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The Baseline, Clinical, and Laboratory Parameters of Breast Cancer Subjects Infected with COVID-19 in Medan, Indonesia

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Abstract

BACKGROUND: Cancer patients may be susceptible to COVID-19 infection due to decreased immune status. Breast cancer is the most common cancer in Indonesia, still has high admission, which increasing the risk of exposure to COVID-19.

AIM: Thus, this study aimed to identify hospitalized breast cancer patients diagnosed with COVID-19 infection 1 year after the pandemic.

METHODS: This is a cross-sectional study that was conducted in the Adam Malik General Hospital in Medan, Sumatera Utara, Indonesia. The enrolled subjects were those who previously histopathologically confirmed with breast cancer and having laboratory-confirmed COVID-19 infection The sources of baseline, clinical, and laboratory data were retrieved from the electronic medical records. Statistical analysis was performed using the SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS: A total of 17 female breast cancer subjects with COVID-19 infection were enrolled in this study. Mostly subjects were multiparity, highest education was junior high school, housewife, menopause, diagnosed in Stage IV, had metastasis in lung, and categorized luminal B with invasive cancer of non-special type. Most subjects showed mild clinical and radiological severity of COVID-19 infection. Low leukocyte, high neutrophil-to-lymphocyte, and high platelet-to-lymphocyte counts were significantly differed between alive and death outcome in the subjects.

CONCLUSION: The baseline and clinical characteristics of female breast cancer subjects with COVID-19 infection were similar to general characteristics in the population. The parameters of leukocyte, neutrophil-to-lymphocyte, and platelet-to-lymphocyte counts could be a valuable predictive parameters of mortality outcomes.

Introduction

The first report of the discovery of COVID-19 in cancer patients was published on February 14, 2020, in China, as many as, 18 patients with a history of cancer were diagnosed with COVID-19. A total of 7 (39%) patients had to undergo intensive care unit (ICU) and/or died [1]. Worsening infection, poorer prognosis, a higher number of ICU admissions, need for mechanical ventilation, and higher mortality were found in the cohort of cancer patients presenting with COVID-19 [2].

The 1st time, Indonesia reported two positive cases on March 2, 2020, and several cases continue to grow. After 3 months, Indonesia has reported 26,473 positive cases, 1613 cases died, 7308 cases recovered, and has declared the COVID-19 pandemic a national disaster. Concerning health issues, the Indonesian government itself has established a public health emergency as stated in the Decree of the Head of the National Disaster Management Agency [3].

Cancer patients may be susceptible to viral infections during a pandemic as a result of decreased immune status caused by cancer treatment, while breast cancer is the most common cancer in Indonesia. The need for inpatient or outpatient treatment for breast cancer patients is also high, even during a pandemic [4]. Despite restrictions on elective surgery and increasing options for conservative therapy, visits to the polyclinic are still high because of the need for chemotherapy, diagnostic assessment, and planning for definitive and emergency surgeries that require patients to continue to come to the hospital. This study aims to identify hospitalized breast cancer patients diagnosed with COVID-19 infection 1 year after the pandemic.

Methods

Study design

This is a cross-sectional study that was conducted in the Adam Malik General Hospital in Medan, Sumatera Utara, Indonesia. This is a tertiary university hospital and the COVID-19 care center in Sumatera Utara. This study has been approved by Local Committee Ethics Review Board, which

waived documentation of informed consent due to its observational design. All female subjects with breast cancer and diagnosed with COVID-19 infection between the June 01, 2020 and May 31, 2021 were included in this study.

Study parameters

The baseline characteristics such as age, parity, education, and menopause status were included in the study. The clinical features such as breast cancer stage, metastasis site, pathological type, molecular subtype, and histological grade were included in the study. The COVID-19 infection features included were clinical severity, radiological severity, the need of mechanical ventilation, mortality status, and comorbidities. The laboratory parameters such as leukocyte count, neutrophil-lymphocyte ratio (NLR), and platelet lymphocyte ratio were included in the study.

Data collection

The sources of data were retrieved from the electronic medical records. The enrolled subjects were those who previously histopathologically confirmed with breast cancer and having laboratory-confirmed COVID-19 infection. Nasopharyngeal swabs were collected and assayed for SARS-CoV-2 RNA by real-time polymerase chain reaction (RT-PCR) assay as previously described. The availability of RT-PCR for the gold standard of COVID-19 diagnostic tools was started from July 01, 2020 in this hospital. COVID-19 was diagnosed based on the criteria published by the WHO and confirmed by RT-PCR assay of nasal and/or pharyngeal specimens. Severe clinical symptoms and (CT)-scan severity score for COVID-19 were defined as the protocol used by the Indonesian Pulmonologist Association. A condition such as comorbidities, history, requiring admission to an ICU for the use of mechanical ventilation, or mortality status was based on medical records.

The baseline, clinical, and laboratory parameters were collected from the medical records. Staging of the disease was based on American Joint Committee on Cancer 8 and the histological grading system was based on the Scarf-Bloom Richardson. The molecular subtypes were determined based on the immunohistochemistry test, classified as luminal A (Estrogen receptor [ER]+ and/or progesterone receptor [PR]+, human epidermal growth factor receptor 2 [HER-2-]), luminal B (ER+ and/or PR+, HER-2-), luminal B HER2 (ER+ and/or PR+, HER-2+), HER-2+/ER- (ER-, PR-, and HER-2+), and triple-negative (ER-, PR-, and HER-2-).

The laboratory parameters were determined from the complete blood count test in the 1st day the patients diagnosed with COVID-19 infection. The leukocyte, neutrophil, platelet, and lymphocyte count were recorded. The neutrophil was divided with the lymphocyte count to obtain NLR. The platelet was divided with the lymphocyte count to obtain platelet-to-lymphocyte ratio.

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). For descriptive analysis, continuous variables were presented as the mean with standard deviation or as median with interquartile range, as appropriate. Categorical variables are presented as numbers (%). The Shapiro–Wilk test was used to test the normality of data.

Results

A total of 17 female breast cancer subjects with COVID-19 infection were enrolled in this study. Two patients were diagnosed with COVID-19 infection in the outpatient department during the consultation for scheduling the neoadjuvant chemotherapy program or surgery, six patients were diagnosed during the screening in Emergency Department, and the others were diagnosed during the hospitalization.

The mean age was 48.71 (SD ± 5.96) years. Mostly subjects were multiparity (70.6%), highest education was junior high school (47.1%), housewife (58.8%), and menopause (58.8%) (Table 1). Thirteen subjects (76.4%) were diagnosed in Stage IV (metastasis) which 76.9% had metastasis in lung. Seven subjects (41.2%) had immunohistochemistry molecular subtype categorized as luminal B. Most subjects had invasive cancer of non-special pathological type (58.8%) (Table 2).

Table 1: Baseline characteristics of breast cancer patients with COVID-19 infection

Variables	n	%
Age (± SD)	48.71 ± 5.96 years old	
Parity		
Nulliparity	1	5.9
Primiparity	4	23.5
Multiparity	12	70.6
Education		
Junior high school	8	47.1
Senior high school	5	29.4
University	4	23.5
Employment		
Housewife	10	58.8
Self-employed	2	11.8
Employee	2	11.8
Farmer	3	17.6
Menopause		
Yes	10	58.8
No	7	41.2

Most subjects had mild clinical severity of COVID-19 infection (41.2%), mild CT scan severity score (41.2%), need for mechanical ventilation (70.6%), and had comorbidities (82.3%). Five from 17 subjects

Table 2: Clinical features of breast cancer patients with COVID-19 infection

Variables	n	%
Stage		
II	2	11.8
III	2	11.8
IV	13	76.4
Metastasis site		
Bone	1	7.7
Lung	10	76.9
Liver	2	15.3
Molecular subtype		
Luminal A	2	11.8
Luminal B	7	41.2
Luminal B HER2	2	11.8
HER2	4	23.4
Triple negative breast cancer	2	11.8
Pathological type		
Invasive ductal carcinoma	6	35.4
Invasive lobular carcinoma	1	5.8
Invasive cancer of non-special type	10	58.8
Histological grade		
Grade 1	7	41.2
Grade 2	3	17.6
Grade 3	7	41.2

had unfavorable outcomes (death, 29.4%) (Table 3). In this study, we also collected data about the laboratory parameters (Table 4). The leukocyte count was significantly lower in death than alive subjects (2.9 vs. 5.7 × 10^9/L; p < 0.0001). The neutrophil-to-lymphocyte count was significantly higher in death than alive subjects (7.73 vs. 2.95 × 10^9/L; p < 0.0001). The platelet-to-lymphocyte count was significantly higher in death than alive subjects (211.6 vs. 127 × 10^9/L; p < 0.0001).

Table 3: COVID-19 infection features of breast cancer patients with COVID-19 infection

Variables	n	%
Clinical severity		
Mild	7	41.2
Moderate	4	23.5
Severe	6	35.3
CT Scan severity score		
Mild	7	41.2
Moderate	2	11.8
Severe	8	47.0
Need for mechanical ventilation		
Yes	12	70.6
No	5	29.4
Mortality		
Alive	12	70.6
Death	5	29.4
Comorbidities		
Yes	14	82.3
No	3	17.7

Discussion

It is suspected that cancer patients may be susceptible to infection during virus epidemics due to their compromised immune status caused by cancer treatment. However, less than half of these infected patients are on active treatment for their cancer. It could be that the activation of the immune system is responsible for the damage caused by SARS-CoV-2 [5]. Many of the deaths from COVID-19 are due to multiple organ dysfunction syndrome rather than respiratory distress, which may be due to the wide distribution of the angiotensin-converting enzyme 2 functional receptor for SARS-CoV-2 in multiple organs. Immunosuppression in cancer patients may be caused by malignancy and anticancer treatments, such as chemotherapy, radiotherapy, or surgery [6].

Table 4: Laboratory parameters of breast cancer patients with COVID-19 infection

Variables	Mortality		p*
	Yes	No	
Leukocyte count	2.9 × 10^9/L	5.7 × 10^9/L	<0.0001
Neutrophil-to-lymphocyte count	7.73 × 10^9/L	2.95 × 10^9/L	<0.0001
Platelet-to-lymphocyte count	211.6 × 10^9/L	127 × 10^9/L	<0.0001

*t-independent.

A prospective study in Paris showed that the incidence of COVID-19 in breast cancer patients was 76 subjects, underwent screening selected based on suspected symptoms or incidentally. The study also showed that the COVID-19 mortality rate in patients with breast cancer was more dependent on comorbidities than the presence of a history of radiation therapy or chemotherapy [7]. Another study in Italy is one of the European countries with the worst impact of the COVID-19 pandemic with a case fatality rate of 11.5%, emphasizing the worse cases of COVID-19 in elderly patients with cancer [8]. Dai *et al*. showed that patients with cancer infected with SARS-CoV-2 tend to have a more severe outcome when compared to patients without cancer. Although COVID-19 is reported to have a relatively low mortality rate of 2% to 3% in general, patients with cancer and COVID-19 not only have a 3-fold increase in mortality compared to COVID-19 patients without cancer [9]. Taken together, these findings suggest that cancer survivors are much more vulnerable in the current COVID-19 outbreak.

In this study, baseline and clinical characteristics of female breast cancer subjects admitted to the hospital were similar to those in general population. Most subjects had mild clinical and radiological severity of COVID-19 infection. Five from 17 subjects had unfavorable outcomes. The interesting informations found were the low leukocyte count, high neutrophil-to-lymphocyte count, and high platelet-to-lymphocyte count that were significantly predict the unfavorable outcomes. Yang *et al*. (2020) in general population infected with COVID-19 showed that elevated NLR (hazard risk 2.46, 95%CI 1.98–4.57) and age (hazard risk 2.52, 95% CI 1.65–4.83) as independent factors for poor clinical outcome of COVID-19 [10]. Zhou *et al*. (2021) showed that much higher mortality was found in COVID-19 patients with cancer compared to that in COVID-19 patients without cancer (11.7% vs. 4.4%, p = 0.028). Furthermore, we found that NLR and C-reactive protein (CRP) were related to death outcome [11]. Zhang *et al*. (2020) also showed that pro-inflammatory neutrophils and CRP can be used as an independent influencing factor for adverse clinical outcome of death in breast cancer subjects with COVID-19 infection [12].

The susceptibility of breast cancer patients to COVID-19 infection was influenced by immunological conditions, but the mechanism was not clearly understood and further studies are needed for the immunological

involvement of breast cancer patients. According to the pathological studies of patients with COVID-19, there was desquamation of pneumocytes and formation of hyaline membranes, implying that the patient is suffering from acute respiratory distress syndrome, induced by a cytokine storm is the main reason for the death of patients infected with SARS-CoV-2. It is possible that immunotherapy induces the release of large amounts of cytokines, which can be toxic to normal cells, including lung epithelial cells, and therefore cause more severe disease. However, in this study, the number of immunotherapy patients was too small; further studies with large case populations need to be carried out in the future [9]. Environmental factors, disease stage, and comorbidities can contribute to symptom severity, mechanical ventilation requirements, and morbidity in this population.

Our study has some limitations, we started this study in June 2020 after our institution used RT-PCR to diagnose COVID-19 disease as a screening and gold standard of diagnosis among our patients, we know that it is too late to use it 4 months after the first case in our city. This study only included our breast cancer patients in 1 year, the bias was probably when the second wave of the outbreak occurred, and yet few numbers of patients who tested or screened for COVID-19. This study was only done in one institution, so there were small samples that were included in the study. For the above limitations, we planned another advanced study with a large sample, prospective method, and additional variables for better results.

Conclusion

The baseline and clinical characteristics of female breast cancer subjects with COVID-19 infection were similar to general characteristics in the population. The parameters of leukocyte, neutrophil-to-lymphocyte, and platelet-to-lymphocyte counts could be a valuable predictive parameters of mortality outcomes.

Data Availability

All the data used to support the findings of this study are included within the article.

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Author Contributions

The authors contributed to the conception and design, data acquisition, data analysis and interpretation, drafting the article, critical revision, and approval of the final version for publication.

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