Annals Of Diabetes, Metabolic Disorders & Control

SCIENTIFIC LITERATURE

Special Issue Article "COVID-19"

Review Article

Gender and Immunosenescence Dependent Progression of COVID-19 Disease in Bangladeshi Population

Fahmida Sultana Rima[1], Rehana Parvin[1*] and Akira Sugawara[2]

[1]Department of Biochemistry and Biotechnology, University of Barishal, Bangladesh

[2]Department of Molecular Endocrinology, Tohoku University Graduate School of Medicine, Japan

ARTICLE INFO

Received Date: May 20, 2022
Accepted Date: June 20, 2022
Published Date: June 22, 2022

KEYWORDS

SARS-CoV-2
Gender
Age
COVID-19
Immune system

Citation for this article: Fahmida Sultana Rima, Rehana Parvin and Akira Sugawara. Gender and Immunosenescence Dependent Progression of Covid-19 Disease in Bangladeshi Population. Annals Of Diabetes, Metabolic Disorders & Control. 2022; 3(1):127

Corresponding author:
Dr. Rehana Parvin,
Department of Biochemistry and Biotechnology, University of Barishal, Barishal, Bangladesh, Tel: +8801788663181;
Email: rehanadu@yahoo.com

ABSTRACT

Novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged from Wuhan, China has spread rapidly around the world with a male bias case fatality rate. The highly infectious Corona Virus Disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2, quickly surges in Bangladesh and the case disaggregated epidemiological data also showed that men, especially the aged men have higher risk of developing this disease. In this review, we aim to highlight the sex specific mechanism, sex hormone modulates innate-adaptive immune response, susceptibility of viral infection in male and female. Alongside, the effect of aging can alter the immune system that reduces ability to fight the infection. Therefore, in this review the impact of gender and age in immunopathogenesis is emphasized in order to improve the therapeutic treatment of COVID-19 disease, which is unique to other studies in respective to Bangladesh.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic, wreaking a global havoc, was declared as pandemic by World Health Organization (WHO) on March 11, 2020 [1]. It is caused by a novel coronavirus (CoV) named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which is reported as a newly identified β (beta) coronavirus [2]. Based on the genomic structure and phylogenetic analysis, this novel coronavirus (2019-nCoV) is most similar (86.9%) to SARS-like CoV sequences, considered as a Severe Acute Respiratory Syndrome (SARS) like virus named SARS-CoV-2 [3]. They cause mostly mild to severe upper respiratory tract illness, enteric, hepatic, systemic and neurologic diseases, in humans and numerous animal hosts (for example, cattle, palm civets, swine, horses, camels, cats, rodents, dogs, bats, ferrets, etc.) [4]. In addition, other systems, like hematological system, complement system, cardiovascular system are also demonstrated in the patients with this novel infection [5,6]. The human coronaviruses were first identified from respiratory infections in adults as well as children in 1960. After two contemporary outbreaks of twenty first century, SARS virus in 2002 and Middle East Respiratory Syndrome (MERS) in 2012 [7], the major scientific interest was strengthened. SARS-CoV-2 is identified as third highly pathogenic human coronavirus [8]. Emergence of the coronavirus was first spotted in Wuhan, Hubei, China in December 2019 [9]. Up to 22nd February of 2021, it has scourged transmission across the globe in 213 countries and territories with a total of 112,007,302 active infection cases and 2,479,067 deaths. The

worldwide case fatality rate is 2.2% due to COVID-19 in comparison with SARS (9.6%), MERS (34%) and swine flu (0.02%) (www.worldometers.info). Since the virus has spread worldwide, the records of infection and death rate are marching up in Bangladesh as well. According to Institute of Epidemiology, Disease Control and Research (IEDCR), the first three cases of COVID-19 were reported on 8th March of 2020. IEDCR has tracked 543,351 active infection cases and the mortality rate is 1.44% in the country on 22nd February of 2021 (www.iedcr.gov.bd).

Patients with COVID-19 often experience asymptomatic or paucisymptomatic forms to clinical conditions, such as dyspnea, Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, coagulopathy, septic shock, and metabolic acidosis, radiological evidence of ground-glass lung opacities compatible with atypical pneumonia etc. [10,11]. However, COVID-19 pandemic has been showing different biological effects on male and female since the emergence [12]. Since sex and gender related factors shape the primary and secondary impact of COVID-19, it plays fundamental roles in this regard [13]. Besides, the immune system of aged person are more prone to the viral attack [14]. Therefore, this review highlights how sex differences in association with age leverage the mechanism of immune system to combat COVID-19 in Bangladeshi people.

Epidemiological evidence of gender and age - based differences in COVID-19

Accumulating the data from different countries [15] including Bangladesh, the COVID-19 incidence and death rates are analyzed in gender and different age groups. The data (Figure 1) of COVID-19 confirmed cases show very little difference in the rate of infection among males and females in Germany, USA, and China. Whereas, in South Asian countries, there is a significant difference in the rate of infection between males and females. We found that males are more susceptible for COVID-19 disease in those countries of South Asia. On the other hand, we found opposite scenario in Italy and South Korea. Therefore, the sex and gender make a difference in the degree of fatality and severity to the disease in this regard.

The reports from Australia highlight that infection rate are higher among males [16], followed by the similar trend in several countries of Europe [17]. On the contrary, 56% of females of South Korea and 51% of females in USA (Figure 1), 62% of females in Netherlands, 63% in Belgium get infected though Case Fatality Rate (CFR) is lower [18]. In addition, the sex ratio also varies with age among COVID-19 patients. Recent data showed that the younger and older women (20-29 years old and 80 years or older) are infected in higher rates than men whereas 0-9 years, 60-69 years and 70-79 years age groups constitute more cases in men [15]. But the mortality rates are higher in older men (60 years or above) in all the countries (Figure 3). Moreover, 58% men are died of COVID-19 in Italy, 55% in USA and the evidence from the available sex disaggregated data clearly indicate that there is a male bias in COVID-19 fatality rates in most of the countries. Prevalence of comorbidities and comorbidities associated risk factors, such as smoking tobacco (36% for men and 7% for women) and alcohol consumption (10.5% for men and 2.3% for women) are reported to be more common in men (WHO), increasing the rate of death globally.

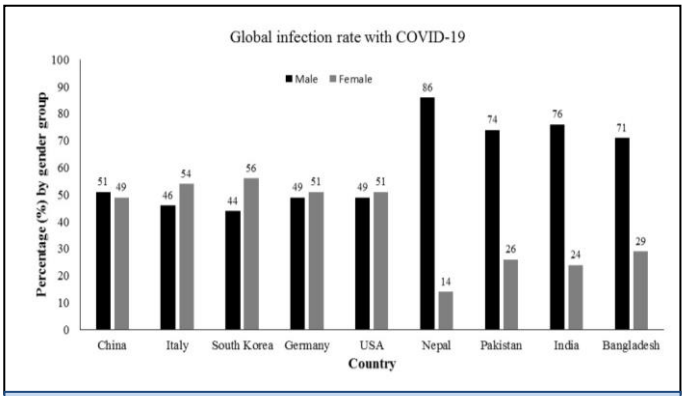

Figure 1: COVID-19 infection rate across different countries on the basis of gender.

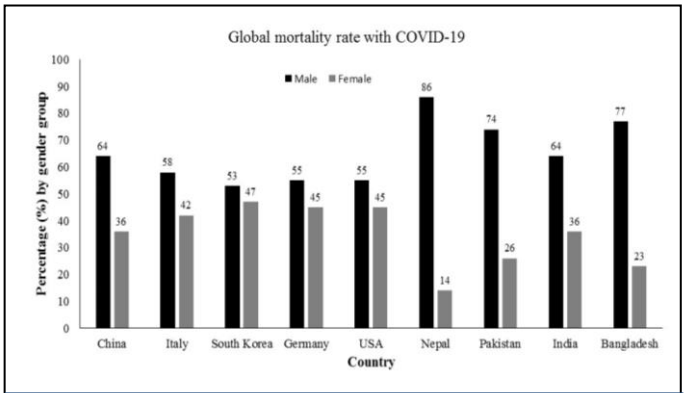

Figure 2: Global mortality rate with COVID-19 across different countries on the basis of gender.

Gender and Immunosenescence Dependent Progression of Covid-19 Disease in Bangladeshi Population. Annals Of Diabetes, Metabolic Disorders & Control. 2022; 3(1):127.

Scenario of COVID-19 cases by age in Bangladesh

SARS-CoV-2 confirmed cases by the age groups indicate that young and working-aged people (from 21 to 40 years) constitute the highest proportion (54.7%) of infected people in Bangladesh (Figure 3). The age distribution of coronavirus patients in Bangladesh is similar with India (which is 60% below age 50) but differs with the England, Germany and Italy. Comparatively young and working-aged people are affected by the COVID-19 (www.worldometers.info) due to young and working aged people in Bangladesh are involved in different volunteer services. Moreover, few people are reluctant to follow the guidelines (staying at home, use of mask, use of hand sanitizer) during the lockdown. In addition, daily wage earners, the low income people along with private sector job holders need to protect their livelihoods which added a percentage [19].

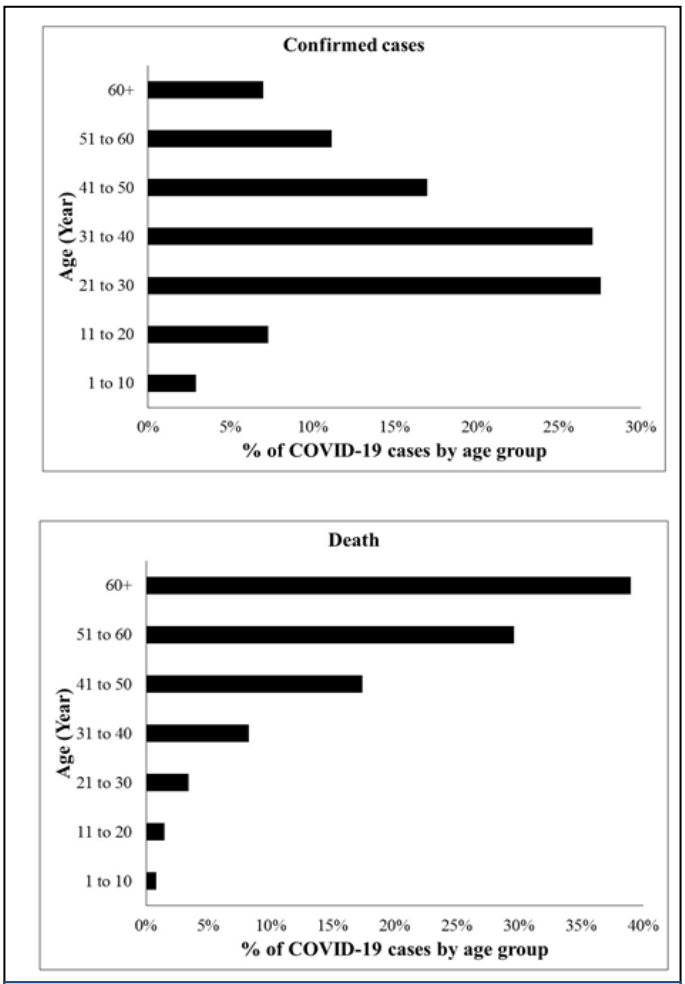

Figure 3: Comparative analyses of COVID-19 case fatality rates as percentage (%) by age group.

Conversely, the severity of COVID-19 in older adults is notable which causes more than 60% of deaths among over 60 years of aged people (Figure 3). Underlying conditions, for instance, cardiovascular disease, diabetes, respiratory illness, higher risk behaviors (i.e., smoking and alcohol use) and other comorbidities raise the risk of severe COVID-19 and COVID-19-related death in old people [20]. It is evident that COVID-19 patients with associated risk factors had a higher mortality rates-10.5% for CVD, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer in Wuhan, China [21]. Moreover, a likely weaker immune system makes it harder for elder adults to fight off the viral infection as well [22].

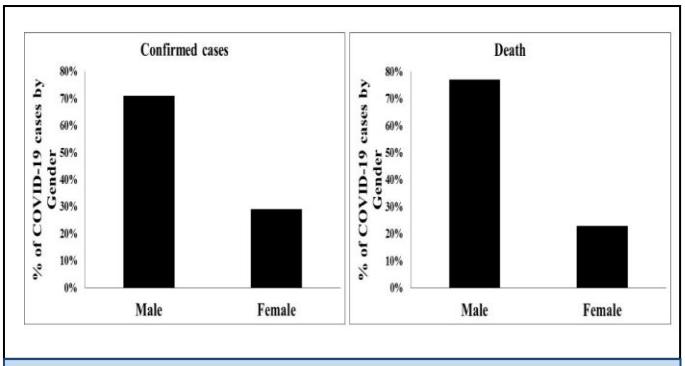

Figure 4: Comparative analyses of percentage (%) of COVID-19 case fatality rates by gender wise.

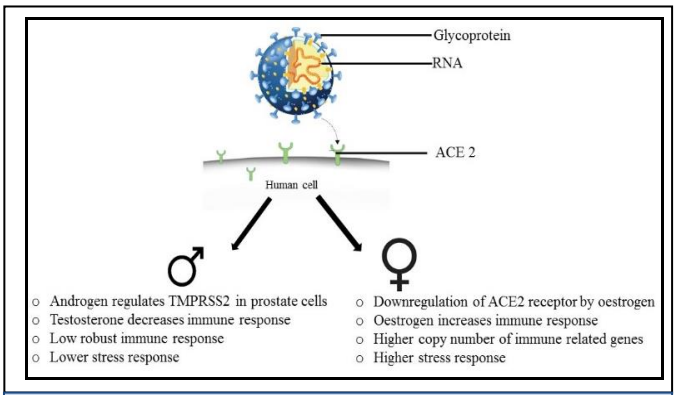

Figure 5: The differential effect of sex hormone in sex biased mortality due to COVID-19 [50].

Scenario of COVID-19 cases by gender in Bangladeshi population

This review also evaluates the current situation in the Bangladesh to determine whether the patterns of infection and mortality in male–female are similar to the above statistics or not. The data of active infection and death cases were retrieved from IEDCR.

Gender and Immunosenescence Dependent Progression of Covid-19 Disease in Bangladeshi Population. Annals Of Diabetes, Metabolic Disorders & Control. 2022; 3(1):127.

The sex-disaggregated data of Bangladeshi population shows that infection rates and death rates are two-folds and four-folds higher for men compared to women (Figure 4), similar with other countries.

One possible explanation can be behavioral and social differences that favor women, for example, follow hand hygiene practices, lower proportion of smoking, use preventive care etc. [23,24]. Sex chromosome genes (XX and XY) together with sex hormones, including oestrogens, progesterone and androgens, also contribute to the differential regulation of immune responses in this regard [25]. Therefore, exploitation of sex associated factors can provide a novel insights into pathogenesis and therapeutic interventions of the disease [17]. In the context of SARS-CoV and MERS-CoV, men were also affected more severely than women [26,27].

Role of sex chromosomes, sex hormones and immunosenescence on progression of COVID-19 disease severity in Bangladeshi population

Potential link of sex chromosomes and its related genes in SARS-CoV-2 infection: Females have two X chromosomes, males have one X and one Y chromosome. There are many immune related genes on the X chromosome that regulate both the innate and adaptive immune responses [28]. The X chromosome, X-linked genes and X Chromosome Inactivation (XCI) mechanisms contribute to the differences in diseases, socioeconomic and behavioral factors between men and women [29,30]. During development of embryo in female, one of the copies of X chromosome is inactivated in XCI [31]. It creates immunological differences between males who are haploid for the X chromosome and females who are functional mosaics for X-linked genes. For example, Toll Like Receptor (TLR) dependent signaling pathway increases during innate immune responses in our body [32]. When RNA viruses, such as SARS-Cov-2 evades, X chromosome encoded TLR7 gene may escape X chromosome inactivation. It leads to higher expression levels of TLR7 in females than males contributing stronger immune responses with faster viral clearance. In addition, X chromosome encoding TLR8, CXCR3, CD40L etc. immune regulatory genes contribute to higher production of type 1 interferon genes. Type 1 interferon proteins are released by stimulation of virus in host [32-34].

A sex difference is also reported with regard to cell mediated immunity components, for example, B cells, CD4+ T cells and CD8+ T cells [35]. Females typically develop higher antibody responses, higher basal immunoglobulin (Ig) levels and higher B cell numbers irrespective of their age [36]. Oestrogens stimulate B cell gene-expression to viral infections by upregulating B cells in females compared with males [37]. At the same time, male and female show different dynamics of CD4+ T cell subsets. Following viral attack, adult female are better protected by producing higher levels of T helper 1 (Th1)-type cytokines (for example, IFNγ) than males [38]. On the contrary, increased level TNFSF13B, CCL14, CCL23, IL-7, IL-16, IL-18 are associated with causing cytokine storm, may lead to damage organ functions. Higher expression of these genes are evident in males, may justify the adverse outcomes with SARS-CoV-2 infection [39]. Higher levels of cytotoxic T cell (CD8+T cells) activity and antiviral genes (such as IFN-γ, RIGI, SPINK5, OAS1 and IFI6) and pro-inflammatory genes (for example, IL12RB2, IL1F5, CXC3CL1, CXCL2 and IL16) are also evident in women compared with T cells from men [40,41]. These may explain why female in comparison to male, clear viral load faster and affect the susceptibility.

Furthermore, the X chromosome encodes approximately 10% of the total genomic miRNAs, which regulates the gene expression by degrading mRNA or by silencing the translation [25,42]. These sex chromosomes associated mechanisms increased susceptibility of SARS-CoV-2 infection in males of Bangladesh, above all worldwide.

Impact of male and female sex hormones in COVID-19 patients: Previous studies demonstrated that male sex hormone (testosterone) may trigger SARS-CoV-2 infection and disease progression whereas female steroid hormones (oestrogen, progesterone) may be responsible for lesser impact of COVID-19 on female [43]. Immunological differences between men and women pertain to the possibility that androgen and progesterone hormone suppress the immune system while oestrogen hormone stimulate the immune responses. For example, Angiotensin-Converting Enzyme 2 (ACE 2), an essential entry receptor for SARS-CoV-2, is expressed in lungs along with Spermatogonia, Leydig and Sertoli cells. ACE2 is considered to modulate testicular function in COVID-19 infected patients which may affect testosterone secretion,

though the pathway is not well established [44,45]. It inhibits the differentiation of T helper 1 (Th1) arm, an important effector cells that act against viral pathogens. Consequently, the reduced level of interferon gamma (IFN-γ), Interleukin-2 (IL-2), Interleukin-10 (IL-10) and Tumor necrosis factor alpha/beta (TNF α/β) make men more vulnerable to SARS-CoV-2 infections [46,47]. Besides, new coronavirus prime the spike (S) protein with the help of the cellular transmembrane serine protease 2 (TMPRSS2) proteins on our lung cells. The transcription of TMPRSS2 gene is modulated by the androgen receptor activity leads to the progression of COVID-19 disease [48,49]. TMPRSS2 inhibitors- nafamostat, camostat, antiandrogens, inhaled corticosteroids etc., are used as a therapeutic drug candidates for the treatment of COVID-19 and these are currently in clinical trials for the development of effective drugs [50,51]. Interestingly, nicotine products, e.g., cigarettes, is supposed to increase the ration of androgen to estrogen and considered as one of the risk factors for the ARDS. Several SNPs found in the Epidermal Growth Factor (EGF) are directly linked with ARDS risks in male but no associations are evident in female. Therefore, men who smoke are associated with higher testosterone, in aggravating the infection [49,52].

The two female sex steroid hormones: oestrogens (17β-oestradiol, E2), and progesterone enable the efficient, intense and prolonged, innate and adaptive immune response in women [53]. Some experiments suggest that SARS-CoV-2 utilize the interferon driven upregulation of ACE2 gene during lung injury [54]. Oestrogens downregulates X chromosome encoded ACE2 gene and turn on sex specific regulation [13,50]. E2 binds to either the oestrogen receptors alpha (ERα), highly expressed on T cells or oestrogen receptors beta (ERβ), highly expressed on B cells [55]. Thus, it raises the level of antibodies by stimulating the humoral response as well as regulates the development of T cells to viral infections. For example, X-encoded immune genes influences the overexpression of CD40LG (also known as CD154, a co-stimulatory molecule) and CXCR3 (chemokine receptor) that leads to differentiation of Th1 arm. This hormone also elevates the level of Natural Killer (NK) cells [13,56]. A recent study showed that COVID-19 patients can also be protected against the disease not only by antibodies but also T-cell mediated immunity which was overlooked previously [57] (Figure 5). This hormone has also antiviral properties in different viral infections including HIV, Hepatitis C Virus (HCV), Ebola virus, and human cytomegalovirus (HCMV), elucidating the reason, why women are less prone to this virus [58].

Moreover, another female steroid hormone, progesterone restrains both innate and cell-mediated immune responses in the body. Like testosterone, the suppression of the Th1 by progesterone favors Th2 cytokine production. Eventually it links to the inhibition of cytotoxic T cells, and modulates the function of NK cells [55,59]. The above-mentioned actions of the steroid hormones may elucidate a potential mechanism of protection in females against SARS-CoV-2 infection. Another research showed that similar coronaviruses, MERS-CoV and SARS-CoV were found to infect more men than women [26]. Study of SARS-CoV infection in a mouse model revealed that male mice were more susceptible to infection than female mice. Therefore, the enhanced susceptibility of male mice to SARS-CoV correlated with extensive alveolar macrophages and neutrophil accumulation in the lungs [60].

Immunological and hormonal role in pregnant women with COVID-19: The data of pregnant women with COVID-19 from different countries showed relatively low mortality rate compared to the patients with hepatitis E virus, influenza A virus, SARS CoV, and MERS CoV [61]. Immune modulating hormones, cytokines and other anti-inflammatory endogenous ligands play important role in reducing the fatality of COVID-19 during pregnancy. Pregnant women with COVID-19 were less likely to cause fever and myalgia compared to non-pregnant women [62]. On the other hand, a report revealed that the rate of susceptibility to be infected by the SARS-CoV-2 or other viruses are greater among pregnant women. But there is still no sufficient evidence to assist the underlying mechanisms [63]. To support the occurrence of less fatality among pregnant women with COVID-19, the possible mechanism lies in the immunological response during pregnancy. The maternal immunological system has triphasic shift. The first state, a proinflammatory in first trimester, is dominated by T-helper/Th-1 and Th-17 production. It causes overproduction of proinflammatory cytokines, including IL-1β, IL-6, Il-8, IL-12, TNF-α, chemotactic cytokines (IFNγ, eotaxin) and growth factors. The second state, anti-inflammatory state

in second trimester is marked by the production of Th-2 and T-regulatory (Tg) cells and overproduction of anti-inflammatory cytokines, including IL-4, IL-5, IL-10, IL-13, and TGF-β. Some placental hormones (estriol, estradiol, progesterone, human chorionic gonadotropin/hCG, prostaglandins, corticosteroid) also augment the Th-2 anti-inflammatory response and inhibit the Th-1 cytokine secretion. Thus it reaches the third state, second proinflammatory state in the peripartum and postpartum period. It has been reported that the activation of immune response to SARS CoV-2 infection is mediated by both proinflammatory (Th-1) and anti-inflammatory (Th-2) mediators, resulting increased production of mixed type of cytokines and chemokines (IL-1ra, IL-2, IL-2R, IL-6, IL-8, IL-17, IL-10, TNF-α, IFNγ, M-CSF, granulocyte colony-stimulating factor/G-CSF) among COVID-19 patients. This bilateral immune activation during anti-inflammatory state (which is dominate during pregnancy period) may reduce the fatality rate among pregnant women with COVID-19. Another important factor for less mortality in pregnancy is that generally women become pregnant under the age of 40 years [61]. The role of age in the progression of COVID-19 disease is discussed further in later section.

Immunosenescence: effects of aging on the immune system: Studies in Bangladesh and the other countries have shown that the mortality rates are higher for men than women in old age. Association of comorbidities with age is reported to influence the severity of the COVID-19 disease. The risk of benign prostatic hypertrophy is also notable in men above the age of 50. Accumulating evidence suggests that increases of TMPRSS2 in prostate cancer also intensify the risk of SARS-CoV-2 infection [44,64]. On the other hand, immunosenescence causes reduction of B and T cells in bone marrow and thymus resulting malfunction of mature lymphocytes. Comorbidities such as diabetes, hypertension, respiratory diseases, cardiac diseases, renal diseases and malignancy etc. are more prevalent in the individuals aged of 50 years or older [65,66]. As a result, the compromised immune system in association with comorbidities cannot perform as robustly as the young individuals, explain the higher mortality rates in elder individuals. At the same time, older women have low female sex hormones, including oestrogen, as women's body go through the menopause phases. Therefore, post-menopausal women are more at risk from COVID-19 than pre-menopausal women [67].

CONCLUSION

In conclusion, the disparities in the sex, gender and age elucidate that why men in Bangladesh are more at risk of dying from COVID-19 disease. The differences in the immune system of male and female shows sex biased pathogenesis from COVID-19. Since three coronavirus outbreaks (SARS-CoV, MERS and SARS-CoV-2) have occurred within past twenty years, the sex specific immune response needs to understand clearly to decrease the case fatality rates in affected patients. Therefore, the gender biased impact of this disease should integrate as a biological variable in fundamental research and provide the treatment against the disease.

CONFLICT OF INTERESTS

All the authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTION

All authors contributed to the critical review of the manuscript. All authors have read and approved the final version of the manuscript.

FUNDING

There is no funding for this review article.

REFERENCES

1. Anjorin A. (2020). The coronavirus disease 2019 (COVID-19) pandemic: A review and an update on cases in Africa. Asian Pacific Journal of Tropical Medicine. 13: 199-203.
2. Pal M, Berhanu G, Desalegn C, Kandi V. (2020). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus. 12: e7423.
3. Zhang L, Shen F, Chen F, Lin Z. (2020). Origin and Evolution of the 2019 Novel Coronavirus. Clinical Infectious Diseases. 71: 882-883.
4. Principi N, Bosis S, Esposito S. (2010). Effects of Coronavirus Infections in Children. Emerg Infect Dis. 16: 183-188.
5. Wang X, Sahu KK, Cerny J. (2020). Coagulopathy, endothelial dysfunction, thrombotic microangiopathy and complement activation: potential role of complement system inhibition in COVID-19. J Thromb Thrombolysis. 15: 1-6.

6. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, et al. (2021). Managing thrombosis and cardiovascular complications of COVID-19: answering the questions in COVID-19-associated coagulopathy. Expert Rev Respir Med. 14: 1-9.
7. da Costa VG, Moreli ML, Saivish MV. (2020). The emergence of SARS, MERS and novel SARS-2 coronaviruses in the 21st century. Arch Virol. 165:1517-1526.
8. Jiang S, Hillyer C, Du L. (2020). Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. Trends Immunol. 41: 355-359.
9. She J, Jiang J, Ye L, Hu L, Bai C, et al. (2020). 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies. Clin Transl Med. 9: 19.
10. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. (2021). Features, Evaluation and Treatment Coronavirus (COVID-19). In: StatPearls. Treasure Island (FL): StatPearls Publishing.
11. Meng H, Xiong R, He R, Lin W, Hao B, et al. (2020). CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan, China. J Infect. 81: e33-e39.
12. Rozenberg S, Vandromme J, Martin C. (2020). Are we equal in adversity? Does Covid-19 affect women and men differently? Maturitas. 138: 62-68.
13. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. (2020). Considering how biological sex impacts immune responses and COVID-19 outcomes. Nature reviews Immunology. 20: 442-447.
14. Leng J, Goldstein DR. (2010). Impact of aging on viral infections. Microbes Infect. 12: 1120-1124.
15. COVID-19: overview and resources - Global Health 50/50.
16. Chen N, Zhou M, Dong X, Qu J, Gong F, et al. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 395: 507-513.
17. Klein SL, Dhakal S, Ursin RL, Deshpande S, Sandberg K, et al. (2020). Biological sex impacts COVID-19 outcomes. PLOS Pathogens. 16: e1008570.
18. Dudley JP, Lee NT. Disparities in Age-specific Morbidity and Mortality From SARS-CoV-2 in China and the Republic of Korea. Clin Infect Dis. 71: 863-865.
19. Anwar S, Nasrullah M, Hosen MJ. (2020). COVID-19 and Bangladesh: Challenges and How to Address Them. Front Public Health. 8.
20. Guan W, Liang W, Zhao Y, Liang H, Chen Z, et al. (2020). Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 55: 200547.
21. Wu Z, McGoogan JM. (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 323: 1239-1242.
22. Lithander FE, Neumann S, Tenison E, Lloyd K, Welsh TJ, et al. (2020). COVID-19 in older people: a rapid clinical review. Age Ageing. 49: 501-515.
23. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. (2000). Gender Differences in the Utilization of Health Care Services. The Journal of family practice. 49: 147-152.
24. Johnson HD, Sholcosky D, Gabello K, Ragni R, Ogonosky N. (2003). Sex differences in public restroom handwashing behavior associated with visual behavior prompts. Percept Mot Skills. 97: 805-810.
25. Bianchi I, Lleo A, Gershwin ME, Invernizzi P. (2012). The X chromosome and immune associated genes. Journal of Autoimmunity. 38: J187-J192.
26. Alghamdi IG, Hussain II, Almalki SS, Alghamdi MS, Alghamdi MM, et al. (2014). The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health. Int J Gen Med. 7: 417-423.
27. Jin J-M, Bai P, He W, Wu F, Liu X-F, et al. (2020). Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health. 8: 152.
28. Brooks WH, Renaudineau Y. (2015). Epigenetics and autoimmune diseases: the X chromosome-nucleolus nexus. Front Genet. 6: 22.

29. Abramowitz LK, Olivier-Van Stichelen S, Hanover JA. (2014). Chromosome Imbalance as a Driver of Sex Disparity in Disease. J Genomics. 2: 77-88.
30. Klein SL, Huber S. (2009). Sex Differences in Susceptibility to Viral Infection. In: Klein SL, Roberts C (editors). Sex Hormones and Immunity to Infection. Berlin, Heidelberg: Springer. 93-122.
31. Panning B. (2008). X-chromosome inactivation: the molecular basis of silencing. Journal of Biology. 7: 30.
32. El-Zayat SR, Sibaii H, Mannaa FA. (2019). Toll-like receptors activation, signaling, and targeting: an overview. Bull Natl Res Cent. 43: 187.
33. Berghöfer B, Frommer T, Haley G, Fink L, Bein G, et al. (2006). TLR7 ligands induce higher IFN-alpha production in females. J Immunol. 177: 2088-2096.
34. Schulz KS, Mossman KL. (2016). Viral Evasion Strategies in Type I IFN Signaling - A Summary of Recent Developments. Front Immunol. 7: 498.
35. Schneider-Hohendorf T, Görlich D, Savola P, Kelkka T, Mustjoki S, et al. (2018). Sex bias in MHC I-associated shaping of the adaptive immune system. PNAS. 115: 2168-2173.
36. Fink AL, Klein SL. (2018). The evolution of greater humoral immunity in females than males: implications for vaccine efficacy. Curr Opin Physiol. 6: 16-20.
37. Suba Z. (2020). Prevention and therapy of COVID-19 via exogenous estrogen treatment for both male and female patients. J Pharm Pharm Sci. 23: 75-85.
38. Klein SL, Marriott I, Fish EN. (2015). Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg. 109: 9-15.
39. Wei X, Xiao Y-T, Wang J, Chen R, Zhang W, et al. (2020). Sex Differences in Severity and Mortality Among Patients With COVID-19: Evidence from Pooled Literature Analysis and Insights from Integrated Bioinformatic Analysis. 43.
40. Klein SL, Flanagan KL. (2016). Sex differences in immune responses. Nat Rev Immunol. 16: 626-638.
41. Qu N, Xu M, Mizoguchi I, Furusawa J, Kaneko K, et al. (2013). Pivotal Roles of T-Helper 17-Related Cytokines, IL-17, IL-22, and IL-23, in Inflammatory Diseases. Clin Dev Immunol. 2013: 968549.
42. Eulalio A, Huntzinger E, Izaurralde E. (2018). Getting to the Root of miRNA-Mediated Gene Silencing. Cell. 132: 9-14.
43. Ma L, Xie W, Li D, Shi L, Mao Y, et al. (2020). Effect of SARS-CoV-2 infection upon male gonadal function: A single center-based study.
44. Chakravarty D, Nair SS, Hammouda N, Ratnani P, Gharib Y, et al. (2020). Sex differences in SARS-CoV-2 infection rates and the potential link to prostate cancer. Communications Biology. 3: 374.
45. Pozzilli P, Lenzi A. (2020). Commentary: Testosterone, a key hormone in the context of COVID-19 pandemic. Metabolism. 108: 154252.
46. Mohamad N-V, Wong SK, Wan Hasan WN, Jolly JJ, Nur-Farhana MF, et al. (2019). The relationship between circulating testosterone and inflammatory cytokines in men. Aging Male. 22: 129-140.
47. Taneja V. (2018). Sex Hormones Determine Immune Response. Front Immunol. 9: 1931.
48. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 181: 271-280.
49. Stopsack KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. (2020). TMPRSS2 and COVID-19: Serendipity or Opportunity for Intervention? Cancer Discov. 10: 779-782.
50. Sharma G, Volgman AS, Michos ED. (2020). Sex Differences in Mortality From COVID-19 Pandemic: Are Men Vulnerable and Women Protected? JACC: Case Reports. 2: 1407-1410.
51. Ragia G, Manolopoulos VG. (2020). Inhibition of SARS-CoV-2 entry through the ACE2/TMPRSS2 pathway: a promising approach for uncovering early COVID-19 drug therapies. Eur J Clin Pharmacol. 1-8.
52. Sheu CC, Zhai R, Su L, Tejera P, Gong MN, et al. (2020). Sex-specific association of epidermal growth factor gene polymorphisms with acute respiratory distress syndrome | European Respiratory Society. 33: 543-550.
53. Khan D, Ansar Ahmed S. (2016). The Immune System Is a Natural Target for Estrogen Action: Opposing Effects of Estrogen in Two Prototypical Autoimmune Diseases. Front Immunol. 6: 635.

54. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, et al. (2020). SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. Cell. 181: 1016-1035.
55. Grandi G, Facchinetti F, Bitzer J. (2020). The gendered impact of coronavirus disease (COVID-19): do estrogens play a role? The European Journal of Contraception & Reproductive Health Care. 25: 233-234.
56. Wang J, Syrett CM, Kramer MC, Basu A, Atchison ML, et al. (2016). Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. Proc Natl Acad Sci USA. 113: E2029-2038.
57. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin J-B, et al. (2020). Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. 183: 158-168.
58. Peretz J, Pekosz A, Lane AP, Klein SL. (2016). Estrogenic compounds reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors. Am J Physiol Lung Cell Mol Physiol. 310: L415-425.
59. Piccinni M-P, Scaletti C, Maggi E, Romagnani S. (2000). Role of hormone-controlled Th1- and Th2-cytokines in successful pregnancy. Journal of neuroimmunology. 109: 30-33.
60. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, et al. (2017). Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. J Immunol. 198: 4046-4053.
61. Berhan Y. (2020). What immunological and hormonal protective factors lower the risk of COVID-19 related deaths in pregnant women? J Reprod Immunol. 142: 103180.
62. (2021). Pregnant women with covid-19 are less likely to have symptoms and may more likely need intensive care. BMJ.
63. Vale AJM, Fernandes ACL, Guzen FP, Pinheiro FI, de Azevedo EP, et al. (2021). Susceptibility to COVID-19 in Pregnancy, Labor, and Postpartum Period: Immune System, Vertical Transmission, and Breastfeeding. Front Glob Womens Health. 2.
64. Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, et al. (2014). The Androgen-Regulated Protease TMPRSS2 Activates a Proteolytic Cascade Involving Components of the Tumor Microenvironment and Promotes Prostate Cancer Metastasis. Cancer Discov. 4: 1310-1325.
65. Bencivenga L, Rengo G, Varricchi G. (2020). Elderly at time of COronaVIrus disease 2019 (COVID-19): possible role of immunosenescence and malnutrition. GeroScience. 42: 1089-1092.
66. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, et al. (2020). COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res. 32: 1599-1608.
67. Oestrogen and Coronavirus. (2020). Megs Menopause Research. MegsMenopause.