

## Gender differences in COVID-19: some open questions

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Coronavirus disease (COVID-19) is the pandemic syndrome associated to the human infection with SARS-CoV-2. This virus belongs to a large and complex family of animal and human viruses, usually responsible for respiratory conditions in humans and gastroenteritis in animals (alfa- and beta-coronavirus). All human coronaviruses are zoonotic, since they originated from animal reservoirs, such as bats or rodents. Crossing the species barriers, the coronaviruses acquire a pathogenic potential in humans, as in the cases of SARS-CoV, that caused an epidemic in 2003, and MERS-CoV, responsible of the human outbreak in 2010. Epidemiological data from those coronavirus epidemics showed that males are significantly more affected than females in the most affected age group (60 and above), and that male patients presented higher fatality rate than female ones.<sup>1,2</sup>

In the ongoing COVID-19 pandemic, caused by SARS-CoV-2, which is closely related to SARS-CoV, with which it shares an 89.10% nucleotide similarity,<sup>3</sup> a gender disparity in severe cases and in case fatality rate has been reported in China, where the infection rate among males and females was similar, but the death rate among males was 4.7% compared with 2.8% for females.<sup>4</sup>

Likewise, in Italy a higher death rate in male patients (14.8%) than in female patients (8.2%) is being reported by the Italian National Institute of Health.<sup>5</sup>

The higher vulnerability to coronaviruses of male patients may be easily explained by a well-known gender disparity in life style, mainly the smoking addiction that, beyond the use of the hands to inhale the smoke, has been suggested to predispose the lungs to inflammation<sup>6</sup> and to contribute to the worse outcome of the SARS-CoV-2 infection in male patients. This is consistent with the higher percentage of male smokers in China (54%) and in Italy (28% of adult males vs 20% of adult females).

But this is not the sole explanation. Several factors can contribute to the observed gender disparity, although experimental data are lacking so far. It is well-known that male and female subjects respond differently to many virus infections, or to pathogens in general. In several species along the evolutionary scale, from fruitflies through birds, reptiles and mammals, up to

human beings, females mount more intense and stronger immune responses, either innate and adaptive, to viral infection, that favors viral clearance.<sup>7</sup> This could also be the case in COVID-19.

In addition, sex hormones have shown to influence sex-specific response to viral infection by directly modulating immune responses. The female estrogen can have pro- or anti-inflammatory activity, depending on the lower or higher physiological levels, respectively, whereas testosterone has anti-inflammatory effects.<sup>7</sup>

Experimental studies in male and female mice<sup>8</sup> infected with SARS-CoV, have shown that male mice have a higher susceptibility to SARS-CoV infection and a higher mortality, compared to females, consistently with the human disease. However, ovariectomy in female mice or treatment with estrogen antagonists increased the death rate of females, which could be rescued by tamoxifen treatment. Those experiments in animal models emphasized an evident protective role of estrogens in coronavirus infection.<sup>8</sup>

Furthermore, a virus targeted mechanism can also be hypothesized. The human angiotensin-converting enzyme 2 (ACE2) is the functional receptor for the severe acute respiratory syndrome coronavirus (SARS-CoV), as well as for the recently identified SARS-CoV-2, and it is an essential enzyme of the renin-angiotensin system (RAS). ACE2 plays a protective role in chronic conditions, like hypertension, cardiovascular diseases and acute respiratory distress syndrome, that are the comorbidities representing the risk of a worse prognosis in COVID-19. The protective role of ACE2 has been evidenced by studies in mice models, showing more severe lung failure upon ACE2 down-regulation.<sup>9</sup> In other respiratory virus infections, such as influenza and respiratory syncytial virus, the administration of recombinant ACE2 appeared to reverse extensive lung damage.<sup>10</sup> SARS-CoV-2 not only binds ACE2 receptor to gain entry into the host cells, but also decreases the level of ACE2,<sup>11</sup> making it unavailable for the lung protective role, and accounting for the severe lung failure observed in some patients. Interestingly, ACE2 is encoded on the X chromosome, in regions usually escaping inactivation of one X chromosome in mammalian XX cells (XCI), a mechanism to maintain gene expression homeostasis, and it

is therefore conceivable that ACE2 is overexpressed in XX cells of female patients, which may thus be protected from the severe outcome and death associated with COVID-19.

It is to be noted that estrogens inhibit the activity or expression of different components of the renin-angiotensin system. In particular, estrogen is able to upregulate the expression of ACE2.<sup>12</sup>

Consequently, hormonal and genetic factors contribute to ACE2 over-expression in female sex. These insights could account, at least partially, for the better outcome and the lower death rate in female COVID-19 patients vs males.

Finally, further studies need to be conducted to evaluate: i) the role of hormone replacement therapy in the protection from respiratory failure in females; ii) the effect of estrogenic agonists that, by increasing the ACE2 expression levels, could be promising in counteracting a worse prognosis in COVID-19; iii) the role of androgen hormones in favoring massive virus spread in the lungs. This notwithstanding, the study of the role of XCI escaping genes, and of their regulators, such as specific X-linked microRNAs, could be a major challenge to understand the sex-specific pathogenic determinants of the COVID-19 disease progression.

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