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# The footprint of androgen sensitive serine protease (TMPRSS2) in gender mortality with COVID-19

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## Abstract

Male gender is an obvious risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and mortality rate is higher in men than women. Undoubtedly, gender-related behavioral factors, such as higher amounts of smoking, alcohol consumption, and biological differences in immune systems could make males more vulnerable. The role of androgen-responsive elements (AREs) of transmembrane serine proteases type II (*TMPRSS2*) gene as one of the major players of male dominance in severe COVID-19 infection has been under appreciated and needs to be clarified.

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## Introduction

The clusters of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the first time was reported in China in December 2019. The spread of the disease has created a huge global public health problem (1). The higher rate of mortality and severity of COVID-19 infection in the male compared to the female has been consistently shown in multiple countries (2,3). The higher mortality rate in men might be explained by higher incidence of high-risk behaviors like alcohol consumption and smoking. The impact of pre-existing diseases such as diabetes, hypertension, cardiovascular disease, and chronic lung disease, and social differences are undeniable (4). It has been shown that male mice had a higher rate of susceptibility to SARS-CoV that was associated with a higher viral load in the accompaniment of extensive infiltration of neutrophils and macrophages into the lungs. Furthermore, administration of estrogen receptor antagonists proved a protective effect of estrogen receptor signaling in female mice. These observations may explain the differences in severity of disease based on gender in humans (5). It has been shown that in women, the higher serum IgG levels in the

## Key point

The androgen-responsive elements (AREs) of *TMPRSS2* gene might be an explanation for severity of COVID-19 infection and higher mortality in men.

early phase of SARS-CoV-2 infection have a significant positive impact in the outcome of COVID-19 infection (6). Sex hormones (androgens, progesterone, and estrogens) and sex chromosome genes have significant roles in the regulation of immune responses between the genders (7, 8). However, the exact underlying mechanism remains obscure and needs further investigation. In this paper, the role of androgen-responsive elements (AREs) of transmembrane serine proteases type II (*TMPRSS2*) gene as one of the major players of male dominance in severe COVID-19 infection has been discussed.

## TMPRSS2 in physiology

Membrane-bound serine proteases are a large family of enzymes with important physiologic roles in activation of extracellular molecule precursors. They have physiologic roles in food digestion, iron homeostasis, spermatogenesis, epithelial barrier integrity,

fluid balance and malignant growth. Viruses hijack the function of these enzymes to facilitate their own entry to the host cells (9-11). TMPRSS2 belongs to a membrane-anchored serine protease superfamily, but its physiological role is not fully understood. The secreted forms of TMPRSS2 have been found in human seminal prostasomes.

### TMPRSS2 and kidney sodium transport

The epithelial sodium channel (ENaC) is naturally expressed on the apical plasma membrane of different tissues such as colon, kidney, and lung. It is a rate-limiting channel for Na<sup>+</sup> absorption. In the airway system, secretion of the thin fluid film is mediated by the apical membrane chloride channels (CFTR) whilst its absorption requires ENaC activity (12,13).

TMPRSS2 upregulates the ENaC activation in renal tubules and in theory, their inhibitors might be a novel therapeutic option for salt-sensitive hypertension (10,14,15). TMPRSS2 as a protease break down the “inhibitory” lock between the  $\alpha$ - and  $\gamma$ -subunits of the ENaC. Therefore, subsequent conformational changes increase Na<sup>+</sup> influx via the channel (14). Over the past two decades, it has been revealed that serine proteases have an important role in ENaC activation and sodium handling; and hypothetically inhibiting the TMPRSS2 might be an option for treatment of salt-sensitive hypertension, a condition in which ENaC are exceedingly activated (14-16).

### TMPRSS2 and viral entry

Several human respiratory viruses (e.g. influenza) use TMPRSS2 to enter the host cells. SARS-CoV, after attaching to ACE2 receptor, utilizes two cellular proteolytic systems to prime its S- protein and subsequent cell entry. Cathepsin L, an endo/lysosomal host cell protease, facilitates the uptake of whole virion into the endosomes of the target cell. The second proteolysis system mediated through TMPRSS2 and facilitates the non-endosome entry of viral genome (11, 17).

### TMPRSS2 gene

TMPRSS2 gene was identified in 1997 (18). The TMPRSS2 gene is around 44 kb in length, is located on human chromosome 21 (21q22.3) and consists of 14 exons. The full-length cDNA encodes a polypeptide with 492 amino acids. Human TMPRSS2 mRNA is expressed in different tissues, especially in epithelial cells of the lung, prostate, breast, bile duct, kidney, colon, pancreas, ovary, stomach, small intestine, and salivary gland. TMPRSS2 is synthesized in the form of inactive zymogens/pro-proteins and then is activated or auto activated by other proteases (19). One of the important characteristics of the TMPRSS2 gene is that several androgen receptor elements (AREs) are upstream

of its transcription starting site. The exact mechanisms are not known, but two AREs at 13 and 60 kb upstream of the TMPRSS2 transcription start site have been described (20, 21). Androgen treatment increases TMPRSS2 zymogen activation in the cell culture and in a mouse xenograft model (22,23). The human TMPRSS2 gene promoter has a 15-bp ARE at position -148 comparative to the putative transcription start site and, TMPRSS2 mRNA expression is consistently elevated in androgen-stimulated prostate cancer (LNCaP) cells (23,24).

### TMPRSS2 and prostate cancer

TMPRSS2 plays an important role in modulating the invasive behavior of prostate cancer (23). Fusion of androgen regulated TMPRSS2 promoter to the ERG oncogene leads to a high ERG expression that consequently intensifies the proliferative speed and invasiveness of prostate cancer. This fusion gene TMPRSS2/ERG (T/E) has been found in up to 60% of invasive prostate cancers and displays the importance of TMPRSS2 gene as an androgen responsive element that conducts the trigger to the fused oncogene (25).

### Conclusion and therapeutic remarks

Male gender is an obvious risk factor for severe COVID-19 infection and male mortality is twice that of females. It seems that ARE in TMPRSS2 gene increases expression of TMPRSS2 in the lung's epithelial surface in males and makes them more susceptible to severe disease. It has been observed that wild type human coronavirus prefers non-endosomal, TMPRSS2-mediated entry rather than cathepsin L mediated-endosomal pathway (26). The inhibitors of TMPRSS2 appear to be a promising approach against SARS-CoV-2 viral infections. Camostat mesylate an FDA-approved medication inhibits the activity of TMPRSS2 enzyme but its entry into the lung is still debatable. Bromhexine hydrochloride, a mucolytic is another TMPRSS2 inhibitor that attenuates prostate cancer metastasis in mice models (27). Its entry into the lung tissue makes it a better potential inhibitor of TMPRSS2 in COVID-19-2 infection (Figure 1).

### Authors' contribution

SZV, RT and MRA designed the study and prepared the first draft. MMSh, RT, AT and HN revised and edited the manuscript. All authors read and signed the final paper.

### Conflicts of interest

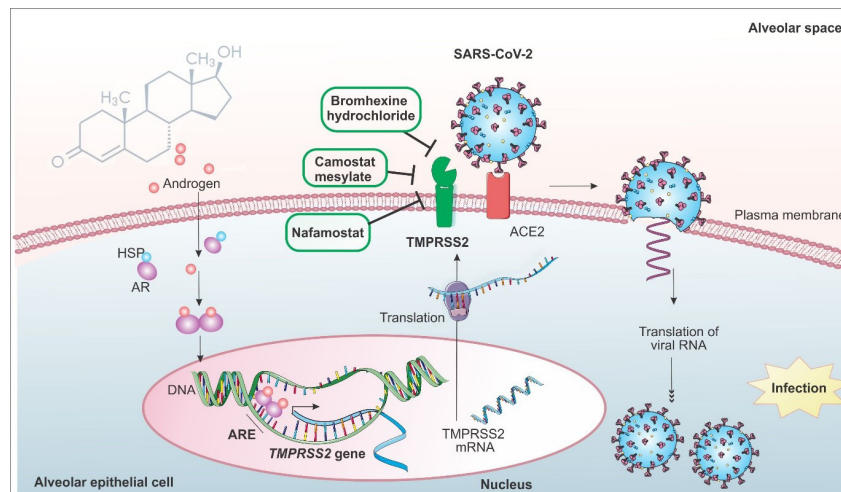
The authors declared no competing interests.

### Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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**Figure 1. Androgen responsive elements (AREs) of *TMPRSS2* gene.** Androgen response elements (AREs) of *TMPRSS2* gene is responsible for higher expression of *TMPRSS2* enzyme on the epithelial cells membrane of respiratory system. It facilitates the non- endosome entry of SARS-Cov-2 into the lung tissue. Possible pharmacologic inhibitors of *TMPRSS2* enzyme have been shown. AREs: Androgen responsive elements, AR: Androgen receptor, HSP: Heat shock protein.

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