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Gender Susceptibility to COVID-19 Mortality: Androgens as the Usual Suspects?

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Abstract

Identification of the causal risk factors of COVID-19 would allow better risk stratification and designing effective therapies. Epidemiological data have shown a higher incidence and mortality of COVID-19 in males compared to females. Here, we have used logistic regression analysis modeling to determine the association between gender and COVID-19 mortality in the Iranian population. The records of 2293 patients with COVID-19 infection were analyzed. The odds of death due to COVID-19 were 1.7 times higher in males compared to females after adjustment for age and background diseases. The gender difference was mainly observed at higher ages, suggesting an adjusted 2.32-fold higher risk of mortality in males aged >59.5 years old compared to females within the same age group. This finding suggests the male gender is a potential predisposing factor for mortality due to COVID-19 infection. The potential role of male hormones, particularly testosterone, as therapeutic targets deserves further investigation.

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Keywords

Coronavirus · COVID-19 · Sex · Mortality · Testosterone · Estrogen · Iran

23.1 Introduction

The rapidly progressing outbreak of coronavirus 2019 (COVID-19) disease has called for attempts to better identify and control the causal risk factors. Consistent with the previous coronavirus outbreaks, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [1, 2], there is a male preponderance in COVID-19 cases. In addition, the case fatality rate (CFR) is significantly higher in males compared to females, according to reports from China [3] and unpublished reports from Italy and the USA. This suggests that males may contract a more severe form of the disease. Iran is also among the countries facing a high disease burden with COVID-19 cases, yet information on the gender difference in mortality rates has not been reported there. Here, we used logistic regression analysis modeling to estimate the crude and adjusted association between gender and mortality in the Iranian population.

23.2 Methods

The records of 2293 patients (mean age 53.7 ± 14.6 years), who were hospitalized in the Baqiyatallah University of Medical Sciences (Tehran, Iran) from February 17 to March 30, 2020, were entered in this analysis. All patients had a diagnosis based by polymerase chain reaction (PCR) or computerized tomography (CT) findings, and men constituted 71.1% of the population group. Out of the 2293 patients, 97 (4.2%) died and the rest of recovered or partially recovered up to March 30, 2020. The most frequent comorbid diseases were chronic heart disease (7.9%) followed by hypertension (6.9%), diabetes (6.4%), cancer (6.3%), chronic lung disease (5.5%), and other chronic diseases (3.1%). Out of the total patient group, 1463 (63.8%) reported no background diseases.

23.3 Results

The results of logistic regression analysis indicated that the odds of death due to COVID-19 infection was 1.7 times higher in males compared to females after adjustment for age and background diseases (Table 23.1). At a defined cutoff of 59.5 years old (selected from a AUC-ROC analysis to predict mortality by age with a sensitivity of 65% and specificity of 68% in the total population), the risk of death for males was 2.32 times higher than that of females at age >59.5 years old, while the between-gender difference was not significant at <59.5 years old. Selecting a cutoff value of 48.6 years old as the average menopause age in the Iranian women, postmenopausal women were found to have significantly higher odds of death compared with premenopausal women. However, applying the same age cutoff for men showed an even greater mortality rate (Table 23.1).

Table 23.1 Association between gender and mortality due to COVID-19 (male vs. female as the reference group)

	Crude model		Adjusted model[a]	
Male vs. female	OR (95% CI)	P-value	OR (95% CI)	P-value
All age groups	1.25 (0.78–1.99)	0.35	1.71 (1.04–2.81)	0.036[a]
Age <59.5 years	0.86 (0.41–1.82)	0.69	1.02 (0.46–2.26)	0.95[a]
Age >59.5 years	1.88 (1.02–3.47)	0.044	2.32 (1.22–4.40)	0.01[a]
All men vs. women <48.6 years	4.12 (1.01–16.95)	0.049	1.39 (0.31–6.12)	0.66[a]
All men vs. women >48.6 years	0.98 (0.61–1.61)	0.95	1.73 (1.03–2.91)	0.039[a]
Age >48.6 vs. <48 years (for women)	4.18 (0.97–17.96)	0.045	4.65 (1.01–21.44)	0.048[b]
Age >48.6 vs. <48 years (for men)	8.43 (3.38–21.03)	<0.001	8.47 (3.39–21.16)	<0.001[b]

[a]Adjusted for age and background diseases
[b]Adjusted for background diseases

23.4 Discussion

The reason behind the observed gender difference is yet to be discovered. However, we elaborate on some lines of evidence which are suggestive of a potential role for sex hormones. The angiotensin-converting enzyme 2 (ACE2) has a key role in the entry of coronavirus particles into the cells and thus in the pathogenesis of the disease. On the other hand, ACE2 reduces angiotensin 2 levels and has a protective effect on the cardiopulmonary system [4]. Therefore, careful evaluation of this double-edged sword among the sexes and age groups can be helpful. There is evidence indicating a higher rate of ACE2 expression in males [5], which can serve as a susceptibility factor for the viral infection. However, the sex-based pattern for ACE2 is still controversial. A recent study using single-cell RNA expression profiling showed that ACE2 is expressed in higher rates in Asian male populations [5]. On the other hand, another recent report (pre-print) showed no effect of gender or age on the ACE2 expression levels in the lung. Surprisingly, another other factor, cigarette smoking, might be more important as it can significantly increase the expression of ACE2 in the lungs [6]. The data for cigarette smoking was not available for our report, although a previous meta-analysis showed a six times higher rate of smoking among Iranian men compared with women [7].

A plausible explanation for the higher rate of ACE2 expression in males could be the action of testosterone [5]. Testosterone can also reduce the immune system responses, while estrogens exert enhancing actions [6, 7]. Estrogens have also been shown to protect against adverse outcomes in SARS [8]. This is consistent with the reports suggesting that the immune response to microbial and viral infections is more efficient in females. Moreover, women elicit a more efficient immune response to influenza vaccination compared with men. The higher testosterone levels in males are predictive of a lower response to vaccination [9]. The male hormone-based pattern of COVID-19 mortality can also explain the extremely lower death rate in children and adolescent groups [10, 11], who have naturally lower levels of testosterone. While epidemiological findings on the gender susceptibility of COVID-19 mortality still need to evolve, early findings might point to a plausible role for sex hormones, particularly testosterone, as a predisposing factor for adverse outcomes. Further investigations on the possible therapeutic impact of intervening androgen and androgen receptor pathways are encouraged (Fig. 23.1).

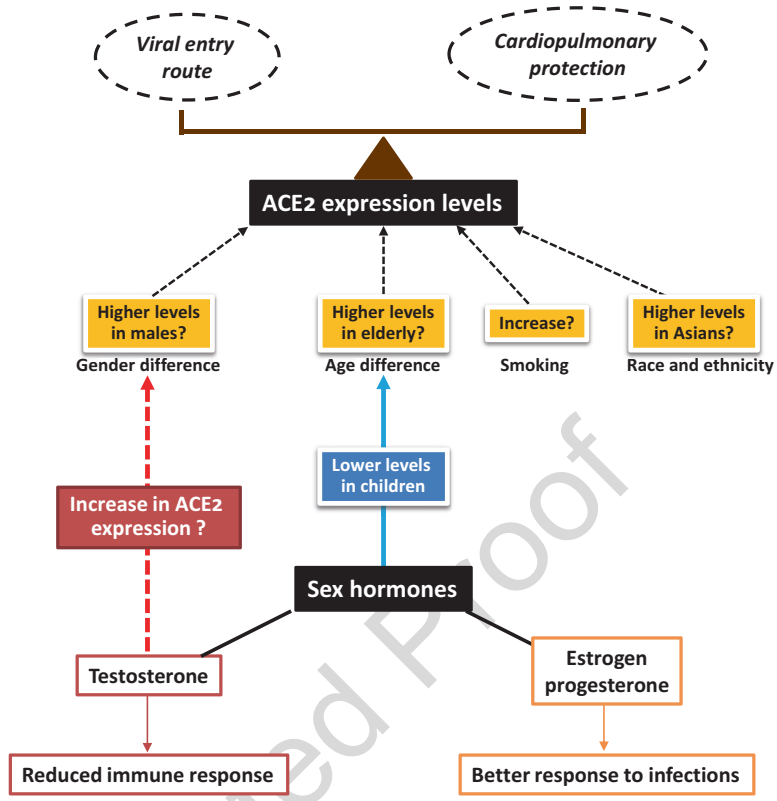

Fig. 23.1 Possible role of sex hormones in COVID-19 infection and several unanswered questions

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