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# Characteristics of COVID-19 cases in Italy from a sex/gender perspective

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**Abstract**

***Introduction.*** Coronavirus disease 19 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). To date, few data on clinical features and risk factors for disease severity and death by gender are available.

***Aim.*** The current study aims to describe from a sex/gender perspective the characteristics of the SARS-CoV-2 cases occurred in the Italian population from February 2020 until October 2021.

***Method and results.*** We used routinely collected data retrieved from the Italian National Surveillance System. The highest number of cases occurred among women between 40 and 59 years, followed by men in the same age groups. The proportion of deaths due to COVID-19 was higher in men (56.46%) compared to women (43.54%). Most of the observed deaths occurred in the elderly. Considering the age groups, the clinical outcomes differed between women and men in particular in cases over 80 years of age; with serious or critical conditions more frequent in men than in women.

***Conclusions.*** Our data clearly demonstrate a similar number of cases in women and men, but with more severe disease and outcome in men, thus confirming the importance to analyse the impact of sex and gender in new and emerging diseases.

**Key words**

- gender
- sex
- COVID-19
- SARS-CoV-2 infection
- coronavirus
- public health

## INTRODUCTION

Coronavirus disease 19 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a newly discovered human coronavirus. It was first reported in December 2019 in China [1], and then spread rapidly worldwide, being declared by the World Health Organization (WHO) a public health emergency of international concern on 30 January 2020 [2]. As to date (30 July 2021) it caused about 200 million cases and more than 4 million deaths worldwide. Most people affected by COVID-19 develop a mild to moderate respiratory illness and they recover without any specific treatment. However, older people and those with pre-existing and/or underlying medical problems, like cardiovascular disease, diabetes, obesity, chronic respiratory disease, and cancer are more likely to develop severe respiratory illness that often requires admission to an intensive care unit (ICU) [1].

Global data strongly indicates that a sex/gender-based disparity exists, with men being at higher risk of infection by SARS-CoV-2, hospitalisation, poor clinical outcomes and death due to COVID-19 than women [3]. Several international studies have reported a male/female ratio of COVID-19 infections and a Case Fatality Rate (CFR, percentage of deaths out of the number of observed cases of infection) that are higher in men as compared to women [4, 5]. In particular, two epidemiological studies from 38 countries reported a mean CFR in men 1.7 times higher than in women [6, 7]. In addition, long-term COVID-19 outcomes after intensive care unit (ICU) admission are worse in critically ill men compared to their female counterparts [8]. Similar sex-based disparities have been previously observed with the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) epidemics [9, 10].

Many factors can contribute to the disparity in disease outcomes observed between adult men and women, including intrinsic differences in innate and adaptive immunity, the role of sex hormones, as well as gender specific differences in behaviours [11]. All these factors confer a protective advantage against COVID-19 to women, which have been reported to have lower viral loads, lesser inflammation, better clinical outcomes and lower mortality as compared to men. Furthermore, it is

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also important to underline that sex differences in COVID-19 clinical outcomes could reflect the difference between women and men in pre-existing comorbidity rates.

To date, data on clinical features and risk factors for disease severity and death in infants, children, and adolescents are still limited, while sex/gender analyses and comparisons with clinical characteristics, disease progression, and outcome, in both adults and children, are almost completely missing. However, it has recently been suggested that male gender is not an independent risk factor of severe COVID-19 in children [12]. Children appear to be less commonly affected by SARS-CoV-2 infection than adults, with a clinical course milder than adults [13, 14], even if a minority of children with COVID-19 require hospitalization, and severe cases have also been reported [15].

Collection, integration and sharing of disaggregated epidemiological data must be promoted to allow the analysis of the risk factors associated to COVID-19, including those related to sex and gender. This could help in the development of adequate therapeutic protocols, more targeted care and prevention strategies for specific groups of patients and population.

In this vein, the current study aims to describe from a sex perspective the characteristics of the SARS-CoV-2 cases occurred in the Italian population from the beginning of its spread in February 2020 until 31 May 2022, and provides insight into sex related issues to explain the disease dynamic in the Italian population.

## MATERIAL AND METHODS

### *Data sources*

We used routinely collected data retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections until 31 May 2022. The Istituto Superiore di Sanità coordinates this system, established on 27 February 2020. Data are collected and entered daily on a secure online platform by the 19 Italian regions and the two Autonomous Provinces (AP), according to an increasingly harmonized track-record [16]. As previously described [17], this surveillance system collects data on all SARS-CoV-2 confirmed cases, following the international case definition that considers as a confirmed case any person with laboratory confirmation of SARS-Cov-2 virus, irrespective of clinical signs and symptoms [18]. Data collected include information on the demographics, clinical outcomes, date of diagnosis, and geographical area of diagnosis. All records are checked for inconsistencies and duplicate by the coordinating centre. The scientific dissemination of anonymised COVID-19 surveillance data was authorised by the Italian Presidency of the Council of Ministers, thus no specific ethics approval was needed.

Data on co-morbidities were available only for deceased patients, for whom a detailed analysis of medical records was carried out by experienced clinicians.

### *Study population and endpoints*

The cases were divided by age from 0 to 90 and over in ten age groups. The case distributions in the study period (epidemic curve) were made by dates of diagnosis and symptom onset. The primary outcome of the study was to outline the epidemiological and clinical characteristics of COVID-19 cases in Italy by sex.

The epidemiological characteristics described were:

1. distribution of the cases in the study period (epidemic curve) and reporting rate of infections (n. of reported cases per 1,000 inhabitants) by region, age and sex;
2. CFR as percentage of deaths among the cases, in general and by age and sex.

Basic clinical information was routinely collected by public health officers through telephone interviews to the cases, usually at the beginning of the quarantine and at the end. Symptoms were self-reported by cases during telephone interview. Clinicians assessed patients with more severe disease. The clinical severity was classified as:

- *asymptomatic*: a case positive to the SARS-CoV-2 molecular testing but without clinical signs;
- *mild:* a case with stable and within normal limit vital signs, and excellent indicators for recovery;
- *severe*: according to WHO (www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2), severe COVID-19 was defined as the presence of any of the following: oxygen saturation <90% on room air; in adults, signs of severe respiratory distress and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) in addition to the signs of pneumonia;
- *critical*: according to WHO critical COVID-19 was defined by the presence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

A patient was considered recovered from the infection if tested negative to a follow up swab.

### *Statistical analysis*

We described the main demographic and clinical characteristics and the distribution of cases over time by sex using counts with percentages and median for categorical and continuous variables, respectively. The comparison by sex and age groups of the main endpoints using Chi-square tests for categorical variables to detect the significant differences ($p < 0.05$) between groups. The statistical package used for the analysis was Stata 16.1 (StataCorp 4905 Lakeway Drive, College Station, Texas 77845 USA). The infection rates were calculated by using the data on the January 1st 2020 Italian population divided by sex and age groups provided by the Italian National Institute of Statistics (www.istat.it/en/). CFR, not accounting for delays, were calculated by age and sex. Chloropleth maps were built with QGIS version 3.10 (https://qgis.org).

## RESULTS

In the period 17 February 2020 to 31 May 2022 in Italy 17,542,535 cases of COVID-19 and 164,071 deaths among cases were reported. On 31 May, 15,448,821 out of 17,542,535 (88.06%) recovered from the infection.

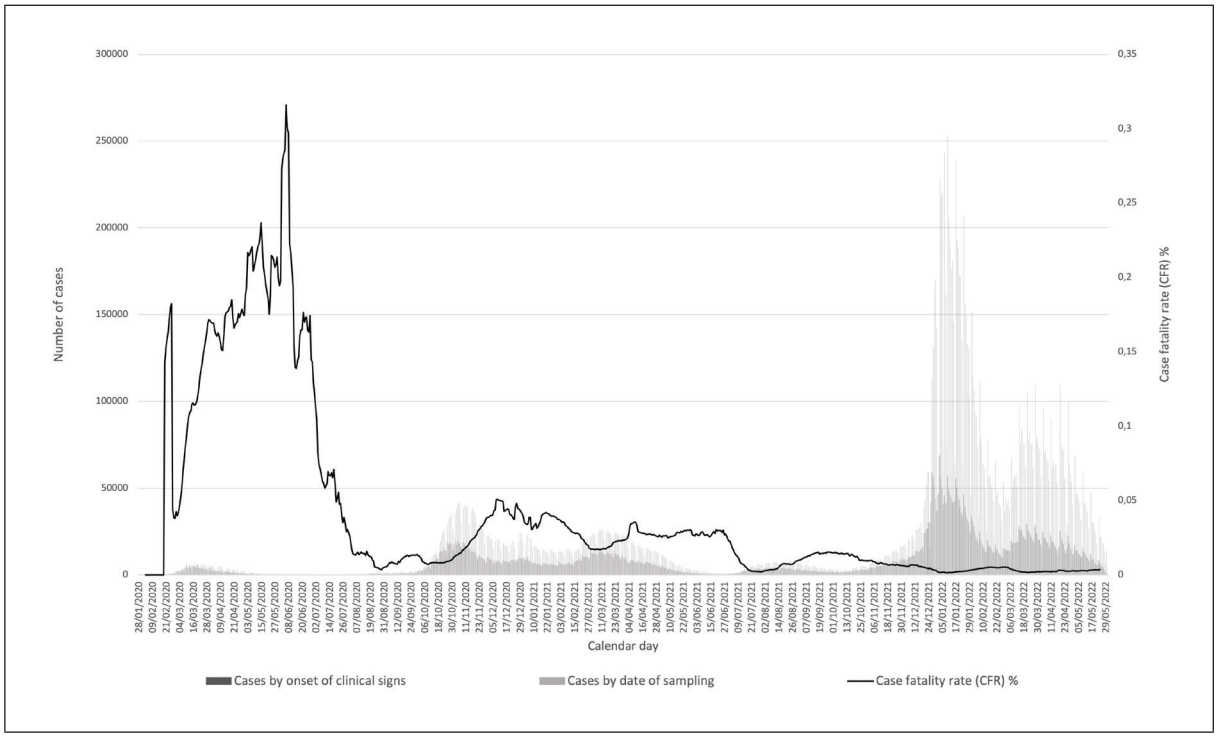


**Figure 1**
SARS-CoV-2/COVID-19 infections from 17 February 2020 to 31 May 2022 in Italy.
Number of cases of SARS-CoV-2/COVID-19 infection diagnosed from 17 February 2020 to 31 May 2022 in Italy (Data from the Italian National Surveillance System of confirmed SARS-CoV-2 infections, Istituto Superiore di Sanità). The number of cases are reported by date of sampling (light grey) and by onset of clinical signs (dark grey). The black line represents the percentage of case fatality rate (CFR).

The distribution of the COVID-19 cases in Italy by date of symptoms onset and by date of sampling is shown in *Figure 1*. As observed in most of the Western European countries, also in Italy the epidemic showed five main waves, with the peak in January 2022. The relatively low number of cases during the first pandemic wave was due to the shortage of diagnostic tests, which were conducted mainly in symptomatic patients. On the contrary, from July 2020 the availability of more testing options (molecular and antigenic) and the abundance of diagnostic kits allowed to extend the screening to positive case contacts and suspected people, even if asymptomatic, consequently the number of positive cases increased. The trend of the weekly-diagnosed cases was similar in male and female patients throughout the observation period, except for the first three months, when there was first an increase in male cases, immediately followed by an increase in female ones (data not shown).

The cumulative COVID-19 infection rate assessed by Italian region *(Figure 2)* showed that the North Western regions were the most affected by the pandemic while the Southern regions were those where the virus circulated the less. The only exception is Valle d'Aosta, the smallest Italian region located in the North-West, mostly covered by Alps Mountains.

The median age of diagnosed cases was 45 years, with no differences between males and females except for the initial period between March and April 2020, when the median age was significantly higher in female (80 years) with respect to male (70 years).

The proportion of the 164,130 deaths due to COVID-19 was higher in men (55.94%) compared to women (44.06%), with the highest number of deaths observed in males aged 80-89 (35,572) *(Table 1)*.

The overall reporting rate in Italy was 290.70 cases/1000 inhabitants, with the highest one (406.67) observed in women aged 10-19. The reporting rates were statistically different between males and females in each age group, as shown in *Table 1*.

The overall CFR was 0.93%, however great differences were observed when age and sex were considered *(Table 1)*. The CFR was substantially <1% in both sexes until the age of 50 years. Over 50 years, the CFR was always higher in men than in women, and this difference increased according to age (from 2.67% at 70 years to 7.66% at 90 years).

From January 2021 the vaccination campaign started and the CFR decreased in both sexes, in particular from July 2021, when the administered vaccine doses were more than 25 million.

In a subset of 8,436 deceased SARS-CoV-2 patients the most common comorbidities diagnosed before the infection were described *(Table 2)*. The mean number of comorbidities was 3.7 (median = 3, SD = 2.1). Overall, 2.9% of the patients presented no comorbidities, 11.3% one comorbidity, 17.9% two, and 67.8% three or more comorbidities. In women (n = 3,424) the average num-

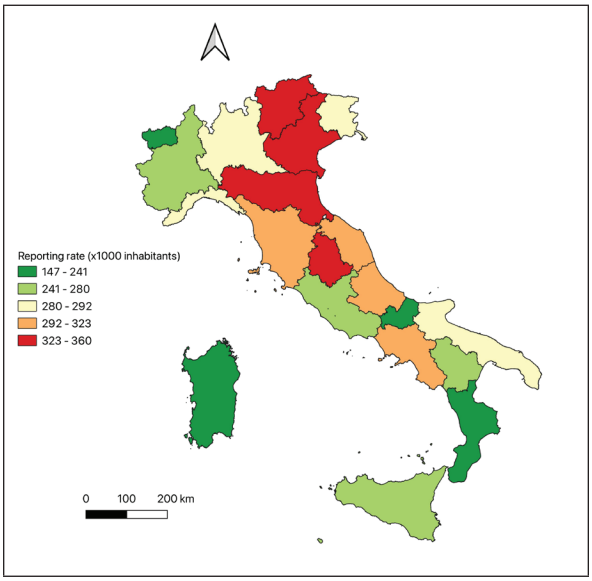


**Figure 2**
COVID-19 cumulative notification rate in Italy.
Choropleth map of the COVID-19 cumulative notification rate in Italy from 17 February 2020 to 31 May 2022.

ber of observed pathologies is 3.9 (median = 4, range 0-12) while in men (n = 5012) is 3.6 (median = 3, range 0-12).

By comparing the frequency of the main comorbidities, the main differences between women and men were observed for ischemic heart disease (23.66% in women and 31.30% in men, p <0.01), dementia (31.98% in women and 17.80% in men, p >0.01) and autoimmune diseases (6.45% in women and 3.51% in men, p >0.01).

In *Table 3*, the total number and the percentage of the different clinical outcomes in COVID-19 patients according to age and sex are reported.

Overall, a higher number of serious and critical cases occurred among men, while asymptomatic and mild cases were more among women. However, considering the age groups, among over 80 years of age the clinical severity was more frequent in women than in men (44.50% of the female severe cases *vs* 35.11% of the male ones; p <0.01). On the contrary, our results showed a higher percentage of male severe cases with respect to female ones, between 40-79 years (57.05% *vs* 43.95%; p <0.01). The reason beyond these two apparently contrasting claims is probably due to the hormonal protection that women have during their fertile period, which disappears after menopause, as treated in the discussion section.

We also observed that in people under 20 years of age the percentage of asymptomatic or mild cases was 99.60%, but this percentage decreased over the age groups, with the lowest value in males over 90 years of age *(Figure 3)*.

## DISCUSSION

In this study, we used data retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections to elucidate features of COVID-19 infection that differ between male and female patients in terms of exposure and outcomes. Our data are consistent with previous reports clearly demonstrating a similar number of cases in women and men, but with more severe disease in men [19-21].

The overall number and proportion of cases of COVID-19 were slightly higher in women than in men, with greatest difference in the age groups from 20 to 60 years. This last result was quite unexpected because women were more likely to agree with the COVID-19 restriction measures and more compliant with such

**Table 1**
COVID-19 deaths, notification rates and case fatality rate by sex and age in Italy

| Age groups | Cases | | | Deaths | | | Reporting rate (x1000) | | | Case fatality rate (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Female | Male | Total | Female | Male | Total | Female | Male | Total | Female | Male | Total |
| 0-9 | 796,775 | 854,017 | 1,650,792 | 16 | 11 | 27 | 322.139 | 326.323* | 324.290 | 0.002 | 0.001 | 0.002 |
| 10-19 | 1,133,915 | 1,140,688 | 2,274,603 | 14 | 16 | 30 | 406.673 | 382.704* | 394.289 | 0.001 | 0.001 | 0.001 |
| 20-29 | 1,089,962 | 1,015,641 | 2,105,603 | 42 | 79 | 121 | 364.650 | 316.182* | 339.544 | 0.004 | 0.008 | 0.006 |
| 30-39 | 1,302,050 | 1,090,096 | 2,392,146 | 158 | 259 | 417 | 370.420 | 306.280* | 338.150 | 0.012 | 0.024 | 0.017 |
| 40-49 | 1,568,264 | 1,300,867 | 2,869,131 | 500 | 1,059 | 1,559 | 337.343 | 283.180* | 310.423 | 0.032 | 0.081 | 0.054 |
| 50-59 | 1,412,128 | 1,242,534 | 2,654,662 | 1,769 | 4,236 | 6,005 | 295.819 | 271.378* | 283.853 | 0.125 | 0.341 | 0.226 |
| 60-69 | 843,040 | 776,569 | 1,619,609 | 4,873 | 11,857 | 16,730 | 220.335 | 221.179* | 220.739 | 0.578 | 1.527 | 1.033 |
| 70-79 | 563,582 | 531,503 | 1,095,085 | 13,538 | 26,926 | 40,464 | 174.185 | 194.904* | 183.661 | 2.402 | 5.066 | 3.695 |
| 80-89 | 394,506 | 287,615 | 682,121 | 30,376 | 35,572 | 65,948 | 182.676 | 206.035* | 191.847 | 7.700 | 12.368 | 9.668 |
| 90 and over | 148,654 | 54,034 | 202,688 | 21,015 | 11,782 | 32,797 | 263.011 | 258.131* | 261.692 | 14.137 | 21.805 | 16.181 |
| Not known | 99 | 105 | 204 | 15 | 17 | 32 | | | | | | |
| **Total** | 9,252,975 | 8,293,669 | 17,546,644 | 72,316 | 91,814 | 164,130 | 298.726 | 282.244* | 290.702 | 0.782 | 1.107 | 0.935 |

Distribution of the number of cases of COVID-19, deaths, infection rates (number of cases/ population), and case fatality rate by sex and age group from17 February 2020 to 31 May 2022 in Italy. Asterisk indicate statistically significant differences between female and male age groups (p>0.01).

**Table 2**
Comorbidities by sex in SARS-CoV-2 positive deceased patients in Italy

| | Total cases | | Women | | Men | |
|---|---|---|---|---|---|---|
| **Number of comorbidities per patient** | **N** | **%** | **N** | **%** | **N** | **%** |
| No comorbidities | 246 | 2.9 | 67 | 2.0 | 179 | 3.6 |
| 1 comorbidity | 955 | 11.3 | 337 | 9.8 | 618 | 12.3 |
| 2 comorbidities | 1,512 | 17.9 | 586 | 17.1 | 926 | 18.5 |
| 3 comorbidities and more | 5,723 | 67.8 | 2,434 | 71.1 | 3,289 | 65.6 |
| **Comorbidities** | **N** | **%** | **N** | **%** | **N** | **%** |
| Ischemic heart disease | 2,379 | 28.2 | 810 | 23.7 | 1,569 | 31.3 |
| Atrial Fibrillation | 2,114 | 25.1 | 901 | 26.3 | 1,213 | 24.2 |
| Heart failure | 1,349 | 16.0 | 623 | 17.8 | 726 | 14.2 |
| Stroke | 950 | 11.3 | 419 | 12.2 | 531 | 10.6 |
| Hypertension | 5,550 | 65.8 | 2,327 | 68.0 | 3,223 | 64.3 |
| Type 2-Diabetes | 2,459 | 29.1 | 934 | 27.3 | 1,525 | 30.4 |
| Dementia | 1,987 | 23.6 | 1,095 | 32.0 | 892 | 17.8 |
| COPD (Chronic Obstructive Pulmonary Disease) | 1,476 | 17.5 | 487 | 14.2 | 989 | 19.7 |
| Active cancer in the past 5 years | 1,362 | 16.1 | 490 | 14.3 | 872 | 17.4 |
| Chronic liver disease | 427 | 5.1 | 145 | 4.2 | 282 | 5.6 |
| Dialysis | 198 | 2.3 | 66 | 1.9 | 132 | 2.6 |
| HIV Infection | 19 | 0.2 | 2 | 0.1 | 17 | 0.3 |
| Autoimmune diseases | 397 | 4.7 | 221 | 6.5 | 176 | 3.5 |
| Obesity | 981 | 11.6 | 391 | 11.4 | 590 | 11.8 |

Distribution by sex of the main comorbidities diagnosed before SARS-CoV-2 infection in a representative subset of SARS-CoV-2 positive deceased patients (n=8436) in Italy.

**Table 3**
Clinical severity of COVID-19 cases by sex and age in Italy

| **Clinical severity** | **Age group (years)** | | | | | | | | | | **TOTAL** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **0-9** | **10-19** | **20-29** | **30-39** | **40-49** | **50-59** | **60-69** | **70-79** | **80-89** | **90 and over** | **Not known** | |
| **Asymptomatic** | 9.72% | 13.03% | 11.24% | 13.12% | 14.86% | 15.44% | 10.17% | 6.92% | 4.24% | 1.26% | 0.00% | 948,037 |
| Female | 8.82% | 12.44% | 11.11% | 13.42% | 15.33% | 15.57% | 10.16% | 6.84% | 4.63% | 1.68% | 0.00% | 502,704 |
| Male | 10.74% | 13.69% | 11.39% | 12.78% | 14.32% | 15.28% | 10.20% | 7.01% | 3.80% | 0.78% | 0.01% | 445,333 |
| **Mild** | 9.90% | 12.70% | 10.65% | 12.78% | 15.60% | 15.82% | 9.68% | 6.90% | 4.63% | 1.34% | 0.00% | 334,800 |
| Female | 8.82% | 11.96% | 10.57% | 13.30% | 16.32% | 16.10% | 9.61% | 6.76% | 4.84% | 1.72% | 0.00% | 183,198 |
| Male | 11.21% | 13.60% | 10.76% | 12.16% | 14.73% | 15.47% | 9.76% | 7.06% | 4.38% | 0.88% | 0.00% | 151,602 |
| **Severe** | 2.61% | 1.36% | 1.99% | 3.62% | 5.08% | 9.71% | 14.05% | 21.96% | 29.59% | 10.05% | 0.00% | 6,777 |
| Female | 2.29% | 1.42% | 2.87% | 4.97% | 4.48% | 7.91% | 11.64% | 19.92% | 31.90% | 12.60% | 0.00% | 3,238 |
| Male | 2.91% | 1.30% | 1.19% | 2.37% | 5.62% | 11.36% | 16.25% | 23.82% | 27.47% | 7.71% | 0.00% | 3,539 |
| **Critical** | 1.43% | 1.43% | 1.43% | 3.17% | 6.95% | 16.04% | 23.19% | 25.33% | 17.26% | 3.27% | 0.51% | 979 |
| Female | 0.81% | 1.89% | 1.89% | 3.50% | 8.36% | 13.75% | 22.37% | 22.37% | 19.68% | 4.58% | 0.81% | 371 |
| Male | 1.81% | 1.15% | 1.15% | 2.96% | 6.09% | 17.43% | 23.68% | 27.14% | 15.79% | 2.47% | 0.33% | 608 |
| **Total** | 9.72% | 13.03% | 11.24% | 13.12% | 14.86% | 15.44% | 10.17% | 6.92% | 4.24% | 1.26% | 0.00% | 2,581,186 |

Clinical severity of COVID-19 cases (in percentage) by sex and age group from 17 February 2020 to 31 May 2022 in Italy (details available for 2581186 cases).

measures than men, according to a recent international survey that included also Italy [22]. Behaviours, occupations, and societal and cultural norms may account for these differences in exposure to SARS-CoV-2 [23]. Indeed, women may have greater exposure then men, probably in relation to their social role of caregivers [19]: about 70% of health and social care workforce are women including frontline healthcare workers [24]. Moreover, women are more likely to care for children and/or other relatives in case of illness [25].

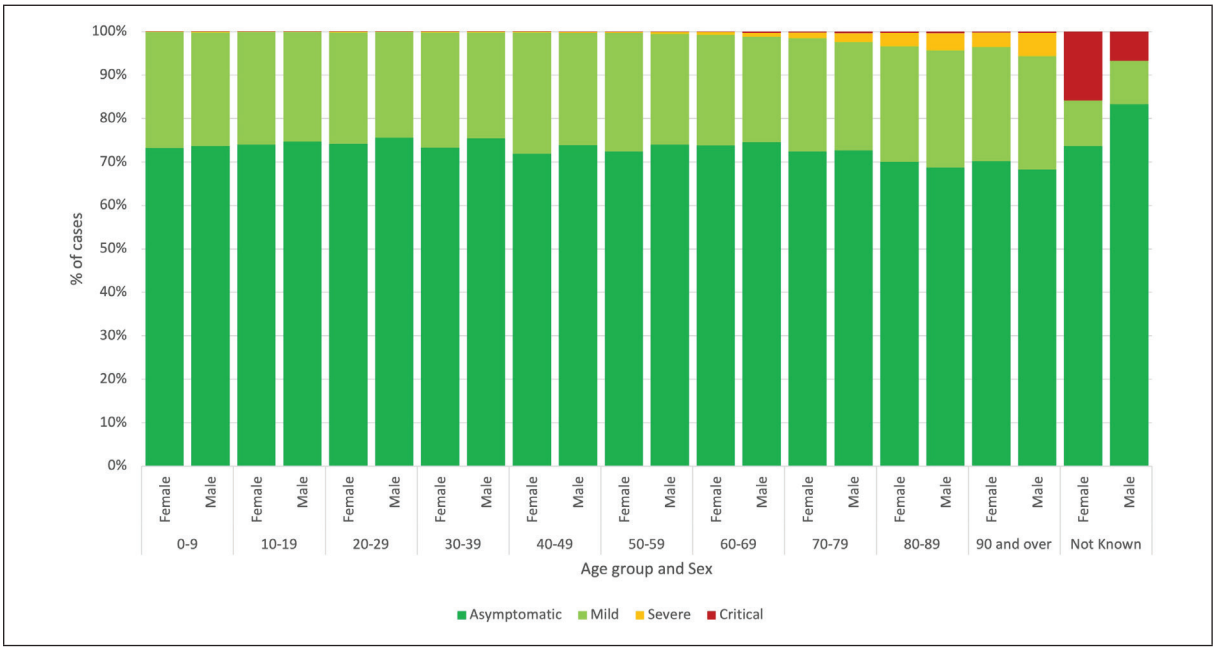


**Figure 3**
COVID-19 clinical cases by age and sex in Italy.
Percentage of COVID-19 cases by clinical severity, age group and sex in Italy from 17 February 2020 to 31 May 2022.

In the general population, we found that the infection rate was higher in women, but changed over 60 years of age, with higher proportion in men than in women. The different infection rate in the over 60 population could be due to both the lower perception of risk and the lower compliance with the restrictive measures of men compared to women. Furthermore, the health conditions of women in this age group are often worse, or perceived as worse than men, causing women to be more concerned about COVID-19 and consequently more compliant with the rules [22]. We also showed that the median age of diagnosed cases in Italy was different in male and female patients only during the first months of SARS-CoV-2 infection, when it was significantly higher in female. This was probably due to a number of outbreaks that occurred in Residential Care Facilities, where the people hosted were mainly elderly women, because of their longer life expectancy than men [26].

This different life expectancy among sexes may play thus a key role in the higher SARS-CoV-2 infections in Italy in women over 90 years of age, which is almost three times higher than in men.

According with previous reports, we found that, despite an equal distribution between men and women, the prevalence of severe symptoms and mortality rate are higher in male patients than in female ones [1, 27]. The Global Health 50/50 research initiative presented results of the Covid-19 sex-disaggregated data worldwide, clearly demonstrating an increased CFR in men in the majority of countries [4]. Our results confirmed that CFR in Italy was higher in men than in women, with significant difference over the 50 years of age. Moreover, a higher percentage of critically diseased men were reported in all the age groups studied, except in over 80 years group, where the greater number of older women affected the results.

Variations in disease severity and mortality rates were suggested to be associated with both gender (sociocultural) and sex (biological) differences [19]. Some social and behavioural habits more common in Italy among males, such as tobacco and alcohol consumption, are closely associated with COVID-19 comorbidities, including cardiovascular and lung diseases [6] and may account for some gender differences.

Sex-related genetic and hormonal factors and different immunological responses may also play a role in the sex bias in COVID-19 patients [28]. Unfortunately, we could not assess the level of sex hormones in the examined cohort because biological samples were not available. However, data from scientific reports strongly suggest that the poorer outcome in men can be explained by the intrinsic differences in innate and adaptive immunity as well as in sex hormones [29]. In particular, a lower testosterone concentration, that is typical of elderly men, has been considered among the risk factors for poor outcomes. The severity of COVID-19 illness, indeed, seems to coincide with the nadir of lifetime testosterone; furthermore, the comorbidities that predispose individuals to increased COVID-19 severity were associated with lower testosterone concentrations [30]. It was also demonstrated that increased estradiol to low testosterone ratio was associated with disease severity, inflammation and mortality in men with COVID-19 [31]. Moreover, a retrospective cohort study [32], showed that high estradiol and low testosterone levels were associated with critical illness in male but not in female COVID-19 patients, thus confirming that disturbance of sex hormone metabolism might represent a hallmark in critically ill men affected by COVID-19.

These results provide a possible explanation for the highest CFR in men over fifty years of age found in the present study.

Finally, our findings on children/adolescent COVID-19 patients confirmed recent results [33] showing that they have milder symptoms compared to adult (more than 99% of the cases under 19 years were asymptomatic or with mild symptoms). The reason for this finding is still unclear, but it could be related to a lesser development, at a younger age, of the angiotensin-converting enzyme (ACE) receptors, the recognised cellular receptor of the SARS-CoV-2 spike protein [34]. Moreover, since a cytokine storm has been involved in the pathogenesis of severe forms of the disease in adults [35], it has been hypothesized that children may have a weaker immune response to SARS-CoV-2 compared with adults [36].

In contrast with adults, in whom older age is an independent risk factor for severity and mortality, very young age seems to be a risk factor for severity in children [12]; however, sex/gender analyses in children are still very scarce.

Our analyses showed some limitations, mainly due to the data access constraint for privacy and data protection reasons. The level of detail in the data did not permit any additional inference about the role of sex and gender in the risk of severe illness and death. On the other hand, our analyses can provide insight into the risk of disease in the different age and sex groups, and speculate on some social and biological aspects potentially related to such risks.

Data collected from the Italian integrated COVID-19 surveillance system during the initial phase of the emergency presented some shortcomings, mainly related to lack of completeness. For this reason, the number of cases during the first pandemic are relatively low. In addition, not all regions reported the date of sampling at the beginning of the outbreak and when missing, we used date of diagnosis to construct epidemic curves. This has limitations because there is a lag between diagnostic sampling and confirmation of laboratory results. However, this interval is expected to be limited to 2-3 days and not to bias excessively the presentation of the time distribution of cases.

In conclusion, our data, retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections until 31 May 2022, further confirm the importance of integrating a sex/gender analysis into future studies, to better understand the complex interaction among sex/gender, age and disease exposure/outcomes. Preparedness and intervention plans for future pandemics should take into account these differences and seek to collect and evaluate data at individual-level by addressing sex/gender differences. These data contribute to provide the scientific basis to enable effective public health measures and specific gender-targeted solutions, also reducing both the social and the economic costs.

### *Authors' contributions*

Conceptualization: LB, MD, PP and CC; methodology: LB, PP, MdM; data collection: extraction and analysis: AB, MdM, MS, SB, MB, DP, CS, MF, MFV, FR, PP; writing - original draft preparation: MD and CC; writing - review and editing: MD, CC, LB, PP and RM; funding acquisition: LB. All Authors have read and approved the final manuscript as submitted.

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### *Data availability statement*

The data presented in this study are freely available on the www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati website (accessed on 18 October 2021).

### *Conflicts of interest statements*

The Authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

### *Ethics approval*

This study was not submitted for approval to an ethical committee because the scientific dissemination of COVID-19 surveillance data was authorized by the Italian Presidency of the Council of Ministers on 27 February 2020.

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