



# Sex hormones, autoimmunity and gender disparity in COVID-19

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## Abstract

The Coronavirus disease 2019 (COVID-19) pandemic has majorly contributed to massive and widespread mortality. Epidemiological data strongly indicates a sex-based disparity in COVID-19 clinical outcomes, with women having lower infection and hospitalisation rates, coupled with better prognosis and lesser mortality. This disparity may be explained by several mechanisms including differences in innate and adaptive immune responses, genetic factors, and an interplay between sex hormones and immune effectors, as well as gender-specific behaviour differences. These pathways, particularly the immunological divergence in response to viral infection, could potentially influence not only COVID-19 pathogenesis and disease course, but also the response to antiviral drugs and vaccines. Furthermore, factors that confer a protective advantage against COVID-19 may be exploited to develop therapeutic strategies to improve clinical outcomes in COVID-19.

**Keywords** COVID-19 · Coronavirus · Gender bias · Sex differences · Clinical outcomes

## Introduction

The Coronavirus disease 2019 (COVID-19) pandemic continues to be a significant cause of morbidity and mortality worldwide in the second year following its inception. Initial demographic accounts from Wuhan, China that indicated a higher mortality in men as compared to women, were further corroborated by numerous epidemiological studies that reported sex-based disparities in disease severity and clinical outcomes of COVID-19 [1].

The Chinese Centre for Disease Control and prevention reported the ratio of male to female COVID-19 infections as 2.7:1, and a Case Fatality Rate (CFR) of 2.8% in males as compared to 1.7% in females, calculated from a group of 72,314 patients in China [2, 3]. This was further supported by the Global Health 50/50 sex-disaggregated data, which indicated 14 male deaths for every 10 female deaths resulting from COVID-19. Epidemiological studies from 38 countries reported a mean CFR in males that was 1.7 times higher than the mean CFR in females, with advancing age being a risk factor for mortality in both sexes [4, 5]. European studies reported greater case fatality rates in males above 20 years, with a cohort study involving 17 million adults in England indicating a significant correlation between male sex and risk of COVID-19-associated mortality, with a hazard ratio of 1.59 [4]. In conclusion, current epidemiological evidence suggests a bias towards males regarding greater susceptibility to both SARS-CoV-2 infection as well as to severe COVID-19 clinical outcomes. While this is concerning, it is unsurprising as similar sex-based disparities were previously also observed in the Severe Acute Respiratory (SARS) and Middle East Respiratory Syndrome (MERS) epidemics [6, 7]. The European League against Rheumatism (EULAR) COVID-19 registry which collected data on COVID-19 in people with rheumatic diseases (RDs) stands out as an exception, with 4018 (65%) of a total 6155 patients with COVID-19 being female. However, since an increased

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incidence of RDs is well-documented in women, this could plausibly bias the sample population, leading to greater COVID-19 being observed in women with RDs, as opposed to a sample from the general population [8]. Furthermore, as per the data from this study, being a male over 65 was identified as the single most important risk factor COVID-19 hospitalisation in people with inflammatory rheumatic and musculoskeletal diseases (RMDs) [9].

A physiological basis for an inherent protective effect against COVID-19 disease severity in females may potentially be exploited to develop a therapeutic intervention for better management of COVID-19. This review investigates the sex-based differences in genetics, behaviour, hormones, and the immune response to suggest a plausible explanation for the gender-based disparity evident in COVID-19 clinical outcomes and mortality [10].

### Search strategy

A literature review was conducted as per the review recommendations by Gasparyan et al. [11]. A search was conducted using PubMed, MEDLINE, EMBASE, ClinicalTrials.gov and SCOPUS databases, using the terms “sex differences OR sex disparity OR gender differences OR gender bias” AND “COVID-19 OR SARS-CoV2 OR SARS-CoV-2 OR novel coronavirus OR nCoV”. Approximately 1500 articles were identified, and ranged from case reports, case series, and letters to the editor, and observational studies to narrative reviews, systematic reviews and clinical trials published till March 26, 2021. Relevant articles were independently reviewed, and information was extracted falling under the different categories of; sex differences in immune response, role of sex hormones in immune response, gender differences in COVID-19 infections and outcomes, COVID-19 and thrombosis, COVID-19 and pregnancy, COVID-19 and autoimmunity and gender differences in the vaccine response.

### Gender-specific differences in immune response

Women are known to inherently mount a stronger innate and adaptive immune response to viral infection. Faster viral clearance and a lower viral load have also been reported in women. However, this enhanced immune response makes women more vulnerable to inflammatory and autoimmune diseases [12].

#### Innate immunity

**Phagocytic responses** Neutrophils and macrophages in females generally have a higher activation and phagocytic activity. Female dendritic cells also have higher TLR-7 and Type 1-IFN response [13]. This may result in prompt

virus sensing and antiviral responses in females in the initial phase of infection.

**Cytokines** Notably, despite more robust immune responses in women, elevated levels of cytokines particularly IL-8 and IL-18 at the baseline, and CCL5 over the disease course were observed in men with COVID-19. This pro-inflammatory cytokine profile was strongly correlated to more severe COVID-19 outcomes, suggesting that deregulated inflammation may turn counterproductive [14]. Interestingly, these cytokine levels were also higher levels of CD14, CD16+ non-classical monocytes. Similarly, in women the production of pro-inflammatory IL-6 in viral infections is lower than in men and is correlated with better COVID-19 outcomes possibly due to reduced inflammation [15].

#### Adaptive immunity

**T cells** CD4+ and CD8+ T cells in women generate more robust responses to viral infections [16]. The Yale study reported lower T cell levels in males with worsening disease as compared to females. Moreover, number of activated CD8 T cells were significantly higher in females [14]. Higher activity of T cells may in turn contribute to potentially better antiviral adaptive immune response in females, which may lead to greater viral clearance.

**B cells and humoral immunity** Women also tend to produce higher titres of antibodies, which remain in the circulation longer, conferring long-lasting protection against COVID-19 infection [14]

These primal differences in the way both sexes react to an inciting event may be ingrained in the differences in the very genetic fabric of both sexes, and their interplay with other potential contributing factors, notably sex hormones.

### Factors determining differences in immune response to SARS-CoV-2

#### Sex chromosome genes

**Immunity-related genes** The possible biallelic overexpression of immune modulatory genes on the X chromosome in females could explain the more robust response of females to viral infection and vaccination and may also confer additional protection against COVID-19 [17].

The endosomal Toll-like receptor 7 (TLR7) is a significant factor involved in the recognition of viral antigens and mounting an effective antiviral immune response [18, 19]. Increased expression of the TLR-7 gene, which is located on the X chromosome, has been reported in women due to the ability of the TLR-7 gene to escape X-chromosome inactivation. Higher TLR-7-driven IFN- $\alpha$  production by

plasmacytoid dendritic cells (pDCs) in response to acute HIV-1 infection has been reported in females as compared to males [18–20]. Rare malfunctioning variants of the TLR7 gene were found in a case series of 4 young male patients, with severe respiratory complications due to COVID-19, with a negative impact on both type I and type II IFN responses [21]. Increased TLR-7 expression may lead to increased cytokine production and faster viral clearance in women. The pandemic has led to the identification of several polymorphisms in men, previously considered to be innocuous subclinical primary immunodeficiencies fairly common in the population, which may now be the very basis of the gender bias in the predisposition to life-threatening COVID-19 [4, 5].

Other genes may also be responsible for the sex-based disparity in immune response to SARS-CoV-2. These may include X-linked genes, including the ones coding for Interleukins, FOXP3, XIST, and TLR-8, which may be similarly upregulated in females due to biallelic expression, as well as Y-linked genes (SRY and SOX9), which would have greater expression in males, and thus may also possibly contribute to lower viral loads and lesser inflammation in females as compared to males [22–29]. Table 1 summarises the genes that may be responsible for the sex-based disparity in immune response as well as their function.

**ACE-2** The angiotensin-converting enzyme 2 (ACE-2) receptor has a major role in the disease pathogenesis of COVID-19, acting as the receptor for viral entry of SARS-CoV-2 into its target cells, primarily alveolar type 2 pneumocytes [30]. However, the ACE-2 receptor also has an important role in organ protection, as it inactivates the active forms, Angiotensin I and II by conversion into Angiotensin 1–9, and 1–7 respectively, and thus reduces the chances of development of pulmonary oedema during COVID-19 [31, 32]. This may explain the apparent paradoxical protective

effect that increased ACE-2 expression may confer against severe COVID-19 clinical outcomes in women, despite acting as the very vessel for its pathogen.

The position of the ACE-2 receptor gene on the X-chromosome, Xp22.2, is such that it escapes X-inactivation in women [33]. Therefore, this leads to increased ACE-2 receptor expression in female type 2 pneumocytes, plausibly allowing the ACE-2 receptors unbound by SARS-CoV-2 Receptor binding domains, to catalytically cleave Angiotensin II and offer protection against pulmonary oedema. The absence of this biallelic expression in men may result in the lack of availability of sufficient free ACE-2 receptors to cleave Angiotensin II, and a resultant reduced protective effect.

### Sex hormones

Another plausible mechanism of gender bias is the obvious difference in sex hormones between the genders, and their effect on innate and adaptive immunity. While androgens like testosterone are known to be immunosuppressive, oestrogen tends to be more versatile in its character, and may enhance or deplete immune response, based on its concentration, distribution, and expression of its receptors [34].

### Role of oestrogen

Oestrogen receptors ER $\alpha$  and ER $\beta$  are found on different lymphoid cells and are involved in their maturation and regulation. Oestrogen is known to play a role in monocyte/macrophage recruitment, and regulation of cytokines and antigen presentation. Oestrogen, through its receptor signalling, has also been shown to promote pattern recognition TLR mediated production of cytokines including antiviral IFN- $\alpha$  by plasmacytoid dendritic cells [34–36].

**Table 1** Genes that may influence sex-based disparity in immune response to SARS-CoV-2

Gene	Function
<b>X-linked genes</b>	
ACE-2	Receptor for SARS-CoV-2 spike (S1) protein, antioxidant, anti-inflammatory
Genes for interleukins e.g. IL2RG gene (encodes interleukin receptor common gamma chain protein)	Cytokines responsible for modulating the immune response
FOXP3, XIST	Transcription factors responsible for the functioning of regulatory T cells (Treg cells)
TLR-8	Endosomal pattern recognition receptor responsible for activation of innate immunity (TLR-8 binds to SARS-CoV-2 ssRNA, recruits MyD88, and activates NF- $\kappa$ B)
<b>Y-linked genes</b>	
TMPRSS2	Promotes entry of SARS-CoV-2
SRY, SOX9	Encodes proteins involved in the immune response to viral infections

*IL2RG* interleukin-2 receptor subunit gamma, *FOXP3* forkhead box P3, *XIST* X-inactive-specific transcript, *TLR-8* toll-like receptor-8, *TMPRSS2* transmembrane protease serine 2, *SRY* sex-determining region on Y chromosome, *SOX9* transcription factor SOX-9, *MyD88* myeloid differentiation primary response 88 protein, *NF- $\kappa$ B* nuclear factor kappa-light-chain-enhancer of activated B cells

Based on the similar trends of higher mortality in males during the SARS-CoV pandemic, male mouse models reported increased viral load, which correlated with higher susceptibility to critical SARS-CoV infection. Additionally, increased mortality was seen in female mice that were ovariectomised or treated with oestrogen receptor antagonists, indicating a protective role of oestrogen signalling in SARS-CoV infection [37]. Thus, it seems plausible that similar protective role of oestrogen may exist in COVID-19 infections.

A cross sectional multicentric study on COVID-19 patients in Wuhan, China, demonstrated that premenopausal women had a milder severity and better outcome of COVID-19 in contrast to men of the same age. Moreover, E2 and Anti-Müllerian hormone were found to be higher in patients with a non-severe disease. The higher E2 levels also correlated with lower IL-2, IL-6, IL-8 and TNF $\alpha$ , suggesting an interplay between the hormonal and immune axis [35]. Oestrogen has also been shown to dampen the production of pro-inflammatory cytokines IL-12 from activated macrophages and IL-6, by directly altering CD16 [35]. This could indicate a possible role of oestrogen in preventing the COVID-19-associated cytokine storm syndrome.

Furthermore, oestrogens have been reported to downregulate the ACE-2 receptor. A recent *in vitro* experiment demonstrated that 17 $\beta$ -oestradiol (E<sub>2</sub>)-medicated normal human bronchial epithelial (NHBE) cells expressed decreased ACE-2 mRNA when compared to controls, in contrast to no effect on TMPRSS2, suggesting that in females, lower levels of ACE-2 might be available for the SARS-CoV-2 virus to act on. However, the study was performed on only four experimental replicates, with NHBE cells from a single female donor, and the concentration of oestrogen used similar to the plasma levels of oestrogen in pregnancy. With current literature not reporting any significant association between pregnancy and a reduced risk of severe COVID-19 outcomes, and previous studies conducted following the SARS-CoV pandemic reporting no gender-related differences in the expression of ACE-2 receptors, further studies are required to elucidate the effect of oestrogen on ACE-2 expression and correlated sex-related differences seen in immune response to COVID-19. [38–40].

### Role of testosterone

Testosterone has a general immunosuppressive role, which may explain the greater susceptibility of males to a more severe disease progression of SARS-CoV-2 infection. Even though the exact mechanism by which androgens dampen the immune system is yet unclear, it has been speculated that testosterone might suppress T<sub>H</sub>2 and Th17 cell function and hence affect the adaptive immune response [41, 42]. Some studies have shown that testosterone might downregulate the production of cytokines such as IFN $\gamma$  and TNF $\alpha$ , and

increase anti-inflammatory cytokines such as IL-10 [43]. Testosterone might also play a positive regulatory role in the expression of TMPRSS2, which enhances viral entry of SARS-CoV-2 [44], suggesting that testosterone could be a possible factor leading to higher cases of COVID-19 and mortality in men as compared to women. On the contrary, a study from Italy on a cohort of 31 COVID-19 patients demonstrated that lower levels of total testosterone and calculated free testosterone at baseline correlated with worsening clinical condition, while also being significantly associated with increased neutrophils and decreased lymphocytes [45]. This implies that within men, lower levels of testosterone might increase the risk of a severe infection.

Although scientific evidence is still not conclusive, with information still evolving regarding the influence of sex hormones in COVID-19, there appears to be significant potential in oestrogen trials for improving immunity in men affected by COVID-19. Table 2 shows a list of ongoing trails for management of COVID-19.

### Gender-specific differences in COVID-19 manifestations

Not only is there an increased mortality observed in men, but a disproportionately high morbidity is seen as well, with the difference in the clinical outcomes between the sexes narrowing as the age increases morbidity increased.

### Thrombosis in COVID-19

The mortality observed in COVID-19 might be attributed to coagulopathies and thrombotic events. In an autopsy series, microvascular thrombosis of pulmonary vasculature was observed, and seven out of 12 patients suffered from deep vein thrombosis, while in another study venous thromboembolism was found in 69% of critically ill patients [46]. A single centre study from Italy reported thromboembolic incidents in 8% of hospitalised patients [47]. Similarly, Tang et al. reported overt-DIC in 71.4% non-survivor patients with COVID-19, while 76% of the non-survivor group were males [48]. The physiological differences between men and women may provide insights to intrinsic protective mechanisms against Thromboembolism that confer a reduced risk of COVID-19-associated coagulopathy in women, and consequently reduced mortality in women.

COVID-19-associated coagulopathy might be explained by rise in inflammatory cytokines during the disease course, increased levels of angiotensin II, increased hypercoagulability and platelet dysfunction, with age and existing co-morbidities such as hypertension being major risk factors [49].

A significant oestrogen-dependent and NO and prostacyclin-independent suppression of neutrophil recruitment and platelet adhesion on endothelial cells, via the

**Table 2** Ongoing trials for management of COVID-19 using oestrogen, progesterone, androgen blockers

Serial number	Title	Design	Interventions and dosing	Status	Country	Clinicaltrial.gov identifier
1	Oestrogen therapy in non-severe COVID-19 patients: proposed treatment scheme in a tertiary hospital	Interventional, randomised/open label controlled trial	EVRA skin patches with norelgestromin 6 mg/ethinyl oestradiol 0.60 mg, (1 patch will be placed every week during 21 days) Control group will receive conventional COVID-19 treatment	Not yet recruiting	Mexico	NCT04539626
2	Selective oestrogen modulation and melatonin in early COVID-19	Interventional randomised, double blind placebo controlled trial phase 2	Active comparator (toremifene + melatonin) will be instructed to take 100 mg oral melatonin on days 1 & 2 (40 mg in the morning and 60 mg in the evening), 60 mg on days 3–14, (20 mg in the morning and 40 mg in the evening), and 60 mg oral toremifene daily days 1–14 Active comparator (melatonin + placebo) will be instructed to take 100 mg oral melatonin on days 1 & 2 (40 mg in the morning and 60 mg in the evening) and 60 mg on days 3–14, (20 mg in the morning and 40 mg in the evening) Placebo comparator (placebo): oral placebo will be used with the same number and appearance to the pills as the interventions	Not yet recruiting	USA	NCT04531748
3	Phase II clinical trial of oestradiol to reduce severity of COVID19 infection in COVID19+ and presumptive COVID19+ patients	Interventional, randomised open label controlled trial phase 2	Experimental group will receive oestradiol 100 µg/day for 7 days through a transdermal patch applied on the skin Control group will receive no intervention	Recruiting	USA	NCT04539329

Table 2 (continued)

Serial number	Title	Design	Interventions and dosing	Status	Country	Clinicaltrial.gov identifier
4	Combination therapy with isotretinoin and tamoxifen expected to provide complete protection against severe acute respiratory syndrome Coronavirus	Interventional randomised open label controlled trial phase 2	Active comparator: 13 <i>cis</i> -retinoic acid doses orally plus tamoxifen orally 80 infected patients will receive tamoxifen 20 mg orally twice daily for 14 days, and after three days of taking tamoxifen, the infected patients will receive 13 <i>cis</i> -retinoic acid (0.5 mg/kg/day in 2 divided doses orally for 14 days) Active comparator: 13 <i>cis</i> -retinoic acid doses aerosolised plus tamoxifen orally 80 infected patients will receive tamoxifen 20 mg orally twice daily for 14 days, and after three days of tamoxifen therapy the infected patients will receive aerosolised 13 <i>cis</i> -retinoic acid in gradual in 2 divided doses increasing from 0.2 mg/kg/day to 4 mg/kg/day as inhaled 13 <i>cis</i> -retinoic acid therapy for 14 days Control group will receive no isotretinoin or tamoxifen treatment	Not yet recruiting	Egypt	NCT04389580
5	A prospective, multicentre, randomised phase II clinical trial of enzalutamide treatment to decrease the morbidity in patients with Coronavirus disease 2019 (COVID-19)	Prospective, randomised (2:1), open label, multicentre, clinical controlled trial	Experimental group will receive 4 × 40 mg enzalutamide tablets orally once daily up to 5 days, to be given only during hospitalisation and stop if starting invasive mechanical ventilation or at discharge from hospital Control group will receive no enzalutamide	Recruiting	Sweden (multi-centric)	NCT04475601
6	A single centre, randomised, controlled trial of the safety and efficacy of progesterone for the treatment of COVID-19 in hospitalised men	Interventional, randomised open label controlled trial phase I	Experimental group: progesterone 100 mg will be administered subcutaneously twice daily for 5 days in addition to institutional standard of care Control group will receive institutional standard of care only	Active, not recruiting	USA	NCT04365127

Table 2 (continued)

Serial number	Title	Design	Interventions and dosing	Status	Country	Clinicaltrial.gov identifier
7	Clinical role of testosterone and dihydrotestosterone and which of them should be inhibited in COVID-19 patients—a double-edged sword?	Interventional randomised open label comparative phase 4 trial	Experimental group will receive aerosolised 13 <i>cis</i> -retinoic acid plus Inhaled testosterone Control group will receive standard of care	Not yet recruiting	Egypt	NCT04623385
8	Efficacy of aerosol combination therapy of 13 <i>cis</i> -retinoic acid and captopril for treating COVID-19 patients via indirect inhibition of transmembrane protease, serine 2 (TMPRSS2)	Interventional randomised (1:1:1), placebo-controlled, proof-of-concept phase 2 trial	Experimental group: infected patients will receive aerosolised 13 <i>cis</i> -retinoic acid in gradual one dose per day increases from 0.2 mg/kg/day to 4 mg/kg/day as inhaled 13 <i>cis</i> -retinoic acid therapy for 14 days plus Inhalation administration by nebulisation captopril 25 mg for 14 days Sham comparator: infected patients will receive the standard therapy for COVID-19 for 14 days	Not yet recruiting	Egypt	NCT04578236
9	Anti-androgen treatment for COVID-19	Prospective, interventional, placebo controlled, double-blinded, randomised parallel assignment study	Experimental: proxalutamide + standard care Proxalutamide (200 mg q.d.) + standard of care Active comparator: standard care	Recruiting	Brazil	NCT04446429

oestrogen-mediated decrease in expression of P-selectin, an adhesion molecule that facilitates leucocyte recruitment has been reported in women [50]. Furthermore, sex-based differences in platelet biology, including platelet receptor signalling, membrane composition, response to nutrients (especially polyunsaturated fatty acids and flavonoids), aggregability, platelet count, as well as the release of thromboxane A<sub>2</sub>, prostacyclin, and serotonin, which confer a protective effect against atherosclerotic plaque formation in women, may explain decreased frequency of coagulopathy-associated mortality in women.

### COVID-19 and autoimmunity

The pro-thrombotic state and diffuse coagulopathy observed in several severe COVID-19 cases bears resemblance to the fatal multi-organ failure in the Antiphospholipid Syndrome (APS) due to activation of inflammatory and thrombotic pathways triggered by autoantibodies. Numerous studies have speculated a correlation of COVID-19-associated coagulopathy to antiphospholipid (aPL) antibodies found COVID-19 patients sera [51]. Previously, autoimmune responses were also found in some studies on SARS-CoV infections, and in general viral infections are known to induce transient production of aPL antibodies [52]. Zhang et al. reported 47% of 66 critical COVID-19 patients having aPLs, out of which the most common were IgA anti- $\beta_2$  GPI antibodies [53]. In a prior study, Zhang et al. had reported multiple infarcts and coagulopathy in 3 severely ill patients with COVID-19, who also tested positive for anti- $\beta_2$ -glycoprotein I IgG and IgA antibodies along with anticardiolipin IgA antibodies [54]. In a cohort of 172 COVID-19 patients, Zuo et al. isolated eight variants of aPL antibodies and identified at least one type of antibody in 52% of the samples, with aCL IgM, aPS/PT IgG and aPS/PT IgM being the most commonly detected. Clinically, greater concentrations of these autoantibodies were associated with significant neutrophil activation including neutrophil extracellular traps (NETs) formation in a process called NETosis, along with increased platelet count and impaired renal function and respiratory complications. Recently, the activation of NETosis in human lymphocytes by SARS-CoV-2 was demonstrated for the first time, in a process associated with increased levels of reactive oxygen species (ROS) in neutrophils. This NET-ROS pathway may possibly be responsible for extensive microthrombus formation, one most insidious and serious complications of COVID-19. Additionally, Zuo et al. reported that IgG from these patients promoted venous thrombosis in mice model studies [51, 55].

These findings suggest that autoantibodies might play a role in the aetiology of COVID-19-associated coagulopathy by potentiating the already existing systemic inflammation

and pro-thrombotic state and consequently lead to a severe form of the disease. It is also known that autoimmune disease are more common amongst women [56]. Further investigation is required to establish the exact basis of autoimmunity in COVID-19 and its influence on sex-based disparity of COVID-19 infections.

### COVID-19 and pregnancy

Current data on COVID-19 suggests that pregnant women face a similar risk to contracting a severe disease as non-pregnant women and the general population [57, 58]. On the contrary, in previous outbreaks of SARS and MERS, pregnant women were found to undergo significant morbidity and mortality, including poor obstetric outcomes and risk of preterm birth [59, 60]. Generally, pregnant women are more susceptible to infections, owing to the physiological cardiopulmonary and immunological changes that occur during pregnancy. The prevalence of a Th2 system in the cell-mediated immune response during pregnancy causes a higher vulnerability to viral infections. In context of COVID-19, the already altered pulmonary function predisposes to a higher risk of developing lung consolidation and respiratory failure [61]. Furthermore, the pro-thrombotic state in pregnancy can lead to significant morbidity due to COVID-19-associated coagulopathy [62]. Although the case fatality rate in pregnant women with COVID-19 seems to be parallel to that in women of reproductive age, some cases have reported a severe COVID-19 sequelae [39]. According to the Centre for Disease Control in the United States, pregnant women required more intensive care unit admissions as compared to non-pregnant women, and often requiring mechanical ventilation [63]. Among foetal complications, preterm births was the most common, however, long-term foetal complications are yet to be seen [59].

### Sex-biased patterns in infectious diseases and vaccine response

Sex-based disparities have been widely researched and reported in susceptibility and outcomes of infectious diseases and efficacy of vaccines [15, 64]. During the SARS outbreak in 2003, case fatality rates were higher in men than in females, and similar trends were seen in the MERS outbreak as well [6]. In HIV infections, studies have shown females to have higher CD4+ counts and stronger activation of CD8+ T cells, coupled with lower viral loads, relating to enhanced innate viral sensing and greater IFN $\alpha$  production [20]. Similarly, in Hepatitis B infection, males have been reported to have higher HBV DNA titres, and an increased susceptibility to developing hepatocellular carcinoma, which has been positively correlated to testosterone concentration and certain androgen receptor genes [65, 66]. Furthermore,



in both adults and children, females were found to generate an increased anti-HBV antibody titre as compared to males [16]. In contrast, while exposure rates to Influenza A viruses are greater in men, higher fatality is reported in younger women [67]. However, females mount a stronger antibody response to the Influenza A vaccine, possibly regulated by greater TLR7 expression and induction of B cells by oestradiol [64]. Hence, several studies have concluded that females tend to produce a more efficacious response to vaccines, although time shall answer this question regarding COVID-19.

### Behavioural risk factors and social constructs

Gendered differences in behavioural risk factors may also be a contributing factor in the apparent differences in mortality between men and women. Smoking has been linked to higher disease severity in COVID-19 and has also been associated with higher expression of ACE-2. Since smoking is more prevalent in men it can predispose men to a worse clinical prognosis [68]. Studies have also shown that women tend to use more healthcare services than men and employ better hygiene practices [69]. A survey from the United States in the at the onset of the pandemic reported that adult men were less determined to observe behavioural changes such as social distancing and wearing masks, and exhibited lesser COVID-19 worry and concern [70]. This may contribute to greater susceptibility to COVID-19 infection in men.

In many parts of the world, including ours, men have a greater proclivity to work outside the home, travel via public transport, and participate in large gatherings such as congregational religious ceremonies as compared to women, inevitably predisposing them to a higher risk of infection due to the greater risk of exposure. However, social constructs and norms, that lead to a disparity in autonomy over healthcare rights and access to healthcare services between the sexes, especially in lower socioeconomic settings, with women often having to bear with delayed hospital visits and inadequate treatment, also merit exploration.

Gender specific behavioural differences seem to only contribute a minor role to COVID-19 sex bias. Physiologically, the interplay between sex hormones and immune effectors primarily drives the drift between sexes in regard to infectious diseases. Guerra-Silveira et al. reported sex-related behaviour differences that lead to differences in exposure-prevalence of diseases, to be significant only in Schistosomiasis and Leptospirosis, while the in the vast majority of diseases, the disparity in incidence and severity of disease was inextricably linked to physiological differences between the sexes. Even though this study primarily investigated the epidemiology of bacterial and parasitic infections such as Tuberculosis and Dengue, the models for disease epidemiology in these high prevalence diseases, may be extrapolated to explain the sex based differences in incidence and clinical outcomes in COVID-19, which is also a high burden disease [71]. Figure 1 summarises the factors influencing sex-based disparity observed in COVID-19.

### Conclusion and implications for the future

Global data strongly indicates that a sex-based disparity exists in COVID-19 clinical outcomes, with men being more affected by initial SARS-CoV-2 infection, hospitalisation and poor clinical outcomes. This sex-based disparity similarly exists in the immune response to infections and inflammatory diseases.

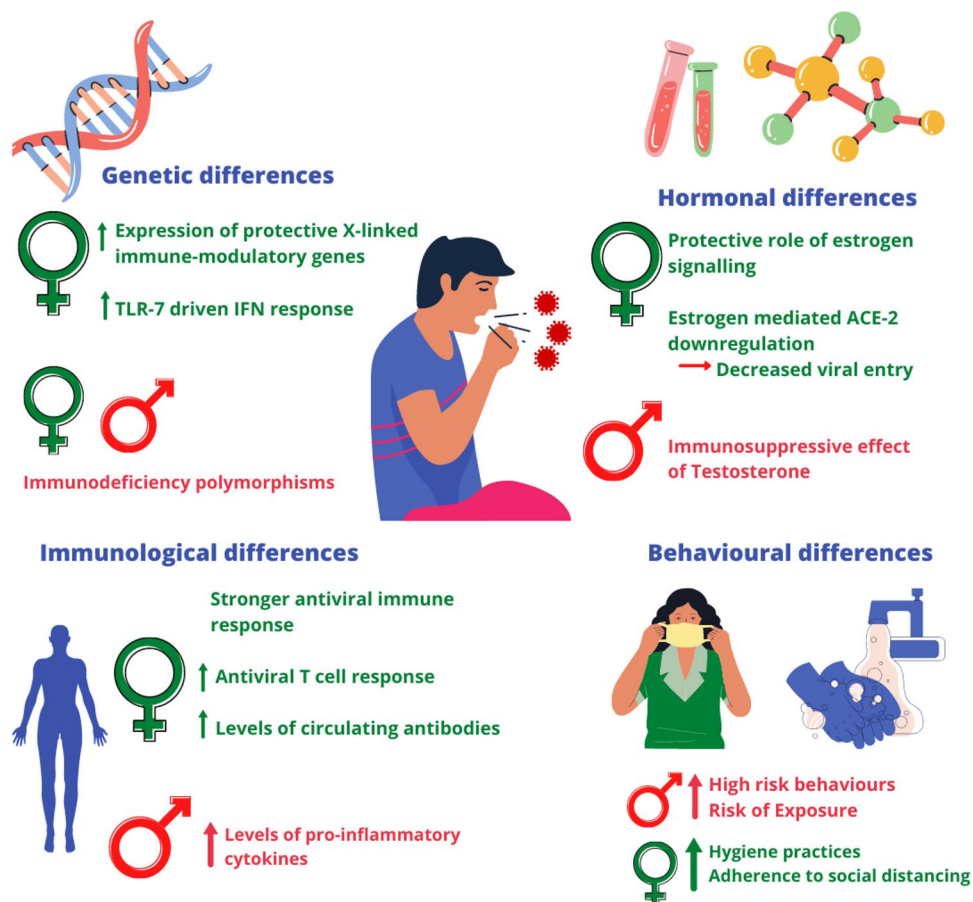
Several factors and mechanisms may explain this disparity, including intrinsic differences in innate and adaptive immunity, plausibly arising from genetic differences in the expression of immune regulatory genes between men and women, the role of crosstalk between sex hormones, as well as differences in gender specific behaviours. These differences confer a protective advantage to women against COVID-19, with women consistently reported to have lower viral loads, lesser inflammation, better clinical outcomes and lesser mortality as compared to men.

These differences, particularly the immunological divergence in response to viral infection, could potentially impact COVID-19 disease course, and antiviral drugs and vaccines. Furthermore, these immunological factors, which confer protection against COVID-19, may be exploited to develop therapeutic strategies to improve clinical outcomes.

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**Fig. 1** Factors contributing to severity of COVID-19 outcomes and mortality in males



## Declarations

**Conflict of interest** The authors declare that there is no conflict of interest.

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