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Review

The role of sexual dimorphism in susceptibility to SARS-CoV-2 infection, disease severity, and mortality: facts, controversies and future perspectives

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ABSTRACT

Former studies have revealed intersex variability in immune response to infectious diseases, including Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological surveillance of the ongoing pandemic has demonstrated a male vulnerability to morbidity and mortality, despite similar infection rates between the two sexes. Divergence in the frequency of comorbidities between males and females, differences in hormonal profile, chromosomal composition and gender behavior have all been proposed as potential causative factors. Data deriving from the immunization process indirectly support the existence of a sex-specific response to SARS-CoV-2, since females apparently produce higher numbers of antibodies while simultaneously exhibiting higher rates of side effects, indicating a stronger immune reactivity to the vaccine's elements. Interpreting intersex differences in immune response to SARS-CoV-2 could lead to a deeper understanding of the COVID-19 pathophysiology and enable healthcare professionals to conduct a more accurate patient risk assessment and better predict the clinical outcome of the disease. This narrative review aims to discuss the pathophysiological and behavioral basis of the disproportionate male morbidity and mortality observed in COVID-19, in the context of most research findings in the field.

It has long been known that the immune responses exerted by the two sexes differ significantly [1]. Accumulating evidence suggests that females produce a more robust immune response, whereas males are in general more susceptible to bacterial, parasitic, and viral infections. A characteristic case in point is the Human Immunodeficiency Virus infection, where numerous studies confirm the presence of the afore-mentioned sex bias [2]. A similar male vulnerability has also been noted in previous outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory syndrome coronavirus (MERS-CoV), both part of the Coronaviridae family, which typically result in respiratory infections. In both cases, a discernible predominance in male susceptibility and mortality was documented [3–5]. Since its identification in December 2019, SARS-CoV-2, a novel type of coronavirus, has caused a global pandemic resulting in over 130 million cases and almost three million deaths worldwide [6]. This virus is the causative agent of coronavirus disease 2019 (COVID-19), a disease that can possibly lead to multiple-system dysfunction. It is most commonly manifested as a severe respiratory disease leading to respiratory failure but can also present with cardiovascular complications, such as myocarditis and pulmonary embolism. Some may argue that the common pathway between these manifestations could be that of a vascular endothelial injury induced by the virus [7]. At the outset of the pandemic (February 2019), early epidemiological data from China indicated a higher mortality rate

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in men compared with women [Case Fatality Rate (CFR) 4.7% vs 2.8%, respectively] [8]. This was subsequently confirmed by a retrospective study of 1591 critically ill Intensive Care Unit (ICU) patients of Lombardy region, Italy, of whom 1304 (82%) were male [9]. As of March 2021, sex-disaggregated data obtained from 12 to 77 countries indicated that men accounted for 64% of ICU admissions and 56% of total deaths, respectively. Interestingly, the infection rate between the two sexes is quite similar (males 49% vs females 51%) [10]. These sex specific differences seem to be age-dependent, mainly manifesting in middle-aged populations [11]. It is hypothesized that this phenomenon could be attributed to sex specific properties, including - but not restricted to—genetic profile, immune system functions and hormone production. On the other hand, conflicting evidence supports that this apparent male vulnerability could be simply a matter of specific gender-related behaviors and habits.

This narrative review aims to discuss the basis of this disproportionate male morbidity and mortality, despite the similar infection rate between the two sexes. The importance of this topic lies in the much-needed in-depth understanding of the COVID-19 pathophysiology, which will potentially enable healthcare professionals to conduct a more accurate risk assessment of the patients and better predict the clinical outcome of the disease. Thus, a more effective patient management could be achieved.

1. Methods

PubMed, Embase, and Google scholar databases were searched to identify relevant papers written in the English language, irrespective of publication status or year of publication. A combination of the following search terms was used: “corona virus”, “sexual dimorphism”, “sex hormones”, “sex/gender differences”. The references of all relevant studies and reviews were scanned for additional articles. The last search was performed in April 2021.

2. Factors affecting sex-specific immunity

2.1. Comorbidities

Throughout the course of the pandemic, several comorbidities such as hypertension, obesity and diabetes, typically manifested at different frequencies between sexes in the middle-aged population, have been identified as risk factors for poor COVID-19 prognosis [12].

According to a systematic review and meta-analysis of seven studies, patients with severe COVID-19 exhibited a higher odds ratio (OR) of hypertension and cardiovascular disease (CVD) [13]. Interestingly enough, numerous studies have shown that males tend to have higher percentages of hypertension than age-matched females throughout the middle ages [14] and therefore theoretically this could cause them to become more susceptible to a severe SARS-CoV-2 infection. In a similar manner, regarding the middle-aged population, male mortality rates of CVD seem to exceed once again those of females, suggesting that males are more affected by CVD. Hence, again males seem to carry an additional burden that predisposes them to poor COVID-19 prognosis [15].

Obesity is another well-studied comorbidity that has been recognized to be independently associated with higher in-hospital COVID-19 mortality [16]. According to the Center for Disease Control and Prevention (CDC), the prevalence of obesity in the United States is higher in male adults of all age groups compared with women [17]. Taking these facts into consideration, it could therefore be postulated that, like hypertension and CVD, obesity may as well act as a male-biased factor that increases the likelihood of men exhibiting a more severe course of disease.

In addition to the foregoing, a meta-analysis of nine studies established a clear link between type 2 diabetes and a higher risk of COVID-19 severe disease and mortality [18]. Data from the CDC 2020 Diabetes update report, here too demonstrate a higher incidence in men (14%) in contrast to that of women's (12%) [19].

Based on the above, it could be argued that the sex-bias regarding COVID-19 morbidity and mortality could be partly attributed to the fact that overall males begin at a less favorable health standpoint, presenting with more risk factors for severe COVID-19. However, according to the sex-disaggregated data that have been presented in the introduction, it appears that the difference in CFR is so remarkable (almost 2-fold in Chinese epidemiological data), that it simply does not suffice to conclude that it is solely inflicted by the comorbidities’ element.

To this adds the fact that, although certain comorbidities may affect the two sexes differently, some studies indicate that in mixed population groups suffering from either diabetes [20] or hypertension [21] men seem to again be more severely affected by COVID-19 than women. Therefore, other factors should definitely be examined in an attempt to fully justify the sexual dimorphism in COVID-19.

2.2. Sex hormones

2.2.1. Estrogen

2.2.1.1. Estrogens and the immune response. There are three major types of endogenous estrogen produced in the human body: estrone (E1), estradiol (E2), and estriol (E3). There is also a fourth type of naturally occurring estrogen called estetrol, but it possesses a weaker potency and it is solely produced in pregnancy. E1 is mostly encountered in postmenopausal women and E3 is the most produced estrogen in pregnant women. Of all three, E2 is the most potent one and is the predominant form in females of reproductive age.

There are two types of estrogen receptors (ERs): nuclear intracellular (ERα and ERβ) and membrane receptors, the latter most commonly acting as G protein-coupled receptors (GPER). Upon their activation, ERα and ERβ target their respective response elements in the deoxyribonucleic acid (DNA) sequence to promote various epigenetic changes, whereas GPERs function via non-genomic signaling.

These receptors are present on the surface of several immune cell types such as natural killer cells, neutrophils, B-lymphocytes (B-cells) and T-lymphocytes (T-cells). In this way, immune cells can be directly affected by the circulating estrogen levels, responding in accordance to the type of receptors they express [22].

For example, in T—lymphocytes, expression of Erα and Erβ and their relative ratio is of crucial significance as it determines the cell's course of action, with the two receptors often displaying antagonistic effects. Namely, Erβ signaling is required for tissue growth factor-β differentiation of T regulatory (T_{reg}) cells, therefore promoting immunosuppression, whereas Erα signaling leads to immune stimulation [23]. However, estrogen signaling is not the only known mechanism promoting T_{reg} cell differentiation. More specifically, a study conducted in vitro showed that testosterone can also lead to the generation of T_{reg} cells from naive T-cells, suggesting an alternative hormone-dependent pathway of immunosuppression in males [24].

Apart from the individual properties of the estrogenic receptors, the level of circulating estrogen also impacts the immune response, since estrogen signaling functions in a dose-dependent manner. At low concentrations, estrogens may stimulate the immune response, whereas at higher concentrations they exert an immunosuppressive function, mimicking the action of glucocorticoids [25]. Estrogens strengthen the immune response by augmenting antibody

production through the enhancement of the somatic hypermutation of immunoglobulins and by increasing the number of antibody-producing cells [26]. As estrogen levels fluctuate throughout the menstrual cycle, women may undergo phases of altered immune reactivity [27].

In this context, females may elicit stronger immune responses compared to their male counterparts, possibly serving the purposes of the evolutionary process. Natural selection may favor females with a more adequate immune system, since during pregnancy and lactation a more intense production of antibodies is needed in order to shield the fetus and - later on - the neonate against infectious diseases, acknowledging that their only protection comes from maternal antibodies [28].

In accordance to the above, one component of the female immune system that is heavily influenced by E2, is antigen presentation and primarily the activity of dendritic cells (DCs). At low doses of E2, DCs are upregulated during inflammation and produce more interferon 1 and proinflammatory cytokines such as interleukin-8 (IL-8), IL-12, IL-6, IL-1β and chemokine ligand 2 [22]. In addition, females are also equipped with a higher number of macrophages, exhibiting a more powerful activity due to a greater density of Toll-like receptors (TLRs), which are activated by estrogens [25,29].

Another notable component of the female immune system is its unique T-cell performance to inflammatory stimuli, which differs when compared to that of males. Regarding this matter, a study concluded that upon stimulation, female T-cells exhibit an augmented expression of certain immune response genes (such as interferon gamma, lymphotoxin beta, granzyme A, and IL-12) and consequently higher levels of their final products than male T-cells. A possible explanation to this apparent sex disparity could be that in half of these overexpressed genes an estrogen response element is located within their promoter region, therefore causing them to be upregulated at higher estrogen concentrations [30]. Apart from that, sex hormones also influence the type of immune response [T helper type 1(Th1) or T helper type 2 (Th2)] that is going to be elicited by the activated T cell. Women, characterized by an estrogenic predominance, tend to favor the development of Th2 responses, therefore shifting the immune response more towards antibody production, further strengthening the humoral immunity [31,32]. On the contrary, men having higher androgen levels tend to favor the development of Th1 responses, which consequently leads to the activation of cytotoxic cells thus promoting the cellular immunity [33].

Alternatively, estrogen signaling may affect immune responses through the induction of the endothelial nitric oxide synthase (eNOS) in the presence of inflammation. This leads to increased nitric oxide (NO) production, which, due to its strong vasodilatory action, facilitates greater blood circulation at the site of inflammation. Thus, the immune response may be rendered more effective [34]. At the same time, the activation of estrogen receptors impedes reactive oxygen species formation, hence exerting an additional anti-inflammatory benefit [35].

2.2.1.2. Estrogen as a modulator of lung inflammation. Estrogen has also been found to play an important role in lung tissue protection by limiting local inflammation. This has been demonstrated in mouse model experiments where female, male and ovariectomized (OVX) female mice were infected with bacterial lipopolysaccharides (LPS). The bronchoalveolar lavage fluid was examined and revealed increased levels of IL-1B in male and OVX female mice. After the administration of E2 in female OVX mice, a reduced level of albumin and LPS-induced lung injury were noted [3]. Since E2 suppresses the production of proinflammatory cytokines, it might be crucial in the prevention of a cytokine storm during lung inflammation in females, which is the main risk factor for COVID-19 mortality [36]. Taking into consideration all of the above, it is evident that estrogen levels are capable of modulating lung inflammation and damage, which could potentially influence the outcome of respiratory diseases such as that of COVID-19 pneumonia caused by SARS-CoV-2.

Estrogens' role has been studied vigorously in several viral infections caused by other subtypes of the Coronaviridae family such as SARS-CoV and MERS-CoV. A case in point that underlines the link between estrogen and SARS-CoV infection is a study conducted on mouse specimens that were infected with mouse-adapted SARS-CoV. More specifically, it was found that even though gonadectomy did not alter the clinical outcome in male mice, ovariectomy or treatment with estrogen antagonists resulted in increased mortality in female specimens. Consequently, it can be strongly asserted that the protective shield that females hold against SARS-CoV can be attributed to the presence of higher circulating levels of estrogen. Another important finding was that the survival difference was age dependent. Particularly in the young and old age groups, the deviation of mortality rates between the two sexes was insignificant, whereas in middle aged mice an extremely noticeable difference was observed, with males presenting a remarkably higher mortality rate than females. These differences can be once again explained by the protective action of estrogens, which safeguard female mice in their middle-aged years, but gradually decline as the animals' transition to perimenopause and menopause state [37].

The above observations refer to mouse species, but several research data suggest a common pattern in humans. In all age groups a male bias in mortality exists, however this predominance is pronounced in the age group of 30–75 years [26]. This was also supported by a study which concluded that young women (0–44 years old) had the lowest SARS-CoV-2 infectivity and mortality rates [3]. At ages 45 to 74, the sex-specific differences in those latter parameters gradually diminished, leading to the loss of this protective shield after the age of 75, where the mortality rate between the two sexes was similar. This could be attributed to the transition to menopause when estrogen levels dramatically drop [38]. Nonetheless, the sex bias is not entirely eliminated even at ages above 75, since postmenopausal women still produce higher levels of estrogen in the form of E1 and via peripheral aromatization [39].

2.2.1.3. The interaction between estrogen and angiotensin converting enzyme 2 (ACE2). Estrogen can also influence the course of SARS-CoV-2 infection through its action on ACE2 gene expression. ACE2 protein acts as the receptor for SARS-CoV-2 cell entry since the viral S-spike protein functions as its ligand [40].

It is known that the pattern of expression of ACE2 is controlled in a tissue-specific manner and is subjected to regulation by ovarian hormones, thus contributing to the sexual dimorphism of the disease. For instance, in a clinical study of human atrial cells of elderly male donors, estrogen increased the ACE2 expression and lowered the ACE/ACE2 ratio, whereas the administration of an ERα antagonist completely revoked these actions [41]. On the other hand, in human bronchial epithelial cells, estrogen has been reported to downregulate the messenger ribonucleic acid (mRNA) expression of ACE2 [40]. Therefore, it could be postulated that estrogens might limit the viral entry in bronchial cells and consequently reduce the viral load. In fact, in an animal study conducted on mice infected with SARS-CoV, lower viral RNA titers could be retrieved from ACE2 knockout mice in comparison with wild-type mice, indicating the important role of ACE2 gene in the in-vivo viral replication [42].

Interestingly, following the binding of SARS-CoV-2, the ACE2 receptor is downregulated causing a shift in the balance of ACE/ACE2 ratio towards the formation of ACE, which results in higher

levels of angiotensin II [29]. This favors pulmonary vasoconstriction and hypertension, deteriorating the clinical course of the infection [43]. This is also supported by a study of critically ill COVID-19 patients where extremely elevated plasma levels of angiotensin II were noted [44]. Thus, the question of whether ACE2 actually possesses a protective role against lung injury is raised.

In an animal model experiment, ACE2 knockout mice were compared with wild-type mice after acid aspiration, a common cause of acute respiratory distress syndrome. The results demonstrated that ACE2 knockout mice had diminished oxygenation and exacerbated lung pathology, manifested by massive lung edema, increased accumulation of inflammatory cells and hyaline membrane formation in comparison with their wild-type counterparts [45].

Thus, a definite relation between ACE2 expression and SARS-CoV-2 clinical outcome has not yet been established, since lower ACE-2 levels may lead to reduced SARS-CoV-2 infectivity, whereas at the same time may promote lung inflammation and increase disease severity by shifting the balance towards the ACE/angiotensin II axis. Nevertheless, the fact that estrogen regulates not only the ACE2 expression but also the entirety of the renin-angiotensin axis is indisputable and this very connection may enhance sex specificity in SARS-CoV-2 infection [41].

2.2.1.4. The link between estrogen and coagulopathy. A main complication of SARS-CoV-2 infection is the occurrence of thromboembolic events due to the presence of a hypercoagulable state [46]. The thrombotic diathesis of SARS-CoV-2 infection may be attributed to molecules that, although generated during the activation of the innate immune system in order to promote the humoral and cellular host defense, can also result in activating the coagulation pathway. This phenomenon is called thromboinflammation and is not specific to SARS-CoV-2. Moreover, some of the pro-inflammatory cytokines produced during inflammation, such as IL-6 activate the endothelial cells and cause endothelial damage, further contributing to the general state of hypercoagulability [47].

In the case of SARS-CoV-2 an additional mechanism for prothrombotic events exists. More specifically, the virus can bind to the ACE2 receptor on the surface of endothelial cells, thus promoting the endothelial inflammation and apoptosis, and ultimately lead to a form of microangiopathic coagulopathy [48]. The thrombi identified in COVID-19 patients are mostly formed in the lung vasculature, regardless of the state of injury of the lung parenchyma [25], but can also be encountered elsewhere [25].

In general females present with lower risk of thrombosis in comparison to males, especially at the premenopausal phase. This potentially illustrates a protective role of estrogen [49]. However, women under the influence of synthetic estrogen, such as those using oral contraceptives, as well as pregnant women, having excessive plasma estrogen concentrations, pose an exception. In fact, under these circumstances women seem to demonstrate a greater thrombotic diathesis, possibly because supraphysiological estrogen has been shown to increase the procoagulant and decrease the anticoagulant factors [50].

A potential way, through which estrogen may partake in the safeguarding of females, is by reducing the platelet aggregation, as first seen in animal experiments [51]. This was later on confirmed by studies conducted on human endothelial cells [52]. Besides, during their premenopausal years, a time period when estrogen levels are within high physiological levels, women seem to exhibit higher fibrinolytic activity, since they possess lower plasma plasminogen activating inhibitor 1 levels [53]. Additionally, estrogen may act indirectly in the preservation of the pulmonary microcirculation through the induction of eNOS. As already mentioned in section 2.2.1.1., estrogen is capable of augmenting the NO bioavailability and thus counteracting the vasoconstricting effects of stress-induced hypoxia, which is a common damage pathway in SARS-CoV-2 infection. At the same time, estrogen also enhances the prostacyclin levels locally, which act in a similar fashion as NO, and decreases the stress-induced production of endothelin-1, a very potent vasoconstrictor. Hence, due to the manipulation of these extremely important vasoactive substances, estrogen plays a pivotal role in the shielding of the endothelial cells of the pulmonary vasculature [25].

2.2.2. Testosterone

Testosterone, being one of the main male sex hormones, has been heavily studied to identify its immune-modulating properties. It is known that testosterone exerts an anti-inflammatory action, possibly induced by the inhibition of the nuclear factor NF-kB pathway [54] This was observed in a clinical study where hypogonadal men suffering from chronic inflammatory conditions were treated with supplemental testosterone. As a result, a reduction in the levels of IL-6 and tumor necrosis factor alpha was observed [55]. Testosterone also possesses an indirect anti-inflammatory function through its conversion to estrogen peripherally, which as already mentioned, impedes hyperactive immune responses [54]. This is a key factor since testosterone levels in males decrease in parallel with the aging process [56]. Therefore, men in older age groups, having lower testosterone levels, are at higher risk of developing a more severe inflammatory response known as cytokine storm, which consists of an excessive pro-inflammatory cytokine production. This was supported by a cohort study among COVID-19 patients at hospital admission which concluded that testosterone levels are negatively associated with C-reactive protein, IL-6 and D-dimers [57], which are all recognized inflammatory biomarkers [58]. The same study also reported that high testosterone levels were correlated with a smaller probability of invasive ventilation [57]. It is important to point out though, that testosterone's role shifts depending on the phase of the disease. It is speculated that during the initial time of infection, when the inflammatory process is of great importance to fight off SARS-CoV-2, higher testosterone levels are of disadvantage since they allow the propagation of infection. As the disease proceeds, the utility of inflammation is diminished, given that it no longer serves as a protective factor against the viral agent. On the contrary, it transforms into a major damaging component that promotes the occurrence of what could be a life-threatening cytokine storm and therefore, during that stage, higher testosterone levels would be of great value due to the induction of immunosuppression [57].

Addressing the matter from a different point of view, an androgen driven COVID-19 theory has been proposed. This theory is based on the fact that the androgen receptor (AR) is the only known promoter of the expression of the Transmembrane Serine Protease 2 (TMPRSS2) gene which encodes the homologous protein, as established in studies of prostate tissue [59]. This protein is a transmembrane serine protease expressed, among elsewhere, in the respiratory tract [60]. TMPRSS2 cleaves both the S-spike protein on the surface of SARS-CoV-2 and the ACE-2 receptor, thus enabling a better interaction between these two structures. This results in an augmented viral entry into the host cell [61]. It has been therefore hypothesized that since higher testosterone levels would lead to a greater expression of TMPRSS2 protease in the prostate tissue by activating the AR, this could also be the case for lung tissue. Since androgen levels are higher in men, the latter are theoretically more susceptible to a SARS-CoV-2 infection and potentially to more severe disease than women [29,62]. Taking it one step further, men that exhibit a hyperandrogenic phenotype (alopecia, acne, oily skin type) could face a higher risk for more severe disease and

hospitalization [62,63]. However, recent studies have indicated that there is no increased expression of TMPRSS2 in the lung tissue of males compared with females, but further research is required to confirm this observation [64]. In parallel to the above, new studies have focused on the impact of estrogenic signaling on TMPRSS2. More specifically, it was observed that 17-b estradiol was also able to downregulate TMPRSS2, challenging the notion that this metalloproteinase is solely affected by androgens [65].

Despite the controversy, solid evidence that androgens are independently linked to a worse outcome of SARS-CoV-2 infection still exists [66]. Statistical data from a study conducted in Italy point out that prostate cancer patients receiving Androgen Deprivation Therapy (ADT) are possibly less susceptible to infection in comparison to prostate cancer patients not receiving ADT (OR 4.95), as well as cancer patients of any other type (OR 4.86) [67]. This is of great interest, since typically people with malignancies are at a higher risk of any type of infection compared to the general population [68].

2.3. The X chromosome factor

In human species, the two sexes are discerned by the possession of two different combinations of sex chromosomes. Females own two copies of the X chromosome and males one X and one Y chromosome [69]. This differentiation on the chromosomal level impacts the capacity of their immune system to fight various groups of pathogens, hence leading to sex dimorphism in immune responses. The X chromosome is not only characterized by a greater dosage of immune-related genes when compared with the Y chromosome but also by differential patterns of gene expression. One example is the TLR gene, which encodes the homologous protein that acts as a pathogen-associated molecular pattern (PAMP) receptor. TLR proteins are responsible for the recognition of pathogens and the promotion of the production of antibodies as well as proinflammatory cytokines that trigger an immune reaction to a possible infectious agent [29,34]. TLR3, TLR7 and TLR9 are female biased genes and primarily provide protection against viruses by tracing the RNA or DNA, whereas TLR2 and TLR4 are male biased and are more targeted towards eliminating bacteria by detecting PAMP structures on the bacterial wall [29]. Consequently, it appears that females are more protected against SARS-CoV-2, as is also the case regarding other viral infections [34]. In addition to these, females may hold another genetic advantage. Since they own two X chromosomes, they possess double quantities of all immune genes. This extra genetic material is balanced by the inactivation of one X chromosome in every female cell by a process called random transcriptional inactivation of the X chromosome. This results in the production of a mosaic in females that generates greater genetic diversity, since both maternal and paternal alleles are preserved and expressed at different cells, enabling them to elicit a more prominent response to infection [34,70]. Moreover, it has been shown that some genes located on the X chromosome, such as TLR7, may escape from this process of inactivation and thus are expressed in higher amounts in females compared with males, contributing to a further strengthening of the female immune system [29].

2.4. Gender behavior

As already discussed, the different rates of infection and mortality that have been observed between genders are mainly attributed to biological factors; yet gender behavior may also partially influence these indexes. In this review, we examine sex and gender separately, since the latter, according to Global Health 50/50 [71] is a socially constructed entity shaped by societal norms that may influence an individual's behavior, their access to health care and the response they will attain form the healthcare system. It has been demonstrated that women are more likely to abide by preventive measures against the spread of the virus such as mask wearing, hand washing and social distancing [72]. As far as mask wearing is concerned, a recent survey carried out in the United States of America highlighted that women exhibited a higher frequency of mask usage (7.6% more than males) [73]. In the same pattern, it has been observed that women tend to engage more than men in the practice of thorough hand washing (OR: 2.39) as well as covering their nose and mouth when sneezing and coughing (OR: 2.12) [74]. Regarding social distancing, here too, women show better compliance with respective governmental instructions and manifest higher odds of keeping 1.5-m distance from others in public spaces [75]. Interestingly enough, according to a research conducted in the Saudi Arabia Kingdom, although there is no statistically significant difference in the knowledge level between men and women in respect to the pandemic, men are less likely to be compliant to preventive measures [76].

Table 1 summarizes the main factors contributing to sexual dimorphism related to COVID-19 morbidity and mortality.

3. Sex-bias in vaccination

The distinct behavior of the immune system between sexes may also be manifested in the case of anti-COVID-19 immunization. As has already been observed with vaccination against other infectious agents such as influenza, hepatitis B, and hepatitis A, women appear to present a stronger immune response than men.

This differential response could be attributed to their unique hormonal milieu. In this setting, the excess of estrogen may aid in mounting stronger immune responses, whereas testosterone exerts its immunosuppressive action by limiting antibody production [77]. Specifically, studies comparing laboratory results between men and women that had previously received influenza shots concluded that females produced higher numbers of neutralizing antibodies [69].

These data are in agreement with results derived from a study regarding H1N1 vaccination in mice models. Concretely, female adult (18–45 years) mice exhibited higher rates of neutralizing seroconversion compared with adult male and aged mice (over 65 years). However, no sex differences were noted when comparing aged female and male mice [78]. This is of great interest since it is known that in aged individual's sex steroid hormone production is blunted [79]. Consequently, this reduction may create a more homogenous hormonal environment, thus alleviating possible differences encountered between sexes during their earlier life stages. One more important finding of the same study is the fact that antibody production was directly associated with hormone levels in a linear fashion in adult mice. More specifically, a positive correlation was noted with estradiol levels in adult females whereas a negative one was observed with testosterone in adult males.

The exact mechanisms through which the steroid hormones alter the vaccination response are still being explored. One interesting theory that has been suggested, regarding the role of testosterone in attenuating the immune response, has focused on the upregulation of a certain complex of genes. These genes are involved in lipid biosynthesis and have been independently associated with poorer vaccination outcomes in males but not in females. They also seem to exert anti-inflammatory actions and appear to be expressed at higher levels in males [80].

Some other studies attempting to explore the sex disparity in immune responses focus on the role of estrogen in promoting the maturation of DCs. In this concept it has been shown that estrogen increases the expression of Major Histocompatibility Complex II

Table 1
Factors contributing to sexual dimorphism related to COVID-19 morbidity and mortality.

Comorbidities
Higher frequency in males:
• Hypertension
• Cardiovascular disease
• Obesity
• Diabetes
Sex Hormones
• Estrogen
• Modulator in lung inflammation
• Interaction with ACE2 gene
• Shield against coagulopathy
• Testosterone
• Dual role in inflammation
• Possible upregulation of TMPRSS2
Genetic - The X chromosome
• Greater dosage of immune-related genes
• Greater diversity due to mosaic of paternal and maternal alleles
Gender behavior
Greater female engagement in:
• Mask wearing
• Hand washing
• Social distancing

Abbreviations: ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2.

molecules on the surfaces of DCs, enabling them to better present the antigens that they have already acquired through the process of TLR7 binding [81]. In this way, females are equipped with higher quality of antigen presentation cells and are potentially capable of better recognizing the vaccine's elements so that they can produce the appropriate immune response.

Additionally, the heightened immune response of females post vaccination could stem from the upregulation of B-cells. Here too estrogen plays a significant role by facilitating the process of the somatic hypermutation and that of immunoglobulin class switching in B-cells. These two processes are vital for the generation of mature functional B-cells and can offer a clear advantage to the female immune response. In addition, it has been demonstrated that menopausal women, who are characterized by a state of estrogen deficiency, exhibit a decrease in the number of B- and T-cells, whereas this is not the case for postmenopausal women receiving hormone replacement therapy [28].

As far as SARS-CoV-2 vaccination is concerned, a study measuring BNT162b2 mRNA vaccine's efficacy by comparing antibody production among different age groups and sexes displayed similar results. In particular, women produced higher antibody titers than men in all age groups and interestingly, this sex-specific difference was substantially pronounced in the age group of 80–89 years. In both sexes, an age-dependent antibody production was noted, as younger participants exhibited not only a greater number of antibodies but also a more rapid response to the vaccine [82].

However, this ability of better antibody production could also act as a liability due to the higher occurrence of adverse reactions in females. Besides, it is well established that this immoderate immune reactivity is to blame for the prevailing incidence of autoimmune diseases in women [77]. Recent events brought to the attention of the global medical community that a similar situation may apply in the case of COVID-19 immunization. In a World Health Organization report, more women declared experiencing adverse effects after the vaccine administration. The majority were classified as non-serious such as pain at the site of injection, fatigue, headache, myalgia, chills, and fever [83].

However, as was first noted in March 2021, a series of cases of thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST) and mesenteric vein thrombosis, as well as cases of disseminated intravascular coagulation began to be documented, almost exclusively in women under the age of 55, linked to the AstraZeneca® vaccine. Some cases of thromboembolism and pulmonary embolism were also reported [84,85]. The exact pathophysiology is yet to be proven, but the proposed mechanism of this side effect could resemble that of heparin-induced thrombocytopenia. In this rare complication of heparin therapy, antibodies against platelet factor 4 are produced, leading to activation of platelets, thrombosis, and subsequent thrombocytopenia [86]. In the case of the AstraZeneca® vaccine, the phenomenon has been named as “vaccine-induced prothrombotic immune thrombocytopenia (VIPIT)” and human intravenous IgG immunoglobulin has been suggested as a potential agent for its management. The confirmation of this theory would be crucial since it would aid in establishing the correct management of the possible thrombotic complications of AstraZeneca vaccine recipients [84]. In a similar way, according to the joint CDC and Food & Drugs administration statement (April 2021), the Janssen (Johnson & Johnson)® vaccine was also linked to cases of CVST and thrombocytopenia with all incidents regarding females between the ages of 18–48 years [87].

However, it still remains to be proved whether women under the age of 55 and between the ages of 18–48 truly represent a risk population for side-effects following vaccination with AstraZenecca® and Janssen (Johnson & Johnson)® vaccines, respectively. Nonetheless, this age and sex specificity could be simply the result of the current strategy of vaccination. The adopted immunization approach in most countries prioritizes people under the age of 65 years and focuses on particular occupational sectors such as healthcare workers and teaching personnel, which happen to be female dominant [88].

4. Discussion

It is evident that many factors play a role in the sexual dimorphism related to SARS-CoV-2 infection. Comorbidities which appear to be more frequent in males, estrogen levels and chromosomal differences, the dual role of testosterone, as well as distinct behavioral practices regarding the pandemic, render the male gender more vulnerable to infection and less likely to survive.

These biological and social factors are in accordance with the globally observed precedence of male mortality, as estimated by epidemiological data, despite the similar infectivity rates between sexes.

However, some aspects need to be further evaluated. For instance, there is an ongoing debate regarding the exact role of ACE2 during SARS-CoV-2 infection. More studies are necessary to clarify the lung-specific pattern of ACE2 expression and the exact relation between ACE2 levels and clinical outcome. An additional point yet to be determined is whether lower levels of testosterone in males favor or deteriorate the clinical outcome in infected individuals. Such a realization would supply additional knowledge which could aid in patient risk stratification.

Furthermore, it is known that women tend to have a better response to vaccines against many viral agents. As COVID-19 immunization continues, the higher percentages of adverse reactions in women pose the question whether this is also the case for SARS-CoV-2. This increased frequency of side effects is possibly caused by an augmented immune activation post injection. Nonetheless, more research is needed to investigate the reasons behind this sex-specific vulnerability and to explore whether the vaccine dosage should be readjusted to better fit the female immune system properties.

In any case, the fact that females exhibit heightened immune reactivity undoubtedly plays an important role in the better disease outcomes regarding SARS-CoV-2 infection and the majority of the studies conducted on this topic concur that one of the primary causative factors of this dimorphism is the female hormonal profile. More specifically, estrogens safeguard women and strengthen their immune system, but their actions are more chronic than acute. Moreover, their use (post menopause) has been restricted due to anticipated risks (mainly of breast cancer). Even if a relative protection against SARS-CoV-2 infection is proven, it is doubted whether they could be eligible as a therapeutic agent. Similarly, given that patients with lower testosterone levels appear to be less susceptible to infection, an alternative hormonal intervention could be that of ADT. However, considering the anticipated side-effects it is questionable whether ADT could be of clinical use as a shield against SARS-CoV-2. TMPRSS2 inhibition could also pose as a potential treatment approach. Regarding the latter, ongoing clinical trials are already testing this hypothesis using the TMPRSS2 inhibitor Camostat Mesylate as a means of restriction of viral entry and therefore infectivity. This could be of extreme importance in lowering the transmission rate in the community. Another inhibitor, currently under investigation, that could also benefit critically ill COVID-19 patients through its action as a TMPRSS2 inhibitor, is Alpha-1 antitrypsin, which protects the airway and reduces lung inflammation. Nonetheless, more in-depth research is required in order for this agent to be of clinical use.

Our literature review bears some limitations due to the recent character of the disease. At present, the number of studies conducted on this topic is restricted and the available data have been provided mostly by retrospective observational studies, whereas very few randomized control trials have been implemented. To overcome these difficulties, in our research we have included studies of other members of the Coronaviridae family as well, such as the MERS-CoV and SARS-CoV, considering their structural and pathophysiological resemblance.

5. Conclusion

In conclusion, it is without doubt that a difference between male and female COVID-19 mortality rates exists, possibly due to variations in the physiology and function of their immune systems. However, clinical trials and animal model experiments are not always sex-balanced and tend to include fewer female subjects. In addition, not all countries include a sex-based distinction regarding their epidemiological data used to monitor the course of the pandemic. Such a lack of information hinders scientific conclusions. Thus, it is of utmost importance that henceforward, sex disaggregated data stand in the epicenter of the research field, thereby shedding more light on COVID-19 pathogenesis and enabling the drawing of more accurate scientific conclusions.

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Author contribution

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Declaration of competing interest

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