

Exploring the relationship between sex and long COVID

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Commentary

In December 2019, an outbreak of pneumonia, of unknown cause and often-fatal evolution, emerged among people linked to a seafood and live animal market in the city of Wuhan, China [1]. Days later, health authorities in that country reported that the epidemic outbreak in that location was caused by a coronavirus, later named SARS CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) [2]. On February 11, 2020, the World Health Organization (WHO) designated the new disease with the acronym COVID-19 (Coronavirus Disease of 2019) [3] and, just a month later, due to its widespread and rapid spread, it was considered a pandemic [4].

The extensive and intense transmission of SARS CoV-2 caused one of the most significant health crises of the present century. In five and a half years of the first outbreak, the high transmissibility of SARS CoV-2 and the emergence of new variants of the virus have facilitated its uninterrupted spread, resulting in the astonishing figure of 777 million confirmed cases and over 7 million reported deaths worldwide [5]. Immense efforts have been made to prevent the spread of COVID-19 and to control the disease in its acute phase, from the implementation of rigorous restriction measures to the introduction of novel vaccines [6,7]. These endeavors have largely succeeded. Today, the transmission of the disease is relatively controlled and the severity of its clinical expression, including its mortality, is lower than before.

Nevertheless, an observation from the beginning of the COVID-19 pandemic has been the occurrence of long-lasting clinical manifestations after the acute phase of the infection has passed. WHO proposes the term post-COVID-19 condition (PCC) to refer to symptoms usually developed 3 months after the onset of COVID-19, with a duration of at least 2 months, and that cannot be explained by an alternative diagnosis [8]. Numerous PCC symptoms, also known as Long COVID symptoms, affecting multiple tissues and organ systems (from respiratory, cardiovascular, neurological, and musculoskeletal symptoms, in both sexes, to perimenopausal and menopausal symptoms, in the case of women), have been described [9,10]. Several reviews have found that up to 50% of individuals who survived a SARS CoV-2 acute infection exhibit Long COVID symptoms from weeks up to one year after [11–13]. Interestingly, the historical data relating to SARS-CoV and Middle East respiratory syndrome-CoV epidemics, the other two major pandemics caused by coronavirus, reveal that these viruses also led to persistent symptoms in infected individuals [14]. Due to its consequences, mainly a notable reduction in the quality of life for the people who suffer from it and an important increase in the use of medical services, Long COVID is a growing health concern [15].

Some mechanisms, or combinations of them, have been mentioned to explain the pathophysiology of Long COVID: viral persistence, long-lasting inflammation, immunological disorders, autoimmunity, reactivation of latent infections, endothelial dysfunction, changes in gut microbiota, and psychological aspects related to the acute phase of COVID-19 [13]. This document later discusses the mechanisms most relevant to sex differences in Long COVID symptom frequency.

Numerous studies have been conducted to identify potential risk factors associated with the development of Long COVID. However, several methodological aspects, mainly differences in the designs of those studies, have led to some divergent and, at times, contradictory results. Despite this, some factors are the most frequently cited: female sex, older age, white ethnicity, previous comorbidities (including obesity and asthma), smoking, longer hospital stay during the acute phase, COVID-19 severity (including stay in intensive care units during the acute phase), higher viral load, and a greater number of onset symptoms during the acute phase [16,17]. Conversely, vaccination against SARS CoV-2 was found to decrease the risk of developing Long COVID symptoms [14].

Regardless of the differences in the results of some reports mentioned previously, female sex, mainly adult women under and near 50 years, is the factor most clearly associated with the development of Long COVID [10,13,14,18,19]. Significantly, two studies have been pivotal in this regard: a systematic review and meta-analysis by Maglietta and colleagues, which included 13,340 patients, and a large analysis and meta-regression by Wulf Hanson *et al.*, which involved more than 2 million patients [18,19]. Both revisions underlined that female sex was significantly associated with the occurrence of Long COVID symptoms. Undoubtedly, a gender factor must be taken into account when analyzing those statistics: compared to men, women are more likely to seek medical help when their health is threatened, which may have increased the Long COVID figures among them.

From a biological perspective, three interconnected groups of aspects have been alluded to explain the sex differences for developing Long COVID:

- A. *Differences in the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors.* These molecules, which are used by SARS CoV-2 to penetrate the cell in which it replicates, play a protective role in some chronic diseases, such as the comorbidities that affect the course of the acute phase of COVID-19. Those differences can explain the higher survival rate during the acute phase of COVID-19 and the higher prevalence of Long-COVID in female sex. Interestingly, high levels of ACE2 expression have been observed in ovarian tissue [20].
- B. *Differences in immune responses between women and men.* At least, three dissimilarities can be mentioned:
 - a. Women develop stronger innate and adaptive immune responses than men do. This fact typically results in both advantageous and disadvantageous consequences. On one hand, it makes females more resistant to infections and better responders to vaccines. On the other hand, it renders them more prone to suffering from clinical entities related to hypersensitivities, particularly autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, among others)

[21,22]. In the specific case of SARS CoV-2 infection, a stronger IgG antibody production in female individuals has been reported, and the evidence suggests that it could contribute to perpetuating disease manifestations or to the development of autoimmune diseases [23–26].

- b. The X chromosome contains the largest number of genes in the human genome related to the expression and control of immune responses [21,27]. Females have two X chromosomes, and although a portion of one of them is inactivated, a significant part of those genes can be expressed doubly, providing females with more robust immune responses [21,27]. The ACE2 gene is located on the X chromosome, a factor potentially contributing to its greater presence in females [28].
- c. Sex hormones also contribute to the differences in immune responses between women and men. Estrogen stimulated immune response, lead to a faster elimination of pathogens and greater efficacy of vaccines in females as mentioned previously [21,27]. Conversely, testosterone has a suppressive effect on immune functions, which explains the greater susceptibility to infections in men [21,27].
- C. *SARS CoV-2 induce sex hormone dysfunction.* Viral infections have the potential to disrupt sex hormone function. For instance, early menopause, menstrual abnormalities, and miscarriage have been reported as part of the evolution of HIV and hepatitis B and C infections [20]. In agreement with these observations, transient disorders in menstruation, along with changes in hormone concentrations, were reported in some patients during the acute phase of the COVID-19 [20]. This observation, which could be related to the presence of the ACE2 receptor in ovarian cells, suggested that a disruption in ovarian hormone production could lead to the development of perimenopausal and menopausal symptoms during the course of SARS CoV-2 infection [10].

Conclusions

For hundreds of years, medical practice has acknowledged age as a key factor influencing diseases progression. However, the understanding and acceptance of how sex and gender variables influence disease presentation, evolution, diagnosis, and treatment is a more recent development. From a global perspective, the COVID-19 pandemic has unequivocally shown the potential for effective medical practice that lies in an appropriate approach to age, sex, and gender. Preventing SARS-CoV-2 infection, and treating the acute and long-term consequences of COVID-19 when infection occurs, necessitates the accurate use of these variables.

Several studies, some mentioned previously, suggest that women have a higher risk of developing persistent symptoms following SARS-CoV-2 infection. From a social perspective, the association of Long COVID with female sex is a threat to the successful performance of female-dominated sectors, such as health and social care, which must be adequately attended by the corresponding authorities and academia. From a medical viewpoint, special attention should be paid to the variable sex for assuring an efficient clinical practice in a context of high Long COVID prevalence. Given the significant overlap between certain Long COVID and perimenopausal/menopausal symptoms (e.g., fatigue, muscle aches, palpitations), clinicians must develop robust expertise to accurately diagnose and manage each condition.

Conflicts of Interest

The author declares no conflict of interest.

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