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Sex Differences on Sars-Cov-2 Infected Patients Admitted in a Spanish Hospital

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ABSTRACT

Background: Sex-dependent and advanced-age-related susceptibilities have been described as risk factors of SARS-CoV-2 infection in epidemiological studies carried out worldwide. Therefore, sex could be a determining factor in the development and outcome of the SARS-COV-2 infection, and its study may be useful for the development of therapeutic strategies aimed at improving the prognosis of the disease.

Aims: To study whether there are differences based on gender in the prognosis of SARS-COV-2 infection in hospitalized patients.

Methods: Retrospective observational cohort study carried out in a Spanish hospital. The statistical analysis determined the differences in characteristics and clinical evolution of the infection segregated by gender.

Results: A total of 255 subjects with SARS-CoV-2 infection, of whom 45% were women, were included. Over 50 years-old group of patients, the percentage of women was significantly greater than men (92.2% vs 80%) and, a higher mortality was observed (20.9% vs. 13.6%). Laboratory tests, radiologic explorations, intensive care unit (ICU) admissions, and ICU length of stay were similar in both genders. The percentage of women admitted to the ICU was higher than that of men (60% vs. 40%).

Conclusions: Women present more severe and more frequent hospital admission at older ages because of SARS-CoV-2 infection, and more risk of admission at ICU. These factors determine that mortality in women was greater than in men. However, this difference was not statistically significant.

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Introduction

The COVID-19 pandemic was declared global health emergency by the WHO on 11 March 2020. This viral infection affects mainly the respiratory tracts acutely and leads to death in approximately 8% of cases globally [1]. Transmission is produced through saliva droplets and contact with the mucosa of infected people. This quickly leads to infection. The incubation period of SARS-CoV-2 is between 2 and 7 days and clinical manifestations are mainly cough, fever, dyspnea, myalgia, diarrhea and general malaise, among other symptoms [2,3]. It is known that the inflammatory response that causes respiratory symptoms is associated to viral load and the delayed onset response associated with interferon type I (IFN-I) [4,5]. Just as with previous SARS epidemics, this disease is age-linked, because the most affected people are aged between 30 and 79 years old [3]. Moreover, the severity of the disease is associated with gender and comorbidities presented by infected individuals [6,7]. Cardiovascular risk factors are more common in males. Lung involvement that leads to pneumonitis and severe respiratory compromise in affected individuals, is associated with different risk factors such as smoking and frequency of hand washing [8,9]. A higher gender-dependent susceptibility of infection in epidemiologic studies carried out in Europe and

China - with a higher percentage of cases in men than in women - has also been reported [10-12]. However, these data differ from those reflected in The Global Health 50/50 Research Initiative, where it is observed that the number of cases between men and women is simila [13]. However, diagnosis of the disease may be biased depending on each country's cultural development. Gender-dependent differences are more marked at elderly ages. However, the cause of the bias in diagnosis between sexes has not been elucidated [9,14,15]. Finally, SARS-CoV-2 infection appears to progress quickly and more aggressively in men who also present a higher probability of hospital admission and death because of the disease; with an increase of 1.5 and 1.8 points, respectively [14,16,17]. These data support the hypothesis that there are biological factors that have an impact on the clinical course of the disease.

Men and women respond differently to viral infections. In general, men do not present a very robust immune response and they are more susceptible to infection than women [4]. Women present higher blood concentrations of immunoglobulins after both the innate and adaptive immune response. These defenses can determine better protection against infectious agents and favor faster viral clearance [4]. For instance, it has recently been observed that women have higher serum concentrations of anti-SARS-CoV-2 IgG during the earliest phase of the disease [18]. This has also been observed in women after seasonal flu vaccination against the influenza virus [14,17].These discrepancies in serum concentrations may play a protective role on disease course in women and hinder the evolution to a more critical phase of the disease or even death.

Multiple factors are involved in the outcome of viral infections in humans. Among the multiple factors that contribute to the severity of infection, there are high titers of viral copies, and concentrations of macrophages/monocytes and neutrophils in the lungs. The rapid viral replication of SARS-CoV-2 together with the delayed IFN-I response subsequent to infection, is associated with a greater recruitment of inflammatory macrophages and monocytes (IMM) that leads to higher levels of inflammatory cytokines and chemokines at the infection site, greater vascular permeability and reduced CD4 and CD8 T lymphocyte response [4,5]. A higher infiltrate of IMM in the lungs has been observed in male patients infected with SARS-CoV-2. Other studies have observed low T cell response negatively correlated with patients' age and, therefore, associated with worse disease prognosis in male, but not in female patients [19]. By contrast, higher levels of innate immune cytokines were associated with worse disease progression in female patients, but not in male patients.

However, estrogens play a protective role in SARS-CoV-2 viral infection because of modified viral replication. Furthermore, estrogens have a modulator effect on migration of macrophages/monocytes that react against infection and are responsible for secretion of inflammatory cytokines such as interleukin-6 (IL-6) and inflammatory chemokines (CCL-2 and CXCL-1) in the alveolar epithelium. This may be translated into lower morbidity in women.

As discussed above, the discrepancies observed between genders in regard to the organic response against viral infection are in part attributable to the genes associated with X chromosome, estrogen receptors that modulate the innate and adaptive immune response and cell immunity [4,17,20]. Estrogens, which are female hormones par excellence, can modulate viral replication thanks to regulated expression of angiotensin converting enzyme 2 (ACE2) [11,14,16,17]. ACE2 is a factor that has been revealed to have a protective role in pathologies such as hypertension, cardiovascular disease, or adult respiratory distress syndrome. These comorbidities are associated with a worse prognosis during SARS-CoV-2 infection. For this reason, we must assume there is an interaction between sex hormones and ACE2 expression, and that their regulated expression mediated by estrogens can, in part, be the cause of differences in the severity of coronavirus infection. However, a second protein required for viral infection - membrane-bound serine protease 2 (TMPRSS2), which is mostly detected in prostate tissue but also in respiratory tract epithelium, has been reported [11,16,17,21]. TMPRSS2 synthesis is regulated by androgens, and the predominance of SARS-CoV-2 infection in males could be partly related to expression of this protein. Suppression of TMPRSS2 expression has demonstrated more susceptibility to viral infection in cellular in vitro experiments [16].

This study highlights that gender is a determining factor for the development and outcome of SARS-CoV-2 infection and may enable devising targeted therapeutic strategies to improve the prognosis of those subjects infected.

Methods

We performed an observational, retrospective cohort study in a Spanish tertiary hospital. The hospital center has 258 ward beds, including 12 Intensive Care Unit (ICU) beds and the health area dependent on the hospital comprises a population of approximately 190,000 inhabitants. The study population include all patients consecutively admitted to a tertiary hospital, with confirmed SARS-CoV-2 virus infection from February 26 to May 20, 2020, both inclusive. Patients aged 18 and over with SARS-CoV-2 virus infection confirmed by polymerase chain reaction (PCR) diagnostic test in a nasopharyngeal exudate or sputum sample, were included. In the event of a negative result, a second test was performed if the patient's clinical symptoms were highly suggestive. Patients who did not give informed consent for SARS-COV-2 infection treatments approved in the hospital protocol, in addition to cases of readmission of a same patient and consideration of the first hospital admission, were excluded. Pregnant or breastfeeding women were excluded. Patients were treated according to medical criteria and protocols, based on recommendations of the health authorities and the scientific evidence available in that moment [22].

Demographic data, comorbidities, clinical symptoms, laboratory results, radiologic tests and treatment for each patient were obtained from the hospital's electronic clinical history. Clinical data were collected by direct download or through individualized manual review of the electronic clinical history. A safe data collection form was designed in the clinical history corporate program for the remaining demographic data, comorbidities, clinical symptoms, and radiologic tests. To ensure correct collection of these forms they were validated by the principal investigators, MRV and DEQ, before incorporating them into the database, with the aim of improving the quality of the data collected and reducing data loss wherever possible. Personal data were broken down and pseudoanonymized in the database for subsequent statistical analysis by an independent expert.

Statistical Analysis

For statistical analysis, quantitative variables are expressed by means of medians and interquartile range (IQR). For the analysis of differences in means the student t and Mann-Whitney U tests were used for normally and non-normally distributed variables,

respectively. Categoric variables are represented as absolute frequencies and percentages. To contrast categoric variables the χ 2 Pearson or Fisher exact tests were used. The Mantel-Haenszel test for trend was also used if necessary. The level of statistical significance adopted for all contrast tests was $P<0.05$. Data were statistically analyzed and processed by means of the statistical package SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY, USA: IBM Corp).

The study protocol was approved on 22 June by the Research Ethics Committee for Medicinal Products (RECm). An exemption to obtain written informed consent from patients was obtained.

Results

A total of 255 inpatients with laboratory-confirmed SARS-CoV-2 infection, of whom 45% were women, were analyzed. Mean (SD) age of the sample was 68.4 (15.9) years. The age difference between both sexes was 2.7 years and was not statistically significant (95%CI 1.3 – 6.6). When stratifying by age, the distribution by sex among infected patients did not differ except for the group of patients over 50 years, where the percentage of women was significantly greater than men (92.2% vs 80%). The recorded characteristics stratified by gender are shown in (Table1). The number of comorbidities per patient does not differ between sexes. Moreover, the most common were cardiovascular risk factors such as HTA, dyslipidemia, diabetes, and obesity. There were no sex differences regarding these common pre-existing chronic pathologies. However, in the group of women, there was a tendency to present more obesity, while the percentage of dyslipidemia was higher in men but did not attain statistical significance.

Table 1: Demographic Characteristics and Comorbidities of Covid-19 Patients Stratified by Gender N (%)

	TOTAL (n=255)	Women (n=115)	Men (n=140)	P
Age, mean (RIQ)	70,0 (55,9-82,1)	71,3 (58,4-82,3)	69,5 (53,6-82,0)	0,18
Hypertension	148 (58,0)	67 (58,7)	81 (57,9)	0,99
Diabetes	65 (25,5)	29 (25,2)	36 (25,7)	0,93
Ischemic heart disease	23 (9,0)	5 (4,3)	18 (12,9)	0,02
Chronic kidney disease	49 (19,2)	25 (21,7)	24 (17,1)	0,35
COPD	21 (8,2)	5 (4,3)	16 (11,4)	0,04
Asthma	19 (7,5)	13 (11,3)	6 (4,3)	0,03
Other chronic lung diseases	24 (9,4)	6 (5,2)	18 (12,9)	0,04
Heart failure	21 (8,2)	15 (13,0)	6 (4,3)	0,01
Cirrhosis	4 (1,6)	3 (2,6)	1 (0,7)	0,33
Neoplasia	31 (12,2)	12 (10,4)	19 (13,6)	0,45
Cardiovascular disease	71 (27,8)	29 (25,2)	42 (30,0)	0,40
Cerebrovascular disease	18 (7,1)	8 (7,0)	10 (7,1)	0,95
Dyslipidaemia	108 (42,4)	44 (38,3)	64 (45,7)	0,23
Tabaquism				
Never smoker	192 (75,3)	107 (93,0)	85 (60,7)	
Smoker	23 (9)	3 (2,6)	20 (14,3)	<0.01
Former smoker	40 (15,7)	5 (4,3)	35 (25,0)	
Obesity (IMC≥30 Kg/m^2)	62 (24,3)	30 (26,1)	32 (22,9)	0,55
HIV	4 (1,6)	3 (2,6)	1 (0,7)	0,33
Inflammatory Bowel Disease	6 (2,4)	5 (4,3)	1 (0,7)	0,09
Autoimmune diseases	15 (5,9)	6 (5,2)	9 (6,4)	0,68
Dementia	27 (10,6)	12 (10,4)	15 (10,7)	0,94
Pulmonary embolism or deep vein thrombosis	4 (1,6)	1 (0,9)	3 (2,1)	0,63
Reumathoid Arthritis	6 (2,4)	4 (3,5)	2 (1,4)	0,41
Chronic treatment*:				
Anticoagulant	30 (11,8)	13 (11,3)	17 (12,1)	0,84
ACEI or ARA II	115 (45,1)	52 (45,2)	63 (45,0)	0,97
Biologic treatments	2 (0,8)	2 (1,7)	0 (0,0)	0,20

*ACEI: Angiotensin converting enzyme inhibitor; ARAII: Angiotensin II receptor blocker.
† Mantel-Haenszel test of trend.

This imbalance between cardiovascular risk factors did not determine a worse prognosis for coronavirus infection. Nevertheless, the smoking rate was significantly higher in men (14.3% vs 2.6% in women), as well as the prevalence of ischemic heart disease (12.9% vs 4.3%, P=0.02). However, these cardiovascular risk factors did not determine higher mortality in men. Conversely, a history of heart failure was more prevalent among women (12% vs. 4.3%, P=0.01), but it was not a determining factor for poor prognosis compared to men. No differences were observed between groups regarding prevalence of ischemic cerebral pathology. In general, only 12% of patients did not present comorbidities, while 51.4% presented 3 or more comorbidities. According to the abbreviated Charlson comorbidity index, the median score was 1 (IQR: 0-2), and 16.5% of patients have a high score. No difference between sexes was detected. The frequency of chronic obstructive pulmonary disease (COPD) was statistically higher in men. Conversely, asthma was statistically higher among women. Finally, no sex differences were found for other important pathologies that could have influenced the outcome of the viral infection such as chronic renal failure or pulmonary thromboembolism. The stratification by sex did not show statistical differences on previous chronic treatments: 11.8% of patients received anticoagulants, 45.1% received Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin II receptor antagonists (ARB), and 0.8% received biologic therapy for inflammatory diseases.

On admission, the most common signs were fever, dry cough, and dyspnea; no sex differences were found on initial clinical symptoms. However, chest pain tends to be more present in women (*P*=0.06) (Table 2). Among the admitted women, there was a greater tendency to present general malaise and headache, whilst men more commonly reported expectoration at the onset of symptoms, perhaps due to the higher prevalence of COPD. Dizziness, sore throat, loss of smell or taste were uncommon, and no statistical differences were found between groups. Most important laboratory findings were alterations on worse disease prognosis factors for SARS-CoV-2 infections, like elevation of acute phase reactants, lymphocytopenia, hypoalbuminemia, hypofibrinogenemia, elevated ferritin and IL-6 levels. Nevertheless, laboratory tests were similar in both sexes. The most common abnormalities on X-ray exploration were ground-glass opacity followed by interstitial pattern. In those patients with worse evolution, chest CT was performed; diffuse interstitial pattern was the most common radiologic finding.

Table 2: Signs and Symptoms of Presentation of Patients on Admission
N (%)

	TOTAL (n=255)	Women (n=115)	Men (n=140)	p
Fever	190 (74,5)	83 (72,2)	107 (76,4)	0,44
Dyspnoea	130 (51,0)	61 (53,0)	69 (49,3)	0,55
Dry cough	156 (61,2)	75 (65,2)	81 (57,9)	0,23
Expectoration	36 (14,1)	14 (12,2)	22 (15,7)	0,42
Odynofagia	19 (7,5)	10 (8,7)	9 (6,4)	0,50
Myalgia	53 (20,8)	27 (23,5)	26 (18,6)	0,34
Headache	28 (11,0)	13 (11,3)	15 (10,7)	0,88
Dizziness	19 (7,5)	9 (7,8)	10 (7,1)	0,84
Diarrhoea	58 (22,7)	25 (21,7)	33 (23,6)	0,73
Chest pain	18 (7,1)	12 (10,4)	6 (4,3)	0,06
Malaise	132 (51,8)	63 (54,8)	69 (49,3)	0,38
Anosmia	18 (7,1)	8 (7,0)	10 (7,1)	0,95
Dysgeusia	19 (7,5)	9 (7,8)	10 (7,1)	0,84

On admission, no sex differences were revealed in the radiologic examinations. The respiratory situation at admission was assessed using the SaFi index (oxygen saturation index/inspired fraction of oxygen) with an average of 442.9 (IQR 148.0 - 457.1) and was similar between sexes. When performing the CURB 65 scale at hospital admission, 34 (13.5%) patients were at severe risk and, therefore, required admission to the Intensive Care Unit (ICU); 28.7% required hospital admission for medium risk, and 56.9% would not have required admission. When this scale was stratified by sex, the most relevant data are found in the medium severity group that determines hospital admission, in which the percentage of men was higher (61.1% vs. 38.9%). Curiously, the percentage of direct ICU patients is higher among women (58.8% vs 41.2%), although this did not attain statistical significance. Most patients received oxygen therapy, oral antibacterial therapy (azithromycin), hydroxychloroquine, glucocorticoid therapy, antiviral therapy (lopinavir-ritonavir) or immunotherapy with tocilizumab, anakinra or baricitinib, but there were no sex differences on treatments received (*P*>0.05). Overall, the median duration of hospitalization was 12 days (mean 12.07), but no sex differences were found. The percentage of patients who required non-invasive ventilation was similar between the sexes (0.9% for women vs 1.4% for men, *P*=1.0). Intensive care unit (ICU) admissions (mean 3.9%) and length of ICU stay (mean 12.07 days) were similar when stratifying by sex. Although statistical significance was not attained, the percentage of women admitted to the ICU was higher compared to men (60% vs. 40%). Finally, case fatality rates (mean 16.9%) were similar between sexes, and in both groups mortality occurred at ages above 50 years. Nevertheless, a total of 43 deaths were recorded. In the group of women was observed a higher mortality (20.9%) proportionally compared to the group of men (13.6%) (Figure 1).

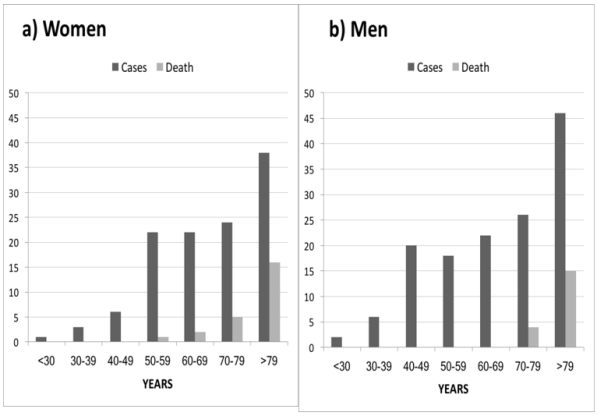

Figure 1: Cases and Death by Gender: a) Women b) Men

Discussion

The mean age in our study was higher compared to Chinese studies [2]. However, European data shows a mean age of infected patients in the general population that is lower than that of our study [23,24]. However, we must consider that severity of the disease is age-associated, and the severity is the essential criteria for hospital admission, whereby our results are in accordance with those reported in previous studies [3,25-28]. Moreover, the percentage of patients affected by coronavirus was similar between men and women. The same was observed for studies in more than 39 countries globally [13]. despite this, in the over 50 age group women showed a higher percentage of cases. Age of presentation of spontaneous menopause is 45 to 55 years with an average of 50-51 years. This is both for the global population and our own setting in which changes occur related to loss of the protective function of estrogen because of a gradual reduction in production in the ovary [29]. On an experimental basis, the organic response to surgical castration has been assessed in studies performed on rats. This has revealed that castrated male rats behave the same way towards viral infection compared to those not chemically or surgically castrated, which is a worse outcome compared to non-castrated rats [4]. Therefore, it appears that estrogens play a protective role against viral infections. However, they are also in part responsible for autoimmune disease, where estrogens facilitate development of immunopathogenic effects in women. This is translated into disordered regulation of the immune system and increased prevalence of autoimmune disease such as systemic lupus erythematosus [14]. Therefore, the decrease in hormones during menopause must be associated with a loss in the protective function of estrogens in women during regulation of ACE2 receptor expression, on the cardiovascular system and infection [16]. This can be accounted for overall in our study by the high percentage of women infected with coronavirus over the age of 50.

Comorbidities, mainly cardiovascular risk factors such as hypertension, are determining factors in the evolution of coronavirus disease because they are related to severity of the infection [2,3,12]. In our study, hypertension was the most common risk factor just as in other studies [2,3,7]. Quantitative differences on the number of comorbidities according to sex have not been observed. We did observe qualitative differences that may be determining factors for morbidity and mortality during coronavirus infection. No differences between sexes among the most common cardiovascular risk factors were observed. However, differences were observed in terms of smoking, which was associated with a greater expression of ACE2, COPD and heart failure that were all more prevalent in males [9,11]. Despite this, this difference was not a determining factor for evolution of the disease in men compared to women. This was because the number of days of admission and percentage mortality were similar between both groups. These results were not detected in accordance with those provided in other studies in which biological differences in sex contributed to a higher mortality in men [16,17]. We did not observe this in our study. According to the results obtained we can state that the qualitative difference in risk factors did not mean that men were more susceptible to presenting more severe or lethal involvement compared to women. Similarly, no differences between sexes were observed for hypertension treatment with ACEI/ARA II, which might entail a risk with a worse outcome.

In accordance with other studies, the most common clinical symptoms were dry cough, dyspnea, fever, and rare gastrointestinal symptoms. Radiologic tests at admission revealed pathologic findings in 86.6% of patients [3]. This is higher than other studies published previously , which may indicate that the disease was at a more advanced phase of evolution because patients recorded on average 7 days of symptoms before going to hospital. Moreover, the pattern of presentation was similar between both sexes, which together with the abnormalities observed in the laboratory data and homogeneous radiologic changes in our sample, was reflected by a similar percentage of cases admitted to the ICU without sex differences. This is the converse of what occurs in other studies where males were more frequently admitted to the ICU [3,30].

The treatment received by patients was prescribed according to therapeutic recommendations for coronavirus infection approved nationally and sex was not a limiting factor in the therapeutic decisions [22,31].

Mortality was similar for both sexes and more noticeable at older ages, such that the average age of patients who died is greater than that of patients who survived as observed in other populations [2,12,17]. However, higher mortality was detected proportionally in the group of women compared to men. This is contrary to other studies, even carried out in Spain ,where women present lower a percentage mortality among patients admitted to hospital because of SARS-CoV-2 [32,33]. In other studies, the females have higher susceptibility of infection but lower severity and fatality [34]. It is possible that the characteristics of our geographic area and older age presented by women admitted to hospital might be determining factors in these results. Other studies have also observed differences in the characteristics of infected patients compared to China [35]. This may explain the differences observed between our and Asian data.

As for the limitations of our study, our population is likely different to others because of the characteristics of our area during the pandemic as the two most important outbreaks of infection were located in a retirement home and in a nearby town to the hospital. This may be a determining factor on the average age of our sample and on treatments provided. It is notable that results are taken from clinical practice in just one center that may cause bias when processed. This is despite having been based on national treatment recommendations. Furthermore, data were collected and analyzed retrospectively, whereby to be able to determine causality relationships a prospective study should be performed and designed prior to collecting data. Finally, it is estimated that 29% of cases analyzed with PCR tests for coronavirus with current diagnostic techniques were false negatives and may lead to a classification bias [36].

In conclusion, we have observed in our cohort that women presented more severity and more frequency of hospital admission at older ages because of SARS-CoV-2 infection. In general, we have not observed other relevant differences between the two genders.

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References

1. Worldometer https://www.worldometers.info/coronavirus/.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, et al. (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 323: 1061-1069.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 382: 1708-1720.
4. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, et al. (2017) Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. J Immunol 198: 4046-4053.
5. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, et al. (2016) Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. Cell host & microbe 19: 181-193.
6. Wu C, Chen X, Cai Y, Xia J, Zhou X, et al. (2020) Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA internal medicine 180: 934-943.
7. Onder G, Rezza G, Brusaferro S (2020) Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA 323: 1775-1776.
8. Cai H (2020) Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med 8: e20.
9. Gagliardi MC, Tieri P, Ortona E, Ruggieri A (2020) ACE2 expression and sex disparity in COVID-19. Cell Death Discov 6: 37.
10. Grasselli G, Pesenti A, Cecconi M (2020) Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. JAMA 323: 1545-1546.
11. Ambrosino I, Barbagelata E, Ortona E, Ruggieri A, Massiah G, et al. (2020) Gender differences in patients with COVID-19: a narrative review. Monaldi Arch Chest Dis 90: 318-324.
12. Li LQ, Huang T, Wang YQ, Wang ZP, Liang, et al. (2020) COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 92: 577-583.
13. Global Health 5050 https://globalhealth5050.org/the-sex-gender-and-covid-19-project/.
14. Cutolo M, Smith V, Paolino S (2020) Understanding immune effects of oestrogens to explain the reduced morbidity and mortality in female versus male COVID-19 patients. Comparisons with autoimmunity and vaccination. Clin Exp Rheumatol. 38: 383-6.
15. Wenham C, Smith J, Morgan R, Gender, Group C-W (2020) COVID-19: the gendered impacts of the outbreak. Lancet 395: 846-848.
16. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL (2020) Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ 11: 29.
17. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL (2020) Considering how biological sex impacts immune responses and COVID-19 outcomes. Nature reviews Immunology 20: 442-447.
18. Zeng F, Dai C, Cai P, Wang J, Xu L, et al.(2020) 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 92: 2050-2054.
19. Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, et.al. (2020) Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature. 588: 315-320.
20. Kovats S (2015) Estrogen receptors regulate innate immune cells and signaling pathways. Cell Immunol 294: 63-69.
21. Goren A, Vano-Galvan S, Wambier CG, McCoy J, Gomez-Zubiaur A et al. (2020) A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain - A potential clue to the role of androgens in COVID-19 severity. J Cosmet Dermatol 19: 1545-1547.
22. Agencia Española de Medicamentos y Productos Sanitarios. https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%e2%80%9119/tratamientos-disponibles-para-el-manejo-de-la-infeccion-respiratoria-por-sars-cov-2/
23. Istituto Superiore di Sanità (ISS). Epidemia COVID-19 2020 https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_16-giugno-2020.pdf.
24. Robert Koch Institute. https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/2020-07-02-en.pdf?__blob=publicationFile.
25. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, et al. (2020) Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 323: 2052-2059.
26. Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, et al. (2020) BMJ Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. Doi: 10.1101/2020.04.20.20072116
27. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, et al. (2020) Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study doi: 10.1136/bmj.m1985.
28. Borobia AM, Carcas AJ, Arnalich F, Alvarez-Sala R, Monserrat-Villatoro J, et al. (2020) A Cohort of Patients with COVID-19 in a Major Teaching Hospital in Europe. Journal of clinical medicine 9: 1-10.
29. Postmenopausia GdTdmy. https://es.cochrane.org/sites/es.cochrane.org/files/public/uploads/GPC_menopausia_definitiva.pdf Barcelona https://es.cochrane.org/sites/es.cochrane.org/files/public/uploads/GPC_menopausia_definitiva.pdf.
30. Zhou F, Yu T, Du R, Fan G, Liu Y, et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1054-1062.

31. Ministerio de Sanidad CyBS. https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Resumen_COVID19_AH-person.
32. Instituto de Salud Carlos III. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/Inf.
33. Jin JM, Bai P, He W, Wu F, Liu XF, et al. (2020) Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Frontiers in public health 8:152.
34. Qian J, Zhao L, Ye RZ, Li XJ, Liu YL. (2020) Age-dependent Gender Differences in COVID-19 in Mainland China: Comparative Study. Clin Infect Dis 71: 2488-2494.
35. Di Stadio A, Ricci G, Greco A (2020) de Vincentiis M, Ralli M. Mortality rate and gender differences in COVID-19 patients dying in Italy: A comparison with other countries. Eur Rev Med Pharmacol Sci 24: 4066-4067.
36. Arevalo-Rodriguez I, Buitrago-Garcia D, Simancas-Racines D, Zambrano-Achig P, Del Campo R, et al. (2020) False-negative results of initial RT-PCR assays for COVID-19: A systematic review. PLoS One 15: e0242958.