

Sex disparity in COVID-19 infection and mortality

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ABSTRACT

The outbreak of Covid-19 is caused by a severe acute respiratory syndrome novel coronavirus 2 (SARS-CoV-2) that was officially reported in China at the end of December 2019, and is now spread across more than 180 countries worldwide. The source of this virus is not very clear; however, many research investigations speculated its origin from an unknown animal to humans. The sweep of viral infection is too high and the number of infected people is doubled every 3-10 days worldwide in the initial 6 months. Early data on Covid-19 suggests a higher infection and mortality rate among males as compared to females. In worldwide data analysis, we found that among European nations, viral infection in females is equal to or more than males, whereas in India, it is approximately thrice among males. When it comes to Covid-19 mortality, males are more susceptible than females across all regions with a few exceptions. In this article, we have discussed likely reasons for sex disparity in Covid-19 infection and mortality with a focus on India.

KEYWORDS: Sex disparity, Covid-19, Susceptibility, India, Europe

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INTRODUCTION

Severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2) is the cause of the present Covid-19 pandemic, resulting in more than 6.9 million cases (6,939,869) in 188 countries with the total number of 400,624 deaths (The center for system sciences and engineering, John Hopkins) as of June 7, 2020. This pandemic situation has put the world on standstill with unprecedented health as well as economic burden and forcing new-ways of daily life for the near future across the globe.

In India, it has been an evolving situation with more than 254,242 cases (7117 deaths) being reported over two months, which is substantially low as compared to the western countries, e.g. the USA, Italy and UK. Till now, it has been attributed to early Nation-Wide-Strict-Lockdown Enforcement (NWSLE) for the first 21 days, which was followed by additional phases of the strict lockdown of 19, 14 and 14 days, respectively. Additional lockdown of 30 days for phase 5 is currently ongoing. This is accompanied by hot-spot identification, sealing containment zones, and isolation and treatment of the patients. Further, finding connected people and self or enforced-quarantine by various administrative entities starting from national-provincial-district-town till the village level, may have effectively contained widespread infections in India.

Infection and mortality

According to the data released by the Ministry of Health, Government of India on April 7, 2020, 76% males were infected compared to 24% females. The data compiled till May 15, 2020, by the Global Health 50/50, (<https://globalhealth5050.org/covid19/>) an independent research initiative, which tracks and compiles information on gender and health on COVID-19 revealed that infections among males are relatively higher than females in most of the Asian and South American countries (Figure 1A). However, in most of the European populations,

infections among females are either equal or more than males (Figure 1B). Indian gender-based data post April 2020 is not yet released. Global Health 50/50 figures on the basis of partial Indian data available till 30.04.2020 showed the death of 64% males and 36% females out of 1075 total deaths. Higher male death as compared to females has been found in almost all affected countries with the exception of Portugal (49% males) and Canada (47% males). The highest death ratio of males to females was found in Thailand (2.8), followed by Greece (2.2), Dominican Republic (2.2), The Netherlands (2.2) and Romania (2.0) (Global health 50/50 <https://globalhealth5050.org/covid19/>). According to the analysis of one of the big datasets published by the Chinese Centre for Disease Control and Prevention (CDC), the infection in men and women in China was nearly equal but the death rate among men was 2.8 per cent, compared with 1.7 per cent among women (Surveillances, 2020). As per the Global health 50/50 data (<https://globalhealth5050.org/covid19/>), in the majority of the countries and among ethnic groups, mortality among males is consistently higher (Figure 2). It is interesting to note that in European countries such as Italy, Spain, France, Switzerland, Sweden, Germany, Austria, The Netherlands and in England, Covid-19 related deaths are higher among males in comparison to females despite higher viral infections among females (Figure 2A). In few countries, such as Estonia, Portugal and Canada, there is marginal (Figure 2B) increase in female deaths. This trend of gender-biased susceptibility and higher vulnerability of males to COVID-19 is puzzling to the scientists across the world. Different research groups all over the world are trying to come up with the possible answers through scientific explanations on the disparity in vulnerability, but also exercising caution before making conclusions. This is largely due to unknown nature, features and behavior of the virus, different immunity responses of the individuals and populations

across the world. Still, there are no common agreeable reasons and the causes for differential susceptibility. However, it is clear that a more severe course of disease manifestation is associated with older age and co-morbidities. The systematic and in-depth scientific investigations taking into consideration of diverse angles will be needed to understand the disparity in male and female susceptibility. Comparative social status,

lifestyle, job profile, health or diseases, hormone and genetics, may have a role in differential susceptibility. With the 1/5th of the world's population and lower healthcare index, India is one of the most susceptible countries. In this work, we evaluated and analyzed the COVID-19 infection as well as mortality rates among males and females.

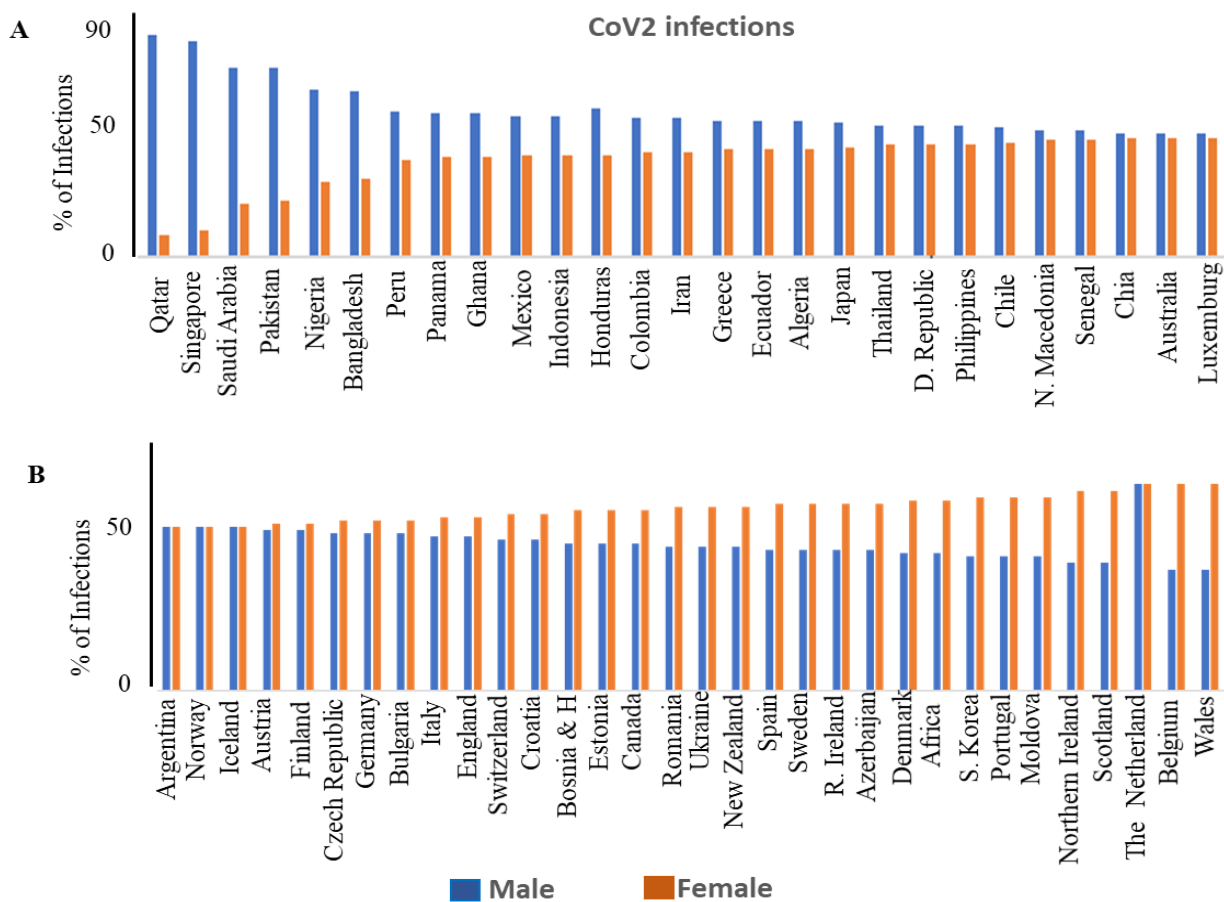
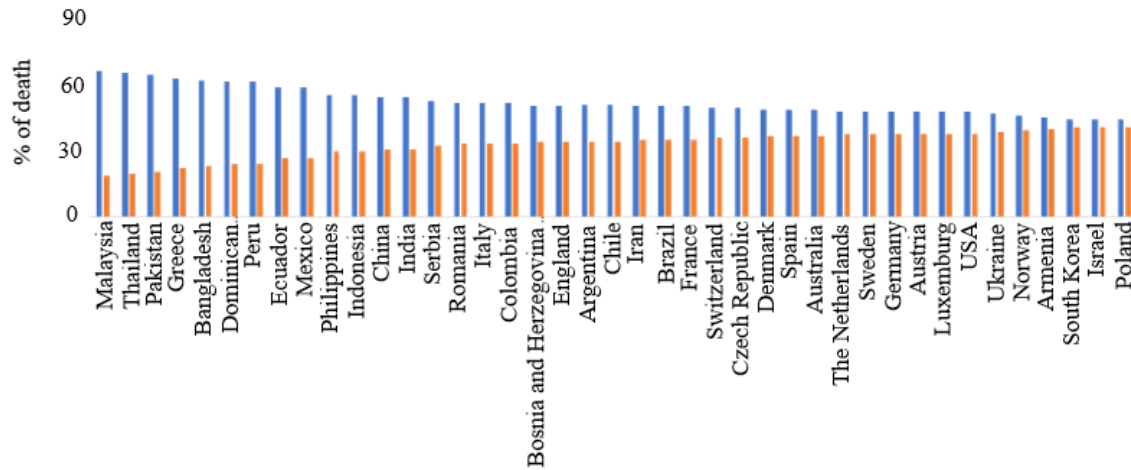


Figure 1: SARS-CoV-2 infections among males and females in various countries. A). Countries with more infections among males. B). Countries with equal or more infections among females. Data source: Global Health 50/50.

A



B

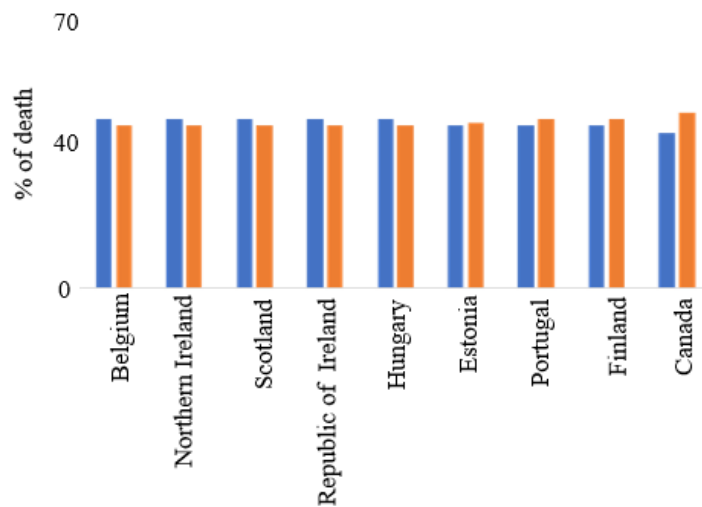


Figure 2: CoV2 infection-related deaths in various countries. A). Countries with less deaths among females. B). Countries with more or less equal deaths among males and females. Data Source: Global Health, 50/50.

Social scenario

Social status, job profile, travel, time of staying indoors or outdoors for work for men and women might be playing an important role in their individual and relative exposure to the virus in various regions. The number of females in education and jobs is comparatively lower than

males in India. Travel time and staying outside the home would be more for men than women. Besides this, the rate of participation in public gatherings and events by males is also comparatively more than females. Therefore, the chances of exposure to infectious particles can be more to males than females.

Moreover, the live-in before marriage in India is socially discouraged, that helps single people to live in isolation. However, relating these factors in the Indian context for Covid-19 susceptibility will be difficult as Indian society is dense and also enjoys more open social gatherings culturally, and therefore the chances of direct and indirect contacts are high. Nevertheless, lifestyle features of males and females in India may have a considerable role in the initial infection, the building of the viral load and thereby differential susceptibility to Covid-19. Addiction to tobacco or alcohol can significantly compromise human lung capacity and overall health. Co-morbidities due to Covid-19 in China were linked to smoking (Rabi et al. 2020), where 54% males compared to 2.6% females smoke tobacco (Liu et al. 2017). In India, 34.6% of adults (out of which 47.9% are males and 20.3% are females) are smokers and 14% adults use smoking tobacco, out of which 24.3% are males and 2.9% are females (India today May 31, 2019). This fits the recent analysis of gene expression data from Gene Expression Omnibus datasets of non-cancerous human lung and bronchial/airway epithelial cells, which shows a modest but significant increase in the expression of ACE2 and TMPRSS2 with smoking, but independent of gender (Baratchian et al. 2020).

Similarly, alcohol addiction poses detrimental effects on health. India's per capita alcohol consumption in the year 2000-2001 was 0.82 liters, which was comparatively lower than per capita consumption in other countries such as Canada (8.26 liters), US (8.51 liters), and UK (10.39 liters) (WHO, 2004). However, the unrecorded per capita alcohol consumption in India after the year 1995 was predicted around 1.7 liters (WHO, 2004). The rate of consumption of alcohol of Indian men is more than women; 21 % of adult men and 2% of women in India consume alcohol as per government statistics (Prasad, 2009). Except in tribal societies, self-restraint about the consumption of alcohol by women is a cultural norm in India (Prabhu et al. 2010). Broad population-level studies have persistently shown

low alcohol consumption rate among Indian women, which ranged between 2 and 5% (Prabhu et al. 2010; Benegal et al. 2005).

The consumption of alcohol in the long term or chronic consumption was linked to heart diseases, liver diseases, liver cirrhosis besides pharynx, oral cavity and lip cancers (WHO, 2004). Alcohol causes 3.2% (~1.8 million deaths) of all annual deaths worldwide accounting for a disease burden of 4.0% (WHO, 2007). A case-control study showed that the consumption of alcohol was harmful to Indian men by increasing the risk of coronary heart disease (CHD) (Roy et al. 2010). Smoking and alcohol are also linked to respiratory diseases. Smoking and overconsumption of alcohol are associated with more than 20% of tuberculosis (TB) disease worldwide (Thomas et al. 2019). Past and current smoking, along with alcohol misuse, has combined effects on increasing the risk of unfavourable outcomes in TB treatment. Therefore, there is an urgent need of innovative interventions that should readily address both co-morbidities (Thomas et al. 2019). Incidentally, deaths occurring due to Covid-19 worldwide comprise a high proportion of co-morbidities. There is a possibility of association between addiction, co-morbidities and Covid-19, which needs further comprehensive investigation.

Gender biased co-morbidities and Covid-19 outcome

The disease progression, severity and mortality due to infectious agent can vary according to age, sex, physical status, underlying conditions, ethnic groups, countries and various other factors. Widespread health impacts have been witnessed due to the Covid-19 pandemic, signifying the people with underlying conditions being particularly the most vulnerable (Kluge et al. 2020). According to a recent report from Italy, co-morbidities and principally non-communicable diseases (NCDs) were found to be the main reason for the death of the majority of patients (96.2%) from Covid-19 (Italy report 2020

www.epicentro.iss.it). In these patients, the most prevailing NCDs were, 69.2%-hypertension followed by 31.8%-type 2 diabetes, 28.2%-ischemic heart disease, 16.9%-chronic obstructive pulmonary disease and 16.3%-cancer (Italy report 2020 www.epicentro.iss.it). The connection of NCDs to Covid-19 vulnerability is also reported in the USA (Richardson et al. 2020), China (Surveillances, 2020) and Spain (Instituto de Salud Carlos III 2020). Older age with pre-existing comorbidities has also played a significant role in several deaths due to Covid-19 (Jordan et al. 2020). According to the WHO report 2015, NCDs (lung and heart diseases, diabetes, stroke and cancer) cause almost 5.8 million deaths in India, which means 1 out of every 4 Indians is at the risk of dying from NCD by the time of reaching 70 years of age. As per the Ministry of Health, Government of India April 2020 statement on COVID-19 pandemic, 86% death cases exhibited co-morbidity related to hypertension, heart-related problems, chronic kidney issues and diabetes. Elderly people form a high-risk population as 63 per cent deaths were observed among them, which comprised 19 per cent of the positive cases. In addition, 37% deaths were of age less than 60 years. About 86% death cases of comorbidities also include young people with comorbidities indicating them as high-risk group for Covid-19. Therefore, taking into consideration of these big numbers, extra precautions will be needed to protect people with underlying comorbidities and prevent them from contracting the virus. The prevalence of NCDs like hypertension, type 2 diabetes, ischemic heart disease, chronic obstructive pulmonary disease and cancer is high in men than women (Jin et al. 2020, Yang et al., 2020). The incidence of cardiovascular diseases is more in males and Covid-19 infected individuals without cardiovascular dysfunctions have a better prognosis; however, these effects till now are under investigation because of their multi-factorial etiology (Conti and Younes, 2020).

Pathophysiology of Covid-19

A variety of different factors at the level of host-pathogen interactions are important for successful entry, adaptation and survival of the infectious agents in the host body. The structure and functional characteristics of infectious agent and response of host decides the course of progression and the severity of the disease. SARS-CoV-2 is a single-stranded enveloped RNA virus that has a positive-sense RNA genome. It has four important structural proteins (envelope (E), membrane (M), spike (S) and nucleocapsid (N)) (Schoeman and Fielding, 2019). Out of these, the N and S proteins play a key role in the entire viral structural development including capsid and host cell attachment, respectively (Siu et al., 2008; Walls et al., 2020). The two host proteins which are responsible for the entry of virus into the host cells are ACE2 and TMPRSS2 (Hoffmann, 2020). The protease (serine protease encoded by TMPRSS2) activates the spike protein to induce virus-cell membrane fusion at the cell surface at ACE2 and facilitates the entry of coronaviruses into the host cell (Shirato K et al. 2013; Gierer S et al. 2013, Hoffman et al. 2020). After the viral antigen is detected, and antigen is presented to the cytotoxic T cells and Natural killer cells, both innate and adaptive immunity get activated. There is an increase in monocytes and macrophages and release of pro-inflammatory cytokines IL-1, IL-6, IL-8 and TNF-alpha. When this immune response is massive, it's called cytokine storm, which can lead to organ failure. In Covid-19 patients, the cytokine storm has been observed due to impaired viral clearance because of low levels of type I interferons (IFN), leading to rapid viral replication in that window during which increased pyroptosis is triggered leading to a massive release of inflammatory mediators (Soy et al. 2020; Coperchini F et al. 2020). This cytokine storm initiates a strong cytotoxic activity through increased neutrophil extracellular traps (NETs) and also directing cytotoxic T cells and NK cells to the infected cells and organs.

Probable molecular basis of gender disparity in Covid-19 outcome

Current data on infection and mortality suggest a clear advantage to women over men in terms of protection against Covid-19. This disparity may be as a result of the presence of advantageous factors in women as compared to men. Studies suggest that there are many differences between men and women in the immune response to Covid-19 infection and inflammatory diseases. Women, compared to men, are less susceptible to viral infections based on different innate immunity (Klein and Flanagan, 2016). The basis of the genetic difference between male and female is always sought after to address the gender disparity to various infections. There are two X chromosomes (46,XX) in women, whereas men have only one (46,XY). The presence of two X chromosomes in women emphasizes the immune system even if one is inactive. An extra X chromosome makes women's immune system stronger than men's (Migeon, 2006; Migeon, 2007). This extra X chromosome is very valuable for crucial functions like building and maintenance of the human brain and immune system (JunXua et al. 2006; Libert et al. 2010). XX chromosomes can be advantageous for women in some aspects. As a result of this, women have less susceptibility to disorders such as colour blindness. Women's immune system battles well against invading infectious microbes and malignant cells. The immune regulatory genes encoded by the X-chromosome in women causes lower viral load levels, and less inflammation than men, while CD4⁺ T-cells are higher with better immune response. In addition, antibodies remain in circulation for longer in women compared to men (Conti and Younes, 2020). Interestingly, ACE2 escapes X chromosome inactivation (Carrel and Willard 2005). In addition, antibodies at high level that remain in circulation for longer are usually produced in women. The women's immune cell activation levels are higher than men's, which is interconnected with the activation of Toll-like receptor 7 (TLR7) and IFN production (Conti and Younes, 2020). Progesterone plays an important

role in immune system modulation and functions apart from its primary sexual role. Progesterone also mediates stimulatory and suppressive roles in immune responses. Progesterone receptors are primarily expressed by T and NK cells, but recent studies detected them on dendritic and mesenchymal stem cells, where they suppress Th₁ cytokine secretion and increase Th₂ cytokine secretion. Progesterone also mediates suppression of T cell cytotoxicity, T-reg cells and inhibits the activity of NK cells by the downregulation of IFN- γ (Butts et al. 2007; Zhao et al. 2012; Enninga E et al. 2014; Arruvito et al. 2008). Moreover, X chromosome has loci which code for the genes implicated in the regulatory cells of the immune system (such as FOXP3, regulator and transcription factor for T-reg cells). Regulatory T-cells (T-regs) modulate the function of effector T cells (by suppressing cytotoxic T cells and other immune effector cells like CD4⁺, CD8⁺ T cells and B cells), either through suppressor cytokines like TGF- β and IL10 or by direct interaction with antigen presenting cells /dendritic cells, thereby helping in overall control of autoimmune responses and chronic inflammation (Caridade et. al. 2013). These differences of hormones may render females for better immunomodulation and suppression of inflammation than males, and hence females are in a better position than males when it comes to managing the cytokine storm and inflammation in the context of COVID-19. Immune system can be influenced by the X-chromosome through action on several other proteins, including CXCR3, CD40L and TLR8, which can be over-expressed in women and influence the response to viral infections and vaccinations. However, women may have to pay the cost for the aggressive immune system by becoming vulnerable to autoimmune diseases. The biallelic expression of X-linked genes can encourage detrimental inflammatory and autoimmune responses (Conti and Younes, 2020). The likelihood of attacking one's own immune system is more in females than males, which happens in conditions such as autoimmune thyroiditis, multiple sclerosis, lupus, Sjögren's

syndrome and rheumatoid arthritis (Moalem, 2020). It has been shown that the pre-condition of autoimmune disease may increase the risk of COVID-19 severity (Favalli EG, 2020). However, the disparity of women vs men for COVID-19 considers all the female populations where the frequency of any autoimmune disease would be obviously very low (Counti and Younes 2020). Nevertheless, these effects are still under study. For a comprehensive view, we rather suggest a dedicated editorial on this topic. As it is very well known that type 1 IFN is antiviral cytokine and is also involved in autoimmune disorders (such as systemic lupus erythematosus –in case of juvenile-onset). The role of IFNs in the context of COVID-19 outcome in female patients would be interesting to explore as plasmacytoid dendritic cells (pDC) from healthy women produce more type 1 IFN upon TLR7 signaling than males (Webb et al, 2019).

A unique human model consisting of Turner syndrome (i.e. female with missing or partially missing X-chromosome) and transgender on cross-sectional hormone therapy (i.e. males by birth on female hormone therapy and females by birth on male hormone therapy with normal pairs of chromosomes) allowed to dissect the direct correlation between X-chromosome numbers and the type 1 IFN response through more activated pDC and higher TLR7 gene expression in immune cells found in females (Webb et al, 2019).

Therefore, it is clear that women who are more prone to the auto-immune disorders (because of more type 1 IFN response), would have more protective first line innate immune response (through TLR7 and type 1 IFN) against the virus, which could very well relate to the gender biased outcome of COVID-19 and is worth investigating further.

Male: An expensive gender

Male is an expensive gender. They need more resources right from the conception to the

adulthood. The biology of this unique phenomenon is not very well understood, but there are scientific evidences in this favour. For example, under stress conditions, pregnant females give birth to more females than males in mice (Dama et al, 2011), in squirrels (Ryan et al., 2012) and humans (Hesketh and Xing 2006) also, i.e. leading to a change in the sex ratio. The quantification of costs for production of female versus male offspring in any given species among mammals is hard (Frank 1990). However, greater nutritional demands, bigger size, and high developmental rates of male offspring usually require greater immediate energy investment (Gomendio et al. 1990; Redondo et al. 1992; Koskela et al. 2009; Ryan et al., 2012). Wars and droughts have been shown to result in altered sex ratio (Hesketh and Xing 2006; Flatø and Kotsadam, 2014). The demography of the Y-chromosome showed a sharp reduction of effective males worldwide during 4-8 thousand years (Karmin et al. 2015). Although different findings show contradictory results for male versus female births (Hesketh and Xing 2006; Flatø and Kotsadam, 2014), the reasons for such sex ratio alterations at birth remain unknown (Hesketh and Xing 2006). It will be interesting to see the effect of overall stress of COVID-19 pandemic on sex ratio at birth. However, it will be difficult to exactly predict the scenario of the sex ratio at birth; nevertheless, from the previous studies, the speculation is that the stress generated because of COVID-19 and associated pandemic situation may skew the sex ratio to more female births. We will have to wait for the actual data that would provide a clear picture in this regard (Dama 2011; Gomendio et al.1990; Redondo 1992; Koskela et al. 2009; Ryan et al. 2012; Hesketh and Xing. 2006)

Conclusion

There is a continuous rise in the number of affected individuals due to COVID-19, warranting for simultaneous and multiple efforts on different fronts of vaccination and drug discovery. Different types of drugs are being constantly tried and

tested in clinical trials. However, drugs with 100% efficacy approved by FDA are not yet available. The current approach is mainly dependent on symptom-based treatment and provision of organ support to the severely affected individuals. Research efforts are underway to discover novel drugs and vaccines against this virus. Certain drugs, for instance, SARS-CoV-2 receptor blockers, hydroxychloroquine (for the treatment of malaria), monoclonal antibodies, anti-IL-1 and anti-IL-6, anti-inflammatories (against rheumatic diseases), the remdesivir (analogue adenosine, effective against ebola), are currently considered promising. However, the side effects of these drugs on humans are a major concern. Plant-based medicines and other natural, non-toxic drugs could find promise as treatment alternatives. Trials of a variety of vaccines are being conducted with a hope to provide protection, but vaccines with full proof accuracy against this virus are yet to be identified. Knowledge about the protective factors in women as compared to men may help in identifying resistance factors and drug targets. Therefore, there is a need for research and development efforts focusing on sex-based disparity in Covid-19 infection and mortality. The outcomes of these findings are anticipated to provide accurate identification of resistance factors and innovative strategies to fight against this dreadful virus.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

BKS and GC conceived the idea and wrote the first draft. DNR and SB performed analysis and prepared figures. All the authors contributed for structuring and improvement of the final draft and the different sections of the draft were further strengthened by authors individually (BKS- social scenario and co-morbidity, GC- genetics and DNR & AR- immunology). All the authors approved the final draft.

Declaration of originality

The authors declare that they have not copied text, figure or data from a particular source without appropriately citing it.

REFERENCES

- Arruvito L, S. Giulianelli, AC, Flores N, Paladino M, Barboza C, Lanari L. et al. . 2008. NK cells expressing a progesterone receptor are susceptible to progesterone-induced apoptosis. *J. Immunol.* 2008; 180:5746–5753.
- Asiel Arce-Sillas, Diana Denisse Álvarez-Luquín, Beatriz Tamaya-Domínguez, Sandra Gomez-Fuentes, Abel Trejo-García, et al. "Regulatory T Cells: Molecular Actions on Effector Cells in Immune Regulation" *J. Immunol Res.* 2016; 1-12.
- Baena E, Shao Z, Linn DE, Glass K, Hamblen MJ, Fujiwara Y. et al. ETV1 directs androgen metabolism and confers aggressive prostate cancer in targeted mice and patients. *Genes & development.* 2013; 27: 683-698.
- Baratchian M, McManus J, Berk M, Nakamura F, Erzurum S, Mukhopadhyay S et al. No evidence that androgen regulation of pulmonary TMPRSS2 explains sex-discordant COVID-19 outcomes. *bioRxiv.* 2020. <https://doi.org/10.1101/2020.04.21.051201>.
- Benegal V, Nayak MB, Murthy P, Chandra PS, Gururaj G. Women and alcohol in India. In, *Alcohol, gender and drinking problems: Perspectives from low- and middle-income countries* World Health Organization. 2005; 89–123.
- Butts CL, Shukair KM, Duncan E, Bowers C, Horn E, Belyavskaya, et al. Progesterone inhibits mature rat dendritic cells in a receptor-mediated fashion. *Int. Immunol.* 2007;19: 287–296.
- Caridade M, Graca L, Ribeiro RM. Mechanisms underlying CD4+ Treg immune regulation in the adult: from experiments to models. *Frontiers in immunology.* 2013 Nov 18;4:378.

- Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature*. 2005;434(7031):400-404.
- Chen J. Pathogenicity and transmissibility of 2019-nCoV—a quick overview and comparison with other emerging viruses. *Microbes Infect*. 2020;22: 69–71.
- Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *Journal of Biological Regulators and Homeostatic Agents*, 2020; 34: (2).
- Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev*. 2020; 53:25-32
- Dama MS, Singh NM, Rajender S. High fat diet prevents overcrowding induced decrease of sex ratio in mice. *PLoS One*. 2011 Jan 25;6(1):e16296.
- Enninga EA, Holtan DJ, Creedon RS, Dronca WK, Nevala S, Ognjanovic, SN, Markovic. Immunomodulatory effects of sex hormones: requirements for pregnancy and relevance in melanoma. *Mayo Clin. Proc*. 2014; 89: 520–535.
- Favalli EG, Ingegnoli, F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 Infection and Rheumatoid Arthritis: Faraway, So Close!. *Autoimmun Rev*. 2020.
- Flatø, M, & Kotsadam A. Droughts and gender bias in infant mortality in Sub-Saharan Africa. 2014 Memorandum.
- Gierer S, Bertram S, Kaup F, Wrensch F, Heurich A, Krämer-Kühl A, et al. The spike protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2, and is targeted by neutralizing antibodies. *J Virol*. 2013; 87:5502–5511.
- Global health 50/50 <https://globalhealth5050.org/covid19/>
- Gomendio M, Clutton-Brock TH, Albon SD, Guinness FE, Simpson MJ. Mammalian sex ratios and variation in costs of rearing sons and daughters. *Nature*. 1990; 343:261-263.
- Hesketh T, Xing ZW. Abnormal sex ratios in human populations: causes and consequences. *Proceedings of the National Academy of Sciences*, 2006;103: 13271-13275.
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271-280
- India today May 31, 2019 <https://www.indiatoday.in/education-today/gk-current-affairs/story/world-no-tobacco-day-34-6-per-cent-adults-in-india-are-smokers-1539130-2019-05-31>
- Instituto de Salud Carlos III. Informe COVID-19 nº 28. 04 de mayo de 2020. Informe sobre la situación de COVID-19 en España. 2020. <https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx> (accessed May 5, 2020).
- Istituto Superiore di Sanità. Characteristics of SARS-CoV-2 patients dying in Italy. Report based on available data on April 29, 2020. COVID-19. 2020. https://www.epicentro.iss.it/en/coronavirus/bollettino/Report-COVID-2019_29_april_2020.pdf (accessed May 5, 2020).
- Jin JM, Bai P, He W, Wu F, Liu X-F, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front. Public Health*. 2020;8:152.
- Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ* 2020; 368: m1198.
- JunXua, Christine M. Disteche. Sex differences in brain expression of X- and Y-linked genes *Brain Research*. 2006;1126: 50-55.
- Kim Y, Jdrzejczak R, Maltseva NI, Wilamowski M, Endres M, Godzik A. et al. Crystal structure of Nsp15 endoribonuclease NendoU from SARS-CoV-2. *Protein Science*. 2020:1-10
- Klein SL, Flanagan KL. Sex differences in immune responses. *Nature Reviews Immunology*, 2016;16: 626.
- Kluge S, Janssens U, Welte T, Weber-Carstens S, Marx G, Karagiannidis C. Empfehlungen zur intensivmedizinischen Therapie von Patienten mit COVID-19 [Recommendations for critically ill patients with COVID-19]. *Med Klin Intensivmed Notfmed*. 2020;115:175-177.
- Konrad HS, Lorelei AM, Emmanuel SA, Peter SN, Philip WK. TMPRSS2 and COVID-19: serendipity or Opportunity for Intervention?. *Cancer Discov* 2020;10:779–82.
- Kluge HHP, Wickramasinghe K, Rippin H, Mendes R, Peters DH, Kontsevaya A, Breda J. Prevention and control of non-communicable diseases in the COVID-19 response. *Lancet*. May 8, 2020
- Koskela E, Mappes T, Niskanen T, Rutkowska J. Maternal investment in relation to sex ratio and offspring number in a small mammal—a case for Trivers and Willard theory?. *Journal of Animal Ecology*, 2009; 78: 1007-1014.
- Libert, C., Dejager, L. & Pinheiro, I. The X chromosome in immune functions: when a chromosome makes the difference. *Nat Rev Immunol* 2010;10:594–604.
- Liu S, Zhang M, Yang L, Li Y, Wang L, Huang Z et al. Prevalence and patterns of tobacco smoking among Chinese adult men and women: findings of the 2010 national smoking survey. *J Epidemiol Community Health*, 2017; 71:154-161.
- Meredith Wadman Sex hormones signal why virus hits men harder. *Science*. 2020;368:1038-1039.
- Migeon BR. The role of X inactivation and cellular mosaicism in women's health and sex-specific diseases. *JAMA*. 2006;295:1428-1433.
- Migeon BR. Why females are mosaics, x-chromosome inactivation, and sex differences in disease. *Gender Medicine*. 2007;4:97–105.
- Moalem, S. Why are so many more men dying from coronavirus. *New York Times*. 2020:April 2. <https://www.nytimes.com/2020/04/02/opinion/coronavirus-men-women.html>
- Karmin M, Saag L, Vicente M, Melissa A. Sayres W, Järve M, et al. A recent bottleneck of Y chromosome diversity

- coincides with a global change in culture. *Genome Research*. 2015;25:459-466.
- Pan PP, Zhan Q T, Le F, Zheng YM, Jin F. Angiotensin-converting enzymes play a dominant role in fertility. *International journal of molecular sciences*, 2013;14: 21071-21086.
- Prabhu S, Patterson SF, David A. Dulmus CN. Ratheeshkumar KS. Prevalence, Nature, Context and Impact of Alcohol Use in India: Recommendations for Practice and Research". *Brown School Faculty Publications*. 2010: 25. https://openscholarship.wustl.edu/brown_facpubs/25
- Prasad R. Alcohol use on the rise in India. *Lancet*. 2009;373:17-18.
- Lu R, Zhao X, Li J, Niu P, Yang B, Wu, et.al. Genomic characterization an epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet*. 2020. 395; 565-574.
- Rabi FA, Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and Coronavirus Disease 2019: What we know so far. *Pathogens*. 2020;9: 231.
- Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;323: 2052-2059.
- Roy A, Prabhakaran D, Jeemon P, Thankappan KR, Mohan V, Ramakrishnan L. et al.. Impact of alcohol on coronary heart disease in Indian men. *Atherosclerosis*, 2010; 210, 531-535.
- Ryan CP, Anderson WG, Gardiner LE, Hare JF. Stress-induced sex ratios in ground squirrels: support for a mechanistic hypothesis. *Behavioral Ecology*, 2012;23:160-167.
- Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. *Virology*. J. 2019;16: 69.
- Shirato K, Kawase M, Matsuyama S. Middle East respiratory syndrome coronavirus infection mediated by the transmembrane serine protease TMPRSS2. *J Virol*. 2013; 87:12552-12561.
- Siu Y, Teoh K, Lo J, Chan C, Kien F, Escriou N et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. *J. Virol*.2008;82:11318-11330.
- Soy M, Keser G, Atagündüz P et al. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol*. 2020: 39;2085-2094.
- Surveillances V. (2020). The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, China CDC Weekly,2020; 8: 113-122.
- The Center for Systems Sciences and Engineering, John Hopkins University Coronavirus COVID 19 Global cases. www.coronavirus.jhu.edu/map.html
- Thomas BE, Thiruvengadam KSR, Kadam D, Ovung S, Sivakumar S et al. Smoking, alcohol use disorder and tuberculosis treatment outcomes: A dual co-morbidity burden that cannot be ignored. *PLoS ONE* 2019;14: e0220507.
- Tomás Redondo and Francisca Castro. Signalling of Nutritional Need by Magpie Nestling. *Ethology*;92.
- Vellingiri B, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B et al. COVID-19: A promising cure for the global panic. *Science of the Total Environment*, 2020;138277.
- Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*. 2020;181:281-292.
- Webb k, Peckham H, Radziszewska A, Menon M, Oliveri P, Simpson F, et al. Sex and Pubertal Differences in the Type 1 Interferon Pathway Associate With Both X Chromosome Number and Serum Sex Hormone Concentration. *Front. Immunol*. 2019;9:3167.
- World Health Organization (2007) Alcohol and Injury in Emergency Departments: A Summary of the Report from the WHO Collaborative Study on Alcohol and Injuries. World Health Organization. Department of Mental Health and Substance Abuse. Geneva.
- World Health Organization (2004). Global status report on alcohol 2004. World Health Organization. Department of Mental Health and Substance Abuse. Geneva.
- World Health Organization. (2015). Noncommunicable diseases progress monitor 2015.
- Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K. et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. *The Lancet Oncology*.2020. DOI: [https://doi.org/10.1016/S1470-2045\(20\)30310-7](https://doi.org/10.1016/S1470-2045(20)30310-7).
- Zhao XL, Liu D, Fan Y. Wang Y, Hu, et al. Progesterone enhances immunoregulatory activity of human mesenchymal stem cells via PGE2 and IL-6. *Am. J. Reprod. Immunol*. 2012; 68: 290-300.
- Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. *BioRxiv*.2020. <https://doi.org/10.1101/2020.01.26.919985>.
- Zheng YY, Ma Y T, Zhang J Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020.
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*