

Epidemiological characteristics of COVID-19 cases in Italy: an analysis from a sex/gender perspective

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Received 29 October 2021; accepted 14 January 2022

Summary. The current study aims to describe the characteristics of the SARS-CoV-2 infection from the beginning of its spread in Italy, in February 2020, up to April 2021 across the tested positive cases in Italy. Global data strongly suggest that a sex/gender-based disparity exists, with men being at higher risk of SARS-CoV-2 infection, hospitalization, poor clinical outcomes and death due to the coronavirus disease 2019 (COVID-19).

With this in mind, we focused on a sex/gender analysis, in order to better understand the role of sex/gender-related determinants in the outcome of COVID-19. We used routinely collected data retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections. Data is collected and entered daily on a secure online platform by the 19 Italian Regions and the two Autonomous Provinces, and all the system is coordinated by the Italian National Institute of Health.

In total, 4,027,075 cases occurred from February 2020 to April 2021, and were included in the analysis. Our results show that in Italy the numbers of SARS-CoV-2 infections are quite similar in women and men, even if some differences in exposure and outcomes between sexes are present. In particular, the case fatality rate over 50 years of age is significantly higher in men than in women, with the difference increasing with age.

These data further confirm the importance of the integration of a sex/gender analysis in future studies, thus enabling effective public health measures and gender-specific solutions.

Keywords. COVID-19, SARS-CoV-2, novel coronavirus, gender.

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly discovered human coronavirus. It was first reported in December 2019, in the city of Wuhan, China,^{1,2} and then spread rapidly worldwide, being declared by the World Health Organization a public health emergency of international concern on 30 January 2020.³ To date (July 5, 2021), it caused more

than 184 million cases and near 4 million deaths worldwide. Most people affected by COVID-19 develop a mild to moderate respiratory illness, and recover without the need of any special treatment. However, older people and subjects with pre-existing and/or underlying medical conditions – like cardiovascular disease, diabetes, obesity, chronic respiratory disease, and cancer – are more likely to develop severe respiratory illness often requiring intensive care.¹

Global data strongly indicates that a sex/gender disparity exists, with men being at higher risk of SARS-CoV-2 infection, hospitalization, poor clinical outcomes and death due to COVID-19 than women.⁴⁻⁶

Several international studies have reported that the male/female ratio of COVID-19 infections and the case fatality rate (CFR) is higher in males than in females.⁷⁻⁹ In particular, an epidemiological study from 38 countries reported a mean CFR in males 1.7 times higher than in females.¹⁰ Long-term COVID-19 outcomes after intensive care unit (ICU) admission are also worse in critically ill men than in their female counterparts.¹¹ Similar sex-based disparities had been previously observed in the severe acute respiratory (SARS) and Middle East respiratory syndrome (MERS) epidemics.^{12,13}

Many factors can contribute to the sex-specific disparity in disease outcomes, including intrinsic differences in innate and adaptive immunity, the role of sex hormones, as well as gender-specific behavioral differences.¹⁴ All these factors confer a protective advantage against COVID-19 to women, who are reported to have lower viral loads, lower inflammation, better clinical outcomes and lower mortality than men.

It is also worth to underline that sex differences in COVID-19 clinical outcomes could be also impacted by pre-existing comorbidities, that are clearly related to the severity of the disease and are usually found in severe and lethal COVID-19 cases.¹⁵ A study explored the presence of pre-existing comorbidities, diagnosed before the infection, in a sample of patients who died from SARS-CoV-2: women had a higher percentage of three or more conditions than men (71% vs 64%).¹⁶

The most common diseases were, in both sexes, ischemic heart disease, atrial fibrillation and type 2 diabetes, even if such non-communicable diseases affect differently the two sexes, males being less frequently but more seriously affected (GBD – Global Burden of Disease – data <http://ghdx.healthdata.org/gbd-results-tool>, accessed 5 July 2021).

A proper understanding of the factors associated with COVID-19 severity and mortality is paramount in order to effectively allocate healthcare resources, implement appropriate preventive and containment measures, and define adequate therapeutic protocols. Among those factors, the role of sex/gender-related determinants in the outcome of COVID-19 needs to be fully understood.

The current study aims to describe the characteristics of the SARS-CoV-2 infection from the beginning of its spread in Italy, in February 2020, up to April 2021 across the tested positive cases in Italy, from a gender perspective.

Methods

Data sources

We used routinely collected data retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections diagnosed up to April 30, 2021. This system, established on 27 February 2020, is coordinated by the Italian National Institute of Health. Data is collected and entered daily on a secure online platform by the 19 Italian Regions and the two Autonomous Provinces, according to an increasingly harmonized track-record.¹⁷ As previously described,¹⁸ this surveillance system collects data on all cases of SARS-CoV-2 infection confirmed by RT-PCR, following the international case definition that considers as a confirmed case any person with laboratory confirmation of SARS-CoV-2 virus, irrespective of their clinical signs and symptoms.^{19,20}

The data collected includes information on demographics, clinical outcomes, date of diagnosis, geographical area of diagnosis and comorbidities.

In the analysis by regional area, three macro areas were considered:

- North, 27,486,438 people (the Regions included are Valle d'Aosta, Piedmont, Liguria, Lombardy, Trentino-Alto Adige, Veneto, Friuli-Venezia Giulia, Emilia-Romagna);
- Center 11,786,952 people (Tuscany, Umbria, Marche, Lazio);
- South and Islands 19,962,823 people (Abruzzo, Molise, Campania, Puglia, Basilicata, Calabria, Sicily and Sardinia).

All records are checked for inconsistencies and duplicate at the coordinating center.

The Italian Presidency of the Council of Ministers authorized the scientific dissemination of COVID-19 surveillance data on 27 February 2020 (Ordinance no. 640).

Study population and outcomes

All cases occurred from February 2020 to April 2021 were included in the analysis (data extracted on June 27, 2021). The following age groups were considered: children and young adults (<40 years of age), middle aged (40-59), elderly (60-79), very elderly (>80). The case distributions in the study period (epidemic curve) were made by date of diagnosis.

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 with interquartile range (IQR) for categorical and continuous variables, respectively. For the calculation of the infection rates, we used the January 1, 2019 data on the Italian population, divided by area, sex and age groups, as provided by the Italian National Institute of Statistics (<https://www.istat.it/en/>).

CFRs, not accounting for delays, were calculated by age and sex.

Results

In total 4,027,075 cases occurred and were included in the analysis, during the studied period. The total number of tests performed was 59,744,776, and the test rates (number of tests/population) by macro area were:

- North = 1.15
- Center = 1.06
- South and Islands = 0.78.

The median age was 47, and the prevalence of females was 51.2%. A total of 120,440 deaths was recorded, with an overall CFR of 3.09%. The trend of the weekly diagnosed cases, showed in Figure 1, was substantially similar in the two sexes throughout the period, except for the first 3 months, where there was a first increase in male cases, immediately followed by an increase in female cases.

The median age of the diagnosed cases (Figure 2) was substantially similar in male and female patients, except for the period between March and April 2020, where it was significantly higher in women (80 years) than in men (70 years).

Table 1 shows the data of all patients divided by gender, geographical distribution and age group. The data shows a higher number of cases in <40-year-old

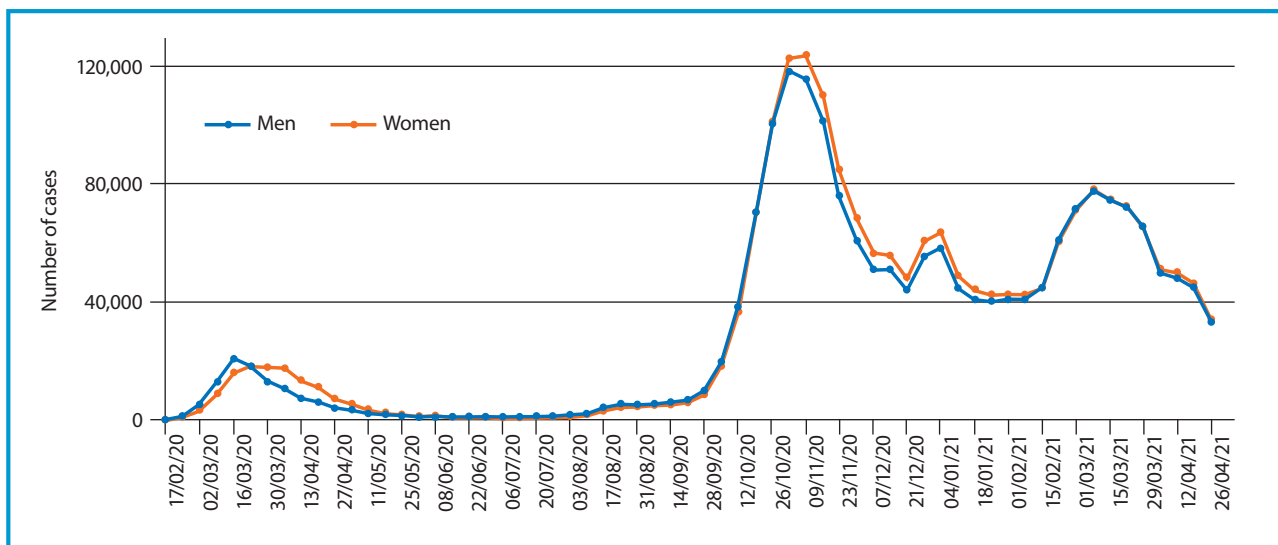


Figure 1. Number of cases of SARS-CoV-2/COVID-19 infection diagnosed from 17/2/2020 to 30/4/2021 in Italy according to sex. The blue line represents men, the orange women. Italian National Institute of Health surveillance data update: 27/6/2021.

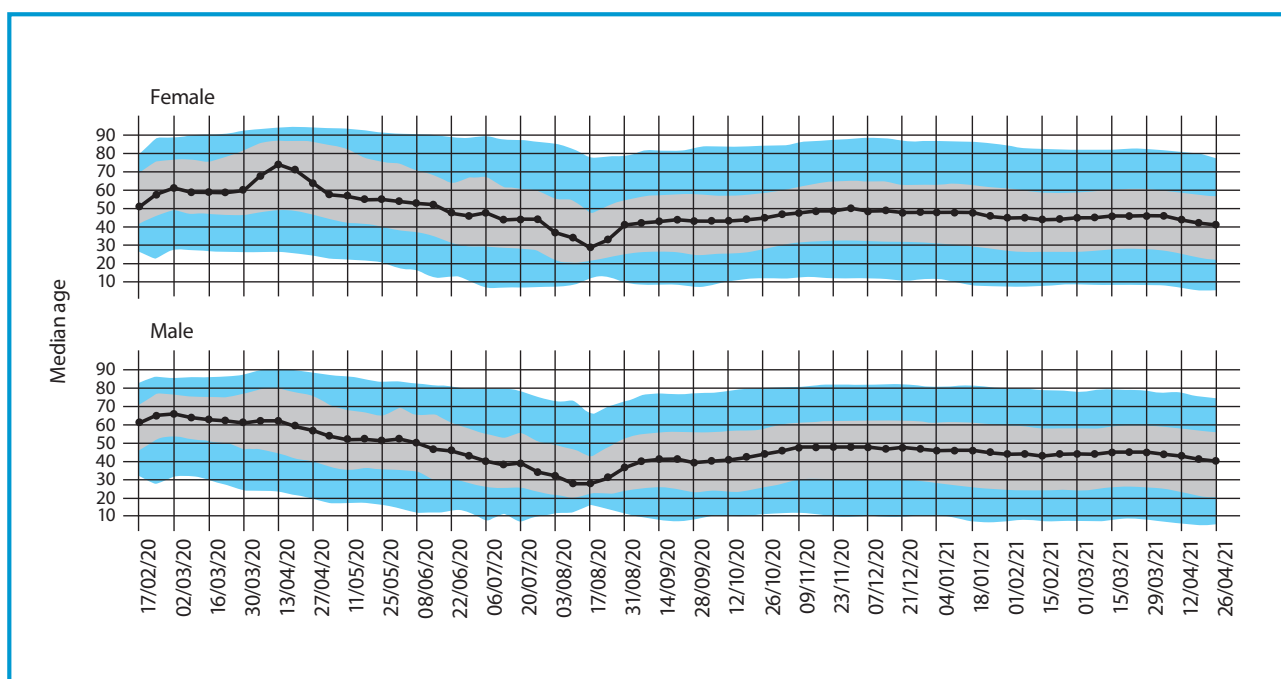


Figure 2. Distribution of the median age of COVID-19 cases by sex from February 2020 to April 2021 in Italy. The grey zone represents the 25-75 percentiles; the blue zone represents the 5-95 percentiles.

men, but the infection rate was higher in women until age <60, after which men resulted the most affected subjects between 60 and 79 years of age. The over-80 group showed a clear prevalence of women (63.4%) compared to men (36.6%). This is probably because women, having a longer life expectancy than men, are more represented in this age group.

We also take into consideration the geographical division in 3 distinct macro areas: North, Center, South and Islands. No differences were found between sexes

in all the three areas (Table 1), even if in the North of Italy a higher infection rate in both sexes occurred, due to the higher virus circulation in this area, especially during the first phase, from February to April 2020.

The CFR showed significant variations in relation to age and sex. The CFR was essentially 0% in both sexes until the age of 50. Over 50, the CFR among males was always higher than that among women, with the difference increasing with age (from 5% at 70 to 15% at 90) (Figure 3).

Table 1. Distribution of the number of cases of COVID-19 and infection rates (number of cases/ population) by sex, age group and geographic areas from February 2020 to April 2021 in Italy (data update: 27/06/2021)

Age groups (years)	Male patients (no. and %)	Female patients (no. and %)	Total patients (no.)	Infection rate (no. cases/1000) in males	Infection rate (no. cases/1000) in females	Infection rate (no. cases/1000) total
<40	793,085 (50.6)	774,769 (49.4)	1,567,862	64.12	65.85	64.96
40-59	651,686 (48.3)	696,793 (51.7)	1,348,482	71.05	73.95	72.52
60-69	232,871 (52.0)	214,732 (48.0)	447,604	66.33	56.12	61.00
70-79	166,762 (50.8)	161,364 (49.2)	328,126	61.15	49.87	55.03
>80	122,617 (36.6)	212,278 (63.4)	334,902	76.38	77.91	77.34
Unknown	46 (46.5)	53 (53.5)	99	-	-	-
North	1,102,823 (48.7)	1,160,188 (51.3)	2,263,030	81.51	81.61	81.56
Center	348,354 (48.8)	365,414 (51.2)	713,768	60.01	58.83	59.40
South and islands	515,890 (49.1)	534,387 (50.9)	1,050,277	51.33	50.66	50.99
Total	1,967,067 (48.9)	2,059,989 (51.1)	4,027,075	66.94	66.51	66.72

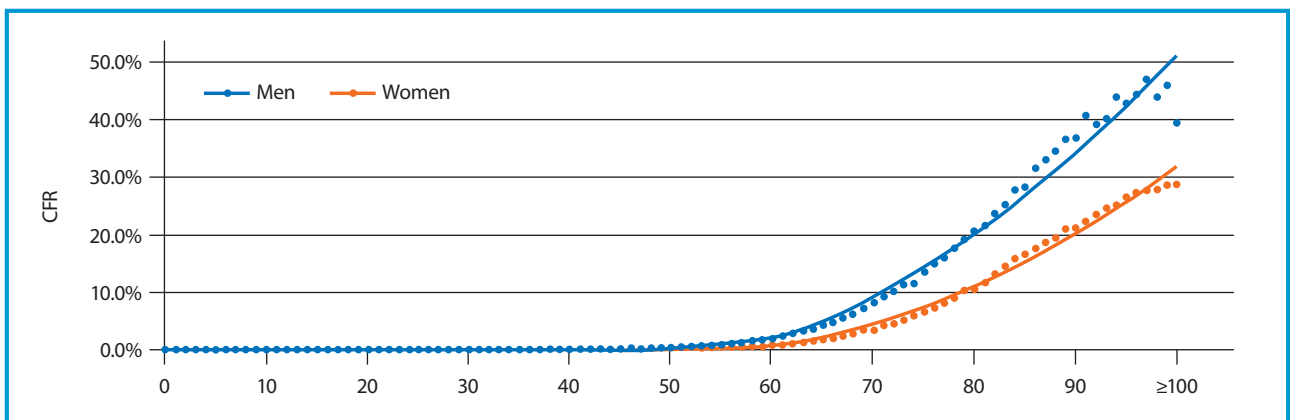


Figure 3. Case fatality rate (CFR) among COVID-19 cases in Italy from February 2020 to April 2021, by age and sex. The blue line and dots represent men, the orange line and dots represent women.

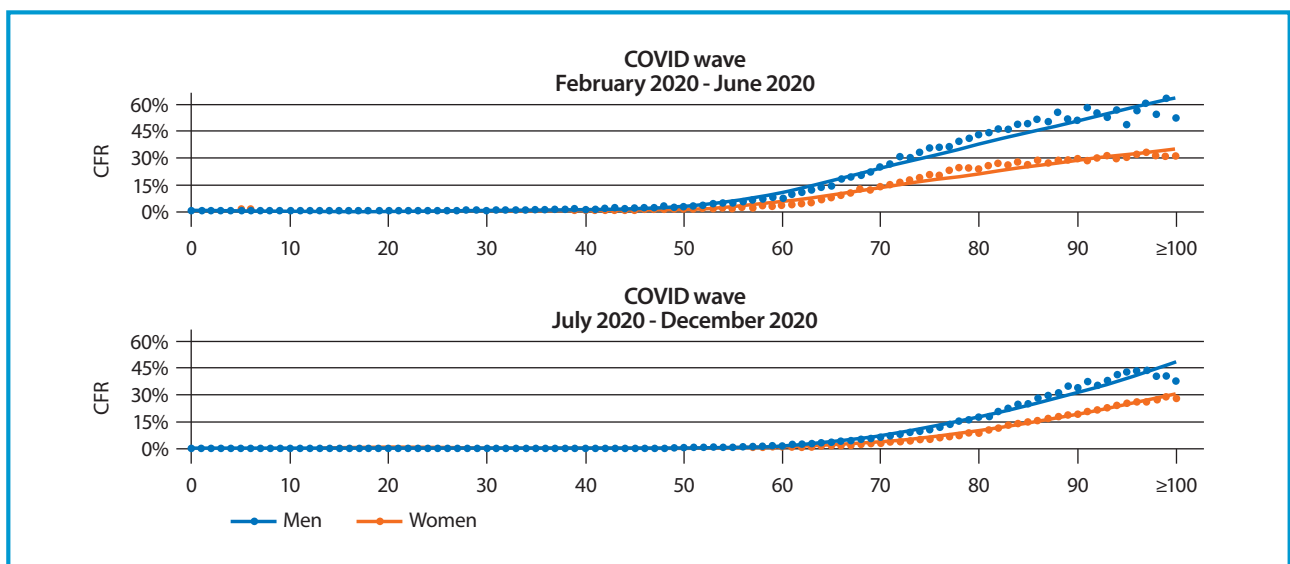


Figure 4. Case fatality rate (CFR) data in Italy in 2020 stratified by COVID-19 waves.

The CFR in the period February-June 2020 was higher compared to the period July 2020-December 2020 (Figure 4), particularly in the elderly (data not shown). In January 2021 the vaccination campaign started, and the CFR showed a steep reduction.

Discussion

Our data seem to support the hypothesis that in Italy COVID-19 does affect both sexes, but with some differences in exposure and outcomes. In the first pandemic period, the median age was significantly higher in women. This was probably due to a number of outbreaks that occurred in long-term care facilities, where many of the hosts were elderly, with chronic diseases and disabilities or health problems, and where women were more represented than men.

Although the numbers of cases were quite similar in women and men, the infection rates by age group showed some differences. These differences in each age group could be driven by the distinct gender-related social roles, which could lead to different exposures to the pathogen. According to the results of an international survey that included also Italy, women were more likely to abide by the COVID-19 restriction measures, and more compliant with such measures than men.²¹ However, in Italy the infection rates in the under 60 population was higher in women than in men.

Gender differences in sociodemographic characteristics or employment status may create different perceptions, and induce different types of behavior; for instance, women perform activities in which the risk of contagion is higher, like caring for the children and the sick at home, and they have higher proportion of health-care workers. The infection rates changed in the 60-79 age group, with higher proportions in men than in women. This can be partly due to the lower risk perception and lesser compliance with the restriction measures of men compared to women. The reduced infection rate in women over 60 could also be related to the fact that women may be more concerned about COVID-19 and more compliant with the rules if they are older, poorer, or in worse health conditions.²¹

The difference in the CFR between February-June 2020 and July-December 2020 probably depends on the lack of knowledge of COVID-19 at the beginning of this pandemic, with particular reference to the therapeutic and prevention options, which caused great difficulty in managing severe cases. Furthermore, in the first period there was a tendency to diagnose symptomatic cases mainly in the over 30 population, while in the subsequent periods the greater availability of diagnostic tools improved the screening; consequently, numerous asymptomatic cases were identified

even in younger subjects at lower risk of complications and death.

The CFR differed by sex, being higher in men than in women, with significant differences among the over 50. A poorer outcome in men has been described, and sex-related genetic and hormonal factors – as well as immunological responses – may play a role in this bias.²²

Angiotensin-converting enzyme 2 (*ACE2*) is a key protein involved in the cell entry of SARS-CoV-2 gene.²³ Since *ACE2*-encoding genes are located on the X chromosome,²⁴ a double copy of *ACE2* in females may compensate for the virus-mediated down-regulation of *ACE2*,²⁵ thus explaining the greater cellular protection in females. It is important to underline that the X chromosome also contains the most prominent immune-related genes in the human genome.²⁶ Therefore females, because of their XX chromosome, develop more robust inflammatory immune responses than males.²⁷

Lower testosterone concentrations – a situation observed in elderly men – was also considered among the risk factors for poor outcomes in men. The severity of COVID-19 seems to coincide with the nadir of lifetime testosterone, and the comorbidities predisposing individuals to an increase in COVID-19 severity are also associated with lower testosterone concentrations.²⁸ A survey showed that an increased estradiol to testosterone ratio during hospitalization was associated with disease severity, inflammation, and mortality in COVID-19 males.²⁹ A recent systematic review investigating risk factors in COVID-19 highlighted that age, sex, obesity, and multiple comorbidities increase the risk of adverse outcomes.³⁰ However, the precise role of sex in such differ-

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ences is still being debated and, in general, the influence of sex and gender on transmission and outcomes depends on the infectious disease, the mechanism of transmission and the interaction between the host and the pathogen. This means that the effects of biological and gender differences vary from disease to disease.

These data further confirm the importance of the integration of a sex/gender analysis in future studies, also investigating the different gender-related social roles, in order to better understand the complex interaction among sex/gender, age and disease exposure/outcomes. These data may provide the scientific basis to enable effective public health measures and gender-specific solutions, also reducing both social and economic costs.

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Author contribution statement: all the Authors participated in conceiving the content of the manuscript and in the final review. Matteo Spuri and Claudia Cataldo contributed equally as co-first authors.

Conflict of interest statement: the Authors declare no conflicts of interest.

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