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# Differences in the clinical course, laboratory and radiological findings of COVID-19 infection between male, female and pregnant patients in demographically homogeneous groups

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## Abstract

**Aim:** This study examines for any differences in the clinical course, laboratory and radiological findings of COVID-19 infection between male, female and pregnant patients in similar age groups.

**Materials and Methods:** This retrospective study involved a review of the data of patients treated between March 2020 and May 2021, included a total of 528 cases (193 pregnant females, 170 non-pregnant females and 165 males) aged 18–40 years with RT-PCR-confirmed COVID-19.

**Results:** A comparison of the three demographically homogeneous groups revealed more common symptomatic infection at admission in the male patient group than in the other two patient groups ($p<0.001$), as well as a longer hospital stay ($p<0.001$) and higher incidences of moderate and severe pneumonia ($p<0.001$) based on radiological findings. In contrast, no significant difference was noted in the intensive care unit admission and mortality rates of the three groups.

**Conclusion:** The results of our study reveal that females have some degree of protection against severe presentations of COVID-19 infection when compared to men. The heterogeneity of immunocompetence and immune response can help to understand the different COVID-19 responses of males and females, and can be used as a guide for disease prognosis and gender-specific treatments.



## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), developed into a global outbreak in less than three months after the first case was reported in December 2019. The disease was declared a pandemic by WHO on March 11, 2020. Since the onset of the COVID-19 pandemic, clinicians and epidemiologists worldwide have observed gender-specific differences in the severity, course and mortality risk of COVID-19. According to the available literature, mortality and morbidity are higher in males than in females. It is a long-known fact that females of reproductive age have a stronger immune response to viral infections than males and postmenopausal females due to their higher estrogen and progesterone levels [1]. Certain physiological changes that take place in the cardiorespiratory and immune systems during pregnancy are known to make pregnant females more susceptible to infections in general [2]. Changes in cellular immunity increase susceptibility to infections with such intracellular organisms as viruses. Unlike with viral epidemics such as SARS and MERS, mortality and morbidity rates were found to be lower in pregnant females with COVID-19, and better perinatal outcomes have been observed with COVID-19 than with SARS and MERS. Previous studies have identified a similar clinical course in pregnant and non-pregnant patients in the same age groups [3], although there have been limited studies to date addressing this subject in literature.

In the present study we examine for any differences in the clinical course, laboratory and radiological findings of COVID-19 infection between male, female and pregnant patients in similar age groups, and the effects of gender and pregnancy on the clinical course of the disease.

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## Materials and Methods

This single-center retrospective study was conducted based on a review the data of inpatients treated in the Bursa City Hospital Infectious Diseases and Gynecology & Obstetrics Clinic between March 2020 and May 2021. The study included a total of 528 cases (193 pregnant females, 170 non-pregnant females and 165 males) aged 18–40 years with no systemic disease and who were unvaccinated. All study patients had COVID-19 infection confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) tests. The study protocol was approved by the Bursa City Hospital Ethics Committee (Decision No: 2021-10/8) and the study was conducted following the principles of the Declaration of Helsinki.

The patients' epidemiological and demographic characteristics, clinical and laboratory parameters, as well as chest radiographs and thoracic tomography scans, carried out as radiological diagnostic tests, were retrieved retrospectively from the electronic medical registry system. The thoracic computed tomography (CT) scans and chest radiographs were evaluated on the Picture Archiving and Communication System (PACS).

The clinical information, laboratory parameters and imaging test results of the patients at the time of hospital admission were assessed. The patients were divided into three groups: pregnant females, non-pregnant females and males, and three groups with a similar mean age and BMI were considered demographically homogeneous groups. WBC, neutrophil, lymphocyte, and platelet counts and percentages, hemoglobin levels from laboratory parameters, ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels from liver function tests, CRP, ferritin, and procalcitonin levels from acute phase reactants, and PT, APTT and INR were compared. Fever, pulse and saturation at the time of admission were recorded. Symptomatic or asymptomatic infection at the time of admission, presenting symptoms, length of hospital stay, need for intensive care and intubation, frequently used medications and additional pathologies were recorded.

All thoracic CT scans and chest radiographs were reviewed by a single radiologist with more than 10 years of experience in thoracic radiology. Pneumonia was classified as mild, moderate or severe based on radiological imaging, with classification made using the RALE Scoring System on chest radiographs. Each lung was assessed individually and scored on a range of 0–4 based on the extent of consolidation or ground-glass opacity and involvement (0: no involvement; 1: less than 25% involvement; 2: 25–50% involvement; 3: 50–75% involvement; and 4: more than 75% involvement) [4].

Thoracic CTs were grouped according to Chest Computed Tomography Score [5]. Accordingly, both lungs were divided into five lobes, and each lobe was assessed individually. The grouping was made based on characteristics such as density, size, and number and distribution of lesions. Assessments of lesion density were based on the proportion of signs such as ground-glass opacity, consolidation, nodules, reticulation, interlobular septal thickening, crazy paving pattern, linear opacities, subpleural line, bronchial wall thickening, lymph node enlargement, pleural effusion and pericardial effusion, which were evaluated according to the international standard terminology defined by the Fleischner Society Glossary [6]. A CT score of 0–5 was assigned to each lobe based on the percentage of the lobe affected: score 0: 0% involvement; score 1: less than 5% involvement; score 2: 25–25% involvement; score 3: 26–49% involvement; score 4: 50–75% involvement; and score 5: more than 75% involvement. The patients were also classified as mild, moderate or severe based on their clinical presentation [7] as follows:

*Mild Illness:* Patients with any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but with no shortness of breath or abnormal chest imaging,

*Moderate Illness:* Patients with evidence of lower respiratory disease during clinical assessment or imaging, and with oxygen saturation of ($SpO_2$) $\geq$94%,

*Severe Illness:* Patients with oxygen saturation of (SpO2) $<$94% (hypoxia), a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of (PaO2/FiO2) $<$300 mm Hg, a respiratory rate of $>$30 breaths/min (tachypnea) or lung involvement of $>$50%.

### *Statistical analysis*

Descriptive statistics of the study data were presented as mean, standard deviation (SD), quartiles, counts and % frequency. The three groups, comprising pregnant females, non-pregnant females of similar age and males of similar age, who had no systemic disease and who had COVID-19, were compared for clinical course, laboratory findings and radiological findings to assess the effects of gender and pregnancy on these measurements. Accordingly, a One-Way ANOVA model was used to compare the three groups for quantitative and normally distributed variables, and a post-hoc Tukey test was used to identify the different groups. A Kruskal-Wallis test was used to compare the quantitative but non-normally distributed variables of the groups, and a post-hoc Dunn test was used to identify different groups. A Shapiro-Wilk test was used to analyze the normality of the quantitative data. Categorical variables and intergroup relations were assessed with a Pearson's Chi-Square test or a Fisher-Freeman-Halton test, depending on the magnitude of frequencies. The statistical significance level was set to $p<0.05$ and the statistics were assessed with IBM SPSS Statistics (Version 23.0. Armonk, NY: IBM Corp.) software.

## Results

The study included a total of 528 patients (193 pregnant females, 170 non-pregnant females and 165 males) aged 18–40 years. None of the study patients had any systemic disease, and all were diagnosed with COVID-19 infection based on PCR testing.

The mean age was 28.53±5.24 years in the pregnant females, 31.15±5.78 years in the non-pregnant females and 32.62±5.09 years in the males ($p<0.001$). The mean BMI was 28.46±4.52 in the pregnant females, 27.04±5.62 in the non-pregnant females and 25.56±4.21 in the males ($p=0.018$). The difference in the mean age and BMI were

**Table 1.** Descriptive statistics on quantitative variables by groups.

| | Pregnant women | | | | | | Non-pregnant women | | | | | | Men | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | | | Percentiles | | | N | | | Percentiles | | | N | | | Percentiles | | | |
| | | Mean | SD | 25th | Median | 75th | | Mean | SD | 25th | Median | 75th | | Mean | SD | 25th | Median | 75th | p |
| AGE* | 193 | 28.53[a] | 5.24 | 24.50 | 28.00 | 32.00 | 170 | 31.15[b] | 5.78 | 27.00 | 32.00[c] | 36.00 | 165 | 32.62[b] | 5.09 | 29.00 | 34.00 | 37.00 | **<0.001** |
| BMI* | 175 | 28.46[a] | 4.52 | 25.59 | 27.97 | 31.20 | 120 | 27.04[b] | 5.62 | 23.32 | 26.41 | 29.49 | 127 | 28.56[a] | 4.21 | 25.83 | 28.38 | 31.14 | **0.018** |
| WBC* | 191 | 7.64[a] | 2.58 | 5.78 | 7.34 | 8.99 | 170 | 5.75[c] | 2.55 | 4.12 | 5.05 | 7.03 | 165 | 6.79[b] | 2.78 | 4.96 | 6.47 | 7.29 | **<0.001** |
| HB* | 191 | 11.34[a] | 1.47 | 10.40 | 11.50 | 12.30 | 170 | 12.56[b] | 1.36 | 11.70 | 12.70 | 13.50 | 165 | 14.91[c] | 1.23 | 14.20 | 14.90 | 15.65 | **<0.001** |
| PLT* | 190 | 209.42[a] | 62.39 | 170.50 | 205.00 | 242.00 | 170 | 236.84[b] | 71.02 | 184.75 | 227.50 | 279.00 | 165 | 230.05[b] | 82.78 | 179.00 | 211.00 | 258.00 | **<0.001** |
| LYMPHOCYTES* | 190 | 1.40 | .64 | .93 | 1.26 | 1.76 | 170 | 1.48 | .65 | 1.00 | 1.39 | 1.88 | 165 | 1.55 | 1.01 | 1.00 | 1.39 | 1.89 | 0.212 |
| LYMPHOCYTES % | 189 | 19.85[a] | 10.00 | 14.15 | 18.30 | 24.10 | 169 | 28.43[c] | 12.83 | 18.80 | 28.00 | 36.10 | 165 | 23.88[b] | 10.71 | 16.30 | 22.20 | 30.25 | **<0.001** |
| NEUTROPHILS* | 189 | 45.17 | 515.34 | 4.07 | 5.40 | 6.97 | 170 | 3.78 | 2.38 | 2.14 | 3.19 | 4.60 | 165 | 10.92 | 81.34 | 3.10 | 4.25 | 5.47 | 0.404 |
| NEUTROPHILS % | 189 | 72.31[a] | 9.12 | 67.45 | 73.40 | 78.20 | 170 | 62.37[c] | 14.19 | 54.85 | 62.85 | 72.55 | 165 | 66.98[b] | 12.46 | 58.40 | 68.80 | 74.95 | **<0.001** |
| AST | 187 | 26.33[a] | 37.53 | 15.00 | 19.00 | 24.00 | 170 | 24.98[a] | 23.33 | 15.00 | 20.00 | 26.00 | 164 | 43.62[b] | 45.17 | 21.00 | 30.00 | 48.00 | **<0.001** |
| ALT | 188 | 23.24[a] | 37.44 | 10.00 | 13.00 | 21.00 | 170 | 23.48[a] | 28.23 | 12.00 | 15.00 | 22.00 | 164 | 51.60[b] | 51.70 | 21.00 | 30.00 | 65.00 | **<0.001** |
| LDH | 128 | 191.79[a] | 60.94 | 157.00 | 183.50 | 209.75 | 101 | 220.95[b] | 102.02 | 158.00 | 190.00 | 268.50 | 93 | 286.72[c] | 116.80 | 213.50 | 257.00 | 330.00 | **<0.001** |
| CRP | 177 | 22.76[a] | 27.12 | 6.05 | 12.70 | 29.45 | 166 | 28.82[a] | 41.23 | 2.78 | 11.55 | 35.58 | 165 | 53.06[b] | 59.16 | 15.30 | 33.10 | 68.25 | **<0.001** |
| FERRITIN | 171 | 64.00[a] | 102.87 | 18.00 | 31.00 | 75.00 | 156 | 119.98[b] | 181.20 | 31.20 | 70.93 | 139.50 | 162 | 524.32[c] | 421.06 | 278.43 | 413.50 | 687.25 | **<0.001** |
| PROCALCITONIN | 132 | .08[a] | .10 | .04 | .06 | .09 | 81 | .15[b] | .65 | .03 | .04 | .07 | 87 | .08[a] | .06 | .04 | .07 | .10 | **<0.001** |
| D-DIMER | 176 | 1.32[a] | 1.12 | .63 | .98 | 1.60 | 163 | .70[b] | 1.20 | .20 | .29 | .54 | 162 | .47[b] | .57 | .20 | .27 | .49 | **<0.001** |
| PT* | 165 | 8.07[a] | .50 | 7.71 | 8.04 | 8.34 | 151 | 8.99[b] | .70 | 8.57 | 8.87 | 9.28 | 154 | 9.13[b] | .79 | 8.64 | 8.98 | 9.57 | **<0.001** |
| APTT* | 162 | 29.93[a] | 4.47 | 26.90 | 29.75 | 32.70 | 151 | 29.59[a] | 4.35 | 26.80 | 29.10 | 32.50 | 154 | 30.79[b] | 4.12 | 27.98 | 30.55 | 33.95 | **0.044** |
| INR* | 164 | .89[a] | .11 | .87 | .90 | .93 | 150 | 1.01[b] | .11 | .95 | .98 | 1.03 | 154 | 1.01[b] | .11 | .97 | 1.01 | 1.06 | **<0.001** |
| SATURATION | 189 | 97.54[a] | 2.14 | 97.00 | 98.00 | 99.00 | 169 | 97.21[a] | 1.83 | 96.00 | 98.00 | 98.00 | 161 | 96.13[b] | 3.13 | 95.00 | 97.00 | 98.00 | **<0.001** |
| PULSE | 189 | 86.84[a] | 12.51 | 78.00 | 84.00 | 90.00 | 168 | 101.72[b] | 19.33 | 89.25 | 100.00 | 115.75 | 159 | 100.26[b] | 17.02 | 89.00 | 100.00 | 113.00 | **<0.001** |
| FEVER | 190 | 36.80 | .63 | 36.40 | 36.70 | 36.90 | 168 | 36.95 | .70 | 36.40 | 36.80 | 37.40 | 162 | 36.74 | .75 | 36.20 | 36.50 | 37.00 | 0.052 |
| LENGTH OF HOSP. STAY | 191 | 6.41[a] | 4.771 | 3.00 | 5.00 | 9.00 | 170 | 5.64[a] | 2.876 | 4.00 | 5.00 | 6.25 | 165 | 6.83[b] | 3.983 | 4.00 | 5.00 | 9.00 | **0.013** |

*: Normally distributed, one-way ANOVA and post-hoc Tukey test were used. Other variables were non-normally distributed, and a: Kruskal-Wallis test and post-hoc Dunn test were used. BMI: Body mass index; WBC: white blood cells; HB: hemoglobin; PLT: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase, LDH: lactate dehydrogenase; CRP: C-reactive protein; PT: prothrombin time; APTT: partial thromboplastin time; INR: International normalized ratio.

not considered to have a significant effect on the clinical measurements. Due to the clinically insignificant difference in age and BMI, the three groups can be considered demographically similar and homogeneous (Table 1). The mean gestational age of the pregnant females at admission was 27.49.91 weeks.

According to the laboratory findings, the mean WBC and neutrophil % were highest in the pregnant female group and lowest in the non-pregnant female group ($p<0.001$ and $p<0.001$). Lymphocyte % was lowest in the pregnant group and highest in the non-pregnant female group ($p<0.001$).

The mean LDH and ferritin were highest in the male patient group and lowest in the pregnant patient group ($p<0.001$, $p<0.001$). The mean AST, ALT and CRP levels and duration of hospital stay were highest in the male patient group, while these parameters were similar in the non-pregnant and pregnant female groups ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.013$). The mean procalcitonin was highest in the non-pregnant female group, but similar in the male and pregnant patient groups ($p<0.001$). The mean saturation was lowest in the male patient group, and similar in the non-pregnant and pregnant female groups ($p<0.001$).

Table 2 presents the descriptive statistics on the categorical variables of the patients, as well as the results of the comparison of the three groups. According to Table 2.

The rate of those with symptoms at admission ($p<0.001$) and the frequency of dyspnea ($p<0.001$) were significantly highest in males and lowest in pregnant females, while the frequency of asymptomatic presentation ($p<0.001$) was significantly highest in pregnant females and lowest in the males. The frequency of mild upper respiratory tract infection symptoms, such as loss of taste-smell and nasal congestion, was significantly higher in pregnant females than in the other two groups ($p<0.001$).

Considering the radiological findings of all three groups, the rates of moderate and severe pneumonia were highest in the male patient group ($p<0.001$). The incidence of severe pneumonia was also higher in the pregnant female group than in the non-pregnant female group ($p<0.001$).No significant difference was noted in the intensive care unit admission, intubation and mortality ratesof the three groups.

The frequency of antibiotic, Favipiravir and steroid use were significantly highest in the male group ($p<0.001$). The rate of additional pathologies was significantly higher in the male group than in the pregnant female group ($p=0.016$).

## Discussion

Our study compared non-pregnant female, pregnant female and male patient groups who were similar in age and BMI, who had no systemic disease and who were unvaccinated, and revealed that symptomatic infection at admission was more common, the incidence of moderate and severe pneumonia was higher, and the hospital stay was longer in the male patient group than in the other two patient groups. Moreover, AST, ALT, LDH, Ferritin and CRP levels were significantly higher and the frequency of antibiotic, antiviral and steroid use was also significantly higher in the male group than in the other two groups.

According to literature, the estimated rate of mortality due to COVID-19 infection is around 3.4%, depending on age, gender and comorbidities [8], with fatalities being most common in older adults, in those with comorbidities or in the immunocompromised, who are most at risk from serious disease. Due to the well-established effects of age and

**Table 2.** Distribution of categories of categorical variables by groups.

| | | Pregnant women | | | Non-pregnant women | | | Men | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | Total | n | % | Total | n | % | Total | p |
| Smoking** | | 15 | 7.8[a] | 193 | 6 | 3.5[ab] | 170 | 4 | 2.4[b] | 165 | **0.040** |
| Medication history* | | 2 | 1.0 | 193 | 3 | 1.8 | 170 | 0 | 0.0 | 165 | 0.283 |
| Symptomatic atadmission** | | 154 | 79.8[a] | 193 | 163 | 95.9[b] | 170 | 164 | 99.4[c] | 165 | **<0.001** |
| Cough** | | 104 | 53.9 | 193 | 105 | 61.8 | 170 | 102 | 61.8 | 165 | 0.206 |
| Fever** | | 44 | 22.8 | 193 | 58 | 34.1 | 170 | 48 | 29.1 | 165 | 0.056 |
| Dyspnea** | | 56 | 29.0[a] | 193 | 69 | 40.6[b] | 170 | 85 | 51.5[c] | 165 | **<0.001** |
| Loss of taste-smell** | | 33 | 17.1[a] | 193 | 11 | 6.5[b] | 170 | 7 | 4.2[b] | 165 | **<0.001** |
| Headache** | | 7 | 3.6[a] | 193 | 25 | 14.7[b] | 170 | 40 | 24.2[c] | 165 | **<0.001** |
| Myalgia** | | 8 | 4.1[a] | 193 | 40 | 23.5[b] | 170 | 46 | 27.9[b] | 165 | **<0.001** |
| GI symptoms** | | 23 | 11.9[a] | 193 | 35 | 20.6[b] | 170 | 37 | 22.4[b] | 165 | **0.020** |
| Sore throat** | | 47 | 24.4[a] | 193 | 31 | 18.2[a] | 170 | 17 | 10.3[b] | 165 | **0.003** |
| Nasal congestion** | | 26 | 13.5[a] | 193 | 3 | 1.8[b] | 170 | 4 | 2.4[b] | 165 | **<0.001** |
| Asymptomatic** | | 37 | 19.2[a] | 193 | 8 | 4.7[b] | 170 | 1 | 0.6[c] | 165 | **<0.001** |
| WBC Group** | <4.49 | 15 | 7.9[a] | 191 | 63 | 37.1[b] | 170 | 23 | 13.9[a] | 165 | **<0.001** |
| | 4.49–12.68 | 168 | 88.0[a] | | 103 | 60.6[c] | | 132 | 80.0[b] | | |
| | >12.68 | 8 | 4.2[a] | | 4 | 2.4[a] | | 10 | 6.1[a] | | |
| Lymphocyte Groups* | <1.26 | 97 | 50.3 | 193 | 76 | 44.7 | 170 | 67 | 40.6 | 165 | 0.190 |
| | 1.26–3.35 | 96 | 49.7 | | 92 | 54.1 | | 95 | 57.6 | | |
| | >3.35 | 0 | 0.0 | | 2 | 1.2 | | 3 | 1.8 | | |
| AST Groups** | <32 | 165 | 87.8[a] | 188 | 150 | 88.2[a] | 170 | 91 | 55.5[b] | 164 | **<0.001** |
| | >32 | 23 | 12.2[a] | | 20 | 11.8[a] | | 73 | 44.5[b] | | |
| ALT Groups** | <31 | 162 | 86.2[a] | 188 | 146 | 85.9[a] | 170 | 88 | 53.7[b] | 164 | **<0.001** |
| | >31 | 26 | 13.8[a] | | 24 | 14.1[a] | | 76 | 46.3[b] | | |
| LDH Groups** | <135 | 22 | 16.1[a] | 137 | 10 | 9.7[b] | 103 | 0 | 0.0[b] | 93 | **<0.001** |
| | 135–214 | 84 | 61.3[a] | | 51 | 49.5[b] | | 24 | 25.8[c] | | |
| | >214 | 31 | 22.6[a] | | 42 | 40.8[b] | | 69 | 74.2[c] | | |
| CRP Groups** | <5 | 34 | 19.2[a] | 177 | 58 | 34.9[b] | 166 | 15 | 9.1[c] | 165 | **<0.001** |
| | >5 | 143 | 80.8[a] | | 108 | 65.1b | | 150 | 90.9[c] | | |
| Ferritin Groups** | <13 | 26 | 15.2[a] | 171 | 13 | 8.3[a] | 156 | 0 | 0.0[b] | 162 | **<0.001** |
| | 13–150 | 131 | 76.6[a] | | 108 | 69.2[a] | | 19 | 11.7[b] | | |
| | >150 | 14 | 8.2[a] | | 35 | 22.4[b] | | 143 | 88.3[c] | | |
| D-Dimer Groups** | <0.5 | 29 | 16.5[a] | 176 | 118 | 72.4[b] | 163 | 125 | 77.2[b] | 162 | **<0.001** |
| | >0.5 | 147 | 83.5[a] | | 45 | 27.6[b] | | 37 | 22.8[b] | | |
| On ANTIBIOTICS** | | 104 | 53.9[a] | 193 | 122 | 71.8[b] | 170 | 142 | 86.1[c] | 165 | **<0.001** |
| On PLAQUENIL** | | 18 | 9.3[a] | 193 | 62 | 36.5[b] | 170 | 23 | 13.9[a] | 165 | **<0.001** |
| On KALETRA* | | 49 | 25.4[a] | 193 | 0 | 0.0[b] | 170 | 0 | 0.0[b] | 165 | **<0.001** |
| On FAVIPIRAVIR** | | 14 | 7.3[a] | 193 | 130 | 76.5[b] | 170 | 164 | 99.4[c] | 165 | **<0.001** |
| On STEROIDS** | | 0 | 0.0[a] | 193 | 45 | 26.5[b] | 170 | 89 | 53.9[c] | 165 | **<0.001** |
| On LMWH** | | 155 | 80.3[a] | 193 | 148 | 87.1[a] | 170 | 156 | 94.5[b] | 165 | **<0.001** |
| On REMDEVISIR* | | 0 | 0.0 | 0 | 2 | 1.2 | 170 | 2 | 1.2 | 165 | 0.998 |
| PATIENTS WITH CT** | | 20 | 10.4[a] | 193 | 160 | 94.1[b] | 170 | 148 | 89.7[b] | 165 | **<0.001** |
| NORMAL CT** | | 1 | 5.0[a] | 20 | 28 | 17.3[b] | 162 | 7 | 4.7[a] | 149 | **0.001** |
| PATIENTS WITH CHEST X-RAYS** | | 90 | 46.6[a] | 193 | 155 | 91.2[b] | 170 | 161 | 97.6[c] | 165 | **<0.001** |
| Normal Chest X-RAY** | | 30 | 33.3[a] | 90 | 39 | 24.2[a] | 161 | 14 | 8.6[b] | 162 | **<0.001** |
| Radiology Pneumonia Groups** | Mild | 77 | 81.1[a] | 95 | 104 | 61.2[b] | 170 | 51 | 30.9[c] | 165 | **<0.001** |
| | Moderate | 12 | 12.6[a] | | 62 | 36.5[b] | | 87 | 52.7[c] | | |
| | Severe | 6 | 6.3[a] | | 4 | 2.4[b] | | 27 | 16.4[c] | | |
| WHO** | Mild | 127 | 65.8[a] | 193 | 70 | 41.2[b] | 170 | 13 | 7.9[c] | 165 | **<0.001** |
| | Moderate | 58 | 30.1[a] | | 96 | 56.5[b] | | 114 | 69.1[c] | | |
| | Severe | 8 | 4.1[a] | | 4 | 2.4[a] | | 38 | 23.0[b] | | |
| Staying in the ICU* | | 7 | 3.7 | 191 | 1 | 0.6 | 170 | 6 | 3.6 | 165 | 0.091 |
| INTUBATED* | | 2 | 1.0 | 191 | 0 | 0.0 | 170 | 3 | 1.8 | 165 | 0.240 |
| ADDITIONAL PATHOLOGY** | | 13 | 6.8[a] | 191 | 15 | 8.8[ab] | 170 | 26 | 15.8[b] | 165 | **0.016** |
| Mortality* | | 1 | 0.5 | 190 | 0 | 0.0 | 170 | 2 | 1.2 | 165 | 0.411 |



*: Fisher-Freeman-Halton Exact test; **: Pearson's Chi-Square test; GIO: gastrointestinal; WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase, LDH: lactate dehydrogenase; CRP: C-reactive protein; LMWH: Low-molecular-weight heparin; CT: Computed tomography; WHO: World Health Organization; ICU: Intensive care unit.

comorbidities on mortality and morbidity, we selected our study population from among young patients with similar BMIs and age, and without any comorbidity.

Various epidemiological studies analyzing cases by gender have identified a significantly higher level of protection against severe disease presentations and the associated outcomes in response to COVID-19 infection among females [9]. Studies of COVID-19 around the world have identified greater disease severity and higher mortality rates in males than in females [10-15], and several national disease control and prevention organizations have reported gender differences in mortality rates (China- 4.7%:2.8%, Italy 10.4%:6.2% and Korea 2.99%:1.91% for males and females, respectively) [11-13]. All these reports suggest that males have poorer clinical outcomes, are more adversely affected, and record higher morbidity and mortality rates than females. Concurring with literature, males in the present study recorded more symptoms, more severe pneumonia and a greater increase in acute phase reactants, in short, poorer clinical outcomes, and, accordingly, longer hospital stays than the two female groups. We further found that the rate of additional pathologies attributable to COVID-19 infection to be higher in males. There was, however, no significant difference in the intensive care unit admission rate, need for intubation or mortality rates of the three groups, which we attributed to the young age of the study population and the low mortality rate.

The difference in sex-specific disease outcomes after viral infections is likely multifactorial and can be attributed to a variety of social, behavioral, biological and systemic factors. High concentrations of E2 (17$\beta$-estradiol) and progesterone (which are even higher during pregnancy) in women help inhibit the production of proinflammatory cytokines by macrophages, and prevent the migration of monocytes and neutrophils to inflamed tissues. CD4+ helper cells are stimulated to produce anti-inflammatory cytokines and regulatory T cells support immune tolerance, while E2 induces antibody production. All these results in a stronger immune response create faster viral clearance and less severe COVID infection in females. Androgens, for example, T/DHT, increase TMPRSS2 expression and ACE2 receptor activity, facilitating viral fusion with host cell membranes. The immunosuppressive effects of T/DHT may contribute to a more severe COVID infection and poorer outcomes in males [16].

A comparison of the pregnant and non-pregnant patient groups revealed asymptomatic infection at admission to be more common in pregnant females. The pregnant patient group presented mostly with upper respiratory tract infection findings, such as loss of taste-smell and nasal congestion, while the rate of dyspnea at admission was the lowest in the pregnant group. Considering the pulmonary findings of the patients, it was found that the incidence of severe pneumonia was lower in the pregnant group than in the male patients, but higher than in the non-pregnant female group. This finding can be attributed to the fact that pregnant patients in our study were mostly in their third trimester. It can be said that patients in the third trimester have more clinical symptoms, and so imaging findings more important in the third trimester, although there were few CT and CXR scans of pregnant females diagnosed between the first and second trimesters in our study. The progressive expansion of the gravid uterus, the resulting insufficient expansion of the rib cage and decreased functional capacity may cause more severe presentations in the third trimester [17-18]. A study comparing pregnant and non-pregnant women infected with SARS-CoV-19 suggested that two-thirds of deaths in the pregnant female cohort occurred in the second or third trimester, when these physiological changes are most pronounced [18].

Pregnancy presents a unique and complex immunological picture; as the maternal immune system must be able to tolerate a "foreign" developing fetus while protecting the mother against infections and supporting the transfer of maternal antibodies to the fetus. To achieve this, host defense and innate immunity elements are modulated during pregnancy [19]. This immunomodulation may increase the susceptibility of pregnant women to viral infections while protecting the fetus [20]. Indeed, it has been shown that pregnant females are disproportionately affected by such respiratory diseases as influenza [20]. Increased morbidity and higher maternal mortality rates were identified during the MERS and SARS outbreaks [21], and so higher mortality rates and a more severe disease course were expected in pregnant females during the COVID-19 pandemic. Studies, to date, however, have not found pregnant women to be at a higher risk of severe disease and complications in terms of maternal mortality and morbidity in COVID-19 infection, unlike with other viral infections [22].

Progesterone, one of the female sex steroids, is known to have immunomodulatory properties that increase during pregnancy. A recent study found that the administration of exogenous progesterone protected female mice against Influenza A virus infection by modulating the infection, improving pulmonary function and inducing pulmonary tissue repair by regulating the epithelial repair pathways, thereby demonstrating the impact of progesterone against viral diseases [23]. In vitro studies have shown that exposure to progesterone may alter the immune environment of various tissues by inhibiting the production of proinflammatory cytokines and increasing the production of anti-inflammatory cytokines, thereby altering the outcome of infections at various mucosal sites [24].

A study involving women with COVID-19 who were grouped according to menstrual status found premenopausal women to have a lower rate of hospitalization, a lower respiratory support requirement and shorter hospital stay durations than postmenopausal women [25]. Another study assessing the safety and potential efficacy of progesterone use in hypoxemic males with severe-to-moderate COVID-19 randomly assigned patients to receive standard COVID-19 therapy plus progesterone or standard COVID-19 therapy alone. After progesterone was administered subcutaneously at 100 mg twice daily for five days, the patients in the progesterone group showed an overall improvement when compared to the control subjects, and required three fewer days of supplemental oxygen and shorter hospitalization durations than the control subjects [26].

Several clinical trials are underway exploring the effect of sex hormone modulators and ACE2/TMPRSS2 inhibitors

in COVID-19 patients, but further studies are needed to identify their circulating levels over the course of the disease and to benefit from sex-based differences.

*Limitations*

The present study has some limitations. First, the study was conducted with a limited number of participants, all of whom were inpatients, and so outpatients were excluded from the study. As the majority of the patients were symptomatic, asymptomatic patients were relatively low in number, which may affect the clinical outcomes of the study.

## Conclusion

Although future studies will further expand our knowledge on disease outcomes, we can conclude that gender has a significant impact on disease outcome, with females having a greater degree of protection than males in COVID-19. This heterogeneity of immunocompetence and immune response can help in understanding the difference in the COVID-19 responses of males and females, and can be used to guide disease prognosis and gender-specific treatments.

*Ethics approval*

The study protocol was approved by the Bursa City Hospital Ethics Committee (Decision No: 2021-10/8) and the study was conducted following the principles of the Declaration of Helsinki.

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