CO-St (COVID 19-study): sex differences in the treatment of COVID-19

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Patient consent for publication: all patients were informed about the study's objectives, procedures, potential risks, and benefits, and they voluntarily agreed to participate by providing written informed consent.

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ABSTRACT

Since December 2019, with the spreading of the pandemic, a lot of medical centers registered data about their patients. In Italy, the most relevant quantity of patients was hospitalized in internal medicine wards. In this observational, retrospective cross-sectional study, all data of the COVID-19 patients admitted to some Lazio hospitals from March 01 to December 31, 2020, were collected, and their epidemiological data, demographics, signs and symptoms on admission, comorbidities, laboratory findings, chest radiography and computed tomography findings, treatment received, and mortality rate were analyzed to find any differences between sexes in terms of disease gravity. Clinician details were registered on a database (one for each hospital). Cost analysis was performed taking into account the length of stay and the employed antiviral drugs, using the point of view of the Italian Healthcare System. A total of 2256 patients with a mean age of 71.01±28.02 years were included. For men, the frequency of hypertension, chronic obstructive pulmonary disease (COPD), use of oxygen therapy, and tocilizumab was significantly higher, and the epidemiological link was related to the rehabilitation ward and community. The length of stay was found to be longer for men than women. No strong difference by sex was observed in terms of death rate. Considering antiviral drugs and hospitalization duration, on average a man costs €591.2 more than a woman. In conclusion, in male patients, hypertension and COPD were observed more frequently, and the epidemiological link was related to the rehabilitation ward and the community. In female patients, the epidemiological link was related to the hospital, and we observed significantly higher atypical chest X-rays. Tocilizumab, oxygen therapy, and antiviral drugs were prescribed more in male subjects. We did not find differences based on sex in other treatments and outcomes. Future studies should be carried out to get a more comprehensive understanding of sex differences in COVID-19 treatment.

Introduction

A new Coronavirus emerged in late 2019 and resulted in several pneumonia cases in China, in the Hubei region.[1] This virus quickly spread to numerous other countries, and in February 2020, the World Health Organization (WHO) defined the disease, triggered by this Coronavirus, as COVID-19.[2,3] On March 11, 2020, the WHO declared the COVID-19 pandemic, with 118,000 cases in 114 countries and 4291 deaths from COVID-19. The analysis by sex did not show significant differences in terms of number of men and women affected by SARS-CoV-2 infection, although the mortality seems to be higher in men. In this regard, it has been reported that the male sex is also more sensitive due to the higher number of smokers in men than in women. Different studies reported that men seem to be more susceptible to COVID-19-related complications, and they represent between 50% and 82% of hospitalized patients.[4-7] Different factors can contribute to the different sex response to COVID-19.[8] In this regard, immune senescence is a major contributory factor increasing susceptibility of older adults to infection.[9] Men experience a stronger 'inflammation' syndrome than women. In terms of COVID-19, it is interesting that the aging lung is characterized by a state of heightened basal inflammation, with levels of interleukin (IL)-6, amongst other cytokines, significantly higher in the bronchoalveolar-lavage fluid of healthy older adults when compared to their younger counterparts.[10]

This report aims to analyze by sex the epidemiologic features, epidemiological links, comorbidity, drug therapy and computerized tomography (CT) findings by sex in COVID-19 patients admitted to different hospitals in Lazio (Italy) from March 01 to December 31, 2020.

Materials and Methods

Sample size calculation

All patients admitted to participating centers were included in the study. According to the protocol approved by the Ethics Committee, the minimum number of patients per center is 250. The number of hospitals involved in the study is equal to 9, whereas the overall number of patients included is 2256.

Study design

In this multi-center retrospective cross-sectional study, we included data on COVID-19 patients. Written informed consent was obtained from the patients for the publication of individual data before enrolment. Different authors were responsible for data gathering. Missing data were obtained by direct communication with attending doctors and other healthcare providers. Sensitivity analysis was carried out to determine the robustness of the study and identify anomalous data.

Study setting and population

We included data from all COVID-19 patients (n=2256) admitted from March 01 to December 31, 2020, to the internal medicine wards of the COVID-19 hospitals in Lazio (Italy) involved in this study. Data were collected from an electronic archive with laboratory confirmation of SARS-CoV-2 infection using real-time reverse transcription polymerase chain reaction (RT-PCR). We excluded all patients with negative laboratory tests for SARS-CoV-2 infection. According to the Italian Government protocol, patients were admitted centrally to the COVID-19 hospitals from the entire region, without selectivity. After the admission to the internal medicine ward, the sample was stratified by sex. Epidemiological data, demographics, signs and symptoms on admission, comorbidities, laboratory findings, chest radiography and CT findings, treatment received, and mortality rate were analyzed by sex. Epidemiologic, demographic, clinical, laboratory, and management (multidisciplinary assessment, delivery methods, and treatments) data from patients' medical records were collected using a checklist from an available clinical data record.

Chest X-ray COVID-19 reporting classification is based upon a recommendation from the Radiological Society of North America as typically having multifocal peripheral opacities with differential diagnosis of drug toxicity, influenza pneumonia, and organizational pneumonia, indeterminate as non-peripheral consolidation with a differential of lots of infectious processes, atypical with uncommon imaging features and negative.[11]

Study protocol

In this study, 2256 patients with a mean age of 71.01 ± 28.02 years were included (56% males).

The incubation period was defined as the interval between the potential earliest date of contact with the transmission source (wildlife or person with a suspected or confirmed case) and the potential earliest date of symptom onset (*i.e.*, cough, fever, fatigue, or myalgia). Laboratory confirmation of SARS-CoV-2 infection was done at COVID-19 hospitals involved in the study using real-time RT-PCR.[9] Other respiratory viruses, including influenza A and B virus, respiratory syncytial virus, parainfluenza virus, and adenovirus were also tested for by real-time RT-PCR. Throat swab specimens from the upper respiratory tract were obtained from all patients at admission and maintained in a viral transport medium. Sputum or endotracheal aspirates were obtained at admission for the identification of possible causative bacteria or fungi. Clinical outcomes were followed up to December 31, 2020. The patient had been discharged from the hospital per the following discharge criteria: body temperature returned to normal for more than 3 days; respiratory symptoms improved significantly; pulmonary imaging showed a significant improvement in acute exudative lesions, and the nucleic acid test of respiratory specimens such as results of sputum and nasopharyngeal swabs were negative twice in a row (sampling interval ≥24 hours). Lazio 2 Ethical Committee approved this study as "55.21 Study", protocol 78111 04/05/2021.

Measures and data analysis

Statistical analysis was performed using R 4.0.0 (released on 2020-04-24). Statistical significance was fixed at 0.05. Categorical variables are reported as absolute and relative frequencies and compared through the Chi-Square test.

Continuous variables are reported as mean ± standard deviation and compared through the Welch *t*-test. Missing data were excluded from the analysis.

Cost analysis was performed using, as a proxy, the hospitalization costs and use of antiviral drugs. The point of view of the Italian national healthcare system was adopted.

Results

Baseline and clinical characteristics

A total of 2256 patients with a mean age of 71.01±28.02 years were included in this study (56% males). Of these, 1405 (62.27%) patients were admitted to COVID-19 hospitals for fever, 425 (18.8%) for dyspnea and 426 (18.8%) for cough. The average incubation period was 7.5±1.0 (range 6-9) days. The mean age in females and males was 70.01±25.01 and 71.02±22.3 years, respectively (p=0.313). Hypertension (51% *vs*. 48%; p<0.001) and chronic obstructive pulmonary disease (COPD) (48% *vs*. 43%; p<0.001) were common in male patients. In the male subjects, the epidemiological link was related to rehabilitation (80% *vs*. 59%; p<0.001) and community (14% *vs*. 4%; p<0.001), whereas in females it was related to hospital contagious (36% *vs*. 5%; p<0.001) (Table 1).

Imaging findings

According to chest CT scan findings, 86% of patients had bilateral pneumonia and the remaining 14.02% had unilateral pneumonia. As shown in Table 2, atypical chest-X rays were more frequent in females (41% *vs*. 16%; p<0.001), compared to male subjects, while abnormal chest CT scans

Table 1. Baseline characteristics of the studied population.

Variable	Total (n=2256)	Male (n=1265)	Female (n=991)	p
Age (year)				
Mean ± SD	71.01 ± 28.02	70.02 ± 25.01	71.01 ± 22.02	0.313
Comorbidity				
COPD, n (%)	1037 (45.96)	607 (47.98)	430 (43.39)	<0.001
Hypertension, n (%)	1127 (49.95)	650 (51.38)	477 (48.13)	<0.001
Other, n (%)	92 (4.07)	8 (0.63)	84(8.47)	<0.001
Incubation period (days)				
Mean ± SD	7.50±1.90	6.3±2.10	9.2±1.10	<0.001
Presenting vital sign				
SBP (mmHg)	130.01±5.10	125.01±3.00	130.01±1.01	<0.001
DBP (mmHg)	75.01±5.00	75.01±3.01	75.01±2.01	>0.999
RR (/minute)	18.01±3.01	15.01±2.02	20.00±1.01	<0.001
PR (/minute)	60.01±2.00	60.01±3.01	60.00±4.00	>0.999
Temperature (°C)	37.70±4.01	38.01±2.00	37.51±1.01	<0.001
Epidemiological links				
Rehabilitation, n (%)	1604 (71.09)	1015 (80.23)	589 (59.43)	<0.001
Community, n (%)	225 (9.97)	180 (14.22)	45 (4.54)	<0.001
Hospital, n (%)	427 (18.92)	70 (5.53)	357 (36.02)	<0.001

SD, standard deviation; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; PR, pulse rate.

Table 2. Differences by gender regarding therapeutic measures, as well as imaging and laboratory findings.

Variables	Male (n=1265)	Female (n=991)	Total (n=2256)	p
Therapeutic measures, n (%)				
TCZ	293 (23.16)	22 (2.21)	315 (13.96)	<0.001
Oxygen therapy	902 (71.30)	609 (61.45)	1511 (66.97)	<0.001
Other	70 (5.53)	360 (36.32)	430 (19.06)	<0.001
Outcomes, n (%)				
Need for intubation	199 (15.73)	210 (21.19)	409 (18.12)	<0.001
Need for ICU admission	215 (16.99)	206 (20.78)	421 (18.66)	<0.001
Mortality	100 (7.90)	102 (10.29)	202 (8.95)	<0.001
Need for antiviral agent	751 (59.36)	473 (47.72)	1224 (54.26)	<0.001
Chest X-ray findings, n (%)				
Atypical	203 (16.04)	406 (40.96)	609 (26.99)	<000.1
Typical	1062 (83.95)	585 (59.03)	1647 (73.01)	<000.1
Chest CT scan, n (%)				
Normal	203 (16.04)	406 (40.96)	609 (26.99)	<000.1
Anormal	1062 (83.95)	585 (59.03)	1647 (73.01)	<000.1
Distribution of abnormalities on chest CT scan, n (%)				
Right lung	300 (23.71)	310 (31.28)	610 (27.03)	<000.1
Left lung	302 (23.87)	307 (30.97)	609 (27.00)	<000.1

TCZ, tocilizumab; CT, computed tomography; ICU, intensive care unit.

were significantly frequent in males (84% *vs.* 59%, respectively, p<0.001) (Table 2).

We did not observe sex differences concerning the type of distribution of abnormalities on chest CT scans and the type of abnormalities on chest CT scans (p=0.190).

Treatment

All patients received antiviral treatment. In male subjects, we detected a higher use of the antiviral drugs (59% *vs.* 47%, p<0.001, respectively), compared to female subjects. Male subjects had a higher need for oxygen therapy (71% *vs.* 61%; p<0.001). Tocilizumab (TCZ) was prescribed more in male subjects (23% *vs.* 2%; p<0.001). No sex differences were observed in other treatments.

Outcomes

At the end of follow-up (December 31, 2020), 9% of patients died. No strong significant differences by sex in the death rate were observed. As reported in Table 2, there were significant sex differences in the need for intubation (21% in females compared to 16% in males, p<0.001), and admission in the intensive care unit (21% in females compared to 17% in males, p<0.001).

Cost analysis

In Italy, every day of hospitalization in an internal medicine ward has an average cost of €546.00.[12] About TCZ 10 mL, National Drugs Agency (AIFA) only allows its use for patients satisfying all the following inclusion criteria: a COVID-19 infection confirmed by microbiological test AND being treated with dexamethasone (or equivalent) AND have C-reactive protein >75mg/L AND oxygen saturation <92% in ambient air OR need for O_2 supplementation AND not treated with an IL-6 inhibitor for COVID-19 during hospitalization and within 24-48 hours of starting respiratory support with high-flow nasal oxygen, continuous positive airway pressure, or mechanical ventilation invasive or non-invasive. Exclusion criteria are: known hypersensitivity to TCZ, a co-existing infection that may have worsened, more than 24 hours have passed since intensive care unit admission or more than 24 hours after starting respiratory support, a baseline alanine aminotransferase or aspartate aminotransferase more than 5 times the upper limit of normal, a platelet count below 50×109/L, absolute neutrophil count at baseline below 2×109/L, a pre-existing condition or treatment that results in ongoing immunosuppression.

Consequently, using AIFA guidelines, the number of patients who can use TCZ is very low; nevertheless, 23.2% of males used TCZ. The cost of every vial is € 211.00.

Discussion

Based on the findings of this study, the differences by sex in the epidemiological link, chest X-ray findings, oxygen therapy, comorbidity, and treatment were observed among patients with COVID-19. In male subjects, the epidemiological link was related to the rehabilitation ward and the community, while in female subjects, the epidemiological link was related to the hospital. In terms of clinical manifestations, the common symptoms of these patients were fever, dyspnea, and cough, and no differences by sex were observed. In our study, we observed that hypertension and COPD were significantly increased in male patients. According to chest CT scan findings, 86% of patients had bilateral pneumonia and the remaining 14% had unilateral pneumonia. Interestingly, we report a significant increase in atypical chest-X ray for female subjects, while TCZ, antiviral drugs, and oxygen therapy were prescribed more in male subjects. We did not observe significant differences by sex in other treatments as well as in the death rate.

Different reasons can describe the sex differences concerning COVID-19 treatment. It is reported that, for both males and females, lung involvement increases significantly as the age increases. Also, it has been described that over 50-year-old males and over 80-year-old females with COVID-19 pneumonia showed the highest chest X-ray scores.[13]

Typical chest X-rays were frequently observed in males compared to female subjects (84% *vs.* 59%, respectively, p<0.001).

Aging is another factor that induces the modification of immune response. In fact, with aging, there is an aberrant chronic low-grade pro-inflammatory state, which may occur to a greater extent in females than in males.[14] In this regard, immune senescence is a major contributory factor in the increased susceptibility of older adults to infection.[15] Concerning epidemiological link, for male subjects, it was related to rehabilitation and community, while for female subjects it was related to hospital admission. Probably, according to the literature,[16] these data are related to hospital contagion. It has been reported that in Italy, about 11% of COVID-19 patients were medical or nurses and about 68% of these are represented by female subjects. These data suggest an intrahospital or unnoticed transmission, with a potential risk of diffusion, and this role drastically exposed the female subjects to contagion.[17] No data in the literature describe the role of an epidemiological link to contagious concerning sex.

Because COVID-19 is an emerging infectious disease, the optimal treatment for affected individuals has not yet been established. In our study, most patients were treated with hydroxychloroquine, lopinavir, remdesivir, TCZ, low-molecular-weight heparin, corticosteroids, and antibiotics. Although remdesivir and other antiviral drugs have been used in the clinical treatment of patients with COVID-19, few data on their safety and efficacy as COVID-19 treatments have been published by sex. In this regard, we report that TCZ was prescribed in 14% of our population. It was prescribed in 23% of male subjects compared to only 2% of female subjects (p<0.001). We do not know the reasons for these differences. Probably, it is correlated with a significant decrease in an adverse reaction in male subjects. Unfortunately, no data is described in the literature concerning the gender differences in the TCZ treatment. There is no data on real life about the effect of sex on TCZ on the inflammatory activity in COVID-19 patients. Fortunately, the clinical characteristics of these patients with COVID-19 are characterized by very good outcomes concerning death by sex. In fact, in our study, only 9% of patients died and we did not observe significant differences by sex in terms of death rate.[18] The clinical significance of this study is to provide an early insight into atypical chest X-ray findings in female patients, not excluding COVID-19 infection. Our study confirmed that the evaluation of TCZ effect in COVID-19

patients by sex requires controlled studies (ideally randomized controlled clinical trials) to evaluate the efficacy and adverse reaction by sex. However, rehabilitation wards, communities, and hospitals can be an unnoticed cause of infection in males or females.

Limitations

The retrospective aspect may introduce selection bias and misclassification/information bias. The representativeness of the sample is significant but not representative of the Italian reality because it is limited to a single region. More infected patients and comparative studies (*e.g.*, cohorts, case-control) should be analyzed to get a more comprehensive understanding of COVID-19 by sex.

Conclusions

This study is one of the few that investigate the relationship between COVID-19, sex medicine, and costs related to hospitalization and care. Men's treatment is more expensive not only because they represent the majority of patients but also because they require longer and more expensive therapies. This study investigates only the costs related to acute care, and it will be necessary to expand it by considering direct and indirect costs related to the sex differences in the treatment of the so-called long covid.

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