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ORIGINAL RESEARCH

Sex differences in hospitalized COVID-19 patients

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Abstract

The novel coronavirus disease (COVID-19) affected females less than males, as demonstrated by sex-disaggregated data present in the literature. During the first wave, females hospitalized at San Raffaele Hospital, Milan, Italy were few in number, presented symptoms later and had less critical clinical conditions than males. The present study aimed to evaluate the epidemiological status of the female population during the second wave, which occurred in Autumn 2020 in Italy. This prospective cohort study included all patients, with a positive real-time reverse-transcriptase polymerase chain reaction for COVID-19, who attended the emergency department or were hospitalized in wards and/or intensive care unit (ICU) from 29th September 2020 to 29th November 2020. A total of 1216 COVID-19 patients were included, of whom 459 (37.8%) were females. The percentage of females admitted was 41.3% in the first period and 36.3% in the second period, without significant increase over time ($p = 0.3$). Females accounted for 25% of all COVID-19 intensive care unit admissions. There was significantly sex-based difference in the overall hospital mortality (4.1% for females and 11.3% for males, $p < 0.0001$). At San Raffaele Hospital, Milan, Italy during the second wave, female patients were few and affected by a less severe form of COVID-19. An increase over time of females hospitalized patients was not reported, unlike what was previously demonstrated during the first wave.

Keywords

COVID-19; Sex-disaggregated data; Sex; Intensive care unit; Critical care; Patient outcome; Italy

1. Introduction

The novel coronavirus disease 2019 (COVID-19) started and spread from China [1] and rapidly turned into a global pandemic, declared by the World Health Organization (WHO) on March 11, 2020 [2].

Since the beginning of the COVID-19 pandemic, case fatality differences were emerging according to sex. Numerous studies tried to investigate these differences to explain why males had worse outcomes than females [3–6]. Since the disease spread across multiple continents, the "Global Health 50/50" initiative presented an overview of sex-disaggregated data worldwide suggesting similar incidence of the disease in women and men, but an increased case fatality in men [7].

During the first COVID-19 wave in our hospital, we observed that women were few in number, presented symptoms later and were less critical than male patients [8].

The present study aims to endorse what has been previously claimed for the first wave regarding SARS-CoV-2 infection in the female population, by analyzing data obtained during the second wave, which occurred in Autumn 2020 in Italy.

2. Materials and methods

This is a prospective cohort study in line with STROBE guidelines [9]. We included all COVID-19 patients admitted to IRCCS San Raffaele Hospital, Milan, Italy from 29th September 2020 to 29th November 2020. Despite the lack of a generally identified second wave, the new increase of infection cases in Italy, after the reduction of notified cases in Summer, suggests the origin of a new COVID-19 wave. This second wave was also observed at the same time at IRCCS San Raffaele Hospital, as shown in the Fig. 1.

All patients enrolled signed a written informed consent. Patients' data were electronically stored: all data were anonymized prior to insertion in the database. Data collection included sex, age, date of admission, admission to emergency department, hospital wards and/or ICU, and mortality rate.

The main catchment area of the hospital includes the metropolitan city of Milan and the whole region of Lombardy. We included in the study all patients who had a positive real-time reverse-transcriptase polymerase chain reaction for COVID-19 from a nasal and/or throat swab and admitted to the emergency department or hospitalized within wards and/or ICU.

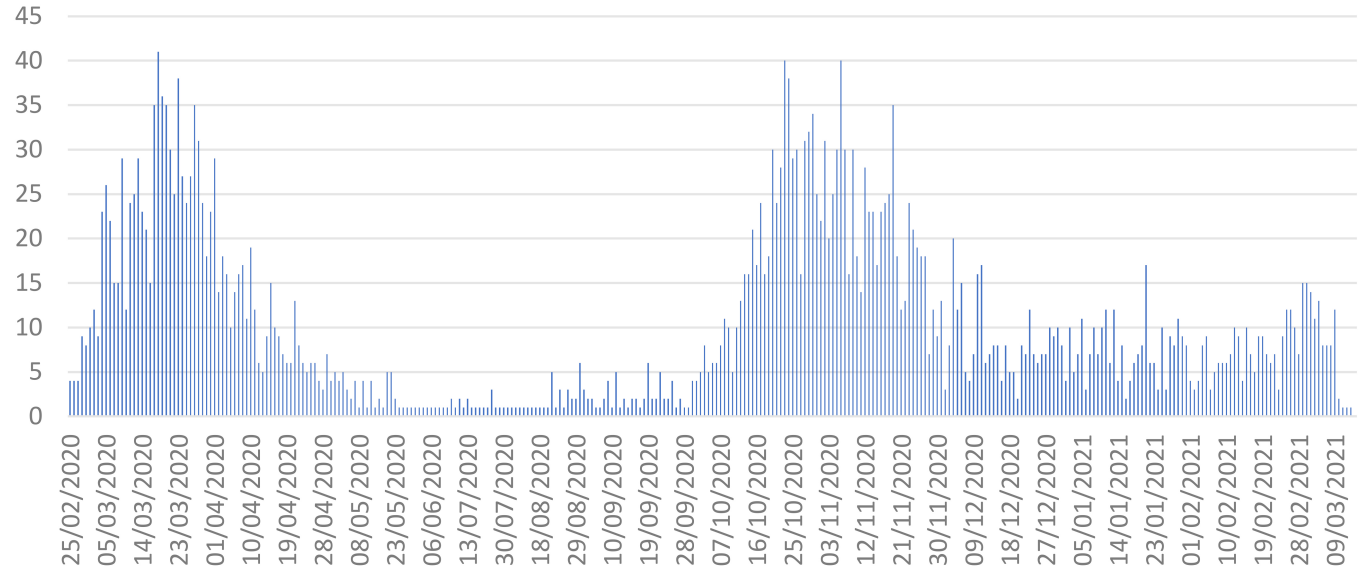

FIGURE 1. Admitted patients to San Raffaele Hospital during COVID-19 pandemic.

Following our previous methodology [8], we divided data into two study periods. Hospitalization occurred during the first 25 days of the second wave (29th September 2020–23rd October 2020) were considered as the first period and those included thereafter were considered as the second one (24th October 2020–29th November 2020).

In order to assess the influence of age-related infection status on outcomes, patients were divided into two groups: young patients aged $\leq$ 55 years and elderly aged >55 years.

Categorical variables were reported as proportions. Continuous variables were presented as mean $\pm$ standard deviation. Chi-square test, Fisher's test, and T student test were used for data analysis using MS Excel (Microsoft Office version 2011; Microsoft Corp., Redmond, WA, USA). A p-value <0.05 was considered statistically significant. Two logistic regression models were performed in order to control the confounding age variable for ICU admission rate and mortality rate.

3. Results

This study included 1216 COVID-19 patients, of whom 459 (37.8%) were females. The mean age was 61.2 $\pm$ 18.9 years, with no differences between females and males (61.7 $\pm$ 17.7 *vs.* 60.4 $\pm$ 20.8 years, respectively, p = 0.3). There was no significant increase (p = 0.3) of the percentage of female patients admitted over time: females were 41.3% (143 of 346) in the first period and 36.3% (316 of 870) in the second period.

A total of 92 patients were admitted to the ICU, of whom females accounted for only 25% (23 of 92). Notably, among male patients the ICU admission rate was 9.1% (69/757), while among female patients the ICU admission was required only in 5% of cases (23/459) (p = 0.008). The mean age of ICU patients was 63.3 $\pm$ 9.1 with no sex-based differences (64.7 $\pm$ 10.4 for females 62.8 $\pm$ 8.7 years for males, p = 0.4). Among young female patients, the ICU admission rate was 2.8% (5/176) compared with 4% among young male patients (11/272) (p = 0.6); among elderly patients, a significantly difference in the ICU admission rate was reported between female and male patients [6.4% (47/283) *vs.* 11.9% (130/486) (p = 0.012)].

Overall hospital mortality was 15.4% (187/1216). Females died less than males: mortality was 4.1% for females (50 deaths) and 11.3% for males (137 deaths) ($p < 0.001$). Young patients died less than the elderly: mortality was 2.2% for young patients (10/448) and 23% for elderly patients (177/768) (p = 0.0001).

Among young female patients, mortality rate was 1.7% (3/176) compared with 2.6% of young male patients (7/272) (p = 0.7); among elderly patients, the mortality rate was significantly different: 16.6% for female patients (47/283) and 26.8% for male patients (130/486) (p = 0.0016).

Lastly, two logistic regression analyses identified sex as an independent predictor of ICU admission rate (odds ratio (OR) 0.52; 95% confidence interval (95% CI) 0.32 to 0.86) and of mortality rate (OR 0.46; 95% CI 0.32 to 0.68).

4. Discussion

4.1 Key findings

We confirmed that in our center we had fewer female patients admitted to the emergency department or being hospitalized for COVID-19 than male (37.8% *vs.* 62.2%) and that they suffered from a less severe disease, as shown by 25% ICU admission rate. ICU admission was needed for 9.1% of hospitalized males compared to 5% of hospitalized females. Interestingly, overall hospital mortality was lower than reported during the first wave. Indeed, in our previous first wave case series overall hospital mortality was 19.5%, while during this second wave overall hospital mortality was 15.4% (176/901 *vs.* 187/1216, p = 0.012), thus suggesting an improvement in medical management over time. Furthermore, among elderly patients, both ICU admission rate and mortality rate were revealed to be increased in males compared to females.

Notably we did not observe an increase of admission rate in females over time, in contrast with what we observed during

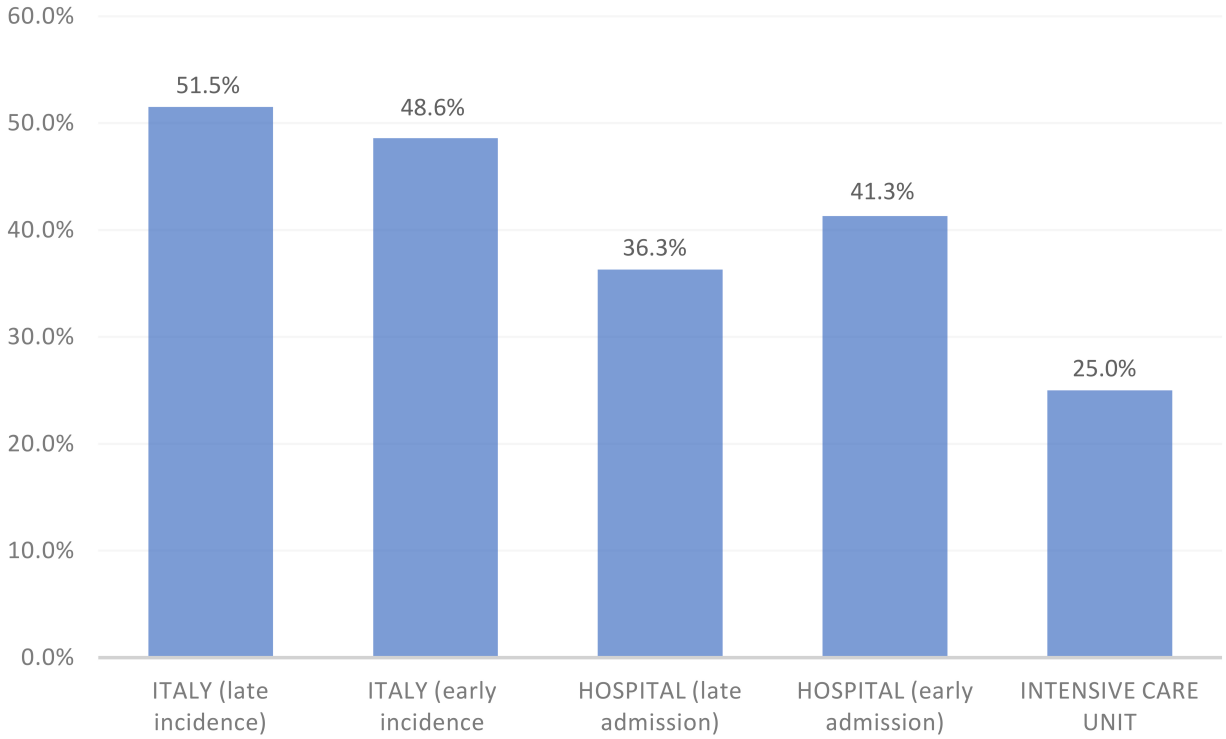

FIGURE 2. Overall percentage of female COVID-19 patients in Italy increase over time (from 48.6% to 51.5%). The percentage of female COVID-19 patients decreased in our hospital from 41.3% in the first study period to 36.3% in the second study period. In the intensive care unit, the percentage of females was only 25%.

the first wave [8]. These findings are coherent with those recorded at the national level: the Italian national statistics found an equal percentage of female COVID-19 cases, 48.6% and 51.5% respectively before and after 23rd October 2020, as shown in Fig. 2 [10].

4.2 Relationship with previous studies

Worldwide, in October 2020 females accounted for 48% of confirmed cases, 46% of hospitalizations, 31% of ICU admissions and 42% of deaths [7].

Since the beginning of the pandemic, in several countries there was the need to collect sex-disaggregated data in order to evaluate the incidence, the mortality rate and the disease treatment according to the sex. Importantly, demographic and clinical data collected globally demonstrated that the rate of COVID-19, including asymptomatic and mild forms, is similar between the sexes [11]. Instead, in our data, which include only patients hospitalized and who had attended emergency room, the percentage of females was lower than that of males both in the first and the second wave. Therefore, it is possible to hypothesize that females are affected by a less precipitating form of disease than men, hence requiring hospitalization and intensive care less frequently than men.

Regarding the other past coronavirus infections, sex differences between infected patients had been reported. For instance, both the 2003 severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) reported a male predominance and a lower case fatality rate in females when compared with males [12, 13].

The first reports of sex bias in COVID-19 patients came from China's Hubei province, where the pandemic has started. A more recent metanalysis by Li *et al.* [14] showed that females represented 40% of the COVID-19 cases.

European data also highlighted a significant male predominance in COVID-19 morbidity and mortality. Hereof, one of the first reports was a retrospective case series from Grasselli *et al.* [15] who reported that 82% of 1591 COVID-19 patients admitted to ICU were males.

In the United States, public sex-disaggregated data on COVID-19 morbidity and mortality showed that men are twice more likely to die from COVID-19 when compared to women [16].

There is a male predominance in almost every country reporting sex-disaggregated data on COVID-19 outcomes. The results reported by these studies are in agreement with those obtained in our center during the second wave. Therefore, we confirmed that sex is a risk factor for a higher severity and mortality in patients with COVID-19. In accordance with our results, the sex-based differences in lethality and ICU admissions may suggest that women are less prone to develop severe forms which lead to death.

4.3 Significance and interpretation of study findings

The reasons for this sex-based tolerance are still unknown. The possible mechanisms involved in this sex bias include social, clinical, immunological, and genetic factors. Generally, several diseases are known to have a higher incidence in men, namely cardiovascular diseases, diabetes, chronic pulmonary disease, hypertension and cancer [17], which were all found to

be linked to a higher case fatality rate for COVID-19 [18].

There is a significant sex bias in the immune response to viral infections. This bias is considered the result of male-female differences in sex chromosomes and sex hormone milieu [11]. In general, female immune system responds to pathogens more efficiently, producing higher amounts of interferon (INF) and antibodies. This effect is primarily mediated by estrogens and attenuated in postmenopausal women [19].

An unchecked inflammatory response and the subsequent cytokine storm is the main cause of severe COVID-19, which damages the lung tissue [20]. A more recent study [21] documented sex differences in immune response during the disease course of COVID-19. Indeed, females have a more robust CD4 and CD8 T cell activation than males during SARS-CoV-2 infection. By contrast, males have higher plasma levels of innate immunity chemokines and cytokines, such as interleukin 8 (IL-8), interleukin 18 (IL-18) and C-C motif chemokine ligand 5 (CCL5), and a poor T cell response. In addition, this poor T cell response was negatively correlated with patients' age, and it was associated with worse disease outcomes in male patients than in female patients.

Emerging evidence suggests that type I IFNs may reduce the virus replication [22]. Notably, a poor INF-I release, associated with an increased production of inflammatory genes, such as *interleukin 6* (*IL-6*), *C-C motif chemokine ligand 2* (*CCL2*), and *C-C motif chemokine ligand 8* (*CCL8*), was observed in response to coronavirus infection [23]. Therefore, the lack of an adequate INF response may represent a deficit in the ability of the immune system to fight COVID-19 infection and prevent severe illness [24].

Toll-like receptor 7 (TLR7) was identified as an important receptor for recognizing and responding to coronavirus infections. In addition, this receptor leads to the production of IFN. Notably, TLR7 seems to be more intensively expressed in females. Consequently, females are more likely to express a higher number of TLR7 which improves the likehood of generating a strong INF response, limiting virus evasion, and accelerating viral clearance [25].

Moreover, high IL-6 level seems to be a good predictor of severity and death in patients with COVID-19 [26]. Interestingly, females express lower levels of IL-6 in response to viral infections [27].

X chromosome inactivation and female mosaicism are particularly relevant to the sex bias observed in COVID-19 outcomes because most of the immune regulatory genes are encoded by X chromosomes, e.g., TLR, costimulatory molecules, and transcription factors. As reported by Raza HA *et al.* [28], there are some Y-linked genes, such as *transmembrane protease serine 2* (*TMPRSS2*), which role is to promote virus entry into the host cells and may highlight sex-based disparity in immune response associated with illness severity. Indeed, the cytokine storm might be influenced by genetic variability and mosaicism.

The sex difference in inflammatory response is largely driven by sex hormones. Physiological levels of estrogens in premenopausal women modulate the immune system, with an anti-inflammatory effect. Instead, low levels of estradiol and high levels of proinflammatory cytokines (IL-6, IL-8, and TNF-a) are reported in postmenopausal women [19, 29].

Firstly, SARS-CoV-2 enters in the pneumocytes via the angiotensin-converting enzyme type 2 (ACE2) receptor. It seems that females have a lower expression of ACE2 in the lungs which may possibly reduce their susceptibility to this coronavirus [30]. Interestingly, Sward *et al*. [31] have reported that females have lower levels of soluble ACE2 when compared to age-matched males. Furthermore, the serum activity of ACE2 is higher in older women (age 55 or older) than in younger women [5]. It is possible to speculate that the increase in ACE2 activity with age might be related to changes in sex hormones, particularly estrogen.

Secondly, ACE2 binds to type 1 angiotensin receptor and activates the nuclear-factor κB pathway, thus inducing vasoconstriction and inflammation [32]. Furthermore, activated estrogen receptor-α mitigates the inflammatory response induced by the nuclear-factor κB pathway and the cytokine production via immune cells (neutrophils, lymphocytes and macrophages) [33].

Finally, SARS-CoV-2 uses TMPRSS2 and a disintegrin and metalloproteinase 17 (ADAM-17) to cleave viral and cellular proteins. Estrogens can also inhibit the TMPRSS2 mRNA translation, reducing its availability to drive the infection of SARS-CoV-2 [34].

4.4 Limitations of the study

Being a single-center study is the primary limitation. However, our findings are supported by numerous studies worldwide. Another limitation is the lack of confounding variables in the database that did not allow us to proceed with a multivariate analysis.

4.5 Future perspectives

Despite this limitation, this observational study stresses again the sex gap in COVID-19 patients and the importance of more adequate treatments empowering precision medicine. Moreover, future studies may be necessary to investigate sex-based differences in immune response to COVID-19 vaccine.

5. Conclusions

We confirmed that female patients are affected by a less symptomatic form of Covid-19, resulting in a reduced rate of hospitalization, an inferior need of ICU admission and a lower hospital mortality.

AUTHOR CONTRIBUTIONS

RS acquired, analysed and interpreted work data, and drafted the manuscript. MBR designed the research study and critically reviewed the manuscript. OB acquired, analysed and interpreted work data, and critically reviewed the manuscript. PC acquired, analysed and interpreted work data, and critically reviewed the manuscript. GL designed the research study, analysed and interpreted work data, and drafted the manuscript. AZ designed the research study and drafted the manuscript. All authors read and approved the final manuscript. All authors take responsibility for all aspects of the work in ensuring that questions related to the accuracy or

integrity of any part of the work are appropriately investigated and resolved.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethical Committee of IRCCS San Raffaele Hospital, Milan, Italy (Reference no. CE 34/int/2020) on March 18, 2020. The study is in compliance with the Declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as one of the Editorial Board members of this journal. We declare that Giovanni Landoni had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to YZ.

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