COVID-19 and Breast Cancer Cross-Talk: Exploring the Role of Tumor-Associated Macrophages

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Abstract:

This study aimed to assess the prognostic significance of CD163+ tumor-associated macrophages (TAMs) density and distribution in breast cancer (BC) patients during the COVID-19 pandemic compared to pre-pandemic periods. A retrospective evaluation was conducted on two groups of BC patients: the study group (during the COVID-19 pandemic, n = 80) and the control group (pre-pandemic, n = 80). Immunohistochemistry was performed for CD163+. The density of CD163+ TAMs was evaluated in intra-tumoral and peri-tumoral areas. A significant association was observed between adverse clinicopathologic parameters and COVID-19-positive patients with poor survival rates. A statistically significant correlation was detected between most unfavorable clinicopathological characteristics and a high density of CD163+ TAMs, particularly intra-tumoral density. Additionally, a high density of intra-tumoral CD163+ TAMs was identified as an independent predictor of shortened overall survival in multivariate analysis (p = 0.014). This study suggested that alterations in the tumor microenvironment of BC may be linked to COVID-19 infection. Moreover, an increased density of TAMs, particularly in intra-tumoral areas, may contribute to tumor burden by promoting tumor progression. These findings underscore the need to consider both the histologic location and infiltration density of TAMs in BC as predictive biomarkers.

Keywords: COVID-19; Breast cancer; Prognosis; CD163+; Tumor-associated macrophages

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Introduction:

COVID-19 (coronavirus disease 2019), caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus, remains a major global healthcare challenge. Although knowledge of the interaction between COVID-19 infection and cancer gradually expands, many questions remain unanswered [1].

One major concern is the biological events that occur during COVID-19 infection and their potential influence on cancer pathogenesis and prognosis. These include immune-mediated inflammation, cytokines release, impaired T-cell activity, and hyperactivation of neutrophils, which may reactivate dormant cancer cells (DBCs), increasing the risk of tumor recurrence and metastasis [2].

Emerging studies have reported high mortality rates in cancer patients infected with COVID-19, likely due to uncontrolled immune cell activation associated with the infection [3].

The long-term consequences of COVID-19 on cancer remain unclear, and no definitive evidence explains how COVID-19 modifies cancer pathophysiology. A plausible explanation is that COVID-19 may create a microenvironment conducive

to tumor progression and metastasis [3, 4]. Understanding the mechanisms of interaction between COVID-19 infection, cancer cells, and the tumor microenvironment (TME) is crucial for evaluating the long-term impact of COVID-19 on cancer patient outcomes.

The significance of TME in breast cancer is rapidly evolving [5]. One of its major components is tumor-associated macrophages (TAMs), which predominantly adopt the M2 phenotype [6].

Little is known about the impact of COVID-19 infection on the breast cancer (BC) microenvironment and its subsequent consequences for patient outcomes. This study aimed to assess the density and distribution of CD163+ TAMs and their prognostic significance in surgically-treated COVID-19-positive patients diagnosed with invasive breast carcinoma, comparing the findings with specimens collected from the pre-pandemic period as a control group.

Patients and Methods:

Patients and tissue samples

A total of 160 patients retrospectively diagnosed with invasive breast carcinoma and who underwent surgical procedures (mastectomy or wide local excision with axillary evacuation) at South Egypt Cancer Institute (SECI) were enrolled in this study. Patients were divided into two groups. The study group (COVID-19-positive/pandemic group) included 80 patients who had tested positive for COVID-19 by PCR before surgery between March 2020 and August 2021. The control group (pre-pandemic group) consisted of 80 patients treated in the pre-COVID-19 period between January 2018 and December 2018.

Clinical variables were obtained from medical records. The eligibility criteria included negative surgical margins, no history of other organ malignancies, no history of neoadjuvant therapy, non-metastatic status at diagnosis, accessible clinical data, and a minimum follow-up of three years. Overall survival (OS) was defined as the period from the date of clinical diagnosis to the date of death or the last clinic visit, while disease-free survival (DFS) was defined as the period from the date of surgery to the date of disease recurrence/metastasis or the last clinic visit.

All included cases were classified as invasive breast carcinoma of no special type (NST) according to the latest 5th edition of the WHO classification of breast tumors. Hematoxylin and eosin (H&E) stained sections were re-evaluated to confirm the histological subtype and to determine Nottingham grade, lymphovascular invasion (LVI), perineural invasion (PNI), coagulative tumor necrosis, presence of ductal carcinoma in situ/ Paget's disease, stromal tumor infiltrating lymphocytes (sTILs), pathological tumor stage (pT), nodal stage (pN) and anatomic stage grouping according to AJCC 8th edition. Immunostained slides were re-evaluated to confirm molecular subtyping. The most representative formalin-fixed, paraffin-embedded (FFPE) block, with minimal necrosis and artifacts, was selected.

Immunohistochemistry technique

According to the manufacturer's protocol, sections of 4 μm thickness were immunostained for CD163 (Clone: EP324, rabbit monoclonal antibody, ready to use, BIO SB).

Evaluation of CD163+ TAMs

Immunostained sections were examined at low power magnification (x100) to identify the area with the highest CD163+ TAMs density, avoiding necrosis and artifacts. The density of CD163+ TAMs was assessed in two areas: the intratumoral area, between tumor nests (TN) in direct contact with tumor cells, and the peritumoral area, within the tumor stroma (TS) [7]. Five hotspots at high-power magnification (x400) were selected to count the number of positive cells, and the average was calculated.

Ten images were captured for each case (five from each intra- and peri-tumoral area) using an Olympus microscope (BX48) and a Toup-Cam Full HD digital camera (XCAM1080PHB model). CD163+ TAMs were manually counted using ImageJ software. The median value for both zones was used to establish the cutoff value to divide patients into low and high groups [8, 9].

Statistical analysis

Statistical evaluations were conducted to summarize quantitative data, including the median (range) and the mean ± standard deviation (SD). For qualitative data, numerical values and percentages were used. A chi-square ($\chi 2$) test was applied to compare categorical data, and the Fisher exact test was used when the expected frequency was below five. The Spearman rho correlation test was implemented to determine the correlation between various variables. Mann-Whitney and Kruskal- Wallis tests were used to compare different groups. OS and DFS analyses were performed using Kaplan-Meier's method with the log-rank test. Cox regression was computed to identify distinct risk factors associated with recurrence. The p-value was calculated for a two-tailed test and considered significant at a level of 0.05. Data management and analysis were performed using SPSS version 22.

Ethical considerations

Ethical approval was granted by the Institutional Review Board (IRB) of the South Egypt Cancer Institute (SECI) under the number SECI-IRB: IORG0006563, approval No: 665.

Results:

Clinical and pathological characteristics

The clinical and pathological characteristics of the two studied groups are presented in Table 1. COVID-19-positive patients were primarily older and exhibited worse clinicopathological characteristics, including multicentric tumors, lymphovascular invasion, higher stage group, progressive disease, and poor outcomes.

The heterogeneous density of CD163+ TAMs according to the tumor location

The densities of intratumoral and peritumoral CD163+ TAMs were significantly higher in COVID-19-positive patients than in pre-pandemic patients (Table 2 and Figure 1).

Association between clinicopathologic characteristics and CD163+ TAMs

The clinicopathological characteristics of all patients with breast cancer and their associations with CD163+ TAMs are summarized in Table 3. In general, most unfavorable clinicopathological characteristics were significantly associated with increased CD163+ TAMs, particularly intra-tumoral density rather than peritumoral density.

Survival analysis

Table 4 summarizes the clinicopathological parameters associated with a poor prognosis of 3-year (36-month) follow-up OS and DFS, as determined by Kaplan-Meier's survival analysis (Figure 2).

Cox regression survival analysis

The significant factors in the Kaplan-Meier analysis were subjected to univariate and multivariate Cox regression analyses to account for confounders during the 3-year OS and DFS (Table 5). The results revealed that intra-tumoral CD163+ TAMs were identified as an independent prognostic factor for OS.

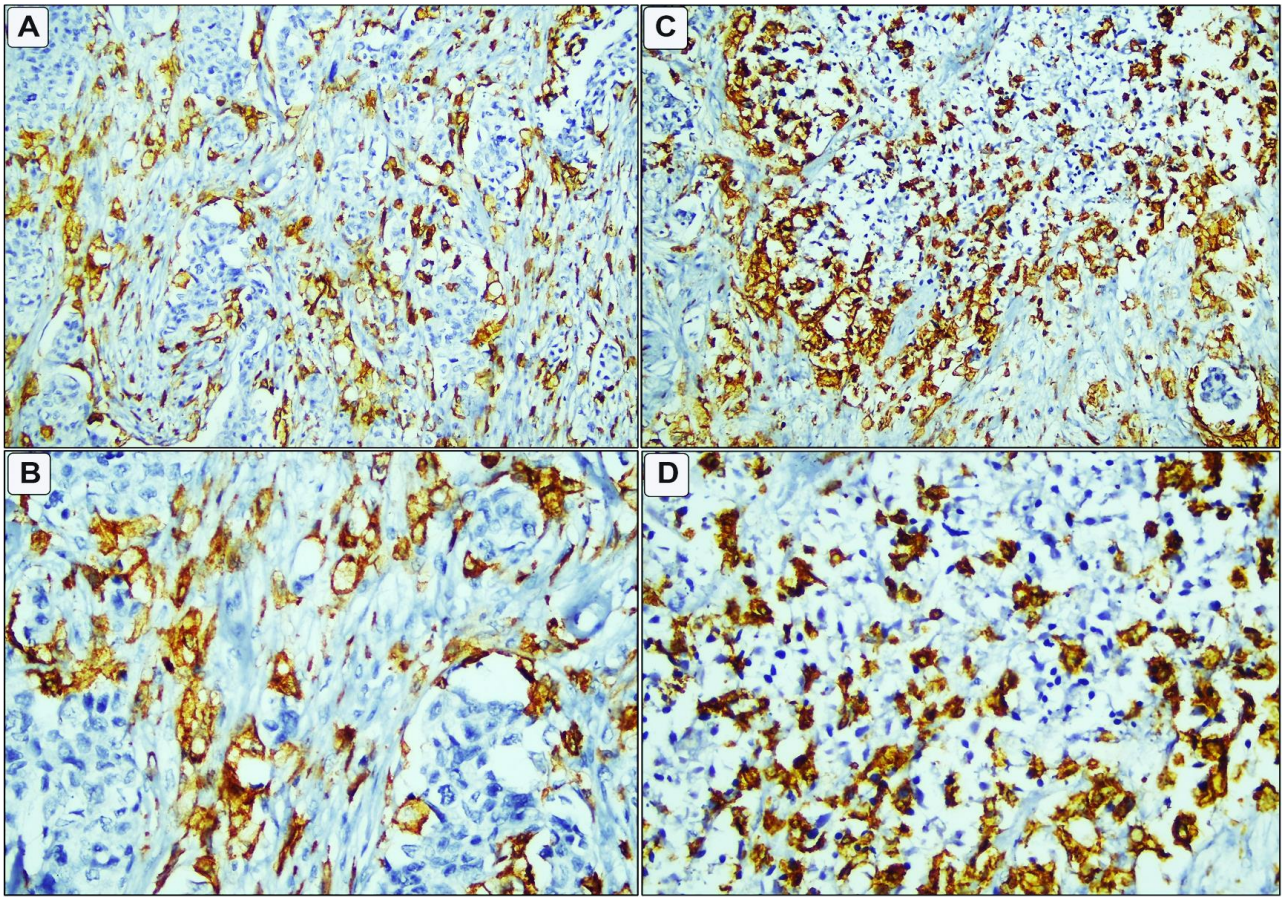

Figure 1: Intra-tumoral CD163+ tumor-associated macrophages: positive CD163 expression in the tumor nest (TN) (A: ×100; B: ×400) and peri-tumoral CD163+ tumor-associated macrophages: positive CD163 expression in the tumor stroma (TS) (C: ×100; D: ×400).

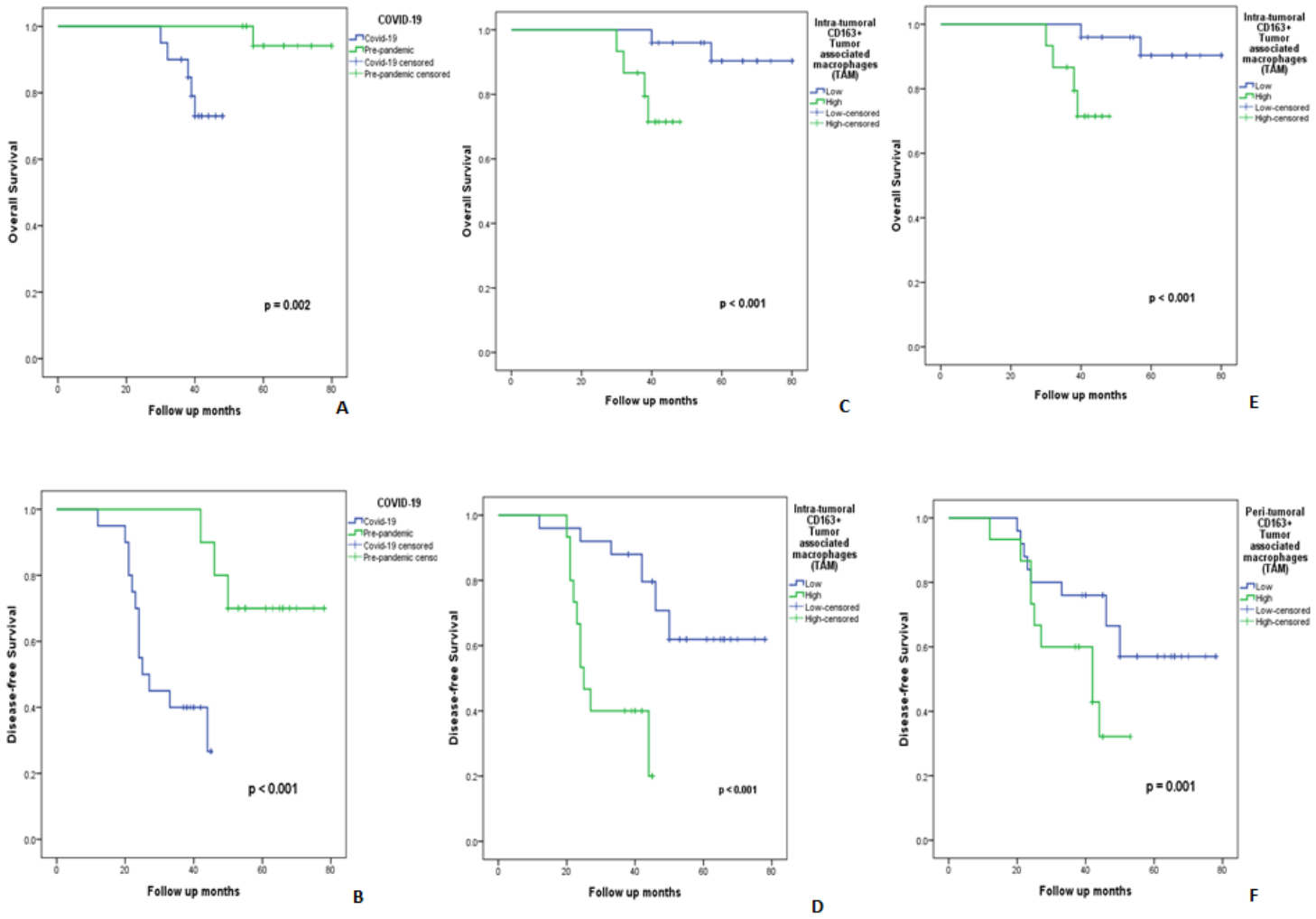

Figure 2: Survival curves among the studied breast cancer patients: (A, B) overall and disease-free survival curves among COVID-19 and pre-pandemic patients, respectively; (C, D) overall and disease-free survival curves of intra-tumoral CD163+ tumor-associated macrophages, respectively; and (E, F) overall and disease-free survival curves of peri-tumoral CD163+ tumor-associated macrophages, respectively.

Table 1: Comparison of clinicopathologic characteristics between COVID-19 positive patients (study group) and pre-pandemic patients (control group)

Variable	COVID-19 positive (n = 80) n (%)	Pre-pandemic (n = 80) n (%)	P-value
Age (y)			< 0.001
• Mean ± SD	54 ± 11.841	43 ± 11.590	
• Median (range)	53.00 (33-77)	41 (30-62)	
Menopausal status			< 0.001
• Pre-menopause	36 (45%)	64 (80%)	
• Post-menopause	44 (55%)	16 (20%)	
Multicentricity			< 0.001
• Unicentric	28 (35%)	72 (90%)	
• Multicentric	52 (65%)	8 (10%)	
Grade			0.570
• G2	60 (75%)	64 (80%)	
• G3	20 (25%)	16 (20%)	
Ductal carcinoma in situ/Paget's disease*			0.632
• Present	44 (55%)	48 (60%)	
• Absent	36 (45%)	32 (40%)	
Perineural invasion			1.000
• Present	32 (40%)	32 (40%)	
• Absent	48 (60%)	48 (60%)	
Lymphovascular invasion			< 0.001
• Present	76 (95%)	16 (20%)	
• Absent	4 (5%)	64 (80%)	
Necrosis			0.570
• Present	20 (25%)	16 (20%)	
• Absent	60 (75%)	64 (80%)	
Stromal tumor infiltrating lymphocytes (sTILs)			0.624
• Brisk (> 50%)	28 (35%)	32 (40%)	
• Non-brisk (≤ 50%)	52 (65%)	48 (60%)	
Pathological tumor (pT) stage			0.002
• T1	12 (15%)	28 (35%)	
• T2	60 (75%)	44 (55%)	
• T3	4 (5%)	8 (10%)	
• T4	4 (5%)	0 (0%)	
Pathological nodal (pN) stage			< 0.001
• N0	16 (20%)	48 (60%)	
• N1	16 (20%)	16 (20%)	
• N2	28 (35%)	8 (10%)	
• N3	20 (25%)	8 (10%)	
AJCC anatomic stage groups			< 0.001
• IA	8 (10%)	12 (15%)	
• IIA	8 (10%)	44 (55%)	
• IIB	16 (20%)	8 (10%)	
• IIIA	28 (35%)	8 (10%)	
• IIIC	20 (25%)	8 (10%)	
Molecular subtyping			
• Luminal A	60 (75%)	58 (72.5%)	0.396
• Luminal B	4 (5%)	4 (5%)	
• Her2 enriched	8 (10%)	4 (5%)	
• Triple-negative	8 (10%)	14 (17.5%)	
Disease recurrence			< 0.001
• Yes	52 (65%)	24 (30%)	
• No	28 (35%)	56 (70%)	

Patients' outcome			0.001
• Died	20 (25%)	4 (5%)	
• Alive	60 (75%)	76 (95%)	
Overall survival			
• Mean ± SD	40.70 ± 4.714	67.20 ± 8.989	
• Median (range)	40.00 (30 – 48)	70.00 (54 – 80)	
Disease free survival			
• Mean ± SD	30.30 ± 10.084	57.70 ± 10.766	
• Median (range)	26.00 (12 – 45)	55.00 (42 – 78)	

Data are presented as mean ± standard deviation (SD) and median (range), or number (percentage). Significance was defined by $p < 0.05$. The p-value was determined by the Mann-Whitney and chi-square tests. Fisher's exact test was used when the expected frequency was less than 5.

* Cases with Paget's disease of the nipple, observed in 5 cases, were included within the DCIS category for statistical purposes. In the absence of underlying invasive carcinoma, both entities are classified as pTis according to the AJCC 8th edition

Table 2: Comparison of intra-tumoral and peri-tumoral $CD163^+$ TAMs between COVID-19 positive patients (study group) and pre-pandemic patients (control group)

	Intra-tumoral $CD163^+$ TAMs			Peri-tumoral $CD163^+$TAMs		
	COVID-19 (n = 80)	Pre-pandemic (n = 80)	P-value	COVID-19 (n = 80)	Pre-pandemic (n = 80)	P-value
Median (range)	43.00 (34 – 60)	16.00 (10 – 24)	< 0.001	23.00 (12 – 41)	18.00 (12 – 32)	0.038
Mean ± SD	44.40 ± 7.148	16.90 ± 5.241		24.15 ± 7.741	19.10 ± 5.884	

Table 3: Association between intra-tumoral and peri-tumoral CD163$^+$ TAMs and clinicopathologic characteristics among all patients (n = 160)

Variable	Intra-tumoral CD163$^+$ TAMs		Peri-tumoral CD163$^+$ TAMs	
	Median	P-value	Median	P-value
Menopausal status and age		0.001		0.672
• Pre-menopause (≤ 50 y)	23.00		20.00	
• Post-menopause (> 50 y)	40.00		22.00	
Multicentricity		< 0.001		0.034
• Unicentric	23.00		20.00	
• Multicentric	40.00		23.00	
Grade		0.077		0.413
• G2	35.00		20.00	
• G3	40.00		20.00	
Ductal carcinoma in situ/Paget's disease		0.638		0.599
• Present	35.00		20.00	
• Absent	35.00		20.00	
Perineural invasion		0.094		0.192
• Present	36.00		22.00	
• Absent	29.00		19.00	
Lymphovascular invasion		< 0.001		< 0.001
• Present	40.00		22.00	
• Absent	18.00		17.00	
Necrosis		0.793		0.248
• Present	39.00		22.00	
• Absent	35.00		20.00	
Stromal tumor infiltrating lymphocytes (sTILs)		0.283		0.148
• Brisk (> 50%)	35.00		19.00	
• Non-brisk (≤50%)	35.00		22.00	
Pathological tumor (pT) stage		0.002		0.110
• T1-T2	29.00		20.00	
• T3-4	41.00		26.00	
Pathological nodal (pN) stage		< 0.001		< 0.001
• Negative (N0)	23.00		19.00	
• Positive (N1-3)	40.00		23.00	
AJCC anatomic stage groups		0.004		0.306
• I	23.00		17.00	
• II	26.00		20.00	
• III	40.00		22.00	
Molecular subtyping		0.487		0.074
• Luminal A	35.00		20.00	
• Luminal B	29.00		22.00	
• Her2 enriched	40.00		24.00	
• Triple-negative	30.00		19.00	
Disease recurrence		< 0.001		0.066
• Yes	40.00		22.00	
• No	23.00		19.00	
Patients' outcome		< 0.001		0.116
• Died	42.00		24.00	
• Alive	29.00		20.00	

Significance was defined by $p < 0.05$. The p-value was determined by Mann-Whitney U and Kruskal-Wallis tests.

Table 4: Three-year overall survival (OS) and disease-free survival (DFS) according to clinicopathologic characteristics among all patients

Variable	Overall survival (OS)		Disease-free survival (DFS)	
	Estimate ± SE	P-value	Estimate ± SE	P-value
Menopausal status and age (y)		0.056		0.260
• Pre-menopause (≤ 50 y)	96.0 ± 2.0		71.1 ± 4.6	
• Post-menopause (> 50 y)	86.2 ± 4.6		53.3 ± 6.4	
COVID-19 status		0.002		< 0.001
• COVID-19	84.7 ± 4.1		40.0 ± 5.5	
• Pre-pandemic	100 ± 0.0		90.0 ± 3.4	
Multicentricity		0.001		< 0.001
• Unicentric	96.0 ± 2.0		82.8 ± 3.9	
• Multicentric	79.0 ± 5.4		33.3 ± 6.1	
Grade		< 0.001		0.868
• G2	93.3 ± 2.3		71.0 ± 4.1	
• G3	77.8 ± 6.9		66.7 ± 7.9	
Ductal carcinoma in situ/Paget's disease		0.323		0.151
• Present	95.7 ± 4.3		62.5 ± 6.7	
• Absent	94.1 ± 5.7		64.7 ± 5.8	
Perineural invasion		0.056		0.917
• Present	87.5 ± 4.1		56.3 ± 6.2	
• Absent	95.8 ± 2.0		69.3 ± 4.9	
Lymphovascular invasion		< 0.001		< 0.001
• Present	86.7 ± 3.6		52.2 ± 5.2	
• Absent	100 ± 0.0		82.4 ± 4.6	
Necrosis		0.088		0.325
• Present	88.9 ± 5.2		54.4 ± 8.3	
• Absent	96.8 ± 1.6		69.7 ± 4.3	
Stromal tumor infiltrating lymphocytes (sTILs)		0.629		0.940
• Brisk (> 50%)	93.3 ± 3.2		73.3 ± 5.7	
• Non-brisk (≤ 50%)	87.8 ± 3.3		68.0 ± 4.7	
Pathological tumor (pT) stage		< 0.001		< 0.001
• T1-T2	94.7 ± 2.6		72.0 ± 3.7	
• T3-4	50.0 ± 3.5		50.0 ± 12.5	
Pathological nodal (pN) stage		0.005		0.402
• Negative (N0)	93.8 ± 3.01		74.0 ± 5.6	
• Positive (N1-3)	86.9 ± 3.5		58.3 ± 5.0	
AJCC anatomic stage groups		0.001		0.011
• I	100 ± 0.0		83.3 ± 7.6	
• II	94.7 ± 2.6		83.1 ± 4.5	
• III	79.4 ± 5.3		40.0 ± 6.3	
Molecular subtyping		0.002		0.018
• Luminal A	96.4 ± 1.8		76.3 ± 3.9	
• Luminal B	50.0 ± 17.7		50.0 ± 17.7	
• Her2 enriched	66.7 ± 13.5		33.3 ± 13.6	
• Triple-negative	81.8 ± 8.2		63.6 ± 10.3	
Intra-tumoral $CD163^+$ tumor-associated macrophages (TAMs)		< 0.001		< 0.001
• Low	96.0 ± 2.0		88.0 ± 3.2	
• High	79.4 ± 5.3		40.0 ± 6.3	
Peri-tumoral $CD163^+$ tumor-associated macrophages (TAMs)		< 0.001		0.001
• Low	92.0 ± 2.0		76.0 ± 4.3	
• High	86.2 ± 4.6		60.0 ± 6.3	

Data are presented as percentage ± standard error (SE). Significance was defined by $p < 0.05$. The p-value was determined using Kaplan-Meier's method with the log-rank test.

Table 5: Cox regression analysis of overall survival and disease-free survival of the study's patients

Variables	Univariate			Multivariate		
	P-value	HR	95% CI	P-value*	HR	95% CI
Overall survival						
COVID-19 (during vs prepandemic)	0.002	0.012	0.000 – 0.464			
Multicentricity (multicentric vs unicentric)	0.001	4.784	1.985 – 11.533			
Grade (G3 vs G2)	< 0.001	3.992	1.790 – 8.903			
Lymphovascular invasion (present vs absent)	< 0.001	5.891	1.955 – 17.752			
Stage grouping	0.001	4.007	1.817 – 8.833	0.023	5.769	1.083 – 23.902
Molecular subtyping	0.002	1.659	1.247 – 2.205			
Intra-tumoral $CD163^+$ tumor-associated macrophages (TAMs) (high vs low)	< 0.001	8.829	2.938 – 26.537	0.013	3.695	1.043 – 15.409
Peri-tumoral $CD163^+$ tumor-associated macrophages (TAMs) (high vs low)	< 0.001	4.689	1.943 – 11.317			
Disease free survival						
COVID-19 (during vs prepandemic)	< 0.001	0.074	0.035 – 0.160			
Multicentricity (multicentric vs unicentric)	< 0.001	3.576	2.241 – 5.707			
Lymphovascular invasion (present vs absent)	< 0.001	2.374	1.464 – 3.850	< 0.001	0.071	0.019 – 0.261
Stage grouping	0.011	1.601	1.113 – 2.303			
Molecular subtyping	0.018	1.361	1.151 – 1.610			
Intra-tumoral $CD163^+$ tumor-associated macrophages (TAMs) (high vs low)	< 0.001	6.007	3.442 – 10.484			
Peri-tumoral $CD163^+$ tumor-associated macrophages (TAMs) (high vs low)	0.001	2.269	1.421 – 3.623			

Significance was defined by $p < 0.05$. The p-value was determined by Cox regression analysis.
CI: Confidence interval; HR: Hazard ratio; Ref: Reference.

Discussion:

The COVID-19 pandemic occurred during a time when the prevalence of breast cancer (BC) was rapidly increasing, raising concerns about the potential interaction between the two diseases. It is hypothesized that severe COVID-19 infection may establish a microenvironment favorable for tumor cell growth and cancer recurrence induced by the infection-mediated activation of several factors implicated in tumorigenesis and disease recurrence [10].

In this study, BC patients who were COVID-19-positive exhibited adverse clinicopathological characteristics compared to the pre-pandemic group. Montopoli et al. reported that women with BC are at higher risk of acquiring COVID-19 and developing more severe infections, with poorer outcomes and higher mortality rates [11].

Furthermore, several studies have supported the findings of this study, noting a significant increase in new metastatic breast cancer, as well as a higher percentage of tumors with advanced stages and nodal metastasis [12-15]. Moreover, Fujita et al. and Sgarzani et al. observed a substantial decrease in breast-conserving surgeries without lymph node dissection, implying a reduction in low-stage diseases during the pandemic [16, 17].

Several explanations for this hypothesis have been proposed in various articles. One explanation relates to the interruption of national breast cancer screening programs during the pandemic. Additionally, delays in patient evaluation of their symptoms due to fear of virus transmission and lockdown measures caused many patients to present with advanced disease [18, 19]. Moreover, Vanni et al. reported that the waiting time between biopsy and surgery was significantly longer during the lockdown period, and this delay may have contributed to a slowdown in treatment [20]. Moreover, it has been proposed that patients with BC might have a higher probability of poor outcomes after being infected with COVID-19 due to immune system impairment related to the tumor itself, viral infection, or anticancer therapy [21].

In addition to the previous explanations, we hypothesize that the relationship between the two

diseases may be due to alterations in the microenvironment of breast cancer tumor cells caused by COVID-19 infection, which affects cancer cell growth, progression, and metastasis.

This hypothesis is based on two rationales. First, lung inflammation has been shown to release damage-associated molecular patterns (DAMPs), which initiate an inflammatory response with overproduction of inflammatory cytokines (e.g., IL-6), sustaining tumorigenesis through direct stimulation of cancer cells and indirect actions on the TME. This, in turn, recruits monocytes and macrophages, inducing epithelial-mesenchymal transition (EMT) and further reawakening dormant breast cancer cells (DBCs) [22, 23]. Second, viral-induced hypoxia has been shown to promote the expression of genes involved in dormancy, EMT, and drug resistance [24]. Therefore, viral-induced inflammation may increase their densities in the tumor cell microenvironment by recruiting blood monocytes and tissue macrophages.

The TME of BC comprises several cell types, with TAMs representing the dominant immune cell population [25]. Most TAMs are associated with the M2 phenotype, which promotes tumor progression through several mechanisms, including the secretion of cytokines like CCL18, CXCL1, and IL-10. In addition, they secrete proteases that degrade the extracellular matrix, inhibit the function of antitumor CD8+ T-cells, and stimulate angiogenesis [26-28]. CD163 is a well-known specific marker for M2-like macrophages [29].

The present study revealed a higher density of CD163+ TAMs in the COVID-19-positive group of BC patients compared to the pre-pandemic group. This result is partially supported by a study conducted by Qin et al., who reported that autopsy results of patients who died from COVID-19 showed a high density of monocytes within lymph nodes, lungs, liver, kidneys, and spleen, where T cells were significantly lacking. Migrating monocytes from the circulation to tissue and further polarization into macrophages were associated with the cytokine storm responsible for multiple organ failure [30].

The current study findings demonstrated that a high CD163+ TAMs density, specifically in the intra-tumoral zone, was linked to adverse clinicopathological parameters, poorer clinical outcomes, and shorter OS and DFS. Moreover, intra-tumoral CD163+ TAMs were identified as an independent predictor of poor outcomes.

Several studies align with our results, confirming the strong association between increased TAM density within the microenvironment of BC and adverse clinicopathological characteristics and its role as an independent prognostic factor for worse OS and DFS [8, 9, 31, 32].

In conclusion, the present study suggests that alterations in the TME of BC could potentially be linked to COVID-19 infection. However, we agree that this hypothesis requires further validation in future studies incorporating additional immune markers and molecular analyses. Moreover, the increased density of TAMs, particularly in the intra-tumoral area, may contribute to the tumor burden by promoting tumor progression, metastasis, relapse, and shortened survival rates. This, in turn, emphasizes the need to consider both the histologic location and the infiltration density of TAMs in BC as predictive biomarkers.

One limitation of the study is that it was conducted in a single institution with a relatively small sample size. More extended follow-up periods would be beneficial in properly assessing the association between BC and COVID-19 infection. Regarding the effect of CD163+ TAM density and distribution, some studies assessed TAMs in different tumor locations (nests and stroma), while others focused solely on the total number of TAMs within the tumor. Additionally, TAMs were assessed using various markers and methodologies. Therefore, reliable labeling markers, standardized procedures, and consistent evaluation across different laboratories are required to ensure consistent and reliable results.

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