

Mini Review

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# Knowledge Gaps of The Morbidity and Mortality of COVID-19: Testosterone & Sex Differences

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## Introduction

The current COVID-19 pandemic has a male bias in morbidity/severity and mortality. This is consistent with previous coronavirus pandemics such as SARS-CoV and MERS-CoV, and viral infections in general (Figure 1). Data from previous coronavirus epidemics-SARS-CoV (2002) and Middle Eastern respiratory syndrome

coronavirus (MERS, 2012) showed differences in their manifestation based on sex, with men being consistently more severely affected than women. Reports of COVID-19 suggest a sex imbalance, with men at a higher risk of more severe disease and increased mortality (Figure 2).

## Influence on COVID-19 Infections & Deaths

Male sex considered a risk factor  
(Batiha et al., 2020)

Androgenic upregulation of angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) (Traish & Morgentaler, 2020)

Possible entry route in testicular cells due to high expression of ACE2 receptor in testes (Batiha et al., 2020)



**Figure: 1** What is the influence of sex and gender on COVID-19 infections and deaths?

It is evident that there is a clear male bias in severity and mortality. In fact, the male sex is considered as one of the risk factors for COVID-19. They are more likely to suffer or to die from complications. There are speculations that testosterone may be responsible for the higher disease burden. Numerous publications have argued that this can be explained by androgenic upregulation of various enzymes. There are concerns that COVID-19 may affect the ability to produce sex hormones. High expression of ACE2 receptor in the testes provides a route for the virus to enter testicular cells and cause damage.

## Influence of Sex & Gender on Immune Response

Different immunological environments where sex hormones play a role (Roved et al., 2016)

Estrogen is immune-enhancing  
Testosterone is immune-suppressing

Gap in healthy life expectancy from gender and sex-related differences

Effect on aging immune system poorly understood (Giebing-Kroll et al., 2015)



**Figure:2** When we look at the influence of sex and gender on immune response as well as susceptibility to infection, we may view males and females as different immunological environments, where sex steroid hormones cause varied responses.

In general, estrogens have immune-enhancing effects making women generally immune-privileged. On the other hand, androgens such as testosterone exert immunosuppressive properties. Gap in healthy life expectancy stems from gender and sex-related differences. However, sex-specific differences in the aging immune system are poorly understood. For example, the potential effects of testosterone replacement therapy on the immune system have not been addressed systematically. But there are implications for clinical trials on combining short-term hormone replacement therapy with vaccinations to improve vaccine efficacy.

Publicly available data from the Global Health 50/50 research initiative showed an increased mortality in men, despite similar numbers of COVID-19 cases in men and women. In addition to mortality, hospitalizations and admissions to intensive care units (ICU) showed men more affected than women (Figure 3). A review of data in several countries showed that there were 50% more men

requiring hospitalization compared to women, with ICU admission being three to fourfold higher. A meta-analysis of 15 independent studies found men had an odds ratio of 1.31 to develop a severe COVID-19 infection compared to women. Early reports by the Centers for Disease Control and Prevention (CDC) observed higher hospitalization rates for men (Figure 4).

## Influence on COVID-19 Infections & Deaths

Exact pathophysiological mechanisms remains incompletely understood (Traish, 2021)

Testosterone treatment may improve clinical outcomes (Alwani et al., 2021)

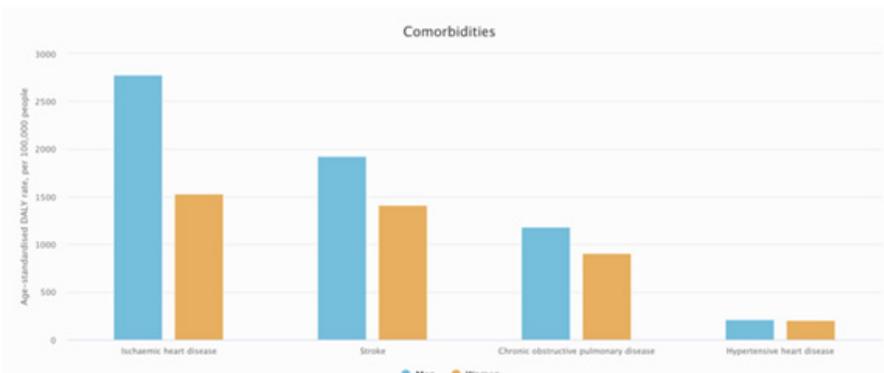
Social, behavioural and comorbidity factors responsible for gender disparities (Traish & Morgentaler, 2020)



**Figure:3** On the contrary, there are solid arguments stating that higher testosterone does not contribute to greater susceptibility, and that there is no significant evidence that the enzymes are associated with disease severity or gender disparity.

The exact pathophysiological mechanisms contributing to COVID-19 susceptibility to infection, severity and mortality remains incompletely understood. In fact, the role of testosterone on the immune response to the virus may be beneficial to patient outcomes potentially suppressing uncontrolled inflammatory responses. There is evidence of possible improvement in clinical outcomes with testosterone treatment in SARS-CoV-2 infected hypogonadal male patients. Gender disparities in COVID-19 infections and deaths can be attributed to social, behavioural and comorbidity factors. For example, men are more likely to be smokers than women.

## Influence on COVID-19 Infections & Deaths



Comorbidities among men and women (Traish & Morgentaler, 2020)

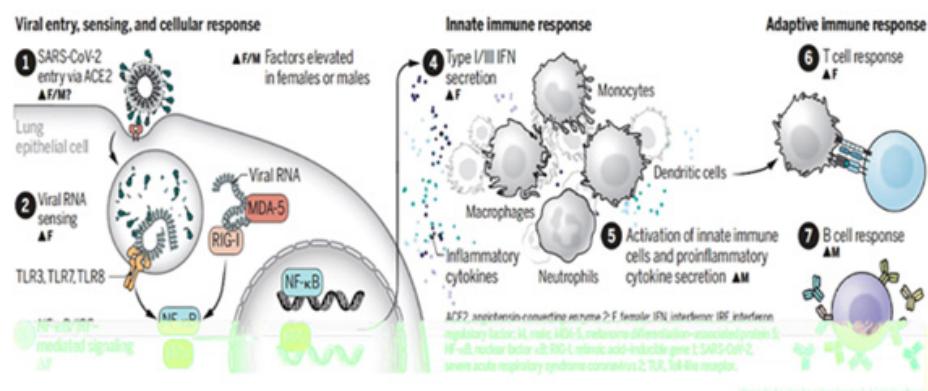
**Figure:4** As evident in the chart here, men have more comorbidities. In general, they do not utilize preventive health services as much as women.

Presence of comorbid conditions has one of the strongest associations with COVID-19 deaths. It is important to look at all sides of the argument as false beliefs in the scientific community can lead to poor judgements and reluctance in investigation of alternative possibilities.

There are, however, some limitations to this data particularly as the interaction between age and sex remains unclear. It was reported that the relative risk of dying from COVID-19 was consistently elevated in men across all age groups with the differences increasing until the age range 60-69 years. Thereafter, the sex difference in survival decreases and was at its lowest for ages  $\geq 80$ . The sex disparities in COVID-19 morbidity and mortality are multifactorial. They may potentially be caused by the sex-differences in comorbidities, behaviors and hormonal influences.

There is a need to collect sex and age-disaggregated data to better understand disease pathology, study the sex differences and guide clinical care. Furthermore, the consistencies with previous coronavirus pandemics may suggest that the public health policies and risk stratification should take sex into consideration for future pandemics. Moreover, more research is needed to clarify inflammatory and immunity disparities to close some knowledge gaps in these concerns (Figures 5 & 6).

## Influence on COVID-19 Infections & Deaths



Sex differences in factors that affect infections & immunity in COVID-19 (Traish, 2021)

**Figure: 5** The figure here shows the sex differences in factors that affect infections & immunity in COVID-19. As you can see, SARS-CoV-2 binds to ACE2 to initiate host cell entry, activating a series of steps. Sex differences may shape the antiviral immune response in each of these steps.

## Some Priority Research Questions

Are sex hormones responsible for disparity in COVID-19 infection severity & mortality?

Will severely ill COVID-19 patients benefit from high-dose testosterone administration?

Can SARS-CoV-2 cause male infertility?



**Figure: 6** The figure here shows the sex differences in factors that affect infections & immunity in COVID-19. As you can see, SARS-CoV-2 binds to ACE2 to initiate host cell entry, activating a series of steps. Sex differences may shape the antiviral immune response in each of these steps.

There is overwhelming evidence to suggest that male gender is at a higher risk of developing more severe Covid-19 disease and thus having poorer clinical outcomes. However, the relationship between testosterone (T) and Covid-19 remains unclear with both protective and deleterious effects on different aspects of the disease suggested. Here, we review the current epidemiological

and biological evidence on the role of testosterone in the process of SARS-CoV-2 infection and in mediating Covid-19 severity, its potential to serve as a biomarker for risk stratification and discuss the possibility of T supplementation as a treatment or preventative therapy (Figure 7).

## Addressing the Knowledge Gaps

Underline the need to collect sex and age-disaggregated data (Alwani et al., 2021)

Implement multidimensional andrological translational research projects

Collaborate internationally for data registry & hormonal studies (Batiha et al., 2020)



**Figure: 7** To address the knowledge gaps, we must:

- underline the need to collect sex and age-disaggregated data to better understand disease pathology and guide clinical care
- emphasize and implement multidimensional andrological translational research projects
- develop international collaborations for data registry, hormonal and genomic studies to better understand the sex difference for COVID-19 health-related consequences

## Acknowledgment

None.

## Conflict of Interest

No conflict of interest.

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