Review Article

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Gender Disaggregation in COVID-19 and Increased Male Susceptibility

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ABSTRACT

Novel coronavirus disease 2019 (COVID-19) is a growing public health crisis. Despite initial focus on the elderly population with comorbidities, it seems that large studies from the worst affected countries follow a sex-disaggregation pattern. Analysis of available data showed marked variations in reported cases between males and females among different countries with higher mortality in males. At this early stage of the pandemic, medical datasets at the individual level are not available; therefore, it is challenging to conclude how different factors have impacted COVID-19 susceptibility. Thus, in the absence of patients' level data, we attempted to provide a theoretical description of how other determinants have affected COVID-19 susceptibility in males compared to females. In this article, we have identified and discussed possible biological and behavioral factors that could be responsible for the increased male susceptibility. Biological factors include - an absence of X-chromosomes (a powerhouse for immune-related genes), a high level of testosterone that inhibits antibody production, and the presence of Angiotensin-converting enzyme 2 (ACE2) receptors that facilitate viral replication. Similarly, behavioral factors constitute - higher smoking and alcohol consumptions, low level of handwashing practices, and high-risk behavior like non-adherence to health services and reluctance to follow public health measures in males.

Keywords: COVID-19; gender; males; sex disaggregation; susceptibility

INTRODUCTION

It is well said that disease has no boundaries, nor does it discriminate between rich or poor. COVID-19 pandemic is one such example which has spread beyond race and creed.[1] Early patients data, 44,672 confirmed COVID-19 cases from China showed higher deaths (63.8% vs. 36.2%) and case fatality rate (2.8 vs. 1.7) in males compared to females.[2] However, the lack of sex-disaggregated data on COVID-19 from the affected countries has caused difficulty drawing a definitive conclusion - whether biological difference relates to the higher infection or death rate. Out of the 210 countries, only 16% have reported robust gender-disaggregated data, mostly from European regions. As gender is a crucial consideration in disease management, we aim to provide some plausible explanations on how biology and other behavioral and social determinants contributed to higher COVID-19 susceptibility in males.

METHODS

A literature review was performed using PubMed and Google Scholar with non-specific combinations of the search strings, including (Severe Acute Respiratory Syndrome Coronavirus 2 OR SARS-CoV-2 OR 2019-nCoV OR coronavirus disease OR COVID-19 novel coronavirus OR ncov OR 2019ncov) AND (sex disaggregation OR gender disaggregation OR sex-disaggregated data OR disproportionate susceptibility OR male susceptibility OR gender-differentiated impacts OR gender inequality). Further relevant information was collected from the Sex, Gender, and COVID-19 project through the 'COVID-19 Sex-Disaggregated Data Tracker', the largest database of sex-disaggregated data on the current COVID-19 crisis collectively recorded by the Global Health 50/50, the African Population and Health Research Center, and the International Center for Research on Women (https://globalhealth5050.org/the-sex-gender-and-

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covid-19-project/). Additional updated information was also collected from the WHO and governments' official webpages. Finally, an independent analysis of the included studies was performed with a secondary reference search for the relevant supplementary information.

GENDER DISAGGREGATION AND COVID-19

As of 24 September 2020, analysis of available data strongly signals the impact of gender in COVID-19; with higher mortality in males.[3] Various biological, behavioral, and social factors could play an essential role in determining increased male susceptibility in COVID-19. We have categorized these factors into biological and behavioral factors, and analyzed them independently below based on the available evidence:

BIOLOGICAL FACTORS

In general, females have more robust innate and adaptive (humoral and cellular) immune responses compared to the males.[4] Many studies have shown that males generally have poorer outcomes and survival rates than females from the illness caused by bacteria and/or viruses, including tuberculosis, parainfluenza, and respiratory syncytial virus.[5-7] This could be attributed to differences in immunological responses and their ability to produce serum antibodies, such as IgM.[7,8] Genetic make-up and concentration of sexual hormones are critical biological factors, which are deemed to provide a stronger foundation for immune response in females than males.[9] COVID-19 is an ongoing crisis, and similar studies are lacking; however, we believe that many of these findings could be reflected in COVID-19 based on the nature of the disease.

GENETIC DIFFERENCES

Sex distinction, either male or female, is based on the presence of X and Y-chromosomes. Females have two sets of X-chromosomes (XX), while males have one X and one Y-chromosome (XY).[10] The X-chromosome houses many immune-related genes responsible for regulating innate and adaptive immune systems.[11] The presence of two sets of X-chromosomes benefits females, and hence, they are immunologically active and hyper-responsive to infectious agents than males. Any deleterious mutation or inactivation in one X-linked gene would result in the total functional loss of protein in males. Still, the loss is compensated in females by homologous X-partner.[7] This means having two sets of X-chromosomes is protective in females as an abnormal alteration in one can potentially balance others. However, such advantages are not available for males. Also, during microbial or viral infections, female immune cells respond faster and more powerfully than males, producing higher amounts of interferon, which are natural proteins that stop viruses from replicating and producing antibodies to neutralize the invaders.[12] Furthermore, SARS-CoV infection was shown to delay the adaptive immune response and prolonged virus clearance.[13] Since males have a naturally slow immune response, the projected ability of SARS-CoV 2 in slowing an immune response, being identical to SARS-CoV, could put males even at higher risk.

HORMONAL INFLUENCE

Hormone, especially sex hormones such as testosterone and estrogen, have a vital role in modulating the inflammatory immune responses.[7] The female sex hormone, estrogen, stimulates the immune system, and fight pathogen faster and aggressively, while the male sex hormone, testosterone, inhibits the immune system.[14] Potluri et al. showed qualitative superiority in antibody response in female mice when compared to the male.[14] In this study, they reported increased vaccine-related antibody responses due to estradiol even after removing gonads in mice. This gender-related antibody response progressively waned over-age. Peretz et al. demonstrated higher viral titers in males' nasal epithelial cells, infected with the influenza-A virus, compared to females when exposed to estrogen receptors.[8] Similarly, a flu vaccine study revealed estrogen-related higher antibody production in females. It showed that males with the weakest response to flu shots have high testosterone and testosterone-induced enzymes.[15] These findings suggest that high levels of testosterone suppress, while estrogen facilitates the immune boost, possibly resulting in more males being affected by SARS-CoV 2.

CELL RECEPTORS

Angiotensin-converting enzyme 2 (ACE2), is an enzyme attached to the cells' outer surface in the lungs, mainly in the type II alveolar cells, which serves as a crucial receptor of SARS-CoV.[16] These receptors are directly linked with viral reproduction and subsequent transmission.[17] Recent studies have reported that SARS-CoV and SARS-CoV-2 share the same receptors (ACE2).[18] The mechanism of action in a mice model demonstrated that SARS-CoV spike protein binding to ACE2 down modulates ACE2 expression and subsequent loss of the expression results in acute respiratory failure.[19] A preliminary study by Zhao et al. on COVID-19

during single-cell RNA-sequence techniques found that expressed ACE2 attached to type II alveolar cells represent many other genes that positively regulate viral entry, reproduction, and transmission.[20] Interestingly, this study also found a larger concentration of ACE2 receptors in males' lungs than females. Likewise, a team of researchers in Spain hypothesized that the androgen receptors genes could be the risk factors for increased severity in males after they observed 71% of the hospitalized COVID-19 male patients were diagnosed with clinically significant androgen receptor alopecia.[21] Although this was a small study with 41 cases and the claim is yet to be validated, it does seem plausible that the difference in gender-based cell receptors could be the reason for higher males' susceptibility in SARS-CoV-2 infection.

COMORBIDITIES

Published literature in COVID-19 has revealed that the chances of contracting COVID-19 are higher among individuals with existing comorbidities, in particular, obstructive respiratory illness, hypertension, and cardiovascular diseases.[22] Notably, the male gender has a higher comorbidity burden globally, partly driven by higher rates of involvement of men in risky behaviors and practices. As existing comorbidities increases the susceptibility to SARS-CoV-2, one of the plausible explanations for the perceived gender disaggregation could be a higher prevalence of comorbidities in males.

BEHAVIORAL FACTORS

Health behavior is one of the most critical elements in the prevention of COVID-19 transmission. Health behavior could be lifestyle choices and personal habits. Smoking, alcohol consumptions, and handwashing practice are crucial to COVID-19 containment.

SMOKING

Smokers are more susceptible to COVID-19.[23] The simple explanation is that COVID-19 affects the respiratory tract and lungs, and most smokers have reduced lungs capacity or pre-existing lungs disease, making them vulnerable to lungs infections. Biologically, smoking also accelerates the ACE2 expression, the receptor for coronavirus.[24] A study by Cai G reported significantly higher ACE2 in current smokers than non-smoker patients infected with COVID-19.[25] Globally, males smoke nearly five times as much as females.[26] The sex difference in the COVID-19 infections might be associated with higher smoking rates in males than in females. Although a systematic review did not show any significant association of smoking and COVID-19, a multivariate analysis reported 14 times the risk of COVID-19 disease progression in a patient with a smoking history.[27,28] The former study had significant limitations, including small sample size.[27] Equally, a survey of 1099 COVID-19 patients in China by Guan et al. showed that 26% of the patients admitted to ICU or on ventilation or died were smokers.[29] Nevertheless, cigarette smoking could also pose an immediate risk, as an indirect lip to lip mucosal contact can enhance viral transmission by sharing contaminated cigarettes.

ALCOHOL CONSUMPTION

Alcohol consumption impairs the immune system, weakens the body's ability to fight infections, delay recovery from tissue injury, and contribute to organ damage.[30] Males are 1.1 to 12.3 times more likely to drink alcohol than females, with higher total per capita alcohol consumption compared to females.[31] According to WHO, global alcohol consumption is attributed to an estimated 2.3 million deaths in males and 0.7 million in females.[32] WHO has issued a public warning to restrict and/or limit alcohol consumption in this coronavirus pandemic.[33] Clinicians have reported the linkage of alcohol consumption with pulmonary disease in COVID-19.[30,34] As males drink more alcohol than females and naturally possess lower immunity,[31] alcohol could enhance the males' susceptibility to COVID-19 and increase its severity, resulting in more deaths. Furthermore, both smoking and alcohol consumption are associated with the risk of developing comorbidities, now related to adverse outcomes in COVID-19.

HANDWASHING

Hand hygiene is the most effective way to curb the spread of infectious diseases, including COVID-19.[35] Effective hand hygiene practices have shown promising results in reducing influenza A virus infection by 51% in 4-6 weeks during the influenza pandemic.[36] Regrettably, the average hand hygiene compliance meeting WHO standard is 39% (range 5 - 89%) among the health workers.[37] Studies have shown significantly low handwashing compliance in males than females in community hospitals (69% vs. 80%) and intensive care units.[38,39] Congruently, hand hygiene practice is even poor among males in general. A study conducted in highway service station restrooms in England reported that only 31% of males wash hands and/or use soap compared to 65% of the females.[40] Similarly, a review of eight studies showed that males washed their hands less often than their female counterparts.[41] This apparent difference in handwashing behavior could be translated into more COVID-19 cases in males.

SOCIAL NORMS AND PRACTICES

Social norms and practices could play a significant role in the transmission of COVID-19. In many societies, females manage the home, while, males go out for a living increasing their risk of exposure to infectious agents.[42] Similarly, more males make up in high-risk professions, such as in the health care setting, except nurses.[43] In many cases, males are also reluctant to use health care services compared to females.[44] Moreover, social distancing is a crucial consideration to curb the spread of COVID-19. Since males are known to be socially deviant and less likely to follow public health advice, like abstinence from social gatherings and congregations, their chance of contracting the infectious disease is relatively high.

RECOMMENDATION

There is progressively stronger evidence to suggest gender disaggregation in COVID-19. These discernible sex disaggregation and increased susceptibility could be attributed to various biological, behavioral, and social factors (Figure 1). Although we understand that the preliminary data could be skewed by notable differences in the coverage of testing and reporting of deaths, the visible differences in disease susceptibility between males and females can not be ignored. Therefore, there is a strong need to consider the gender-based biological and behavioral differences in disease susceptibility to target public health measures and save more lives in this global COVID-19 emergency.

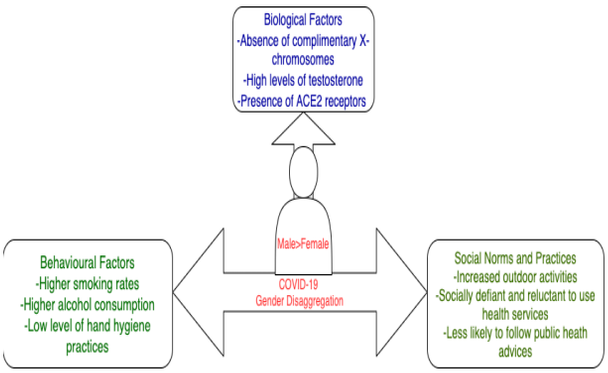

Figure 1. Figure showing various biological, behavioral, and social factors that determine the gender disaggregation in COVID-19.

CONCLUSIONS

An interplay between biological, behavioral, and social factors determines the increased susceptibility of males in COVID-19.

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