

COVID-19: Gender and Outcomes

Subjects: [Infectious Diseases](#)

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The existence of differences in susceptibility to SARS-CoV-2 infection between males and females in both incidence and outcomes is well documented in the scientific literature. These differences, which are still underestimated, may have important implications in terms of prevention, diagnosis, and treatment of COVID-19, with significant prognostic consequences. The greater severity of the infection observed in males, even more so if they are elderly, would seem, according to current knowledge, to be due to multiple influences: immunological and endocrinological, but also genetic and behavioral.

immunosenescence

coronavirus

Angiotensin Converting Enzyme 2 (ACE2)

dendritic cells

estradiol

Since the outbreak of the current pandemic, it has been clear that the severity of infection was greater in older people, depending on the burden of comorbidities ^[1], and most likely related to the decay of immune functions, referred to as immunosenescence, which occurs as the physiological aging process advances. The latter is characterized by a progressive failure of innate and especially acquired immunity, secondary to the decreased availability of naïve peripheral T and B cells, which tend to be gradually depleted by repeated microbiological exposure throughout life ^[2]. This depletion is accompanied by the expansion of some memory cell subsets, which leads to a significant imbalance in the relationship with naïve cells. The result is a reduced availability of cells oriented towards immune responses to new pathogens and an increased susceptibility to infection ^{[3][4]}.

Another widely recognized aspect of the aging process is the profound structural changes that occur to the rib cage (stiffening from calcification and kyphosis from osteoporosis), reducing its compliance and impairing the complete emptying of the lungs at expiration with an increase in residual volume. There is also an increase in the size of the distal airspaces due to the loss of supporting tissue and a progressive reduction in the strength of the respiratory muscles. These effects reduce the reserve capacity of the whole system, increasing the vulnerability to functional failure in situations of increased ventilatory demand ^[5].

The aforementioned issues do not discount the weight of comorbidities on the severity of the infection. In the cohort of patients evaluated by Grasselli and co-workers, about 1550 subjects were admitted to the Intensive Care Unit (ICU), and at least one comorbidity was recorded in 68% of cases ^[6].

A lower percentage (23.7%) was reported in Guan's study of 1099 patients. However, in this cohort, the infection was classified as severe in only 173 patients ^[7].

The data on the type of preexisting disorder is also of significance. Case fatality is highest in patients with defined comorbidities, such as cardiovascular disease, diabetes mellitus, hypertension, chronic respiratory disease, and cancer ^[8]. Of these, hypertension is the most common in patients with COVID-19 and hypertensive patients have a higher disease severity and admission rate to the ICU than those with normal blood pressure ^{[6][9]}.

Therefore, since hypertension has a higher prevalence in males than in females, at least until the onset of menopause ^[10], the possible link between hypertension and the severity of COVID-19 should also be investigated. According to some authors, it should be attributable to endothelial dysfunction, which preexists with the infection but promotes its progression through a state of hypercoagulability, and to dysregulation of the Renin-Angiotensin System (RAS). The latter would be favored by downregulation of the ACE2 enzyme, on the surface of pneumocytes, with reduced production of Ang 1-7 and an increase of the pro-oxidative and pro-inflammatory actions of Ang II ^[11].

However, even irrespective of age and comorbidities, the greater severity of infection observed in males, makes this subset at higher risk for admission to the ICU ^{[6][12]}, as well as having a higher mortality rate ^{[13][14]}.

This was also supported by Peckam's meta-analysis, which selected 107 studies from all over the world with a total of 3,111,714 patients. The analysis shows that males and females are at equivalent risk of infection, with males being associated with the development of severe disease as measured by admission to the ICU ^[15].

Although the current epidemiological situation is in constant evolution, the trend does not seem to have changed substantially.

In England, the majority of deaths in COVID-19 patients (99%), from March 2020 to April 2021, occurred in adults aged 45 years and older, and from this threshold age, most deaths were in males ^[16].

In Italy, the most recent data provided by the National Institute of Health document that the number of positive swabs is higher in females between the ages of 20 and 55. Conversely, the incidence curves of hospital admissions, including those in the ICU, begin to differ after the age of 40, with a greater slope in males than in females ^[17].

The aim of this entry is to explore the above gender-correlated differences, with particular focus on risk factors that are thought to have the greatest impact on important clinical outcomes.

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