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Sex and gender differences in COVID-19: a narrative review

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Summary. The coronavirus disease 19 (COVID-19) pandemic is a major challenge for all healthcare systems, as well as for social stability and the economy. The clinical spectrum of COVID-19 is: asymptomatic; mild to moderate; severe; and critical disease, leading to different fatality rates. Although countless studies have been published to better understand the pathophysiology of this infectious disease, the mechanisms of action of the virus, and the immunological responses, further research is needed to unravel the precise host factors determining COVID-19 susceptibility and severity. A considerable interest from the media and the general public has focused on the disproportionately high COVID-19-related mortality in men. This sex discrepancy may be attributed to biological, genetic and lifestyle differences between males and females, since sex is one of the variables affecting innate and adaptive immune responses, resulting in sex-specific outcomes in patients with infectious and autoimmune disorders. Therefore, in this paper we will review the available data on sex- and gender-related differences in COVID-19 susceptibility and severity.

Keywords. Sex, gender, SARS-CoV-2, COVID-19, genetics, immune response, hormones, risk factor, morbidity, mortality.

Introduction

The World Health Organization (WHO) have reported approximately 300 million cases of confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and 5.7 million deaths from coronavirus disease 19 (COVID-19).[1] The pandemic has had a catastrophic effect on society, healthcare systems and the economy, and still represents a major challenge as a fourth wave is now involving many Countries, despite the availability of a vast array of effective vaccines. The clinical spectrum of COVID-19 ranges from asymptomatic to critical, going through mild to moderate and severe, with a fatality rate between 1 and 10%. Most disparities seem related to the variable size of the denominators, including the number of subjects tested, demographics, ethnicity, organization of healthcare systems and viral variants.[2] Although numerous studies have been published to better understand the pathophysiology of this infectious disease, the mechanisms of action of the virus and the immunological responses, further research is needed to unravel the precise host factors determining COVID-19 susceptibility and severity. According to emerging evidence, the most commonly described risk factors are older age, comorbidities (eg., chronic lung disease, cardiovascular disease, hypertension, diabetes, obesity and cancer), and ethnicity.[3,4] Moreover, a considerable interest from the media and the general public has focused on the disproportionately high COVID-19-related mortality in men. This discrepancy may be due to biological, genetic and lifestyle differences between the sexes, making men more vulnerable to both infections and non-communicable diseases.[5] Villani et al. reported both higher crude mortality rates (CMR) and case fatality rates (CFR) in males than females during the COVID-19 pandemic in Italy, this data being confirmed for all age groups.[6] A meta-analysis of over 3 million reported global cases demonstrated that, although no difference can be seen in the proportion of males and females with confirmed COVID-19, men are almost three times more likely to require intensive treatment unit (ITU) admission (odd ratio - OR, 2.84; 95% CI, 2.06-3.92) and higher odds of death (OR, 1.39; 95% CI, 1.31-1.47) than women.[7] The authors of this paper, however, used the term 'anecdotal' to describe currently available data on sex-differences in COVID-19, as sex is still not routinely reported in all available regional and national data.[7] In addition, 'sex' and 'gender' are frequently used interchangeably, in both literature and clinical practice. On the contrary, the sex of an individual is defined by a differential organization of chromosomes, reproductive organs, and sex steroid levels. Hence, it is distinct from gender, which includes behaviors and activities that in humans are determined by society or culture. Therefore, gender differences are separate from – but complementary to – biological sex differences.[8] Male and female differences in immunological responses, disease prevalence and severity, as well as morbidity and mortality may be influenced by both sex and gender, with sex contributing to the physiological and anatomical differences that affect the exposure, recognition, clearance, and even the transmission of microorganisms. By contrast, gender may reflect behaviors that affect the exposure to microorganisms and the access to healthcare or health

seeking behaviors that may have an impact on the course of the infection.[9] Therefore, the aim of this article is to review the available data on sex- and gender-related differences in COVID-19 susceptibility and severity.

Sex- and gender-related differences in pathophysiology

There are several underlying differences between the physiological functions of males and females. This aspect denotes a different incidence and severity of the most common and major diseases, such as cardiovascular, musculoskeletal and immune disorders up to lifespan regulation.[10,11] For example, 80% of patients with osteoporosis are women and, similarly, about 80% of patients suffering from autoimmune diseases are females, while cardiovascular diseases occur at least a decade earlier in men than women.[12] The term "gender health paradox" has been coined to denote the evidence that, in general, men have a lower life expectancy than women, but women spend their extra years with higher levels of illness.[13] Globally, men's life expectancy is 5.1 years lower than women's,[6] despite the establishment of focused Men's Health charities and equality legislation, namely the Equality Act.[14]

In addition to physiological variables, the use of healthcare services by men is a further contributing factor to gender-related differences. Women use primary care services more frequently than men, but increased hospital admissions in men have been reported,[15] with crude consultation rate being 32% lower in men than in women, with the greatest sex gap in primary care consultations among subjects between 16 and 60 years.[16] In the case of COVID-19, the data collected revealed that the associated gap between men's and women's recorded case and death rates from COVID-19 are larger than expected in countries where women's rights are less protected and women do not have access to personal finance and education.[17] In such extreme healthcare-related settings, women cannot afford testing and hospitalization, and need to rely on their relatives' benevolence for help; this, in turn, may result in underreported female cases and deaths from COVID-19.[17] Biological and genetic mechanisms have been reported to contribute to the disproportionate male mortality from COVID-19. In particular, immunological defense and immune responses, genetics, and hormones have been suggested as major factors in sex-related differences in COVID-19.

Immunology

The mortality rate associated with viral infections is generally higher in men than in women, with such discrepancy being attributable to differences in the immunological responses of the two sexes. In particular, sex-related differences exist in both the innate and adaptive immune response.[18] As is well known, interferon-α (IFNα) is required for the immunological defense against viral infections, in which it acts via the activation of dendritic cells, the stimulation of IFNα and the activation of both CD8*T cells and natural killers.[19] A sex-dependent pathway has been identified, which induces IFNα, while the production of IFNα by peripheral blood leukocytes is higher in women than in men after stimulation.[19] Sex differences in both the innate and adaptive immune system have been previously reported, and may account for the female advantage in COVID-19. Within the adaptive immune system, females have higher numbers of CD4+ T cells, a more robust CD8+ T cell cytotoxic activity and an increased B cell production of immunoglobulin than males.[9] Other data suggests that females produce a greater humoral response to viral infections than males, a conclusion supported by vaccination studies, where higher antibody responses to influenza vaccination have been reported.[20] In COVID-19 patients with severe disease, females exhibited higher antibody response than males, with antibodies also appearing at the earlier phases of the disease. These results were also consistent with other studies describing higher antibody levels (including more functional antibodies) in adult females compared to adult males.[21] However, other studies reported conflicting results and, in particular, in COVID-19 convalescent plasma donors, increased antibody responses across the serological assays were found in males.[22] In our studies, we did not observe any sex-related difference in antibody levels and kinetics, both in the natural infection and after vaccination,[23,24] while some sex-related differences in humoral response seem to be due to confounding variables, namely smoking habits. According to Nomura et al., in particular, the most important factors associated with low antibody titer six months after the second dose of the mRNA-based BNT162b2 COVID-19 vaccine were age and smoking, though the latter was the most important factor that could be avoided in order to maintain a higher antibody titer.[25] Moreover, systematic reviews and meta-analyses highlighted substantial evidence gaps in COVID-19 vaccine research, although some studies failed to find significant differences in the efficacy of vaccines, especially in younger populations.[26,27] Of the 75 clinical trials on COVID-19 vaccines evaluated in a recently published systematic review, only 24% presented their main outcome data disaggregated by sex, and only 13% included any discussion on the implication of the study for women and men.[28] A systematic review and meta-analysis found lower vaccination intentions among women than men, with an OR of 1.41 (95% CI, 1.28-1.55). Subgroup analyses revealed that gender effects were even higher among healthcare workers compared with unspecific populations.[29] Interestingly, Cavaleri re-

ported that, during this ongoing pandemic, large clinical trials aimed at supporting the approval of vaccines and therapeutics included women to an adequate extent.[30] In actual fact, however, the emergent cases of thrombosis with thrombocytopenia with the two approved viral vectored vaccines were more frequently reported in females than males, stressing the need to further characterize the incidence of this risk by age and gender. Ughi et al. reported an association between the development of non-serious adverse events with young age, low body mass index (BMI), previous history of SARS-CoV-2 infection and female gender. In particular, female gender and previous SARS-CoV-2 infection were independently associated with the risk of developing suspected adverse events.[31] Once again, these findings emphasize the inadequate reporting of sex and gender dimensions in clinical research, including COVID-19.

Genetics

Genetic differences between males and females are well recognized, and a body of evidence has been collected even in COVID-19, starting from the X chromosome. Multiple genes playing an essential role in both the innate and adaptive immune response to viral infections are located on the X chromosome. The gene encoding the angiotensin converting enzyme 2 (*ACE2*), i.e., the main SARS-CoV-2 receptor, is located on chromosome X region p22 and may be over-expressed in females.[12] SARS-CoV-2 binds to ACE2 as a cell entry receptor via the receptor binding domain (RBD) of the viral spike protein (S-protein). It has been discussed whether a high *ACE2* expression poses a risk of severe disease, as more receptors are available for virus entry, or if it may instead be protective. In COVID-19, a reduction in the components of the alternative renin-angiotensin system (RAS axis), including ACE2 and angiotensin,[1-7] has been reported by Viera et al.[32] Consequently, increased inflammation, thrombosis and angiogenesis may occur in patients infected with SARS-CoV-2, thus requiring further research on interactions of the RAS and COVID-19, mainly in the context of novel vaccines and proposed medications.

Another study reported higher serum ACE2 levels in men than in women with heart failure, leading the authors to postulate that the increased concentrations of serum ACE2 may contribute to explain the sex discrepancies seen in COVID-19.[33] However, no further studies confirmed this hypothesis. The lung expression of the *ACE2* gene decreases with age, prevalently in men.[34] This aspect, together with a potential double expression of the *ACE2* gene in women, could explain the higher COVID-19 pulmonary mortality and morbidity in elderly men. Therefore, expression patterns of the cellular ACE2 enzyme and *ACE2* gene expression and/or polymorphisms may influence both the susceptibility and outcome of COVID-19 disease. In particular, an ACE2 variant (rs190509934:C) has been found to reduce the risk of SARS-CoV-2 infection, but not the severity of the disease.[35]

Transmembrane serine protease 2 (*TMPRSS2*), located on chromosome 21 region 21q-22.3, is another important gene in SARS-CoV-2 biology. This gene encodes the transmembrane serine protease 2, involved in the entry of coronaviruses, including SARS-CoV-2, into host cells, by catalyzing the cleavage of the two subunits (S1/S2) within the S-protein.[4] *TRMPRSS2* expression is regulated by androgens and promoted through androgen receptor. Significantly lower levels of TRMPRSS2 transcripts have been reported in men with castrated testosterone levels secondary to treatment with either estradiol or the luteinizing hormone (LH)-releasing hormone agonist leuprolide, compared to untreated subjects.[4] Since first- or second-generation androgen-deprivation therapies (ADTs) decrease TMPRSS2 levels, and although cancer patients have an increased risk of SARS-CoV-2 infection compared with non-cancer patients, prostate cancer patients receiving ADT appear to be partially protected from SARS-CoV-2 infection.[36] A further US study, which included 58 patients with prostate cancer and SARS-CoV-2 infection, revealed that ADT was associated with lower rates of hospitalization and oxygen requirement, thus suggesting that ADT may limit severe COVID-19 complications.[37] Genetic factors have been reported to influence also the geographical spread of COVID-19. A common 1245 A→C missense-encoding single nucleotide polymorphism in 3β-hydroxysteroid dehydrogenase isoenzyme-1 (HSD3B1) has been found to alter androgen physiology and accelerate the development of castration-resistant disease.[4] As previously reported, this may influence the susceptibility to – and development of – severe COVID-19 in males; notably, this polymorphism is mainly found in the Italian and Spanish populations.[38] Genome-wide association (GWAS) and whole-exome sequencing (WES) studies are being increasingly conducted to identify host genetic factors associated with the course of SARS-CoV2 infection. In particular, researchers have recently identified two genomic regions that encompass the genes involved in type I IFN antiviral immunity. Inborn errors of immunity (IEIs), in fact, may favor the development of more severe and potentially lethal forms of COVID-19.[39] Nakanishi et al. reported the results of a meta-analysis on the association between a common genetic risk locus (chromosome 3 locus tagged by rs10490770);[40] this major common COVID-19 genetic risk factor was found to be associated with increased risks of morbidity and mortality, which are more pronounced among individuals aged 60 years or younger. However, they did not evaluate sex-related differences, once again highlighting the scarce consideration of sex as a fundamental variable, not only in 'old', but also in recent research.[40] A recently published

review on host genetic factors determining the susceptibility and severity of COVID-19 has collected the available data on polygenic risk scores (PRSs) related to COVID-19, which should then provide important public health advice during the pandemic, by facilitating the identification of high-risk individuals and populations. Even this review, however, underlines the scarce concern assigned to sex-related issues, because only a few studies have disaggregated data considering gender as an independent variable.[41]

Endocrine factors

Androgens have been postulated to contribute to the severity of COVID-19 infection, by providing one of the mechanisms by which men are more likely to become severely ill. As previously discussed, androgen-deprivation therapies (ADTs) were found to decrease the expression of TMPRSS2, thus lowering the vulnerability to SARS-CoV-2 infection. The production of cytokines and chemokines by innate immune cells also differs between sexes. Activation of toll-like receptor 9 (TLR9) with viral or synthetic ligands in peripheral blood mononuclear cells (PBMCs), collected from human males, is associated with a greater interleukin-10 (IL-10) production, which in turn is positively correlated with androgen concentration in males.[9] Androgens, including dihydrotestosterone (DHT) and testosterone, are present at higher concentrations in post-pubertal men than women, and generally suppress immune cell activity, while *in vivo* exposure to testosterone reduces natural killer (NK) cell activity. In addition, testosterone and dihydrotestosterone (DHT) increase the synthesis of IL-10 and the transforming growth factor-β (TGFβ), thus triggering anti-inflammatory responses via androgen receptor signaling.[9] In COVID-19, the observed effect of testosterone in reducing the number of CD8*T cells provides further evidence on the role of androgens in sex-related differences in morbidity and mortality. However, the role of androgens remains controversial, while its anti-inflammatory action should be considered as beneficial. The role of estrogens is another interesting issue. Experimental data in urine studies showed that male mice are at higher risk of SARS-CoV-2-related mortality than female mice (90% versus 20%).[5] In addition, ovariectomy or treating female mice with an estrogen receptor antagonist increased mortality, indicating a protective effect of estrogen receptor signaling in SARS-CoV-2 infected mice. The authors' conclusions were that "taken together, these data suggest that sex differences in the susceptibility to SARS-CoV-2 in mice parallel those observed in patients, and also identify estrogen receptor signaling as critical for protection in females".[42] Estrogens, therefore, may confer a protective effect against SARS-CoV-2, though further studies are needed to evaluate the clinical outcomes in patients undergoing hormone therapies, both women taking estrogen receptor antagonists and men taking exogenous estrogens. Evidence suggests that 17β-estradiol regulates many aspects of the innate and the adaptive immune systems, including stimulation of pro-inflammatory cytokines, increasing neutrophil value and promoting the differentiation of bone marrow precursor cells and monocytes into dendritic cells.[43] Moreover, androgens have been observed to increase IL-10 levels, which expresses anti-inflammatory properties, therefore limiting the host immune response to pathogens. Furthermore, testosterone has been observed to reduce the number of circulating $CD8^+$ T cells.[5]

Collectively, these data highlight the fact that sex differences in hormones may result in altered immunological responses which, in turn, might also account for sex differences in COVID-19 susceptibility, disease severity and clinical outcomes.

Conclusions

Sex differences in the prevalence and outcomes of infectious diseases occur at all ages, with an overall higher burden of bacterial, viral, fungal and parasitic infections in human males.[9] Previous coronavirus outbreaks demonstrated the same sex bias. For example, the Hong Kong SARS-CoV-1 epidemic showed an age-adjusted mortality risk ratio of 1.62 (95% CI, 1.21-2.16) in males.[44] The Saudi Arabian MERS outbreak in 2013-2014 was associated with a case fatality rate of 52% in men, but was nearly half in women (i.e., 23%).[45] This data suggests that while socio-economic factors may be influencing some aspects of the coronavirus outbreaks, important differences in immune response between males and females are likely to be driving factors behind the significant sex bias observed during this COVID-19 pandemic. Sex differences in the innate and adaptive immune system have been previously reported, and may account for the female advantage in COVID-19. Females have higher number of CD4+T cells, more robust CD8+T cell cytotoxic activity, and an increased B cell production of immunoglobulin compared to males.[7] Females, therefore, have an increased capacity to mount humoral immune responses than males. They produce more type 1 IFN, a potent anti-viral cytokine, upon toll-like receptor 7 sensing of viral RNA than males, which is important for an early response in COVID-19. The increased production of IFN in females is associated with both the sex hormone concentration and the number of X chromosomes.[46] Therefore, the complex interplay between genetics, hormones and immune system may explain the sex-related differences in susceptibility and severity of COVID-19, as shown in Figure 1. However, further research would be needed, since the current evidence indicates

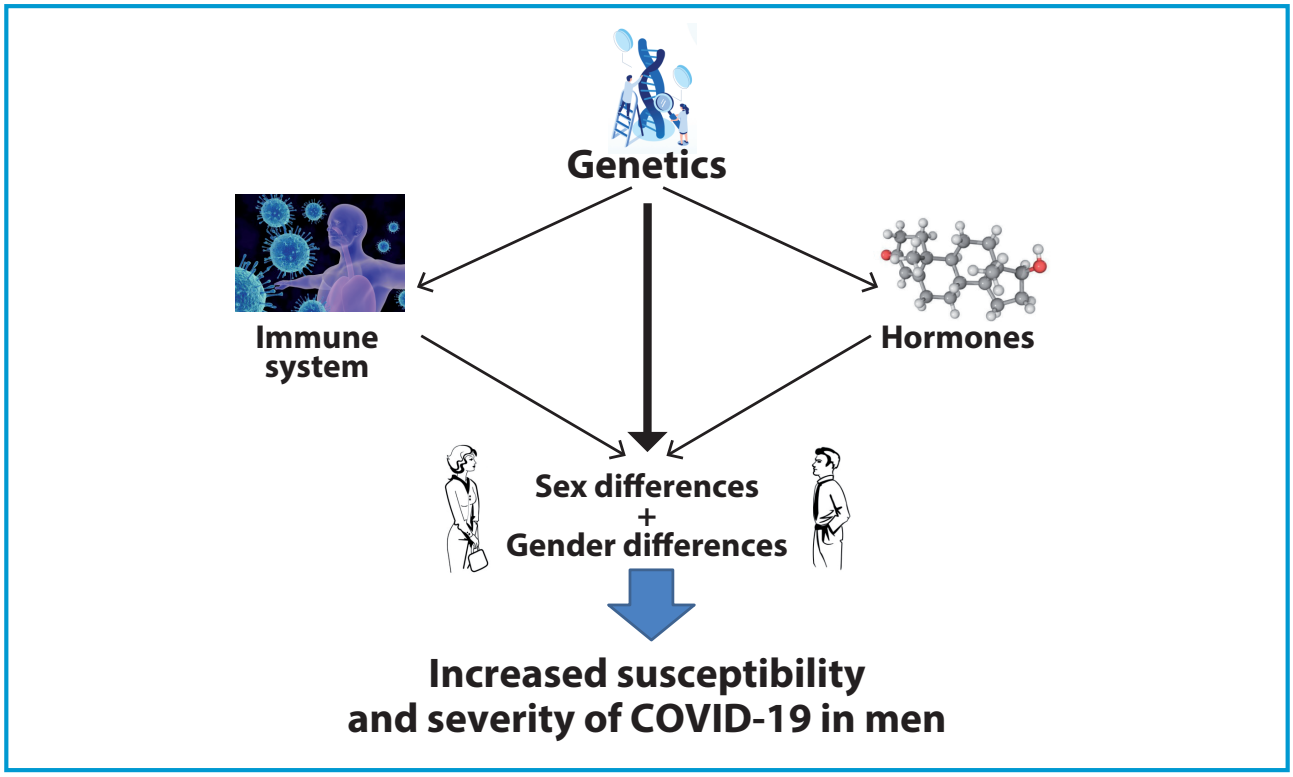

Figure 1. The interplay between genetics, immune system, hormones and gender differences in COVID-19.

that only a few studies have been planned, or possess disaggregated data to evaluate sex-related differences. Gender-based socio-cultural and behavioral differences could contribute to the sex difference seen in COVID-19 severity. Men are more likely to smoke, although smoking has not emerged as a clear risk factor for progression towards severe disease.[47] Men are less likely to wash their hands with soap after entering a restroom and, in many cultures, men may be more likely to leave the house and enter crowded areas.[48] Unequal access to healthcare and testing between sexes may cause a deviation towards a male bias in infection rates. The data, however, shows no difference in the numbers of infected cases between sexes overall, so much so that gender differences in hygiene behaviors and testing are unlikely to completely explain the sex disparity in disease severity. Regional gender differences in health-seeking behaviors and access to care may predispose men towards an earlier access to hospital and ITU admission.[6] The Gender Impact Assessment (GIA) highlighted inequalities in accessing the vaccination campaign for informal caregivers and healthcare workers outside hospitals versus hospital-based healthcare professionals, thus offering new information about the current knowledge gaps.[49]

In conclusion, male sex has been identified as a risk factor for both morbidity and mortality in COVID-19, and this finding has important implications in the clinical and social management of both the disease and the pandemic. This gender disparity has also been attributed to a historic failure to invest in male health.[5] However, the lack of adjustment for different variables in many studies limits our capability to accurately predict the role of sex in disease severity and, even more importantly, to better unravel the complex interplay of genetic, hormonal and immunological variables underlying sex-related differences.

Key messages

- Male sex is a risk factor for both morbidity and mortality in COVID-19.
- Sex differences in both innate and adaptive immune responses may account for the female advantage in COVID-19.
- However, the complex interplay between genetics, hormones and immune system may better explain the sex-related differences in susceptibility and severity of COVID-19.
- Gender-based socio-cultural and behavioral differences could contribute to the sex-difference observed in COVID-19 severity.
- Further research is needed as only a few studies have been planned, or possess disaggregate data to evaluate sex-related differences.

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