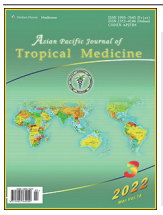

Review Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995−7645.340567

5-Years Impact Factor: 2.285

Sex differences in SARS−CoV−2 infections, anti−viral immunity and vaccine responses

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ABSTRACT

The COVID-19 pandemic has revealed sex-based differences in anti-viral responses, with a higher rate of SARS-CoV-2 infections as well as a higher rate of morbidity and mortality in men than in women. Males and females also show disparate immune responses to COVID-19 infection, which may be important contributors to lower rates of infection, disease severity and deaths in women than in men. Here, the authors review sex differences in SARS-CoV-2 infections, anti-viral immunity and vaccine responses, putting forth the importance of sex, the underappreciated variables in vaccine response and disease infectivity.

KEYWORDS: SARS-CoV-2; Antiviral immunity; Sex based mitochondrial differences; Vaccine responses; Innate immunity; Sex differences; COVID-19 pandemic

1. Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged as the novel pathogen of the coronavirus disease-2019 (COVID-19) pandemic which has emaciated the world, affecting every age-group of humans across the globe. Ever since the emergence, there has been a substantial international effort to understand the virus, the depth of its pathogenicity, the disease it causes and the type of target population which have got affected the most out of this viral infection. Undoubtedly, the global vaccination programs have substantially reduced the fatal outcomes, but the slow coverage of vaccine across the human population around the world has been a concern. Additionally, response to disease and susceptibility to severity has been associated with demographics, sex differences and associated risk behaviors. The unraveling of the etiology and epidemiology behind the COVID-19 pandemic has plunged a spotlight on the sex based disparities of the disease, implicating the essence of sex differences as evident from greater disease severity and higher death rates amongst men than women across the pandemic[1−3]. Given the pre-existing comorbidities, sex-influenced biological factors like physiology and host immune responses could be determining in such a sex difference towards SARS-CoV-2 infection.

In the current article, we have discussed the essence of sex differences in SARS-CoV-2 infections and its fondness for males, putting forth the significance of sex-differences, the under touched biological parameter in the magnitude of infectivity, immunity

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How to cite this article: Mohanty A, Sawhney A, Gupta S, Rao V, Govindaraj P, Mohanty S, et al. Sex differences in SARS-CoV-2 infections, anti-viral immunity and vaccine responses. Asian Pac J Trop Med 2022; 15(3): 97-105.

Article history: Received 27 January 2022 Revision 27 March 2022
Accepted 28 March 2022 Available online 30 March 2022

and mortality during the COVID-19 pandemic. The endocrine and genetic bias of the SARS-CoV-2 in causing exacerbated fatal consequences in male *versus* female patients has been unraveled. In this regard, the untouched role of mitochondrial differences in both sexes as a hidden secret behind the robust immunity and effective immune response towards COVID-19 vaccines has been brought to the spotlight. The sex differences in response to COVID-19 vaccines are being discussed in this article, providing an insight into the national and international status of COVID-19 infections.

2. Endocrine and genetic basis of immunological differences between males and females-innate immunity differences

In relation to SARS-CoV-2, the accumulation of reports and epidemiological data indeed confirms that, in agreement with other respiratory inflammatory diseases and consistent with previous Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus infections, the new coronavirus preferentially affects males than females that show a better prognosis.

We discussed potential sex-specific mechanisms modulating the course of disease, such as hormone-regulated expression of genes encoding for the SARS-CoV-2 entry receptors angiotensin-converting enzyme (ACE) 2 receptor and transmembrane serine protease 2 (TMPRSS2), as well as sex hormone-driven innate and adaptive immune responses and immunoaging[4,5].

2.1. Genetics and its contribution to immune differences between men and women

The presence of two X chromosomes in women emphasizes the system albeit one is inactive. The immune regulatory genes encoded by X chromosome in female causes lower viral load levels and less inflammation in men, while the $CD4^+$ T cells are higher with better immune response. In addition, women generally produce higher levels of antibodies which remain within the circulation longer. The levels of activation of the immune cells are higher in women than in men, and it is correlated with the trigger of toll like receptor (TLR) 7, therefore the production of interferon gamma (IFNγ). TLR7 is higher in women than in men and its biallelic expression results in higher immune responses and increases the resistance to viral infections. TLR7 is expressed in the innate immune cells which recognize the single "stranded" RNA virus by promoting the assembly of antibodies against the virus and the generation of pro-inflammatory cytokines including IL-6 and IL-1 family members. In women , the assembly of inflammatory IL-6 after virus infection is less than in men and is usually correlated with better longevity[6]. Notably, the severity of clinical manifestations in COVID-19 patients presented as a cytokine storm correlates with significantly higher levels of IL-6. The magnitude of inflamm-aging shows a disparity between older men and women with much higher levels of IL-6 detected in aged men compared with age-matched women who might face more negative outcomes with COVID-19 infections with pre-existing co-morbidity[7,8].

Loci on X chromosome code for the genes involved within the regulation of immune cells like FOXP3, and transcription factor for Treg involved in virus pathogenesis. The X chromosome influences the immunity by working on proteins, including TLR8, CD40L and CXCR3 which are over-expressed in women, and can influence the response to viral infections and vaccinations[6].

2.2. Genetics behind sex-based differences in COVID-19 immune responses

In COVID-19 infection, women demonstrate lower plasma viral loads than men, while $CD4^+$ T cells are higher, demonstrating a higher response of the immune system in women. In addition, after vaccination, women generally produce in the circulation higher levels of antibodies, which have longer life than in men. The immune regulatory genes encoded by the X chromosome in the female cause lower viral load levels, inflammation and death after COVID-19 infection[6].

The surface of SARS-CoV-2 interacts specifically with ACE2 through its receptor-binding domain (RBD) of the S-protein, which is critical to the success of the viral infection. The affinity between ACE2 and the RBD of the SARS-CoV-2 is 10-20 times higher than that of previous SARS-CoVs, which also explains its higher aggressive performance. Moreover, the ACE2 peptidase domain, assigned to angiotensin-Ⅰ to angiotensin 1-9 cleavage, also makes a direct binding site for SARS-CoV-2 S-proteins available. In addition to the peptidase domain, a neck domain is crucial for the ACE2 dimerization process and stability. A scientific survey of XCI that integrated transcriptomes with genomic data identified ACE2 as a tissue-specific gene that showed moderate male-biased expression in lungs, higher male-biased expression within the intestine, and weak male-biased expression in Epstein-Barr virus-transformed lymphocytes. This could also implicate the lower ACE2 expression in females thanks to the mixture of the 2 X-linked

genes compared to the expression arising from the X-linked and a Y homolog in males. Alternatively, the predominant male-biased expression of ACE2 could be explained by increased ACE2 activity in males partially driven by sex hormones, because it has recently been demonstrated in mice kidneys[9].

SARS-CoV-2 enters the pneumocyte *via* the angiotensin-converting enzyme type 2 (ACE-2) receptor and leads to the downregulation of ACE-2 levels. ACE-2 plays a protective role by converting angiotensin Ⅱ into vasodilatory and less immune augmenting variants of angiotensin. The activation of the nuclear factor κB by angiotensin Ⅱ binding type 1 angiotensin receptors in the lung to induce vasoconstriction and inflammation *via* activation of the pathway, increases cytokine synthesis. Lung parenchyma inflammation is attributed to increased pulmonary vessel permeability caused by low ACE-2 and high angiotensin Ⅱ levels.

The cytokine storm from an unchecked inflammatory response is the proposed mechanism of severe COVID-19 that damages the lung tissue, rendering some patients' condition severe enough to require assisted ventilation and causing a high percentage of mortality in cases[10].

Higher plasma levels of innate immune cytokines such as IL-8 and along with more robust induction of non-classical monocytes are reported in males. By contrast, female patients are delineated to have more robust T cell activation than male patients during SARS-CoV-2 infection. It was observed that a poor T cell response negatively correlated with patients' age and was associated with worsening disease outcomes in male patients as compared to females. Female patients with higher levels of innate immune cytokines demonstrated worse disease prognosis in comparison to males. These uncovering observations provide a possible explanation for the observed sex biases in COVID-19 and provide an important basis for the development of a sex-based approach to the treatment differences between male and female patients with COVID-19[11].

Furthermore, sex hormones induced activation of immune cells are higher in females than in males, and this is in correlation with TLR7 activation and IFN production. The COVID-19 infection induces immune cells to produce cytokines like IFNs which have antiviral properties and can modulate the immune response, even if it is highly pro-inflammatory[6].

An inverse correlation between ACE2 levels and SARS-CoV-2 prognosis is proven by the unpredicted higher expression of ACE2 in females, the inverse age-dependent ACE2 expression significantly reduced by the presence of diabetes, and the ACE2 suppression by inflammatory cytokines. In contrast with the assumption that high ACE2 is a culprit in COVID-19 outcome, it actually plays a protective role against SARS-CoV-2 fatality, *i.e.* it is also strengthened by the ACE2 intrinsic anticoagulant properties. Sex hormones which tend to decrease with age counteract the ACE2 suppression caused by SARS-CoV-2 mediated repression of ACE2[9].

Although controversial, the role of angiotensin Ⅱ type 1 receptor blocker (*e.g.*, losartan) in patients chronically treated with, is supposedly bound to show a better prognosis after being infected with SARS-CoV-2. The rationale behind this standpoint is that SARS-CoV-2 down regulates the ACE-2, hence increasing the availability of proinflammatory Ang Ⅱ, which binds to angiotensin Ⅱ type 1 receptor and causes lung damage[10].

3. Mitochondrial differences in vaccine responses–the sex–based differences in COVID–19 infections

The severity of clinical outcomes in men compared to women upon coronavirus infection leading to higher mortality and morbidity in males has raised many fundamental questions on the sexual dimorphism of SARS-CoV-2[1]. The discrepancy in the sex-based bias towards the criticality of symptoms and more severities in males could be attributed to a compromised immune system that is heavily reliant again on the mitochondrial function. In general, preserving a healthy mitochondrial system could be proved as the key in resisting the virus both directly or indirectly toward mounting an effective vaccine response. Thus, the mitochondrial health of an individual could possibly be the determining factor towards antiviral immunity and effectiveness of a vaccine. The SARS-CoV-2 is known to orchestrate the host cells bioenergetics and redox status in order to replicate and augment the rates of viral infection. In the occurrence of a viral infection, mitochondria are known to participate in immunity by engaging the interferon system, altering their structure, and inducing programmed cell death[12]. Recently, a study highlighting the protein interaction mapping of SARS-CoV-2, predicted the direct interaction SARS-CoV-2 proteins such as the non-structural proteins 4 and 8, and ORF9c with host mitochondria[13](Figure 1). This leads to a hypothesis that a possible mitochondrial "hijacking" by SARS-CoV-2 to be a key factor in the pathogenesis of this virus[14]. Justifiably, the patients with severe symptoms could be facing the brunt of sub optimal mitochondrial support in the form of direct mitochondrial anti-oxidants, or indirect anti-viral, or anti-inflammatory responses, viral replication inhibitors *etc*. mitigated as metabolic and non-metabolic functions of mitochondrial nexus

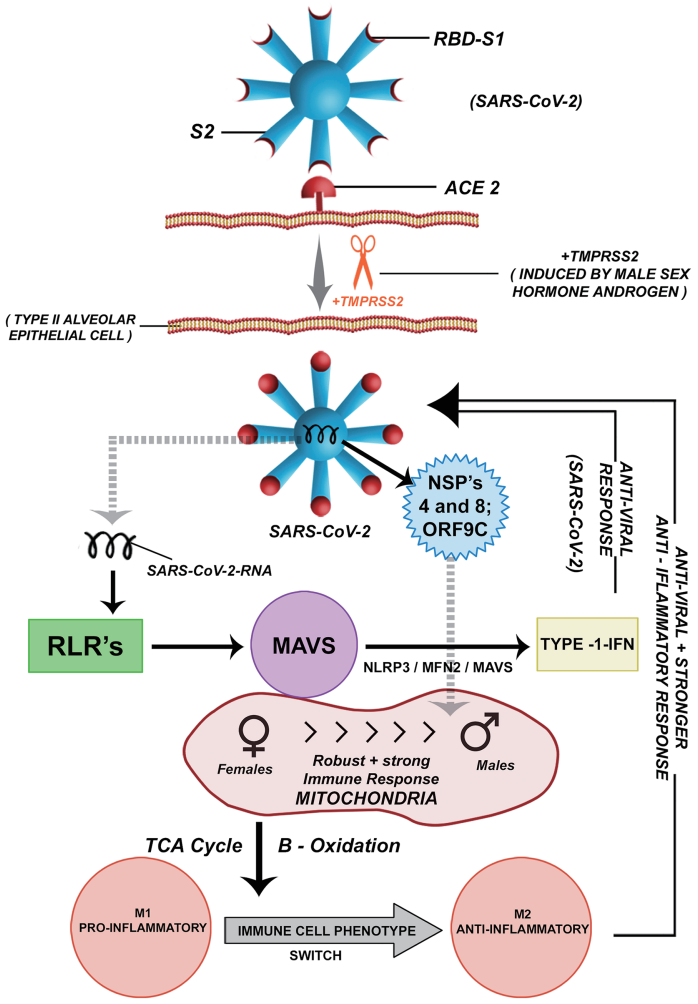

Figure 1. Mitochondria and anti-viral SARS-CoV-2 response. The entry of the SARS-CoV-2 into the target cell such as type Ⅱ alveolar epithelial cells is facilitated by androgen induced serine protease, trans-membrane serine protease 2 (TMPRSS2). The presence of SARS-CoV-2 is sensed by retinoic-acid-inducible gene-Ⅰ (RIG-Ⅰ) like receptors (RLRs), major sensors of viral RNA. The antiviral protein mitochondrial anti-viral signalling protein (MAVS) on the outer mitochondrial membrane (OMM) gets activated which then forms the NLRP3/MFN2/MAVS inflammasome complex to induce type 1-IFN anti-SARS-CoV-2 response. The mitochondria can ensue the shift of the respiratory dependency of the host cells from the tricyclic antidepressant (TCA) cycle to β-oxidation aiding in the macrophage or immune cell phenotype switch from pro-inflammatory (M1) to the anti-inflammatory (M2) phenotype, a possible anti-SARS-CoV-2 response adapted by robust mitochondria as seen in athletes and females as compared to males.

in the cells. The confounding link comes from the evidence of more robust mitochondria in females with a substandard mitochondrial quality which suffices for the longer life span of females than males[15]. A profound sex specific behavior is reminiscent of the maternal inheritance of mitochondria exerting differential effects in males and females. While the speculations predicted that the involvement of TMPRSS2 receptor in facilitating COVID-19 infections[14], TMPRSS2 the androgen induced hormone, not estrogen, is reported to localize to the mitochondria regulating mitochondrial function by acting on the estrogen related receptor alpha, which is a nuclear receptor that regulates the transcription of mitochondrial functions and energy[14,16,17]. Therefore, it seems rational to visualize that the SARS-CoV-2 entry to the host cell like the type Ⅱ alveolar epithelial cells facilitated by TMPRSS2 could have an indirect link with the mitochondria. Additionally, a study by Singh *et al.* showed SARS-CoV-2 utilizing the double-membrane vesicles derived from mitochondrial membranes to hide and protect itself inside the cell[14]. The ACE-2 receptors used by the SARS-CoV-2 blocks the availability of ACE-2, that influences mitochondrial functions and this might impair the adenosine triphosp production leading to the severer COVID-19 symptoms. The mitochondria have a functional angiotensin system[18,19] and angiotensin-(1-9), a product of ACE-2 which probably inhibits the mitochondrial

fission in the heart and checks the cellular respiration rate and ATP production, thereby favouring mitochondrial fusion event and also indirectly regulating inflammatory responses and protecting against cardiac hypertrophy[20]. The mitochondrion has evolved to be an epicentre of antiviral defence due to the primary involvement of mitochondrial outer membrane protein, mitochondrial antiviral signalling (MAVS) molecule that mediates the induction of type Ⅰ interferon response post recognition of the invasive viral RNA by the retinoic acid-inducible gene-Ⅰ (RIG-Ⅰ) like receptor (Figure 1) [21,22]. Thus, MAVS mediated signalling by mitochondria could prove vital for COVID-19 infection wherein the SARS-CoV-2 virus directly infects alveolar macrophages inducing them to switch on the cytokine storm in the lungs[23].

Although, the role of RNA viruses like influenza virus and their impact on mitochondrial fusion mediated inflammation *via* the NLRP3/MFN2/MAVS inflammasome complex is well known[24], the impact of ACE-2 on mitochondrial dynamics and inflammation is still under investigation. Interestingly, the transition of respiratory dependency from the broken trichloroacetic acid cycle to β-oxidation can empower the mitochondria to mitigate the immune cell type switch from the pro-inflammatory macrophage phenotype to the anti-inflammatory[25,26](Figure 1) and this could be a possible antiviral response adapted by robust mitochondria especially seen in athletes and females as compared to males. The viral replication and its survival therefore depend also on the energy produced by host mitochondria giving open vistas for targeting the mitochondrial bioenergetics as a probable antiviral therapeutic option.

Another aspect of sex-based differences which influences this inequality by SARS-CoV-2 is the hormonal impact of sexes on COVID-19 infections. The male androgen, TMPRSS2 favours the onset of inflammatory processes by facilitating virus entry and interestingly, well known inflammatory conditions occurring more frequently in men like cardiovascular diseases (*i.e.*, atherosclerosis and dilated cardiomyopathy), many cancers (*i.e.*, lung, liver and stomach) and other co-morbidities like male-dominant autoimmune diseases (*i.e.*, type Ⅰ diabetes and myocarditis) are leading causes of COVID-19 associated death in men[27–31]. In contrast, inflammatory diseases that occur more often in women tend to be chronic with lower mortality like most autoimmune diseases, allergy and asthma[27,32] and so did the case of less observed mortality in COVID-19 infections. The role of mitochondrial dynamic processes like mitochondrial fission/fusion cannot be side-lined especially in the context of SARS-CoV-2 viral infection which is another RNA virus with life threatening mitochondrial dynamics mediated inflammatory consequences.

Sexual dimorphism in mitochondrial functions can also lead to such imperfections in metabolic fitness between males and females, for instance, the females have an edge over males with respect to elevated oxidative capacities as described in many tissues such as liver and brain seen in the rodent studies. Observations in mouse brain reflected that the mitochondria of female rodent brains displayed[33] higher electron transport chain activity and adenosine triphosphate production[34] and greater functional capacities than their male counterparts[35]. Support in this aspect was also reinforced with higher mitochondrial enzyme activities such as citrate synthase, succinate dehydrogenase, and mitochondrial reductase in post-mortem human brains found in female brains than the males[36]. This indicates a less oxidative damage to female brain mitochondria than males irrespective of the age[37].

In addition to the sex based differences in oxidative capacities in men and women that can be attributed to estrogens promoting mitochondrial biogenesis, efficiency, and protection against oxidative stress[38], other studies have shown a lower production of mitochondrial free radicals that contribute to reactive oxygen species mediated cell death in females than males, and females also harbor a higher content of antioxidant enzymes than males[39–42]. In total, all this implies that the male androgen hormone TMPRSS2 facilitate the SARS-CoV-2 entry, making easy grounds for its entry and also augmenting post viral inflammatory complications in contrast to estrogens that support the enhanced mitochondrial anti-inflammatory and antioxidant events, justifying the sex-based discrimination in COVID-19 associated mortalities in this pandemic. Thus, a compromised mitochondrial functional activity resulting from genetic factors, aging associated comorbidities, and lifestyle, could have a decisive consequence not only on the resistance to the virus but also on the ability to mount an effective response to a vaccine. Hence, the severity of viral infection in males with more co-morbidity and less efficient immune system compared with a more robust mitochondrial functional reservoir in females, leading us to speculate that women are perceptibly expected to mount a more protective and long lasting anti-viral immune response against the ongoing COVID-19 vaccinations.

4. Sex differences in response to COVID–19 vaccines

While men are more susceptible to infections, females depict a higher rate of autoimmune diseases and also mount superior immunity in response to vaccinations. Sex-based vulnerability

to SARS-CoV-2 infection and the severity of COVID-19 disease are likely linked to better innate and adaptive immune response of females and the sex related differences in cytokine release and inflammatory response.

The present review focusses exclusively on two kind of vaccines commonly used in India: Covishield and Covaxin. Covishield which is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus vector encoding the S glycoprotein of SARS-CoV-2 and Covaxin which is an inactivated virus developed using whole-virion inactivated vero cell derived platform technology.

4.1. Covaxin

The TLR7/8 agonist adjuvant in the inactivated vaccine formulation induces Th1 biased antibody responses, causing an increased IgG2a/IgG1 ratio and increase in SARS-CoV-2 specific IFN-γ-producing CD4 T lymphocyte response. TLR7/8 agonists induce dendritic cells to generate a strong type Ⅰ interferon response and monocyte-macrophages to facilitate the development of Th1 biased immunity. Antigen formulated with Algel-IMDG skewed towards Th1 mediated response and induced strong T cell immunity, showing elevated levels of IFNγ-producing CD4 cell population. A combination of both humoral and cell-mediated immune response is a desirable COVID-19 vaccine result. It is the TLR7/8 agonists as an adjuvant in SARS-CoV-2 vaccine formulation which will minimize the Th2 response and control the ADE/ERD, if any. All the three inactivated whole virion SARS-CoV-2 vaccine candidates in our study showed 100% seroconversion with high titers of antigen binding and neutralizing antibody responses. The secretion of antiviral cytokines such as IL-2, IL-4, IL-6, IL-10, IL-17, TNF-α, and IFNγ were observed on days 7 and 14 (7 days after the 1st & 2nd dose) of vaccination with Algel-IMDG adjuvant formulations. Further, IFN-alpha might contribute to the activation of the first line of defense mechanisms, which lead to enhanced activation of antigen-presenting cells, such as dendritic cells or macrophages. It is reported that TLR recognition in innate cell population drives early type Ⅰ IFN production, thereby promoting viral clearance and the early production of pro-inflammatory cytokines.

The X-linked gene expression of TLR-7, TLR-8, CD132, and CD40 in both innate and adaptive immune cells and modulators of NF-kappa-B transcription factor gives females a super-added benefit. A higher $CD4^+$ cell counts, $CD4^+/CD8^+$ ratio and a better cytotoxic T- and T-suppressor cells is expected in females. Estrogen modulates the function of both $CD4^+$ and $CD8^+$ T-cells and myeloid cell lines by increasing the expression and release of Th1 pro-inflammatory cytokines (IL-12, TNF-α, and IFN-γ) and reducing the release of Th2 anti-inflammatory cytokines IL-10, IL-4 and TGF-β. Since females tend to control T cell expression and show a higher $CD4^+/CD8^+$ ratio, it is postulated that females respond better to Covaxin than males. Estrogen modulates the antigen recognition response by acting on TLR7, which causes the dendritic cell induced increased production of INF-α. This regulation highlights the role that endocrine regulation plays in the immune response which leads to sex-specific disease outcomes[43].

4.2. Covishield

The spike S1 protein is an external protein on SARS-type Ⅱ-coronavirus which helps it enter cells through the interaction of subunit of spike protein and ACE2 receptor in the host. Covishield causes the S glycoprotein expression on cells which locally stimulates neutralizing antibody and cellular immune responses as an active immunity. Geometric mean antibody titres of IgG antibodies against spike (S) protein were comparable between the injected and non-injected groups at baseline, *i.e.* day 1 increased significantly after each dose of vaccine in both sexes (males and females). There was 100% seroconversion in both the sexes on day 57 as well. The four structural proteins expressed on SARS-CoV-2: N (nucleocapsid), E (envelope), S (spike), and M (membrane) proteins are potential antigens which induce neutralizing antibodies and provide protective function[44,45].

The affinity of the spike protein RBD of SARS-CoV-2 has been shown to be very high for the ACE2 receptor and structural mimics to RBD can be used to block access to the entry receptor, *i.e.*, human ACE2 receptor[46]. The receptor binding domain of the spike protein from SARS-CoV has been shown to block the virus from accessing the ACE2 receptor in cell culture[47]. As spike proteins of coronaviruses are the most important antigenic determinants known to trigger neutralizing antibodies, spike proteins can be used as antigens for developing vaccines[45,48]. Spike protein RBD sequences are relatively conserved, and they can activate extremely effective neutralizing antibodies against this virus, which has been elucidated by the monoclonal antibodies isolated from the inactivated virus-immunized human and mice antibody libraries[47,49]. The RBD of this virus S protein plays dual function as important domain for receptor binding of this virus and a significant neutralization determinant element of SARS-CoV-2. So the proteins that contain the RBD region or vectors encoding the spike protein RBD can be foreseen as an effective vaccine candidate. The limitations of requirements for multiple

booster shots and adjuvant selection still exist, as with any other subunit vaccines[44,50,51].

The relative efficiency of these two vaccines in generating and mounting effective immune response is now well known although unprecedented data is yet to prove the hypothetical belief that Covaxin would produce better immunity in females as compared to males and needs detailed investigation in large cohort.

Work on animal models to provide evidence of COVID-19 severity in men and women has thrown out exciting results. Recent attempts to validate the sex dependency on the severity of lung disease in males have given unexplored leads and insightful clinical observations using an experimental animal model such as golden Syrian hamster. In one such approach attempt to examine the interrogation of biological sex as a factor with COVID-19, Dhakal *et al.*[52] reported that female hamsters show lower morbidity, developing less extensive pneumonia, and greater antibody response to SARS-CoV-2 than male hamsters. The authors also found that females had higher and broader humoral response than males during SARS-CoV-2 infection. Intriguingly, the female hamsters showed a greater cross-reactive antibody response, IgM, IgA, and IgG antibody responses against the receptor-binding domain of the spike protein (S-RBD) and its variants (anti-S-RDB IgG, wild type, N501Y, Y453F, N439K, and E484K). It becomes imperative to unravel the role of androgen treatment in impacting the humoral response and unravel likely mechanism(s) fundamental to sex differences of SARS-CoV-2 such as genetics (X-inactivation, genetic variants, and epigenetics), microbiome (metabolomics), sex hormones (androgen, estrogen, and estrous cycle), metabolism (biological sex differences in adipose tissue distribution, visceral and subcutaneous), and aging.

5. Conclusions

Given the sex differences in COVID-19 health outcomes, it becomes extremely important that countries collect, analyse and publish sex-based differences and disaggregated data on COVID-19 to facilitate adoption of effective public health measures that will help in mitigating the adverse health outcomes of this pandemic. In the current scenario of vaccine response, as the only saviour strategies against the existing COVID-19 health emergency, it becomes imperative to highlight the evidence-based sex differences in anti-SARS-CoV-2 immune response and vaccine responses. Not surprisingly, for most of the countries, the sex-disaggregated data is lacking, and the need of the hour is to segregate the added data and information by sex in epidemiological reporting and research findings. The awareness of the clinicians of sex differences in vaccine developments through the reported information in scientific studies published in peer-reviewed journals is a must to address vaccine misinformation and cater to the queries and concerns that underappreciated sex as a biological variable in COVID-19 pandemic. Our understanding of sex-based biological factors will help us guide effective therapies for this virus and enhance precision of personalized medicine and will bring lucidity in the necessary guidelines of vaccination protocols. It will also unravel the prevalent mysteries about the need of boosters for women with more robust immune responses and the post vaccination consequences such as adverse effects and how they impact anti-COVID immunity and immune responses.

Conflict of interest statement

The authors declare that there is no financial and non-financial conflict of interest.

Acknowledgments

Mr. Karan Gaur is deeply acknowledged for his contribution in making the figure.

Funding

There is no funding source or financial support available from any grant or institutional support for the design and for the publication process of this manuscript.

Authors' contributions

A.M. conceptualised, designed and wrote the manuscript, A.S. also participated in the conceptualisation and writing of the manuscript, S.G. contributed in writing one section of the manuscript, V.R., G.P, S.M. and V.J. helped in proof reading and editing the manuscript.

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