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Invited Editorial

COVID-19: Is there a weaker sex?

Int

Sex is one of the most relevant factors often associated with health, disease severity, mortality, and life expectancy [1]. From neonatal diseases to non-communicable disorders, men often have higher risks and poorer prognosis; however, the causes of these disparities are still subject to debate [2–7]. In this context, the new coronavirus disease of 2019 (COVID-19) has again called attention to these differences, mainly due to the observations of a higher level of complications and fatality rates among men [8]. According to data from the Global Health 50/50 initiative, which collects sex-disaggregated information from COVID-19 cases worldwide, from the 75 countries reporting case and death data by sex, 63 revealed a male:female ratio of mortality over 1, three countries having a value of 1 and only nine a ratio below this mark (Fig. 1). Furthermore, a recent study observed that although the male: female ratio of deaths per 100,000 individuals varied by age, the probability of death remained higher in males across all age categories [9]. In addition, a recently published study from India revealed that the magnitude of the differential risk by sex was higher as age increased, suggesting a role of age in this association [10]. Beyond these population observations, several studies have concluded that male sex is a risk factor for COVID-19 adverse outcomes, even in multivariate analyses after adjusting for potential confounders [11–14]. The association between male gender and adverse outcomes, such as mortality, seems consistent across all geographical areas, as revealed by several meta-analyses [15–18].

The reasons for this trend are likely to be multifactorial, including physiological factors, lifestyle, and socio-cultural behaviors [19] (Fig. 2). The physiological differences between the sexes may initially be directly involved in this differential risk of COVID-19 adverse outcomes [20]. For example, recent evidence has suggested that SARS-CoV-2 expression may induce angiotensin-converting enzyme-2 (ACE-2) downregulation due to the binding of the viral spike protein to its receptor, then promoting a decrease in the angiotensin- [1–7] production [21]. In this context, there is evidence suggesting an important role of sex hormones in the regulation of ACE-2 in a tissue-specific manner [20]. For example, female mice were observed to have a higher expression of ACE-2 in adipose tissue compared with male mice, leading to higher levels of Ang- [1–7], which in turn were associated with lower levels of hypertension, another risk factor for COVID-19 negative outcomes [22,23]. Similarly, higher testosterone levels in males may be related to a higher risk of coagulation disorders, resulting in complications such as venous thromboembolism and systemic embolisms, which are frequently observed in severe COVID-19 patients [24,25].

Furthermore, differences in the immune responses against SARS-CoV-2 between sexes may also play an important role. Takahashi et al. observed that men had higher plasma levels of IL-8 and IL-18, along with a more potent induction of non-classical monocytes among patients with moderate COVID-19 who had not received immunomodulatory medications [26]. On the other hand, women had a more robust CD8 T cell activation. In this study, poor T cell responses were associated with disease progression in males, while higher cytokine levels were predictors of worsening of clinical status in females [26]. In addition, females may produce larger amounts of neutralizing antibodies, as evidenced by the study of Zeng et al., in which the concentration of IgG antibodies against SARS-CoV-2 was higher in women, especially during the early phase of the disease [27]. Finally, several studies have supported the direct role of sex hormones in immune responses. For example, the phytoestrogen silibinin was shown to reduce the expression of the pro-inflammatory cytokines IL-17 and TNF-α, potentially reducing the risk of complications such as the cytokine storm observed in cases of severe SARS-CoV-2 infection [28].

On the other hand, lifestyle differences between the two sexes need consideration. Women tend to have a healthier lifestyle than men, with lower frequencies of smoking and heavy drinking [29]. This is reflected in a lower prevalence of classic cardiovascular (CV) risk factors, mostly before the menopausal transition [30]. Furthermore, adipose tissue distribution differences may also impact the outcome of COVID-19, as abdominal adiposity has been identified as an independent predictor of pulmonary function in several studies [31–33]. Nevertheless, recent studies have concluded that CV risk factors may have a stronger association with CV disease in women, highlighting the need for sex-specific analyses to clarify the reason for this trend [34,35].

Finally, socio-cultural variables are paramount to explain these differences. At first, the estimated global ratio of female to male labor force participation for 2020 was around 0.6, positioning work-related transmission as a relevant factor supporting male higher risk in several occupational groups [36]. Similarly, school closures have forced -more often- women to provide care for their children and immediate families, potentially inducing them to stay at home [37]. Furthermore, religious restrictions for women could play a role in the spread of the virus. For example, in certain cultures, facial covering is relatively common; therefore, women are likely to be less exposed to air-borne pathogen transmission, also being less prone to touching their faces [38]. In addition to this, men with voluminous facial hair might have limitations with mask fit, causing increased exposure to the virus and air leakage during non-invasive positive pressure ventilation [39].

From a behavioral perspective, men are usually more likely to engage in health-related risk activities, increasing their exposure to the virus [29]. On the other hand, women tend to be more cautious and tend to have better hygiene knowledge and practice [40]. In addition, women may have a lesser risk of contagion through distancing from

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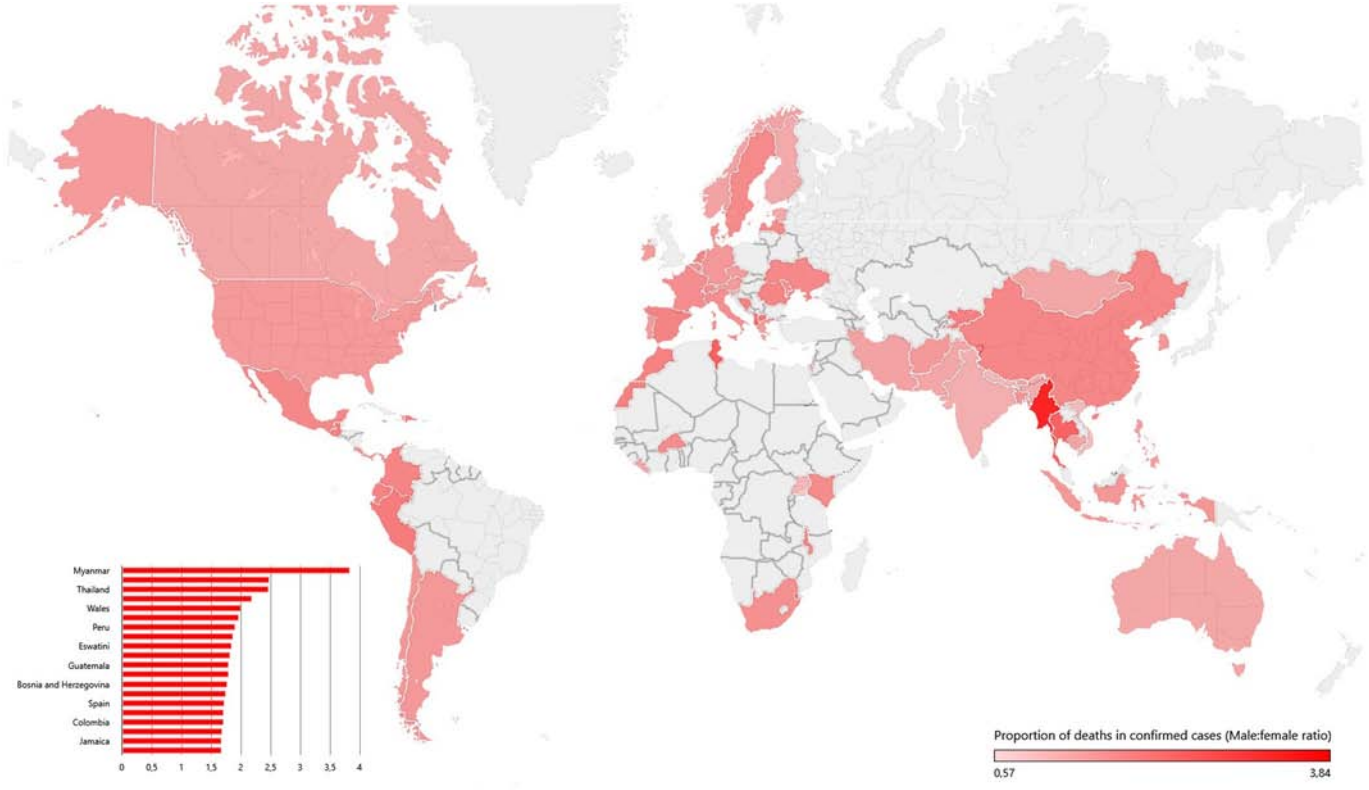

Fig. 1. Male to female ratio of deaths in COVID-19 confirmed cases. Source: [44].

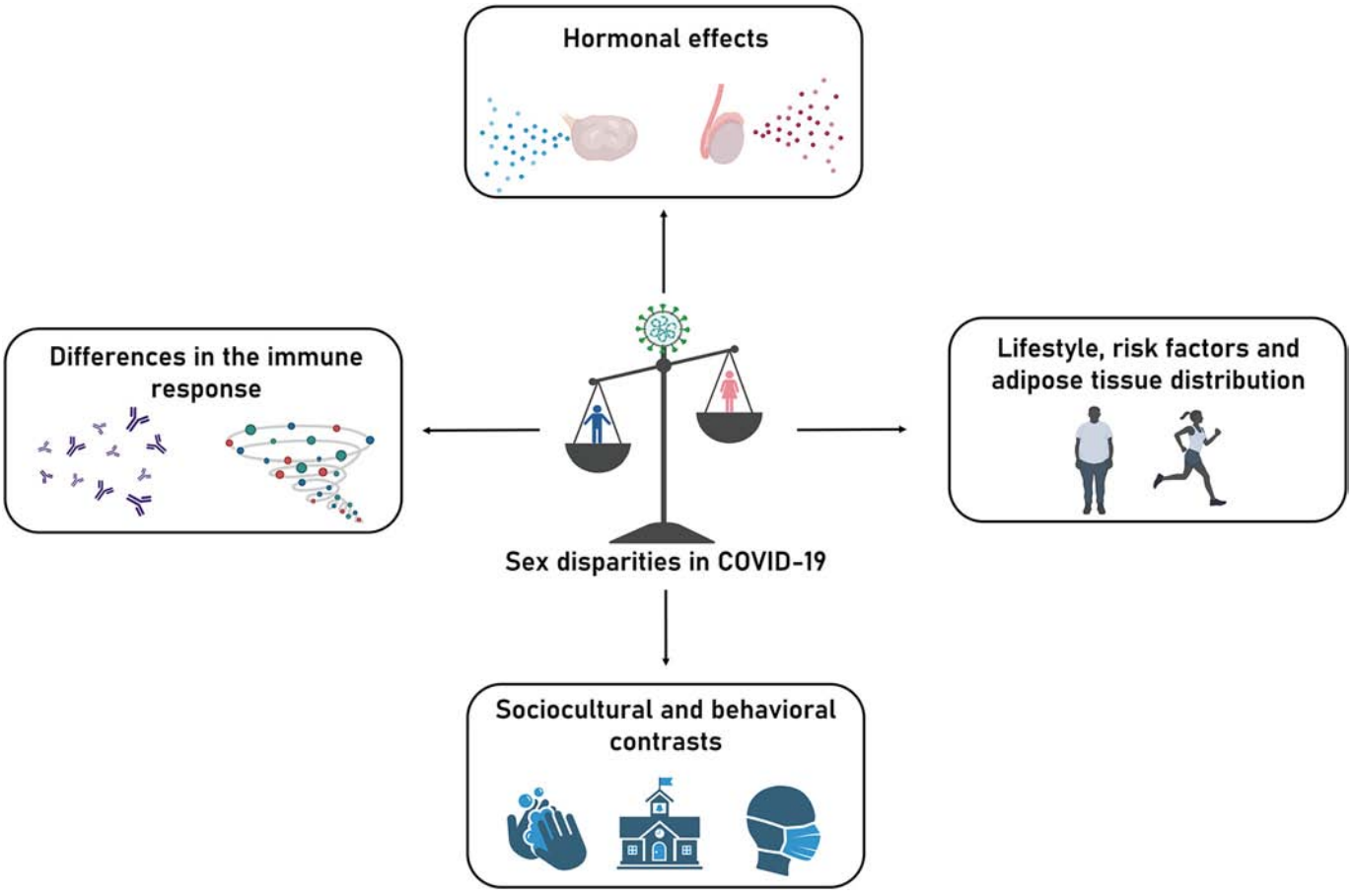

Fig. 2. Summary of the potential mechanisms and variables involved in the sex differential between men and women regarding COVID-19 adverse outcomes. Source: Authors. Created with BioRender.com

men or separation from the broader workforce and community in some cultures. Moreover, women are less inclined to seek medical attention in some settings, which may favor a potential underrepresentation in data collected regarding infection incidence in selected regions [41,42]. Finally, education has been identified as a factor influencing health outcomes in several clinical conditions; however, gender studies have revealed a larger effect on men's mortality than women' s [43]. Therefore, more research is needed to assess the role of education in COVID-19.

Considering all these differences, it is essential to take a sex- and gender-based approach to the identification, diagnosis, treatment, and overall management in the COVID-19 pandemic to elucidate further additional pathophysiological mechanisms and socio-cultural variables that may play a role in the differential expression of SARS-CoV-2 infection by sex, ultimately leading to an optimal prevention and care.

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