

BMJ Open Sex and gender differences in COVID-19: an Italian local register-based study

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ABSTRACT

Objectives The present study aimed to explore differences in COVID-19 outcomes between male and female cases in the Apulian District of Foggia, Italy.

Design and setting We performed a retrospective epidemiological study among all COVID-19 confirmed cases that occurred in the Apulian District of Foggia from 29 February to 30 June 2020. The surveillance data from a regional registry (GIAVA-COVID) were used.

Main outcomes The main outcome measures were the proportion of hospitalisations, virus clearance and the case fatality rate.

Results A total of 1175 cases (50.7% female; median age: 55 years) were identified among 55 131 tests performed. The proportion of hospitalisation with COVID-19 diagnosis was 45.4% in men versus 37.9% in women ($p<0.01$), while the average length of stay in hospitals was 31.3 ± 14.6 days in women versus 26.8 ± 14.4 days in men ($p<0.01$). The proportion of cases who achieved virus clearance was higher in women (84.2%; days to clearance: 28.0 ± 12.1) than in men (79.3%; days to clearance: 29.4 ± 12.9 ; $p<0.05$). Men were associated with a significantly higher risk of dying from COVID-19 than women (case fatality rate 16.1% vs 10.4%; $p<0.01$). The mean time, from diagnosis to death, was 14.5 ± 14.4 days in women compared with 10.6 ± 10.7 days in men ($p<0.01$). The male sex, age ≥ 55 years and presence of at least one underlying comorbidity significantly raised the risk of hospitalisation, persistent infection and death ($p<0.05$).

Conclusions This study suggests that more attention should be paid to sex as a variable for the interpretation of COVID-19 data. Sex-disaggregated data will help clinicians to make appropriate patient-tailored medical decisions.

INTRODUCTION

SARS-CoV-2 is a novel coronavirus causing the current pandemic, which has resulted in millions of infections and hundreds of thousands of deaths worldwide. As of 10 March 2021, a total of 3 069 625 cases of confirmed SARS-CoV-2 have been reported in Italy with a case fatality rate (CFR) of 3.2%.¹

The clinical manifestations of SARS-CoV-2 vary from asymptomatic infection to severe or critical disease.²

Strengths and limitations of this study

- This study provides sex-disaggregated data of COVID-19 cases at a district level, in Italy, contributing to a better understanding of who is being impacted the most by the pandemic and promoting a patient-tailored treatment approach.
- The robust methodology of the present study enabled to accurately correlate the case demographics with COVID-19 clinical response.
- The data related to the viral clearance, which reflect the diversified course of the disease according to the individual immune response, are confirmatory of sex difference in COVID-19.
- The data collected are highly homogeneous as they are strictly related to the first epidemic wave and provide an accurate picture of the impact of sex and age on COVID-19 outcomes in Italy during the initial phase of the pandemic.
- As the majority of the sex-disaggregated data available in the literature, the data presented in our study are not adjusted for lifestyle, profession, social or behavioural differences.

Older age and comorbidities such as hypertension, cardiovascular disease, diabetes and chronic respiratory disease are associated with severe disease and death.^{3–5} Sex and gender have been identified as additional risk factors contributing to heterogeneous COVID-19 outcomes.² Indeed, several studies have reported sex bias in COVID-19 case fatalities. It is observed that men have a higher risk of developing a severe form of the disease compared with women, highlighting the importance of sex-disaggregated data of COVID-19 cases.⁶ The initial reports from China followed by data from several European countries have shown similar numbers of confirmed cases between men and women.^{7 8} However, the severity of COVID-19, measured as hospitalisation, admission to intensive care units (ICUs) and fatality rate, is twofold higher in men than women.^{8 9} Studies in China, South Korea, USA, UK and Italy



have reported higher CFRs and worst disease outcomes in male cases than in female cases.^{7 10-14} In some of these studies, the higher fatality rate in men was observed even after adjusting for confounding factors such as age and comorbidities.^{7 14} Additionally, in Italy, the higher fatality rate in men (age range: 40–80 years) is confirmed when the healthcare worker population is selectively studied.¹

The reasons for the differences in COVID-19 outcome and progression between men and women remain unclear. On one hand, biological factors, such as chromosomal and hormonal differences between men and women, may influence their susceptibility to infections, immune responses and progression of the disease.^{6 9 15 16} On the other hand, gender-related factors including psychological, social and behavioural differences between men and women may affect SARS-CoV-2 exposure, presence of comorbidities, treatment initiation and compliance, and COVID-19 mortality.^{17 18}

In this study, we used the surveillance data from a regional registry containing all confirmed cases of COVID-19 that occurred in the Foggia District (Apulia region, Italy), as of late June 2020, after the end of the first epidemic wave. We aimed to explore the sex differences in hospitalisation, virus clearance and deaths.

METHODS

Study population and design

We conducted a retrospective epidemiological study among COVID-19 cases that occurred in the Foggia District, Apulia region, Italy, from 29 February to 30 June 2020. Foggia District is the third largest Apulian District, with an estimated population of 616310 residents (51% women) as of 1 January 2020.¹⁹

We used the surveillance data from a regional registry (GIAVA-COVID), which was developed based on the WHO Go.Data outbreak investigation tool to manage the emergency.²⁰ GIAVA-COVID includes functionalities for investigation and follow-up of cases and contacts, contact tracing, laboratory and clinical data collection. The collected information includes age, sex, residence location, date of disease onset, date of diagnosis, date of hospital admission, date of COVID-19 test results (positive or negative), date of death, presence of underlying diseases, case outcomes (hospitalisation, virus clearance and death) and disease severity (mild, moderate, severe or critical).²¹ The disease classification was duly updated according to clinical evolution of each case.

This study included all laboratory-confirmed cases defined as any person meeting the laboratory criterion (ie, detection of SARS-CoV-2 nucleic acid or antigen in a clinical specimen).²²

The proportion of hospitalisation was defined as the proportion of infected individuals undergoing hospitalisation among the total number of infected individuals. The proportion of individuals who achieved virus clearance was defined as the proportion of clinically recovered individuals with laboratory evidence of viral RNA

clearance from the upper respiratory tract (two serial negative PCR tests at least 24 hours apart) among the total number of infected individuals. The CFR was defined as the proportion of deaths among the total number of confirmed cases.

Statistical analysis

Categorical variables were summarised as counts and percentages in each category. Data for continuous variables were expressed as medians (IQRs and means (\pm SD)). Normality of data was tested by the Kolmogorov-Smirnov test. Differences in continuous variables were assessed with Student's t-test or Mann-Whitney U test, depending on whether continuous variables were normally distributed or not, respectively. Significant differences in categorical variables were assessed using the χ^2 test or Fisher's exact test when appropriate and the OR with 95% CI. Multivariate logistic regression analysis was performed to evaluate whether demographics (sex: male vs female; age group: above vs below the median age) and clinical characteristics (presence vs absence of at least one underlying medical condition) were independently associated with hospitalisation, virus clearance and deaths. The analysis was conducted with STATA/SE V.15.0.

RESULTS

Between 29 February and 30 June 2020, a total of 1175 cases (50.7% female; median age: 55 years, IQR: 40–71 years) were diagnosed with COVID-19 in the Foggia District, Apulia region, Italy. The female positivity rate was 2.02% among 29475 tests performed, and the male positivity rate was 2.25% among 25656 tests performed (χ^2 $p > 0.05$).

Comparison of demographics and clinical characteristics of men versus women are shown in [table 1](#). A total of 373 cases (31.7%) had underlying medical conditions, including cardiovascular disease (63.3%), diabetes (19.6%), chronic pulmonary disease (13.9%), cancer (10.7%), neurological diseases (9.9%), chronic kidney disease (9.4%) and obesity (with body mass index between 30 and 40 kg/m² or higher) (6.7%). Nearly 50% of cases were asymptomatic or with mild disease, 14.4% had moderate disease, 20.9% developed a severe disease and 3.2% progressed to a critical stage. There was no significant difference in age, underlying comorbidities (with the exception of diabetes) and disease severity distributions between the male and female groups ([table 1](#)).

The proportion of hospitalisation among COVID-19 cases was estimated to be 41.6%, with a significant difference observed between men (45.4%) and women (37.9%; $p < 0.01$). While the average length of stay in hospitals was significantly higher in women (31.3 \pm 14.6 days) than in men (26.8 \pm 14.4 days; $p < 0.01$), there were more women aged ≥ 55 years hospitalised ($p < 0.01$). The proportion of cases who achieved virus clearance was 82%, higher in women (84.2%; days to clearance: 28.0 \pm 12.1) than in men (79.3%; days to clearance: 29.4 \pm 12.9; $p < 0.05$). A

Table 1 Comparison of characteristics between male and female COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Male	Female	Total	OR (95% CI)	χ^2	P value
No. of cases (%)	579 (49.3)	596 (50.7)	1175			
Median age (IQR), years	56 (40–70)	54.5 (38–74)	55 (40–71)			
Mean age (\pm SD), years	54.3 \pm 21.1	54.5 \pm 22.6	54.4 \pm 21.8			0.4291
Age group, no. (%)						
0–9	14 (2.4)	16 (2.7)	30 (2.6)	Ref.		
10–19	23 (4.0)	22 (3.7)	45 (3.8)	1.19 (0.43 to 3.34)	0.1	0.7061
20–29	43 (7.4)	53 (8.9)	96 (8.2)	0.93 (0.38 to 2.30)	0.03	0.8571
30–39	57 (9.8)	64 (10.7)	121 (10.3)	1.02 (0.42 to 2.47)	0.00	0.9655
40–49	91 (15.7)	95 (15.9)	186 (15.8)	1.09 (0.47 to 2.57)	0.05	0.8184
50–59	105 (18.1)	108 (18.1)	213 (18.1)	1.11 (0.48 to 2.59)	0.07	0.7874
60–69	96 (16.6)	64 (10.7)	160 (13.6)	1.71 (0.72 to 4.07)	1.84	0.1747
70–79	71 (12.3)	69 (11.6)	140 (11.9)	1.17 (0.49 to 2.81)	0.16	0.6874
80–89	64 (11.1)	72 (12.1)	136 (11.6)	1.01 (0.43 to 2.44)	0.00	0.9689
\geq 90	15 (2.6)	33 (5.5)	48 (4.1)	0.52 (0.18 to 1.48)	1.88	0.1705
Comorbidity, no. (%)						
None	388 (67.0)	414 (69.5)	802 (68.3)	Ref.		
At least one comorbidity	191 (33.0)	182 (30.5)	373 (31.7)	1.1 (0.86 to 1.43)	0.75	0.3860
Cardiovascular disease	126 (66.9)	110 (60.4)	236 (63.3)	1.27 (0.81 to 1.97)	1.23	0.2682
Diabetes	49 (25.7)	24 (13.2)	73 (19.6)	2.27 (1.29 to 4.01)	9.20	0.0024
Chronic pulmonary disease	30 (15.7)	22 (12.1)	52 (13.9)	1.35 (0.72 to 2.58)	1.02	0.3132
Cancer	23 (12.0)	17 (9.3)	40 (10.7)	1.32 (0.65 to 2.75)	0.71	0.3994
Neurological diseases	15 (7.9)	22 (12.1)	37 (9.9)	0.62 (0.29 to 1.30)	1.87	0.1715
Chronic kidney disease	22 (11.5)	13 (7.1)	35 (9.4)	1.69 (0.78 to 3.78)	2.10	0.1475
Obesity	13 (6.8)	12 (6.6)	25 (6.7)	1.03 (0.42 to 2.55)	0.01	0.9345
Other metabolic diseases	5 (2.6)	10 (5.5)	15 (4.0)	0.46 (0.12 to 1.52)	2.00	0.1575
Liver disease	10 (5.2)	4 (2.2)	14 (3.8)	2.45 (0.69 to 10.91)	2.38	0.1228
Disease severity, no. (%)						
Asymptomatic	92 (15.9)	113 (19.0)	205 (17.4)	Ref.		
Critical	23 (4.0)	15 (2.5)	38 (3.2)	1.88 (0.88 to 4.11)	3.15	0.0760
Severe	126 (21.8)	120 (20.1)	246 (20.9)	1.28 (0.87 to 1.90)	1.80	0.1796
Moderate	80 (13.8)	89 (14.9)	169 (14.4)	1.10 (0.72 to 1.69)	0.23	0.6348
Mild	165 (28.5)	197 (33.1)	362 (30.8)	1.02 (0.72 to 1.47)	0.03	0.8718

Ref., reference group.

total of 155 deaths occurred among all cases for an overall CFR of 13.2%. Men were associated with a significantly higher risk of dying from COVID-19 than women (16.1% vs 10.4%; $p < 0.01$). The mean time, from diagnosis to death was higher in women (14.5 \pm 14.4 days) compared with men (10.6 \pm 10.7 days; $p < 0.01$) (table 2).

The male sex, age ≥ 55 years and underlying comorbidities (presence of at least a condition among those listed in table 1) significantly raised the risk of hospitalisation, persistent infection and death ($p < 0.05$; table 3).

DISCUSSION

Our registry-based surveillance study of 1175 COVID-19 cases, well characterised from both demographic and clinical points of view, highlighted a male bias in COVID-19

outcomes. Based on the herein presented data, men are more likely to be hospitalised than women, and the proportion of male cases achieving virus clearance is lower compared with female cases. Furthermore, men require longer periods to achieve virus clearance, have a higher fatality rate and faster progression to death.

A male bias (male-to-female ratio > 1.1) in COVID-19 mortality is currently reported in 75 of the 94 countries that have provided sex-disaggregated data (as of 10 March 2021). At the global level, a higher number of men are hospitalised or admitted to ICU compared with women.²³ Additionally, several studies have demonstrated that men with COVID-19 are at higher risk of death and severe form of infection than women.^{24 25} A recent meta-analysis of 3111714 reported global cases demonstrated that,

Table 2 Comparison of outcomes between male and female COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Male	Female	OR (95% CI)	χ^2	P value
Hospitalisation, no. (%)	263 (45.4)	226 (37.9)	1.36 (1.07 to 1.73)	6.81	0.0091
Mean age (\pm SD), years	66.2 \pm 16.0	70.2 \pm 18.8			0.0053
Mean length of stay in hospital (\pm SD), days	26.8 \pm 14.4	31.3 \pm 14.6			0.0032
Median length of stay in hospital (IQR), days	24 (17–35)	29 (19–41)			
Virus clearance (yes), no. (%)	459 (79.3)	502 (84.2)	0.72 (0.53 to 0.97)	4.84	0.0278
Mean time-to-virus clearance (\pm SD), days	29.4 \pm 12.9	28.0 \pm 12.1			0.0432
Median time-to-virus clearance (IQR), days	25 (18–35)	27 (19–37)			
Deaths, no. (%)	93 (16.1)	62 (10.4)	1.65 (1.15 to 2.36)	8.21	0.0042
Mean time to death (\pm SD), days	10.6 \pm 10.7	14.5 \pm 14.4			0.0282
Median time to death (IQR), days	8 (3–16)	10 (4–23)			

while there is no difference in the proportion of male and female COVID-19 cases, men have higher odds of death (OR=1.39; 95% CI 1.31 to 1.47) compared with women.²⁶ Similarly, our study presents a comparable proportion of women and men with confirmed COVID-19 (50.7% vs 49.3%) and similar rates of positivity for infection (2.02% vs 2.25%, $p>0.05$). Therefore, the observed differences cannot be attributed to a prevalence of COVID-19 in the male sex.

The sex distribution of confirmed cases observed in the Foggia District, Apulia region is in line with the overall sex distribution of cases observed in Italy and other European countries.^{1 8 27} Although in the early phase of the pandemic in Italy, a higher prevalence of COVID-19 was observed in men compared with women; this disproportion became less evident with the progression of the pandemic. This variability may be explained by the different surveillance approaches adopted during the pandemic since a symptom-based screening led to an underestimation of asymptomatic to mild cases during the first epidemic wave. In Italy, after the end of the first epidemic wave (30 June 2020), a higher number of male cases was observed in the 0–9, 10–19, 60–69 and 70–79 years age groups (52.7%, 50.1%, 59.5% and 57.1%, respectively) compared with female cases, whereas a nearly four times higher number of female cases was observed in the >90 years age group.²⁸ On the contrary, as of 10 March 2021, the number of confirmed COVID-19 cases is slightly higher in women both in the overall

Italian territory (51.4% in women vs 48.6% in men) and in Apulia (51.6% in women vs 48.4% in men).^{1 29}

Differences in disease incidence, morbidity and mortality between sexes have also been observed in other infectious diseases such as the severe acute respiratory syndrome coronavirus and the Middle East respiratory syndrome coronavirus with men being more susceptible than women to the infection and having a worse outcome.^{30 31} The difference in mortality between men and women suggests that women are either less prone to develop severe complications or are less likely to die because of severe complications.³²

The reasons behind these sex-related differences are probably pathogen-specific and of multifactorial origin.²⁵ The three main determinants so far proposed to explain male–female disparities in SARS-CoV-2 infection are differences in immune function associated with the X chromosome, the effects of sex hormones, gender-related behavioural and sociocultural differences.^{2 6 15 16} For example, the localisation of ACE2 and Toll-like receptor 7 genes in the X chromosome and the monoallelic versus the biallelic presence may help explain the increased risk of COVID-19 for males compared with females.³³

From a biological point of view, women seem to have a stronger immune system, weaker cytokine-based proinflammatory response and lower levels of ACE2, an essential component for the entrance of COVID-19 into the cells.^{2 15 34–36} In this context, oestrogens seem to play a key protective role. Oestrogen levels vary with age, rising in

Table 3 Multivariate logistic regression analysis of demographics and clinical characteristics of COVID-19 cases in the Foggia District, Apulia region, Italy

Characteristics	Hospitalisation		Virus clearance (no)		Deaths	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (male vs female)	1.52 (1.15 to 2.20)	0.003	1.51 (1.08 to 2.09)	0.014	2.33 (1.52 to 3.58)	0.000
Age group (\geq 55 years vs <55 years)	1.83 (1.68 to 1.99)	0.000	1.62 (1.47 to 1.78)	0.000	2.62 (2.22 to 3.07)	0.000
At least one comorbidity (yes vs no)	1.99 (1.47 to 2.69)	0.000	1.63 (1.16 to 2.29)	0.004	1.94 (1.28 to 2.93)	0.002

prepubertal individuals and decreasing with age. Thus, the age-associated decline in oestradiol levels might be an explanation for the higher susceptibility and severe progression of COVID-19 in older subjects.³⁷

Our study highlights that, alongside sex, age and comorbidity are risk factors increasing hospitalisation and death and decreasing virus clearance. That COVID-19 severity increases with age became evident since the beginning of the pandemic. Early studies from China and Italy showed that older age was associated with a greater risk of developing acute respiratory distress syndrome, severe lung disease and death.^{5 10} A recent meta-analysis of 55 studies and 10 014 COVID-19 cases confirmed that older age (≥ 50 years), together with comorbidities, significantly affects the prognosis and severity of COVID-19.³ A further study investigated whether male bias in COVID-19 mortality was maintained at every age. It analysed data collated by the National Institute for Demographic Studies from national statistical agencies across England and Wales, France, Germany, Italy, the Netherlands, Portugal, Korea and Spain, including a population of 194 349 591 men and 201 715 364 women from the beginning of the pandemic until 21 June 2020. The overall male-to-female mortality sex ratio per 100 000 population was 1.4 (crude ratio 1.3). This ratio varied with age: 0.81 for subjects aged 0–9 years; 1.9 in the 40–49 year age group; 2.3 in the 50–59 year age group; 2.6 in the 60–69 year age group; and 1.65 in subjects older than 80 years.³⁸ How the male versus female difference in mortality, hospitalisation and virus clearance progresses with age is an aspect that warrants further investigation. In this context, stratification of the sex-disaggregated data provided in our study by age group could be relevant to better understand to what extent women are genetically protected from COVID-19. Interestingly, in our study, the stratification of the population by a cut-off age of 55 years highlighted a higher hospitalisation rate in the subgroup of women aged ≥ 55 years, suggesting the role of the reduction of hormonal protection with age.

One of the main hypotheses that have been postulated to justify the observed sex heterogeneity in the immune response to SARS-CoV-2 infection is the different genetic profile. Increasing evidence from patient populations highlights a substantial contribution of human genetic factors to the diversified susceptibility to SARS-CoV-2 infection and/or COVID-19 severity. In this context, a differential response to COVID-19 has also been observed among individuals with ethnicity-based differences in their genetic profile.³³ For instance, the distribution of the gene cluster on chromosome 3, that has been recently identified as the major genetic risk factor for severe COVID-19, differs among populations of different ethnic background (ie, Asian, European and African populations).³⁹

Lastly, gender-related differences in lifestyles and social roles require careful considerations as they are believed to greatly influence the onset, course and outcome of COVID-19. It has been proposed that smoking and

alcohol consumption, alongside poor eating habits, more frequently found in men than women, may lead to a higher incidence of comorbidities in men compared with women explaining the higher male mortality observed on a global level.^{17 40} However, it must be noted that no significant difference in underlying comorbidities (except for diabetes) between men and women was found in our study. There may be other behavioural and social differences favouring women as men are more reluctant to follow hand hygiene and seek preventive care.⁴¹ However, women might be more easily exposed to SARS-CoV-2 infection in both professional and household settings. Indeed, women represent 70% of the health and social care workforce and more often care for household members with COVID-19.^{17 40}

The present study aimed to explore the differences in hospitalisation and death between men and women at the local level taking into consideration COVID-19 confirmed cases in the Apulian District of Foggia. The results are in line with what observed on a national and global level. Hospitalisation and death are hard outcomes for monitoring the course and severity of the disease. Furthermore, sex difference in virus clearance represents an added-value outcome of our study as it expresses the immune response of the host.

However, it should not be neglected that one of the main limitations of our study is that the presented data are not adjusted for lifestyle, profession, social or behavioural differences, all relevant factors that could change the interpretation of the data and could further emphasise the male bias in COVID-19 severity and fatality. This limitation is a common feature of the majority of sex-disaggregated data currently available. Indeed, due to practicability and ethical reasons, no prospective study comparing an equal number of men and women under equal conditions of viral exposure has been conducted to date. Therefore, we highlight the need of taking into account the social, familiar and professional roles, alongside biological variables, in order to fully understand the differences in COVID-19 outcome between men and women.

The main strength of our study consists in its robust methodology, which enabled an accurate evaluation of the correlation between the case demographics (especially gender) and COVID-19 clinical response. Specifically, the collection of viral clearance data highlights a statistically significant male-to-female difference and provides a plausible explanation for the observed diversified course of the disease. Furthermore, the data collected in our study are highly homogeneous as they are strictly related to the first epidemic wave and provide an accurate picture of the impact of sex and age on SARS-CoV-2 infection response in Italy during the initial phase of the pandemic. The ethnic composition of the population included in our study is also highly homogeneous and likely well representative of the Italian population or other Mediterranean European populations.

CONCLUSIONS

Despite a comparable incidence of COVID-19 among the two sexes, a male bias in COVID-19 mortality is observed in the majority of the countries with available sex-disaggregated data. Our study provides sex-disaggregated data for the COVID-19 cases of the Apulian district of Foggia, Italy. It demonstrates that male sex, alongside older age (age ≥ 55 years) and presence of at least one comorbidity, is associated with a greater risk of hospitalisation and death, and lower virus clearance. Therefore, more attention should be paid to sex as a variable for the interpretation of COVID-19 data. This study will help clinicians to make appropriate patient-tailored medical decisions based on patient sex, age and comorbidities. Future investigations providing data adjusted for gender-related factors (social, familiar and professional roles) are warranted.

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Contributors FF and RP conceptualised and designed the work, analysed and interpreted data and wrote the manuscript. DM and PLL supervised the study, coordinated regional data collection and provided statistical support. SLC, TS and VD interpreted the results and critically reviewed the advanced version of the manuscript. All authors approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with the principles expressed in the Declaration of Helsinki 1975, as revised in 2008. As this study constituted public health surveillance, ethical approval from institutional review board was not required. All data were provided and analysed anonymously.

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