

Gender differences in COVID-19 patients: a regional survey among physicians of Internal Medicine Wards

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ABSTRACT

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has infected millions of individuals around the World. Hypertension (HT), chronic heart disease (CHD), and diabetes mellitus (DM), particularly in the elderly, increase susceptibility to SARS-CoV-2 infection. However, conflicting results [such as coronavirus 2019 (COVID-19) disease vulnerability, case fatality, *etc.*] have been reported about the response to infection and COVID-19 outcomes in men and women. Therefore, understanding predictors of Intensive Care Unit (ICU) admission might help future planning and management of the disease. We conducted a multicenter survey about COVID-19 involving internists from Internal Medicine Wards. This survey indirectly allowed us to analyze the information of 2400 patients hospitalized in 35 wards of Internal Medicine of the Campania Region between July and October 2020. Our investigation has detected that the infection is more frequent in males, and the number of male patients hospitalized in ICU is also higher than females, with a large proportion of hypertensive patients. Extensive prospective studies are required to confirm this finding and explore the mechanisms for which hypertensive males are exposed to a higher proportion of admission to ICU and higher case fatality rates.

Introduction

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has infected millions of indi-

viduals worldwide: up to 22nd November about 58 million cases have been reported, with more than one million deaths.¹ The elderly and people with chronic conditions, such as hypertension and diabetes mellitus, show increased morbidity and are more likely to be hospitalized and admitted to Intensive Care Units (ICUs). These considerations seem to be particularly true for hypertensive patients.²⁻⁴ The analysis by gender has reported a similar number of men and women affected by SARS-CoV-2 infection, although mortality seems higher in men. In this regard, it has been reported that the male gender is also more sensitive due to the higher number of smokers in men than in women.⁵ In addition to lifestyle habits, other gender-related aspects - including metabolism, immunologic reactivity, and drug response- have been described as potential explanations for these observations.⁶ These preliminary findings highlight the need to identify the predictors of admission to ICU, which, appropriately diversified by gender, can be useful for managing SARS-CoV-2 infection.

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Materials and Methods

We conducted a multicenter survey involving physicians who attended to patients affected by coronavirus disease 2019 (COVID-19) and hospitalized in

Campania in July–October 2020. The physicians are not included in the study population for evaluating the outcome, case fatality *etc.* Only the respondents who answered all the questions were included in the final sample, pre-specifying that the average time to complete the survey was ten minutes and that the participants would receive no incentive for its completion. Among the 85 wards of Internal Medicine in the region, 35 of them (41%) have agreed to join the study. The database was too big to be included in the article. Moreover, to better explain the kind of data, we specify that the data set consists of 2400 records, *i.e.*, every hospital that had answered the survey. For each hospital, the returned data (the answers) were continuous data (*e.g.*, the number of male nurses, the number of female patients, *etc.*) It is performed under article 89 of the General Data Protection and Regulation, which allows the processing of personal data for archiving

purposes in the public interest, scientific or historical research purposes, or statistical purposes, provided that technical and organizational measures are in place to ensure the principle of data minimization.^{7,8} An online questionnaire was distributed among the Internal Medicine wards to collect epidemiological, clinical, and outcomes data about COVID-19 patients, followed throughout their hospital stay, starting from the Emergency Room. Patients have been pseudonymized by assigning each one an identification code. Every Internal Medicine Ward specified at least one physician, trained in processing the information, collected and developed on 26 items. Twenty-four of these items describe a gender perspective (12 items for men and 12 for women) (Table 1). For example, it was surveyed, in relation to gender, how many health workers were currently on the ward; how many patients hospitalized from February 1 to date have been tested pos-

Table 1. Items included for the study.

Item	Questions	Mean (standard deviation)
A	Male physicians	5.8 (3.9)
B	Female physicians	4.6 (5.6)
C	Physicians and nurses	12.3(9.2)
D	Female nurses	13.2 (8.2)
E	Male patients admitted to Internal Medicine Ward	9.5 (7.7)
F	Female patients admitted to Internal Medicine Ward	8.8 (8.4)
G	Male physicians positive for SARS-CoV-2	0.8 (1.3)
H	Female physicians positive for SARS-CoV-2	0.5 (0.9)
I	Male patients positive for SARS-CoV-2	8.1 (14.3)
J	Female patients positive for SARS-CoV-2	7.3 (13.6)
K	Male patients positive for SARS-CoV-2 have died	1.6 (2.5)
L	Female patients positive for SARS-CoV-2 have died	1.0 (1.7)
M	ADE COVID-19 related treatments have been recorded in male patients	0.4 (0.9)
N	ADE COVID-19 related treatments have been recorded in female patients	0.2 (0.4)
O	COVID positive male patients have required resuscitation therapy	1.7 (2.8)
P	COVID positive female patients have required resuscitation therapy	1.0 (2.0)
Q	COVID positive male patients had P/F values <300	6.3 (10.7)
R	COVID positive female patients had P/F values <300	3.2 (6.4)
S	COVID positive male patients had P/F values >300	4.1 (7.0)
T	COVID positive female patients had P/F values >300	3.9 (7.3)
U	COVID positive male patients had CRP values between 0.5-10 mg/mL	3.5 (7.5)
V	COVID positive male patients had CRP values between 0.5-10 mg/mL	3.7 (7.8)
W	COVID positive male patients had CRP values >10 mg/mL	6.4 (9.8)
X	COVID positive female patients had CRP values >10 mg/mL	3.8 (6.3)
Y	COVID positive male patients presented some comorbidities >3	7.2 (12.3)
Z	COVID positive female patients presented some comorbidities >3	5.4 (9.9)

ADE, adverse drug events; CRP, C-reactive protein.

itive for COVID-19 (diagnosis confirmed by RT-PCR performed on nasopharyngeal or throat swab samples); among them, how many have died and how many COVID-positive patients had P/F values <300 or >300 ; as well as how many patients showed C-Reactive Protein values between 0.5-10 mg/mL and how many above 10. The number of comorbidities per patient was also assessed, including hematological or oncological morbidities. Ultimately, we collected outcomes, such as hospital discharge, admission to ICU, or death. The electronic data were transmitted with the modern cryptography systems over the web and stored in a locked, password-protected computer. All collected records were then quality checked by two authors (T.C. and V.D.P.). Statistical analysis was performed using R version 4.0.0 (released on 2020-04-24). Statistical significance α was fixed to 0.05. Numerical variables were reported as mean (SD) and compared through paired t-test.

Results

On 35 hospital wards, the data of 2400 records (Table 1). While the difference between the two sexes regarding the positivity of the swab is not statistically significant, the difference in mortality is at the border of significance. Similarly, at the threshold of significance, the difference between COVID-positive males and females in need of admission to ICU. However, among patients admitted to ICU, the number of comorbidities was higher; overall, the number of morbidities was higher in COVID-positive males than in females (7.2 compare 5.4, $P<0.05$). Also, in the context of comorbidities, the number of COVID-positive males with more than 3 morbidities was higher than the number of COVID-positive females. Furthermore, the gender difference in the exchange parameters was very significant since positive males with a P/F <300 were almost twofold compared to females (6.3 in males compared to 3.2 in females; $P<0.05$). A similar gap was recorded for the two sexes concerning C-reactive protein, for values >10 mg/mL (6.4 in males compared to 3.8 in females; $P<0.05$) (Table 2).

Discussion

We observed that males had a significantly higher proportion in COVID-19 infection than females with a higher fatality rate. Therefore, in our cohort and in agreement with those from other groups, the male gender is a risk factor for a poor clinical outcome.¹¹ In particular, in males, a P/F ratio <300 and higher C-reactive protein levels were more frequent. In addition, it has been widely reported that male patients were more frequently admitted to ICU,¹² although this

feature, in our survey, is at the border of significance. The explanation for the greater vulnerability of males to SARS-CoV-2 infection with a worse outcome remains largely unknown.¹²⁻¹⁴ In this regard, some hypotheses can be advanced both in an immuno-biological key. With aging, the functional competence of immune responses decreases, and this reduction is more remarkable in males.⁶ These functional changes, involving innate immunity and acquired specific immunity cells, are likely to increase the risk of autoimmune diseases and cancer.¹⁵⁻¹⁷

With regard to gender, significant differences between the two sexes have been reported. For example, it has been observed that the activity of pattern-recognition receptors, production of acute phase proteins (e.g., TNF- α), and phagocytosis are higher in females than males.¹⁸⁻¹⁹ These features could explain a more vigorous response to microbial invasions and a more efficient elimination of microorganisms. In particular, the high production of IL-6 in adipose tissue can act as a stimulus for hepatocytes to produce acute phase reactants such as C-reactive protein.²⁰ The increased expression of adipose tissue, which is observed in the male with senescence, could be an additional factor in promoting the increase of C-reactive protein levels in baseline and even more so following an inflammatory trigger.²¹ According to literature search, our data involved high levels of IL-6 and P/F ratio <300 in the male gender, as a crucial factor of the negative outcome. However, our data are in accordance with other studies about ICU admission in male patients.¹² Besides a wide range of factors, sex should be one of the criteria to consider to select the appropriate therapies for the *right* patient. That is why there is a need for extensive, unbiased studies that also account for gen-

Table 2. Paired t-test.

Items comparison by Table 1	Mean of differences	P
A-B	1.1	0.151
C-D	-0.9	0.591
E-F	0.6	0.552
G-H	0.2	0.056
I-J	0.8	0.576
K-L	0.6	0.055
M-N	0.2	0.163
O-P	0.8	0.055
Q-R	2.9	0.034
S-T	-0.1	0.835
U-V	-0.2	0.617
W-X	3.0	0.007
Y-Z	1.8	0.037

der differences, to find patient-tailored therapies. Our study has several limitations. First, the use of questionnaires may allow a certain level of uncertainty, especially for the risk of incomplete responses. The online survey is designed with closed-ended questions, all of which are required for final validation, thus reducing this hazard. Second, the survey includes hospitalized patients and assesses clinical features and outcomes only of patients with the confirmed disease by nasal or pharyngeal swabs. Therefore, we might have missed those patients with early infection and negative tests. Third, this study was conducted in few hospitals; the sample size and selection bias might limit therefore interpretation of our findings.

Conclusions

SARS-CoV-2 is a novel coronavirus that emerged in Wuhan (China) markets in late December 2019. It induces predominantly respiratory symptoms, but also other manifestations are possible, for example, cardiologic or neurological. The prognosis is worse in the elderly and in multimorbid subjects, but there is also an important prognostic difference according to sex. In this matter, since the beginning of the outbreak, there has been increased morbidity and mortality among males. Concurrently, the number of males admitted to the ICU for COVID-19 is also higher. Our survey has confirmed this gender difference in the distribution of the disease, extending it to health care workers of the internal medicine ward, which are mainly represented by males among the medical staff.

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