Review Article

Gender and genetic factors impacting COVID-19 severity

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Abstract

COVID-19 pandemic is a cause of global concern and is impacting lives and economy globally. Infection due to SARS-CoV-2 leads to varied clinical manifestations, which can vary from asymptomatic to severe acute respiratory syndrome and death. The clinical features are proposed to depend upon various host factors, namely, gender and genetic factors. The significantly high mortality among males has revealed the role of gender, androgens, age, genetics, and risk factors in determining the severity of COVID-19 among the population. The interplay of various host factors and their association with clinically severe infections is crucial for our understanding of COVID-19 pathogenesis. A PubMed and Google scholar search was made using keywords such as "COVID-19 + sex differences," "COVID-19 + androgens," "COVID-19 + ACE2 receptor," and "COVID-19 + smoking alcoholism pregnancy." The articles which highlight the association of gender and genetic factors to COVID-19 were selected and included in our study. It is mainly the primary care or family physicians who act as the first contact of COVID-19 patients. With the recent increase in SARS-CoV-2 infections in the Indian subcontinent and probability of upcoming surges, it has become imperative to understand its interaction with the various gender and genetic factors to devise effective triage and management protocols. Our review highlights the possible mechanisms by which these factors impact the severity of COVID-19. A better understanding of these factors will be of immense help to primary care physicians.

Keywords: ACE-2, androgen, COVID-19, host genetic factors, SARS-CoV-2

Introduction

The pandemic due to SARS coronavirus-2, coronavirus disease-19 or COVID-19 is a cause of global concern and is impacting lives and economy globally. As of 5th July, 2021, over 183 million cases are reported globally with about 30.5 million from India. It has also resulted in 3.97 million deaths worldwide.[1] Currently, many countries have reported a second wave of infection with India reporting more than 4 lakhs COVID-19 cases daily, in May, 2021. Infection due to SARS-CoV-2 leads to varied clinical manifestations, which can vary from asymptomatic to severe acute respiratory syndrome and death. The degree of severity has been reported to be different in different geographical locations with a mortality rate of 0.7 deaths per 100,000 in South Korea to 86.8 per 100,000 in Belgium.[2]

Various host factors that have been attributed to COVID-19 disease severity are male gender, old age, patients with diabetes mellitus, hypertension, and cardiovascular diseases.[3] Worldwide higher risk of severe disease and mortality are reported among males, including in India.[4,5] Globally, males have been shown to have significantly higher mortality compared to females with about 1.17 million deaths reported among males as compared to 900,000 deaths among females.[6] Similarly in India, 68% of mortality due to COVID-19 was among men while women constituted 32% of the total deaths reported.[7] The comparative mortality depending on gender is depicted in Figure 1.

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Received: 27-04-2021 **Revised:** 08-07-2021
Accepted: 10-07-2021 **Published:** 29-11-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_769_21

How to cite this article: Ranjan J, Ravindra A, Mishra B. Gender and genetic factors impacting COVID-19 severity. J Family Med Prim Care 2021;10:3956-63.

A higher percentage of severe disease among males has also been reported in other coronaviruses like severe acute respiratory syndrome coronavirus (SARS-CoV)[8] and Middle East respiratory syndrome coronavirus.[9] Several studies have attributed different host factors for severity.

The importance of primary care physicians was highlighted during the second wave of COVID-19 in India. Nonavailability of hospital beds and scarcity of equipment such as ventilators to the patients in need were commonly seen during the second wave.[10] Family physicians or primary care physicians play a key role in COVID-19 management. They help in the early diagnosis of the disease, in assessing the clinical severity of COVID-19 among the patients, and are also responsible for triaging patients and providing emergency care, thus, decreasing the burden on hospitals.[11] A better understanding of various gender and genetic factors among these physicians will be of immense help in devising effective patient management and triage strategies. The present review describes the various gender and genetic factors impacting COVID-19 disease.

Methodology

A literature search was performed using Google Scholar and PubMed. Keywords "COVID-19 + sex differences," "COVID-19 + androgens," "COVID-19 + ACE2 receptor," and "COVID-19 + smoking alcoholism pregnancy" were used. The articles which highlight the association of host factors to COVID-19 were selected and included in our study.

Discussion

Host receptors

SARS-CoV-2, the etiological agent of COVID-19 is a positive-sense RNA virus of 29,903 bases, belonging to the genus Betacoronavirus. The virus genome encodes for spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. Spike proteins are projected from the envelope and are mainly responsible for the entry of virus into the host cells.[12]

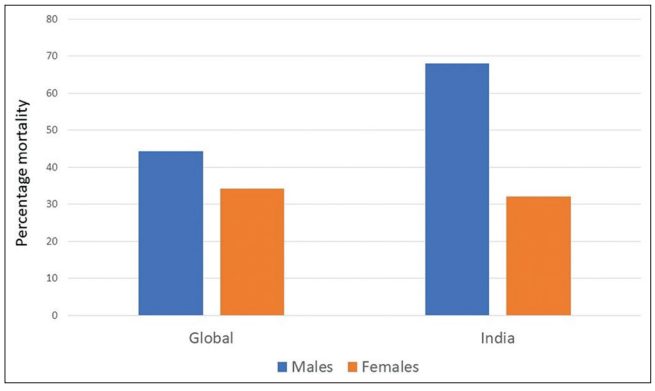

Figure 1: Gender disparity in COVID-19 mortality (Based on the data available from [6] & [7])

The entry of virus to host cell is mediated by the binding of the receptor-binding domain (RBD) of the spike protein of virus to the peptidase domain of the angiotensin-converting enzyme-2 (ACE-2) receptor on the host cell.

The spike protein (S-protein) is a clove-shaped homo trimer composed of a monomer made up of two segments S1 and S2. The S1 forms the ectodomain, while S2 forms the stalk, transmembrane, and intracellular domain. The RBD lies in the S1 part of the S-protein. RBD is composed of core domain and receptor binding motif, which is an extension of the RBD. S-protein is primed by transmembrane protease, serine 2 (TMPRSS2). It clips S2 and exposes viral fusion peptide and results in viral fusion to the plasma membrane. The S1 subunit of the virus attaches to the ACE-2 receptor to gain entry into the cells. Single nucleotide polymorphisms (SNPs) are the mutations, which result in the production of different proteins, different susceptibilities to infections, and can also affect the disease severity. SNPs of TMPRSS2 gene, namely, rs2070788 and rs383510, have been reported to increase the susceptibility of the host to influenza virus by increasing the expression of TMPRSS2 Figure 2 depicts the factors influencing TMPRSS2 expression.[13] Chiappelli has hypothesized that the same can also be extrapolated to the COVID-19, wherein the same SNPs can be associated with increased severity of infection,[14] whereas a study by Hussain *et al*.[15] has shown that SNPs in ACE-2 region, rs73635825 (S19P) and rs143936283 (E329G), result in decreased susceptibility to SARS-CoV-2. This is because of decreased binding affinity of these residues with SARS-CoV-2. It is hypothesized that S-protein also binds to basigin, which is also called extracellular matrix metalloproteinase inducer (EMMPRIN), i.e. CD147 present on the host cell surface, and leads to invasion of virus into the cell.[16] Overexpression of EMMPRIN in the cells can promote SARS-CoV-2 viral infection by facilitating the entry of SARS-CoV-2 in cells.[17]

Gender and sex hormones

Increased susceptibility of males to SARS-CoV-2 is attributed to androgens such as testosterone and dihydrotestosterone. Androgens bind to androgen receptors (ARs) which in turn act as an enhancer to the promoter-bound RNA polymerase machinery. This activates the expression of TMPRSS2 [Figure 3].[18] More

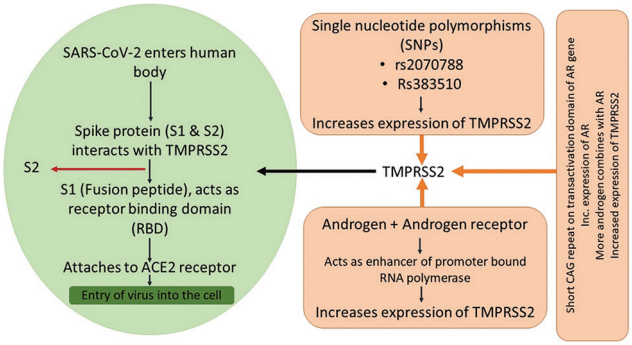

Figure 2: Factors influencing TMPRSS2 expression

S1/S2 regions are primed by the TMPRSS2 and more viruses gain entry into the host cells through ACE-2 receptors. The effect of androgen on susceptibility to COVID-19 infection is substantiated by the studies wherein patients with androgenic alopecia are found to have a severe infection.[19] Patients on androgen deprivation therapies (ADT) for prostate cancer are reported to have lower severity of infection.[20] A significant reduction in ICU admissions due to COVID-19 was observed among males taking antiandrogens such as dutasteride or finasteride by Goren *et al*.[21] This is due to the downregulation of TMPRSS2 by the use of AR antagonists, which in turn leads to lower disease severity by the decreased entry of SARS-CoV-2 into the cells.

AR is hypothesized to play a major role in disease severity in the case of COVID-19 infection. The gene for AR is present on X-chromosome Xq 11-12 and is comprised of three domains: ligand-binding domain, DNA-binding domain, and transactivation domain. The N-terminal of the later domain contains the DNA segment known as cytosine, adenine, guanine trinucleotide repeats or CAG repeats in a polymorphic polyglutamine (polyQ) tract.[22] The polymorphism of CAG repeats has been shown to be responsible for different rates of COVID-19 mortality among various racial populations. Normally, this CAG segment is repeated 11–31 times within the gene. The longer length of CAG repeats results in the decreased transactivational activity of ARs.[23] The short length of CAG repeats is associated with androgenic alopecia and is also proposed to lead to increased disease severity.[24] This is due to the fact that the short CAG repeats display higher expression of AR genes, generating an increase number of functional AR leading to higher sensitivity for androgen and thereby an increase in the viral entry in the host cells. A more severe disease leading to mortality is also predominantly noted among African-Americans having AR gene polymorphism with shorter CAG repeats.[25]

In contrast, recent study by Baldassarri *et al*.[22] shows that the presence of shorter polyQ tract among the European males led to better protection from COVID-19 among them. This was postulated to be because of proinflammatory action of long polyQ repeats, leading to more severe inflammatory response. Thus, more studies are required to better understand its relationship with COVID-19.

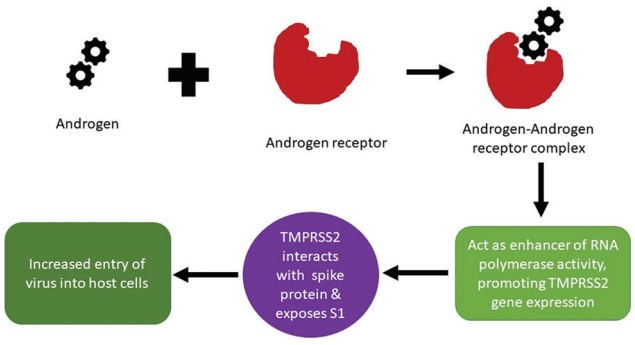

Figure 3: Androgen-androgen receptor complex acting as enhancer to promote TMPRSS2 expression

Gender and immune response

Immune response in both sexes differs because of the expression of different toll-like receptors (TLR). A higher expression of TLR-2 and TLR-4 is seen among males, while females show a higher expression of TLR-3, 7, and 9.[26] TLR-4 has a high affinity for S-protein of SARS-CoV-2.[27] Stimulation of TLR-4 has been shown to result in a strong cytokine response,[28] which can be one of the possible reasons for more severe infections among men. However, in females even though TLR-7 expression is higher, the production of proinflammatory cytokine IL-6 is lesser.[29] This might explain milder infections in females.

Additionally, in males, androgens lead to increased neutrophils which translates to increased interleukin and tumor growth factor-β production[30] leading to cytokine storm.[31] In females, estrogen is associated with T-cell proliferation and X-linked genes are said to increase the immune response.[26] This might be a reason for milder disease among females.

Estrogens decrease the production of proinflammatory cytokines (mediated by Th1) and increase the production of antiinflammatory cytokines.[32] Estrogen receptors (α and β) are present on B cells. Estrogen combines with these receptors and upregulates the expression of B-cell lymphoma-2 (Bcl-2), SHP-2, and CD22. Increased expression of these proteins is associated with decreased apoptosis.[33] This can increase the survival of B-cells and provide a protective antibody response to the viral infections.[34]

High level of estrogen among African women has also been proposed to be protective against severe COVID-19. Estrogen decreases endoplasmic reticulum (ER) stress by activating unfolded protein response pathway and restores ER integrity. This in turn decreases SARS-CoV-2 multiplication in the cells leading to lesser severity of infection.[35]

X-chromosome

Genes present on X-chromosome have an influence on the immune response.[36] X-chromosome has been studied for its effects in disease outcomes of HIV and various other viral infections.[37] The presence of pattern recognition receptor (PRR) genes (TLR-7 and 8), AR gene, ACE-2 gene, and genes for various interleukins (IL-RAP1, IL2-RG) on X-chromosome are responsible for its relationship with innate and adaptive immunity.[38] TLR-7 activity has been shown to have an influence on the disease severity of COVID-19. Viral infections such as influenza promote TLR-7 expression. On binding with a ligand, TLR-7 activates the myeloid differentiation response gene 88 (MyD88) pathway and activates IFN regulatory. This results in the production of proinflammatory cytokines. TLR-7 also stimulates B-cells to increase antibody production.[39] In a recently published study, loss-of-function variants of TLR-7 on X-chromosome have been detected in patients with severe

COVID-19.[40] Impaired Interferon-I and Interferon-II responses were also reported among these individuals, signifying a decreased immune response.

MicroRNAs (miRNAs) are double-stranded, non-coding small RNAs, which control gene expression, regulate protein synthesis, and are supposed to play a role in immunity.[41] There are about 112 miRNAs, which are encoded by X-chromosome but only about 2 miRNAs are present on Y-chromosome. Thus, variations in regions of X-chromosome, which encode for these miRNAs, can have an influence on COVID-19 disease progression.[42]

Age

Children are found to be less affected with COVID-19 with majority of them presenting with milder symptoms.[43] Macias-Parra *et al*.[44] and Jat *et al*.[45] in their studies have found that majority of children presented with mild symptoms and had a better prognosis. It has been postulated that the presence of lesser ACE-2 receptors (leading to decreased viral entry into host cells) and a higher activity of the innate immune system because of more proportion of natural killer cell and lymphocytes (resulting in more viral lysis)[46] can be the reason behind less severe infection in children.[47]

Neutrophils in children show weak bactericidal effects and decreased chemotaxis.[48] Macrophages and monocytes are also immature and have decreased TLR-4 expression, resulting in lower cytokine responses.[49] The majority of severe clinical manifestations of COVID-19 are because of the cytokine storm. A lower cytokine response can also be considered as one of the causes for less severe infection among pediatric population.

Other factors such as a high level of melatonin, immunomodulatory effects of other vaccines, and difference in microbiota are also proposed to have a protective effect on children. Melatonin is known to block CD147, which facilitates entry of SARS-CoV-2 into cells and also decreases expression of ACE-2 on cell surface by inhibiting calmodulin. This in turn can result in decreased virus entry into the cells. Since children are known to have higher levels of melatonin, they are postulated to have less severe infections. Vaccination among children for various infections is known to produce cross-reacting antibodies, which also has a protective action from SARS-CoV-2. Certain studies have also shown that children are colonized with a heavy load of viruses and bacteria and hence competition among these and SARS-CoV-2 might lead to a lesser entry of it in the human cells and thus resulting in milder infections.[50]

A thorough understanding of the factors influencing disease progression in children is of vital importance. It will help in devising better treatment strategies for pediatric COVID-19.

Host genetic factors

HSD3B1 gene

The genetic makeup of the host also plays a vital role in determining the severity of the illness. *HSD3B1* gene encodes for 3β-hydroxysteroid dehydrogenase-1, which transforms dehydroepiandrosterone into more active androgens. There are two forms of *HSD3B1* gene, i.e., adrenal permissive HSD3B1 (1245C), which encodes for enzyme which is resistant to degradation, and adrenal restrictive form, which encodes for enzyme which is degraded easily. The presence of an adrenal permissive form of this gene might lead to increased androgen production and thus impacting disease severity. It can also result in associated features such as androgenic alopecia.[51] Spain recorded one of the highest COVID-19 mortality rates worldwide, i.e. 544 per million population in the initial phases of the pandemic, as compared to other European countries.[52] This could be due to the prevalence of adrenal permissive *HSD3B1* allele among the Spanish population.[53]

Genetic variants

In recent studies, genetic variants (a group of alleles present on various chromosomes) are found to be associated with COVID-19 severity.[54] *DNAH7* gene encodes for dynein axonemal chain 7. It is a component of ciliary axonemes. Variations in *DNAH7* can result in decreased mucociliary clearance and eventually severe COVID-19 symptoms.[55] *CLUAP1* gene is responsible for the formation of clusterin-associated protein 1, which helps in ciliogenesis.[56] *CLUAP1* gene containing the super variant SNP rs2301762 can lead to alteration in the functioning of cilia and is known to be associated with severe disease.[57] Moreover, the effect of SARS-CoV-2 on cilia can be gauged by the fact that COVID-19 infection leads to ciliary dysregulation and anosmia.[58]

Acute myocardial damage has been reported among certain COVID-19 patients.[59] Genes *DES* and *SPEG* can be associated with cardiomyopathies and cardiac manifestations of the infection. Gene *DES* and gene *SPEG* encode for muscle-specific intermediate filament and muscle-enriched protein kinase, respectively.[60] SNPs in Chr2_221 located near the genes *DES* and *SPEG* are associated with cardiomyopathy. This can also be enhanced by SARS-CoV-2 leading to acute damage of the myocardial tissues.[59]

COVID-19 leads to platelet activation and may predispose patients to various thrombotic diseases.[61] *STXBP5* encodes for syntaxin 1 binding protein. It promotes platelet secretion and is associated with thromboembolic disorders.[62] Chr6_148 is a super variant, which contains 101 SNPs. These SNPs are present in *STXBP5* gene (89 in STXBP5 and 6 in STXBP5-AS1). Mutations in *STXBP5* predispose to venous thromboembolic disease and might result in increased mortality in COVID-19 patients.[54]

Another genetic factor influencing disease severity is *WSB1* gene. It functions as receptor binding molecule of interleukin-21 (IL-21).[63] Three variant SNPs are found on Chr17_26, which includes SNP rs60811869 which is an expression quantitative trait locus of *WSB1* gene. Genetic variations in this region will also result in higher mortality among COVID-19 patients due to an altered immune system.

Of late, C9orf72 gene, which is an autophagy gene and is associated with vesicular trafficking and lysosomal activity, has also been shown to affect outcomes in COVID-19. It is responsible for the degradation of inflammatory mediators like TLRs. There are many hexanucleotide repeat expansions, which are present in it. Intermediate repeats (repeats of >10) show a higher degree of methylation among them and can result in severe infection due to decreased degradation of the inflammatory markers.[64]

Ellinghaus *et al*.[65] have recently shown that 3p21.31 gene cluster has a significant association with severity in COVID-19 positive patients with respiratory failure. This is a cluster of six genes, namely, *SLC6A20*, *LZTFL1*, *FYCO1*, *CXCR6*, *CCR9,* and *XCR1*. *SLC6A20*, which encodes for sodium-amino acid transporter, forms a complex with ACE-2 and facilitates entry of SARS-CoV-2. Increased expression of this gene can lead to more entry of the virus into the cell. Other genes in the cluster such as *LZFTL1* and *CXCR6* are to influence ciliogenesis and activity of natural killer cells. A variation in the genetic components of these genes can also have an effect on disease progression.[66] Various genome-wide association studies have been undertaken to ascertain the effect of different genetic variations on COVID-19. SNP rs11385942 on chromosome 3 has been identified as a risk variant in such studies, signifying the role of host genetics on COVID-19 severity.[67]

Pregnancy

Physiological conditions such as pregnancy are also postulated to have effects on COVID-19 infection. Usually, an increase in ACE-2 is seen during pregnancy and this poses a greater risk of acquiring SARS-CoV-2 infection during pregnancy.[68] A decrease in Th1 response compared to Th2 response is observed during pregnancy, which might lead to lesser clearance of virus-infected cells and severe COVID-19 infection.[69] Other factors that can result in severe COVID-19 in gravid females can be a decrease in natural killer cells and reduced dendritic cells. These need to be studied further to accurately ascertain the relationship between these immunological changes and the severity of COVID-19.[69]

Risk factors

Habits such as smoking and alcoholism are attributed to increased severity of many viral infections, possibly due to reduced level of natural killer (NK) cells among people who smoke.[70] Similarly, other habits such as substance abuse can also have an effect of COVID-19 infections.

Smoking

Smoking is found to have a direct relationship with the worsening of COVID-19 symptoms in the majority of studies.[71] Benzano *et al*.[72] in their study found a significant correlation between smoking and COVID-19 severity with about 82% patients with severe COVID-19 being smokers.

This can be due to the upregulation of ACE-2 receptors in current smokers, which result in increased uptake of the SARS-CoV-2 virus by the host cells.[73] Recent studies have also demonstrated that a significant increase in ARs and ACE-2 receptors is seen among elderly male smokers.[18] This can in turn lead to an increase in viral entry into cells and severe clinical manifestations of the disease. This is corroborated in the study by Maggi *et al*.[74]

In contrast, Purohit and Panda in their study showed a protective influence of smoking against SARS-CoV-2 infection. The probable causes for such an observation could be squamous cell metaplasia (SQM) and ACE-2 expression. SQM is seen among smokers and usually results in the altered cell surface, which could hamper the entry of the virus into the cell. Certain studies have also shown that nicotine decreases the expression of ACE-2, hence decreasing infection. Further analysis of smoking and its effect on COVID-19 is still warranted to better understand the interplay of various factors.[75]

Alcoholism and substance abuse

Alcohol consumption is known to reduce immunity to viral infections and makes the host more vulnerable to COVID-19.[76] This was substantiated by Saurabh *et al*.[77] in their study, wherein alcohol consumption was found to be a risk factor for the development of symptomatic COVID-19. Substance abuse leads to cardiomyopathy, lung injury, and pulmonary hypertension, which results in a bad prognosis of COVID-19 infection.[78] This has been substantiated in studies by Wang *et al*.[79] and Althobaiti *et al*.[80]

Figure 4 depicts the summary of gender and host genetic factors influencing COVID-19 severity.

Conclusion

Host factors such as *TMPRSS2* and *ACE-2* expression, androgen, and ARs play a major role in contributing to higher severity and mortality in male gender. Understanding the interplay of gender and host genetic factors influencing COVID-19 mortality is the need of the hour to devise appropriate management and research should be carried out to find out the role of antiandrogen in decreasing the severity of COVID-19. It will also be of immense help for primary caregivers to devise effective triage and management protocols for future COVID-19 surges.

Key Messages

- Gender and genetic factors influence the severity of COVID-19.
- The presence of androgens in males has shown to be a risk factor for severe SARS-CoV-2 infection.
- Antiandrogens or ADT as used in prostate cancer can also be used for the treatment of COVID-19.
- X-chromosome carries genes that are responsible for immune response.

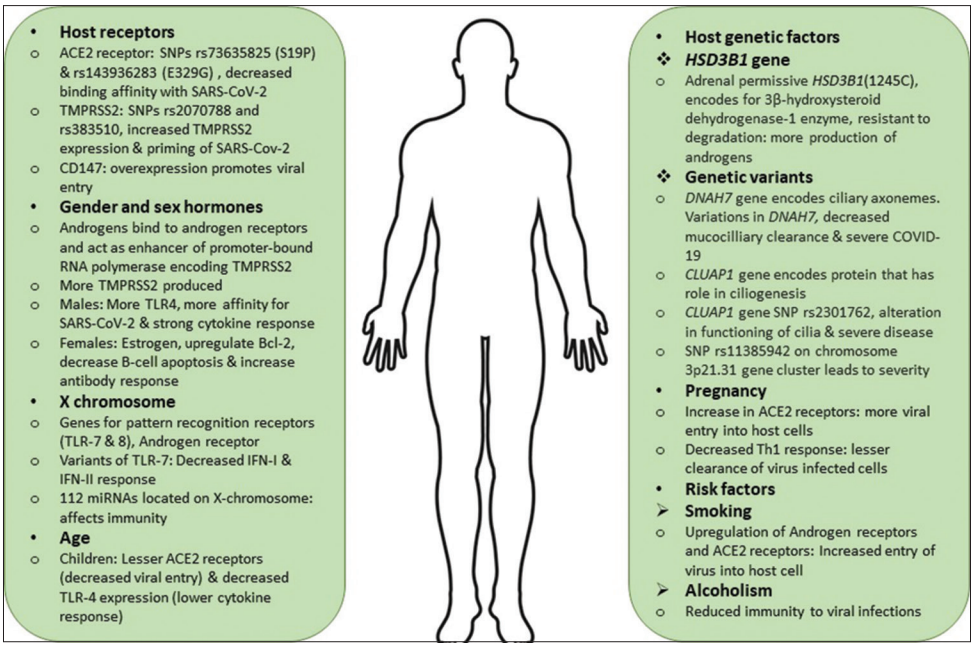

Figure 4: Summary of gender and genetic factors influencing COVID-19 severity

- Estrogen is protective against severe COVID-19.
- Children usually have milder symptoms because of the presence of higher proportion of lymphocytes, high level of melatonin, and cross protection conferred by other vaccines.
- Genetic variation among hosts, i.e. SNPs in *DNAH7, DES, SPEG, STXBP5,* and chromosome 3 cluster of genes influence the disease severity of COVID-19.

Acknowledgement

None

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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