Gender differences in patients with COVID-19: a narrative review

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Abstract

In December 2019 a novel coronavirus emerged in Wuhan, China causing many cases of severe pneumonia. World Health Organization (WHO) named this disease Coronavirus Disease 2019 (COVID-19). The infection has rapidly spread across China to many other countries, and on March 12, 2020 the WHO declared pandemic outbreak of COVID-19. As of May 16, 2020, COVID-19 has been diagnosed in more than 4,490,000 patients, associated to 305,976 deaths worldwide; in Italy 224,760 COVID-19 cases have been reported with 31,763 deaths. The main routes of transmission are respiratory droplets and direct contact with infected people, so numerous prevention strategies are employed to mitigate the spread of disease, including social distancing and isolation. The aim of this narrative review is to underline gender differences in epidemiology, etiopathogenesis, risk factors, clinical presentation, diagnosis, prognosis and mortality of patients infected with SARS-CoV-2. Currently data on the sex indicators for admitted or deceased patients are only available, but there is no analysis about other gender indicators. The data considered in our study are the only currently available in the literature, but it is appropriate to implement a specific analysis with all gender indicators to identify appropriate strategies. Moreover, the evaluation of a health service efficiency is a key element to define gender outcomes. Knowing the gender differences in COVID-19 outbreak would be a fundamental tool to understand the effects of a health emergency on individuals and communities as well as to carry out effective and equitable policies, public health measures and targeted solutions.

Introduction

In December 2019, a series of pneumonia cases caused by a novel coronavirus (later referred to as SARS-CoV-2) emerged in Wuhan, China. World Health Organization (WHO) named this disease as Coronavirus Disease-2019 (COVID-19) on February 11, 2020. The infection has rapidly spread across China to many other countries, and on March 12, 2020 the WHO declared pandemic the COVID-19 outbreak [1]. As of May 16, 2020, COVID-19 has been diagnosed in more than 4,490,000 patients and associated with 305,976 deaths [2] worldwide; in Italy 224,760 cases with 31,763 deaths [3] have been reported.

The main routes of transmission are respiratory droplets and direct contact with infected people. The COVID-19 virus spreads through droplets from mouth or nose when an infected person coughs or sneezes. Governments of many countries implemented several restrictive measures to contain the spread of the infection, including careful infection control, contact tracing, social distancing and isolation.

It has been estimated that the median incubation period is 5.1 days and that 97.5% of the infected subjects will develop symptoms within 11.5 days of infection. Patients infected with SARS-CoV-2 can present a wide range of symptoms ranging from mild to severe. Fever, cough, and shortness of breath are the most common symptoms [4]. It has also been reported that about 2–10% of the patients with COVID-19 had gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain [4]; diarrhea and nausea preceded the development of fever and respiratory symptoms in 10% of patients [4]. Other symptoms were hyposmia or anosmia, gustatory dysfunction, and conjunctivitis.

The RT-PCR detection of viral nucleic acid test on samples from oro/rino-pharyngeal swab test was the most reliable established laboratory diagnosis method for SARS-CoV-2.

To date, there are no specific vaccines nor treatments available for COVID-19. Several studies are ongoing to evaluate effective therapeutic strategies and specific protocols.

The aim of this narrative review is to underline gender differences in epidemiology, etiopathogenesis, clinical presentation and mortality of patients infected with novel coronavirus. Recognizing gender differences in COVID-19 is a fundamental tool in understanding the primary (health protection) and secondary (social, economic) effects of this health emergency on individuals and communities, and creating effective and equitable policies as well as targeted solutions.

Methods

Studies were identified through Pubmed systematic research until May 7, 2020. The search keywords were "SARS-CoV 2", "COVID-19", "gender", "estrogen", "androgen" and "coronavirus". The studies were selected and reviewed for potential inclusion. Studies written in languages other than English were excluded. Two authors (IA and EB) reviewed all study abstracts. Studies were included if they analyzed gender differences in SARS-COV-2 infection. All selected studies are qualitatively analyzed.

Epidemiology

Many studies underlined that in China men were more infected by COVID-19 (51%) [5] than women, most patients were aged 30-79 years [6] and the elderly with comorbidities had more severe conditions [7].

The study of Huang et al. [8] on 41 inpatients with laboratory-confirmed COVID-19 infection, showed that most of the infected patients were men (73%), the median age of infected patients was 49.0 years (IQR 41.0–58.0) and less than half of infected men had underlying diseases (32%), including diabetes (20%), hypertension (15%), and cardiovascular disease (15%).

Wang's study [7] enrolled 69 patients with confirmed SARS-CoV-2, of whom 32 patients (46%) were men, and 37 patients (54%) were women, the median age of the patients was 42.0 years and the elderly and the patients with underlying comorbidities developed severe conditions. Chen conducted a retrospective, single-centre study [9] and observed a greater number of men than women in the 99 cases of 2019-nCoV infection, in fact 32% were female and 68% were male with a mean age of 55·5 years. None of the 99 patients were medical staff. About half of patients (51%) had chronic diseases, mainly cardiovascular and cerebrovascular diseases and diabetes. Wang [4] performed a retrospective study which included 138 hospitalized patients with confirmed COVID-19 of whom 45.7% were women and 54.3% were men; the median age of inpatients was 56 years (IQR, 42-68; range, 22-92 years). The retrospective study by Zhou et al. [10] included 191 inpatients with COVID-19 with a median age of 56·0 years (IQR 46.0–67.0), ranging from 18 years to 87 years; 72 (38%) were females and 119 (62%) were males. The meta-analysis conducted by Li [11] confirmed these studies, in fact showed that males took a larger percentage in the sex distribution of COVID-19 patients (60%). In a study [12] of 1099 patients with COVID-19 from 552 hospitals in 30 provinces in China, 58% of the patients were men and 41.9% of the patients were female and the median age of the patients was 47 years. Only one study of 140 patients with

COVID-19 in China [13] found an equal distribution by sex, in fact an approximately 1:1 ratio of male (50.7%) and female (49.3%) COVID-19 patients was found, with an overall median age of 57.0 years and the majority (70%) of them were more than 50 years old.

The Report of the WHO-China Joint Mission on COVID-19 [14] as of 20th February 2020, showed that the median age was 51 years with the majority of cases (77.8%) aged between 30-69 years; among reported cases, 51.1% were male, 77.0% were from Hubei and 21.6% were farmers or laborers by occupation.

The Korean Report [15] showed that in total confirmed cases, two peaks of age groups were 20 years and 50 years; among the confirmed cases in Gyeonggi-do where the third-highest number of patients was observed, the peak age group was 30 years. Moreover, only 37.7% were male in total confirmed cases, but among the confirmed cases in Gyeonggi-do, 59.1% were male. The distribution may reflect the movement and the social activities of individuals in different societies. The female prevalence in Korean COVID-19 patients of 20 years old is probably due to the outbreak in a religious group, whose demographic composition includes women mostly.

In Italy, first data reported in Lombardy Region reported a major prevalence of COVID-19 pneumonia in men and older patients. The retrospective observational study conducted by Grasselli [16] showed that males were 82% (1304 of 1591 patients), while females were 18% (287 of 1591 patients). The median age was 63 years. In particular, in the age groups 51-60, 61-70 and 71-80, the majority of patients were men (83%, 81% and 82%, respectively) versus women (17%, 19% and 18%, respectively). Patients in these age groups had more comorbidities, in particular hypertension was the most common comorbidity, followed by cardiovascular disease and hypercholesterolemia. In a review conducted by Lovato [17], 57.5% of a total of 1556 hospitalized patients with COVID-19 were males and the mean age was 49.1 years. According to the ISTAT-ISS report published on May 4th 2020 [18], 52.7% of the COVID-19 cases were female and the median age was 62 years. In the age groups 0-9 years, 60-69 and 70-79 years, a greater number of cases of males was observed. In the age group >90 years, the number of females was more than triple compared to males probably due to the clear prevalence of women in this age group.

Also interesting are data about medical staff: from 7th January to 11th February 2020 Chu [19] conducted a retrospective study among all 54 hospitalized medical staff from Tongji Hospital diagnosed with COVID-19. Most of those cases were from other clinical departments (39 cases - 72.2%) rather than emergency department (2 cases - 3.7%) or medical technology departments (10 cases - 18.5%). There were categorized as common-type 11 out of 54 patients with COVID-19, while 40 as severe-type, and 3 as critical-type. Among 11 common-type patients, 5 cases (45.5%) were females and 6 cases (54.5%) were males. Unexpectedly, the median age for the common-type patients was significantly older than severe/critical-type patients (47 years vs 38 years; p=0.015). Such differences may be explained by the lower ratio of elderly people among the medical staff and by the longer work time and higher work intensity of the medical staff aged 38 years or so. More male patients (30/43, 69.8%) were found with severe/critical-type as compared with females (13/43, 30.2%). All 54 patients conducted SARS-Cov-2 nucleic acid tests, but only 38 were positive for the tests. The 16 patients negative for SARS-Cov-2 tests, showing typical pathological changes in CT-scans were however diagnosed as COVID-19. The median age of patients positive (39 years) for SARS-Cov-2 tests was comparable to patients negative (46 years) to the tests. In both groups higher pro-

portion of male patients were observed, in *positive* for SARS-Cov-2 tests: 24 M (63.2%) and 14 F (36.8%), in *negative* for SARS-Cov-2 tests 12 M (75%) and 4 F (25%).

Physiopathology

Full-genome sequencing and phylogenic analysis indicated that the coronavirus that causes COVID-19 is a beta-coronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses), but in a different clade. The structure of the receptor-binding gene region is very similar to that of the SARS coronavirus, and the virus has been shown to use the same receptor, the angiotensin-converting enzyme 2 (ACE2), for cell entry [20,21].

ACE2 is widely distributed in the heart, kidney, lung, and testis and may show differences in different ages and sexes. SARS-CoV-2 invades human alveolar epithelial cells through ACE2 [22]. Interestingly, one study [23] found that the expression of ACE2 was more elevated in Asian men, which might be the reason for the higher prevalence of COVID-19 in this subgroup of patients than in women and patients of other ethnicities. ACE2 has been shown to play a protective role in acute respiratory distress syndrome. In fact, upon ACE2 down-regulation, mice showed more severe lung failure [21]. A study [24] in animal models underlined that ACE2 expression is dramatically reduced with aging in both genders: young-adult *vs* old p<0.001 (by 78% in male and 67% in female, respectively) and middle-aged *vs* old p<0.001 (by 71% in male rats and 59% in female rats, respectively). Given that COVID-19 prognosis is related to age and sex, ACE2 expression appears to be higher in young people than in elderly individuals and higher in females than in males and circulating ACE2 activity is increased in patients with cardiovascular complications [25]. The binding of SARS-CoV-2 spike protein to ACE2 has been shown to downregulate ACE2 and, in turn, to decrease angiotensin production. This mechanism may be involved in the pathogenesis of pulmonary hypertension and insufficiency caused by SARS-CoV-2 infection [26].

In a study on SARS-CoV-2 infection, Channappanavar *et al.* [27] showed that male mice were highly susceptible to this virus compared with age-matched female mice, confirming even in this infection, the protective function of ACE2. Estrogen, the main female sex hormone, is able to upregulate the expression of ACE2 [28] supporting the higher ACE2 expression in young women.

Another key discovery in understanding the mechanism of SARS-CoV-2 infection involves the role of the transmembrane serine protease 2 (TMPRSS2), a cell surface protein that is expressed by epithelial cells of specific tissues including those in the aerodigestive tract. Coronaviruses as well as influenza viruses critically depend on TMPRSS2 for viral entry and spread in the host. As a first step enabling host cell entry, the viral hemagglutinin protein attaches to ACE2 expressed on respiratory epithelial cells. In a second step, hemagglutinin is cleaved to activate internalization of the virus. This second step is dependent on the host cell, particularly TMPRSS2. Understanding how TMPRSS2 protein expression in the lung varies in women and men could reveal important insights into differential susceptibility to coronavirus infections. The strong regulation of TMPRSS2 by androgens have raised the hypothesis that the male predominance in the COVID-19 pandemic could partially be explained by TMPRSS2 [29,30]. Hence, also in this context, a link to genetic variations in the androgen receptor and COVID-19 disease severity has been suggested [31].

However, constitutive expression of TMPRSS2 in lung tissue does not appear to differ between men and women and low levels of androgens present in women may suffice to sustain TMPRSS2 expression [32]. In addition, TMPRSS2 expression levels may be also regulated by estrogen signaling [33].

Other biological factors may contribute to the disparity in sex-specific disease outcomes. In particular women, compared to men, have a better outcome of viral infections due to a stronger innate and acquired immune response. Sex-specific steroids play a role in this sex dimorphism in immune response with estrogens as immune enhancers and androgens as immune suppressors. Furthermore, the role played by X-linked genes (TLR-7, TLR8, CD40L, FOXP3 and CXCR3), which modulate the innate and adaptive immune response to virus infection and influence the immune response [34,35], is important.

The presence of two X chromosomes in women could lead to an over-expression of these X-linked immunoregulatory genes. As a consequence, women may have lower viral load levels than men, higher number of CD4+ T cells and higher levels of antibodies. In this context, the role played by the molecule Toll like receptor 7 (TLR7) [36] is very important.

The expression level of TLR7 in innate immune cells, is higher in women than in men leading to a higher immune response and viral infection resistance. TLR7 recognizes single strand RNA virus promoting the production of antibodies against the virus. Of note, in COVID-19 the presence of high levels of IL-6 and other inflammatory cytokines (the cytokine storm) is associated with a worse prognosis [37].

Interestingly, in women the production of inflammatory IL-6 after viral infection is lower than in males and is often correlated with a better longevity [38].

Risk factors

According to Italian data published on April 6th 2020 by the Istituto Superiore di Sanità (ISS), an overall prevalence of obesity of 10.0% was found among 1290 deceased patients, for whom medical records were available [39]; likewise, 72.1% of 775 patients in UK, with confirmed COVID-19 were overweight or obese and among patients with BMI >30 who had undergone intensive care, 60.9% of them died, according to the Intensive Care National Audit & Research Centre (ICNARC) report on COVID-19 in critical care of United Kingdom (27 March 2020) [40]. These data suggest that obesity may be a risk factor for severe COVID-19 infection. Actually, obesity induces the immune dysregulation that appears, at least in part, to mediate the progression to critical illness and organ failure in a proportion of COVID-19 patients. In addition, increased levels of circulating pro-inflammatory cytokines, such as TNF-α, IL-6, or C-reactive protein, have been reported in overweight and obese adult individuals. This may be a pro-inflammatory milieu that could be further exacerbated by COVID-19, possibly explaining the increased risk of severe outcome of COVID-19 in obese subjects. Given that overall more women are obese than men in developing countries, treatment of COVID-19 patients should be aware of the associated risk [41,42].

Smoking could be another risk factor of COVID-19 disease. It is related to higher expression of ACE2 [43]. The study conducted by Cai [44] did not find significant disparities in ACE2 gene expression between Asian and Caucasian groups, patients older and younger than 60 years, and men and women. This study observed significantly higher ACE2 gene expression in former smoker's lung compared to non-smoker's lung and found higher

ACE2 gene expression in Asian current smokers compared to non-smokers but not in Caucasian current smokers. In the studies conducted by Zhang [13] and by Guan [12] the percentage of current smokers' patients was low (1,4 and 12,6, respectively) and could not explain the association between smoking and the prevalence of SARS-CoV-2. However, Guan's study [12] there was an association between smoking and the severity of COVID-19 (11.8% of patients with non-severe disease were smokers *vs* 16.9% with severe disease), but this data was not significative. For this reason other studies are needed to clarify the relation between smoking and prevalence or severity of COVID-19.

Hypovitaminosis D represents a risk factor for viral acute respiratory infection and COVID-19 [45]. In particular, vitamin D has three main mechanisms by which it reduces the risk of viral infection [46]. The first one consists in the physical barrier: vitamin D contributes to maintain junction integrity that could be broken by viruses. The second one regards the role of vitamin D in the enhancement of innate immunity and in the induction of antimicrobial peptide production, such as human cathelicidin, LL-3, and defensins [47]. Finally, vitamin D reduces the cytokine storm induced by the innate immune system, inhibiting the expression of pro-inflammatory cytokines and increasing the expression of anti-inflammatory cytokines [48].

The inter-individual variance in vitamin D status could be involved in pulmonary inflammation and viral pathogenicity [49]. To note, serum vitamin D levels decrease with age, and this may be linked to the increased lethality of COVID-19 with age. Moreover, vitamin D levels were significantly reduced in both men and women with obesity. However, compared to women, serum vitamin D was consistently lower in men, irrespective of obesity and type 2 diabetes [50]. Hence, a link among vitamin D, gender, and COVID-risk should be considered and vitamin D supplements could be a valid adjuvant for prevention of this severe infection, in particular in elderly men [51].

Clinical presentation

In a multicenter European study [52] including 417 patients, the mean age was 36.9±11.4 years (range 19–77) and 263 females and 154 males were enrolled: European (93.3%), South American (2.7%), Sub-Saharan African (2.2%), Black African (1.4%), Asian (0.2%), and North American (0.2%). The females were proportionally more affected by hyposmia or anosmia compared to males (p<0.001). Similar results were found for gustatory dysfunction (p=0.001). There are no gender-related data of eyes' involvement.

The retrospective study of Mo [53] included 155 patients with confirmed COVID-19 and showed that the patients with "refractory" COVID-19 were often male with manifestations of anorexia and fever on admission. Those patients received oxygen, expectorant and adjunctive agents (p<0.05) when considering the factors of disease severity on admission, mechanical ventilation, and ICU transfer.

Comorbidities

In the study conducted by Grasselli in Lombardy (Nothern Italy) [16] hypertension was the most common comorbidity (49%), followed by the cardiovascular disease (21%), hypercholesterolemia (18%) and diabetes (17%). Those data were similar to two Chinese studies [4,12] in which a history of chronic obstruc-

tive pulmonary disease was only reported in 4% of the patients, *i.e.* more hypertensive, significantly older and died in the intensive care unit (ICU) patients.

A review conducted by Cheng [21] underlined that the poor prognosis of patients with COVID-19 was related to factors such as male sex, age >60 years, underlying diseases (hypertension, diabetes and cardiovascular disease) and complicating secondary acute respiratory distress syndrome (ARDS). Although COVID-19 is predominantly a respiratory illness, a large number of COVID-19 patients exhibit severe cardiovascular damage and those with pre-existing CVD appear to have an increased risk of death.

Individuals with diabetes mellitus had also a significantly increased risk of hospitalization and death in the pandemic COVID-19. It was not fully understood if diabetes constitutes an increased risk of infection but it was known that individuals with diabetes had a dysregulated immune system and were more susceptible to infections. Moreover, type 2 diabetes had been associated with reduced ACE2 activity in late diabetes [54].

The sex differences in clinical outcomes could also be cause by pre-existing comorbidities, such as hypertension, cardiovascular disease and diabetes, which were almost always present in severe and lethal COVID-19 cases and tended to be more frequent and more severe in men [55].

Diagnosis

In the study conducted by Liu [56], 4880 cases (2251 male and 2629 female) with respiratory infection symptoms or close contact with COVID-19 patients in hospital in Wuhan were tested for SARS-CoV-2 infection by the use of quantitative RT-PCR (qRT-PCR) on samples from the respiratory tract. The positive rate was significantly higher in men (40.43%) than in women (36.71%) and increased from 24.9% (age 18-30) to 61.81% (age >70), confirming that male patients and older population had significant higher positive rates.

Prognosis and mortality

Based on the available data, older male adults and people of any age who have chronic underlying morbidities might be at higher risk for severe illness and fatal outcome from COVID-19.

The meta-analysis conducted by Li [11] suggested that the discharge rate of patients with COVID-19 was 52%, with a fatality rate of 5%. 31.5% of the deceased patients were frail and had one or more of the following cases: advanced age (>60 years), cancer, more underlying diseases, or major infections.

The retrospective study conducted by Zhou *et al*. [10] showed that the female fatality rate was 30%, while that of the males was 70% and confirmed that death, in patients with COVID-19, was associated with increased age.

The retrospective study conducted by Chen [57] recruited 799 inpatients of whom 113 died, with a mortality rate of up to 14.1%, and 161 were discharged. The median age of deceased patients (68 years) was significantly older than total recovered patients (51 years). The male sex was more predominant in deceased patients (83; 73%) than in recovered patients (88; 55%). Chronic hypertension (48%) and other cardiovascular comorbidities (14%) were more frequent among deceased patients than recovered patients (24% and 4%, respectively).

The prospective study conducted on COVID-19 pneumonia by Du [58] included a total of 179 patients (54,2% M, 45,8% F) with a mean age that was 57.6 years. Survivors were 158 (88.8%) of whom male (55.1%) and female (44.9%). Mortality in male patients was 47.6% and in female patients 52.4%. The patients in the deceased group were much older than those in survivor group (70.2±7.7 years *versus* 56.0±13.5 years, p<0.001). The authors identified four risk factors: age ≥65 years, preexisting concurrent cardiovascular or cerebrovascular diseases, $CD3^+CD8^+$ T cells ≤75 cell μl^{-1}, and cardiac troponin I ≥0.05 ng·ml^{-1}; the latter two factors were better predictors for mortality in COVID-19 pneumonia patients.

Dudley *et al.* [59] showed in China a peak morbidity in the 50-59 years cohort, while in the Republic of Korea in the 20-29 years cohort. In the systematic review of Fu *et al.* [60] the overall estimated proportion of severe cases and case-fatality rate was 25.6% and 3.6% respectively. The case fatality rate and laboratory abnormalities were higher in severe cases, in patients from Wuhan, and in older patients, but did not differ by sex. The report of the WHO-China Joint Mission on COVID-19 [14] confirmed that the mortality rate was greater in males (4.7 %) than in females (2.8%). The Korean Report [15] showed that the case fatality rate increased with older age. The case fatality rate of persons 50 years or older was higher than that of persons younger than 50 years (1.2% *vs* 0.2%, p=0.0017). There were no sex differences.

In Italy, deaths are similar to China with fatalities mostly in the elderly with known comorbidities [61]. According to the ISS report [62] based on available data on May 7th, the mean age of patients dying for COVID-19 was 80 years (median age 81 years) and women were 39.1%. Deceased women had an older median age than men (85 *vs* 79 years). There were no sex differences about the most common pre-existing chronic pathologies in deceased patients.

Conclusions

In our review we underlined that in China men were more infected by COVID-19 than women. Most patients were aged 30–79 years, and men with underlying diseases, including diabetes, hypertension and cardiovascular disease developed severe condition with an increased mortality rate. Instead in Korean outbreak, two peaks of age groups were described: 20 years and 50 years, with a predominance in the age group of the 20-year-olds. Predominance in the age group of the 20 year-olds and females may be linked to the outbreak in a religious group in Daegu; moreover, the case fatality rate of persons 50 years or older was higher than that of persons younger than 50 years.

In Italy, in particular in Lombardy region, men were more infected by COVID-19 than women, the median age was 63 years and deaths are similar to China with deaths mostly in the elderly with known comorbidities. Many factors can contribute to disparity in sex-specific disease outcomes such as sex-specific steroids and activity of X-linked genes which modulate the innate and adaptive immune response to virus infection and influence the immune response. Moreover, the male predominance in the COVID-19 pandemic could partially be explained by TMPRSS2. The females were proportionally more affected by hyposmia or anosmia and gustatory dysfunction compared with males. There were not available data about eyes' involvement. The sex differences in clinical outcomes could be also caused by pre-existing comorbidities, such as hypertension, cardiovascular disease and diabetes, which were almost always present in severe and lethal COVID-19 cases and tended to be more frequent and more severe in men.

Because a specific treatment is not yet available, more clinical and basic research regarding gender and other prognostic factors for individualized risk assessment and management strategies are crucial. Currently, there is only data available on the sex indicator for admitted or deceased patients. There is no data about domestic isolation and there is no analysis about other gender indicators.

The data considered in our study are the only currently available in the literature, but it is appropriate to implement a specific analysis with all gender indicators to identify appropriate strategies. Moreover, the evaluation of the health service efficacy is a key element in determining gender outcomes.

In our opinion, it is very important to carry out a gender analysis of data about COVID-19 as well as other specific studies to evaluate gender differences. Knowing the gender differences in COVID-19 outbreak would be a fundamental tool to understand the effects of a health emergency on individuals and communities as well as to carry out effective and equitable policies, public health measures and targeted solutions.

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