

Novel Coronavirus Disease (COVID-19) in Italian Patients: Gender Differences in Presentation and Severity

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Abstract

Background: In the first wave of the novel coronavirus (severe acute respiratory syndrome coronavirus 2) infections, Italy experienced a heavy burden of hospital admissions for acute respiratory distress syndromes associated with the novel coronavirus disease (COVID-19). Early evidence suggested that females are less affected than males.

Objective: This study aimed to assess the gender-related differences in presentation and severity among COVID-19 patients admitted to IRCCS San Raffaele Hospital, Milan, Italy.

Materials and Methods: This prospective observational study included all patients admitted to the hospital between February 25 and April 19, 2020, with a positive real-time reverse-transcriptase polymerase chain reaction for COVID-19. The following data were collected: date of admission, gender, age and details of intensive care unit admission and outcomes.

Results: A total of 901 patients with COVID-19 were admitted to the hospital and provided consent for the study. Of these, 284 were female (31.5%). The percentage of admitted female patients significantly increased over time (25.9% of all admissions in the first half of the study period vs. 37.1% in the second half; $P < 0.001$). Females accounted for 14.4% of all COVID-19 intensive care unit admissions. There was no gender-based difference in the overall hospital mortality: 20.1% for females and 19.2% for males ($P = 0.8$).

Conclusions: In our hospital, which was in the epicenter of the first wave of COVID-19 pandemic in Italy, female patients were few, presented late and were less critical than male patients.

Keywords: COVID-19, critical care, gender, intensive care unit, Italy, severity

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INTRODUCTION

The novel coronavirus (COVID-19) continues to affect the world's population, and current data suggest that females are less affected than males, including differences in the severity of

the disease.^[1-3] Indeed, in a meta-analysis that included >7000 COVID-19-positive patients from various studies conducted worldwide, 53% were male and 47% were female.^[4]

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Understanding the reasons behind these differences may help gain knowledge regarding both the disease and host response and consequently with the treatment for COVID-19. Besides the challenge, this pandemic gives a unique opportunity to study an infectious disease from the very beginning.

In this report, we describe the male-to-female ratio in a large teaching hospital^[5] in Italy that serves as a COVID-19 referral center during the pandemic and also show trends over time and disease severity.

MATERIALS AND METHODS

This prospective study included all COVID-19 patients admitted to IRCCS San Raffaele Hospital, Milan, Italy, between February 25 and April 19, 2020, who provided written informed consent for participation. The study was approved by the Ethical Committee of IRCCS San Raffaele Hospital, Milan, Italy.

The main catchment area of the hospital includes the metropolitan city of Milan and the whole region of Lombardy, but frequently, patients from other regions of Italy are also admitted. Admission criteria did not differ for male and female patients.

Data collection included the date of admission, gender, age and details of intensive care unit (ICU) admission and outcomes. Data were categorized into two equal study periods, wherein admissions from February 25 to March 21 were considered as the first half and those included thereafter were considered as the second half. All included patients had a positive real-time reverse-transcriptase polymerase chain reaction for COVID-19 from a nasal and/or throat swab. Chi-square test was used for data analysis using MS Excel (Microsoft Office version 2007; Microsoft Corp., Redmond, WA, USA). $P < 0.05$ was considered statistically significant.

RESULTS

This study included 901 COVID-19 patients, of which 617 (68.5%) were male. The mean age was 65.3 (± 15.1) years, with no difference between females and males (66.6 ± 16.1 years vs. 64.7 ± 14.6 years, respectively). In terms of distribution by age, an almost equal number of patients were aged ≤ 65 years (hereafter referred to as “young”) and > 65 years (hereafter “elder”) (441 and 460, respectively). Overall, there was no difference in the rate of young and elder patients among the first and the second half of hospital admissions (young patients: 212/451 vs. 229/450 in the first and second half, respectively; elder: 239/451 vs. 221/450, respectively).

There was a significant increase ($P \leq 0.001$) in the percentage of female patients admitted over time: females represented 25.9% (117 of 451) of the patients in the first half and 37.1% (167 of 450) in the second half [Figure 1]. When stratified by age, the admissions increased among both young and elder females (young: 49 of 212 in the first half vs. 79 of 229 in the second half, $P = 0.008$; elder: 68 of 239 in the first half vs. 88 of 221 in the second half, $P = 0.01$).

A total of 111 patients were admitted to the ICU, of which females accounted for only 15.3% (17). The mean age of these patients was 61 ± 11.2 years, with no gender-based differences (61 ± 8.4 years for females vs. 61 ± 11.6 years for males).

Overall hospital mortality did not differ according to gender: 20.1% for females (57 deaths) and 19.2% for males (119 deaths) ($P = 0.8$). The mortality rate was significantly different when compared by age group, regardless of the gender: 8.6% for young patients (38/441) and 30% for elder patients (138/460) ($P < 0.001$). Among young female patients, the mortality rate was 10.9% (14/128) compared with 7.6% among young male patients (24/313) ($P = 0.3$); among elder female patients, the mortality rate was 27.6% (43/156), and it was 31.2% among elder male patients (95/304) ($P = 0.41$).

DISCUSSION

In our center, the number of COVID-19 female patients hospitalized were fewer (31.5%), had delayed clinical presentation (as suggested by admissions rates of 25.9% in the first half vs. 37.1% in the second half) and suffered from a less severe form of the disease (14.4% ICU admission rate).

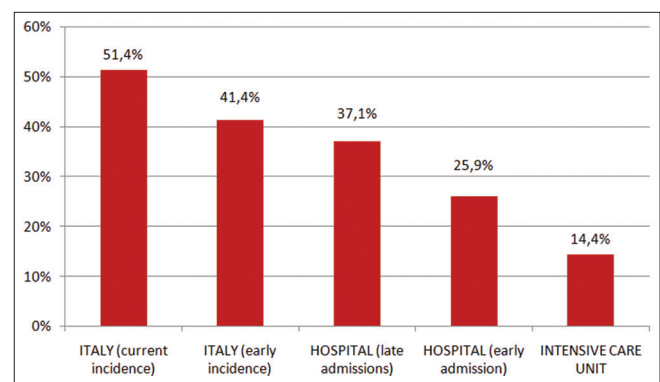


Figure 1: Overall percentage of female severe acute respiratory syndrome coronavirus 2-positive patients in Italy increased over time (from 41.4% to 51.4%). The percentage of COVID-19 female patients increased in our hospital from 25.9% in the first half to 37.1% in the second half of the study period. In the intensive care unit, the percentage of females was only 14.4%

Interestingly, the time-dependent increase in the female cases observed in our hospital was evident also in the Italian national statistics: 41.4% of confirmed cases were female up to March 21, but this percentage increased to 51.4% by April 24, 2020 (in Italy, females comprise 51.6% of the overall population).^[6] Similarly, these findings are also comparable with data from China: 48.6% of the Chinese COVID-19 patients are females, which corresponds to the 48.2% overall female population of the country.^[7]

National data take into account all COVID-19-positive cases, including asymptomatic and mild forms. The authors speculate that suffering from less severe infection with delayed clinical presentation, females get tested later for the disease, and thus are later recorded in statistics, as well as require hospitalization less frequently (as seen in our hospital, where they only accounted for 31.5% of all cases). Even when hospitalized, the unfavorable evolution of the pathology in females is not as common as in males, as confirmed by the lower ICU admission rate (14.4% in our hospital).

A clear understanding of this gender gap in COVID-19 infection and outcome is lacking, although several hypotheses have been made in recent literature.^[8-14] Several hormonal, biological and behavioral factors may be involved to explain this difference. Many pathological conditions are known to have a higher incidence in males, such as cardiovascular diseases, trauma accidents, sepsis and septic shock,^[15] with animal studies showing that females may have beneficial immunologic and cardiovascular responses to infections.^[16,17] Previous data from septic shock patients showed a male prevalence between 54% and 61% for this life-threatening condition,^[18] and although the reason for this gender-related inconsistency has not been determined, evidence suggests that different hormonal settings (with estrogens being the most involved) are intimately involved in the immune response difference.^[19]

Insight into pathogenesis of COVID-19 may be crucial to understand the gender gap. In affected patients, the host response to the viral infection seems to be a determinant in the development of the severity of the disease, toward a dysfunctional immune reaction, involving a hyperinflammation and cytokine storm. Cytopathic viruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) may cause a highly inflammatory form of apoptosis in the airway epithelial cells of infected subjects, which is known as pyroptosis. This mechanism triggers the subsequent inflammatory response responsible for the above-cited cytokine storm.^[8]

Increased levels of cytokines and chemokines are a hallmark of severe disease, and interleukin (IL)-6 plasma levels were found to be higher in nonsurvivors than in survivors from a cohort of COVID-19 Chinese patients.^[9]

Moreover, both the 2002 SARS-CoV-1 epidemic and the current SARS-CoV-2 pandemic interact with the renin-angiotensin-aldosterone system. The two viruses share 76% of protein identity, thus explaining the reason both interact with the cellular receptor angiotensin-converting enzyme 2 (ACE2) through which these viruses seem to gain entry in the host. Notably, females were found to have lower expression of this receptor in the lungs,^[20] possibly reducing their susceptibility to this coronavirus. Furthermore, ACE2 binds to type 1 angiotensin receptor and activates the nuclear-factor κ B pathway, thus inducing vasoconstriction and inflammation.^[21] However, despite these findings, the regulation and expression of the ACE2 gene, which is located on the X chromosome, remain to be further understood. In addition, to complete the infection of the host, SARS-CoV-2 requires the cleavage of viral and cellular proteins, performed by the TMPRSS2 and ADAM17 co-receptors. Possibly, estrogens are capable of inducing the inhibition of TMPRSS2 microRNA (mRNA) translation, thus reducing its availability to drive the infection of SARS-CoV-2.^[13] Furthermore, ADAM17 is also involved in the activation of proinflammatory cytokines and cytokine receptors.

Posttranscriptional modulation of gene expression can further be regulated by sex hormones (estrogen, progesterone and androgen) and by mRNAs, where the X chromosome is particularly enriched of mRNAs. With regard to sex hormones, progesterone, by mitigating the inflammatory response inhibiting the proinflammatory cytokines (IL-1 β and IL-12) and by promoting anti-inflammatory cytokines (IL-4 and IL-10) through T-helper 2 cells, might play a role in the prevention of severe outcome of COVID-19.^[14,22,23] At the same time, periovulatory dosages of estrogen may inhibit IL-6, IL-8 and tumor necrosis factor- α .^[24] In addition, activated estrogen receptor- α is capable to mitigate the inflammatory response induced by NF- κ B and the cytokine production via immune cells (neutrophils, lymphocytes and macrophages).^[25]

The findings of this study need to be considered in light of the study's limitations. The study presents data from a single referral center; nonetheless, the male-female ratio of our hospitalized patients reflects the national statistics. Second, a patient's admission to ICU was limited to the availability of beds. Notably, this issue was not specific to our center,

but this problem was experienced by all referral hospitals involved in the management of COVID-19 patients. Despite the limitations, the findings from this observational study focus on the gender gap in COVID-19 patients, which may trigger the development of more adequate treatments empowering precision medicine.

CONCLUSIONS

According to the observations of this study, female patients are affected by a slower and possibly less symptomatic form of the disease, resulting in a reduced and delayed rate of hospitalization and an inferior requirement for ICU admission.

Ethical considerations

This study was approved by the Ethical Committee of IRCCS San Raffaele Hospital, Milan, Italy (Reference no. CE 34/int/2020) on March 18, 2020. All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki, 2013.

Peer review

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: Clinical response to viral infection. *J Biol Regul Homeost Agents* 2020;34:339-43.
- Pérez-López FR, Tajada M, Savirón-Cornudella R, Sánchez-Prieto M, Chedraui P, Terán E. Coronavirus disease 2019 and gender-related mortality in European countries: A meta-analysis. *Maturitas* 2020;141:59-62.
- Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender differences in patients with COVID-19: Focus on severity and mortality. *Front Public Health* 2020;8:152.
- Galbadage T, Peterson BM, Awada J, Buck AS, Ramirez DA, Wilson J, et al. Systematic review and meta-analysis of sex-specific COVID-19 clinical outcomes. *Front Med (Lausanne)* 2020;7:348.
- Zangrillo A, Beretta L, Silvani P, Colombo S, Scandroglio AM, Dell'Acqua A, et al. Fast reshaping of intensive care unit facilities in a large metropolitan hospital in Milan, Italy: Facing the COVID-19 pandemic emergency. *Crit Care Resusc* 2020;22:91-4.
- EpiCentro. Sorveglianza Integrata COVID-19 in Italia [Internet]. Available from: https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_24aprile%20ITA.pdf [Last accessed 2020 Oct 01].
- The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) China, 2020. *China CDC Weekly* 2020;2:113-22.
- Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. The trinity of COVID-19: Immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363-74.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 2020;395:1054-62.
- Capuano A, Rossi F, Paolisso G. Covid-19 kills more men than women: An overview of possible reasons. *Front Cardiovasc Med* 2020;7:131.
- Zeng F, Dai C, Cai P, Wang J, Xu L, Li J, et al. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: A possible reason underlying different outcome between sex. *J Med Virol* 2020;92:2050-4.
- Al-Lami RA, Urban RJ, Volpi E, Algburi AM, Baillargeon J. Sex hormones and novel corona virus infectious disease (COVID-19). *Mayo Clin Proc* 2020;95:1710-4.
- Pontecorvi G, Bellenghi M, Ortona E, Carè A. microRNAs as new possible actors in gender disparities of Covid-19 pandemic. *Acta Physiol (Oxf)* 2020;230:e13538.
- Salvati L, Biagioni B, Vivarelli E, Parronchi P. A gendered magnifying glass on COVID-19. *Clin Mol Allergy* 2020;18:1-1.
- Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: Final data for 2014. *Natl Vital Stat Rep* 2016;65:1-22.
- Angele MK, Wichmann MW, Ayala A, Cioffi WG, Chaudry IH. Testosterone receptor blockade after hemorrhage in males. Restoration of the depressed immune functions and improved survival following subsequent sepsis. *Arch Surg* 1997;132:1207-14.
- Kuebler JF, Jarrar D, Toth B, Bland KI, Rue L 3rd, Wang P, et al. Estradiol administration improves splanchnic perfusion following trauma-hemorrhage and sepsis. *Arch Surg* 2002;137:74-9.
- Campanelli F, Landoni G, Cabrini L, Zangrillo A. Gender differences in septic intensive care unit patients. *Minerva Anestesiol* 2018;84:504-8.
- Kotimaa J, Klar-Mohammad N, Gueler F, Schilders G, Jansen A, Rutjes H, et al. Sex matters: Systemic complement activity of female C57BL/6J and BALB/cJ mice is limited by serum terminal pathway components. *Mol Immunol* 2016;76:13-21.
- Li Y, Zhou W, Yang L, You R. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. *Pharmacol Res* 2020;157:104833.
- Jia H. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease. *Shock* 2016;46:239-48.
- Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016;16:626-38.
- Szekeres-Bartho J, Wegmann TG. A progesterone-dependent immunomodulatory protein alters the Th1/Th2 balance. *J Reprod Immunol* 1996;31:81-95.
- Straub RH. The complex role of estrogens in inflammation. *Endocr Rev* 2007;28:521-74.
- Biswas DK, Singh S, Shi Q, Pardee AB, Iglehart JD. Crossroads of estrogen receptor and NF-kappaB signaling. *Sci STKE* 2005;2005:pe27.