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A large-cohort retrospective study of metastatic patterns and prognostic outcomes between inflammatory and non-inflammatory breast cancer

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Abstract

Background and aims: Breast cancer-related death is attributable mainly to metastasis. Inflammatory breast cancer (IBC) is an infrequent subtype of breast cancer that shows a relatively high rate of metastasis. In this study, we aimed to compare the metastatic patterns and prognostic outcomes of IBC and non-inflammatory breast cancer (non-IBC).

Methods: We extracted data between 2010 and 2014 from the Surveillance, Epidemiology and End Results (SEER) database. The Chi-square test and Fisher's exact test were used to compare the categorical parameters among different groups. Logistic regression was applied for multivariate analysis. The Kaplan–Meier method and multivariate Cox regression models were performed to analyze prognosis.

Results: We enrolled 233,686 breast cancer patients between 2010 and 2014 in our research, including 2806 IBC and 230,880 non-IBC patients. Compared with the non-IBC group, the IBC group tended to have a higher incidence of the human epidermal growth factor receptor 2 positive (HER2+) and triple-negative breast cancer (TNBC) subtypes, older age, a higher rate of unmarried status, a lower incidence of black race, poorer tumor differentiation, larger tumor sizes, and a higher frequency of regional lymph node invasion. IBC and non-IBC shared similar trends in molecular subtypes among different metastatic organs. The percentage of the hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–) subtype decreased gradually in patients with lung (IBC 42.5%, non-IBC 55.7%), distant lymph node (IBC 41.5%, non-IBC 54.6%), liver (IBC 31.1%, non-IBC 46.7%), and brain (IBC 30.6%, non-IBC 47.9%) metastases compared with that in patients with bone (IBC 50.8%, non-IBC 69.0%) metastasis in both cohorts. In both the IBC and non-IBC cases, the proportion of visceral metastases increased in the TNBC subtype, especially brain metastasis (IBC 26.4%, non-IBC 21.2%), which had the largest increase. The frequencies of all sites (bone, lung, liver, brain, and distant lymph node) in IBC were much higher than those in non-IBC (bone: IBC 21.1%, non-IBC 3.0%; lung: IBC 11.4%, non-IBC 1.4%; liver: IBC 9.6%, non-IBC 1.2%; brain: IBC 2.6%, non-IBC 0.3%; distant lymph node: IBC 12.9%, non-IBC 1.0%). The most frequent bi-site metastasis was the bone and liver (IBC 2.5%, non-IBC 0.3%), and the most frequent tri-site combination was the bone, lung, and liver (IBC 1.1%, non-IBC 0.2%). Kaplan–Meier curves and multivariate Cox regression models suggested that the IBC cohort had poorer overall survival [hazard ratio (HR) 1.602, 95% confidence interval (CI) 1.496–1.716, $p < 0.001$] and breast cancer-specific survival (HR 1.511, 95% CI 1.402–1.628, $p < 0.001$) than the non-IBC cohort. Furthermore, univariate and multivariate analyses indicated that IBC was an independent prognostic factor in patients with different metastatic sites.

Conclusion: IBC and non-IBC patients presented with different metastatic frequencies, clinical features and prognostic outcomes. Our findings provide more information for therapeutic decision making and clinical study designs.

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Introduction

Breast cancer is the most common neoplasm in women.[1] Breast cancer-related death is attributable mainly to metastasis.[2] Despite the rapid advances in treatment methods in recent years, the prognostic outcome for metastatic breast cancer patients remains frustrating.[3] Thus, a deep understanding of distant metastatic patterns is beneficial for diagnostic and therapeutic decisions in clinical practice.

Cancer metastasis is a multistep process that involves the escape of tumor cells from the primary location, systemic translocation in the body, and adaptation to the foreign microenvironment of distant sites.[4] The spread of cancer cells is mediated by the interaction between tumor cells (seeds) and the microenvironment of the host organ (soil).[5] Extensive studies have clarified several stages of the invasion-metastasis cascade, including epithelial-mesenchymal transition, angiogenesis, and immune invasion.[6] Moreover, host organs could develop premetastatic niches and be prepared for cancer cell colonization.[7] Therefore, specific organ microenvironments seem to be hospitable for the colonization and growth of certain types of cancer cells.[8] By elucidating the distribution of metastatic sites in breast cancer, we can obtain a better understanding of the "seed and soil" interaction.

Inflammatory breast cancer (IBC) is an invasive type of breast cancer.[9] IBC is characterized by tumor embolism of the dermal lymphatics, resulting in the rapid onset of skin changes. Compared with non-inflammatory breast cancer (non-IBC), IBC tends to show unfavorable prognosis, attributable mainly to a high risk of early distant metastasis.[10] According to previous studies, more than 80% of IBC patients were reported to have regional lymph node invasion, and 30% presented with distant metastasis at the time of diagnosis.[11] Therefore, it is vital to perform careful screening and start precise treatment for IBC.

Among different metastatic sites, bone seems to be the most frequent lesion for breast cancer.[12] Several studies have indicated that breast cancer patients with bone metastasis survived longer than patients with visceral metastasis.[13] Another retrospective study suggested that IBC patients with bone metastasis had a poorer prognosis than non-IBC patients with bone metastasis.[14] Moreover, IBC patients have a relatively high risk of visceral metastasis and brain metastasis, leading to a dismal prognostic outcome.[15,16]

However, the metastatic profiles of IBC and non-IBC and their comparisons still need further elaboration. The clinical and prognostic values of different metastatic lesions need to be illustrated. Thus, in our research, we compared distant metastatic patterns between IBC and non-IBC, by analyzing accessible information from the Surveillance, Epidemiology and End Results (SEER) database. We also aimed to clarify the impact of IBC on prognosis in patients with different metastatic lesions.

Methods

Cohort population

A population-based retrospective study was conducted with data from the SEER national database. The patient selection process is illustrated in Figure 1. A total of 233,686 patients with a diagnosis of breast cancer between 2010 and 2014 were enrolled in this research. Patients were excluded if their metastatic status, follow-up information, or molecular type was unknown. Patients were classified into the IBC group and the non-IBC group. Data on metastasis to the bone, lung, liver, brain, and distant lymph node (DL) were recorded in the database.

Ethics statement

This research was based on publicly available data from the SEER database (https://seer.cancer.gov/), and a data use agreement was assigned. This study received exemption from ethics approval by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. The requirement for informed consent was also waived by the ethics committee of Ruijin Hospital because no direct interaction with patients was performed and no personal identification was applied in this study.

In addition, this research was conducted in compliance with the Declaration of Helsinki.

Statistical analysis

We used descriptive statistics to summarize the patients' clinical characteristics. The Chi-square test and Fisher's exact test were used to compare the categorical parameters among different groups. Logistic regression was applied for multivariate analysis. Overall survival (OS) and breast cancer-specific survival (BCSS) were compared by the Kaplan–Meier method and log-rank test. We also performed multivariate Cox regression models to assess independent prognostic factors. A two-sided p value < 0.05 was defined as statistically significant. We used GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) and SPSS 22.0 (SPSS Inc. Chicago, IL, USA) to perform statistical analyses.

Results

Patient characteristics

In total, 233,686 breast cancer patients were finally enrolled in our research, including 2806 IBC and 230,880 non-IBC patients. The detailed baseline clinical characteristics are described in Table 1. Parameters including molecular subtype, age, marital status, race, grade, tumor size, and regional lymph node invasion showed significant differences between the two groups. Compared with the non-IBC group, the IBC group tended to have a higher incidence of the human epidermal growth factor receptor 2 positive (HER2+) and triple-negative breast cancer (TNBC) subtypes, older age, a higher rate of unmarried status, a lower incidence of black race, poorer tumor differentiation, larger tumor sizes, and a higher frequency of regional lymph node invasion. Regarding therapies, fewer IBC patients underwent surgery and more IBC patients received chemotherapy and radiation therapy than non-IBC patients.

Among all the included patients, 11,439 patients (4.9%) were recorded as having distant metastasis at the time of diagnosis. Based on metastasis data extracted from the SEER database, the five metastatic lesions (bone, brain, liver, lung, and DL) accounted for 94.4% (10,804/11,439) of all metastatic cases. Bone, which accounted for 65.9% (7543/11,439) of all metastatic cases, was the most frequent metastatic lesion. The brain was the least frequent lesion, accounting for 7.1% (816/11,439).

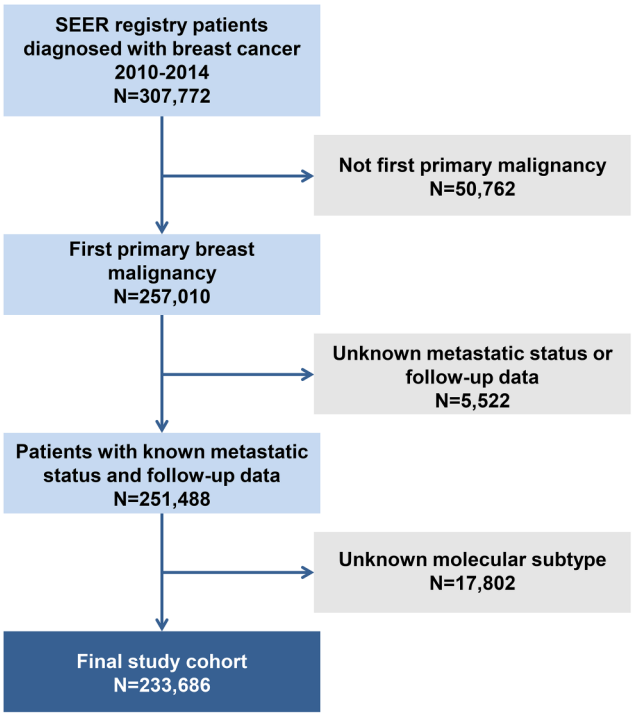

Figure 1. Flowchart of the patient selection process in this study. SEER, Surveillance, Epidemiology and End Results database.

Metastatic patterns

The frequencies of different sites were compared between IBC and non-IBC. The metastatic rates of all sites in IBC were much higher than those in non-IBC (Figure 2). To further validate this finding, multivariate analysis was performed to adjust for confounding variables including age, race, marital status, molecular subtype, grade, tumor size, regional lymph node invasion, and therapies. The results demonstrated that the IBC group tended to have more bone metastasis [odds ratio (OR) 2.082, 95% confidence interval (CI) 1.846–2.348, $p < 0.001$], lung metastasis (OR 1.802, 95% CI 1.567–2.073, $p < 0.001$), liver metastasis (OR 1.531, 95% CI 1.319–1.777, $p < 0.001$), brain metastasis (OR 1.321, 95% CI 1.012–1.725, $p = 0.041$), and DL metastasis (OR 2.868, 95% CI 2.500–3.290, $p < 0.001$) than the non-IBC group (Table 2). Regarding metastatic distribution, both IBC and non-IBC shared similar trends, indicating that bone was the most common lesion in both IBC (21.1%) and non-IBC (3.0%) patients (followed by DL, lung, liver, and brain).

Table 1. Baseline clinical characteristics of IBC and non-IBC patients in the SEER database.

Characteristics	IBC (*n* = 2806)	Non-IBC (*n* = 230,880)	*p*
Molecular subtype			<0.001
HR+/HER2−	1118 (39.8%)	169,803 (73.5%)	
HR+/HER2+	521 (18.6%)	24,599 (10.7%)	
HR−/HER2+	482 (17.2%)	10,457 (4.5%)	
TNBC	685 (24.4%)	26,021 (11.3%)	
Age			<0.001
<50	831 (29.6%)	51,616 (22.3%)	
51–65	1178 (42.0%)	89,982 (39.0%)	
⩾65	797 (28.4%)	89,282(38.7%)	
Marital status			<0.001
Married	1291 (46.0%)	127,478 (55.2%)	
Unmarried	1379 (49.1%)	91,183 (39.5%)	
Unknown	136 (4.9%)	12,219 (5.3%)	
Race			<0.001
White	2130 (75.9%)	182,143 (78.9%)	
Black	474 (16.9%)	23,017 (10.0%)	
OthersΔ	202 (7.2%)	25,720 (11.1%)	
Grade			<0.001
I	73 (2.6%)	50,591 (21.9%)	
II	709 (25.2%)	97,249 (42.1%)	
III	1637 (58.3%)	72,869 (31.6%)	
Unknown	387 (13.8%)	10,171 (4.4%)	
Size (cm)			<0.001
<2.0	244 (8.7%)	125,928 (54.6%)	
2.0–4.9	659 (23.5%)	80,215 (34.7%)	
⩾5.0	1114 (39.7%)	19,857 (8.6%)	
Unknown	789 (28.1%)	4880 (2.1%)	
Regional lymph node invasion			<0.001
N0	344 (12.2%)	154,765 (67.0%)	
N1	1279 (45.6%)	54,595 (23.7%)	

(Continued)

Table 1. (Continued)

Characteristics	IBC (*n* = 2806)	Non-IBC (*n* = 230,880)	*p*
N2	506 (18.0%)	12,298 (5.3%)	
N3	611 (21.8%)	7516 (3.3%)	
NX	66 (2.4%)	1706 (0.7%)	
Surgery			<0.001
Yes	1809 (64.5%)	214,167 (92.8%)	
No	997 (35.5%)	16,713 (7.2%)	
Chemotherapy			<0.001
Yes	2395 (85.4%)	95,740 (41.5%)	
No	411 (14.6%)	135,140 (58.5%)	
Radiation therapy			0.384
Yes	1599 (57.0%)	129,672 (56.2%)	
No	1207 (43.0%)	101,208 (43.8%)	

ΔOthers include American Indian, AK Native, Asian, and Pacific Islander.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer; SEER, Surveillance, Epidemiology and End Results; TNBC, triple-negative breast cancer.

Table 2. Multivariate analyses of the impact of IBC on different metastatic sites.

Variable	Metastatic site	OR	95% CI	*p*
IBC *versus* non-IBC	Bone	2.082	1.846–2.348	<0.001
	Lung	1.802	1.567–2.073	<0.001
	Liver	1.531	1.319–1.777	<0.001
	Brain	1.321	1.012–1.725	0.041
	DL	2.868	2.500–3.290	<0.001

Adjusted for age, race, marital status, molecular subtype, grade, tumor size, regional lymph node invasion, and therapies.
CI, confidence interval; DL, distant lymph node; IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer; OR, odds ratio.

We further explored the impact of molecular subtypes on metastatic sites in IBC and non-IBC cases (Figure 3A,B). For all patients with metastasis, the percentage of hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–) was much lower in IBC patients (42.6%) than in non-IBC patients (61.6%). The percentage of the HR+/HER2– subtype gradually decreased in patients with lung (42.5%), DL (41.5%), liver (31.3%) and brain (30.6%) metastases compared with bone (50.8%) metastasis in the IBC cohort. The same trend of the HR+/HER2– subtype was found in the non-IBC cohort. Compared with the whole cohort, the percentage of HR+/HER2+ and hormone receptor negative (HR–)/HER2+ subtypes increased most in patients with liver metastasis in both the IBC (HR+/HER2+: 24.4%, HR–/HER2+: 21.5%) and non-IBC (HR+/HER2+: 23.9%, HR–/HER2+: 15.1%) groups. We also

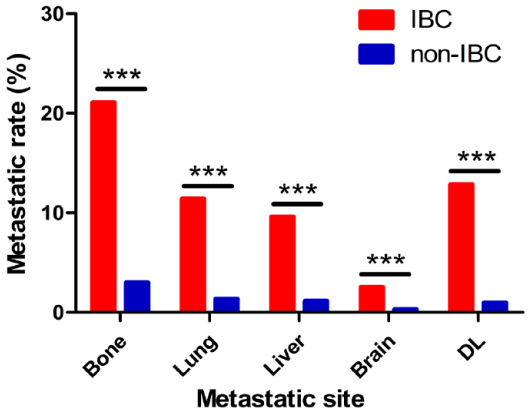

Figure 2. Comparison of the frequencies of different sites between IBC and non-IBC.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$
DL, distant lymph node; IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer.

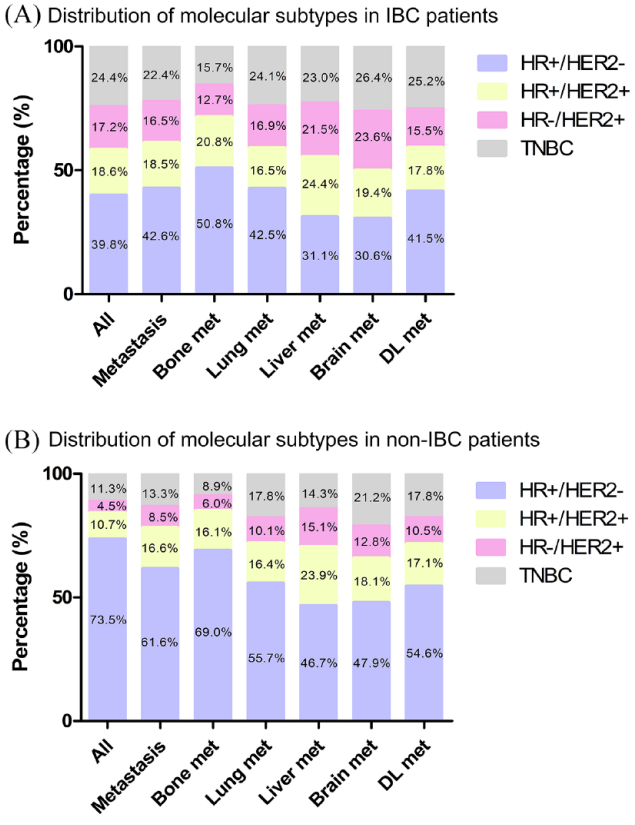

Figure 3. Distribution of molecular subtypes in IBC (A) and non-IBC (B).
DL, distant lymph node; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IBC, inflammatory breast cancer; MET, metastasis; non-IBC, non-inflammatory breast cancer; TNBC, triple negative breast cancer.

found that, in both IBC and non-IBC cases, the proportion of visceral metastases increased in the TNBC subtype, especially brain metastasis (IBC: 26.4%, non-IBC: 21.2%), which had the largest increase.

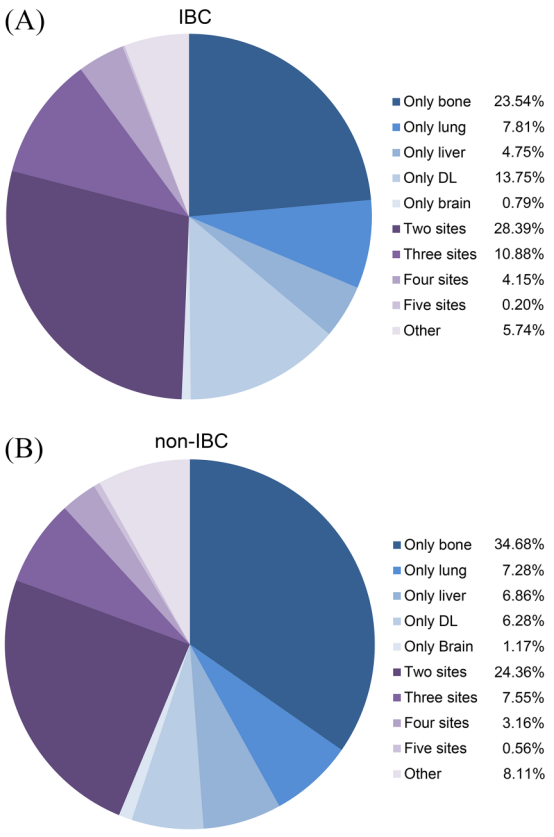

Figure 4. Relative rates of single-organ and multi-organ metastatic sites in IBC (A) and non-IBC (B).
DL, distant lymph node; IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer.

Combination of metastases

A large number of patients show multiorgan metastasis at the time of diagnosis. Pie charts illustrating the relative rates of single-organ and multi-organ metastases are shown in Figure 4. In the IBC cohort, bone, and DL were the two leading sites for single-site metastasis (Figure 4A). However, in the non-IBC group, only bone was the leading lesion for single-site metastasis (Figure 4B). For co-metastases, the bi-organ pattern (IBC: 28.4%, non-IBC: 24.4%) showed predominance over the tri-organ (IBC: 10.9%, non-IBC: 7.6%), tetra-organ (IBC: 4.2%, non-IBC: 3.2%), and penta-organ (IBC: 0.2%, non-IBC: 0.6%) patterns.

The frequencies of all possible combinations of the five metastatic lesions were compared between the IBC and non-IBC cohorts (Table 3). The most

Table 3. Frequencies of combined *de novo* metastases.

Features	IBC (*n* = 2806)		non-IBC (*n* = 230,880)		*p*
	Number	(%)	Number	(%)	
One site					
Only bone	238	8.482	3616	1.566	<0.001
Only lung	79	2.815	759	0.329	<0.001
Only liver	48	1.711	715	0.310	<0.001
Only brain	8	0.285	122	0.053	<0.001
Only DL	139	4.954	655	0.284	<0.001
Two sites					
Bone and lung	62	2.210	736	0.319	<0.001
Bone and liver	69	2.459	702	0.304	<0.001
Bone and brain	17	0.606	151	0.065	<0.001
Bone and DL	65	2.316	384	0.166	<0.001
Lung and liver	23	0.820	168	0.073	<0.001
Lung and brain	5	0.178	47	0.020	<0.001
Lung and DL	31	1.105	236	0.102	<0.001
Liver and brain	3	0.107	18	0.008	0.002
Liver and DL	11	0.392	82	0.036	<0.001
Brain and DL	1	0.036	16	0.007	0.186
Three sites					
Bone and lung and liver	32	1.140	351	0.152	<0.001
Bone and lung and brain	7	0.249	71	0.031	<0.001
Bone and lung and DL	26	0.927	16	0.007	<0.001
Bone and liver and brain	4	0.143	53	0.023	0.005
Bone and liver and DL	26	0.927	172	0.074	<0.001
Bone and brain and DL	4	0.143	28	0.012	0.001
Lung and liver and brain	2	0.071	17	0.007	0.022
Lung and liver and DL	8	0.285	73	0.032	<0.001
Liver and brain and DL	1	0.036	6	0.003	0.081

(Continued)

Table 3. (Continued)

Features	IBC (*n* = 2806)		non-IBC (*n* = 230,880)		*p*
	Number	(%)	Number	(%)	
Four sites					
Bone and lung and liver and brain	10	0.356	77	0.033	<0.001
Bone and lung and liver and DL	27	0.962	189	0.082	<0.001
Bone and lung and brain and DL	1	0.036	41	0.018	0.398
Bone and liver and brain and DL	2	0.071	15	0.006	0.017
Lung and liver and brain and DL	2	0.071	8	0.003	0.006
Five sites					
Bone and Lung and liver and brain and DL	2	0.071	58	0.025	0.162

DL, distant lymph node; IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer.

frequent bi-site metastasis was the bone and liver (IBC: 2.5%, non-IBC: 0.3%). The most frequent tri-site combination was the bone, lung, and liver (IBC: 1.1%, non-IBC: 0.2%). Significant differences existed between the two groups in the frequencies of most of the metastatic combinations.

In addition, the interactions among these metastatic lesions were further analyzed (Figure 5A–E). IBC patients with bone metastasis had a higher rate of metastasis to the liver (6.1%) than DL (6.0%), lung (5.5%) and brain (1.7%). However, non-IBC patients with bone metastasis had a higher incidence rate of lung metastasis (0.8%) than metastasis to the liver (0.7%), DL (0.5%) and brain (0.2%). Patients with liver, lung, brain or DL metastasis all had a higher incidence rate of bone metastasis than other lesions. We also noticed that the liver preferentially co-metastasized with bone in the IBC and non-IBC cohort. Brain metastasis was specifically associated with bone and lung metastases.

Survival

In our research, 974 deaths in the IBC cohort (34.7%) and 16,829 deaths in the non-IBC cohort (7.3%) were observed. The Kaplan–Meier curves suggested that the IBC cohort had poorer OS and BCSS than the non-IBC group (Figure 6A,B). The multivariate analyses further confirmed IBC as an independent prognostic factor for OS [hazard ratio (HR) 1.602, 95% CI 1.496–1.716, $p < 0.001$] and BCSS (HR 1.511, 95% CI 1.402–1.628, $p < 0.001$) (Table 4, Supplemental Table S1). We assessed the impact of IBC on patient survival according to different molecular subtypes. The IBC cohort showed poorer OS and BCSS than the non-IBC cohort in all molecular subtypes, including HR+/HER2–, HR+/HER2+, HR–/HER2+ and TNBC (Supplemental Figure 1A,B).

Moreover, univariate and multivariate analyses were performed to assess the impact of IBC on the prognosis of patients with different metastatic sites. The Kaplan–Meier curves indicated that the IBC group had poorer OS and BCSS than the non-IBC group at different metastatic sites, including bone, lung, liver, and DL (Supplemental Figure S2A,B). The multivariate analysis further indicated that IBC was an independent prognostic factor for OS in different metastatic sites, including bone (HR 1.366, 95% CI 1.213–1.539, $p < 0.001$), lung (HR 1.178, 95% CI 1.010–1.374, $p = 0.037$), liver (HR 1.349, 95% CI 1.144–1.591, $p < 0.001$), and DL node (HR 1.236, 95% CI 1.044–1.463, $p = 0.014$) (Table 5). For BCSS, IBC was also an independent predictive factor in patients with bone metastasis (HR 1.363, 95% CI 1.202–1.546, $p < 0.001$), lung metastasis (HR 1.228, 95% CI 1.047–1.441, $p = 0.012$), liver metastasis (HR 1.358, 95% CI

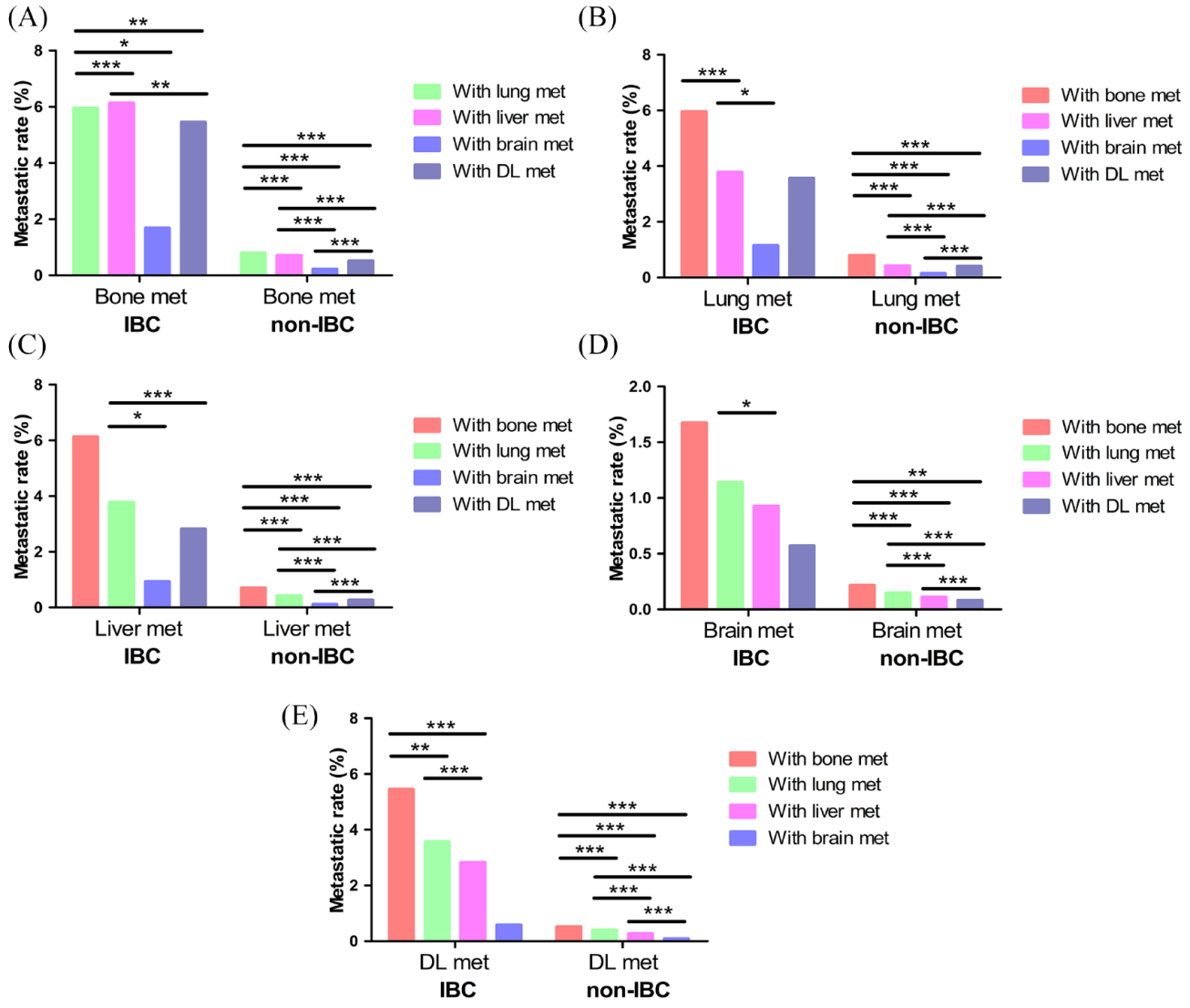

Figure 5. Comparisons of co-metastatic rates in IBC and non-IBC. (A) Bone metastasis with other sites; (B) Lung metastasis with other sites; (C) Liver metastasis with other sites; (D) Brain metastasis with other sites; (E) DL metastasis with other sites.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
DL, distant lymph node; IBC, inflammatory breast cancer; MET, metastasis; non-IBC, non-inflammatory breast cancer.

1.143–1.612, $p < 0.001$), and distant lymph node metastasis (HR 1.214, 95% CI 1.015–1.452, $p = 0.034$) (Supplemental Table S2).

Discussion

Distant metastasis remains a vital problem in breast cancer, contributing to the majority of cancer-related deaths. Among all types of breast cancer, IBC is a fatal subtype with a high frequency of early distant metastasis. Therefore, it is important to compare the metastatic patterns between IBC and non-IBC. In the present research, we mainly achieved the following: (a) elaborated the distribution of single-site metastases; (b) clarified the impact of molecular subtypes on metastatic sites; (c) identified the patterns of co-metastases; and (d) compared prognostic outcomes and clinicopathological features between IBC and non-IBC. To the best of our knowledge, our research is the first comprehensive, population-based study comparing metastatic profiles between IBC and non-IBC. Thus, we hope that our research could be helpful in future clinical and translational studies in breast cancer.

By comparing the metastatic frequencies between IBC and non-IBC, we suggested that

Table 4. Univariate and multivariate analyses for OS.

Clinicopathological characteristics	Univariable analysis *p*	Multivariable analysis	
		Hazard ratio (95% CI)	*p*
IBC/non-IBC	<0.001		<0.001
non-IBC		Reference	
IBC		1.602 (1.496–1.716)	<0.001
Age	<0.001		<0.001
<50		Reference	
50–64		1.256 (1.198–1.317)	<0.001
⩾65		2.557 (2.443–2.675)	<0.001
Marital status	<0.001		<0.001
Married		Reference	
Unmarried		1.468 (1.422–1.516)	<0.001
Unknown		1.213 (1.136–1.295)	<0.001
Race	<0.001		<0.001
White		Reference	
Black		0.616 (0.575–0.660)	<0.001
OthersΔ		0.849 (0.815–0.884)	<0.001
Molecular subtype	<0.001		<0.001
HR+/HER2–		Reference	
HR+/HER2+		0.908 (0.862–0.958)	<0.001
HR–/HER2+		1.255 (1.177–1.337)	<0.001
TNBC		2.430 (2.332–2.532)	<0.001
Grade	<0.001		<0.001
I		Reference	
II		1.173 (1.113–1.237)	<0.001
III		1.836 (1.737–1.941)	<0.001
Unknown		1.464 (1.366–1.569)	<0.001
Size (cm)	<0.001		<0.001
<2.0		Reference	
2.0–4.9		1.829 (1.758–1.904)	<0.001
⩾5.0		2.711 (2.582–2.847)	<0.001
Unknown		2.227 (2.087–2.376)	<0.001

(Continued)

Table 4. (Continued)

Clinicopathological characteristics	Univariable analysis *p*	Multivariable analysis	
		Hazard ratio (95% CI)	*p*
Regional lymph node invasion	<0.001		<0.001
N0		Reference	
N1		1.483 (1.428–1.541)	<0.001
N2		2.186 (2.071–2.307)	<0.001
N3		2.775(2.625–2.933)	<0.001
NX		1.927(1.773–2.094)	<0.001
Bone metastasis	<0.001		<0.001
No		Reference	
Yes		1.791 (1.703–1.884)	<0.001
Brain metastasis	<0.001		<0.001
No		Reference	
Yes		2.370 (2.160–2.601)	<0.001
Liver metastasis	<0.001		<0.001
No		Reference	
Yes		2.208 (2.078–2.346)	<0.001
Lung metastasis	<0.001		<0.001
No		Reference	
Yes		1.421 (1.340–1.508)	<0.001
DL metastasis	<0.001		0.171
No		Reference	
Yes		1.048 (0.980–1.121)	0.171
Surgery	<0.001		<0.001
No		Reference	
Yes		0.303 (0.291–0.316)	<0.001
Chemotherapy	<0.001		<0.001
No		Reference	
Yes		0.610 (0.588–0.632)	<0.001
Radiation therapy	<0.001		<0.001
No		Reference	
Yes		0.650 (0.630–0.672)	<0.001

ΔOthers include American Indian, AK Native, Asian, and Pacific Islander.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer; OS, overall survival; TNBC, triple-negative breast cancer.

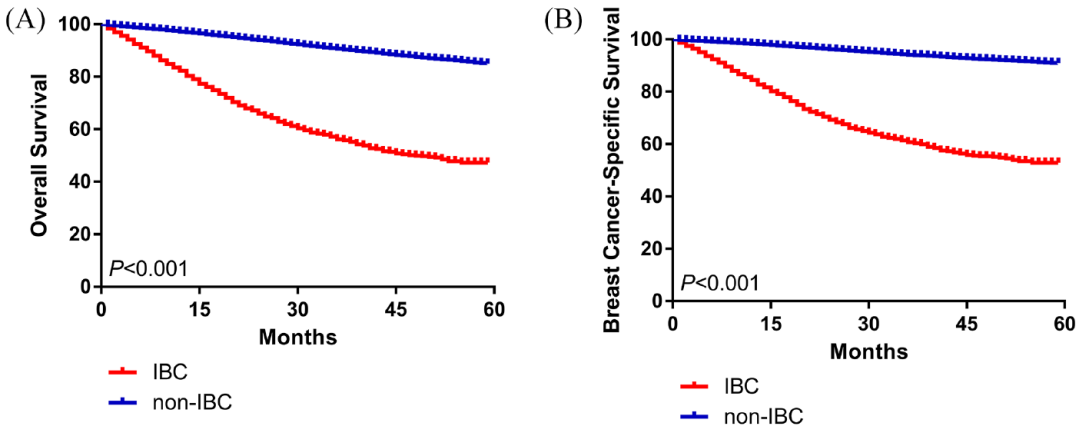

Figure 6. Kaplan–Meier curves of the impact of IBC on overall survival (A) and breast cancer-specific survival (B). IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer.

Table 5. Multivariate analyses of the impact of IBC on overall survival inpatients with different metastatic sites.

Variable	Metastatic site	OS	
		HR (95% CI)	*p*
IBC *versus* non-IBC	Bone	1.366 (1.213–1.539)	<0.001
	Lung	1.178 (1.010–1.374)	0.037
	Liver	1.349 (1.144–1.591)	<0.001
	Brain	1.143 (0.845–1.545)	0.386
	DL	1.236 (1.044–1.463)	0.014

Adjusted for age, race, marital status, molecular subtype, grade, tumor size, regional lymph node invasion and therapies. CI, confidence interval; DL, distant lymph node; HR, hazard ratio; IBC, inflammatory breast cancer; non-IBC, non-inflammatory breast cancer; OS, overall survival.

the metastatic rates of all sites in IBC were extraordinarily higher than those of non-IBC. Adjusting for confounding clinical variables, multivariate analyses further demonstrated that the inflammatory nature of IBC increased the metastatic frequency in all sites. Consistent with the results reported in previous publications, the bone and brain were the most and least frequent lesions, respectively, in the whole breast cancer cohort.[17] We further studied the relationship between molecular subtype and metastasis. In both groups, the percentage of the HR+/HER2– subtype decreased in patients with lung, DL, liver, and brain metastases compared with bone metastasis. Previous studies have suggested that TNBC has a relatively high rate of brain metastasis,[18,19] and our study also indicated that the proportion of visceral metastases increased in the TNBC subtype, especially brain metastasis, which showed the largest increase.

Of note, approximately 30% of patients with distant metastasis developed more than one metastatic lesion. Therefore, we analyzed the patterns of combined metastases in the IBC and non-IBC groups. It was suggested that DL was the leading site of single-site metastasis in IBC but not in non-IBC, which could be attributed to the clinical characteristics of tumor infiltration in lymphatics and regional lymph node invasion. Consistent with the findings in other solid tumors, the bi-organ pattern was far more common than the tri-organ, tetra-organ and penta-organ patterns in both inflammatory and non-inflammatory breast cancer.[20,21] Among all combined metastases, the most frequent bi-organ metastatic

pattern was the bone and liver, and the most frequent tri-organ metastasis was the bone, lung, and liver. Moreover, brain metastasis was preferentially correlated with bone and lung metastasis. The above results indicated that clinical physicians need to be aware of the possibility of combined metastases in different sites and make more accurate diagnoses and treatments for multiorgan metastasis.

We further focused on clinicopathological parameters and their prognostic significance in the two cohorts. Several clinical features including molecular subtype, age, marital status, race, and grade varied between the two groups. Compared with the non-IBC cohort, the IBC cohort had a higher incidence of the HER2+ and TNBC subtypes, older age, a higher rate of unmarried status, a lower incidence of black race, poorer tumor differentiation, larger tumor sizes, and a higher frequency of regional lymph node invasion. Notably, the IBC cohort tended to have a higher incidence of unmarried status, which could have several reasons. A possible explanation for this result may be the psychosocial perspective. Lacking support from spouses, unmarried patients may suffer from psychological stress, which alters neuroendocrine mediators, metabolic status, and immune system, thus facilitating tumor initiation and progression.[22–24] Distressed psychological status may lead to bad habits, such as smoking and excessive alcohol consumption, also resulting in the development of cancer.[25–27] Another finding is that marriage could increase the possibility of early diagnosis. Adekolujo *et al.* and Hinyard *et al.* found that unmarried patients showed a higher risk for late-stage diagnosis of breast cancer compared with married patients.[28,29] Moreover, marital status partially reflects financial status, which could affect routine clinical visits and the quality of medical care. Several previous studies have indicated that IBC contributes to a large proportion of breast cancer in low-income populations.[30,31] Regarding therapies, fewer IBC patients undergo surgery and more IBC patients undergo chemotherapy than non-IBC patients, which is due mainly to the tumor biology and metastatic potential of IBC. Moreover, univariate and multivariate analyses suggested that the IBC group showed poorer prognosis than the non-IBC group. In addition, adjusting for clinical and treatment variables, we found that IBC was an independent prognostic factor for patients with different metastatic sites.

We believe that our research could be conducive to the clinical practice. First, clinical and molecular subtypes could help clinicians recognize patients at high risk for distant metastasis. Second, knowledge of the patterns of site-specific metastases would improve study designs for precision medicine. Third, patients with bone-only metastasis may benefit from primary tumor operation and show favorable prognostic outcomes.[32]

As far as we know, this is the first population-based study summarizing the metastatic patterns in IBC and non-IBC. However, several potential limitations may exist in this retrospective study. The first limitation may be the retrospective nature of this study. Second, the SEER database only includes metastatic data in five sites (bone, lung, liver, brain, and DL node). However, we found that these five lesions accounted for 94.4% of all metastatic patients, and few patients with metastasis in other lesions were missing. Third, since detailed information on metastasis and molecular subtype was provided by the SEER database from 2010, we enrolled patients only between 2010 and 2014. Furthermore, the majority of the included cases were Caucasian and black, so the results needed to be validated in external cohorts, especially in Asian cohorts. Additionally, some patients may develop metachronous metastasis, which was unknown from the SEER database. Thus, we suggest that further prospective studies be performed to validate our findings.

In summary, in this population-based retrospective study, we compared metastatic patterns between IBC and non-IBC cases. We found that IBC and non-IBC patients presented with different metastatic frequencies, clinical features, and prognostic outcomes. Our findings provide more information for therapeutic decision making and clinical study designs.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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