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Gender differences in death rates due to the COVID-19 pandemic in Italy

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Summary. Italy was the first European country hit by the COVID-19 pandemic. As of March 3, 2021, the Italian national surveillance system had registered 2,953,120 cases and 96,977 deaths, with gender differences both in terms of cases and deaths. Therefore, the aim of this observational ecological study is to analyze gender differences during the first year of COVID-19 pandemic in Italy in terms of crude mortality rate (CMR) and case fatality rate (CFR).
We collected data from the official database of the Italian National Institute of Health (*Istituto Superiore di Sanità* – ISS). We considered the two waves of the pandemic, using the date between the two peaks that had the trough (lowest number of deaths) for a 7-day average to separate the two periods). Then, we calculated the CMR and CFR by age group for males and females, considering three periods: overall, first wave and second wave.
Our study shows that male gender reported both higher CMR and CFR than female, and this data is confirmed for all the age group. Although many demographic, socioeconomic, hormonal, genetic, and epigenetic factors may explain these differences, further studies are required in order to understand the pathophysiological mechanisms underlying gender differences in CMR and CFR due to COVID-19.

Keywords. Crude mortality rate, case fatality rate, COVID-19, gender differences, pandemic.

Differenze di genere nei tassi di mortalità dovute alla pandemia di COVID-19 in Italia

Riassunto. L'Italia è stata il primo paese europeo colpito dalla pandemia di COVID-19. Al 3 marzo 2021, il Sistema nazionale di sorveglianza registrava 2.953.120 casi e 96.977 decessi, con differenze di genere per entrambi. Pertanto, lo scopo di questo studio ecologico osservazionale è quello di analizzare le differenze di genere durante il primo anno di pandemia di COVID-19 in Italia in termini di *crude mortality rate* (CMR) e di *case fatality rate* (CFR).
Una volta raccolti i dati dal database ufficiale dell'Istituto Superiore di Sanità (ISS), abbiamo considerato le due ondate della pandemia, utilizzando – per separare i due periodi – la data tra i due picchi che aveva avuto il minor numero di morti per una media di 7 giorni. Quindi, abbiamo calcolato il CMR e il CFR per gruppo di età per maschi e femmine, considerando tre periodi: totale, prima ondata e seconda ondata.
Il nostro studio dimostra che gli uomini presentano valori di CMR e di CFR più elevati rispetto alle donne e che tali dati sono confermati in tutte le fasce di età. Diversi fattori demografici, socioeconomici, ormonali, genetici ed epigenetici potrebbero essere responsabili di queste differenze. Sono dunque necessari ulteriori studi per comprendere i meccanismi fisiopatologici alla base delle differenze di genere nei CMR e CFR dovute al COVID-19.

Parole chiave. Tasso di mortalità, tasso di letalità, COVID-19, differenze di genere, pandemia.

Introduction

Italy was the first European Country hit by the COVID-19 pandemic and, as of March 3, 2021, the Italian national surveillance system had registered 2,953,120 cases and 96,977 deaths.[1] One year later, it is possible to evaluate the evolution of the pandemic and its impact in terms of cases and deaths in Italy. In particular, attack rate, crude mortality rate (CMR) and case fatality rate (CFR) allow to understand the trend of the pandemic,[2-5] despite some limits related to these indicators, such as the dependence on case and death definitions, the modalities of – and delays in – data collection and the capacity of the healthcare systems to identify positive cases.[6,7] In particular, especially during the first wave of the pandemic, the CFR could be overestimated, due both to the impossibility of detecting all positive cases (limited diagnostic capability, especially for people with mild symptoms or asymptomatic)[8,9] and the definition of case: indeed, cases can be defined either as the total cases (every confirmed case) or as closed cases (only those who have recovered or died).[9] On the other hand, the CFR could be underestimated, due to time-lag bias associated with diagnosing and reporting cases.[9] Despite all these limitations, the CFR calculated per total cases still appears to be a good tool to express the fatality of the disease.[9] In particular, we considered the CFR defined by the World Health Organization, as well as the Italian National Institute of Health (*Istituto Superiore di Sanità* – ISS)[10] as the proportion of individuals diagnosed with a disease who die from that disease, in order to differentiate this indicator from the infection fatality ratio (IFR).[11]

Moreover, specific variables – such as age, gender and the presence of comorbidities – should be always considered as factors that could affect case and death distri-

bution.[5] In particular, Italy is a Country of about 60 million people, with one of the highest life expectancy in the world (85.2 years for women and 80.8 for men), despite significant differences between Regions.[12]

The aim of this study, therefore, is to evaluate the evolution of the COVID-19 pandemic in Italy, highlighting gender differences during the year of the pandemic in terms of attack rate, CMR and CFR.

Data and methods

In this observational ecological study, we compared the cumulative number of positive cases due to COVID-19, the CMR and the CFR in women and men in Italy during the first year of pandemic. In order to calculate the CMR and CFR, we collected the number of cases and deaths from the official database of the ISS.[10] Rates were calculated with reference to the national population by age and gender, as estimated as of January 1, 2020. The CMR was calculated as the total number of deaths from COVID-19 against the total Italian population (x100,000), while the CFR as the percentage of COVID-19 deaths against the total number of confirmed positive cases.[11] Rates were calculated for gender and specific age groups (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, >90). We obtained the age and gender distribution from the Italian National Institute of Statistics (ISTAT).[13] In order to compare the CMR between the two waves of pandemic, we used the date between the two peaks that had the trough (lowest number of deaths) for a 7-day average to separate the two periods: in this way, we considered the end of the first wave on August 18,[14] due to the availability of data from the ISS. As for the CFR, due to the possible over/underestimation,[8,9] we only reported the trend from the beginning of the pandemic to March 2021. In particular, we considered for each month the last monthly report provided by ISS (dates between the 25th and the 30th day of the month).

Results

Out of a total of 2,953,120 cumulative positive cases in Italy, 49.9% are women, with an overall median age of 44 years.[1] In particular, considering the specific age groups, the main differences are observed in the 80-89 and >90 age groups, where the female gender accounts for 59.3% and 76.8% of cases, respectively. This figure can be explained by the longer life expectancy of women, which therefore determines the presence of a greater number of female individuals in the Italian population in these age groups (in the 80-89 group, about 60% are women, while in the >90 group this percentage is over 75%).[13] Considering instead the youngest population, up to the age of 30, men present a greater prevalence (51.9%, 52.1% and 50.4% in the 0-9, 10-19 and 20-29 age groups, respectively).

The median age of death from SARS-CoV-2 infection is 83, with 43.9% of women. In addition, women dying from COVID-19 are older than men (median age, 86 vs 80). Although the median age of COVID-19 cases changed during the pandemic (62 years in the first months, 33 in August 2020 and 46 in March 2021), the median age at death, however, did not change, thus confirming the highest number of deaths (and therefore the highest CFR) of SARS-CoV-2 in the elderly.

In this context, it is possible to calculate the CMR and CFR of COVID-19 by gender and age. In particular, the overall CMR and CFR in Italy are, both in the first[15] and second wave,[16] among the highest in Europe and, at the beginning of March 2021, they are 160.7/100,000 and 3.3%, respectively.[1]

The CMR varied greatly during the pandemic. In particular, during the first wave the overall CMR reached a value of 59.4/100,000, while in the second wave (beginning of March 2021) this value is almost double, being equal to 101.3/100,000.

However, significant differences are evident when considering gender and age groups. In particular, the overall CMR is much higher in males than in females (185.2/100,000 vs 137.4/100,000). Considering the different age classes, between 0 and 29 years of age there are no differences between genders, with values lower than 0.9/100,000. From age 30 onwards, however, the differences between genders are evident, and tend to increase with age. The male gender always presents a higher CMR, with peaks of 1,566.6/100,000 (almost double the value of 852.8/100,000 of the female gender) between the age of 80 and 89, and values of 3,199.8/100,000 for people >90 (compared to 2,318.3/100,000 in females). However, even considering the youngest groups (30-79), important differences are evident (Table 1). We observed these age differences in CMR among male and females also comparing the two waves: during both the first and the second period, the CMR was higher in the male gender in all age groups (Table 2). Moreover, comparing the two waves, there is a huge increase in CMR in both genders, especially among the elderly. Indeed, while the CMR increased by less than 1/100,000 in the age groups 0-9, 10-19, 20-29, 30-39, and less than 10/100,000 in the age groups 40-49 and 50-59, considering the >60 group there is an important difference between the first and the second wave: in males the CMR increased from 77.6/100,000 to 115.3/100,000 (age group 60-69), from 236.8/100,000 to 352.1/100,000 (70-79), from 575.1/100,000 to 991.5/100,000 (80-89) and from 991.3/100,000 to 2208.5/100,000 (>90). We observed the same trend in females, albeit with lower values: from 22.6/100,000 to 39.8/100,000 (60-69), from

Table 1. Overall crude mortality rate (x100,000) in Italy by gender and age groups as of March 2021

Age group	Male	Female	Overall	Male/Female (x100)
0-9	0.2	0.2	0.2	63.0
10-19	0.2	0.2	0.2	112.3
20-29	0.9	0.7	0.8	132.9
30-39	3.2	1.0	2.6	159.4
40-49	12.3	5.3	8.8	232.0
50-59	50.3	17.5	33.6	287.7
60-69	192.9	62.5	124.9	308.8
70-79	589.0	230.7	394.5	255.3
80-89	1566.6	852.8	1133.0	183.7
>90	3199.8	2318.3	2556.5	138,.0
Total	185.2	137.4	160.7	134.8

Table 2. Variation of crude mortality rate (x100,000) in Italy by gender and age groups during the first wave, the second wave and overall

Age group	First wave		Second wave		Overall	
	Male	Female	Male	Female	Male	Female
0-9	0.0	0.1	0.1	0.1	0.2	0.2
10-19	0.0	0.0	0.2	0.2	0.2	0.2
20-29	0.4	0.1	0.6	0.6	0.9	0.7
30-39	1.2	0.7	1.9	1.3	3.2	2.0
40-49	4.9	1.9	7.4	3.4	12.3	5.3
50-59	20.6	6.3	29.8	11.2	50.3	17.5
60-69	77.6	22.6	115.3	39.8	192.9	62.5
70-79	236.8	88.9	352.1	141.7	589.0	230.7
80-89	575.1	308.3	991.5	544.4	1566.6	852.8
>90	991.3	798.5	2208.5	1519.8	3199.8	2318.3
Total	69.8	49.5	115.4	87.9	185.2	137.4

88.9/100,000 to 141.7/100,000 (70-79), from 308.3/100,000 to 544.4/100,000 (80-89) and from 798.5/100,000 to 1519.8/100,000 (>90) (Figure 1).

Considering the CFR, Italy initially presented high values, equal to 10.6% in March 2020 and 14.5% at the end of June (the highest value during the pandemic). Considering gender differences, as of March 2021, a higher CFR is observed in men than in women (3.8% vs 2.8%). Furthermore, the CFR is higher in men in all age groups, and the difference is particularly evident in the 70-79 (12.7% vs 6.3%), 80-89 (26.5% vs 15.3%), and >90 (38.6% vs 22.9%) age groups. The same figure was observed considering the trend from the beginning of the pandemic up to March 2021 (Figure 2).

Discussion

In this study we analyzed the gender differences in terms of COVID-19 CMR and CFR in Italy, comparing the two waves of the pandemic. Despite their limits, these indicators allow to evaluate the trend of the pandemic one year after its start.[9] In particular, the male gender reported both higher CMR and CFR than the female one, and this figure is confirmed considering all age groups. These data confirm what has been shown in previous coronavirus outbreaks (SARS and MERS), where an increased susceptibility and mortality was observed in men.[17,18]

Furthermore, considering COVID-19, it has been observed in many other Countries that males present high-

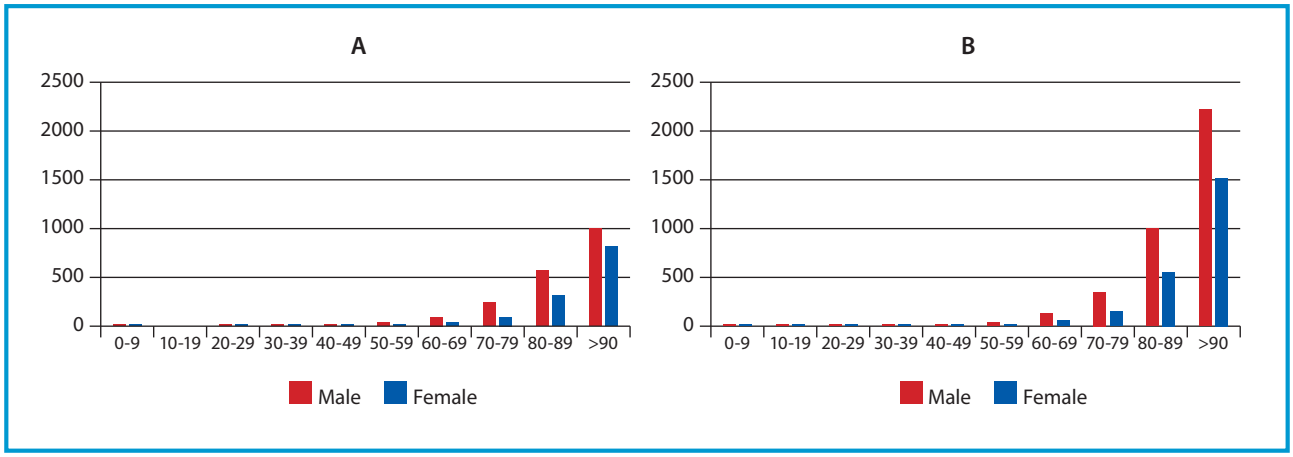

Figure 1. Crude mortality rate (x100,000) in Italy by gender and age groups during the first (A) and second (B) wave.

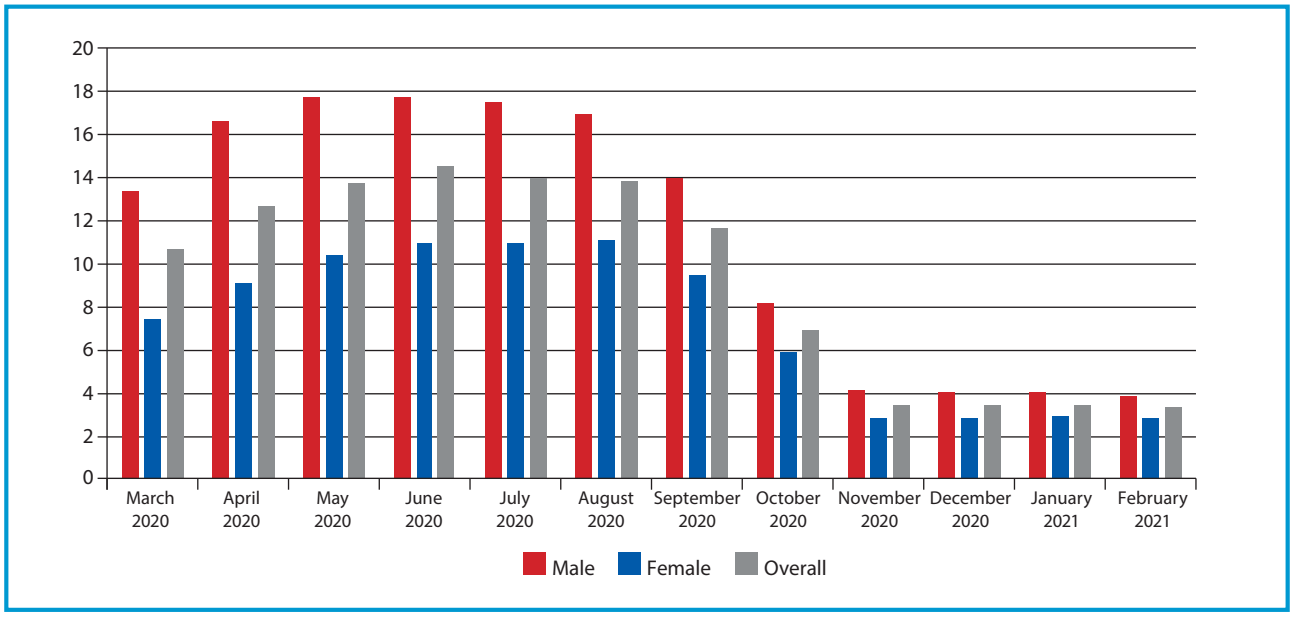

Figure 2. Case fatality rate (x100) in Italy by gender and during the period March 2020-February 2021.

er CMR and CFR than women,[19,20] and that biological sex and the sociocultural aspects of gender may explain these differences in terms of CMR and CFR.[21] In particular, although the prevalence of COVID-19 is lower in men than in women, CMR and CFR are higher among men, and many factors – such as demographic, socioeconomic, hormonal, genetic, epigenetic – may affect immune response.[22] Moreover, while analyzing CMR and CFR, the presence of comorbidities should be considered.[23] In Italy, in a sample of 6,713 deaths, 98.0% and 96.2% of the deaths in women and men, respectively, had at least one comorbidity (70.1% of women and 64.2% of men had 3 or more comorbidities).[24] Specifically, a total of 66.7% of patients had hypertension, while other frequent conditions were type 2 diabetes and ischemic heart disease (29.3% and 27.9%, respectively).

Key messages

- Crude mortality rate (CMR) and case fatality rate (CFR) are two important indicators that allow to understand the trend of the COVID-19 pandemic.
- Age, gender and the presence of comorbidities should be always considered as factors that could affect case and death distribution.
- In Italy the male gender reported both higher CMR and CFR than the female one, and this figure is confirmed considering all age groups during both the waves.
- It is important to understand the pathophysiological mechanisms underlying gender differences in CMR and CFR in order to implement policies that protect the most vulnerable people.

However, further researches are required to understand the pathophysiological mechanisms underlying gender differences in CMR and CFR due to COVID-19, in order to provide the best possible access to healthcare and treatments, and to implement health policies that protect the most vulnerable groups of the population.

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