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Mini Review

Addressing Sex and Gender Bias in COVID-19 Epidemiology in Bangladesh

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A B S T R A C T

Sex and gender are recognized as a vital factor in the infectious disease epidemiology, and disease outcomes, and these two factors also appear to hold for severe acute respiratory syndrome (SARS-CoV-2) infection. Evidence from COVID-19 infection in Bangladesh showed that a variation number of cases and deaths between the sex differences in immune responses to viruses and gender related risk factors among the male and female, but more severe outcomes in aged men of cases and deaths in 31~40 and 61~70 years respectively than female. However, the previous research dataset in the different parts of world evidenced that the men's are vulnerable compare to women's. Similar trends to observe in Bangladesh datasets in COVID-19 epidemiology. Male and female represented 71% and 29% of total reported confirmed COVID-19 cases in Bangladesh, respectively. Moreover, different levels of angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMRSS2) enzymes play important role in COVID-19 infection of men and women. In addition, the effects of testosterone on ACE2 levels and the presence of ACE2 genes on the specific X-chromosome should not be ignored. In fine, this mini-review focuses on sex and gender variations in patients with an infectious disease of COVID-19 epidemiology in Bangladesh. The information of sex differences and age dependence might contribute to proper management and treatment of COVID-19 in Bangladesh.

Introduction

In Wuhan, the capital of China's Hubei-Province; a new coronavirus of severe acute respiratory syndrome coronavirus (SARS-Cov-2) appears consequence series of infections in the lower respiratory-tract, just at the close of 2019. WHO has formally termed the latest SARS-CoV2 viral disease 'COVID-19' on the 11th of February 2020 (Guo Y-R *et al.*, 2020). Since the officially confirmed pathogenic factors were released on the 7th January 2020 and their genome sequence was posted upon that internet web resource virological.org2; three days later, their four genome sequences database were published by GISAID (which offers unrestricted entry to influenza-virus genomic information) on 12 February 2012. The genome sequences recommend the viral intimately allied with SARS-CoV. Coronaviruses has a single-stranded RNA genome in the positive(+ve) sense, infecting humans as well as a wide variety of species (Tyrrell *et al.*, 1966). The four types of coronavirus (a, b, g, and d) have previously been identified. There are two kinds of human coronavirus such as coronavirus A (Human coronavirus-229E and NL63) and coronavirus B (MERS-Coronavirus, SARS-Coronavirus, Human coronavirus-OC43, and Human coronavirus-HKU1) are the (Perlman S *et al.*, 2009). An initial devastating problem was reported on the11th of January 2020. In the case of the massive Chinese transition, the Pandemic erupted mostly during the Chinese New Year. Other country's problems were also reported in people who mostly returned from Wuhan in a few other Chinese provinces (Bastola *et al.*, 2019). The overall amount of verified cases was three hundred and forty were published on January 22, 2020, and six patients were declared dead. The existence of a novel coronavirus 2019 human infection from China was confirmed by Thailand, Japan, and Korea on January 13th, 16th, and 21st respectively. Currently, nCoV-19 expanded everywhere throughout the globe to an area including counties of two hundred. Coronaviruses have risen

repeatedly in various places around the globe throughout the last several years. During the first decade of the twenty-first century, the SARS coronavirus syndrome (SARS-CoV) infected approximately 8,422 people worldwide, resulting in 916 deaths. Middle East Coronavirus Respiratory Syndrome (MERS-CoV) was identified for the first time in science in 2012, with a total of 1,401 people infected and 543 (roughly 39 percent) of them dying (World Health Organization, MERS-CoV). According to the WHO, there have been confirmed (102,083,344) COVID 19 cases with 2,209,195 deaths as of 31 January 2021, while the United Nations, the hardest hit country, has claimed 25,676,612 (164,415) cases with 433,173 (3,521) deaths. The third highest cases were 9,118,513 cases (59,826) and the second highest deaths were 222,666 (11,119) deaths followed by India 154,274 (127) concurrently with cut-offs.

The several evidences for potential sex differences in the COVID-19 pandemic are continuing to evolve. In a study from China showed that males tend to higher disease severity compared to females; and individuals with comorbidities had a higher critical illness, but a similar observation was not showed for females (Jin *et al*., 2020; Meng *et al*., 2020). Besides a preliminary evidence of variety immune reactions to SARS-CoV-2 between males and females has been demonstrated (Yale *et al*., 2020). Moreover, male sex gender-related behaviors such as smoking, drinking, the propensity to seek hospital care and presence of comorbidities could affect the outcome of COVID-19, the increased risk of death seen in males across several different cultures in the world point to biological risk determinants (Vahidy *et al*., 2020). However, from 8 March 2020 to 31 January 2021, five hundred thirty-five thousand one hundred thirty-nine (535,139) COVID-19 were confirmed in the DGHS press release in Bangladesh, including 8,17 deaths in connection with the RT-PCR, Gen Expert and Rapid Antigen test (CFR 1.52 percent) and the total of confirmed cases COVID-19 recorded, males account for 71 percent and 76 percent. In this review, we try to summarize the WHO report on the basis of age-sex distribution of COVID-19 case and death, 08 March 2020 to 31 January 2021, in Bangladesh. The information associated with COVID-19 are important for take initiative prevention and management strategies in Bangladesh.

Sex differences in covid-19 epidemiology and case fatality in Bangladesh

According to 31 January 2021 confirmed cases for male and female (figure 1 and 2), seven age groups had been categorized to describe the infection rate of COVID-19. In male, 0.9, 2.5, 11.8, 19.7, 14.3, 12, and 19.7% cases were confirmed respectively in the age group of 1-9, 10-19, 20-29, 30-39, 40-49, 50-59 and 60-69 years (figure 1). On the other hand 0.7, 2.2, 6.2, 6.7, 5.3, 4.6 and 0.6% cases were found respectively in female (figure 2). The highest case for male 19.7% was reported in the age group of 30 to 39 years old and in female highest case 6.7% was reported in the same age group. Male and female represented 71 and 29% of the of total reported confirmed COVID-19 cases, respectively.

In both male and female active cases, hospitalizations, recover and mortality records are presented in figure 2 & 3. Among them the highest death rate was reported at 24.7% in the 60 to 69-year-old age group in males, while the highest death rate was reported at 7.0% in females in the same age group. Furthermore, 0.2% of death cases in both male and females were found in the age group of 1-9 years, 0.4 and 0.3% found in the age group of 10-19, 0.8 and 0.7% found in the age group of 20-29, 2.7 and 1.5% found in the age group of 30-39, 6.2 and 2.2% found in the age group of 40-49, 15.6 and 5.2% found in the age group of 50-59, 18 and 4.7% found in the age group of 70-79% respectively in male and female. Furthermore, 2.4% death occurs in the age group above 80 years old male.

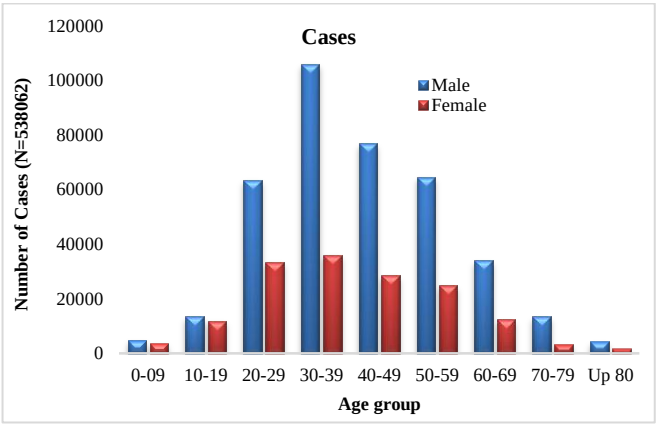

Figure 1: The sex and age distribution of COVID-19 cases in Bangladesh as of January 31, 2021

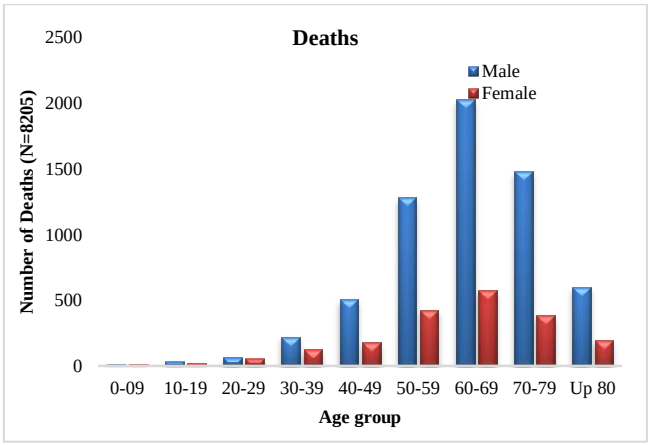

Figure 2: Graph information on sex and age distribution of COVID-19 deaths in Bangladesh as of January 31, 2021

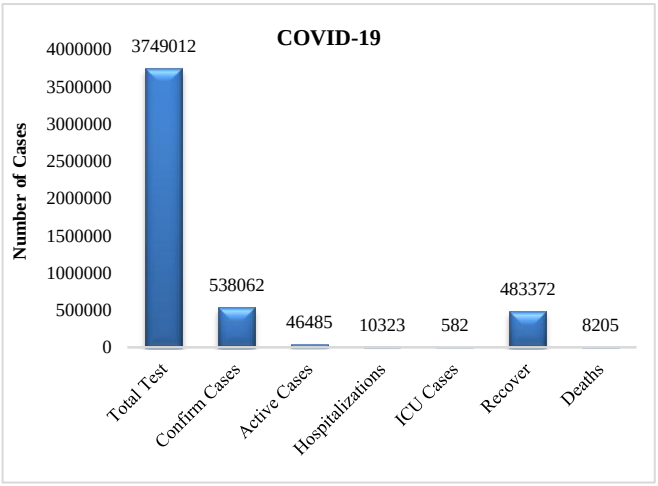

Figure 3: Male and female of COVID-19 total test, confirm cases, active cases, hospitalizations, ICU cases, recover and deaths in Bangladesh as of January 31, 2021

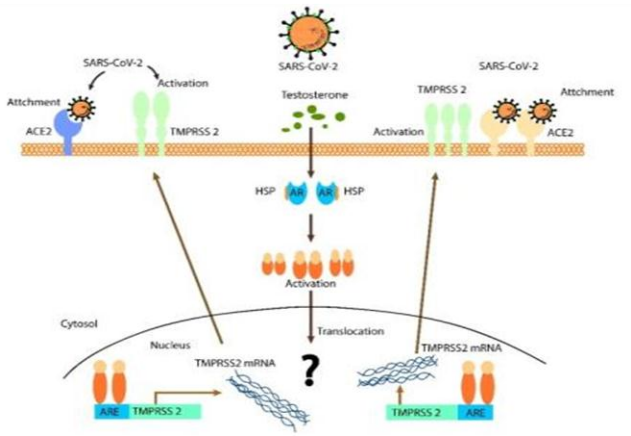

Figure 4: Sex differences in angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) regulations

Male and female represented 76 and 24% of the of total reported confirmed COVID-19 deaths respectively (https://www.who.int/bangladesh/emergencies/coronavirus-disease-(covid-19)-update). The highest 72,314 COVID-19 survey in China recorded that cases of suspected or confirmed death were considerably higher for men than in women (men: 63.8% women: 36.2%). Another study in Italy, among first 827 COVID-19 deaths, 80% were men and 20% were women. Similar findings have been identified in a sample of 3,912 English and Wales's patients died of SARS-CoV-2 (Scully *et al.*, 2020). Besides, in China the fatality rate reported the infected men (2.8%) compare to women (1.7%) with severity and fatality rate was high men versus women (Gebhard *et al*., 2020). While age progression is linked to a higher death risk in both sexes, male discrimination remains apparent. The COVID-19 study from Italy, Spain, Germany, Switzerland, Belgium and Norway indicates men fatality rates are greater than women among all age groups older than 20 years (Marina *et al.*, 2020).

Sex differences in angiotensin converting enzyme (ACE) 2 and transmembrane protease serine 2 (TMRSS2) regulation

The entry receptor and hormone genes are the responsible factor for the sex-related of COVID-19 disease severity such as the encoding genes of hormone-regulated expression, angiotensin converting enzyme (ACE) 2 receptor and TMPRSS2 as well as sex hormone-driven innate and adaptive immune responses, immunoaging and so on (Gebhard *et al*., 2020). SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMRSS2) enzyme as receptor to bind with a cell. As this ACE2 gene is on the X-chromosome, females may be heterozygous about the enzyme and males are homozygous (Gemmati *et al.*, 2020). ACE2 is an outer membrane protein which is found in different types of cells; adipose tissue, heart, spleen, blood vessels, kidneys, liver, lungs, and bladder (Jia *et al*., 2016, Li *et al*., 2020). The spike (S) protein of SARS-CoV-2 binds to the ACE2 receptor of the cell and invades the target cell. In both healthy and diabetic states, women have higher levels of circulating ACE2 than men, according to recent research. Other studies have discovered that older women have higher ACE2 serum activity than younger women (Li *et al.*, 2020).

The second important protein for SARS-CoV-2 to invade a cell is transmembrane protease serine 2 (TMRSS2), expressed in the cell epithelium and most of the human prostate cancer metastases predominantly. TMPRSS2 is a testosterone-regulated gene that may be more exposed in men than in women (Tomlins *et al.*, 2005). TMPRSS 2 actually aids SARS-CoV-2 priming with target cells. The presence of testosterone in the cell facilitates in the activation of androgen receptors (ARs) through heat shock proteins (HSPs) (figure 4). These ARs are then phosphorylated and translocated into the nucleus, where they help the cell's TMPRSS 2 protein translate faster. Finally, a large numbers of TMPRSS 2 spreads at the outer membrane of the cell and activate the spike proteins of SARS-CoV-2 (Gebhard *et al.*, 2020).

Sex differences in immune responses to viruses

The susceptibility of men and women to viral infections varies, leading to sexual disparities in disease severity and seriousness (Barna *et al*., 1996). Gender and sex may have a variety of effects on men and women's unequal vulnerability to infectious diseases caused by viruses. Humans, for example, discovered that women with human immunodeficiency virus (HIV) proliferate at a rate that is more than 40% lower than men. Despite having less transmitting HIV RNA than men, women have 1.6 times the risk of developing AIDS when their HIV RNA loads are compared to men's (Klein *et al*., 2015). Even if the sensitivity to influenza A is frequently greater in men, fatalities are noticed to be higher in women's results of exposure to pathogenic influenza A viruses (WHO; 2010). By contrast, the prevalence of surface antigen serum hepatitis B virus (HBV), titers of HBV-DNA, and hepatocellular carcinoma development are higher amongst men than women (Tsay *et al.*, 2009).

Innate viral recognition and responses and downstream adaptive immune responses vary among women and men throughout viral infections. Innate immune cells, particularly monocytes, macrophages, and dendritic cells (DCs), and inflammatory immune responses, typically have more numbers and involvement in women relative to men (Souyris *et al.*, 2018). Toll-like receptor (TLR), used to detect single-stranded RNA viruses, including coronaviruses. The TLR7 gene can evade the suppression of the X chromosome and increase the level of TLR7 in women in comparison to men (Berghöfer *et al.*, 2006). In vitro exposure of TLR7 ligands to peripheral-blood mononuclear cells (PBMCs) leads to increased interferon-α (IFNα) synthesis from woman cells, as compared to man cells (Klein *et al.*, 2010).

In terms of adaptive immune responses, women have a higher humor and cell-mediated immune response than men for antigenic stimulation, vaccination, and infection (Butterworth *et al*., 1967). Almost all basal immunoglobulin levels, as well as antibody response levels, are significantly higher in women than in men (Cook *et al*., 2008). The most expression levels genes in B cells in adult women are significantly more regulated than in men, according to global analyses of B-cell signatures (Fan *et al*., 2014). Research studies have shown that mans had lower CD3 +, CD4+: CD8 +, and T type 1 (Th1) cell aids than women (Wikby *et al.*, 2008). The sexual differences in immune responses can also be caused by polymorphisms of sexual chromosomes along with autosomal genes that express immune proteins (Poland *et al.*, 2008). Age is also a factor in sexual differences in cardiac tissue immune response. Since then, it has been demonstrated that in old age, women with myocardium

develop strong chronic immune reactions (de Arellano *et al.*, 2019).

Gender-related risk factors and impact

During this COVID-19 pandemic, women have a lower fatality rate in serious cases than men. Coronavirus affects men more than it affects women. Though the exact cause is unknown, some gender-related risk factors play a significant role in these disparities (figure 5) (Dana *et al.*, 2020). Men and women are distinguished by the human sex chromosomes X and Y. Men have only one copy of the X chromosome and one copy of the Y chromosome, while women have two copies of the X chromosome (Schurz *et al.*, 2019). Because some genes encoded by the X chromosome are related to immune responses, women have less inflammation and a lower viral load than men. Women's immune cells can be activated more than men's, and this is linked to INF (interferon) production and TLR-7 stimulation (toll-like receptor-7). In comparison to men, women have a higher level of T cell activation, which results in a faster immune response to coronavirus (Takahashi *et al.*, 2020). The X chromosome is more functional in women which are highly dense with immune-associated cells, this makes women greatly stronger in rapid immune responses (innate and adaptive) compared to men (Sharma *et al.*, 2020). Also, sex hormones make women stronger than men in case of viral infection. Estrogen increases immune responses as well as rapid pathogen decline and effective vaccination while inhibitory roles are played by testosterone for immune responses. It may a valid reason for men's higher fatality rate (Klein *et al.*, 2010). Hypertension, chronic lung disease, cardiovascular disease, such comorbidities are possible fatal risk factors for severe COVID-19 patients (Martinez-Ferran *et al.*, 2020). Lifestyle, behaviors like drinking and smoking are higher in men than women. This lifestyle plays a vital role in developing such comorbidities. These comorbidities rate is higher in men than women worldwide. This also makes men more vulnerable to COVID-19 than women (Klein *et al.*, 2020, Penna *et al.*, 2020).

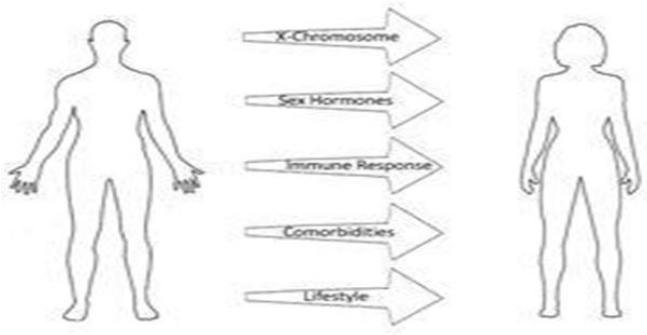

Figure 5: Information on COVID-19 associated gender related risk factors heir impact

Conclusion

Studies performed in Bangladesh by COVID-19 patients found that men are more vulnerable compared to women to develop the disease. In addition, cases of death in male patients are higher than in female ones. Sex as a significant variable should also be given more consideration. By looking at COVID-19 literature, it can be inferred that some sex-related variables are used to determine the outcomes of the patients. Older age, male sex with acute illness severity has been with increased mortality risk. This study shows that different levels of male and female sex hormone enhances or protective immune response, receptor protein such as ACE2 in men and women, the effects of testosterone on ACE2 levels, and the ACE2 gene location on the X-chromosome should not be ignored. However, findings or draw hypothesis in this area are limited and further studies are required to draw a conclusion.

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Author Contributions

MAAM planned and designed the project and writing the main manuscript. MAAM, MLR, MMR, MEA, ANH, MLK, MRS, MRK and MAI contributed in reviewing relevant literature and drafting of the manuscript. MLR, MMR designed figures. All authors approved the final version for submission.

Conflicts of Interest

Authors declared that they have no conflict of interest.

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