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# Gender Differences in Coronavirus Disease-19 (COVID-19) in Tunisian Population

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**Abstract**

Introduction: The aim of our study was to determine if the gender influences the clinical presentation and/or the outcome of the new coronavirus disease 2019 (COVID-19) in Tunisian population. Methods: Prospective cross-sectional study including 143 patients with confirmed COVID-19 infection, admitted in the Pneumology Department of the Military Hospital of Tunis between September 2020 and January 2021, during the first infection-wave. Results: There were 99 men (69.2%) and 44 women (30.8%) with a mean age of 61.66 years: 61.66 years for men and 61.68 years for women, and a sex-ratio of 2.25. The clinical presentation of the infection was significantly more severe in men: Tachycardia>100 bpm (15.2% Vs 2.3%, p=0.034), neurological symptoms (5.1% Vs 4.5%, p=0.008) and oxygen desaturation<90% (19.2% vs. 20.5%, p=0.002). Radiologically, pulmonary involvement was more severe in men with significantly more bilateral damage: 75.8% Vs 59.1%, p=0.048, and pulmonary embolism: 9.1% Vs 6.8%, p=0.045. Men have received more second-line antibiotic (ATB) treatment (Quinolones, Tetracyclines…) with a prolonged ATB course duration. Furthermore, they needed more systemic corticosteroids compared to women. Severe complications, Intensive care unit (ICU) admission, and in-hospital mortality were significantly higher in men compared to women: 16.2% Vs 15.9%, p=0.006, 21.2% Vs 22.7%, p=0.017, and 10.1% Vs 6.8%, p =0.055 respectively. Conclusion: In our study, men affected with COVID-19 were more prone to severe infection forms, leading to higher ICU admissions, severe radiological lesions, greater use of antibiotics and worse outcomes.

**Keywords:** COVID-19, gender, SARS-CoV2, severity, prognosis, Tunisia

## 1. Introduction

Since the Outbreak of the new coronavirus disease-19 (COVID-19) pandemic, the virus has affected 527,971,809 persons, resulting in 6,284,871 deaths in the world (Biancolella M, Colona VL, Mehrian-Shai R, Watt JL, Luzzatto L, Novelli G & et al., 2022). The trend now is to seek for a gender-disaggregated data, to understand the biology of the disease and assess the adequate treatment (Ueyama H, Kuno T, Takag H, Krishnamoorthy P, Vengrenyuk Y, Sharma SK & et al., 2020).

Gender Differences are likely due to a Behavioral, Genetic and Hormonal gap between both sex, as well as distinct biological pathways related to SARS-CoV-2 virus. Some studies have suggested worse outcomes among

men affected with COVID (Ueyama H, Kuno T, Takag H, Krishnamoorthy P, Vengrenyuk Y, Sharma SK & et al., 2020; Ferretti VV, Klersy C, Bruno R, Cutti S & Nappi RE., 2022). However, very few cross-sectional studies were published between countries (Feng H, Gan CCR, Leiva D, Zhang BL & Davies SE., 2022; Fortunato F, Martinelli D, Lo Caputo S, Santantonio T, Dattoli V, Lopalco PL & et al., 2021; Undurraga EA, Chowell G & Mizumoto K., 2021). The results remain controversial (Mangia C, Russo A, Civitelli S & Gianicolo EAL., 2020).

We aimed to study the clinical, biological, radiological, and therapeutic features, as well as the outcomes (complications & death), according to gender.

## 2. Methods

It is a prospective, cross-sectional study, including 143 patients with confirmed COVID-19 infection, admitted in the Pneumology Department of the Military Hospital of Tunis. The data were collected from September 2020 up to January 2021 in an electronic database, during the first infection-wave.

Each patient was subjected to a thorough clinical examination, blood samples, electrocardiogram, and an enhanced Chest CT-Scan. The infection was confirmed by a nasal Polymerase Chain Reaction (PCR) sampling to screen for (COVID-19).

We assessed the clinical, biological, and radiological findings upon admission and during the follow-up.

Inclusion criteria were patients aged over 18 years, infected with SARS2-CoV-2 confirmed by a nasal PCR, and admitted in our Military Hospital. Exclusion criteria were missing data or patient's refusal to participate to our study. The patient's consent was obtained orally, as they were discharged, and the Military Hospital Ethics Committee has approved our study.

We divided our sample in 2 Groups according to gender: G1=Male and G2=Female.

We used the latest Version of SPSS (V26) to analyze the data. The normality of the variables was tested using the Ghauss Test.

The normally-distributed continuous variables distributions were represented as means, medians, and standard-deviation. We used the Student's T-Test for the comparison between these variables.

The Variables, that don't follow the Normal Distribution, were shown as medians and interquartile ranges (IQR).The Mann-Whitney U Test was used to correlate these variables.

The Categorical variables are showed as absolute frequencies and percentage. To compare them, we used the Chi-Square test or Fisher's exact test.

A multivariate regression analysis was performed to highlight the correlation between the (clinical, biological, radiological…) data and the outcomes (complications & death).

Statistical significance was settled as ($p<0.05$).

## 3. Results

There were 99 men (69.2%) and 44 women (30.8%) with a mean age of 61.66 years: 61.66 years for men and 61.68 years for women (Table 1).The sex-ratio was 2.25.The COVID infection rate remained more frequent in men, in all age-groups, as shown in (Figure1).

As regards with the lifestyle, the smoking rate was greater among men 46 (46.5%) vs 2 (4.5%), p=0.000. None of the women was addicted to alcohol (p=0.106) (Table 2).

Concerning the comorbidities, men had more serious past medical history like type 2 diabetes: 26 (26.3%) vs 10 (22.7%), p=0.04), chronic cardiac disease: 5 (5.1%) vs 0 (0%), p=0.129, arrhythmia: 6 (6.1%) vs 0 (0%), p=0.095, cancer: 5 (5%) vs 2 (4.8%), p=0.017, and COPD: 6 (6.1%) vs 2 (4.5%, p=0.032. Whereas, women had more asthma: 12 (27.3%) vs 4 (4%), p=0.000) (Figure 2).

Regarding the Clinical Findings, women were referred to us for more uncommon patterns such as digestive symptoms (vomiting: 9 (20.5%) vs 8 (8.1%, p=0.089 or anosmia/agueusia: 9 (20.5%) vs 14 (14.1%). While, men had more severe clinical presentation as shown in table 3.

As regards with the lab tests, men are found to have higher systemic inflammation protein (CRP, IL6, and Fg) levels and prognostic biomarkers (D-Dimer, Pro-BNP) levels, than those reported in women. The High-Sensitive (HS) Troponin level was similar between both groups (Table 4).

As regards with CT findings, we noticed more severe radiological lesions (multifocal, bilateral, and extended) in men as shown in (Table 5). Moreover, the enhanced CT-Scan revealed a pulmonary embolism in 12 cases (9 men vs 3 women, p=0,031).

According to CT-Scan findings, the infection was considered as severe in 41 cases (27 men vs 14 women), and

critical in 17 cases (10 men vs 7 women) (Figure 3).

Concerning the treatment, men have received more second-line antibiotic (ATB) treatment (Quinolones, Tetracyclines…), with a prolonged ATB course duration (Table 6). Furthermore, they needed more systemic corticosteroids (compared to women).The anticoagulant treatment was more prolonged (for curative reasons) in the first group. They needed more advanced ventilation support such as (NIV, Optiflow, and IMV) to be in a stable condition as shown in (Table 6).

Remission rate was higher in women compared to men. Unfortunately, 23 cases presented complications needing an ICU admission: 16 men vs 7 women, p=0.009. Besides, we reported also 13 deaths related to COVID infection: 10 men vs 3 women, p=0.045 (Figure 4, Table7).

**4. Discussion**

In our study, we noticed that the smoking rate was greater among men. Interestingly, the patients of the first group (G1) had more serious comorbidities. They presented with more severe clinical presentations, with a higher rate of ICU admissions. They had higher biological markers like (D-Dimer & Pro-BNP), and systemic inflammation protein levels (CRP, Il6, & Fg), known to be associated with a severe COVID-infection and worse outcomes. They needed more systemic treatments with a prolonged ATB course duration and more advanced resuscitation strategies for to be in a stable state. It is so important to underline that they had more severe complications with a higher death rate, as described above.

Our results are in accordance with the literature (Ueyama H, Kuno T, Takag H, Krishnamoorthy P, Vengrenyuk Y, Sharma SK & et al., 2020; Ferretti VV, Klersy C, Bruno R, Cutti S & Nappi RE., 2022; Feng H, Gan CCR, Leiva D, Zhang BL & Davies SE., 2022; Fortunato F, Martinelli D, Lo Caputo S, Santantonio T, Dattoli V, Lopalco PL & et al., 2021; Undurraga EA, Chowell G & Mizumoto K., 2021). In fact, in Ueyama H et al meta-analysis including 15 observational studies, men were more prone to develop severe forms of COVID-19 infection (Ueyama H, Kuno T, Takag H, Krishnamoorthy P, Vengrenyuk Y, Sharma SK & et al., 2020).

We attempted to understand the underlying mechanisms of such correlation. First, unhealthy lifestyle and social habits may contribute to a worse baseline Health status (Khunti K, Singh AK, Pareek M & Hanif W., 2020; Pflugeisen BM & Mou J., 2021). In fact, we reported more current smokers and severe comorbidities in G1.This may result in a weaker immune response towards pathogens (Khunti K, Singh AK, Pareek M & Hanif W., 2020). In our study, men had more serious clinical presentations and severe complications during the hospital-stay.

Second, women are thought to have a stronger immune response. This statement can be explained by the Biological differences between both sex. In fact, recent studies suggest that Hormones may participate in this huge gap between genders. In fact, Estrogen may enhance both innate and adaptative immune response (Fidecicchi T, Fruzzetti F, Lete Lasa LI & Calaf J., 2022). During the humoral response, it may increase the level of antibodies, as well as the number of cell-producing antibodies. Moreover, researchers have demonstrated that macrophages phagocytic capacities are more efficient in women. This finding could explain a faster viral clearance, and clinical remission in the second group, as described in our study (Fidecicchi T, Fruzzetti F, Lete Lasa LI & Calaf J., 2022; Falahi S & Kenarkoohi A., 2021).

Inversely, Testosterone may have immunosuppressive effects. It is known to be associated with a higher viral load and a decrease in viral clearance. However, a large German Cohort Study has reported low-Testosterone level in confirmed COVID-19 patients, admitted in ICU. Thus, the correlation between androgen level and the severity of the disease has not been established yet (Pradhan A & Olsson PE., 2020).

Additionally, recent studies suggest that this gender-dismorphic response towards SARS2-infection could be explained rather by the genetic constitution of each sex (XX in women and XY in men). As the X-chromosome encodes for many immune genes like the immune recognition receptors (PAMPS, TLRs, ACE2…). Hence, a missing X-chromosome may lead to a worse immune response. Researchers have demonstrated that women have different subtypes of Toll Like-Receptors « TLRs », such as (TLR2,7,9) than those found in men (TLR 2,4). This is so important as the affinity of TLRs towards pathogens is different. They suggest that women TLRs recognize well the viral pathogens, whereas those in men identify better the bacterial pathogens (Foresta C, Rocca MS & Di Nisio A., 2021).

It is interesting to underline that the testis has been involved recently in this biological analysis, since it is an immune-preferred organ. Researchers have found high Angiotensin Converter Enzyme 2 (ACE2) levels in the testis (He W, Liu X, Feng L, Xiong S, Li Y, Chen L & et al., 2020). ACE2 is a mainstream protein in SARS2-COVID infection. It is a receptor involved in COVID19 recognition and entry to the infected cells. It mediates also the immune response, leading to an increased viral transmission. Researchers have isolated SARS2-COVID particles in the testis (Leydig cells, Sertoli, seminifer ducts...), in histological samples. This may explain an increased viral load and a delay in viral clearance in men, as reported in our study (Testis Involvement Theory) (He W, Liu X, Feng L, Xiong S, Li Y, Chen L & et al., 2020). They even suggest that the testicles may

play the role of a « virus reservoir », resulting in a delay in clinical remission and worse outcomes among men in our study. The issue of a possible sexual transmission of this virus, as well as the impact on the fertility is still raised. We do recommend monitoring the gonad function, during the follow-up especially in men.

Third, the behavioral studies attempted to explain this gender imbalance towards COVID-19. We think that women are more aware towards risk and adopt preventive strategies, like withdrawal from competitions despite pricing. This may result in a higher rate of infection among men, as seen in our study (Pflugeisen BM & Mou J., 2021; Galasso V, Pons V, Profeta P, Becher M, Brouard S & Foucault M., 2020; Kowalik Z & Lewandowski P., 2021).

Psychological analyses have revealed that men often think to be stronger and less exposed to worse outcomes than women, especially in our Arab countries. Whereas, women are more sensitive towards danger, and have a higher level of anxiety. Thus, the Death rate is often greater in men (Ferretti VV, Klersy C, Bruno R, Cutti S & Nappi RE., 2022; Mangia C, Russo A, Civitelli S & Gianicolo EAL., 2020), as reported in our study. Besides, they don't adhere to the hygienic measures (wearing protective masks, washing hands, distancing…) and to restrictive decisions, as well as women do (Pflugeisen BM, Mou J., 2021; Griffith DM, Sharma G, Holliday CS, Enyia OK, Valliere M, Semlow AR & et al., 2020).

## 5. Conclusion

To conclude, men affected with COVID were more prone to severe infection forms, leading to higher ICU admissions, severe radiological lesions, greater use of antibiotics and worse outcomes in our study. We do advocate for a gender-based responsive approach to tailor the best treatment. The behavioral and biological pathways seem to be rigorous, with new insights towards this « tricky » virus.

**Conflicts of Interest**: None

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## Abbreviations

**ACE**: Angiotensin Converter Enzyme, **ATB**: antibiotic, **Covid-19**: Coronavirus disease 2019, **COPD**: Chronic Obstructive Pulmonary Disease, **CRP**: C-Reactive Protein, **CT**: Computed tomography, **Fg**: Fibrinogen, **HS-Troponin**: High-Sensitive Troponin, **ICU**: Intensive care unit, **IL6**: Interleukin 6, **IMV**: Invasive Mechanical Ventilation, **NIMV**: Non Invasive Mechanical Ventilation, **pro-BNP**: pro-brain natural peptide, **SARS-CoV-2**: Severe Acute Respiratory Syndrome Coronavirus-2, **PCR**: Polymerase Chain Reaction, **TLRs**: Toll Like-Receptors, **TNF-alpha**: Tumor Necrosis Factor Alpha.

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