



Opinion

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Understanding SARS-CoV-2 infection in males

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Abstract

The worldwide spread of the emerging respiratory disease produced by SARS-CoV-2 has become a matter of great concern to public health. The expression of the viral receptor ACE2 in the male reproductive tract arises hypothesis about a possible targeting to testicular tissue during the infection and further implications to male fertility. However, current data of whether the virus is present or not in the seminal fluid is contrasting. Objectives: The propose of this opinion article was to describe the impact SARS-CoV-2 infection in males. We analyze SARS-CoV-2 infection and the sex differential epidemiological impact in 3 185 468 cases from 53 countries. Although men and women seem equally susceptible to infection, SARS-CoV-2 elicits worsening outcomes in males; the mean proportion of deaths in confirmed cases (male:female ratio) is 1.5 (95% CI: 1.39 – 1.62). To date, evidence shows that the stronger inflammatory response in men is a marker of disease severity and mortality, and systemic inflammation might be correlated to the altered hormone profile in male patients. More high-quality information regarding the pathophysiology of the infection and gender disparity is needed to understand the higher mortality rates in men.

Keywords: COVID-19, SARS-CoV-2, Spermatozoa, Male, Testosterone, Proinflammatory cytokines,

INTRODUCTION

Recent studies have shown high expression of ACE2 RNA in the human male reproductive tract, mainly in spermatogonia, Leydig and Sertoli cells in the testes, and in a smaller proportion the expression of the transmembrane serine protease 2, essential for the viral S protein cleavage and further viral membrane fusion, suggesting that SARS-CoV-2 could target male reproductive system tissues. Thus, it is hypothesized that SARS-CoV-2 may bind to ACE2 in testicular tissue [1] and prostate [2], providing a site for viral infection.

In previous observational studies, SARS-CoV-2 RNA in semen was not detected, whether at the acute or recovery phase of the disease. However, the virus could be detected in prostate and testicle in deceased patients with COVID-19 [3]. Recently, the presence of the viral RNA in semen samples was confirmed in patients at the acute and convalescent stages of the disease, with no association among test results and patients age, clinical history of the illness and urogenital diseases [4].

On the other hand, serum sexual hormone profile is shown to be altered in COVID-19 patients in a sex specific way, leading to higher susceptibility to severe illness and overall worse outcomes in male patients. Specifically, testosterone that has been speculated to play a crucial role in modulating the expression of proinflammatory markers such as IL-1, IL-6 and TNF- α as observed in *in vitro* evidence and human T replacement therapy [5], was found negatively correlated with IL-2 and IFN- γ in male, in contrast to the increased female levels of serum testosterone that were correlated with the proinflammatory cytokines IL-1 β , IL-6 and IL-12 [6], suggesting that sex-related hormone levels and the proinflammatory status in SARS-CoV-2 infected patients could be associated with the gender.

It thus seems that testosterone could influence the immunopathological responses in COVID-19 according to its serum levels, with low T having harmful effects as it might be associated with increased proinflammatory mediators. Indeed, T also boosts regulatory T cells differentiation that mitigates inflammatory states and also suppresses T helper 17 cells that are shown to have a pathological role in COVID-19 as it favors strong inflammatory responses that cause lung epithelium damage and further lung injury. Hence, T deficiency in older men and those with comorbidities such as obesity and cardiovascular diseases that are known to be related to hypogonadism may precisely predispose to a systemic dysregulated inflammation and consequent poor prognosis in men with COVID-19 [7]. Furthermore, hypogonadism or its aggravation could also be hypothesized to result from direct testicle damage during the SARS-CoV-2 infection since the virus RNA can be found in semen, for which patients would have raised

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gonadotropins as compensatory feedback to maintain testosterone levels, as it was pointed out in the Ma L. *et al.* research [8], where the serum luteinizing hormone (LH) and T were proved to be increased and decreased respectively, and T/LH and follicle stimulating hormone (FSH)/LH ratios were significantly reduced in males with COVID-19.

When comparing the number of COVID-19 cases to June 24, 2020, in 53 countries [9] that distributed the cases and deaths per sex, which represent 3 185 468 cases, is observed that men die more than women, corresponding 60% of deaths to male ($p < 0.0001$ vs women); the mean proportion of deaths in confirmed cases (male:female ratio) 1.5 (95% CI: 1.39 – 1.62) (Fig 1.). This data leads to the assumption that SARS-CoV-2 elicits a more severe clinical course in males, leaving them at a disadvantage compared to females.

Otherwise, SARS-CoV-2 can theoretically cross the blood-testis barrier in a systemic inflammation environment, promoted by the high concentration of proinflammatory cytokines that have shown to play a crucial function in modulating spermatogenesis and causing sperm abnormalities in animal models. These inflammatory cytokines observed in the hyperinflammatory state in patients infected with SARS-CoV-2 can affect male reproduction. Also, the shift to proinflammatory cytokines can affect the maintenance of the normal tolerance microenvironment and the secretion of peptide hormones in the testis, leading to modified sperm parameters and to the

suppression of Leydig cells development that results in detrimental effects on the testosterone production [10].

Thus, low testosterone levels observed in men with COVID-19 may be related to several conditions, including the cytokine storm, increasing age, patients' comorbidities, and even primary hypogonadism due to possible damage to testis cells. However, the presence or absence of the virus in semen may not be dependent on these particular characteristics. So, it is essential to determine the variables underlying SARS-CoV-2 infection and if it is the viral loads itself that harm the testis hormone profile or if there are other factors inherent to the infection involved in the disturbance of male hormone levels such as the excessive release of proinflammatory cytokines.

Since most of the research conducted to identify the SARS-CoV-2 RNA in semen and its consequences have severe limitations and a substantial risk of bias, further studies with greater and more diverse sample sizes and longer follow-up to patients should be carried out. These studies should assess viral loads and shedding, complete male sex related hormone profiles, semen parameters, and perform a full examination of the genitourinary and reproductive system function to understand the impact of SARS-CoV-2 on male fertility. Furthermore, it is important to clarify if the sexual intercourse truly represents a potential route of transmission of the infection, and so implement protective measures such as abstinence or the usage of condoms in the sexual activity in acutely infected or recovering COVID-19 patients.

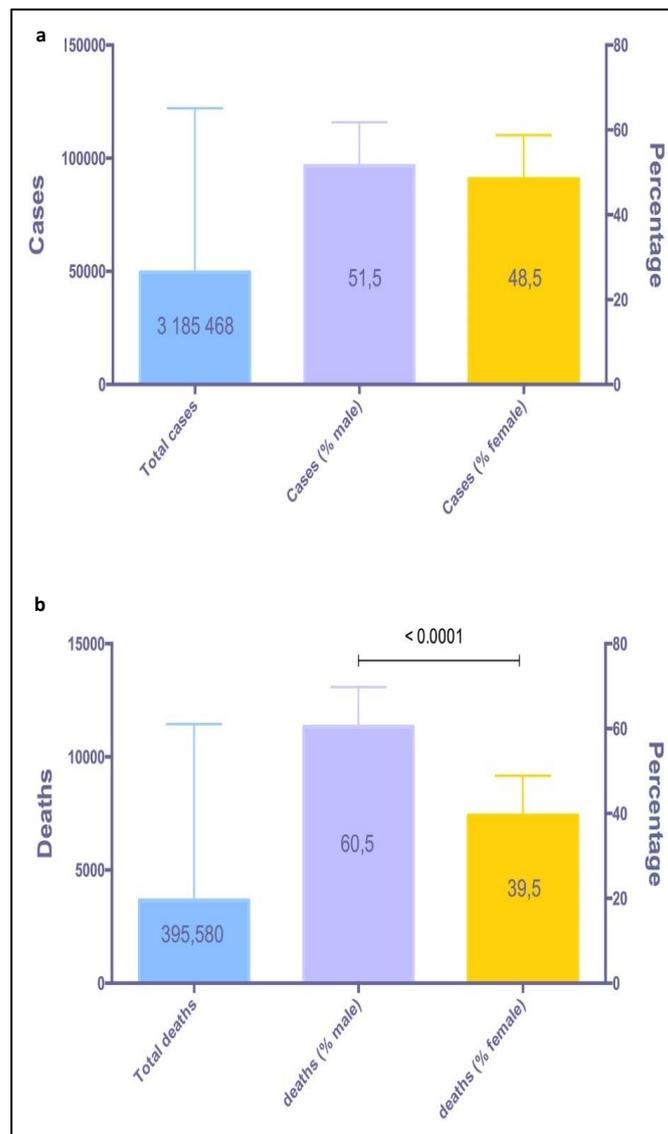


Figure 1: (a) The bar graph shows confirmed SARS-CoV-2 cases differentiated by sex in 47 countries ($p = 0.958$). (b) The bar graph describes Wilcoxon signed-rank test for deaths SARS-CoV-2 cases separated by sex in 47 countries ($p < 0.0001$).

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