autoantibodies to interferon)</li> <li>- Decreases responsiveness of certain types of T cells and decreased antibody response</li> <li>- Enhances TMPRSS2 (a transmembrane protease that aids the entrance of ACE-2–bound viral complexes into cell)</li> <li>- Elevated levels can decrease immune response to certain vaccines</li> <li>- Age, diabetes, obesity, hypertension, and sleep apnea can all decrease testosterone levels</li> <li>- In RAAS system, increases renin levels, and tips the balance toward inflammation and vasoconstriction by activating ACE/Ang II/ATR-1 axis</li> <li>- Low testosterone levels have been associated with increased risk for ICU admission and death in COVID-19 patients, possibly by increasing IL-6 and further decreasing effective T-cell response</li> </ul>

ACE = angiotensin-converting enzyme; ATR = angiotensin II receptor; ICU = intensive care unit; IFN = interferon; IL = interleukin; NK = natural killer; RAAS = renin-angiotensin-aldosterone system; TLR = Toll-like receptor; TMPRSS = transmembrane protease serine; TNF = tumor necrosis factor.

males.<sup>28</sup> The natural aging process and the secondary effects of hypertension, obesity, and diabetes may cause the testosterone level to fall. In males, a lower testosterone level can shift the immune response toward an increased production of pro-inflammatory cytokines. Obese men may get a “double hit” as adipose cells convert testosterone to estrogens, predominantly estradiol, leading to the production of

more activated inflammatory cytokines. As the testes contain significant amounts of ACE-2 receptors, it has also been theorized that gonad function and testosterone production may be further impaired in males with SARS-CoV-2 infection (Ma L, Xie W, Li D, et al. Effect of SARS-CoV-2 infection upon male gonadal function: a single center-based study. <https://doi.org/10.1101/2020.03.21.20037267>. Submitted.).

A study of testosterone levels in admitted patients with COVID-19 found that more than half of men admitted to hospitals with active infection had evidence of hypogonadism (testosterone level of <300 ng/dL) and that the risk for ICU admission was inversely correlated with circulating levels (Schroeder M, Tuku B, Jarczak D, et al. The majority of male patients with COVID-19 present low testosterone levels on admission to intensive care in Hamburg, Germany: a retrospective cohort study. <https://doi.org/10.1101/2020.05.07.20073817>. Submitted.).<sup>32</sup> Some have recommended testosterone supplementation in infected, morbid men with a low serum testosterone level.<sup>32,33</sup>

### Biological Sex and the Maladaptive Immune Response

There has been speculation over the past few months that seriously ill patients with COVID-19 may be experiencing *cytokine storm*, a hyperactive immune response associated with an increased expression of inflammatory mediators such as interferons, tumor necrosis factor, and interleukins (ILs), leading to a hyperinflammatory state and end-organ damage.<sup>34</sup> This assumption has been challenged, given that blood levels of multiple inflammatory cytokines are significantly lower in some patients with severe COVID-19 compared to ill non-COVID ICU patients.<sup>35</sup> Perhaps it may be more accurate to describe patients with COVID-19 as having a “maladaptive immune response.”

Patients with COVID who become severely ill have different patterns of immune response: Severely ill women produce more pro-inflammatory cytokines, while severely ill men, especially if they are older, produce a lesser adaptive T-cell response.<sup>36</sup> About 14% of patients with severe COVID-19 may have either a maladaptive genetic variant for interferon or actual autoantibodies against interferon, obstructing its role in communicating with other immune cells.<sup>37,38</sup> Males reportedly are more likely to have these autoantibodies against interferon.<sup>38</sup> Males with severe disease may have a greater SARS-CoV-2 antibody response (Grzelak L, Velay A, Madec Y, et al. Sex differences in the decline of neutralizing antibodies. <https://doi.org/10.1101/2020.11.12.20230466>. Submitted.).<sup>39</sup> Importantly, this response may be short-lived, as antibody levels in males may fall more precipitously than do those in females

(Grzelak L, Velay A, Madec Y, et al. Sex differences in the decline of neutralizing antibodies. <https://doi.org/10.1101/2020.11.12.20230466>. Submitted.). These considerations become relevant in the identification of the ideal candidates for convalescent serum donation and the appropriate timing intervals for vaccine redosing.

### Biological Sex Differences in Clinical Manifestations and Laboratory Evaluation

Patients infected with SARS-CoV-2 have an asymptomatic incubation period of approximately 5 days and are at greatest risk for viral shedding in the 1–2 days prior to symptom development; symptomatic male and female patients with COVID-19 commonly experience cough, fever, shortness of breath, headaches, myalgias, vomiting, diarrhea, and abdominal pain.<sup>40</sup> Women report more initial symptoms of hyposmia, anosmia, and gustatory dysfunction than do men.<sup>7,41</sup> Cutaneous manifestations of COVID-19 include viral exanthem, urticaria, and papules; differences by sex have not been well studied.<sup>42</sup> Women may have a greater prevalence of the peculiar chilblain-like rash that has become better known as “COVID toes.”<sup>42,43</sup>

Neurologic symptoms are common and can range from mild headache and dizziness to encephalopathy, cerebral thrombosis, and neuropsychiatric disorders, with one study suggesting that 13% of hospitalized patients have significant new neurologic disorders with 2 days of admission.<sup>44</sup> Overall, in men, severe symptoms are more likely to develop, and men are at greater risk for hospitalization, ICU utilization, and death.<sup>45</sup>

With regard to laboratory testing, investigators from Brazil reported that both infected women and men had lower concentrations of platelets, basophils, eosinophils, and lymphocytes, and higher erythrocyte sedimentation rate, C-reactive protein (CRP),  $\gamma$ -glutamyl transferase, alanine aminotransferase, fibrinogen, and ferritin than did patients without COVID-19 (Ten-Caten F, Gonzalez-Dias P, Castro I, et al. In-depth analysis of laboratory parameters reveals the interplay between sex, age and systemic inflammation in individuals with COVID-19. doi:2020.08.07.20170043. Submitted.). Men had higher overall CRP, erythrocyte sedimentation rate, alanine and aspartate aminotransferase,  $\gamma$ -glutamyl transferase, ferritin, fibrinogen, lactate

dehydrogenase, and activated partial thromboplastin time versus in women, serum calcium and sodium concentrations were greater, and lactate dehydrogenase and activated partial thromboplastin time remained elevated throughout hospitalization (Ten-Caten F, Gonzalez-Dias P, Castro I, et al. In-depth analysis of laboratory parameters reveals the interplay between sex, age and systemic inflammation in individuals with COVID-19. doi: 2020.08.07.20170043. Submitted.). Markers of immune-mediated responses were more frequently observed to be elevated in patients with COVID-19 requiring ICU admission (Ten-Caten F, Gonzalez-Dias P, Castro I, et al. In-depth analysis of laboratory parameters reveals the interplay between sex, age and systemic inflammation in individuals with COVID-19. <https://doi.org/10.1101/2020.08.07.20170043>. Submitted.). Furthermore, IL-8 and IL-18 levels were increased in men with COVID-19, while CD8 T cells were increased in women.<sup>36</sup> For the clinician, in addition to hypoxia, biomarkers of vascular injury such as troponin (cardiac), IL-6 and CRP (inflammation), and D-dimer (coagulation) serve as predictors of prognosis in patients with COVID-19 (Ten-Caten F, Gonzalez-Dias P, Castro I, et al. In-depth analysis of laboratory parameters reveals the interplay between sex, age and systemic inflammation in individuals with COVID-19. <https://doi.org/10.1101/2020.08.07.20170043>. Submitted.).

### Biological Sex and Venous Thromboembolic Events

Venous thromboembolic events (VTEs) are common in COVID-19 and found to be associated with adverse outcomes.<sup>46</sup> In one study, ICU patients infected with SARS-CoV-2 had a 27% prevalence of VTEs and an almost 4% prevalence of arterial thrombosis.<sup>47</sup> In addition to being vulnerable to the conventional clotting risks of all immobilized, severely ill, hospitalized patients, sick patients with COVID-19 are at risk for immunothrombosis attributable to microangiopathic dysfunction from endothelial cell activation causing overexpression of prothrombotic and procoagulant molecules (eg, von Willebrand factor), and reduced anticoagulants (eg, antithrombin III, protein).<sup>48</sup> This exaggerated coagulopathic state leads to the formation of fibrin clots, and subsequently, as these clots start to dissolve, an elevated D-dimer. As a significantly elevated D-dimer has been associated

with disease severity, the use of a D-dimer may help in prognostication and in the early initiation of anticoagulation.<sup>46</sup> This immunothrombosis may not be unique to COVID-19 and may be associated with other viruses, such as H1N1 and Dengue fever.<sup>49</sup> Clotting issues may not develop early in the disease course. The PEPCOV study (Association Between Pulmonary Embolism and COVID-19 in Emergency Department Patients Undergoing Computed Tomography Pulmonary Angiogram),<sup>50</sup> conducted in 6 countries and 3253 patients, showed that the clotting risk in patients with SARS-CoV-2 infection in the emergency department was similar to the rate in noninfected patients, with both around 15%.

Concerning possible BSDs in VTE risk in patients with COVID-19, a meta-analysis of data from patients with severe disease showed no BSDs in D-dimer elevation.<sup>8</sup> With regard to the prevalence of clot, however, a meta-analysis of data from 33,970 patients (60.1% men) revealed that hospitalized men with COVID-19 were 1.5-fold more likely to experience a VTE compared to women.<sup>9</sup> Plus, a recent study from 6 emergency departments in New York, New York, that compared the percentage of patients with confirmed pulmonary emboli (PE) in April–May 2019 to the percentage during that same time period in 2020 found BSDs in PE prevalence.<sup>51</sup> The percentage of men with PE increased from 35% to 59%, and contrary to findings from the PEPCOV study, the overall PE rates doubled—34/446 in 2019 versus 87/464 in 2020—with 60% of patients testing positive for SARS-CoV-2 infection in 2020.<sup>51</sup>

Although the mechanism of these differences in clotting is unclear, testosterone may play a role, especially if it is being supplemented. A 2019 study showed that males receiving testosterone supplementation, regardless of whether they had documented hypogonadism, were at twice the normal risk for VTE.<sup>52</sup> This association may become particularly relevant if studies confirm a benefit of testosterone supplementation in severely ill male patients with COVID-19.

A different theory for potential BSDs in VTE risk was recently suggested by Garvin et al,<sup>53</sup> who used a supercomputer to analyze cell gene expression in bronchial lavages of patients with COVID-19 and found that the peptide thymosin- $\beta$ 4, which assists in fibrinolysis, appeared to have greater expression in cells in females. The gene encoding thymosin- $\beta$ 4 is located on the X chromosome and escapes X inactivation;



thymosin-β4 is already being studied for use in CVD, and as it down-regulates pro-inflammatory cytokines and chemokines, there is interest in using it in patients with COVID-19.<sup>53</sup>

**Biological Sex Differences in Cardiovascular Manifestations of COVID-19**

The previously noted “endothelial disease” and its associated widespread hyperinflammatory and coagulopathic pathology can lead to injury throughout the body.<sup>54</sup> This includes cardiac damage, cerebral thrombosis, and disruption of the endothelial barrier in the lungs. Patients with CVD are not at higher risk for infection; however, they are at higher risk for hospitalization and adverse outcomes.<sup>48</sup> Men have even worse endothelial pathology when infected with COVID-19 if they have underlying hypertension, obesity, and known CVD.<sup>55</sup>

Cardiac injury, defined as a troponin elevation in the >99th percentile, is associated with higher

mortality in patients with COVID-19 and is more commonly seen in men.<sup>56</sup> Elevated troponin increases the risk for malignant arrhythmias and heart failure. Acute respiratory distress syndrome (ARDS), acute kidney injury, and coagulopathy in patients with COVID-19.<sup>57</sup> SARS-CoV-2 binds to ACE-2 receptors on the myocardium, causing both overstimulation and dysregulation of the renin-angiotensin-aldosterone system (RAAS), contributing to vasoconstriction and a pro-inflammatory state.<sup>58</sup> RAAS changes are influenced by sex chromosomes and hormones because the tissue distribution of ACE-2 receptors differs between women and men (Table III).

Whether sexual dimorphisms in ACE-2 directly contribute to the sex-specific severity and mortality seen with COVID-19 remains unclear.<sup>48</sup> Further confounding matters is the complicated relationship between RAAS and the kinin-kallikrein system, with some suggesting that once RAAS is dysregulated it disrupts the delicate balance of bradykinin

Table III. Sex and gender difference in ACE-2, the binding site of the SARS-CoV-2 virus.<sup>19,48,58–62</sup>

General Population	Effects in Males	Effects in Females
Acts as the fulcrum of RAAS, separating the vasoconstrictive/pro-inflammatory axis from the vasodilatory/anti-inflammatory axis, by converting Ang II (which is vasoconstrictive when bound to ATR-1) into Ang (1–7) (which is vasodilatory when bound to Mas receptors);	Testosterone tips the balance of RAAS toward the (potentially cardiotoxic) vasoconstrictive/pro-inflammatory axis by increasing renin and activating the ACE/Ang II/ATR-1 axis;	Estrogen tips balance of RAAS toward the (cardioprotective) vasodilatory/anti-inflammatory axis by decreasing renin, increasing angiotensinogen, ACE, Ang I, aldosterone, and Ang (1–7) and enhancing binding at ATR and MasR (which are both vasodilatory);
Decreased ACE or ACE-2 levels can lead to excessive amounts of bradykinin and increased vascular permeability, as the RAAS and kinin–kallikrein systems are closely interwoven;	Testosterone enhances TMPRSS-2, a transmembrane protease, that aids viral bound ACE-2 into cells; Serum (unbound) ACE-2 levels are greater in males than females with congestive heart failure;	Gene for ACE-2 is encoded on X chromosome, allowing a second copy of gene in females;
ACE-2 expression is enhanced in smokers;	Significant amounts of ACE-2 in testes;	Progesterone competes with aldosterone for the mineralocorticoid receptor;
Children may have decreased ACE-2 expression in nasal mucosa	ADAM-17 (which cleaves ACE-2 from cell membranes, leading to increased plasma ACE-2 levels) is increased in testes	

ACE = angiotensin-converting enzyme; ADAM-17 = ADAM metallopeptidase domain 17; Ang = angiotensin; ATR = angiotensin II receptor; MasR = Mas receptor; RAAS = renin-angiotensin-aldosterone system; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; TMPRSS = transmembrane serine protease.

production/degradation, leading to excessive bradykinin levels and vascular leakage and inflammation.<sup>53</sup> SARS-CoV-2 infection also leads to an imbalance in T-cell activation, increasing IL-6 and other pro-inflammatory markers in the myocardium. On serial assessments, troponin elevations have been found to be correlated directly with IL-6 elevations in patients with COVID-19.<sup>59</sup>

The cause of cardiac injury is uncertain and can occur in the absence of obstructive coronary artery disease. Proposed mechanisms include direct virus invasion leading to extensive inflammation (eg, myocarditis), or a secondary myocardial stress resulting from extensive lung injury, or a consequence of the maladaptive immune response.<sup>48</sup> Cardiac complications usually occur 2 weeks after infection, lending support for the maladaptive immune response mechanism, as peak windows of viral invasion have already passed—this window is important to know for the clinician assessing these patients and in seeking evidence of myocardial injury when patients with COVID-19 present with chest pain.<sup>48</sup> Data from a few case reports do not support a diagnosis of myocarditis on endomyocardial biopsy, thus raising the possibility of additional mechanisms, such as microvascular dysfunction, takotsubo, arrhythmias, or tamponade, with COVID-19.<sup>60,61</sup>

An increased prevalence of takotsubo or stress cardiomyopathy has been reported with COVID-19.<sup>62</sup> Although takotsubo is generally much more common in women, there has not been a sex difference in prevalence among patients with COVID-19.<sup>62</sup> SARS-CoV-2 affects macrophages that are involved with the conducting cells of the AV node which express ACE-2, precipitating arrhythmias including atrial fibrillation, sinus tachycardia, complete heart block, and cardiac arrest; to date, no sex differences have been found in the prevalence of arrhythmias.<sup>48</sup> However, most antiviral therapies have a QTc-prolonging effect that needs to be monitored as women in particular are at higher risk for drug-induced QTc prolongation than men.<sup>48</sup>

### Biological Sex and Pulmonary Manifestations of COVID-19

SARS-CoV-2 binds to ACE-2 receptors on the epithelial cells of the pulmonary vasculature, inducing a vigorous immune response, edema, and respiratory failure, and patients with obesity are at significantly

increased risk for lung damage and severe disease because of chronic inflammation, dysregulated immune response, and respiratory compromise (from atelectasis, decreased lung compliance, hypoventilation, and reduced chest wall compliance).<sup>63</sup> This amplified inflammatory response can lead to abnormal pulmonary perfusion, impaired fibrinolysis, and an increased risk for other comorbid conditions.<sup>63</sup> The pro-inflammatory effects of obesity can be augmented in obese men, whose testosterone levels are often lower and estrogen levels higher than those in nonobese men.<sup>63</sup> In addition, ACE-2 expression is also increased in adipose tissues, which can act as a major reservoir of pro-inflammatory markers, including IL-1 and IL-6.<sup>64</sup> In females, estrogen may provide protection by helping to shift the RAAS pathway toward activation of angiotensin (1–7) through the Mas receptor, which protects the endothelial barrier in acute lung injury, and by increasing nitric oxide release and decreasing platelet aggregation.<sup>65</sup>

There are known sex-based differences in lung physiology, including airway caliber, accessory muscle mechanics, lung volumes, diaphragmatic excursion, and abdominal fat distribution.<sup>66</sup> These differences may affect the management of patients with severe COVID-19. For example, older data suggest that males with ARDS are at greater risk for ventilation-associated pneumonia after intubation.<sup>67</sup> More recent research has suggested that testosterone replacement may help men with severe chronic obstructive pulmonary disease, possibly via an anti-catabolic effect on the respiratory muscles.<sup>68</sup> Conversely, a 2019 study found that in patients intubated for ARDS, 74% of males versus only 50% of females received ventilation at appropriate lung-protective, low-volume settings.<sup>69</sup> Shorter women appeared to be at particular risk for being placed on ventilation at unnecessarily high volumes, underscoring the importance of using height to estimate ideal body weight when setting ventilator parameters.<sup>70</sup>

During the initial stages of the pandemic, it was common practice to intubate mildly hypoxic patients, even if they clinically appeared otherwise well; however, as this practice did not appear to benefit many patients, strategies to help avert early intubation have become increasingly popular.<sup>71</sup> Previous research on ARDS has shown that proning intubated patients can significantly decrease mortality.<sup>72,73</sup> A meta-analysis of data on proning spontaneous-breathing patients with COVID-19

suggested an improvement in oxygenation and likely a decreased need for subsequent intubation.<sup>71</sup> The physiologic advantage of proning appears to be an overall improvement in ventilation/perfusion matching that can enhance oxygenation.<sup>74</sup> Data are scarce on whether proning equally benefits males and females. In the 2017 meta-analysis of data from >2100 proned, mechanically ventilated patients with ARDS, outcomes data were not sex-disaggregated, and published data on proned patients with COVID-19 are thus far limited.<sup>71,73,75</sup>

Although there are S/G differences in the need for ICU admission, once in a unit there are no S/G differences in mortality, as shown by a recent global meta-analysis involving data from >16,000 patients with COVID-19.<sup>76</sup> A total of 69% of ICU-admitted patients were male, there were no S/G differences in ICU mortality, ~68% of patients overall required intubation, and 28% died.<sup>76</sup>

### Long Haulers: Patients With COVID-19 and Persistent Symptoms

“Long-haulers” are individuals who have had SARS-CoV-2 infection and experience lingering symptoms beyond what is typical of most viral illnesses.<sup>77</sup> The prevalence of long-haulers is variable. A report in the *British Medical Journal* estimated that ~10% of infected patients go on to have residual symptoms, while a Centers for Disease Control and Prevention–administered phone survey involving ~274 symptomatic, nonhospitalized patients with SARS-CoV-2 infection found that 35% still reported symptoms 2–3 weeks after testing positive.<sup>78,79</sup>

The pathophysiology leading to symptoms in long-haulers is poorly understood. Theories include a hidden persistent reservoir of virus that intermittently sheds, immune reactions to residual viral particles, a hyperactive inflammatory response involving bradykinin with increased endothelial permeability, and an autoimmune response.<sup>53,80,81</sup> Long-haulers can have a myriad of different symptoms, including dysautonomia, myalgic encephalomyelitis, severe fatigue, difficulty sleeping, headache, anxiety, and shortness of breath, despite normal oxygen levels.<sup>80</sup>

Unfortunately, several factors complicate the study of long-haul patients, most importantly the challenges of confirming previous SARS-CoV-2 infection. Many long-haulers are not tested during the initial illness due to test scarcity or because they were not sick

enough to require hospitalization. In addition, many patients may lack evidence of residual elevated antibody concentrations.<sup>82</sup> The absence of reliably persistent markers of previous infection make it particularly difficult to distinguish those with previous exposure/falling concentrations or false-negative tests from those with unrelated conditions.

Although the current identification and understanding of potential S/G differences in long-haulers are still in their infancy, women appear to be at much greater risk for persistent symptoms (Sudre CH, Murray B, Varsavsky T. et al. Attributes and predictors of long-COVID: analysis of COVID cases and their symptoms collected by the COVID Symptoms Study app. <https://doi.org/10.1101/2020.10.19.20214494>. Submitted).<sup>80</sup> As many of the long-haul syndromes overlap with those associated with myalgic encephalomyelitis/chronic fatigue syndrome or fibromyalgia syndromes, there has been growing research interest in this potential connection.<sup>80</sup> Historically, myalgic encephalomyelitis affects a greater number of women (3:1 ratio), frequently develops after an infectious exposure, and has defied straightforward objective diagnoses.<sup>83</sup> BSDs in myalgic encephalomyelitis/long-haul symptomatology may likely be amplified by BSDs in pain physiology and nociception.<sup>84</sup> Due to an increasing prevalence of long-haulers, more hospital systems are developing post-COVID clinics.<sup>80</sup> Hopefully, these clinics will drive research to better define the prevalence, physiology, and treatment options in these patients.

### Biological Sex Differences in Drug Therapies for COVID-19

Known BSDs in the immune response to new antigens such as SARS-CoV-2, along with documented BSDs in pharmacokinetics and adverse drug reactions, have the potential to lead to BSDs in the efficacy and adverse effects of medications used for treating COVID-19.<sup>85,86</sup> The paucity or absence of sex-disaggregated data to compare benefits or adverse effects of novel COVID-19 treatments creates major knowledge gaps that will continue to widen and affect the lives of both women and men as the pandemic continues.

### The Influence of Gender on COVID-19

Socially constructed roles and expectations may influence the COVID-19 pandemic in many important ways. Specifically, gendered behaviors, occupations,

and habits are likely to affect disease risks and outcomes. For instance, men are more likely to use nicotine,<sup>87</sup> women are more likely to seek out medical care, and older women are more likely to live alone and experience social isolation.<sup>88</sup> There also appear to be gender differences in risk tolerance: A study in US men found that they were more likely to downplay the potential risk of the virus and are less likely than women to report avoiding large public gatherings or close physical contact with those outside the home.<sup>89</sup> Similar patterns of gender-based public health choices were apparent when hand-washing and mask-wearing are examined; one study demonstrated that women were 50% more likely to wear a mask than were men (Haischer M, Beilfuss R, Hart M, Opielinski L, Wrucke D, Zirgaitis G et al. Who is wearing a mask? Sex-, age-, and location-related differences during the COVID-19 pandemic. <https://doi.org/10.1101/2020.07.13.20152736v3>. Submitted.). Age can be an additional modifier; for example, older men may perceive their risk for COVID-19 to be higher than do younger men, yet be less willing to commit to behavioral changes and to engage in preventive measures such as hand-washing.<sup>90</sup> Messaging targeted to improving compliance with public health measures must consider that the values and motivators of different groups may be deeply affected by gender identities and other sociocultural characteristics.<sup>91</sup>

Worldwide, gender influences occupational trends and can greatly affect susceptibility to COVID-19; for instance, in the United States, over 75% of health care workers are women, and women are more likely to be defined as “essential workers.”<sup>92</sup> Men are more likely to be employed in jobs that are associated with a greater risk for death from COVID-19, such as food processing, transportation, delivery, warehousing, construction, and manufacturing.<sup>93</sup>

Gender relations and positive and negative externalities must be considered when governments formulate policies. For example, stay-at-home orders may put individuals at increased risk for domestic violence, and early research has demonstrated that the prevalence and severity of physical intimate-partner violence has significantly escalated during the pandemic in the United States and worldwide.<sup>94</sup>

## CONCLUSIONS

The evidence presented here underscores the critical importance of including S/G variables in future

COVID-19—related research to ensure that care is optimized in all patients infected with SARS-CoV-2. Mitigation of the S/G-based outcomes that result from health disparities requires a multipronged approach. There must be gender equity in leadership positions, ensuring that sex and gender are considered *de facto* as variables for inclusion and analysis in scientific research, policymaking, and task-force initiatives.<sup>95</sup>

## DISCLOSURES

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**APPENDIX 1****Definitions**

*Biological sex* refers to an individual's innate combination of sex chromosomes and hormones and is usually binary-male versus female whereas *Gender* refers to a social construct that is heavily influenced by societal roles and expectations and occurs along a spectrum bracketed by “man” and “woman”.<sup>9</sup> When a clinically important medical outcome is noted to differ between men, women, and non-binary individuals (MWN), it is helpful to determine if that difference is rooted in biological sex or gender identity. In reality, this can often be quite difficult. Gender influences start before birth (i.e. gender reveal parties or sex-selective abortions) and gendered experiences can affect exposure rates to different toxins and pathogens. In addition, even if MWN are exposed to the same infection or carcinogen, their physiological response may be quite different due to biological sex-based differences (BSD) in epigenetics that influence which genes are expressed in response to the trigger. Rather than thinking of sex and gender as two distinct entities separated by a vertical line, it is more helpful to consider them as being part of a circle that is continuously looping.