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Original Article

Comparative study of the severity of Covid-19 infection between female and male patients

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Abstract

Background: Different studies have identified the prognostic factors of COVID-19 infection. These studies have revealed that COVID-19 infection is more severe in males than in females. The aim of our study was to compare the severity of COVID-19 infection between males and females in terms of clinical, biological, radiological, and evolutionary aspects.

Methodology: This is a cross-sectional observational study conducted in patients hospitalized with COVID-19 infection over a 6-month period from 1 August 2021 to 1 February 2022.

Results: The comparison of clinical, biological, radiological, and evolutionary severity factors of covid-19 infection between the two sexes revealed that this infection was more severe in males. Statistically significant differences were noted for the rate of high dimers (p =0.01) and for lung involvement greater than 25% on chest CT (Computed tomography) (p =0.008).

Conclusion: The severity of covid-19 infection in men is due to biological differences between men and women in the renin-angiotensin system, the immune system, genetics, and sex hormones. Further research into the pathophysiological mechanisms behind this finding is needed.

Keywords: COVID-19, Gender, Severity, Biological Differences.

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Introduction

The human coronaviruses (CoV) are an important cause of community respiratory tract infections. The symptoms associated with CoV infection were first described more than 40 years ago [1]. In December 2019, cases of pneumonia associated with the emergence of a new coronavirus called SARS-CoV-2 were detected in China. [2] Since then, the disease has spread rapidly, resulting in millions of cases and thousands of deaths worldwide. The World Health Organization (WHO) declared the disease a pandemic on March 11, 2020 [3].

The clinical presentation of COVID-19 varies from asymptomatic or pauci symptomatic to severe forms [4]. Although a large majority of COVID-19 patients present with a mild to moderate form of the disease, many patients present with severe forms with complications that require hospitalization or cause the death of the patients [5, 6].

Different studies have identified prognostic factors for progression to severe disease and mortality for patients diagnosed with COVID-19 [7], pointing to the differences between young and old, male, and female. Interestingly, COVID-19 infection has shown a higher severity and mortality in males compared to females [8], which according to the literature can be explained by differences in the renin-angiotensin-aldosterone system, and the entry of SARS-Cov-2 viral cells, the immune system, the genetic system, and sex hormones [9-11].

Little study has been done on the difference in severity between the sexes in patients with COVID-19, which motivated us to carry out a study with the aim of comparing the severity of COVID-19 infection between men and women on the clinical, biological, radiological, and evolutionary aspects in patients hospitalized at the Hassan II Hospital in Agadir.

Methodology

It is a cross-sectional observational study conducted among patients hospitalized for COVID-19 infection in the pneumology department of the Hassan II University Hospital of Agadir. Data collection was carried out over a period of 6 months from August 1, 2021, to February 1, 2022. We included in our study patients whose diagnosis of COVID-19 infection was confirmed by molecular examination (RT-PCR or equivalent test) or by a rapid antigenic test. Any suspected case with CT images suggestive of COVID-19 with one of the following criteria: contact with a confirmed case during the contagious period or the presence of an epidemiological link with a cluster or a health professional working in a health care structure or in a laboratory [12]. Patients with incomplete files were excluded.

The data were collected via a pre-established data collection form prepared following a literature review, containing three parts: the first part concerns the sociodemographic and clinical information of the participants, including age, sex, patient history (toxic antecedents, respiratory antecedents, co-morbidities), clinical signs (fever, headaches, dry cough, etc.), the motive for hospitalization, physical examination (general examination, respiratory examination performed on admission). The second part concerns the paraclinical information, such as a thoracic CT scan and biological parameters. The third part consists of collecting information on the evolution of the patients.

The severity criteria in our study were defined as follows: the presence on admission of signs of respiratory distress, arterial saturation <90%, respiratory rate >30 cycles per minute, cardiac rate >100 beats per minute, chest CT damage >25%, CRP (C-reactive protein)>50 mg/l, low prothrombin level < 60%, dimers > 1000 G/l, hyperleukocytosis > 1000 l [13], occurrence of thromboembolic complications or death during hospitalization, occurrence of sequalae respiratory failure after hospital discharge.

The data collected was entered into Excel and analyzed using SPSS 16.0. Qualitative variables were represented as numbers and percentages, and quantitative variables were represented as mean and standard deviation. A subgroup analysis was performed to compare the two sexes. The KHI 2 test, or Fisher's exact test, was used to compare the percentages. The significance level was set at 0.05.

The data collection was carried out with respect to the anonymity of the patients. Written consent has been obtained from patients participating in the study or from their families.

Results: A total of 194 patients with COVID-19 in the Hassan II hospital in Agadir were included in this study. The sex ratio (male/female) was 1,2 with an average age of 60.2 years (18-89 years) for males and 57.8 for females (17-85 years).

The medical history

The toxic antecedents were identified only in the men: chronic smoking, 18.3%, alcohol 3%, and others in 1%. As for respiratory history, 6.2% of the women were asthmatics 3.06 % of the men; 5.1%, 1%, and 4% of the men had COPD (chronic obstructive pulmonary disease), a history of pneumothorax, and common pulmonary tuberculosis, respectively, while no cases of these antecedents were detected in the women. Diabetes was identified in 22 % of the men versus 19 % of the women; hypertension in 13.2% of the men versus 13% of the women; heart disease in 11 % of the men and 4.1% of the women; liver disease in 1.9% of the men and 1% of the women.

Clinical data

Clinically, the arterial oxygen saturation in the ambient air of the patients in this study was divided into three ranges: 80–90%, 90–95%, and 95–100%. According to the results obtained, 11.2 % and 30.6% of the men had saturations below 90% and between 90-95%, respectively. Saturation above 95% was found in 58.1%, while for women, only 4.1 % had saturations below 90%, 27% had saturations between 90% and 95%, and most (69%) had saturation levels over 95% (figure 1).

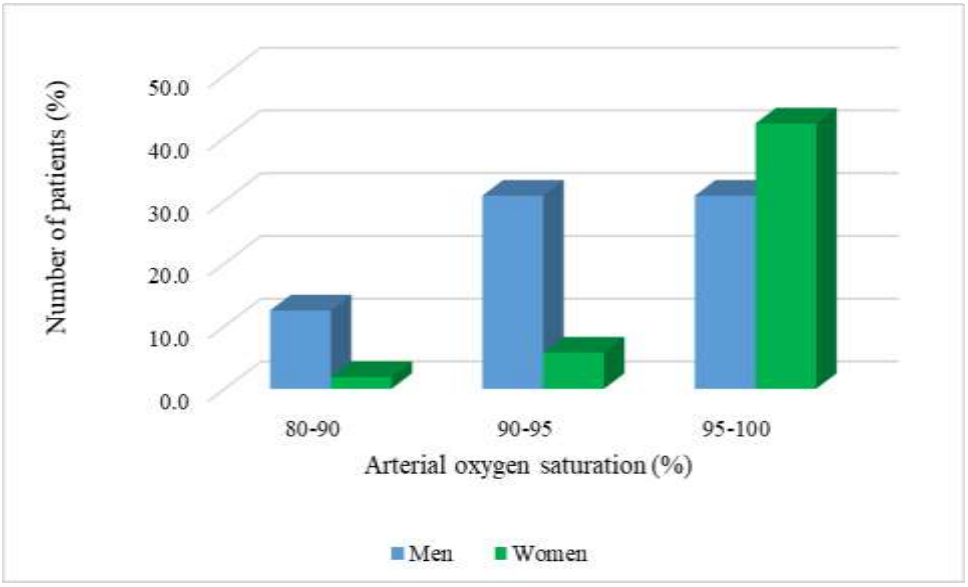

Figure 2: COVID-19 patients' respiratory rates.

Most patients had a normal cardiac rate. Only one case of bradycardia was reported in women. Tachycardia above 90 beats/m was found in 61% of men and 50% of women.

Radiological data

Chest CT revealed an estimated involvement of less than 25% in 16.2% of men compared to 42.2 % of women. Involvement between 25%–50% and 50%–75% was almost similar between the two sexes. An estimated involvement of more than 75% was noted only in men (7%) (figure 3).

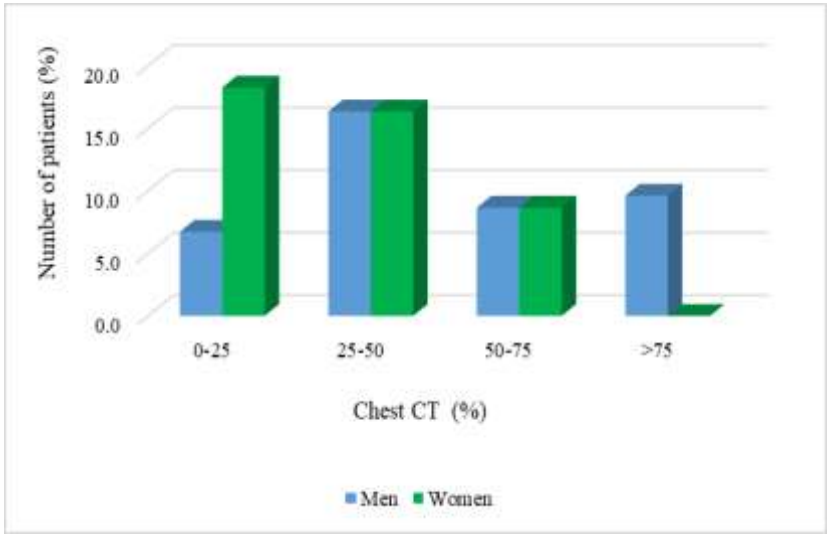

Figure 3: Chest CT scan at the time of infection of COVID-19 patients

Biological data

On the biological plan, the comparison of the results of the blood count, CRP, LDH (Lactate dehydrogenase), ferritinemia, creatinine, fasting glycaemia, D-Dimer, and prothrombin rate between the male and female sex is summarised in the table below (table 1).

Table 1: Biological examination of Covid-19 patients.

	Gender Number (Percentage)	
	Men	**Women**
Hyperleukocytosis	56 (57.1)	45 (46.8)
Leukopenia	4 (4.1)	4 (4.2)
Anemia	8 (8.1)	13 (13.5)
Trombopenia	2 (2.0)	4 (4.3)
Increased CRP ≥ 40 mg/l	66 (67.3)	57 (59.2)
Increased LDH	23 (23.4)	15 (15.6)
Increased ferritinemia	27 (27.5)	25 (26)
Increased Creatinine	11 (11.2)	7 (7.2)

Hyperglycemia	24 (25.5)	18 (19.1)
Increased d-dimer	48 (49)	22 (23.9)
Low prothrombin rate	2 (7.1)	0 (0.0)

The Evolution of the Patients

The evolution was marked by the occurrence of chronic respiratory failure only in men (2%). The rate of thromboembolic complications was approximately the same in both sexes, while the death rate was higher in men (5.1 %) compared to women (3.1 %) (figure 4).

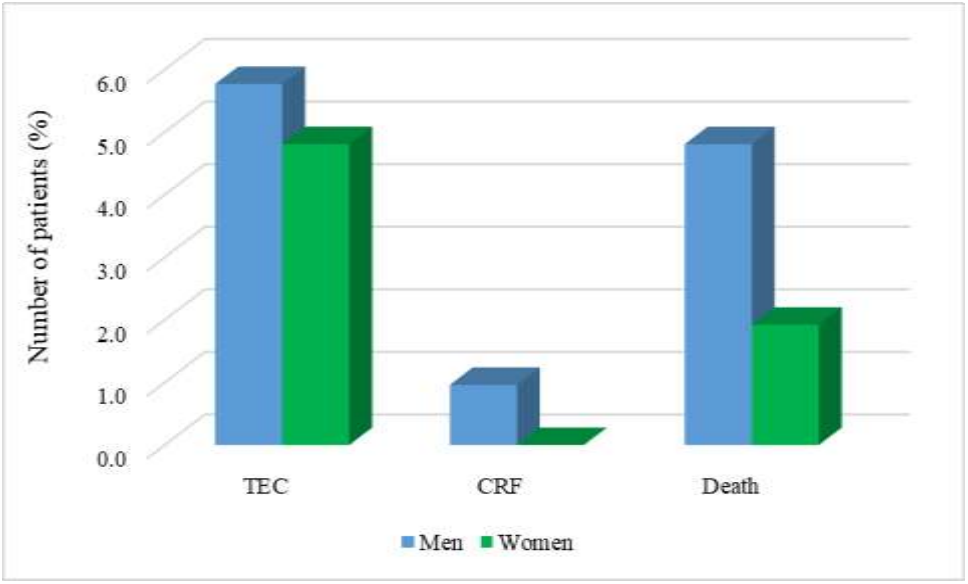

Figure 4: Evolution of COVID-19 patients.

(TEC: thromboembolic complications. CRF: chronic respiratory

Comparison of severity factors of COVID-19 infection

Concerning the severity factors of COVID-19 infection, a gender comparison was made which revealed a higher rate in men than in women for most of these factors. Statistically significant differences were noted in the rate of high dimers (p =0.01) and in the proportion of patients with lung involvement greater than 25% (p =0.008) (table 2).

Table 2: Comparison of COVID-19 infection severity factors

	Participants (N=194)		
	Gender (%)		***p***
	Men	**Women**	
Signs of respiratory struggle	11.2	5.2	0.13
SaO2 <90	11.2	4.1	0.19
Respiratory rate >20 cpm	28.5	14.5	0.09

heart rate >90 bpm	61.0	50	0.28
Leukopenia	4.1	4.2	0.68
Elevated CRP ≥ 40 40 mg/l	67.3	59.2	0.26
Elevated D-dimer	49.0	23.9	0.01
Low prothrombin rate	7.1	0.0	0.65
Chest CT involvement more than 25%	83.8	57	0.008
Thromboembolic complications	12.2	10.4	0.77
Death	5.1	3.1	0.22

Discussion

Several studies have analyzed the risk factors for COVID-19 that predispose patients with COVID-19 to present with a severe form of the disease, for which clinicians should focus on identifying patients at high risk at an early stage. These studies have identified that older age, the presence of cardiac comorbidities, arterial hypertension, diabetes, immune deficiency, elevated LDH and CRP levels, high transaminases, procalcitonin, creatinine, and D-dimer levels are associated with the severity of COVID-19 [14-16].

In our study, we investigated the impact of the gender factor on the severity of COVID-19 infection based on a comparison of clinical and paraclinical signs of severity and outcome in males and females and concluded that males have a more severe form of COVID-19 infection, which is consistent with the results of other studies that have reported that the mortality rate of males was much higher than females of all ages [17-19].

Toxic habits, including chronic smoking, were identified just in males, considering the effect of toxic habits on the respiratory system most affected in the case of COVID-19 infection, which could explain the severity of covid-19 infection in males in our series [20]. The prevalence of diabetes and hypertension described as risk factors for the severity of COVID-19 infection [21] was equal in both sexes in our series, while cardiovascular comorbidities were more identified in the male sex.

SARS-CoV-19 and CVD have a common characteristic [22-26], Angiotensin-Converting enzyme 2 (ACE2) is implicated in the pathogenesis of both diseases, To facilitate entry into cells, SARS-CoV-2 binds to specific cell surface receptors, such as ACE2 [27-30], The infection generally begins in the oropharynx or nasopharynx and then spreads to tissues that express ACE2 in the superior airways and lungs, ACE2 is a key negative regulator of the renin-angiotensin aldosterone system (RAAS), counterbalancing the actions of ACE [31], and acts by converting angiotensin II to angiotensin I, which attenuates the deleterious effects of Ang II by causing a range of effects on the cardiovascular system, including vasodilation, myocardial protection and anti-arrhythmic, anti-inflammatory, anti-hypertensive, anti-thrombotic and inotropic effects by nature [32, 22].

Indeed, the genes encoding ACE2 are located on the X chromosome, suggesting a higher expression potential in women [33]. Nevertheless, reports from several preclinical studies indicate that ACE2 expression is often higher in men [34-36]. An analysis of a sample of lungs from patients with co-morbidities that predispose to severe Covid-19 infection shows higher expression of ACE2 [37].

Biologically, in our series, men had elevated levels of inflammatory markers compared to women, including hyperleukocytosis, and increased CRP and LDH, and in another study, men had remarkably elevated CRP and procalcitonin levels compared to women [38].

The morbidity and mortality associated with COVID-19 are mediated by intense inflammation stimulated by the virus. increased levels of inflammatory biomarkers and cytokines, generally referred to as the "cytokine storm". The cytokine storm is consistently associated with more severe COVID-19 disease. Among those presenting with an excessive inflammatory profile were elderly patients and men [39-41].

Males with severe COVID-19 are reported to have higher CRP concentrations than females, irrespective of age and comorbidities [42], which is in accordance with the results of our series. Data indicate that males with COVID-19 have many pro-inflammatory cytokines, including CCL14 (Chemokine C-C Motif Ligand 14), CCL23, IL-7 (interleukins-7), IL-16, and IL-18, the latter possibly contributing to their higher susceptibility to developing cytokine storm [43].

Concerning the biological markers of coagulation in our series, men had higher d-dimer levels than women with a statistically significant difference ($p = 0.01$), low prothrombin levels were identified just in men, and consequently, men had more thromboembolic complications. In another study, it was observed that d-dimers were elevated in more than half of the patients with severe COVID-19 but with no difference between the sexes and that thrombocytopenia was a predictive factor for death following COVID-19 infection [44].

In studies of Covid-19 patients with coagulation dysfunction, the composition of the patient population includes more male patients, reflecting the severity of Covid-19 infection in male patients [45-47]. The underlying mechanism of coagulopathy in COVID-19 patients has not yet been elucidated, but it is hypothesized that a disproportionate inflammatory response leads to endothelial cell dysfunction and a pro-thrombotic state [48].

The expression of the ACE2 receptor on endothelial cells results in endothelitis, which can cause extensive organ damage, sudden vasoconstriction, abnormal angiogenesis, microthrombosis formation, and ischaemia [48-50]. In addition, patients with severe COVID-19 develop a hypercoagulable state [51], which is also demonstrated by increased levels of factor VIII and von Willebrand factor, a slight decrease in anti-thrombin III activity [52], and inactivation of the fibrinolytic system [53]. These disturbances are probably the basis of venous thrombosis. Arterial thrombosis, which can present as ischemic stroke, mesenteric ischemia, or acute limb ischemia, can be explained by the phenomenon of free-floating thrombi observed in COVID-19 infection [54-58].

The constitution of the sex chromosomes could also be important for the outcome of the disease between the two sexes. Females have two copies of the X chromosomes while males have only one X chromosome that contains a high density of genes related to the immune system, which is responsible for one of the differences in the innate and adaptive immune responses between the two sexes [59, 60].

Many sex differences in the manifestation of infectious diseases have long been attributed to the influence of sex hormones. Endogenous oestrogens can improve the severity of influenza infections in mice by reducing the release of chemokines and pro-inflammatory cytokines [61-64]. Interestingly, men with prostate cancer undergoing androgen deprivation therapy appear to be protected from SARS-Cov-2 infections, highlighting the potential of androgens to modulate susceptibility and disease progression [65-67].

Conclusion

Based on our study and the available literature, it appears that COVID-19 infection is more severe in males. This has been explained by biological differences between men and women. These include the renin-angiotensin-aldosterone system and the entry of SARS-Cov-2 viral cells, the immune system, the genetic system, and sex hormones. Further research on the prognostic factors of COVID-19 infection specific to each gender and the pathophysiological mechanisms explaining this outcome is needed to improve the management and outcome of patients diagnosed with COVID-19.

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Conflicts of interest

There are no conflicts of interest.

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