

## Genetic and Hormonal Susceptibilities to SARS-CoV-2 and Severe COVID-19

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### Mini Review

Over the course of the COVID-19 pandemic it has been acknowledged by a variety of sources that elevated SARS-CoV-2 infection rates were observed in biological males when compared to biological females. While the incidence of COVID-19 in biological males versus biological females varies based on region and date of data collection, a study of approximately 1,100 patients from 30 provinces in China reported that 58% of COVID-19 patients were male [1]. An early hypothesis regarding non-genetic factors contributing to this sex predisposition was that smoking may be a contributing factor, as the smoking rate among Chinese men in 2018 was more than 22 times that of women [1]. This relationship was explored in multiple studies enrolling cohorts of Asian men, and although none resulted in statistically significant correlations, smoking is likely one of many comorbidities that contributes to increased severity of COVID-19 worldwide [2]. While correlations between older age and COVID-19 severity have also been explored, it appears that males are more prone than females to severe disease phenotype, independently of age [2]. An anthropological approach has also been employed, considering the impacts of gender norms and cultural habits across different countries and regions of interest in relation to disease susceptibility and severity. In addition to likelihood of smoking, behaviors such as compliance with hygienic procedures, the maternal/child-care related expectations of women, and the working role of men have all been speculated to contribute to the sex predisposition of SARS-CoV-2 [1,2].

Severe inflammatory responses such as elevated cytokines, chemokines, and growth factors have all been reported in patients infected with SARS-CoV-2 [3,4]. Across all humans, up-regulation of interferon-I (IFN-I) proteins IFN $\alpha$  and IFN $\beta$  is a standard immune response against viral infections [4]. Early into the pandemic, IFN-I pro-inflammatory signaling was detected in a SARS-CoV-2-infected mouse model, specifically in mice who express human angiotensin-converting enzyme-2 (ACE2), the receptor used for viral entry into human hosts [3, 5]. ACE2 alone is not always sufficient for viral entry, however, as entry is sometimes enhanced by transmembrane serine protease-2 (TMPRSS2) [5]. Entry of SARS-CoV-2 may be enhanced when TMPRSS2 cleaves ACE2, mediating viral pathogenesis and progressing the disease [5]. Furthermore, the gene encoding ACE2 is located on the X chromosome, render-

ing biological males as homozygous, while biological females may be heterozygous [5]. The phenotypic variation in female ACE2 proteins may contribute to the lower-case positivity rates and therefore reduced disease burden of COVID-19 in female versus male patients.

The differential immune responses of men and women must not be overlooked in assessing the processes which underlie the imbalance in mortality of male versus female COVID-19 patients. A variety of modalities have been used to immunophenotype these sex differences, one of which being assaying plasma cytokines and chemokines [3]. In a cohort of 39 patients (17 male, 22 female) matched by age and body mass index (BMI), all of whom were screened for 71 cytokines and chemokines in their blood plasma, investigators found that pro-inflammatory cytokines IL-8 and IL-18 were significantly higher in male patients than female patients at baseline [3]. When the data were adjusted for age and BMI, while the statistical significance between the male and female pro-inflammatory cytokine response was lost, it was revealed that male patients maintained a significantly higher response compared to healthy controls, while female patients lacked a significant pro-inflammatory cytokine response compared to healthy female controls [3]. Although the sexes display comparable levels of innate immune cytokines and chemokines while infected, a significant disparity in immune response both at baseline (increased IL-8, IL-18) and during disease progression (increased CCL5) within the male cohort likely contributes to increased severity of disease. The rationale for the reduced pro-inflammatory cytokine response in female patients at baseline is unclear, but perhaps females mount alternative immune responses such as virus-specific antibodies that prevent production of potentially harmful cytokines and chemokines in excess [6]. Of note, female patients who expressed higher innate immune cytokines and chemokines at baseline also exhibited worsening clinical disease outcomes, much like the male patient cohort [3].

It is hypothesized that testosterone may contribute to modulating expression of TMPRSS2, which could subsequently lead to poorer clinical outcomes for biological males [5]. Additionally, aging biological men are often characterized by decreased testosterone levels, which often translate to an increased pro-inflammatory condition [5]. Both of these scenarios – high and low testosterone – have a negative bearing on the clinical disease progression for males. On the contrary, estrogen is known to have profound effects on the innate immune system

including suppression of IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , as well as stimulation of CD4+ T-helper cell production, which in turn leads to an increase in anti-inflammatory cytokines [6]. Further, increased estrogen levels are known to promote antibody production by B cells, assisting in developing a specific response to pathogens such as SARS-CoV-2 [6]. In a mouse model, estrogen was found to decrease cytokine storm in the lungs and inhibit viral replication and cytopathic effects, all of which are associated with milder COVID-19 progression [6]. In comparison with the effects of testosterone, estrogen clearly has a large benefit for individuals with infectious diseases or otherwise challenged immune systems, assisting in tolerance and eventual clearance of COVID-19 in female patients with sufficient to high levels of estrogen.

Based on the factors discussed herein, one viable option for anti-COVID-19 therapy may include recombinant IFN-I proteins as a single agent and/or in combination with other antiviral therapies, as the role of the interferon response in the different stages of SARS-CoV-2 infection appears to be more complex than for other viral infections, such as influenza virus [4]. While preliminary trials have investigated these therapeutic regimens, additional stratification may be necessary to determine which patient cohorts will respond best to these therapies, as IFN-I proteins have been found to exacerbate inflammation in certain patient subgroups [4]. For this reason, it is also critical to continue investigating the potential use of JAK inhibitors, which interfere with the IFN-I pathway and could prevent further aggravation of IFN-I's pro-inflammatory properties [4].

Additionally, TMPRSS2 inhibitors have been indicated and approved for use for patients with prostate cancer; it has been suggested that use of these therapeutics for patients with COVID-19 may be beneficial in preventing cleavage of ACE2,

thereby preventing viral entry and thwarting infectious pathogenesis [5]. Finally, it is known that estrogen can suppress inflammation, reduce viral titers, and hasten pathogen clearance [5, 6]. Similarly, it is suggested that estrogen may even increase the effects of vaccinations [5], pointing to another avenue by which COVID-19 eradication may be accelerated. Although COVID-19 is a novel virus, the global urgency with which countless research endeavors have been conducted illuminates a diverse array of potential paths forward which may curb the global impacts of the disease. Acknowledging the non-genetic and genetic differences between males and females, and their downstream effects on host immune response and disease susceptibility, is paramount in tailoring medical treatment to the individual patient in pursuit of the best clinical outcome achievable for that patient.

## References

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