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REVIEW ARTICLE

Why are Men more susceptible to COVID-19: A narrative review of current global knowledge

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Abstract: Since its inception on December 2019, COVID-19 epidemic now has been titled a global emergency. Rich literature on the global descriptive epidemiology of the cases has shown that the burden of COVID-19 epidemic in terms of both morbidity and mortality is more pronounced among men. Physiological and genetic traits along with numerous differences in social and cultural profile of men are attributed to this discrepancy. This review attempted to delineate various proposed explanations for the observed gender-differences in COVID-19 morbidity and mortality.

Keywords: COVID-19; survival; men; Iran

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1. Introduction

In early December 2019, an outbreak of a novel coronavirus disease (COVID-19) emerged in Wuhan city and rapidly spread throughout China and the world (1). The exponential and rapid growth of the epidemic has made the World Health Organization to announce COVID-19 outbreak as the sixth public health emergency of international concern on 30 January 2020, following H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019) (2). Epidemiologic evidence shows that the trend of the incidence of COVID-19 largely follows exponential growth, so that by 1st of April 2020, the number of confirmed cases worldwide has exceeded 823,626 confirmed and 40,598 deaths (3). Although the situation is evolving and further updated data are required to confirm, the calculations show that the mean basic reproduction number (R0) was estimated to range from 2.24 [95% confidence interval (CI) 1.96–2.55] to 3.58 (95% CI 2.89–4.39), associated with two- to eight-fold increases in the reporting rate (4, 5). The current estimate of the mean incubation period for COVID-19 is 6.4 days, ranging from 2.1 days to 11.1 days (2.5th to 97.5th percentile), with potential asymptomatic transmission (6). Iran identified the COVID-19 epidemic by two deaths on 20th February 2020 and currently it is ranked among the 15 first countries with the highest morbidity and mortality in the world. A glance on the descriptive epidemiology of the cases in Iran shows that the mean age of the cases was 52.7 years. Interestingly, compared to women, men can acquire CoV infection up to 13% higher and may die from the disease 29% more (Table 1) (7) . Meanwhile, identification of risk factors for morbidity and mortality from CoV is urgently warranted not only to define clinical and epidemiological characteristics more precisely, but also to facilitate control and containment measures to cease the epidemic (1). Despite this need, gender-dependence nature of the COVID-19 epidemic has been the focus of little literature. Therefore, this review is prepared to address the COVID-19 epidemic among men. To prepare this narrative review, the major international (including Medline, Scopus, and Clarivate Analytics) and national (Magiran, SID) electronic databases were searched to obtain published research with the keywords including COVID-19, CoV infection, Corona Virus, Respiratory virus, gender-difference, and male susceptibility. Studies with the aim to explain gender variations or male susceptibility to CoV infection were as priority. In addition to published literature, opinions of experts in the field of men's health and infectious diseases were collected and summarized.

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2. Male susceptibility to Corona Virus (CoV) infection

Epidemiological studies show sex-specific differences in the incidence and Case Fatality Rates (CFRs) in human hosts after CoV infection, with males experiencing higher CFRs compared with females (8, 9). Investigations from mainland China showed that men manifest more serious forms of the disease during COVID-19 epidemic compared to women. Although age was comparable between men and women in the deceased or the survived group, the proportion of male was higher in the deceased group than in the survived group (70.3 vs. 50.0) (10, 11). Male dominance in cases of COVID-19 has been reported by other countries as well (12-14). Published factsheets by the Iranian ministry of health & medical education show that throughout the COVID-19 pandemic, men acquire the CoV disease 13% more and die of the disease 29% more than women (7). The sex-dependent increase in disease severity after pathogenic CoV infection was more pronounced with advancing age (15). Results from Iranian patients have shown that compared to women, there was a male dominance in morbidity among age groups of 30-39 and 40-49 years old and in mortality among 50-59 and 60-69 years old. A report of one tertiary hospital in Tehran city (Shohadaye-Tajrish Referral Hospital) showed that during 41 days (until the date of the final drafting of this article), a total of 1100 cases of CoV have been admitted to the hospital with a male-to-female ratio of 1.7 (from official weekly reports of the corresponding hospital). The reasons behind gender discrepancy in morbidity and mortality from CoV infection are not fully explored. A few in vitro studies have attempted to find the answer while epidemiologic evidence is still hugely lacking. Therefore, the rest of this review addressed two broad categories of explanations based on genetic traits and social characteristics. Although, more basic and clinical research regarding the role of gender for individualized treatment and risk prediction is needed.

2.1. Genetic and physiologic explanation

Similar to SARS, CoV attacks cells via the same receptor, ACE2. It has previously reported that high protein expression of ACE2 receptor in specific organs correlated with specific organ failures indicated by corresponding clinical parameters in SARS patients (16, 17). 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 (18). Apart from ACE2 expression, expressions of pro-inflammatory cytokine (IL-6) and chemokine (CCL2 and CXCL1) are also presented as the possible mechanism for higher susceptibility to CoV infection among male. It is reported that following CoV challenge, the levels of these cytokines and chemokines remained elevated or even increased in lungs of male mice compared with females, suggesting a prolonged inflammatory response in male mice (19). Corona virus predominantly replicates in airways and alveolar epithelial cells (20) while estradiol concentrations are higher in female mice (21). Estrogen signaling in females may directly suppress SARS-CoV replication via effects on cellular metabolism. Moreover, high viral RNA levels in the lungs of male mice may stimulate TLR7 on IMMs, resulting in elevated pro-inflammatory cytokines and chemokines (22). Higher virus titers and increased IMM and neutrophil infiltration in the lungs suggest the contribution of multiple factors to the disease severity observed in male mice. Increased numbers of IMMs and neutrophils in SARS-CoV infected males correlated with elevated levels of pro-inflammatory cytokines and chemokines in the lungs of male mice are also reported from other studies. These cells also produced more of these inflammatory mediators in male mice compared with female mice. Further, increased numbers of IMMs in ovariectomized mice compared with intact female mice suggest that estrogen signaling in females suppressed the accumulation and function of IMMs in the lungs (23) . The higher expression of ACE2 in men can be regarded as an explanation to the higher mortality among them, though further research on the mechanism is needed. Another factor that could contribute to different outcomes of CoV disease between men and women is the direct cytopathic effect that is due to higher virus loads in males(24). Human studies are also conducted to find the link between male gender and susceptibility to CoV infection. Multiple factors have been identified that contribute to disparity in sex-specific disease outcomes following virus infections. Sex-specific steroids and activity of X-linked genes, both of which modulate the innate and adaptive immune response to virus infection, may influence the immune response (25, 26). Meanwhile, some studies used simulations of body response to other infectious pathogens to the problem in hand. Similar to HIV infection, it is shown that 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 provided protection against HIV infection in female patients (27). Additionally, 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. Similarly, it has been shown that treating with estrogen reduces the levels of TNF and CCL2 and, thus, protects against influenza virus infection(28, 29). In summary, results of genetic studies show that male gender is probably more susceptible to CoV infection compared with age-matched females. These results are in accordance with what is previously been observed in SARS and MERS studies in humans, showing

Table 1: Gender stratified distribution of morbidity and mortality of CoV infection in Iran by 31^{st} March 2020

	Men N(%)*	Women N(%)
CoV morbidity	23730 (53.2)	20876 (46.8)
CoV mortality	1637 (56.5)	1261 (43.5)

*based on the total number of cases reported from the Ministry of Health and Medical Education.

that there is a trend toward sex-specific disease outcomes in middle-aged individuals compared with younger individuals (8, 15, 30). Nonetheless, considering unique characteristics of infectious diseases, there are still many research opportunities on the role of genetic traits on pathogenesis of CoV infection in humans. So far, the role of ACE2, IMMs, cytokines and inflammatory biomarkers are partially explored while personalized medicine and prevention measures would require more insights into genome-wide association studies.

2.2. Epidemiologic explanation

To our surprise, sex-differences in the distribution of CoV infection in human population received little attention from epidemiologic perspective. Despite ample epidemiologic evidence on the description of COVID-19 cases and fatalities, proposed hypotheses on the observed differences are scarce. It is frequently reported that differences in morbidity and mortality from COVID-19 were less apparent in individuals aged over 75 years, possibly because of the enhanced mortality in elderlies, regardless of sex (13, 30). On the other hand, balanced sex distribution of cases in advanced ages might be due to the presence of other co-morbidities and underlying diseases, which affects the survival equally. For instance, unstratified on gender, cardiovascular disease and hypertension were the most common underlying diseases, followed by diabetes mellitus among Iranian adult patients (7) . Thus, it is likely that the effects of genetic traits (presumably ACE2) enhancing susceptibility in men are antagonized by the clinical profile of the patients, leading to sex-independent prognosis among elderlies. This explanation is in accordance with studies from China suggesting that COVID-19 is more likely to affect older cases with comorbidities, and can result in severe and even fatal respiratory diseases such as respiratory distress (10, 11, 18). Another plausible explanation is the relationship between CoV infection and tobacco smoking. Studies on the clinical management of the disease have demonstrated that smoking is related to higher expression of ACE2 (the receptor for severe acute respiratory syndrome coronavirus 2), so that might also be a reason for observed sex-differences in COVID-19 prevalence and severity (31). Consistent to the observation in China (31), the sex predisposition in the distribution of CoV infection might be associated with the much higher smoking rate in men. One study (preprint) found that despite similar expression of ACE2 between men and women, it was significantly higher in current smokers of Asian ethnicity than non-smokers (32). Other studies, mainly in China, have also shown a trend towards an association between smoking and severity of COVID-19 (33, 34); nevertheless, the current literature does not support smoking as a predisposing factor in men for infection with CoV. Additionally, reports on the distribution of COVID-19 cases with regard to smoking status are not prepared in Iran yet. To establish whether tobacco smoking contributes to susceptibility to COVID-19 among men, strong local evidence of an association between smoking and prevalence or severity of COVID-19 in Iranian men are highly warranted. On another perspective, higher incidence rate of CoV in men might be due to higher social interactions in work places. National office for statistics reported that men comprises of 81 percent of workforce in Iran during 2018-19; while more than 50 percent of them are employed in service occupations. Therefore, there is a higher likelihood for men to acquire CoV infection due to higher social interactions in work environments. Another common yet, forgotten aspect of the issue is the masculinity and social norms among men that hinder them from seeking medical help in times of need. It is well-known that due to social and physiologic characteristics, men tend to overlook their health and are incline to seek medical help. This picture adds up to the previous problem of higher social movements, which leads to more contact of healthy people with asymptomatic or mildly symptomatic patients in community(35). In summary, apart from genetic factors, there seems to be a constellation of demographic and social factors contributing to higher incidence and mortality rates among men. Taking into account the role of gender in the progression of COVID-19 epidemic may contribute greatly to the control and containment measures, which itself would help combating the pandemic.

3. Conclusion

Corona virus has a less fatality rate compared to other viruses in the family such as SARS or MERS; nevertheless, it shows unique propagation behaviours in human societies that make epidemic control measures difficult. Our review showed that current knowledge supports the premise of higher susceptibility of men to CoV infection, which is mainly attributed to genetic traits and social profile. Health policy makers and public health practitioners must take into ac-

count individual differences in the course of epidemic control.

4. Appendix

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4.2. Authors Contributions

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4.4. Conflict of Interest

The authors declare that there is no conflict of interest in the publication of this paper.

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