



Article

Gender-Based Differences by Age Range in Patients Hospitalized with COVID-19: A Spanish Observational Cohort Study

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Abstract: There is some evidence that male gender could have a negative impact on the prognosis and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The aim of

the present study was to compare the characteristics of coronavirus disease 2019 (COVID-19) between hospitalized men and women with confirmed SARS-CoV-2 infection. This multicenter, retrospective, observational study is based on the SEMI-COVID-19 Registry. We analyzed the differences between men and women for a wide variety of demographic, clinical, and treatment variables, and the sex distribution of the reported COVID-19 deaths, as well as intensive care unit (ICU) admission by age subgroups. This work analyzed 12,063 patients (56.8% men). The women in our study were older than the men, on average (67.9 vs. 65.7 years; $p < 0.001$). Bilateral condensation was more frequent among men than women (31.8% vs. 29.9%; $p = 0.007$). The men needed non-invasive and invasive mechanical ventilation more frequently (5.6% vs. 3.6%, $p < 0.001$, and 7.9% vs. 4.8%, $p < 0.001$, respectively). The most prevalent complication was acute respiratory distress syndrome, with severe cases in 19.9% of men ($p < 0.001$). In men, intensive care unit admission was more frequent (10% vs. 6.1%; $p < 0.001$) and the mortality rate was higher (23.1% vs. 18.9%; $p < 0.001$). Regarding mortality, the differences by gender were statistically significant in the age groups from 55 years to 89 years of age. A multivariate analysis showed that female sex was significantly and independently associated with a lower risk of mortality in our study. Male sex appears to be related to worse progress in COVID-19 patients and is an independent prognostic factor for mortality. In order to fully understand its prognostic impact, other factors associated with sex must be considered.

Keywords: SARS-CoV-2; coronavirus; COVID-19; Spain; gender differences

1. Introduction

Since the first cases of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were described in China in December 2019, this virus has spread worldwide. As of January 2021, there have been more than 94 million confirmed infections, and over 2 million deaths worldwide. It has a 2.2% fatality rate [1–3].

Over 29.7 million infections have been recorded in Europe. In Spain, the first confirmed SARS-CoV-2 infection was reported on 31 January 2020, and since then, Spain has been one of the countries most affected by this pandemic, with 2,252,164 confirmed cases and 53,314 deaths as of 16 January 2021 [3,4].

The initial reports from China pointed to a difference in the number of cases detected and the fatality rate between the sexes. However, few reports have addressed this disparity in COVID-19 incidence and disease course according to sex; most of the studies that have been published so far indicate that male gender is linked to more serious forms of the disease, but more thorough investigation is necessary. As the disease has spread across multiple countries, the Global Health 50/50, an independent research initiative for gender equality, presented an overview of sex-disaggregated data from countries worldwide. Though a similar numbers of cases have been recorded in women and men, the fatality rate is higher among men; in January 2021, the number of COVID-19 deaths worldwide was divided into approximately 777,000 men, 578,000 women, and 633,000 deaths for which the sex was unknown. Nevertheless, sex-disaggregated data are still not provided by all countries, and the number of cases and the case fatality rate vary significantly by region [2,5,6].

In Spain, the Spanish Society of Internal Medicine (SEMI, for its initials in Spanish) has sponsored the SEMI-COVID-19 Network. The SEMI-COVID-19 Registry involved gathering detailed information on a large cohort of hospitalized patients. In this work, statistical analyses were carried out on data on baseline characteristics, comorbidities, clinical presentation, laboratory and radiological data, treatments received, clinical progress, complications, the need for ICU admission, and in-hospital mortality [7].

The aim of this study was to analyze the differences in the clinical characteristics, progress, and mortality rate of patients with COVID-19 according to sex. Understanding sex-based differences in this disease is essential for the expansion of the knowledge of the

etiopathogenesis and epidemiology of the virus, as well as to more precisely analyse the social and economic impact that COVID-19 has on both patients and communities [1,8].

2. Materials and Methods

2.1. Study Design

This work is a multicenter, observational, cohort study of patients hospitalized due to COVID-19 in Spain. The Spanish Society of Internal Medicine is the sponsor of the nationwide SEMI-COVID-19 Registry, which retrospectively collects patient data. The specific characteristics of the registry have been described in previous works [7].

2.2. Population and Inclusion Criteria

The SEMI-COVID-19 Registry included data on hospitalized patients over 18 years of age with microbiologically-confirmed SARS-CoV-2 infection. All of the patients who were discharged or deceased after hospital admission with confirmed SARS-CoV-2 infection were candidates for inclusion. The infection was confirmed by a polymerase chain reaction (PCR) test of a nasopharyngeal, sputum, or bronchoalveolar lavage sample, or a positive result on a serological test with compatible symptoms.

In this work, the data on all of the patients in the registry were analyzed in order to examine the differences between men and women. The inclusion criteria were: (a) an age of 18 years or older; (b) a confirmed diagnosis of COVID-19; (c) a first hospital admission to a Spanish hospital participating in the study, and (d) a hospital discharge or a hospital death. The exclusion criteria were patients with incomplete data, and those who did not provide consent.

The data analyzed included baseline characteristics, comorbidities, clinical and radiological presentation, laboratory data, treatment, complications during hospitalization, and in-hospital mortality.

This record began collecting patients in March 2020, and we are currently still collecting data from hospitalized patients. The data in our study correspond to the first wave of patients hospitalized by COVID from March 2020 until July 2020.

2.3. Ethical Aspects

The SEMI-COVID-19 Registry and the studies related to it were approved by the Provincial Research Ethics Committee of Málaga (Spain). All of the included patients or their legal representatives gave their informed consent. In cases in which there were biological safety concerns, or in which the patient had already been discharged, consent was obtained verbally and noted on the patient's medical record.

2.4. Data Analysis

The patients were divided into two groups: a male group and a female group.

The normality of the continuous variable distributions was verified using the Kolmogorov–Smirnov test. Data that follow a normal distribution are shown as means and standard deviations (SD), whereas data that follow a non-normal distribution are shown as medians and interquartile ranges (IQR). The comparisons between the groups for the normally distributed continuous variables were made using Student's t-test. In cases in which the variables did not follow a normal distribution, the Mann-Whitney U test was used.

The categorical variables are expressed as absolute frequencies (n) and percentages (%). In order to compare the categorical variables, we used the chi-square test or Fisher's exact test. The relationship between the variables and mortality was calculated using a multivariate logistic regression model which included the variables of gender, age, dependency, comorbidity, fever, dyspnea, confusion, tachypnea, severe acute respiratory distress syndrome [ARDS], radiological affection, and radiological worsening at 7 days.

Statistical significance was established as $p < 0.05$. The statistical analyses were performed using SPSS version 25.0.

3. Results

A total of 13,090 patients were included in the SEMI-COVID-19 Registry as of 2 June 2020. Of them, this work analyzed data on 12,063 patients, of which 6853 were men (56.8%). Figure 1 shows the patient inclusion flowchart.

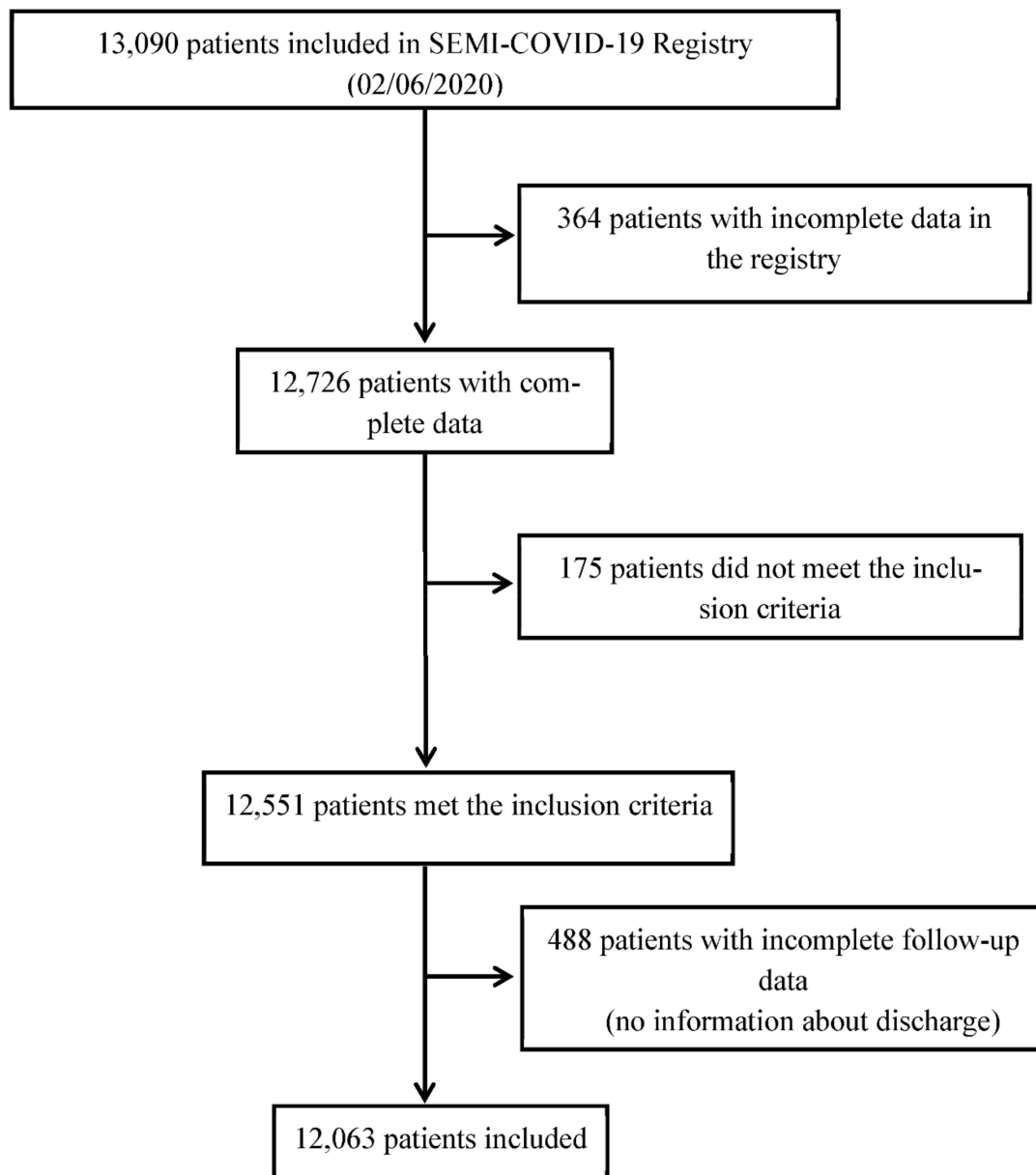


Figure 1. Patient inclusion flowchart.

3.1. General Data at Baseline

In our study population, the women were older than the men, with a mean age of 67.9 vs. 65.7 years ($p < 0.001$). The notable findings on the baseline characteristics and comorbidities include a higher smoking rate observed among men (6.9% vs. 3.3%; $p < 0.001$) and a higher percentage of women with obesity (22.3% vs. 20.5%; $p = 0.022$). Severe dependency was more frequent in women (10.1% vs. 5.1%; $p < 0.001$). All of the data on the baseline characteristics and comorbidities are shown in Table 1.

Table 1. Baseline characteristics and comorbidities of the study patients.

	Male <i>n</i> = 6853 (56.8%)	Female <i>n</i> = 5210 (43.2%)	Total <i>n</i> = 12063	<i>p</i> -Value
Age, mean (SD)	65.7 (15.8)	67.9 (16.9)	66.7 (16.3)	<0.001
Smoker, <i>n</i> (%)	445 (6.9)	167 (3.3)	612 (5.3)	<0.001
Obesity, <i>n</i> (%)	1265 (20.5)	1052 (22.3)	2317 (21.2)	0.022
Arterial hypertension, <i>n</i> (%)	3422 (50.0)	2636 (50.7)	6058 (50.3)	0.453
Dyslipidemia, <i>n</i> (%)	2699 (39.5)	2052 (39.5)	4751 (39.5)	0.997
Atrial fibrillation, <i>n</i> (%)	786 (11.5)	554 (10.7)	1340 (11.1)	0.145
Severe dependency, <i>n</i> (%)	346 (5.1)	516 (10.1)	862 (7.3)	<0.001
Charlson Comorbidity Index, mean (SD)	3.57 (2.76)	3.59 (2.60)	3.58 (2.69)	0.729
Anxiety, <i>n</i> (%)	323 (4.7)	636 (12.3)	959 (8.0)	<0.001
Depression, <i>n</i> (%)	418 (6.1)	844 (16.3)	1262 (10.5)	<0.001
Neurodegenerative disease, <i>n</i> (%)	524 (7.7)	606 (11.7)	1130 (9.4)	<0.001
Rare disease, <i>n</i> (%)	111 (1.6)	90 (1.7)	201 (1.7)	<0.001
Dialysis, <i>n</i> (%)	79 (1.2)	43 (0.8)	122 (1.0)	0.109

SD: standard deviation.

3.2. Symptoms upon Admission

With regard to the clinical presentation of COVID-19, symptoms such as a cough, fever > 38 °C, dyspnea, tachypnea and oxygen saturation < 92% were more frequent among men, whereas milder symptoms such as odynophagia, ageusia, anosmia, arthralgia, headache, and abdominal symptoms were more frequent among women.

On the chest X-rays, bilateral involvement was more common than unilateral involvement. Bilateral condensation and bilateral interstitial infiltrates were significantly more frequent in men (31.8% vs. 29.9%; *p* = 0.007 and 53.7% vs. 48.6%; *p* < 0.001, respectively). Table 2 describes the clinical presentation of the COVID-19 disease, and the main differences observed between the groups.

Table 2. Clinical presentation.

	Male <i>n</i> = 6853 (56.8)	Female <i>n</i> = 5210 (43.2)	Total <i>n</i> = 12,063	<i>p</i> -Value
Symptoms				
Dry cough, <i>n</i> (%)	3996 (58.5)	3011 (58.1)	7007 (58.3)	<0.001
Productive cough, <i>n</i> (%)	1152 (16.9)	723 (13.9)	1875 (15.6)	<0.001
Fever > 38°, <i>n</i> (%)	4650 (68.1)	2976 (57.4)	7626 (63.5)	<0.001
Ageusia, <i>n</i> (%)	414 (6.2)	381 (7.6)	795 (6.8)	0.005
Anorexia, <i>n</i> (%)	1267 (18.9)	1063 (20.9)	2330 (19.8)	0.008
Headache, <i>n</i> (%)	729 (10.8)	635 (12.4)	1364 (11.5)	0.007
Diarrhea, <i>n</i> (%)	1473 (21.7)	1285 (24.9)	2758 (23.1)	<0.001
General malaise, <i>n</i> (%)	663 (9.9)	805 (15.9)	1468 (12.5)	<0.001
Vomiting, <i>n</i> (%)	377 (5.6)	506 (9.9)	883 (7.4)	<0.001
Abdominal pain, <i>n</i> (%)	376 (5.6)	402 (7.8)	778 (6.5)	<0.001
Arthralgia, <i>n</i> (%)	2043 (30.2)	1610 (31.5)	3653 (30.8)	0.158
Anosmia, <i>n</i> (%)	385 (5.8)	331 (6.6)	716 (6.1)	0.089
Asthenia, <i>n</i> (%)	2878 (42.7)	2266 (44.4)	5144 (43.4)	0.072

Table 2. Cont.

	Male <i>n</i> = 6853 (56.8)	Female <i>n</i> = 5210 (43.2)	Total <i>n</i> = 12,063	<i>p</i> -Value
Odynophagia, <i>n</i> (%)	631 (9.4)	531 (10.4)	1162 (9.8)	0.062
Dyspnea, <i>n</i> (%)	3971 (58.2)	2960 (57.2)	6931 (57.8)	0.265
Physical Examination				
Confusion, <i>n</i> (%)	713 (10.6)	702 (13.7)	1415 (11.9)	<0.001
Tachypnea, <i>n</i> (%)	2173 (32.6)	1505 (29.8)	3678 (31.4)	0.002
Hypotension (SBP < 100 mmHg), <i>n</i> (%)	358 (5.5)	331 (6.7)	689 (6.0)	0.006
Tachycardia (>100 bpm), <i>n</i> (%)	1502 (22.8)	1075 (21.5)	2577 (22.2)	0.103
Oxygen saturation < 92%, <i>n</i> (%)	2363 (35.6)	1569 (31.1)	3932 (33.6)	<0.001
Wheezing, <i>n</i> (%)	355 (5.3)	359 (7.1)	714 (6.1)	<0.001
Rales, <i>n</i> (%)	757 (11.4)	517 (10.2)	1274 (10.9)	0.045
Crackles, <i>n</i> (%)	3504 (52.8)	2648 (52.4)	6157 (52.7)	0.666
Radiological Data				
Unilateral condensation, <i>n</i> (%)	1224 (18.0)	885 (17.3)	2109 (17.7)	0.071
Bilateral condensation, <i>n</i> (%)	2158 (31.8)	1526 (29.9)	3684 (31.0)	0.007
Unilateral interstitial infiltrates, <i>n</i> (%)	700 (10.3)	547 (10.7)	1247 (10.5)	0.194
Bilateral interstitial infiltrates, <i>n</i> (%)	3647 (53.7)	2481 (48.6)	6128 (51.5)	<0.001
Unilateral pleural effusion, <i>n</i> (%)	192 (2.8)	152 (3.0)	344 (2.9)	0.587
Bilateral pleural effusion, <i>n</i> (%)	89 (1.3)	96 (1.9)	185 (1.6)	0.012
Radiological worsening *, <i>n</i> (%)	2255 (43.6)	1343 (35.9)	3598 (40.4)	<0.001
Laboratory Data				
Lymphocytes < 1500/mm ³ , <i>n</i> (%)	5771 (84.8)	4101 (79.9)	9872 (82.7)	<0.001
LDH > 300 IU/L, <i>n</i> (%)	3377 (56.9)	2255 (51.1)	5632 (54.4)	<0.001
D-Dimer > 500 ng/mL, <i>n</i> (%)	3148 (59.7)	2417 (61.5)	5565 (60.4)	0.084

* Radiological worsening at follow-up at 7 days, discharge, or death. LDH: lactate dehydrogenase; SBP: systolic blood pressure. bpm: beats per min. mmHg: millimeters of mercury.

3.3. Treatments

The data regarding the treatment received were also analyzed. Systemic steroids were widely used, with higher frequency among men, a finding that was statistically significant (38.7% vs. 30.5%; $p < 0.001$). Men required non-invasive mechanical ventilation (NIVM) and invasive mechanical ventilation (IMV) more frequently than women (5.6% vs. 3.6%, $p < 0.001$, and 7.9% vs. 4.8%, $p < 0.001$, respectively). Oxygen via high-flow nasal cannula was also used more frequently in men (9.4% vs. 7.2%, $p < 0.001$) and prone positioning was used in 12.5% of men and 7.2% of women ($p < 0.001$). Full anticoagulant doses of low-molecular-weight heparin (LMWH) were more frequently administered in the male group (11.8% vs. 9.0%; $p < 0.001$). The complete data on the treatments, including the other types of treatments prescribed during hospitalization, can be seen in Table 3.

Table 3. Treatment during admission.

	Male <i>n</i> = 6853 (56.8)	Female <i>n</i> = 5210 (43.2)	Total <i>n</i> = 12,063	<i>p</i> -Value
Most Used Treatments				
Hydroxychloroquine, <i>n</i> (%)	5931 (86.9)	4353 (84.1)	10,284 (85.7)	<0.001
Lopinavir/ritonavir, <i>n</i> (%)	4438 (65.1)	2954 (57.1)	7392 (61.7)	<0.001
Remdesivir, <i>n</i> (%)	42 (0.6)	16 (0.3)	58 (0.5)	0.016
Interferon beta-1B, <i>n</i> (%)	943 (13.9)	481 (9.4)	1424 (11.9)	<0.001
Tocilizumab, <i>n</i> (%)	738 (10.9)	324 (6.3)	1062 (8.9)	<0.001
Systemic steroids, <i>n</i> (%)	2632 (38.7)	1571 (30.5)	4203 (35.2)	<0.001
Chloroquine, <i>n</i> (%)	313 (4.6)	215 (4.2)	528 (4.4)	0.243
Colchicine, <i>n</i> (%)	60 (0.9)	45 (0.9)	105 (0.9)	0.959
Immunoglobulins, <i>n</i> (%)	35 (0.5)	15 (0.3)	50 (0.4)	0.061
Anakinra, <i>n</i> (%)	45 (0.7)	15 (0.3)	60 (0.5)	0.005
Baricitinib, <i>n</i> (%)	29 (0.6)	11 (0.1)	40 (0.3)	0.043
Oseltamivir, <i>n</i> (%)	66 (1.0)	36 (0.7)	102 (0.9)	0.109
Inhaled beclomethasone, <i>n</i> (%)	390 (5.8)	284 (5.6)	674 (5.7)	0.593
Antibiotics				
Beta-lactams, <i>n</i> (%)	5188 (76.2)	3642 (70.4)	8830 (73.7)	<0.001
Macrolides, <i>n</i> (%)	4223 (62.1)	3013 (58.4)	7236 (60.0)	<0.001
Quinolones, <i>n</i> (%)	894 (13.3)	645 (12.6)	1539 (13.0)	0.268
Respiratory Therapies				
NIMV, <i>n</i> (%)	384 (5.6)	187 (3.6)	571 (4.8)	<0.001
IMV, <i>n</i> (%)	541 (7.9)	249 (4.8)	790 (6.6)	<0.001
High flow nasal cannula, <i>n</i> (%)	640 (9.4)	368 (7.2)	1008 (8.5)	<0.001
Prone positioning, <i>n</i> (%)	851 (12.5)	370 (7.2)	1221 (10.2)	<0.001
Other Treatments During Admission				
ACEI, <i>n</i> (%)	672 (9.9)	421 (8.2)	1093 (9.2)	0.001
ARB, <i>n</i> (%)	703 (10.4)	535 (10.4)	1238 (10.4)	0.965
ASA, <i>n</i> (%)	962 (14.3)	581 (11.4)	1543 (13.1)	<0.001
Statins, <i>n</i> (%)	967 (14.4)	642 (12.6)	1609 (13.6)	0.005
Vitamin K antagonists, <i>n</i> (%)	109 (1.6)	91 (1.8)	200 (1.7)	0.516
DOAC, <i>n</i> (%)	127 (1.9)	80 (1.6)	207 (1.7)	0.190
LMWH: Prophylactic doses, <i>n</i> (%)	4354 (64.2)	3435 (66.7)	7789 (65.3)	0.139
LMWH: Full anticoagulant doses, <i>n</i> (%)	797 (11.8)	464 (9.0)	1261 (10.6)	<0.001
LMWH: Intermediate doses, <i>n</i> (%)	500 (7.4)	294 (5.7)	794 (6.7)	<0.001
Ibuprofen, <i>n</i> (%)	65 (1.0)	46 (0.9)	111 (0.9)	0.771
Other NSAIDs, <i>n</i> (%)	285 (4.2)	215 (4.2)	500 (4.2)	0.934

NIMV: non-invasive mechanical ventilation; IMV: invasive mechanical ventilation; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin ii receptor blockers; ASA: acetylsalicylic acid; DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; NSAIDs: nonsteroidal anti-inflammatory drugs.

3.4. Outcomes

Regarding complications during hospitalization, men suffered more complications. Acute respiratory distress syndrome (ARDS) was the most common complication, and severe ARDS was more frequently in men (19.9% vs. 14%, $p < 0.001$). Men needed ICU admission more often than women (10% vs. 6.1%, $p < 0.001$), and presented higher in-

hospital mortality (23.1% vs. 18.9%, $p < 0.001$). Table 4 details the data on complications during admission, ICU admission, and in-hospital mortality.

Table 4. Complications, ICU admission rate, and in-hospital mortality.

	Male <i>n</i> = 6853 (56.8%)	Female <i>n</i> = 5210 (43.2%)	Total <i>n</i> = 12,063	<i>p</i> -Value
Complications				
ARDS mild, <i>n</i> (%)	602 (8.9)	380 (7.4)	982 (8.2)	<0.001
ARDS moderate, <i>n</i> (%)	570 (8.4)	311 (6.0)	881 (7.4)	<0.001
ARDS severe, <i>n</i> (%)	1352 (19.9)	722 (14.0)	2074 (17.4)	<0.001
Acute kidney injury, <i>n</i> (%)	1082 (15.9)	609 (11.8)	1691 (14.1)	<0.001
Bacterial pneumonia, <i>n</i> (%)	806 (11.9)	480 (9.3)	1286 (10.8)	<0.001
Multi-organ failure, <i>n</i> (%)	505 (7.4)	252 (4.9)	757 (6.3)	<0.001
Sepsis, <i>n</i> (%)	481 (7.1)	267 (5.2)	748 (6.3)	<0.001
Shock, <i>n</i> (%)	366 (5.4)	173 (3.4)	539 (4.5)	<0.001
DIC, <i>n</i> (%)	89 (1.3)	41 (0.8)	130 (1.1)	0.007
Acute myocardial infarction, <i>n</i> (%)	67 (1.0)	28 (0.5)	95 (0.8)	0.007
Peripheral arterial disease, <i>n</i> (%)	43 (0.6)	13 (0.3)	56 (0.5)	0.003
Heart failure, <i>n</i> (%)	398 (5.9)	333 (6.5)	731 (6.1)	0.176
Atrial arrhythmia, <i>n</i> (%)	251 (3.7)	179 (3.5)	429 (3.6)	0.462
Ventricular arrhythmia, <i>n</i> (%)	27 (0.4)	9 (0.2)	36 (0.3)	0.031
Myocarditis, <i>n</i> (%)	74 (1.1)	43 (0.8)	117 (1.0)	0.159
Seizures, <i>n</i> (%)	38 (0.3)	34 (0.3)	72 (0.6)	0.484
Ischemic stroke, <i>n</i> (%)	36 (0.5)	30 (0.6)	66 (0.6)	0.712
Hemorrhagic stroke, <i>n</i> (%)	7 (0.1)	1 (0)	8 (0.1)	0.149
VTE: DVT, <i>n</i> (%)	29 (0.4)	23 (0.4)	52 (0.4)	0.892
VTE: PE, <i>n</i> (%)	103 (1.5)	66 (1.3)	169 (1.4)	0.281
VTE: DVT + PE, <i>n</i> (%)	9 (0.1)	7 (0.1)	16 (0.1)	0.964
ICU Admission Rate and in-Hospital Mortality				
ICU admission, <i>n</i> (%)	684 (10.0)	318 (6.1)	1002 (8.3)	<0.001
In-hospital mortality, <i>n</i> (%)	1547 (23.1)	962 (18.9)	2509 (21.3)	<0.001

ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.

We analyzed the age and sex distribution of the reported COVID-19 deaths in our study, as well as ICU admission by age subgroups. A complete picture of the results can be seen in Figures 2 and 3. In both data sets, men have a higher mortality and income rate in the ICU. Most of the deceased were over 85 years of age, in both groups, men and women (52.2% vs. 41.2%, $p < 0.001$). It is important that when we compare the graphs, the percentages should be related to the size of the population in each subgroup, since it is notable that, as age increases, the gender gap is more noticeable despite the fact that women are in the majority in the upper age groups, and—in our study—also present greater dependence than men. Regarding mortality, the differences by gender are statistically significant in the age groups from 55 years to 89. If we take into account the ICU admissions, the differences are significant from 45 to 74 years, except in the age group of 50 to 54 years. It is important to note that the age group with the greatest difference with a great statistical significance is that of 70 to 74 years (15% vs. 8.3%, $p < 0.001$).

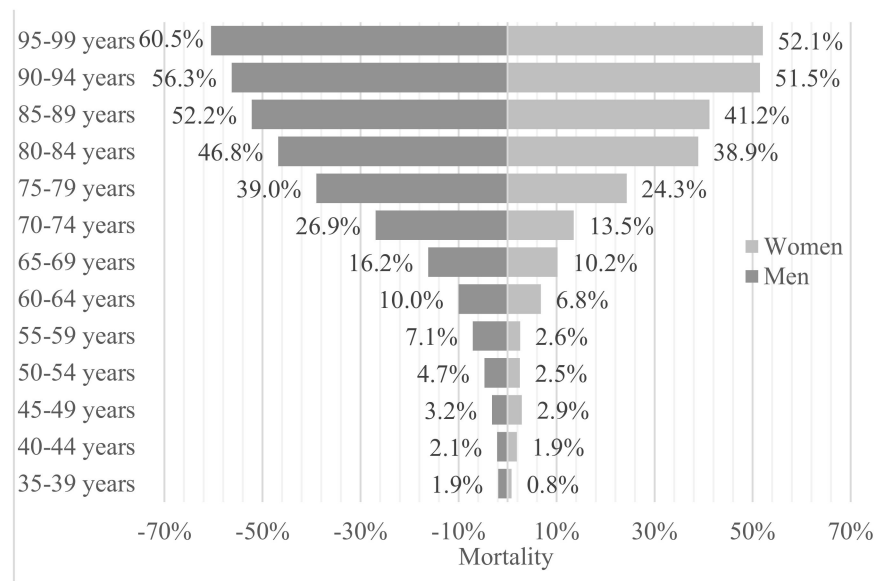


Figure 2. Mortality between the sexes according to age range.

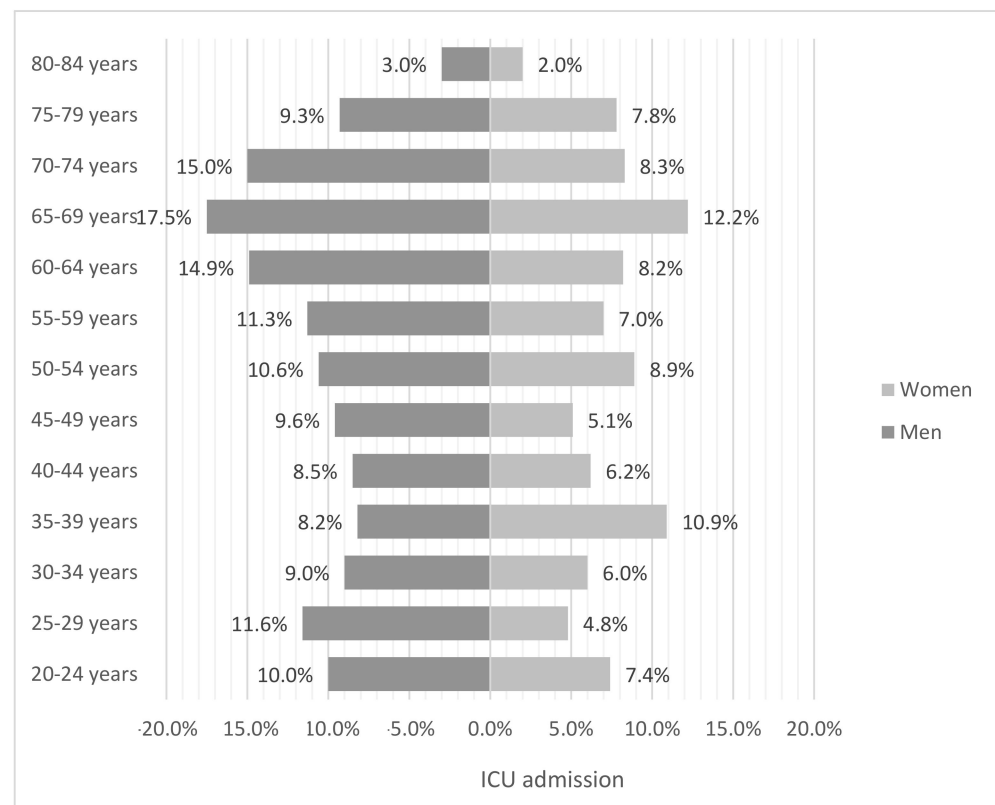


Figure 3. Intensive Care Unit (ICU) admission by sex and age range.

3.5. Risk Factors for Mortality

A multivariate analysis was conducted in order to analyze the associations between some of the aforementioned variables and mortality. The variables of age, moderate and severe dependence, a Charlson comorbidity index above 3 points, confusion, tachypnea, radiological worsening at seven days, and severe acute respiratory distress syndrome were independently associated with higher mortality in the multivariate analysis. Therefore, our analysis shows that female sex was significantly and independently associated with a lower risk of mortality in the patients admitted for SARS-COV-2 infection (Hazard Ratio

(HR) 0.771; confidence interval (CI) 95% 0.642–0.925, $p = 0.005$). In this analysis, fever, dyspnea, and bilateral radiological involvement were not shown to be independent factors of mortality. Table 5 details the multivariate analysis of the selected variables in relation to mortality.

Table 5. Independent variables associated with in-hospital death.

Mortality	Univariate Analysis		Multivariate Analysis	
	HR (CI 95%)	<i>p</i> -Value	HR (CI 95%)	<i>p</i> -Value
Gender (female)	0.777 (0.710–0.851)	<0.001	0.771 (0.642–0.925)	0.005
Age	0.920 (0.916–0.924)	<0.001	0.945 (0.936–0.954)	<0.001
Moderate dependency	5.749 (4.970–6.650)	<0.001	2.808 (2.049–3.847)	<0.001
Severe dependency	1.203 (1.005–1.439)	0.044	1.405 (1.004–1.967)	0.047
Charlson Comorbidity Index < 3 points	9.759 (8.668–10.988)	<0.001	3.431 (2.673–4.403)	<0.001
Fever > 38 °C	0.812 (0.727–0.907)	<0.001	0.907 (0.724–1.135)	0.393
Dyspnea	2.097 (1.095–2.308)	<0.001	1.173 (0.968–1.422)	0.104
Confusion	6.321 (5.619–7.111)	<0.001	2.264 (1.781–2.877)	<0.001
Tachypnea > 20 bpm	4.049 (3.687–4.446)	<0.001	1.321 (1.096–1.592)	0.003
Severe ARDS	4.757 (4.015–5.638)	<0.001	7.942 (6.084–10.366)	<0.001
Bilateral pneumonia	1.386 (1.216–1.579)	<0.001	1.168 (0.898–1.519)	0.247
Radiological worsening at 7 days of hospitalization	5.003 (4.424–5.658)	<0.001	2.352 (1.956–2.828)	<0.001

ARDS: acute respiratory distress syndrome.

4. Discussion

Since the onset of the COVID-19 pandemic, and since the first studies on the disease were conducted, a greater vulnerability to the disease and its complications, as well as a higher mortality rate, have been observed in men compared to women. Along these lines, this work has found that men with COVID-19 had complications more often, had a higher rate of ICU admission, and had a higher mortality rate compared to women.

Our data coincide with those reported in other studies. In Italy, a study comparing different variables that analyzed the effect of COVID-19 on daily deaths per 100,000 people of all genders and ages showed 30% higher mortality in men compared to women, with this difference becoming notably more striking in those aged 60 years and older. Worldwide, it is estimated that twice as many men die due to COVID-19 than women, according to data from the European Center for Disease Prevention and Control [9,10].

In the UK, researchers at the Intensive Care National Audit and Research Centre analyzed a sample of 7542 critically ill patients with confirmed COVID-19 and found that 5389 of these patients were men and 2140 were women. They also found that men were more likely to die in the ICU, with 51% of the men who were admitted dying compared to 43% of the women [11].

One of the first studies on the differences between men and women with COVID-19 was a retrospective analysis of 168 patients, which evaluated the differences between the clinical characteristics of critically ill patients according to sex. Again, its age- and comorbidity-adjusted results also found higher mortality and a worse prognosis among men [12].

In a recent meta-analysis on COVID-19, the authors confirmed the higher mortality of men over women. They placed particular importance on external factors that could contribute to this increase in deaths, especially in terms of habits and lifestyles. For example, one of the works included was a Chinese study in which the prevalence of smoking among men was ten times higher than that in women, which could have a negative impact on their health status. This could therefore entail a prior deteriorated health status that could condition greater severity of infection in men [13,14].

In our work, it is striking that even though the women in the study were older than the men, and had a higher percentage of severe dependence, coupled with the fact that both groups had similar percentages of comorbidities, the men had greater mortality and a higher number of ICU admissions. However, it is true that the men arrived at our

hospital in worse condition and with more serious symptoms than the women, and a greater percentage of the men had established bilateral pneumonia upon admission.

Another important finding of our work concerns the differences in the treatments received according to sex. A greater use of systemic treatments and respiratory therapies was observed in the male group compared to the female group. In regard to this finding, we hypothesize that the men in our study were younger than the women, and thus had a higher life expectancy; therefore, they may have been administered more treatments.

Alternatively, another explanation for why men had worse clinical progress than women may be due to reasons that are not yet clearly defined.

It is important to note, in our study, that the differences in mortality in terms of gender are greater and statistically significant according to the older age of the patients. Thus, we find similar data in the literature, as in a study with a sample of patients in New York, in which increasing age and male sex are independent factors associated with worse in-hospital evolution [15].

In another study carried out with a sample of Italian patients, the authors concluded that men from the age of 50 and women from the age of 80 had a worse prognosis in terms of radiological evolution (although the sample of men was almost three times larger than that of women), and if we look at the data of our study, in men, the percentage of higher mortality begins to be notably different from the other age ranges after 55 years, and in women after 75 years, which could overlap with the conclusions of the Italian study [16].

A meta-analysis that included 60 studies and more than 50,000 patients found that age played an important role in the analysis by subgroups, as although advanced age supposes an independent risk of mortality or worse prognosis, if other factors were taken into account, such as smoking or dyspnea on admission, mortality was higher in younger patient groups, and they concluded that these two factors are associated with a worse prognosis in populations with less exposure to the main risk factors for mortality from COVID-19, that is, elderly patients, a high proportion of men, and a high prevalence of comorbidities [17].

In another study with Canadian patients, they compared differences between women and men in different age groups in terms of hospital admission, ICU admission, time to recovery, and mortality, and found that there were large differences in women under 30 years of age and men of the same age in terms of hospitalization and admission to the ICU, and observed that, from the age of 60, there was a significant decrease in mortality in women compared to men of the same age group. They concluded that estrogens in women after puberty and before menopause could play a fundamental role, and that there may be a possible mechanism between estrogen levels and mortality/time to recovery that is not yet well defined, although in women aged over 60 years there would have to be other additional factors [18].

In China, in a study of 80,000 patients, patients older than 60 years had a 9.9 times greater risk of dying than patients younger than 30 years. Regarding the differences by gender, women presented less severity of the disease in all age ranges except those between 20 and 29 years. Regarding mortality, in all age groups, it was lower in women, with this difference being statistically significant from 30 years [19].

In another meta-analysis with 59 studies and more than 36,000 patients included, men demonstrated more severe forms of SARS-CoV-2 disease than women in all age groups. In addition, men had a higher ICU admission and mortality rate than women. In this meta-analysis, patients in both groups (men and women) older than 70 years had a worse prognosis, higher mortality, and a higher rate of admission to the ICU than those younger than 70 years [20].

Another interesting study on laboratory hematological parameters in COVID-19 infection suggests that it is important to carry out studies that analyze the differences in these parameters between men and women, as these results could be valuable to determine why the disease manifests itself in men more seriously than in women. In our study, men

had higher lymphopenia and higher lactate dehydrogenase (LDH) and D-dimer levels, with these results being statistically significant [21].

This leads us to wonder whether men have worse progress solely due to their sex, or whether there are other intervening factors. Some possible factors can be observed in the multivariate analysis conducted in this study, such as older age, radiological worsening at seven days, and confusion at the onset of the disease. Indeed, our data show that men develop more symptoms—such as a cough, fever, and tachypnea—at the onset of the disease than women.

Delving deeper into the influence that comorbidities and lifestyle can have on COVID-19 infection according to gender, one study in the literature examined the differences between females and males among COVID-19 patients in China. In this work, the men were more likely than the women to have two or more major comorbidities. Of those with COVID-19 and chronic obstructive pulmonary disease, 83.3% were men. Males represented 58.9% of those with diabetes, and 62.1% of those with some type of cardiovascular disease. Several studies have shown that, in places where mortality is higher in men than in women, men largely show behaviors that can worsen health, such as smoking, poor diet, or a sedentary lifestyle, along with their related comorbidities. Indeed, in our study, more men were smokers than women. An analysis of other lifestyle factors that were not assessed in our registry would be an interesting future line of research [22–24].

Finally, there are studies that attempt to explain this bias between men and women according to physiopathogenesis and innate characteristics of biological sex. In the literature consulted, we found several articles that defend the notion that women have a better immune response to external pathogens, and many of the genes that regulate this immune response are found on the X chromosome. Hormones could also play a fundamental role; estrogens could be beneficial in improving the immune response, as they enhance the proliferation of T lymphocytes and attenuate the cytokine storm, while testosterone in men could have a certain negative effect [25,26].

Another study by Haitao et al. on the mechanisms by which biological sex can influence the prognosis of COVID-19 disease concluded that the greater severity and mortality in men compared to women is most likely due to a combination of factors: on the one hand, differences regarding behavior and lifestyles and, on the other hand, comorbidities that affect men to a greater extent. They conclude that biological sex differences could affect the risk of contracting the disease, its physiopathogenic mechanisms, and its severity due to, among other causes, the fact that men are more likely to develop the dreaded cytokine storm associated with a higher lethality of the virus [27].

Another possible explanation is that sex differences in COVID-19 could be related to different angiotensin converting enzyme 2 (ACE2) receptor expression, as several studies have shown a greater presence of ACE2 receptor receptors in the Leydig cells and kidneys of men due to mechanisms possibly explained by hormonal differences. This is why diffuse alveolar damage is the main cause of morbidity and mortality in SARS-CoV-2 infection. Older age is also related to a higher expression of ACE2 receptors, although a greater number of specific studies are necessary in order to be able to develop a definitive theory. A study that began before the COVID-19 pandemic which aimed to investigate patients with heart failure and ACE2 found that men, older patients, and those with more comorbidities had higher concentrations of ACE2. These results were validated with another control group of more than 2000 patients. It was suggested that, perhaps, this was the reason why men are more susceptible to contracting the infection and presenting with worsening symptoms than women [26,28].

The data in this study are from the ‘first wave’ of contagions in Spain. Today, the SARS-CoV-2 epidemic continues to progress exponentially, and it is necessary to learn from past mistakes in order to improve the treatment of this disease. It is clear that some gender-related aspects—such as comorbidities or lifestyle choices like active smoking, which are more common among males—refuted in our study may play a key role in the higher percentage of ICU admission and higher mortality of men compared to women,

although other circumstances related to biological sex that are not analyzed in our registry should be taken into account as possible endpoints in future studies.

The strength of this study is that it is a multicenter study which included a large number of patients. On the other hand, there are limitations, as statistically more complete and advanced studies with larger sample sizes are required due to the overwhelming incidence of the disease. Furthermore, the retrospective nature of the study, and the fact that the vast majority of the patients in this study were Caucasian, that all required hospital admission, and the unknown real spread of COVID-19 among outpatients, mean that our results cannot be easily extrapolated to the general population.

5. Conclusions

Male sex seems to be related to worse progress in the SARS-CoV-2 disease. Men present with more symptoms at the disease's onset, have more complications during hospitalization, require a greater number of treatments, are more frequently admitted to the ICU, and have a higher mortality rate. Male sex and older age seem to be independent prognostic factors for mortality, but—in order to fully understand its impact on the prognosis of the disease—we must always consider other factors associated with sex.

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Appendix A

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H. U. de A Coruña. A Coruña

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Hospital Público de Monforte de Lemos. Monforte de Lemos

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H. U. Lucus Augusti. Lugo

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H. Virgen de los Lirios. Alcoy (Alicante)

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Hospital Clínico Universitario de Valladolid. Valladolid

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Hospital do Salnes. Vilagarcía de Arousa

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H. de la Axarquía. Vélez- Málaga

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H. Virgen del Mar. Madrid

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