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Men with COVID-19 die. Women survive

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ABSTRACT

The severity and mortality rate of COVID-19 differ between the sexes. Several biopsychosocial determinants may account for the better outcomes in women. The notion that sex steroid hormones account for the gender disparity is reasonable but not proven; the same is true of the role of menopause as a risk factor. A retrospective analysis of patients (\(n=1764\)) hospitalized in Italy showed a higher mortality (HR 1.58, 95%CI 1.30–1.91, adjusted for age and multi-comorbidities) in males only after the age of 65 (the rate is twice as high in the 65–79-year age group and 1.5-fold higher in those aged over 80). The higher mortality of men is mostly evident among those aged over 65 years, long after the average age of menopause.

1. Introduction

Biological sex influences immune responses and specific risk factors for SARS-CoV-2 infection. Both biomedical and psychosocial determinants contribute to the gender issue of the COVID-19 pandemic in terms of incidence, fatality, long-term sequelae and immunological response to vaccines [1,2]. Therefore, stratification of data by sex and not only by age is mandatory in every trial in order to gain a deep understanding of the interplay between genetic sex, sex hormones and resiliency to SARS-CoV-2 infection. Whether menopause, an estrogen deficiency state favoring the Th1 innate cellular response and usually occurring at midlife, should be considered a risk factor for disease state and severity in women remains to be fully elucidated [3].

Males with COVID-19 display greater upregulation of pro-inflammatory cytokines and most of the biomarkers tested in the context of the risk of infection and the severity of COVID-19 differ by sex at baseline within healthy populations [1,3]. Indeed, two primary receptors for priming and cellular invasion, angiotensin-converting enzyme-2 (ACE-2) and type II transmembrane serine protease (TMPRSS2), are more prevalent in males than in females [1,3]. However, several comorbidities and risk factors are also overrepresented in men than in women and may explain the gender disparity in mortality [1]. In addition, X-linked gene expression may serve better survival of women playing a possible role in the course, outcomes, and prognosis for COVID-19\textsuperscript{1,3}. On the other hand, women displayed a higher infection rate due to a more frequent exposure to SARS-CoV-2\textsuperscript{1}.

Here, we present a single-center retrospective analysis of patients admitted to the Hub COVID-Hospital IRCCS San Matteo Foundation (Pavia, Italy) in Lombardy, Italy, where the first case of COVID-19 in Italy (on February 20, 2020) was diagnosed. Stratification by sex and age will allow further exploration of the potential role of menopause in the progression to severe Covid-19 illness.

2. Methods

We retrieved demographic characteristics, number of comorbidities and survival status of patients hospitalized at IRCCS San Matteo Foundation (Pavia, Italy) for COVID-19 in a pre-vaccination era (between February and December 2020) and included in the local SMAtteo COvid19 RGistry (SMACORE). We compared 30-days mortality between males and females, overall and by age groups (18–49, 50–64, 65–79, 80+ years). The cut-off of 50 years reflects the epidemiological reality of menopause in our country. Local ethics committee (IRCCS San Matteo Foundation, Pavia, Italy) approved this observational research.
Fig. 1. Comparison of 30-days mortality between males and females COVID-19 patients. (A) Overall survival in males and females adjusted for age groups and presence of multi-comorbidities. (B) Subgroup analysis by age groups showing mortality rates in males and females: rates per 100 person years are reported with 95% confidence interval. (C) Forest plot showing in each age group the effect of gender on mortality adjusted for presence of multi-comorbidities resulting from four bivariable Cox models. The Hazard Ratios (HR) with their 95% confidence interval in Log scale are shown.
3. Results

A total of 1764 patients [696 (39%) females and 1068 (61%) males] hospitalized for COVID-19 were enrolled and followed for a median time of 14 days (IQR: 9–24 days). Females were significantly older than males [median age (IQR): 74 (58–84) vs 69 (58–78) years respectively, \( p<0.001 \); 1434 (81%) patients had multiple comorbidities, with no difference between gender both overall (\( p = 0.755 \)) and in each age group. Overall, COVID-19 mortality was 27.7% (488 patients). We observed 4 cases in the 18–49 years group; 39 in the 50–64, 192 in the 65–79 and 253 in the 80+ group. Males were 321 (30%) and females were 167 (24%). At Cox multivariable analysis males had a higher mortality (HR 1.58, 95%CI 1.30–1.91, \( p<0.001 \), after adjustment for age and multi-comorbidities) (Fig. 1A). In the pre-defined subgroup analysis by age groups (Fig. 1B), difference in mortality rates was only observed in patients aged 65 or more. Mortality, adjusted for comorbidities, was twice as higher in males in the 65–79 and 1.5 higher in the 80+ group (Fig. 1C). Similar findings were obtained when adjusting for intubation.

4. Discussion

Our analysis showed that fewer women than men were hospitalized for COVID-19. In spite of being older, women displayed a lower mortality (similar to the findings reported in another study conducted in Lombardy [4]) but differences compared to men were evident only over the age of 65 years and persisted over the age of 80 years. Whether this gender disparity reflects genetic fingerprints or results from low testosterone levels predicting the most severe clinical outcomes in men [5] remains to be determined.

A recent multicenter retrospective cohort study conducted in China showed no difference in hospital mortality in premenopausal women (cut-off ≤55 years of age according to the previous epidemiological data from China) compared with the same age men, whereas there was a significant difference in women over 55 (postmenopausal) in respect with men of the same age group [6]. Interestingly, differences in mortality between premenopausal and postmenopausal women were not significant, questioning the role of estrogen in the gender gap in COVID-19 pandemic death rates [6]. Our data reporting a similar mortality rate in the age range 50–64 between men and women seems to confirm that hormonal changes occurring around the menopause do not promote worse outcome in the short term. Potential limitations of the present analysis were using 50 years as a crude proxy for menopausal status and lacking information on the use of exogenous hormones (contraception or menopausal treatments) in our sample. We believe that only studies including women across the menopausal transition or comparing postmenopausal women taking or not hormone therapy will allow clarifying whether circulating estrogens account for the gender disparity in COVID-19 infection severity, mortality and other long-term outcomes.

We can conclude that the higher mortality of men is mostly evident over 65 years, long after the average age of menopause. A combination of biological, behavioral, and psychosocial factors may account for gender disparity. Anyway, be that as it may, sex-disaggregated data can help to prioritize public health interventions and to guide vaccine intentions.

Contributors

Virginia V. Ferretti participated in the study design, performed the data analysis and drafted the manuscript.

Catherine Klersy participated in the study design, supervised the data analysis and critically revised the manuscript.

Raffele Bruno participated in the care of hospitalized patients.

Sara Cutti collected the data in the local SMAtteo COVID19 Registry (SMACORE).

Rossella E. Nappi participated in the study design, critically revised the data and wrote the final version of the manuscript.

All authors gave final approval of the version to be published.

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Ethical approval

This study was approved by the local ethics committee (IRCCS San Matteo Foundation, Pavia, Italy).

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Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The data are impossible to anonymize.

Declaration of competing interest

The authors declare that they have no competing interests.

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