



Are we equal in adversity? Does Covid-19 affect women and men differently?

Serge Rozenberg^{a,*}, Jean Vandromme^a, Charlotte Martin^b

^a Department of Gynaecology-Obstetrics, CHU St Pierre, Université Libre de Bruxelles, Vrije Universiteit Brussel, Brussels, Belgium

^b Department of Infectious diseases, CHU St Pierre, Université Libre de Bruxelles, Brussels, Belgium



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ABSTRACT

Background & objectives: This article examines whether women are less prone than men to Covid-19 infections and their complications.

Data sources: We reviewed available databases and searched systematically for publications. To be taken into account, data had to be broken down by gender. There was no study evaluation nor quantification synthesis, due to the large heterogeneity of the studies. Nineteen databases were selected. 73 publications were considered and 33 were selected, to which 12 more were added.

Results: Globally, the proportion of men and women who tested positive is comparable. However, men are about 60 % more likely to be severely ill or to die from the complications of Covid-19 than are women.

Limitations: The study was hampered by a large heterogeneity in testing and reporting of the data.

Conclusions: Although in the pandemic men die more frequently than women from Covid-19, it is not clear whether this is due to biological differences between men and women, differences in behavioral habits, or differences in the rates of co-morbidities.

Implications of key findings: Countries and studies should report their data by age, gender and co-morbidities. This may have implications in terms of vaccination strategies, the choice of treatments and future consequences for long-term health issues concerning gender equality.

1. Introduction

Unfortunately, it is well known that we are not all equal in adversity. It has been reported that older people and those with preexistent co-morbidities are at higher risk of dying from Covid-19 in the pandemic [1–3]. It is also possible that ethnic origin influences the prognosis of the Covid-19 infection, since diseases like diabetes and hypertension are more frequently found among patients of African origin [4]. Currently, it is unclear whether there is a direct link between race or ethnicity and the outcome of COVID-19 infection or whether race is a confounding factor due to the hidden effects of diabetes or hypertension, which are more prevalent, for instance, in the Afro-American population. [4]. The availability of health care resources may also play a major role, since access to health care systems may vary between countries or regions, but may also vary within a region according to socioeconomic factors or the presence of chronic diseases [5]. Analyses stratified by those factors should be carried out for the pandemic's data. The first publications from China and Italy reported higher fatality rates, due to the pandemic, in men than in women [6,7]. Following

these publications, some authors suggested that the reduced susceptibility of women to viral infections could be attributed to the protection from the X chromosome as well as from sex hormones, which play an essential role in innate and adaptive immunity [8]. Therefore the current gender difference in the response to the pandemic raises a number of questions: here are a few of them.

Are women and men similarly vulnerable or is there a difference in susceptibility?

Are the biological and clinical immune responses identical? Are symptoms in women and men similar? What is the proportion of men and women who are hospitalized and transferred to intensive care units (ICU)? Are the responses to treatment and the recovery patterns similar in men and women? Are the fatality rates identical? And finally will the response to vaccines be comparable in men and women?

We review only some of the currently available data, notably the sex-difference in susceptibility to the Covid-19 infection and the concomitant risk of death. Indeed, it will not be possible to determine whether biological and clinical immune responses are the same in women and men until data becomes available regarding the cytokine

* Corresponding author.

E-mail address: serge_rozenberg@stpierre-bru.be (S. Rozenberg).

ratios are not well known. The reasons are, first, that the denominators of incidence and prevalence are not defined, mainly because random sampling of the population has not been carried out (samples are selective as mentioned previously) and secondly, multivariate analyses are needed to determine the exact effect of COVID-19 on adverse outcomes, given other risk factors such as gender, age or comorbidities.

We did however search national databases and registries that presented data in relation to gender. When possible, we further sought to classify the data by age and comorbidities. Male hospitalization rates were higher than female ones, in all countries which reported them, ranging from 55 % to 62 % (Table 1) [10,11,16,17,20,22]. The proportion of male admissions to the ICU was even higher ranging from 65 % to 74 % [10,11]. Throughout Europe, 73 % of all ICU admissions were for men (Table 1) [9,12]. Most, but not all, of early publications from China reported that men presented three times more often prolonged SARS-CoV-2 RNA shedding, had twice the risk of developing kidney disease as well as more frequent refractory pneumonia and metabolic associated fatty liver disease (MAFLD) [29–34]. Similarly, in the Seattle and New York areas more men (63 % and 76 %) were admitted to the ICU [27,35]. In our own hospital the first 272 patients that were admitted had a median age of 60 years; 45 % had hypertension, 30 % diabetes and 20 % cardiovascular diseases. Sixty-six percent of these patients were men. Fifty seven out of 272 were admitted to the ICU, of which 63 % were men (personal communication).

3.3. What are the fatality rates for men and women?

Reported death rates vary tremendously between countries. But almost all of the data that broke numbers down by gender, reported a higher proportion of deaths among men than among women (ranging between 59 % and 69 %) (Table 1). With the exception of India and Pakistan, all other countries reported a male to female death ratio ranging between 3 and 1.1. Even in countries where fewer male than female cases were reported the death rates were still higher for males (Table 1).

The first report from China quoted a death rate of 2.8 % in men and 1.7 % in women [6]. In other series in China, more men than women died (73 % vs 27 %), and had higher fatality rates (3.6 % vs 1.6 %) [36–40]. This was also the case in Australia, Austria, Belgium, Denmark, France, Germany, Italy, Europe (in general), Seattle and New York (Table 1). In Italy, at all ages the lethality rate of Covid-19 was higher for men than for women (globally 13.3 % vs 7.4 % at ages 40–49: 1.1 % vs 0.4 %, 50–49 2.9 % vs 0.9 %, 60–69: 8.6 % vs 4.2 %, 70–79 23.1 % vs 13.9 %, 80–89 34.1 % vs 21.2 %, and above 90 : 36.6 % vs 21.4 % [23].

In New York, men accounted for 60.3 % of deaths and women for 39.7 %. An even higher proportion of men were admitted to the ICU (76.5 % vs 33.5 %), while more women were being discharged and more men died in each age class. [28]. Nevertheless, there is still a lack of data classified by age, sex and comorbidities.

4. Discussion

Earlier publications reported that men were more frequently infected with COVID-19 than women, with men accounting for 60 % of infected patients [8]. This has also been reported for MERS-COV and SARS-COV [8]. Nevertheless, these data should be interpreted with great caution. Indeed, other publications did not report sex differences among people with seasonal coronaviruses and respiratory illnesses: among 84,957 episodes of respiratory illness, in Scotland, between 2007 and 2015, the global sex distribution was approximately equal, with 51.6 % of patients being female [38]. However, these authors reported greater numbers among males than females for certain infections such as CoV-229E, CoV-OC43, CoV-NL63 and influenza, with higher hospitalization and mortality rates in men [38]. Furthermore, there is a marked heterogeneity concerning the current pandemic as to

who is being tested. In Iceland, a large proportion of the population has been tested (148 people per thousand inhabitants), whereas in other countries only severely symptomatic patients have been tested (11 per thousand in France). The number of tests is constantly increasing. The “picture” that we report here, therefore only reflects the situation at the beginning of May 2020. But if we rely on the most comprehensive available data, there seems to be no important difference in terms of infection prevalence between men and women (women have a 2 %–8 % lower exposure rate than men in some countries). The South Korea data are an exception. Indeed, in this series of 4,212 patients, only 37.7 % of the infected ones were male [29]. But the authors provided an explanation: the discrepancy was probably due to an increase of infected women, in a religious group of Daegu [29]. The Belgian data also are somewhat particular because they present data by sex and age group. They found a higher rate of infections in women before the age of 60 and a lower rate thereafter. It is possible, however, that these data are biased by the higher rate of women working in hospitals and more prone to be infected therefore [39,40]. About 70 % of confirmed infected health workers were found to be women, in Spain, the USA, Italy and Germany [9–12,21–23].

We don't know much yet about the spectrum of symptoms in men and women. One series of 263 (63.1 %) women and 154 men (36.9 %) mildly-to-moderately affected patients, by COVID-19, reported that women were significantly more affected by olfactory and gustatory dysfunctions than men [41].

We did find data broken down by sex, for patients requiring hospitalization in some countries or areas (Denmark, France, New York, Belgium) [11,16,17,20,27]. In these areas, more men were hospitalized than women (between 57 % and 74 %). Similarly, in all countries reporting death rates from Covid19 infections, by sex, more men died than women (60 %–70 % of men) (Table 1) [11].

These data need also to be interpreted cautiously. There are many diverse ways to evaluate Covid-19 related mortality. For instance, the fatality ratio (the number of deaths divided by the number of confirmed cases) depends on how many tests are performed. When extensive screening occurs, the fatality ratio is lowered (Austria, Germany, Finland) [9–11,15,21]. On the other hand, the mortality rate will rise, when deaths suspected to be related to Covid -19, in patients untested for the presence of the virus, are attributed to the pandemic (this is what happened in Belgium where about half of the deaths occurred in geriatric living facilities, but only 11 % of the patients who died had been tested for Covid 19) [16]. The fatality rate also depends on the country's age pyramid (the older the population the higher the rate). This was the case in Italy [23].

As suggested by others, the difference in vulnerability towards the pandemic could be due to biological differences between men and women. But whether men are more susceptible to an infection or its increased severity, or whether women have some natural protection against these viruses, is not clear [42].

It has been previously reported that men suffering from all-cause infectious sepsis have a 70 % higher mortality rate than women and this is also the case for SARS and MERS respiratory infections (21.9 % vs 13.2 %) [43,44]. Women seem to have a more robust immune system [45]. It has been reported that women have stronger immune responses to infections and vaccinations than men. This is, among other factors, due to the documented effects of estrogens, progestogens and androgens [45]. For instance, estrogens suppress T and B cell lymphopoiesis and activates B cell function. Estrogen enhances humoral responses, B cell differentiation and immunoglobulin (Ig) production [45]. The difference in gender immune responses may also have a role in why women have a higher incidence (up to 15 times more for thyroiditis) of autoimmune diseases [45].

The presence of two X chromosomes in women emphasizes the immune system even if one is inactive. The immune regulatory genes encoded by X chromosome in women has been associated with lower viral load levels, and less inflammation in women than in men, with