# Sex-Related Differences in COVID-19 Lethality

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## Abstract

Many Western countries have been affected by the outbreak of COVID-19. Italy has been particularly hit at the beginning of the pandemic, immediately after China. In Italy and elsewhere women seem to be less affected then men by severe/fatal COVID-19 infection, regardless of their age. Despite the evidence that women and men are different fort this infection, very few studies consider different therapeutic approaches for the two sexes. Undoubtedly, understanding the mechanisms at the bases of these differences may help to find appropriate and sex specific therapies. Here we consider that other mechanisms but estrogen protection are involved. Several X-linked genes (such as ACE2) and Y-linked genes (SRY, SOX9) may explain sex differences. Cardiovascular comorbidities are among the major enhancers of virus lethality. In addition, the number of sex-independent non-genetic factors that can change susceptibility and mortality is enormous, and many other factors are likely to be considered, including gender and cultural habits in different countries.

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ABSTRACT

Many Western countries have been affected by the outbreak of COVID-19. Italy has been particularly hit at the beginning of the pandemic, immediately after China. In Italy and elsewhere women seem to be less affected then men by severe/fatal COVID-19 infection, regardless of their age. Despite the evidence that women and men are different fort this infection, very few studies consider different therapeutic approaches for the two sexes. Undoubtedly, understanding the mechanisms at the bases of these differences may help to find appropriate and sex specific therapies. Here we consider that other mechanisms but estrogen protection are involved. Several X-linked genes (such as ACE2) and Y-linked genes (SRY, SOX9) may explain sex differences. Cardiovascular comorbidities are among the major enhancers of virus lethality. In addition, the number of sex-independent non-genetic factors that can change susceptibility and mortality is enormous, and many other factors are likely to be considered, including gender and cultural habits in different countries.

**Key words:** Cardiovascular comorbidities, ACE, ACE2, Androgens, Estrogens

**Introduction**

The outbreak of novel coronavirus disease 2019 (COVID-19) quickly turned into a pandemic, and Europe and U.S.A. have been particularly affected [Zhou et al. 2020b]. Sex differences are emerging in terms of *case fatality* (deaths/reported cases), and sex disaggregated data are now starting to be available for many countries. Looking at male/female ratio for death in confirmed cases it appears that the ratio is always above 1.1 in 34 out of the 35 countries that provide sex disaggregated data (only for Pakistan, the ratio is 0.9). Many European countries (Spain, Italy, England, Belgium, Greece, Denmark and The Netherlands) have a male/female ratio for death in confirmed cases equal or above 1.7 (*https://globalhealth5050.org/covid19/*, accessed on May 13th 2020). In particular, on May 11, 28.903 COVID-19 positive patients had died in Italy (Table 1). Their mean age was 80 years (median 81, range 0-100, IQR 74 -87) (https://www.iss.it/coronavirus, accessed on May 13[th]2020). Deceased women were 10.934 (lethality 9.6%), whereas men were 17.018 (lethality 17.1%). For 951 Italian deaths, sex was not reported. The difference in lethality between sexes seems to suggest that women are less prone to develop severe complications that ultimately lead to death. The reasons for this

sex-based tolerance are still unknown. Among Italian patients in the range 10-49 years, deceased women were about 84 over 32.345 (0.26% lethality), while in the range age of 50-90 years they were 7975/67.263 (11.9% lethality). Of note, men had a 0.89% lethality (225 deaths over 25276 cases) in the range 10-49 years and 21.8% (15236/69844) in the range 50-90 years. Therefore, lethality seems to increase with age in both sexes, but it is 3.42 folds higher in young men than young women (10-49 years), and 1.84 folds in older men than in older women (50-90 years) (https://www.iss.it/coronavirus, accessed on May 13th 2020).

Although these are cumulative/raw data, they confirm that there is a reduced susceptibility of females to severe COVID-19 infection. Due to the differences between pre and post-menopausal phases [Horstman et al. 2012], it is reasonable to speculate that the potential role played by hormones may be present in protecting against severe outcome, but it is not the only factor. Therefore, we need to consider other possible reasons for this difference in sex-related lethality. First, is this difference confirmed also in populations from other countries? According to the latest publications, such differences in lethality between the 2 sexes have been shown elsewhere (see Table 1 and*https://globalhealth5050.org/covid19/*). For instance, in a number of different articles from China, similar data are reported [Chen et al. 2020a; Chen et al. 2020b; Guan et al. 2019; Huang et al. 2020; Wang et al. 2020; Zhou et al. 2020a]. In these studies, severe or deceased patients admitted to intensive care units (ICUs) were prevalently men, while women ranged between 30% [Huang et al. 2020] and 42.2% [Guan et al. 2019]. In the largest study available from China [Guan et al. 2019;], quite similar percentages to those reported for deceased women in Italy have been observed. Yet, in this latter study, the median age of patients was 47 years (IQR, 35-58), and the distribution between sexes according to age was not reported. For the US, sex disaggregated data on case fatality are not available, but deaths were 57% for males and 43% for women (*https://globalhealth5050.org/covid19/*, accessed on May 13th 2020).

To sum up, currently available studies suggest that both young and older females are less susceptible to severe infection outcomes, regardless of their nationality. Both hospitalization in ICUs and death rates are different between sexes (https://globalhealth5050.org/covid19/ and Table 1). Similar observations were already reported for other coronavirus epidemics [Channappanavar et al. 2017].

Despite this striking evidences for this infection, very few studies consider different therapeutic approaches for the two sexes. As no specific therapeutics are yet proposed to treat Covid-19 and control disease evolution, a better understanding of the pathogenic mechanisms in the two sexes induced by SARS-CoV-2 is mandatory to characterize new targets.

### Why Are Less Women Than Men Dying of COVID-19?

Both young and old women are dying less than matched age males. Beside hormone differences, which, however, do not appear to be the only factor, there are different potential mechanisms that may explain why women are less prone to severe COVID-19 infections.

The expression and activity of two factors may be considered, namely angiotensin-converting enzyme-2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2) [Cheng et al. 2015; Kuba et al 2005]. While ACE2 is the receptor for the spike (S) protein of coronaviruses, TMPRSS2 splits the S-protein at sites S1/S2 and S2, favoring the attachment and fusion of the virus to cell membranes, respectively. ACE2 is largely expressed in organs mainly targeted and damaged by SARS-CoV-2 [Pagliaro and Penna 2005]. Both ACE2 and TMPRSS2 have been proposed as modulators of the different susceptibility to SARS-CoV in both sexes [Hoffmann et al. 2020]. Indeed, the expression of ACE2 seems reduced in post-menopausal women. However, in some studies, no differences were detected for ACE and ACE2 between the 2 sexes, while a lower ACE2 serum activity was observed in younger compared to older women [Fernández-Atucha et al. 2017]. ACE2 is located on the X chromosome, and is one of the genes escaping X inactivation [Tukiainen et al. 2017]. Therefore, it can be hypothesized that the second X chromosome could protect women from fatal polymorphisms that make the infection more aggressive in males, *e.g.* by favoring viral binding. Indeed, in a recent study, worse outcome in older COVID-19 patients has been attributed to the presence of lower ACE-2 levels and the subsequent upregulation of Angiotensin II (Ang II) proinflammatory pathways throughout the body, which could make patients more prone to systemic "deleterious" effects of Ang II [AlGhatrif et al.

2020]. ACE and ACE2 and their major products, Ang II and Ang-1-7, respectively, are linked in a sort of ying/yang process, when one decreases the other increases and *viceversa* [Pagliaro and Penna 2005; Koni and Miyamori 2007; Wakahara et al. 2016; Wang et al. 2015, 2016]. Whether ACE2 levels in the lung are related to the susceptibility and severity of COVID-19 infection is a matter of investigation [Gheblawi et al. 2020], and men may have higher expression of ACE2 in the lungs compared to women [Zhao et al. 2020], with potential important consequences on COVID-19 infections. Moreover, the different roles of membrane bound ACE2 and circulating ACE2 should be considered. Indeed, it has been proposed that soluble ACE2 could quench the coronavirus by limiting its attachment to cellular ACE2 [Monteil et al. 2020]. It is unknown whether circulating ACE2 levels in the two sexes are different. This would be an important piece of information as circulating ACE2 quenching the virus may limit the possibility for the virus to target other organs.

Although some animal and human studies suggest that TMPRSS2 is involved in determining severity of influenza [Cheng et al. 2015; Sakai et al. 2015], its role during coronavirus infections and in the modulation of COVID-19 severity is still unclear. Nevertheless, we must consider that TMPRSS2 is a testosterone regulated gene and may have a higher expression in men than in women [Tomlins et al. 2005].

Moreover, several other X-linked genes (such as ILs, FOXP3XIST, TLR7) and Y-linked genes (SRY, SOX9) may explain sex differences [Ghosh and Klein 2017]. These and other immune regulatory genes encoded by the X and Y chromosomes may explain lower viral loads and reduced inflammation in women compared to men [Conti and Younes 2020]. In particular, the two X chromosomes seem to regulate the immune system even if one of them is inactive. The X chromosome regulates the immune system also acting on other proteins, including CD40L, CXCR3 and TLR8. These can be up-regulated in women and can determine the response to viral infections as well as to vaccinations. A Differentially Expressed Genes (DEGs) network was constructed to identify a specific gene signature characterizing SARS-CoV-2 infection [Fagone et al. 2020]. Intriguingly, ten DEGs were modulated by sexual hormones, as Androgen Receptor regulated 6 DEGs (while CCL20 and CXCL1 genes were upregulated; THBD, HEY2, BBOX1 and MYLK were downregulated genes); whereas Estrogen Receptor 1 regulates 4 DEGs (while C3 and EDN1 genes were upregulated; PDK4 and VTCN1 were downregulated DEGs). Also, $CD4^+$ T cells number differs between sexes being higher in women with a better immune response [Conti and Younes 2020]. Finally, the number of sex-independent non-genetic factors that can change susceptibility and mortality is enormous, and many other factors are likely to be considered, including gender and cultural habits in different countries. For example, an Outbreak in the Republic of Korea determined a high incidence of case in women due to social and religious events occurring in those days. [Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020].

### Sex, Cardiovascular disease and Covid-19

Cardiovascular disease is more prevalent in males, and subjects with cardiovascular dysfunction infected with SARS-CoV-2 have a worse prognosis. Among the deceased Covid-19 patients in Italy, less than 4% had no co-morbidity, while more than 60% had three or more comorbidities. Among these, cardiovascular comorbidities were the most represented. These include arterial hypertension (about 70% of deceased patients), followed by ischemic heart disease (about 30%), atrial fibrillation (about 20%), and heart failure (about 15%) (https://www.iss.it/coronavirus, accessed on May 13[th]2020). Most of the deceased patients were elderly (over 65 years) and obese (in the Italian report, obesity is present in 12% of the deceased patients). All these conditions are characterized by a deranged ACE/ACE2 ratio [Koni and Miyamori 2007; Colucci et al 2011; Wang et al. 2015, 2016; Santos et al 2013, Wakahara et al. 2016;]. It appears that a deranged ACE/ACE2 ratio is responsible for a high incidence of dramatic ARDS and cardiovascular complications and the high lethality of Covid-19. Downregulation of ACE2 has been observed in pulmonary arterial hypertension and cigarette smoker patients [Yuan et al 2015; Horn et al 2020]. Therefore, we wonder if it is worth trying to reestablish an adequate ACE/ACE2 ratio to have better outcomes in Covid19. Indeed, Covid-19 depletes and downregulates ACE2 [Moccia et al 2020]. Therefore, a potential therapy could be the administration of drugs that activate ACE2, which has anti-inflammatory effects (Fig 1). Of note exercise is a natural way to increase the ACE2/ACE ratio [Crisafulli and Pagliaro 2020].

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## Proposed drugs

Drugs that can increase ACE2 activity include losartan (NCT04312009, NCT04311177, NCT04340557, NCT04343001; clinicaltrials.gov), diminazene diaceturate, resorcinolnaphthalein, and xantenone [Li et al. 2020]. Furthermore, recombinant ACE2 has been proposed in both pneumonia [Khan et al. 2017] and Covid-19 [Monteil et al. 2020].

Currently, remdesevir, used against ebola, chloroquine/hydroxylchloroquine, used against malaria [Yazdany and Kim 2020; Luo et al. 2020], are being used for Covid-19 patients. A "cytokine storm" has been proposed several times as responsible of Covid- 19 lethality [Moccia et al. 2019]; therefore the anti-IL-6 receptor antibody, tocilizumab (used for the treatment of rheumatoid arthritis and CRS after CAR-T therapies), has been proposed in many clinical studies, and it is now in Phase II and Phase III studies in Covid-19 patients [Alvi et al. 2019; Lu et al. 2020; Luo et al. 2020]. Monoclonal antibodies, anti-IL-1 and anti-IL-6 and plasma derived from Covid-19 recovered patients have been proposed (*https://www.sciencenews.org/article/coronavirus-covid-19-can-plasma-recovered-patients-treat-sick*). Other anti-inflammatory drugs, comprising JAK inhibitors, and glucocorticoids may also be useful [Zhang et al. 2019]. Coagulopathies are also a prominent aspect of severe Covi-19 patients. Thus, anticoagulant treatment may decrease mortality [Tang et al. 2020]. While waiting for vaccines and new therapeutic strategies to fight this terrible pandemic different old antiviral options are under clinical trial as combination therapies. These include hydroxychloroquine given alone or with azithromycin, and remdesivir, as well as lopinavir/ritonavir alone or with interferon (ClinicalTrials.gov identifier: NCT04332094; NCT04332107; NCT04322123; NCT04335552; NCT04336332; NCT04339816). To the best of our knowledge none of these studies considered different therapeutic approaches for men and women. Moreover, for many of these drugs the effects on ACE/ACE2 ratio is unknown.

A recent study [Fagone et al. 2020] investigated the transcriptomic profile of primary human lung cells upon infection with SARS-CoV-2. In this study the transcriptomic profile of lung tissue from healthy women and men were compared with the transcriptomic induced by Covid-19. It emerged that at ages 40-60 years, the transcriptomic feature of female lung tissue was more similar to those induced by Covid-19 than in male tissue. The authors suggest that a lower threshold of acute response to SARS-CoV-2 infection in men may at least partly explain the lower lethality in women. Nevertheless, the potential factors that might induce this" COVID-19-resistant lung phenotype" in middle-aged women is not clear. In this study targeting the mammalian target of rapamycin (mTOR) pathway using sirolimus, appeared to be a promising therapeutic approach to fight Covid-19. Also mitogen-activated protein kinase kinase (MEK), I kappa B Kinase (IKK) and serine-threonine kinase (AKT) inhibitors have been proposed as candidate drugs [Fagone et al. 2020]. Of note some of these enzymese are linked to ACE2 anti-inflamamtory action [Dhawale et al. 2016]. Nevertheless, this study does not envisage different therapeutic approaches for men and women.

In conclusion, all the above mentioned drugs would warrant clinical studies. In particular, drugs that can affect ACE/ACE2 ratio may be considered (Fig 1). Besides a plethora of factors that may influence the outcome, sex must be one of the criteria to consider in order to select the appropriate therapy for the appropriate patients. Indeed, given the striking differences in lethality between the two sexes, we believe that studying the sex differences may help to find the appropriate therapies for all. Only large unbiased studies considering all the factors and hypotheses mentioned here concerning sex differences may explain why women are less at risk of dying from COVID-19 and might help to find the patient tailored therapy.

ships/conditions/circumstances that present a potential conflict of interest.

## Acronyms List

ACE: angiotensin-converting enzyme

ACE2: angiotensin-converting enzyme-2

AKT: serine-threonine kinase

Ang II: angiotensin II

CAR-T: chimeric antigen receptor T-cells

Covid-19: coronavirus disease 2019

CRS: cytokine release syndrome

DEGs: differentially expressed genes

ICUs: intensive care units

IKK: I kappa B Kinase

MEK: mitogen-activated protein kinase kinase

mTOR: mammalian target of rapamycin

TMPRSS2: transmembrane protease, serine 2

## Legend

**Fig 1** Possible pivotal role of ACE2/ACE ratio in therapies against Covid-19 in the two sexes.

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**Same or different therapy against Covid-19 in the two sexes?**

Higher
ACE2/ACE ratio
Less Severe
Covid-19

Lower
ACE2/ACE ratio
More Severe
Covid-19
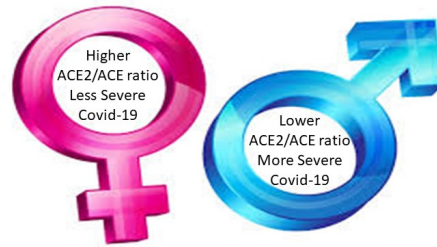
**Can administration of drugs that upregulate ACE2
have anti-inflammatory effects?**

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