Chemotherapy Increases the Risk of Developing Severe Illness in Breast Cancer Patients with COVID-19: A Multi-Center Retrospective Study in Hubei, China

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Research article

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Abstract

Background: The COVID-19 pandemic is a significant worldwide health crisis. Patients with malignancy are considered at substantially increased risk of infection and poor outcomes. Breast cancer patients with COVID-19 represent an urgent clinical need. This study aimed to identify clinical characteristics of breast cancer patients with COVID-19 and risks associated with anti-cancer treatment.

Methods: This multicenter retrospective cohort study included 45 breast cancer patients with laboratory-confirmed COVID-19 at seven designated hospitals in Hubei, China. The medical records of breast cancer patients were collected from the records of 9559 COVID-19 patients from 13th January, 2020 to 18th March, 2020. Univariate and multivariate analyses were performed to assess risk factors for COVID-19 severity.

Results: Of 45 breast cancer patients with COVID-19, 33 (73.3%) developed non-severe COVID-19, while 12 (26.7%) developed severe COVID-19, of which 3 (6.7%) patients died. The median age was 62 years, and 3 (6.7%) patients had stage IV breast cancer. Most patients developed fever (37, 82.2%), and most had bilateral lung involvement on chest CT (36, 80.0%). Univariate analysis showed the age over 75 and Eastern Cooperative Oncology Group (ECOG) score were associated with COVID-19 disease severity (P<0.05). Multivariate analysis showed patients received chemotherapy within 7 days had a significantly higher risk for severe COVID-19 (logistic regression model: RR=13.886, 95% CI 1.014-190.243, P=0.049; Cox proportional hazards model: HR=13.909, 95% CI 1.086-178.150, P=0.043), with more pronounced neutropenia and higher LDH, CRP and procalcitonin levels than patients else (P<0.05).

Conclusions: The severity of COVID-19 in breast cancer patients was associated with baseline factors of the age over 75 and ECOG score, but not with tumor characteristics. Chemotherapy within 7 days before symptom onset was a risk factor for severe COVID-19, reflected by neutropenia and elevated LDH, CRP and procalcitonin levels.

Background

The current coronavirus disease 2019 (COVID-19) pandemic has been active worldwide since December 2019, a period of more than half a year, which brought unprecedented challenges to health care system. As of 2nd August, 2020, the total number of laboratory-confirmed cases has risen sharply to over 18 million globally, with 688354 (3.7%) deaths [1-3]. The increasing number of newly diagnosed and hospitalized patients with COVID-19 has brought unprecedented challenges and changes to health care systems. According to the previous study, patients with malignancy are more susceptible and vulnerable to SARS-CoV-2 infection than those without cancer[4]. Even though some treatment regimen and recommendations had been proposed for cancer patients during epidemic，nevertheless, it was still necessary and important to realize the core risk factors for COVID-19 in the real world.

Some researchers have conducted studies to characterize cancer patients with COVID-19[5-12]. Approximately 1-2.5% of COVID-19 patients had cancer, and their mortality rate ranged from 11.4-28.6%,

which is much higher than that of the general population [4-12]. Regrettably, many of these studies described in general and ignored effects of different cancer types. As the most common cancer among women, breast cancer has a long treatment cycle resulting in immunosuppression and increased risk of infection[13], thus individuals with breast cancer are at increased risk of SARS-CoV-2 infection and should be given more attention. In our previous study, breast cancer patients had the highest proportion among all cancer patients with COVID-19 [9]. Their mortality rate was 14%, far below the average of general cancer patients (28%) [5, 9]. A study from Paris suggested that the severity of breast cancer patients with COVID-19 resided more in comorbidities[14]. However, our previous study found that cancer patients with anti-cancer treatment had a poorer prognosis, which prompted us to find the relationship between disease severity and anti-cancer treatment among breast cancer population.

This study aimed to identify the epidemiological and clinical characteristics of breast cancer patients with COVID-19 and risks associated with anti-cancer treatment. This is a multi-center retrospective study of 45 breast cancer patients with laboratory-confirmed COVID-19 identified among 9559 COVID-19 patients in seven hospitals in Hubei, China.

Patients And Methods

Study design and participants

In this multi-center retrospective study, 45 breast cancer patients diagnosed with laboratory-confirmed COVID-19 (40 cases from our previous study and 5 from two other hospitals) were identified among 9559 COVID-19 cases admitted between 13th Jan and 18th March, 2020 to seven designated hospitals in Hubei, China (Cancer Center of Union Hospital, Western District of Union Hospital, Red Cross Hospital of Union Hospital and The Central Hospital of Wuhan, all of which are affiliated with Tongji Medical College of Huazhong University of Science and Technology; Jinyintan Hospital; Renmin Hospital of Wuhan University and the First Renmin Hospital of Jingzhou). The clinical outcomes of the patients were followed up to 15th April, 2020. This study was approved by the ethics committee of Union Hospital, Tongji Medical College of Huazhong University of Science and Technology (NA2020-0078).

Study definitions

Patients with the pathological diagnosis of breast cancer and laboratory confirmation of SARS-CoV-2 were included. COVID-19 was diagnosed by RT-PCR of nasal or pharyngeal specimens on criteria of World Health Organization[3], or antibody IgM and IgG based on criteria by National Health Commission(NHC) of China[15]. According to Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (v7.0 Feb 8, 2020) by NHC[15], upon admission, severe cases were characterized as oxygen saturation≤93% at rest or chest imaging with lesion progression>50% within 24-48 hours. Critical cases, such as the patients with respiratory failure and requiring mechanical ventilation, shock, or organ failure requiring intensive care unit (ICU) care. We categorized severe/critical cases into the severe group, and mild/moderate cases

into the non-severe group. Breast cancer staging was based on American Joint Committee on Cancer (AJCC) guidelines [16].

Data collection

Demographic information, clinical manifestations, physical signs, laboratory results, chest radiographs, treatments and outcomes were extracted from electronic medical records using a standardized data collection form and cross-checked by two trained researchers. Clinical outcome data were collected up to 15th April, 2020.

Statistical analysis

Continuous variables, not normally distributed, were expressed as the median and interquartile ranges (IQR) and compared using Mann-Whitney U test. Categorical variables were noted as number (%) and compared by the χ^2 test or Fisher's exact test. The risk ratio (RR) and 95% confidence interval (CI) from univariate and multivariate logistic regression models explored risk factors of COVID-19 severity. The hazard ratio (HR) and 95% CI from Cox proportional hazards model were represented effects of risk factors over time. Statistical analyses were conducted using SPSS statistics 22.0 and SAS 9.4 software. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of breast cancer patients with COVID-19

In this study, 45 breast cancer patients with COVID-19 were selected (Table 1), of which 40 (88.9%) patients diagnosed by PCR and 5 (11.1%) patients diagnosed by positive serum antibody plus chest CT radiography indicative of COVID-19. And 12 (26.7%) patients were categorized into the severe group, while the rest into the non-severe group (73.3%). All patients were females with no smoking history; the median age was 62 years (54.0-70.5 years) (Table S1). The severe group had higher proportion of patients older than 75 years in compared with the non-severe group (P<0.05).Only 4.4% (2/45) of patients had ECOG scores higher than score one. More than half of cases had underlying diseases (60.0%), mainly hypertension (31.1%). As for characteristics of breast cancer, 3 (6.7%) cases were diagnosed with stage IV disease, 31.6% with HER2 over-expression, and 55.3% with estrogen receptor (ER) positive. Among all patients, 51.5% (23/45) received anti-cancer treatment within one month before symptom onset, and 33.3% (15/45) within one week, including chemotherapy (4/45, 8.9%), surgery (2/45, 4.4%), radiotherapy (2/45, 4.4%), targeted therapy (2/45, 4.4%) and endocrinotherapy (7/45, 16.3%). Patients undergoing anti-cancer treatment within 7 days aged from 24 to 69 years old, three of which treated with taxane-based chemotherapy, and the one left was treated with anthracycline-based chemotherapy. (Table S2)

Typical symptoms at illness onset were fever (82.2%), cough (75.6%) and dyspnea (42.2%) (Table 1 and Table S1). Dyspnea and expectoration were more common in the severe group than in the non-severe group (P<0.05). Body temperature upon admission and during hospital stay was significantly higher in

the severe group (P<0.05) (Table S1). Both the four patients who received chemotherapy within 7 days had fever (Table S2).

Laboratory results, CT imaging findings and patient outcomes

The laboratory tests performed upon admission showed that the levels of neutrophils and platelets in the severe group were significantly lower than those in the non-severe group (P<0.05) (Table 1 and S1). In contrast, the levels of LDH, AST and CRP in the severe group were significantly higher than those in the non-severe group (P<0.05) (Table 1 and S1, Fig .2).

On chest CT scans, 80.0% (36/45) of patients showed bilateral involvement (Table 1). The typical patterns were ground-glass opacity (29/42, 69.0%), diffused patchy shadowing (6/42, 14.3%) and local patchy shadowing (5/42, 11.9%) (Figure 1, Table S1). However, there was no statistically significant different radiography between the severe group and the non-severe group (Table A).

Treatments for COVID-19 included physical therapy and medical therapy in routine, including physiotherapy and medical therapy (Table S1). During hospitalization, 7 patients developed complications, mainly with ARDS (4/41, 9.8%), and 4 patients developed severe events (4/45, 8.9%), including admission to ICU, mechanical ventilation, or death [4] (Table S1). Three patients (6.7%) in the severe group had died as of April 15th, 2020; one of these patients had received chemotherapy within 7 days prior to symptom onset (Table 1).

Risk factors for disease severity

To explore clinical factors affecting COVID-19 severity, univariate and multivariate logistic regression models were applied. In the univariate logistic analysis, the age over 75 and ECOG score were associated with disease severity (P<0.05) (Fig 2). Notably, chemotherapy within 7 days showed a tendency towards association with severe illness (P=0.051). After adjusting for age and other anti-cancer treatments within 7 days (including surgery, radiotherapy, targeted therapy and endocrinotherapy), patients undergoing chemotherapy within 7 days had a significantly higher risk of severe illness (RR=19.457, 95% CI: 1.147-329.997, P=0.040) (Table 2). Moreover, among patients with ongoing anti-cancer treatment within one month, the multivariate Cox proportional hazards model showed chemotherapy within 7 days was an independent risk factor for developing severe illness after adjusting for age (HR=13.909, 95% CI 1.086-178.150, P=0.043) (Table 3, Fig 3.A).

Correlations of chemotherapy with laboratory findings

Next, we evaluated the correlation of chemotherapy and laboratory findings. The results showed patients undergoing chemotherapy within 7 days had higher levels of leukocyte and neutrophil counts, LDH, CRP and procalcitonin levels than other patients (P<0.05) (Fig 3.B, Table S3).Similar results were observed between the severe and non-severe groups, that is, neutrophil and platelet counts, LDH, CRP and procalcitonin levels were statistically significant (P<0.05) (Fig 3.C, Table S3).

Discussion

With the rapid progression of COVID-19 worldwide, it is inevitable that large numbers of cancer patients will be affected by this pandemic [5-10]. This leads to grave concerns about standard-of-care treatment regimens in COVID-19 era and the adoption of protective measures, such as postponing active cancer treatments. However, it is impossible to provide a set of universal guidelines for all types of cancer, especially for patients receiving active life-saving therapy or undergoing active treatment to achieve a probable cure. Breast cancer, the most common malignancy among women, is commonly identified in early stages, with slow progression and high chance of cure [17]. Based on our recent report, we focused on effects of COVID-19 on breast cancer patients and determined risk factors for severe COVID-19 in this population.

By now, several studies for epidemiological characteristics of COVID-19 in cancer patients have been published, but most of them focused on general cancer patients, only two reports for breast cancer [5-10, 14, 18]. Remarkably, breast cancer patients with COVID-19 had lower disease severity and mortality when compared with general cancer patients. Compared with the similar works of breast cancer patients with COVID-19 in the world, the mortality in our study was 6.7%, which is similar to that in Vuagnat's study(6.7%) and higher than Kalinsky's study(3.7%) [14, 18]. These different outcomes among breast cancer patients could be explain by the different regional distribution and availability of medical cure, testing methods, subtypes and virulence of SARS-CoV-2. A current report indicated the SARS-CoV-2 variant with Spike D614 to G614 increased the infectivity of the COVID-19.[19] However, the mortality of our study (6.7%) was much lower than that of general cancer patients (11.4-18.6%) [5, 8-10]. Besides, as to disease severity, 26.7% of breast cancer patients in our study had severe disease, which still lower than that of general cancer patients observed by H. Zhang (47.8%), Ma (54.1%), and Dai (34.3%) [7, 8, 20]. In addition, there was a similar trend in the comparison of critical case rates. 8.9% (4/45) breast cancer patients developed events of admission to ICU/ mechanical ventilation/ death in our study, lower than that of general cancer patients in study of L. Zhang (53.6%), and Liang (39%) [5, 6]. The discrepancies above may be due to different strategies for combating the pandemic, cancer types, basic characteristics (e.g., sex, age, general health and comorbidities), etc. Taken together, cancer type seems to be a major determinant of mortality rate, and we can speculate that breast cancer patients with COVID-19 have better outcomes than that of general cancer population.

It seems that recent sessions of chemotherapy or other anti-cancer treatment are a risk factor for the severity of COVID-19 in cancer patients [5, 6, 9]. A study by L. Zhang indicated that undergoing anti-cancer treatment within 14 days mattered [6], and our previous study showed chemotherapy within 4 weeks was a risk factor for fatal outcomes [9]. Notably, in this study, we observed breast cancer patients undergoing chemotherapy within 7 days were more likely to get severe disease, not 2 or 4 weeks. This discrepancy of timing may be due to different cancer types, anti-cancer strategies and intensities. Breast cancer patients are generally female, relatively young, with no history of smoking [17, 21-23], indicating a better baseline condition. Moreover, they are relatively treated with mild chemotherapy regimens, in which induced haematological disorders resolve in approximately one week [24]. Breast cancer patients have

been reported with better prognosis and faster recovery form chemotherapy when compared to those with other solid tumor, such as lung cancer [25].Our study focus on the relationship between anti-tumor treatment and disease severity of breast cancer patients with COVID-19. Remarkably, according to deliberate univariate and multivariate analysis, our study identified the risk and effect of chemotherapy to severe COVID-19 in breast cancer patients, reaching a profound and meaningful conclusion and emphasizing the effect of cancer therapy. Noteworthy, in Vuagnat's study, univariate analysis showed that the ongoing cancer therapy (within 30 days) was not associated with disease severity, and there were no further analysis into cancer therapy within 7 or 14 days. Besides, the number of patient events in their study was too small to have multivariate analysis[14]. In addition, our study demonstrated the age over 75 as a distinct risk factor of severity, which shared a similar results with Vuagnat's report (age over 70).

Laboratory examinations on patients undergoing chemotherapy within 7 days showed distinct abnormalities in infection indicators (neutrophil counts, CRP, LDH, procalcitonin) compared with those not receiving chemotherapy within 7 days, which consistent with laboratory changes found in severe patients to a rather large extent. It has been reported that neutropenia is linked to chemotherapy effects of myelosuppression [26-28], which in turn worsens the immune condition. Additionally, the immunosuppression by chemotherapy possibly prolonged the time of viral shedding [29], which provided an explaination for our study, indicating chemotherapy within 7 days led to myelosuppression and secondary infection, resulting in an aggravated illness and poor outcome of COVID-19.

Therefore, our results can serve as a basis for proposing some recommendations for oncologists. Since intravenous chemotherapy has been identified as a potential risk factor, oral chemotherapy agents [30-33] or other treatment including radiotherapy, surgery and endocrinotherapy should preferentially be administered to contain tumor progression. If active chemotherapy must be administered, measures should be taken under strict assessments of individuals, for example, less-toxic agents in myelosuppression [34-37], intensive examinations before and after chemotherapy, prophylactic administration of G-CSF [38-40], and close monitor for any symptoms indicative of SARS-CoV-2 infection for at least 7 days.

To the best of our knowledge, this is the first report of clinical characteristics and risk factor analysis for breast cancer patients with COVID-19 in Asia. However, this study has several limitations. First, the sample size of 45 cases was somehow insufficient to be significant or skewed in some respects. Only two patients received targeted therapy, which was too limited to be analyzed in multivariate models. Thus, more patients undergoing anti-cancer treatment should be included, especially those with targeted therapy. Second, this study did not delve into different regimens of chemotherapy, and extended follow-up and close observation are recommended. In addition, how to balance a delay in cancer treatment against the risk of contracting COVID-19 remains unsettled.

Conclusions

In this study, we focused on the clinical characteristics and potential risk factors for COVID-19 in breast cancer patients. Compared with other aggressive types of cancer, breast cancer had lower rates of COVID-19-related mortality and severity, the latter of which was related to the age over 75 and ECOG score. In addition, receiving chemotherapy within 7 days before symptom onset was tightly associated with severe COVID-19 in breast cancer patients, reflected by abnormalities in infectious indicators, indicating that the ideal preventive care and supportive treatments are warranted.

Abbreviations

COVID-19: Coronavirus Disease 2019

CT: Computed tomography

ECOG: Eastern Cooperative Oncology Group

RR: Risk ratio

HR: Hazard ratio

CI: Confidence interval

LDH: Lactic dehydrogenase

CRP: C-reactive protein

PCT: Procalcitonin

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

RT-PCR: Real time Polymerase Chain Reaction

NHC: National Health Commission

ICU: Intensive care unit

AJCC: American Joint Committee on Cancer

IQR: Interquartile ranges

HER2: Human epidermal growth factor receptor 2

ER: Estrogen receptor

AST: Aspartate aminotransferase

ARDS: Adult respiratory distress syndrome

G-CSF: Granulocyte colony stimulating factor

Declarations

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AVAILABILITY OF DATA AND MATERIALS

All data generated and/or analyzed during this study are included in this published article.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

YZ and CC had the idea and designed the study. JW, MW, JL, XW, LP, YH, HY, and ZX contributed to the acquisition of the data. JW and PX summarized the data and made statistical analysis. JW, MW, JL, PX, YZ, and CC were involved in data interpretation. JW and MW drafted the manuscript. YZ, CC, JL, XW, CL, and ZX critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This COVID-19 registry was approved by the ethics committee of Union Hospital, Tongji Medical College of Huazhong University of Science and Technology (NA2020-0078).

CONSENT FOR PUBLICATION

Not applicable.

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Tables

Table 1.

Clinical Characteristics and Outcomes of Patients

Characteristics	Disease Severity			
	All Patients (*N*=45)	Non-Severe (*N*=33)	Severe (*N*=12)	*P* value
Age (years)				0.020
≤ 75	41 (88.9%)	32(97.0%)	8 (66.7%)	
> 75	5 (11.1%)	1 (3.0%)	4 (33.3%)	
ECOG Score				0.067
0-1	43 (95.6%)	33 (100%)	10 (83.3%)	
≥2	2 (4.4%)	0 (0%)	2 (16.7%)	
Comorbidities	27 (60.0%)	21 (63.6%)	6 (50.0%)	0.409
Hypertension	14 (31.1%)	11 (33.3%)	3 (25.0%)	0.865
Diabetes	7 (15.6%)	5 (15.2%)	2 (16.7%)	>0.999
Chronic Cardiovascular Disease (not including hypertension)	6 (13.3%)	5 (15.2%)	1 (8.3%)	0.921
Hepatitis	4 (8.9%)	3 (9.1%)	1 (8.3%)	>0.999
Cancer (not including breast cancer)	3 (6.7%)	3 (9.1%)	0 (0%)	0.553
Chronic Cerebrovascular Disease	1 (2.2%)	1 (3.0%)	0 (0%)	>0.999
AIDS	1 (2.2%)	0 (0%)	1(8.3%)	0.267
Others	7 (15.6%)	6 (18.2%)	1 (8.3%)	0.733
Stage				>0.999
I-III	42 (93.3%)	31 (93.9%)	11 (91.7%)	
IV	3 (6.7 %)	2 (6.1%)	1 (8.3%)	
Her-2 expression				0.232

HER-2(+)	12 (31.6%)	8 (26.7%)	4 (50%)	
HER-2(-)	26 (68.4%)	22 (73.3%)	4 (50%)	
Hormone receptor status				>0.999
ER(+)	21 (55.3%)	17 (56.7%)	4 (50%)	
ER(-)	17 (44.7%)	13 (43.3%)	4 (50%)	
Anti-cancer within 1 month				0.928
Yes	23 (51.1%)	17 (51.5%)	6 (50.0%)	
No	22 (48.9%)	16 (48.5%)	6 (50.0%)	
Chemotherapy within 1 month				0.556
Yes	7 (15.6%)	4 (12.1%)	3 (25.0%)	
No	38 (84.4%)	29 (87.9%)	9 (75.0%)	
Anti-cancer within 7 days [a]	15 (33.3%)	9 (27.3%)	6 (50.0%)	0.153
Surgery	2 (4.4%)	1 (3.0%)	1 (8.3%)	>0.999
Chemotherapy	4 (8.9%)	1 (3.0%)	3 (25.0%)	0.090
Radiotherapy	2 (4.4%)	1 (3.0%)	1 (8.3%)	>0.999
Targeted therapy	2 (4.4%)	0 (0%)	2 (16.7%)	0.067
Endocrinotherapy	7 (16.3%)	6 (19.4%)	1 (8.3%)	0.676
Main symptoms				>0.999
Fever	37 (82.2%)	26 (78.8%)	11 (91.7%)	0.577
Cough	34 (75.6%)	24 (72.7%)	10 (83.3%)	0.734
Dyspnea	19 (42.2%)	10 (30.0%)	9 (75.0%)	0.019
Laboratory findings				

Neutrophil <1.8* 10^9/L	6 (13.3%)	2 (6.1%)	4 (33.3%)	0.042
LDH> 250 U/L	14 (35.9%)	5 (17.9%)	8 (81.8%)	<0.001
AST> 40 U/L	10 (25.0%)	4 (13.8%)	6 (54.4%)	0.025
CRP> 10 mg/L	23 (47.7%)	14 (42.4%)	9 (81.8%)	0.055
CT changes				0.448
Unilateral	9 (20.0%)	8 (24.2%)	1 (8.3%)	
Bilateral	36 (80.0%)	25 (75.8%)	11 (91.7%)	
Clinical outcomes				0.016
Discharge	42 (93.3%)	33 (100%)	9 (75.0%)	
Death	3 (6.7%)	0 (0%)	3 (25.0%)	
a: One patient received chemotherapy and targeted therapy together, another patient received radiotherapy and targeted therapy together.				

Table 2.

Logistic Multivariate Analysis of Risks for COVID-19 Severity in 45 Patients

Clinical Factors	**RR**	**95% CI**	***P* value**
Age	1.027	0.960-1.099	0.436
Chemotherapy within 7 days	19.457	1.147-329.997	0.040
Other anti-cancer treatment within 7 days[a]	1.938	0.342-10.994	0.455
a: Other anti-cancer treatment includes surgery, radiotherapy, targeted therapy and endocrinotherapy.			

Table 3.

Cox Proportional Hazards Analysis of Risks for COVID-19 Severity in Breast Cancer Patients[a]

Clinical Factors	**HR**	**95% CI**	***P* value**
Age	0.914	0.821-1.017	0.100
Chemotherapy within 7 days	13.909	1.086-178.150	0.043
a: Breast cancer patients with COVID-19 who undergoing anti-cancer treatment within one month			

Figures

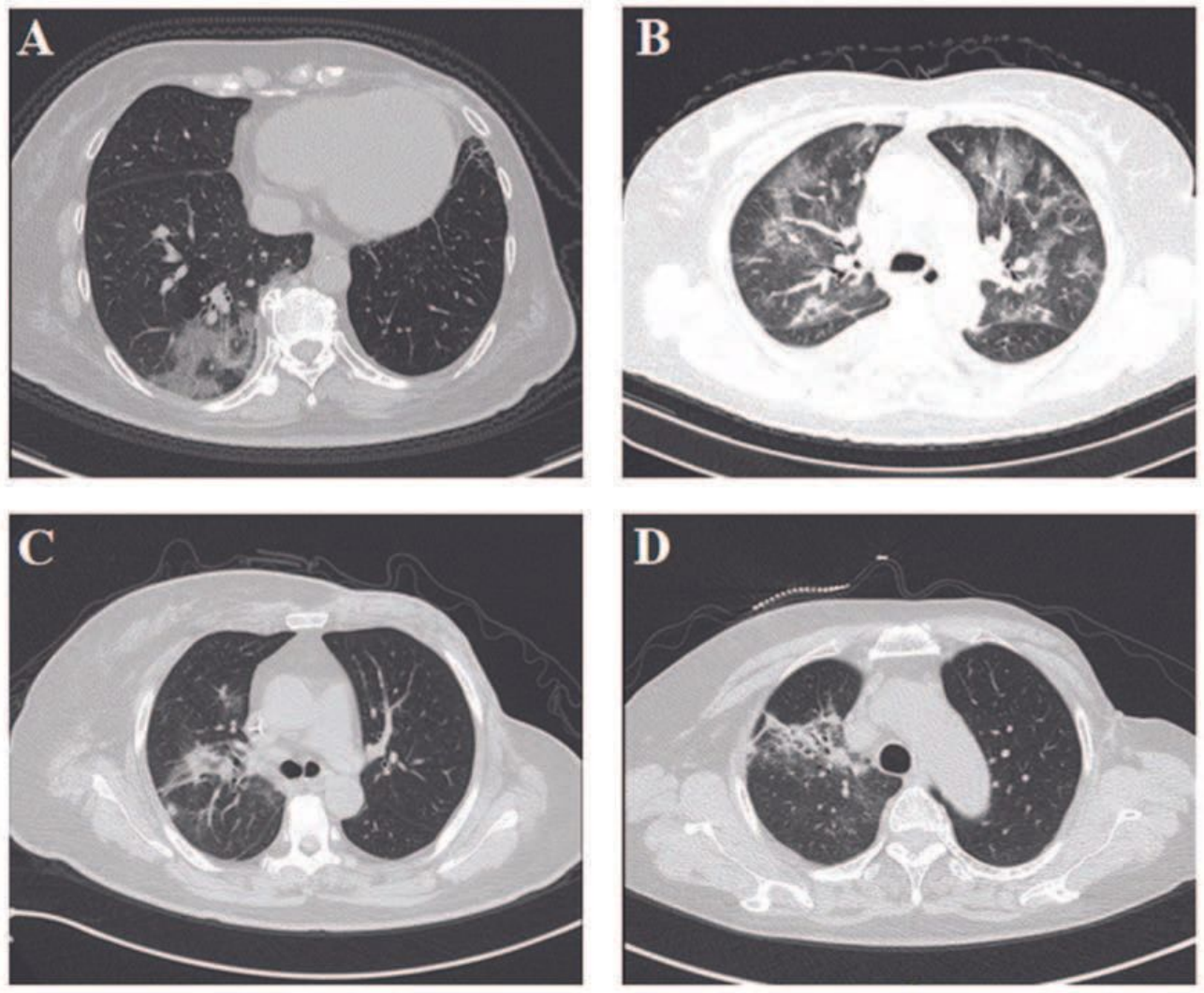

Figure 1

Typical radiologic findings of chest CT scan A. Sporadic patchy ground-glass opacities in the right lower lobe. B. Diffuse patchy ground-glass opacities bilaterally. C. A mixed pattern of ground-glass opacities and consolidation in the right lung. D. Patchy consolidation in the right upper lobe with obvious predominant reticular change.

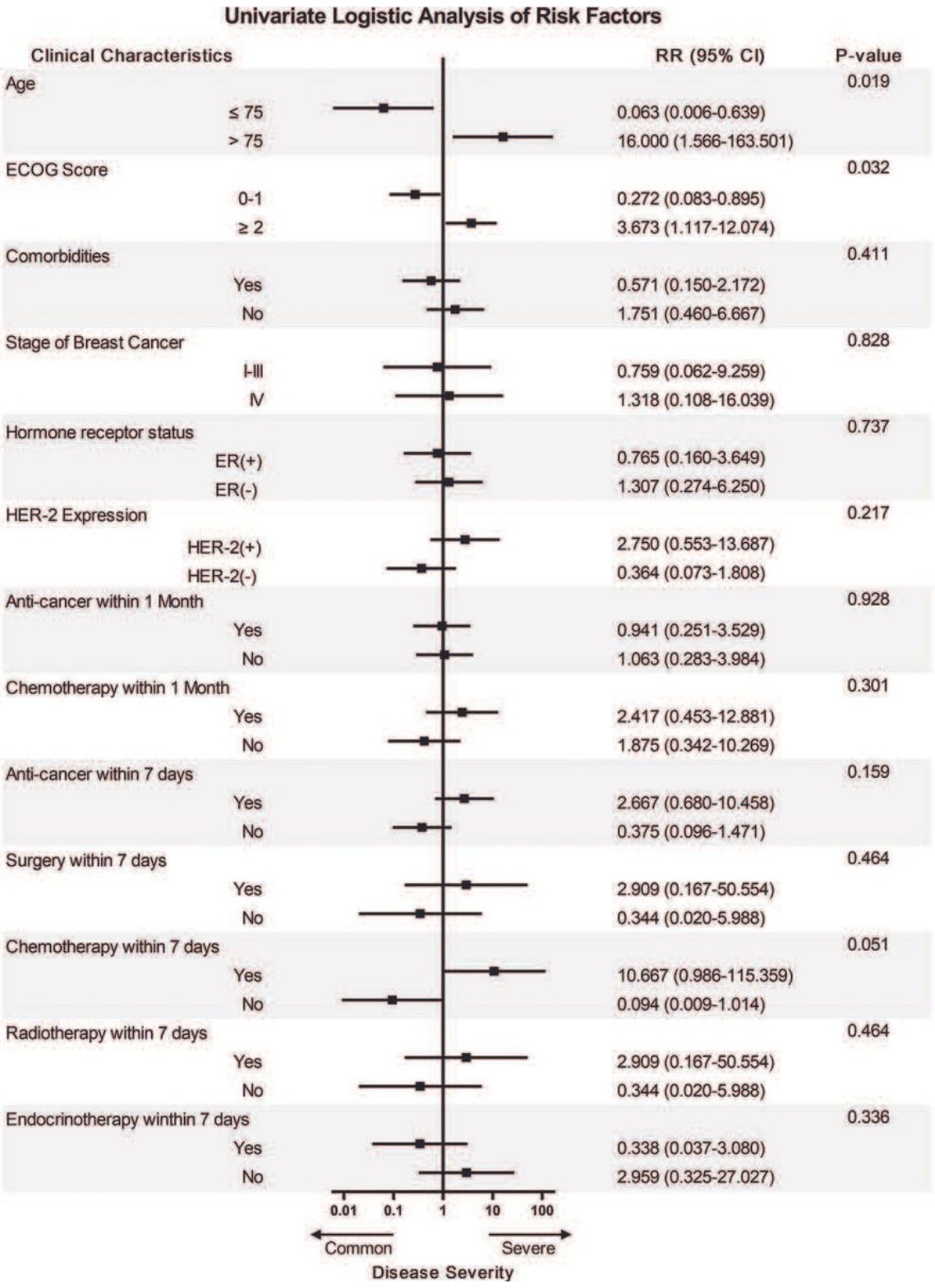

Figure 2

Forest Plot of Univariate Analysis for Clinical Characteristics as Potential Risk Factors

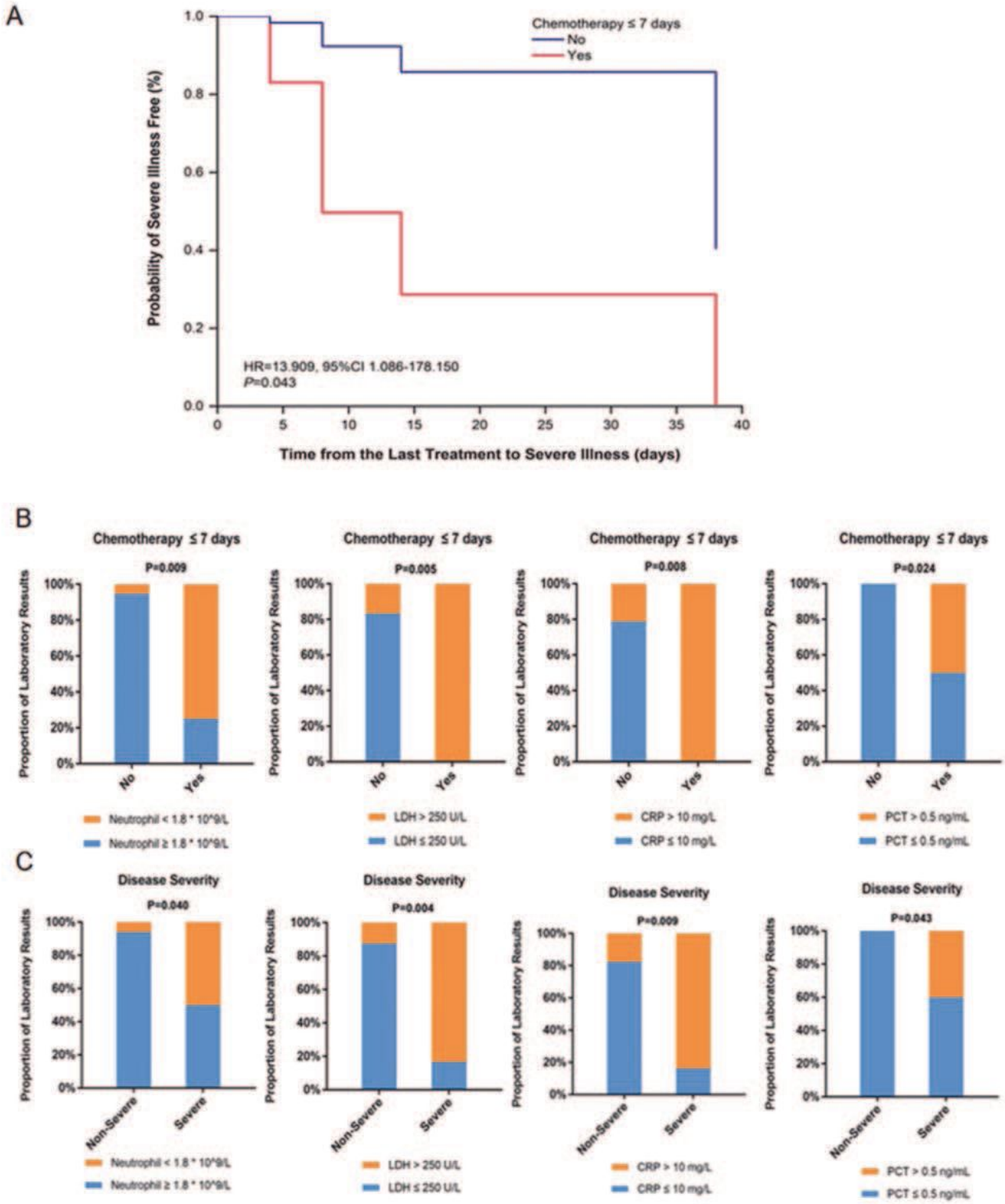

Figure 3

Chemotherapy, State and Disease Severity A. Cox survival analysis for the risk of severe illness with chemotherapy within 7 days. Breast cancer patients with COVID-19 who underwent chemotherapy within 7 days had a higher risk of developing severe illness. B. Patients treated with chemotherapy within 7 days before symptom onset had distinct abnormalities in neutrophils, LDH, CRP and procalcitonin (PCT). C. The severe group of patients who underwent chemotherapy within 7 days showed significant differences

in neutrophils, LDH, CRP and PCT. * The results in Fig C were analyzed in the population of patients who received anti-cancer treatment within one month before symptom onset.

Supplementary Files

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- BCRSupplementaryfilestables1.docx