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Gender Differences in Covid-19 Infected Patients: Focus on the Male and Female Susceptibility to Covid-19 and Mortality Rate

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***Abstract*— The outbreak of Novel Coronavirus (SARS-CoV-2) Disease (COVID-19) has put the whole world on alert. Epidemiological data from the 2002-2003 SARS epidemic and the recent SARS-CoV-2 pandemic indicate that there may be sex-dependent differences in disease susceptibility and mortality rates. We therefore aim to compare the susceptibility of COVID-19 and mortality rate on gender basis and give reasons for the disparity. We extracted theepidemiological data from different countries showing differences in susceptibility and mortality rate of disease based on gender then did an empirical study on the reasons for the disparity. Results: Males are more susceptible to COVID-19 compared to females. This is attributed to immunological advantages produced by estrogen hormone, X-chromosome and differences in the ACE2 receptors.**

In conclusion, apart from exposure, smoking and social cultural risk factors subjected men on COVID-19, their susceptibility to the disease is caused by immunological and hormonal risk factors. This study will greatly help in developing gender sensitive medications or vaccines for COVID 19 and fine-tune response policies.

***Index Terms*— Susceptibility; Mortality; COVID-19; SARS-CoV-2**

I. INTRODUCTION

In early December 2019, an outbreak of a novel coronavirus disease (COVID-19) occurred in Wuhan city and then rapidly spread throughout China, putting the world on alert. High-throughput sequencing has revealed a novel β-coronavirus that is currently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhu *et al.,* 2020) which resembles severe acute respiratory syndrome coronavirus (SARS-CoV) (Drosten C *et al.*, 2003).

The coronavirus belongs to a family of viruses that may cause various symptoms such as pneumonia, fever, breathing difficulty, and lung infection (WMHC, 2020). These viruses are common in animals worldwide, but very few cases have been known to affect humans. The World Health Organization (WHO) used the term 2019 novel coronavirus to refer to

coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December 2019 (Li Q *et al.*, 2020). Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. It was suggested that the population most at risk may be people with poor immune function such as older people and those with renal and hepatic dysfunction (CDC, 2020).

The best way to prevent and slow down transmission is be well informed about the COVID-19 virus, the disease it causes and how it spreads. Protect yourself and others from infection by washing your hands or using an alcohol-based rub frequently and not touching your face.

Susceptibility seems to be associated with age, biological sex, and other health conditions (Fehr AR et al, 2017). Emerging evidence suggests that more men than women are infected, potentially due to sex-based immunological (Chen *et al.*, 2020), or gendered differences, such as patterns and prevalence of smoking (Liu *et al.*,2010). This sex-dependent increase in disease severity after pathogenic COVID-19 infection is more pronounced with advancing age (Karlberg *et al.*, 2004).

II. METHODS AND MATERIAL.

A. Epidemiological Data

The Chinese health authority has announced that the total number of confirmed cases on the Chinese mainland has reached 76,936, and 2,442 people have died of the disease as of Feb 23. Among the 2,442 deceased patients, most were men (National Health committee of PRC, 2020). Men were more susceptible and two-thirds of the deaths were males.

A recent report (23 April 2020) from the Italian National Institute of Health shows that of 23 188 deaths from COVID-19 infection in Italy, approximately 70% were in men. In the United States, provisional death counts for COVID-19 from February to April 2020 similarly indicate a sex bias in fatality rates: Of 37 308 deaths reported by the National Center for Health Statistics, 59% were in men. Similar trends have been reported in China (Dudley *et al.*,2020) and South Korea (Bartz*et al.*,2020).

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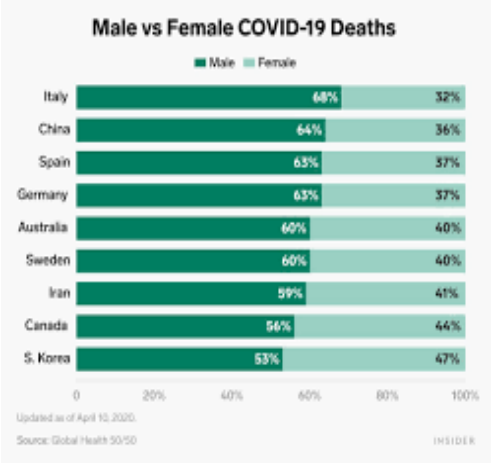
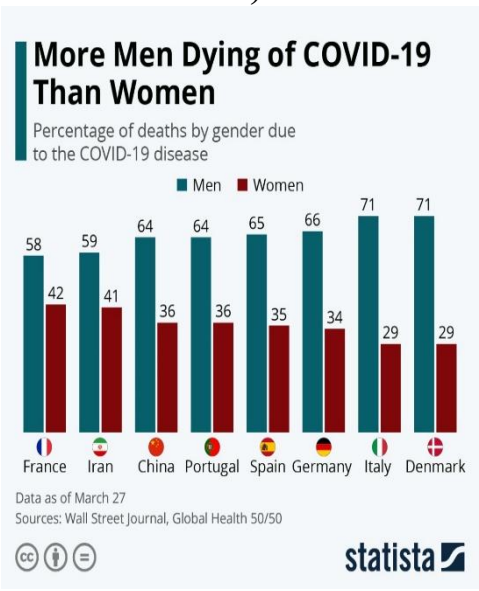
B. Graphical data



Graph 1; A graph showing COVID-19 deaths in different countries based on gender as at April 10th,2020. (*Extracted from Global Health 50/50)*



Graph 2; A graph showing percentage of deaths by gender due to COVID-19 in different countries by March 27th, 2020. (*Extracted from wall street journal, Global Health 50/50*)

III. DISCUSSION

Males and females respond differently to many RNA and DNA virus infections (Klein *et al.*, 2016). In general, males generate less robust immune responses and are more susceptible to a variety of infectious agents (Ouman *et al.*, 2015). In contrast, females mount stronger innate and adaptive immune responses and are relatively resistant to virus infections (Hannah *et al.*,2008).

Sex-specific disease outcomes following virus infections are attributed to sex-dependent production of steroid hormones, different copy numbers of immune response X-linked genes, and the presence of disease-susceptibility genes in males and females (Robinson *et al.*, 2011). Sex-specific steroids and activity of X-linked genes, both of which modulate the innate and adaptive immune response to virus infection, influence the immune response (Klein *et al.*, 2016). High copy numbers of TLR7 (located on the X-chromosome) and elevated IRF-7 expression in females induce increased IFN-b production by plasmacytoid dendritic cells and provides protection against SARS-CoV-2 infection (Meier *et al.*, 2009). In the current study using mice of different sexes, mRNA levels of IFN-b were equivalent during all time points examined. However ,although proinflammatory cytokine (IL-6) and chemokine (CCL2 and CXCL1) expression was similar in both sexes early (16, 24, and48 h.) after SARS-CoV challenge, the levels of these cytokines and chemokines remained elevated or even increased in the lungs of male mice compared with female mice at 72 h , suggesting a prolonged inflammatory response in male mice.

Although testosterone suppresses innate immune responses, hormones such as estrogens have disparate functions with an immune-suppressive effect at high concentrations and immunostimulatory activity at low concentrations (Malkin *et al.*, 2004). Estrogen signaling also promotes adaptive T cell responses in female by increasing neutrophil accumulation (Robinson *et al.*,2014). Estrogens are known to suppress monocyte–macrophage recruitment by downregulating CCL2 expression during inflammation and inhibiting TLR4-mediated NFkb activation in macrophages via suppression of micro-RNAs, such as let7a and miR-125b (Zhang *et al.*, 2001).Similarly, estrogen reduces the levels of TNF and CCL2 and, thus, protects females from SARS-CoV-2 virus infection (Robinson *et al.*, 2011).

Recently, (Li *et al.*, 2003) identified a metallopeptidase named angiotensin converting enzyme 2 (ACE2), isolated from SARS-CoV permissive Vero-E6 cells, that effectively binds to the S1 domain of the SARS-CoV protein. ACE2 transfected 293T cells formed multinucleated syncytia with cells expressing S proteins. The virus was shown to replicate effectively in ACE2-transfected, but not in mock-transfected 293T cells. ACE2 antibodies, but not ACE1 antibodies, blocked the viral replication on Vero E6 cells7. These data indicated convincingly that ACE2 is a functional receptor for SARS-CoV as well as COVID-19. (Yang *et al.*,2010) reported that high protein expression of ACE2 receptor in specific organs correlated with specific organ failures indicated by corresponding clinical parameters in SARS patients. Interestingly, the ACE2 gene is located on the X-chromosome and it has been shown that circulating ACE2 levels are higher in men than in women (Patel *et al.*, 2013).

It has been shown that ACE2 plays a protective role in chronic pathologies, like hypertension, cardiovascular diseases, and acute respiratory distress syndrome, that are the comorbidities representing the risk of worse prognosis in COVID-19. The protective role of ACE2 has been evidenced by studies in mice models, showing more severe lung failure upon ACE2 down-regulation (Kuba *et al.*, 2005).Estrogen hormone participate in the upregulation of ACE2 expression and activity levels (Silva *et al.*, 2017). This might explain the relative protection of female vs. male in COVID-19 infection. Taken together, this evidence seems to indicate that the putative sex predisposition to COVID-19, with men being more susceptible, might be reflective of a peculiar ACE plasma profile. Therefore, male patients may be more prone to be susceptible and die from SARS-CoV-2 because of the high expression of ACE2.

IV. CONCLUSION AND RECOMMENDATIONS.

Conclusion; Men are more susceptible to COVID-19 females. Holding exposure, smoking habits and social cultural habits constant, the susceptibility is attributed to immunological and hormonal differences with females. This study will greatly help in developing gender sensitive medications or vaccines for COVID 19 that will target ACE-2 receptors and fine-tune response policies based on gender.

Recommendations; Many countries do not report their COVID-19 cases and deaths disaggregated by sex (separately for women and men), and many more do not report data disaggregated by both sex and age. There is also limited data available on testing in men and women. The study recommends that countries report COVID-19 data with gender disparity.

The study also recommends further research on the ACE-2 receptors in target for COVID-19 vaccine and drug production.

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