

## Factors affecting COVID-19 disease severity in breast cancer patients: Single-Center experience

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### ABSTRACT

**Objective:** Coronavirus disease-19 (COVID-19) is one of the large-scale pandemics affecting the whole World. Breast cancer is the most common cancer in women. This study aims to examine the factors that may be effective on COVID-19 disease severity in breast cancer patients.

**Material and Methods:** This study was carried out as a single-center and retrospective study with a total of 65 patients with a pathological diagnosis of breast cancer who were hospitalized between April 2020 and June 2021. The patients were divided into two groups, mild and severe. 35 patients were in the mild group and 30 patients were in the severe group. Patients with oxygen saturation below 93 percent, needing non-invasive or invasive mechanical ventilation, acute respiratory distress syndrome, shock, and multiple organ failure were included in the severe group.

**Results:** A total of 17 parameters that may affect disease severity were analyzed. As a result of the univariate analysis performed to evaluate the potential factors that may affect the severity of the disease, statistically, significant differences were found: the patient had diabetes mellitus ( $P=0.050$ ), the neutrophil count increased during hospitalization ( $P=0.002$ ), the lymphocyte count decreased at admission ( $P=.0001$ ), high d-dimer level during hospitalization ( $P=0.007$ ), lymphocyte to monocyte ratio above 2.55 ( $P=0.016$ ).

**Conclusion:** As a result, the presence of diabetes mellitus, neutrophilia, lymphocytopenia, high D-dimer, and increased lymphocyte to monocyte ratio in patients with breast cancer may aggravate the course of COVID-19 disease. These parameters may be predictive for closer follow-up in terms of clinical deterioration of the patients.

**Keywords:** COVID-19, breast cancer, inflammatory indices.

### INTRODUCTION

COVID-19 continues to be one of the most important health problems in the world since its emergence. COVID-19 morbidity and mortality in cancer patients are higher than in other populations. The mortality rate for COVID-19 in non-cancer patients is 12.5 % (1).

The mortality rate for COVID-19 in cancer patients is 11.5-28.6 %. These studies are not specific to the cancer subtype (2-4). Breast cancer is the most common cancer in women. It is usually diagnosed at an early stage, grows slowly, and has a high survival rate. However, previous studies have shown that the mortality rate in patients with breast cancer is lower than in patients with COVID-19 with other cancers (4-6).

In cancer patients, the immune system is suppressed. This may be due to the cancer's effect or anti-cancer treatments. Advanced age and the presence of comorbidities increase the morbidity and mortality of COVID-19 in cancer (7,8). The inflammatory response accompanying viral infection is extremely important in determining the severity of the clinical course of COVID-19. This inflammatory response; excessive secretion of cytokines leads to macrophage and granulocytes mediated cytokine storm (9,10). Recently published studies have shown that various inflammatory parameters and indices may affect the prognosis during COVID-19 (11-13). However, the clinical course may differ in cancer patients due to the effect of anti-cancer therapy, cancer itself, or an inadequate immune response (14).

This study aimed to investigate the factors that may cause the severe course of COVID-19 disease and follow-up in the intensive care unit in patients with breast cancer.

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## MATERIAL and METHODS

**Study Design:** This study was retrospective and single-center. Patients who received inpatient treatment for COVID-19 in the service or intensive care unit at Mersin City Training and Research Hospital between April 2020 and June 2021 and who were positive for reverse transcriptase PCR on nasopharyngeal swabs were included in the study. Of the 14410 patients diagnosed with cancer or COVID-19 with the hospital electronic ICD-10 code, 251 adult patients with COVID-19 and cancer disease were identified. Among 251 cancer patients, 65 patients with pathological diagnoses of breast cancer were included in the study. Demographic characteristics, cancer diagnoses, hemograms, and biochemistry results of the patients included in the study were obtained from the electronic information system. Inflammation-based indices were calculated for each patient.

The patients were divided into two groups the mild and severe course. Patients with an oxygen saturation level below 93 percent who were monitored and treated in the intensive care unit and showed a more than 50% increase in chest imaging lesions within the first 24-48 hours and required non-invasive or invasive mechanical ventilation, had acute respiratory distress syndrome, were in shock, and had multiple organ failure were classified as severe cases.. The remaining patients were included in the mild course. 35 patients were in the mild course group, and 30 were in the severe course group.

**Statistical analysis:** Whether the variables were suitable for normal distribution was tested with the Shapiro-Wilk test. Variables with normal distribution are given with mean±standard deviation values. Variables with non-normal distribution are given with median (minimum-maximum) values. Categorical variables are given with frequency and percentage values. All data were uploaded to the statistical software program package (SPSS) version 26.0. Kaplan-Meier univariate logistic regression analysis was used to identify possible factors that may affect disease severity.  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 65 patients were included in the study. Thirty patients were in the severe course group and thirty-five were in the mild course. The mean age of the patients was 57.8 (36-91). All of the patients consisted of female patients. 32 patients were in the metastatic stage. Of the non-metastatic patients, 3 were stage 1, 16 were stage 2, and 14 were stage 3. 17 patients had received chemotherapy in the last 28 days. 2 patients had received radiotherapy in the last 28 days. 49 of the patients had at least 1 co-morbid disease as hypertension, diabetes mellitus, and coronary artery disease. The mortality rate was 33% (22 patients). All the severe group patients were hospitalized in the intensive care unit. All of the patients who died were in the severe group. Demographic characteristics, laboratory parameters, and inflammatory indices of the patients in the mild and severe groups are shown in Table 1.

The 6 parameters that were statistically significant as a result of the univariate analysis performed to evaluate the potential factors that may affect the severity of the disease were as follows: the patient had diabetes mellitus ( $P=0.050$ ), increased neutrophil count during hospitalization ( $P=0.002$ ), decreased lymphocyte count at admission ( $P=0.001$ ), high d-dimer level during hospitalization ( $P=0.007$ ), lymphocyte to monocyte ratio above 2.55 ( $P=0.016$ ).

When the effect of chemotherapy and radiotherapy history in the last 28 days on disease severity was examined, no statistically significant difference was found. There was no statistically significant difference between advanced age and disease severity.

**Table 1.** Clinical characteristics and laboratory parameters of patients

Parameters	All patients (N=65) n.%	Severe group (n=30) n.%	Non-severe group (n=35) n.%	P-value
Age (< 65 / ≥65 )	42(65.6)/23(35.4)	18/12(60/40)	24/11(68.6/31.4)	0.379
Comorbidities (0-1/≥2)	40(61.5)/ 25(%38.5)	13/17 (43.3/56.7)	27/8(77.1/229)	0.491
Hypertension (yes/no)	35(53.8)/30(46.8)	19/11(63.3/36.7)	16/19(45.7/54.3)	0.474
Diabetes mellitus (yes/no)	19(29.2)/46(70.8)	9/21(30/70)	10/25(28.6/71.4)	<b>0.050</b>
Cardiovascular disease (yes/no)	21(32.3)/44(67.7)	12/18(40/60)	9/26(25.7/74.3)	0.130
Receiving chemotherapy in the last 28 days (yes/no)	17(26.2)/48(73.8)	10/20(33.3/66.7)	7/28(20/80)	0.289
Receiving radiotherapy in the last 28 days (yes/no)	2(3.1)/63(96.9)	0/30(0/100)	2/33(5.7/94.3)	0.859
<b>Laboratory parameters (median, min-max)</b>				
Total white blood cell count( $\times 10^3/\mu\text{L}$ )	7.10(0.18-22)	10(0.18-22)	5.9(2.52-14)	0.800
Hemoglobin (g/dL)	11.6(4.4-14.7)	10.6(4.4-14.7)	12(6-14.5)	0.070
Platelet count ( $\times 10^3/\mu\text{L}$ )	225(14-749)	205(14-575)	249(61-749)	0.945
Neutrophil ( $\times 10^3/\mu\text{L}$ )	4.9(0.05-18.4)	7.87(0.05-18.4)	4.5(1.52-11.5)	<b>0.002</b>
Lymphocytes ( $\times 10^3/\mu\text{L}$ )	1.1(0.02-5)	0.8(0.02-5)	1.4(0.45-2.8)	<b>0.001</b>
Monocytes ( $\times 10^3/\mu\text{L}$ )	0.39(0.08-1.96)	0.44(0.08-1.8)	0.31(0.1-1.96)	0.173
D-dimer (mg/L)	1.2(0.15-80)	3.4(0.4-36)	0.9(0.15-80)	<b>0.007</b>
Neutrophil:lymphocyte ratio (NLR) (<6/ ≥6)	4.14 (0.64-45.71)	12.5(0.64-45.71)	2.85(1.06-11.9)	0.519
Platelet:lymphocyte ratio (PLR) (<270/ ≥270)	191.42(11-1500)	252(11-1500)	159.28(88.9-680.9)	0.709
Lymphocyte: monocyte ratio (LMR) (<0.255/ ≥0.255)	3.18(0.25-14)	1.63(0.25-7.45)	4(1-14)	<b>0.016</b>

## DISCUSSION

Shortly after the COVID-19 disease emerged, it rapidly affected the whole world. Therefore, the incidence of COVID-19 has increased in cancer patients. Breast cancer is the most common type of cancer in women and the mortality rate due to the disease is low. Previous studies on cancer patients showed that COVID-19 mortality is higher in patients with hematological and lung cancer [4-6]. When we look at the literature, most of the studies on COVID-19 in cancer patients were conducted in mixed cancer groups. There are only three studies covering patients with breast cancer [15-17]. Previous studies have shown that the mortality rate is lower in patients with breast cancer [15]. While the mortality rate was 6.5% in the study of Wei J et al., it was 22% in our study. The high mortality rate can be attributed to the higher number of patients in our study and the high number of metastatic stage 4 patients. Similar to the study of Wei J et al., in our study, no correlation was found between chemotherapy and radiotherapy treatment in the last 28 days and the severity of COVID-19 [15].

In our study, when the relationship between comorbidities and the severity of COVID-19 was examined, no significant relationship was found between hypertension and coronary artery disease. This situation is similar to the results of other studies [15,17]. Our study found a statistically significant relationship between Type 2 diabetes mellitus and COVID-19 disease severity ( $P=0.050$ ). In the other 2 studies, no significant relationship was found between diabetes mellitus and the severity of COVID-19 ([15,16]. Another study showed that it worsens the course of hyperglycemia and COVID-19 [18]. These results are similar to our study. But that study was done in patients without cancer. New studies are needed to clarify this situation.

Our study found a statistically significant relationship between neutrophilia and lymphopenia and the severity of COVID-19. These results are similar to those of Wei et al. similar to work [15].

In our study, D-dimer levels were significantly higher in the severe group than in the mild group. In one study, high d dimer was associated with mortality in COVID-19 patients. But that study was done on patients without cancer [19]. There are no studies in the literature on D-dimer and COVID-19 in patients with breast cancer. Elevated D-dimer may be associated with increased cancer hypercoagulability and COVID-19 coagulability. These patients should be followed closely in terms of thrombotic events.

Our study evaluated the effect of inflammatory indices on disease severity. There are no previous literature studies evaluating the inflammation associated with COVID-19 in patients with breast cancer. In our study, no statistically significant correlation was found between the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio and the severity of COVID -19. A statistically significant correlation was found between the lymphocyte/monocyte ratio and COVID-19 ( $P=0.016$ ). There are no studies on this subject in the literature yet.

This study has several limitations. The first is that it is retrospective, and the second is that the number of patients is small.

## CONCLUSION

Consequently, our study found that the presence of diabetes mellitus, increased levels of neutrophils, decreased levels of lymphocytes, high levels of D-dimer, and an elevated lymphocyte-to-monocyte ratio in breast cancer patients during COVID-19 disease could worsen the progression of the illness. These parameters may be predictive for closer follow-up of patients in terms of deterioration in clinical severity. More recent studies are needed.

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**Ethical approval:** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. Ethics committee approval dated 03.08.2022 and numbered 2022/537 was obtained from Mersin University Ethics Committee before starting the study

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