LETTER TO THE EDITOR

Sex and gender differences in the outcome of patients with COVID-19

To the Editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is a new wave of emerging infections that the world is struggling with. There are many unanswered questions in this regard, including sex-specific outcome in coronavirus disease 2019 (COVID-19).

The clinical consequences of SARS-CoV-2 infection vary from asymptomatic to severe or critical. Nearly 80% of cases are asymptomatic or with mild symptoms, 15% have severe disease and 5% become critical. Gender and age are major risk factors for SARS-CoV-2 infection. In addition to the effect of these factors on the prevalence of SARS-CoV-2, the clinical outcome varies according to both sex and age. One study found that in similar age groups, outcomes of COVID-19 were more severe in men compared to women, as observed in SARS and Middle East respiratory syndrome infections. Other investigators reported that the highest mortality rate was found in older men with underlying diseases. Another study also reported that men with COVID-19 had worse outcomes. In several countries, outcomes of COVID-19 were more severe in men compared to women, as observed in SARS and Middle East respiratory syndrome infections. These studies suggest that men are more susceptible to SARS-CoV-2 infection and its clinical outcomes are more severe in men than in women. The potential factors influencing these gender-dependent differences, should be clarified. Numerous factors, such as the immune system, sex hormones, physiological factors, lifestyle, and sociocultural behaviors are likely to be responsible for these differences. Here we refer to some influential factors:

One of the possible factors causing different outcome of patients with COVID-19 between two sexes is the immune system. In dealing with viral infections, women’s immune systems act differently from men, which create a stronger immune response leading to viral clearance. In general, antibody production level is higher in women compare with men and last longer.

Differences in women’s immune responses can be related to sex hormones and factors related to chromosome X. Estrogen modulates pro-inflammatory responses as well as immune regulatory genes are located on chromosome X so it can be assumed that, the cytokine storm linked to immune dysregulation, occurs less in women compared with men.

So far, researchers believe that the cytokine storm is responsible for lung tissue damage and immunopathogenesis of COVID-19 infection. Interleukin-6 is an important component of the cytokine storm and the driving force of the storm, as its level in men is higher than in women. High levels of interleukin 6 in men may be related to worse outcomes against women, can indicate a higher risk of cytokine storm formation in male patients.

One study showed that levels of neutralizing antibodies are higher in women with severe COVID-19 than its level in men. Also, immunoglobulin G (IgG) antibody has been identified more frequently in the early stages of COVID-19 infection in women, indicating that production of antibodies, specially IgG, in the early days of infection may prevent the disease from progressing and getting worse.

In short, more antibody production and a lower chance of immune dysregulation in women, may explain the gender differences of outcome during COVID-19 infection according to the immune system.

The second factor related to outcome, is the gender-specific difference in the respiratory tract properties. It may be worth noting that men’s lungs are larger than women’s and is a larger fertile ground to support more SARS-COV-2 replication in men. Elevated virus replication leads to higher viral load and exacerbation of the COVID-19 disease.

Another factor is angiotensin-converting enzyme 2 (ACE2) as a viral receptor. There is conflict in evidence about ACE2 expression levels and its exact role (protective or not) in COVID-19 infection. ACE2, on the one hand, is a receptor for virus entry to cells, and its higher expression as a viral receptor should exacerbate the infection. On the other hand, it is a key enzyme that prevents lung damage. ACE2 role in the pathogenesis of SARS-COV-2 remains a mystery. One study indicates men have more ACE2 on the endothelium of the pulmonary vessels than women, and has a widespread distribution in men's lungs that at least five different cell type express this receptor, while fewer types of cells in women’s lungs expose ACE2. Since the lung is the main tissue involved in the COVID-19 pathogenesis, a further expression of the ACE2 in this site can lead to an increase in the disease severity.

A recent study reported that ACE2 had a higher expression in different tissues of women, and also believe that high levels of ACE2 in women play a protective role against the COVID-19 infection.

ACE2 has two biological forms, membrane-bound and a soluble form. The membrane-bound form acts as a virus receptor, and its presence exacerbates infection outcome, while its soluble form prevents the virus from attaching to cells and plays a protective role, like neutralizing antibodies. Circulating ACE2 level (soluble form) appears to be higher in women and children than in men, so may play a
protective role in these subjects by Competitive inhibition of virus attachment and entry to the target cells. Circulating ACE2 level can act as a contributing factor in determining the disease severity.

It is recommended that more studies should be designed and implemented in the area of ACE2 role, protective or damaging, in pathogenesis and outcome of COVID-19 infection.

Among other factors that cause sex differences in the outcome of COVID-19, sex hormones should not be overlooked. As mentioned previously, sex hormones affect immune responses. Some studies suggested, estrogen therapy has remarkable role in developing a protective immune responses against COVID-19. 

Due to the age-dependent decrease of sex hormones in older people, these hormones can be suggested as therapeutic options, and may help to reduce inflammation in elderly patients with COVID-19.

The higher mortality rate in men seems to be partly related to the frequency of underlying diseases. One of the most common co-morbidities in the development of severe COVID-19 is cardiovascular disease and also testosterone activates the main pathway of myocardial inflammation while estrogen has a protective effect on cardiovascular disease.

Another cause of gender-based disparities is lifestyle, such as smoking. According to one study, COVID-19 was more severe in smokers than in non-smokers, since men are more likely to smoke than women, smoking can be a potential factor in this disparity.

Although we pointed out some possible factors contributing to sex and gender-based discrepancy, but since age is also a risk factor for COVID-19 severity and mortality, comparison of the COVID-19 outcome in both sexes should be performed after age matching.

Shahab Falahi1
Azra Kenarkoohi2

1Zoonotic Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran
2Department of Microbiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran

Correspondence
Azra Kenarkoohi, Department of Microbiology, Faculty of Medicine, Ilam University of Medical Sciences, 6939177143 Ilam, Iran.
Email: a.kenarkoohi@gmail.com

REFERENCES
1. Rokni M, Ghasemi V, Tavakoli Z. Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: comparison with SARS and MERS. Rev Med Virol. 2020;30(3):e2107.
2. Liu R, Han H, Liu F, et al. Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clin Chim Acta. 2020;505:172-175.
3. Singh S, Chowdhry M, Chatterjee A, et al. Gender-based disparities in COVID-19 patient outcomes: a propensity-matched Analysis.
4. Nikpouraghdam M, Farahani AJ, Alishiri G, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: a single center study. J Clin Virol. 2020.
5. Wenham C, Smith J, Morgan R. COVID-19: the gendered impacts of the outbreak. Lancet. 2020;395(10227):846-848.
6. GlobalHealth5050. COVID-19 sex-disaggregated data tracker. Sex, gender, and COVID-19. 2020. http://globalhealth5050.org/covid19
7. Jin J-M, Bai P, He W, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health. 2020; 8:152.
8. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents. 2020;34:2.
9. Zeng F, Dai C, Bai P, et al. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between sex. J Med Virol. 2020.
10. LoMauro A, Aliverti A. Sex differences in respiratory function. Breathe. 2018;14(2):131-140.
11. Zhao Y, Zhao Z, Wang Y, et al. expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. BioRxiv. 2020.
12. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-422.
13. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med. 2020;35:1-5.
14. Chen J, Jiang Q, Xia X, et al. Individual variation of the SARS-CoV2 receptor ACE2 gene expression and regulation. Preprints. 2020.
15. Ciglia E, Vecchione C, Puca AA. COVID-19 infection and circulating ACE2 levels: protective role in women and children. Front Pediatr. 2020;8:206.
16. Suba Z. Prevention and therapy of COVID-19 via exogenous estrogen treatment for both male and female patients. J Pharm Pharm Sci. 2020; 23:75-85.
17. Di Florio DN, Sin J, Coronado MJ, Atwal PS, Fairweather D. Sex differences in inflammation, redox biology, mitochondria, and autoimmunity. Redox Biol. 2020;31:101482.
18. Brown LM, Gent L, Davis K, Clegg DJ. Metabolic impact of sex hormones on obesity. Brain Res. 2010;1350:77-85.
19. Al-Lami RA, Urban RJ, Volpi E, Albargi AM, Bailleulonge J, eds. Sex hormones and novel corona virus infectious disease (COVID-19). Mayo Clinic Proceedings. Elsevier; 2020.
20. Ruggieri A, Gagliardi MC. Gender differences in COVID-19: some open questions. Italian. J Gender-Specific Med. 2020;6(2):49-50.