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Methodological Considerations for Design of Studies Investigating Gender Differences in COVID-19 Mortality

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Commentary
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Commentary

Clinical [1], genetic [2] and epidemiologic [3] literature is increasing exponentially with papers on possible association between sex-related differences in ACE2 activity and higher mortality in men versus women with COVID-19. Surprisingly, a balanced holistic approach is lacking in published reports, contemporary clinical trials, registered clinical trials, meta-analyses and review papers.

In this short methodological commentary, I would like to suggest some factors to consider in the design of clinical and epidemiological studies that might help to differentiate physiological sex-mediated mortality rate differences between men and women from those that might be due to behavioral and life-style-mediated issues and those that might be due to the genuine individual genetic susceptibility/receptivity. Also, I suggest some brief statistical strategies that can improve future study designs.

Just very recently, Gemmati, et al. [4] discussed COVID-19 and individual genetic susceptibility/receptivity. They hypothesized that the double X-chromosome in women might be protective against SARS-CoV-2 compared to the single X-chromosome in men. While their hypothesis may be correct, there may be other critical modifying factors that might help to explain the COVID-19 mortality rate differences between men and women. Gemmati, et al. [4] have suggested that their hypothesis should be demonstrated by dedicated clinical epidemiological studies in genetically selected patients, however, they have not considered the possibility that genuine/functional interaction or modification effect between individual genetic susceptibility/receptivity and individual confounding factors such as different adherence to COVID-19 protocols with regards to risk perception associated with COVID-19 variants may exist which may obscure and counterbalance any conclusion. This is especially relevant if we are considering translating hypothetic molecular mechanisms to clinical epidemiological studies and eventually those in a clinical setting.

Furthermore, throughout the literature it has been vaguely proposed that sex-related differences in ACE2 activity may contribute to higher mortality in men versus women with COVID-19 [1]. I would like to clarify some of their significant conclusions and suggest future studies and clinical trials to consider/differentiate between physiological gender-mediated mortality rate differences between men and women with that of behavioral and life-style-mediated ones.

For instance, some authors Salah and Mehta [1] have hypothesized that possibly the worse outcomes in men with COVID-19 compared to women is due to higher prevalence of hypertension and heart failure among men compared to women. While their hypothesis can be partly true, it may not explain and account for the whole COVID-19 mortality rate differences between men and women. Indeed, ignoring recently known reasons may contribute to weak study designs, improper data interpretations and strategies to target COVID19.

Most recent cohort [5] and emergency room [6] studies have failed to show a statistically significant predictive

value for "viral load" that predicts COVID-19 severity and mortality. This may change, as the effect of the higher viral load associated with the Delta variant is assessed in the future. Whether or not individuals take steps to reduce their exposure to this more transmissible variant may impact their outcome, should they become infected.

With the emerging Delta variant, individuals' personal network characteristics and patterns of COVID-19 protocol compliance is rapidly changing, mainly because of improvement in knowledge, attitude, and practice (KAP) and higher risk perception, particularly males, towards COVID-19.

Secondly, Salah and Mehta [1] paper has not considered genuine immunological and hormonal gender differences at all. Sex-based immunological differences have been suggested to contribute to variations in the susceptibility to infectious diseases and responses to vaccines in males and females [7]. Estrogen, as the sex hormone, interacts with the renin-angiotensin-aldosterone system, which is considered as one of the most important pathways in COVID-19 infectivity, and thus modulates the vasomotor homeostasis. Conversely, testosterone enhances the concentrations of the two most critical molecules, i.e., angiotensin-converting enzyme 2 and the transmembrane protease serine-type 2, and thereby increasing viral load and delaying viral clearance in men as compared with women [8].

On the other hand, major differences exist between men and women in terms of life style and social behavior. For example, higher levels of both active and passive smoking [9-11] and drinking [12,13] among men compared to women. Also, there are recent studies [14,15] reporting that women have more responsible attitude toward the COVID-19 than men. Collectively, a cavalier attitude among men regarding mask wearing, hand washing, social distancing and a willingness to observe home quarantine protocols may negatively affect their COVID-19 risk profile [16]. This however is beginning to change too. As the new papers show, a different trend is emerging: the population KAP towards COVID-19 is rapidly changing in gender [17,18] and age [19,20] groups.

Recent studies investigating knowledge, attitude, precautionary practices and degree of fear related to COVID-19 demonstrate that with increasing risk perception, adherence to prevention and control measures of COVID-19 in Iranian men is significantly improved compared to the past [17]. Surprisingly, opposite results are reported from other countries such as Cameroon [18]. In the USA, during the early phase of the COVID-19 outbreak, older adults perceived the risks of COVID-19 to be higher than did younger adults. Contrary to this, older males were comparatively less worried about COVID-19 than their younger counterparts. In comparison to the other participants, older males had also implemented the fewest behavior changes [19]. In other words, individual protective measures can further complicate the previously established genetic susceptibility or environmental influences on virus infection and/or SARS progression, thus as the authors [4] state, a wide and heterogeneous epidemiological and geographical distribution of absolute numbers and percentages of infected cases is now emerging.

In order to come to a better understanding of how different patterns of compliance with COVID-19 preventive and control measures affect genetic, clinical and epidemiological studies, the possible interaction or modification effect between extensive list of confounding variables as well as other factors such as the role of ACE1/ACE2 genes, immunity, inflammation and coagulation should be concomitantly considered in future studies. In other words, it is very important that future studies include all important variables and control for all confounding factors and perform a causal mediation analysis in order to get a big picture to control/treat/prevent COVID-19 both at individual and pandemic levels.

Therefore, in order to avoid artifactual results and to eliminate possible confounders, I suggest future studies perform critically important yet sadly less used analyses such as mediation analysis, casual mediation analysis, counterfactual mediation analysis and counterfactual causal mediation analysis. Meanwhile, retrospective data or clinical/epidemiologic studies can provide preliminary insights for further future mediation analyses into how levels of behavioral variability interact with individual genetic susceptibility/receptivity.

Such data collection strategy is cost-effective, quick and easy to perform, and more patients can be recruited [21]. A correct risk attribution is essential to tailor the best treatment for each patient. This will also help to remove barriers and facilitators to populational adherence to prevention and control measures of COVID-19 and possibly other respiratory infectious diseases that may occur in the future.

In conclusion, it is important that future studies consider both genetic and physiologic variables as well as confounding behavioral factors that might impact our understanding of COVID-19, which in turn may facilitate the discovery of better preventive measures and therapeutic agents for the management of this terrible pandemic.

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Letter refers to published article without new subjects.

Disclosure Statement

I declare that I have no competing interests.

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