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Original article

Clinicopathological characteristics and survival outcomes in breast carcinosarcoma: A SEER population-based study

Shuchen Lin [a, b, 1], Chang Liu [a, b, 1], Zhonghua Tao [a, b], Jian Zhang [a, b], Xichun Hu [a, b, *]

[a] Department of Medical Oncology, Fudan University Shanghai Cancer Center, 270 Dong'an Road, Shanghai, 200032, China
[b] Department of Oncology, Shanghai Medical College, Fudan University, 130 Dong'an Road, Shanghai, 200032, China

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ABSTRACT

Objectives: Carcinosarcoma of the breast is a rare disease. Its clinicopathological features and prognosis are not well defined. The aim of this study was to compare the clinicopathological features and clinical outcome between breast carcinosarcoma and breast invasive ductal carcinoma (IDC).
Materials and methods: Patients with breast carcinosarcoma and breast IDC were identified through the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015. Then a comparison was conducted between these two groups. Propensity score matching (PSM) was performed to balance the effects of baseline clinicopathological differences. The Cox proportional hazard model was used to identify potential prognostic factors of breast carcinosarcoma.
Results: In total, we identified 63 patients with breast carcinosarcoma and 200,596 cases with breast IDC. Comparing with IDC, breast carcinosarcoma was significantly correlated with higher grading, higher staging, larger tumor size, lower lymph node involvement, and a higher proportion of triple negative breast cancer (TNBC), suggesting a significantly worse clinical outcome. After adjusting for the uneven clinicopathological variables with PSM, significant differences were still observed between these two histology types. Subgroup analysis further showed that carcinosarcoma-TNBC has an inferior clinical outcome compared with IDC-TNBC. Finally, we identified independent prognostic factors, namely, stage, tumor size, and distant metastasis.
Conclusion: It is concluded that breast carcinosarcoma has distinct clinicopathological features and a significantly worse clinical outcome than common IDC.

1. Introduction

Breast carcinosarcoma is a rare histological cancer that occurs in 0.08%–0.2% of all cases of breast cancer [1]. It was first reported by Halpert B and Young MO in 1948 [2]. In the World Health Organization (WHO) breast cancer classification (2003), breast carcinosarcoma was characterized as infiltrating carcinoma mixed with heterologous malignant mesenchymal component and was defined as a subtype of metaplastic carcinoma. The term "metaplastic carcinoma" refers to a heterogeneous group of neoplasms characterized by an intimate admixture of adenocarcinoma with dominant areas of spindle cell, squamous, and/or mesenchymal differentiation [3]. In 2012, WHO published a revised classification for metaplastic carcinoma. In this edition, "breast carcinosarcoma" is replaced by "metaplastic breast cancer with mesenchymal differentiation", and other subtypes of metaplastic breast cancer are squamous cell carcinoma, low-grade adenosquamous carcinoma, spindle cell carcinoma, and fibromatosis-like metaplastic carcinoma [4]. Compared with invasive ductal carcinoma (IDC), the most common type of breast cancer, patients diagnosed with metaplastic carcinoma are more likely to have larger tumor size, less lymph node metastasis, a higher histology grade and percent of triple negative breast cancer (TNBC), and a worse clinical outcome [5–7].

Due to the specific histologic feature, breast carcinosarcoma may have different biological characteristics when compared with IDC. Because of the rarity of breast carcinosarcoma, previous publications about this disease were a few small sample size retrospective analyses [8–14] and a few case reports [15–20]. From these limited studies, it appears that breast carcinosarcoma is always aggressive, poorly differentiated, and hormone receptor-

* Corresponding author. Department of Medical Oncology, Fudan University Shanghai Cancer Center, 270 Dong'an Road, Shanghai, 200032, China.
E-mail address: huxichun2017@163.com (X. Hu).
[1] Shuchen Lin, and Chang Liu equally contributed to this work.

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Abbreviations

BCSS	Breast cancer cause-specific survival
CS-TNBC	carcinosarcoma-TNBC
CS-non TNBC	carcinosarcoma-non TNBC
IDC	Invasive ductal carcinoma
OS	Overall survival
PSM	Propensity score matching
SEER	Surveillance, Epidemiology, and End Results
TNBC	Triple negative breast cancer
TNM	Tumor Node Metastasis

negative [8,10]. Some reports showed that patients with carcinosarcoma had worse survival than other subtypes of metaplastic carcinomas [8,11]; however, one report showed that carcinosarcoma shared a similar clinical outcome with other metaplastic carcinomas [10]. Until now, accurate information concerning the comparison of breast carcinosarcoma and breast IDC has been unavailable.

The aim of the study was to perform a comparison of the prognosis between breast carcinosarcoma and breast IDC, and to further identify the underlying prognostic clinicopathological factors.

2. Methods

2.1. Patients

The Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2015 was used to collect patients' clinicopathological features and survival data. This database includes authoritative information about cancer incidence and survival data from 18 population-based cancer registries, covering approximately 34.6% of the U.S. population [21]. Since the HER2 information was available after 2010, we collected the SEER patients diagnosed between 2010 and 2015. Other selection criteria were as follows: breast cancer as the only cancer diagnosis, Tumor Node Metastasis (TNM) stage I–IV and pathologic confirmation of carcinosarcoma (ICD-0-3 8980/3, and 8981/3) and infiltrating duct carcinoma, not otherwise specified (ICD-0-3 8500).

2.2. Clinicopathological characteristics

To investigate the clinicopathological characteristics of carcinosarcoma and infiltrating duct carcinoma of the breast, the following information was obtained: age, race, marital status at diagnosis, laterality, grade, TNM stage, tumor size, nodal stage, metastasis status, breast molecular subtype, surgery treatment with either mastectomy or breast-conserving surgery, radiation therapy, chemotherapy, cause of death, and survival (months). Patients were categorized into four subtypes: HR + HER2-, HR + HER2+, HR-HER2+, HR-HER2- (triple negative).

2.3. Statistical analyses

Breast cancer cause-specific survival (BCSS) was defined as the time from the date of diagnosis to the date of death from breast cancer. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death due to any cause or the last follow-up. Clinicopathological characteristics were compared between carcinosarcoma and infiltrating duct carcinoma by Pearson chi-square and Fisher's exact probability tests. The univariate Cox proportional hazard model was applied for identifying prognostic factors. Kaplan-Meier plots and log-rank tests were performed to compare BCSS and OS among different groups. Propensity score matching was conducted to calibrate the effects of the baseline of clinicopathological differences. All the statistical analyses and graphics were performed with the SPSS statistical software, version 22.0 (IBM Corp, Armonk, NY) and R statistical software (version 3.6.0. http://www.R-project.org/).

3. Results

3.1. Patient, clinical, and tumor characteristics

Between the years 2010 and 2015, a total of 63 patients with breast carcinosarcoma and 200,596 with breast IDC were identified in our study. The detailed clinicopathological characteristics are summarized in Table 1. There were significant differences between carcinosarcoma and IDC, including Grade, AJCC stage, T stage, N stage, molecular subtype, and treatment options. Compared with IDC, patients with carcinosarcoma had higher grade (III–IV, 87.3% vs. 36.8%, P = 0.000), higher stage (II–IV, 88.9% vs. 49.3%, P = 0.000), larger tumor size (>2 cm, 84.2% vs. 40%, P = 0.000), lower lymph node involvement (negative, 77.8% vs. 66.3%, P = 0.040), and higher proportion of TNBC (68.3% vs.12.3%, P = 0.000). There was no significant difference in the rate of distant metastasis (M1, 7.9% vs. 5.0%, P = 0.247). Concerning treatment options, patients with carcinosarcoma were more likely to receive mastectomy (73.0% vs. 35.6%, P = 0.000) and chemotherapy (73.0% vs. 44.2%, P = 0.000), while less likely to receive radiotherapy (30.2% vs. 52.1%, P = 0.001).

3.2. Comparison of survival between breast carcinosarcoma and breast IDC

Based on the Kaplan–Meier plot, carcinosarcoma showed a significantly worse clinical outcome than breast IDC (Fig. 1, both P < 0.0001). The 4-year BCSS rate in carcinosarcoma and IDC was 49.6% and 91.3%, respectively, and the 4-year OS rate in carcinosarcoma and IDC was 46.2%, and 87.4%, respectively. Since TNBC was a poor prognostic molecular subtype for breast cancer, and 68.3% of carcinosarcomas were TNBC, we further compared BCSS and OS among the following subgroups: IDC- TNBC, IDC-non TNBC, carcinosarcoma-TNBC (CS-TNBC), and carcinosarcoma-non TNBC (CS-non TNBC). The results are presented in Fig. 2. Patients with CS-TNBC and CS-non TNBC have similar BCSS and OS (both P > 0.05). These two groups displayed worse clinical outcomes than those with IDC- TNBC and IDC-non TNBC (both P < 0.05).

Since the uneven baseline characteristics may have a marked impact on the survival outcomes, we performed a 1:5 (carcinosarcoma/IDC) propensity score matching analysis to the utmost to eliminate the baseline variations. Eleven patients with carcinosarcoma were excluded due to lack of definite baseline characteristics. Finally, 260 IDC patients were selected to match 52 carcinosarcomas. No significant differences were observed for all of the baseline variations between the matched groups (Table 2). The patients with carcinosarcoma exhibited a poorer clinical outcome than IDC patients. The 4-year BCSS rate in carcinosarcoma and IDC was 50.1%, and 76.9%, respectively (P = 0.0018, log-rank test), and the 4-year OS rate in carcinosarcoma and IDC was 47.0% and 69.3%, respectively (P = 0.0048, log-rank test) (Fig. 3).

Then we used the same strategy to match CS-TNBC. Finally, we obtained 37 patients with CS-TNBC and 185 matched patients with IDC-TNBC. No significant differences were observed for all of the baseline variations between the two groups (Table 3). We observed an inferior outcome for CS-TNBC compared with IDC-TNBC. The 4-

Table 1
Baseline characteristics of patients with carcinosarcoma and invasive ductal carcinoma (IDC).

Characteristics	Carcinosarcoma (n = 63) No	Percent (%)	IDC (n = 200,596) No	Percent (%)	P
Age					0.314
< 60 years	36	57.1	100,937	50.3	
≥60 years	27	42.9	99,666	49.7	
Race					0.208
Black	13	20.6	23,467	11.7	
White	44	69.8	155,335	77.4	
Other	6	9.5	20,268	10.1	
Unknown	0	0	1533	0.8	
Grade					0.000
I	0	0	39,131	19.5	
II	1	1.6	80,147	40.0	
III	51	81.0	73,320	36.5	
IV	4	6.3	616	0.3	
Unknown	7	11.1	7389	3.7	
Laterality					0.904
Left	31	49.2	101,726	50.7	
Right	32	50.8	98,728	49.2	
Others	0	0	149	0.1	
Marital status					0.087
Married	29	46.0	111,103	55.4	
Unmarried	33	52.4	79,152	39.5	
Unknown	1	1.6	10,348	5.16	
Stage					0.000
I	7	11.1	101,726	50.7	
II	39	61.9	67,115	33.5	
III	12	19.0	21,722	10.8	
IV	5	7.9	10,040	5.0	
T stage					0.000
T0	0	0	172	0.1	
T1	9	14.3	118,921	59.3	
T2	25	39.7	61,002	30.4	
T3	19	30.2	10,848	5.4	
T4	9	14.3	8443	4.2	
Unknown	1	1.6	1217	0.6	
N stage					0.040
N0	49	77.8	133,012	66.3	
N1	7	11.1	49,603	24.7	
N2	4	6.3	10,804	5.4	
N3	2	3.2	6278	3.1	
Unknown	1	1.6	906	0.5	
Metastasis					0.247
M0	58	92.1	190,563	95.0	
M1	5	7.9	10,040	5.0	
Molecular subtype					0.000
HR + HER2-	13	20.6	130,044	64.8	
HR-HER2+	2	3.2	10,670	5.3	
HR + HER2-	2	3.2	23,571	11.8	
Triple negative	43	68.3	24,628	12.3	
Unknown	3	4.8	11,690	5.8	
Surgery					0.000
No surgery	4	6.3	14,961	7.5	
breast-conserving surgery	13	20.6	113,776	56.7	
Mastectomy	46	73.0	71,424	35.6	
Unknown	0	0	442	0.2	
Radiation					0.001
Yes	19	30.2	104,458	52.1	
No/unknown	44	69.8	96,145	47.9	
Chemotherapy					0.000
Yes	46	73.0	88,600	44.2	
No/unknown	17	27.0	112,003	55.8	

year BCSS rate in CS-TNBC and IDC-TNBC was 58.9% and 81.7%, respectively (P = 0.0032, log-rank test), and the 4-year OS rate in CS-TNBC and IDC-TNBC was 53.9% and 75.2%, respectively (P = 0.0071, log-rank test) (Fig. 4).

3.3. Identifying prognostic factors for carcinosarcoma

We also explored the potential prognosis factor in breast carcinosarcoma using univariate Cox regression analysis. As shown in Table 4, stage, tumor size, and distant metastasis were all significantly associated with poor BCSS and OS. Other factors such as grade (P = 0.028, grade III, HR = 0.246, 95% CI, 0.070–0.859), N stage (P = 0.003, unknown, HR = 73.170, 95% CI, 4.503–1189.004), and molecular subtype (P = 0.009, unknown, HR = 10.759, 95% CI, 1.806–64.103) were also prognostic factors for OS.

4. Discussion

Breast carcinosarcoma is a rare disease. Only 358 patients were registered in the SEER database between the years 1973 and 2015.

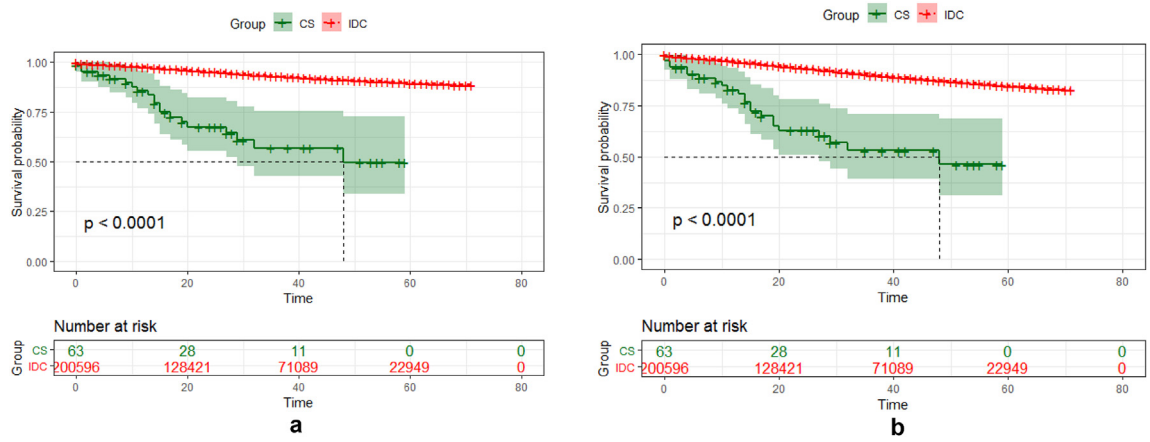

Fig. 1. Kaplan–Meier curves showing a comparison of cancer cause-specific survival (a) and overall survival (b) between invasive ductal carcinoma (IDC) and carcinosarcoma (CS).

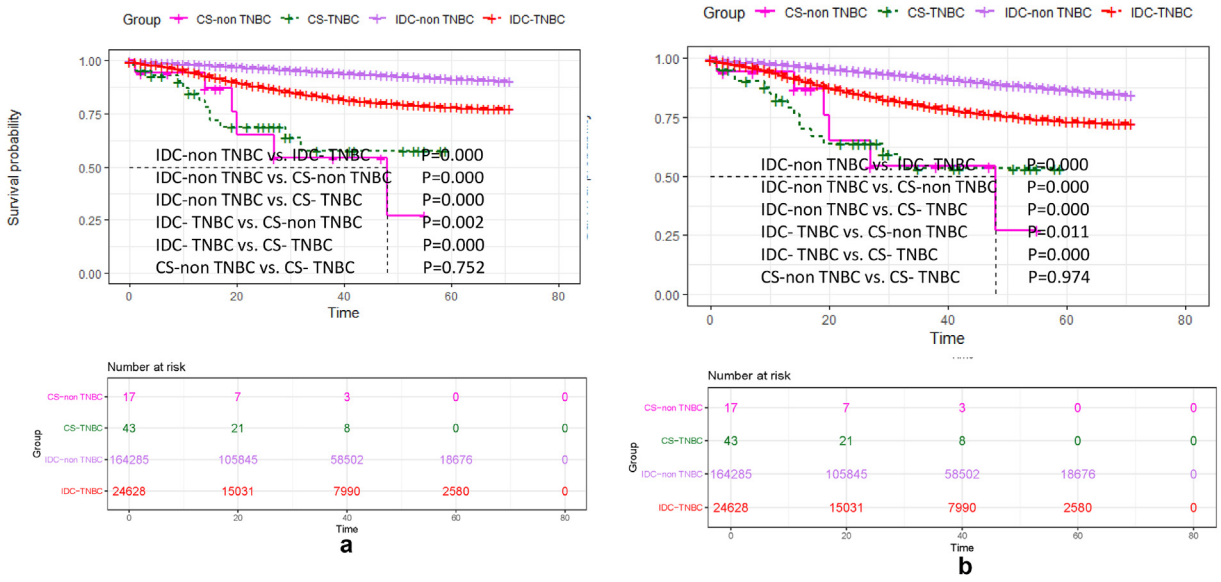

Fig. 2. Kaplan–Meier curves showing a comparison of breast cancer cause-specific survival (a) and overall survival (b) among invasive ductal carcinoma–non TNBC (IDC-non TNBC), IDC-TNBC, carcinosarcoma-non TNBC (CS-non TNBC), and carcinosarcoma-TNBC (CS-TNBC).

Because Her-2 is an important molecular subtype factor and this information is only available after 2010, we collected the SEER patients diagnosed between 2010 and 2015. Finally, only 63 patients with breast carcinosarcoma were identified in the present study.

Our study showed that the 4-year BCSS rate and OS rate of carcinosarcoma was 49.6% and 46.2%, respectively. This poor clinical outcome was similar to other reports [8,13]. Some studies further conducted a comparison of breast carcinosarcoma with other subtypes of breast metaplastic carcinoma. Hennessy et al. [10] found that carcinosarcoma shared similar clinicopathological features with breast metaplastic carcinoma. Tseng et al. [11]analyzed 1501 patients with breast metaplastic carcinoma from the SEER database, and they found that patients with carcinosarcoma had a worse disease-specific survival and overall survival compared with patients with metaplastic NOS. Our study showed that not only the whole carcinosarcoma group, but also the TNBC subgroup, uniformly showed a significantly worse clinical outcome than IDC. To the best of our knowledge, this is the first study comparing the prognosis of breast carcinosarcoma with IDC.

In the present study, we found that carcinosarcoma has distinct clinicopathological features. Compared with IDC, breast carcinosarcoma was correlated with higher grade, higher stage, larger tumor size, lower lymph node involvement, and a higher proportion of TNBC. In addition, carcinosarcoma showed a significantly worse clinical outcome than IDC. It appears that these aggressive clinicopathological features may be the cause of the poor outcome of carcinosarcoma. Then we used PSM to adjust for the uneven clinicopathological values, and a significant difference for the prognosis was still observed. To our knowledge, there have been no studies on breast carcinosarcoma that take advantage of PSM. Subgroup analysis for CS-TNBC and IDC-TNBC also showed similar results. All together, these results mean that a poor clinical outcome is characteristic of carcinosarcoma. However, few studies have focused on the molecular mechanism of breast carcinosarcoma. To improve the clinical outcome, further fundamental and clinical studies are required to explore the underlying molecular mechanism of breast carcinosarcoma.

Recently, Kennedy et al. [14] analyzed 329 early/or locally advanced breast carcinosarcoma patients from 2004 to 2012

Table 2
Baseline characteristics of patients with carcinosarcoma and invasive ductal carcinoma (IDC) in 1:5 matched group.

Characteristics	Carcinosarcoma (n = 52) No	Percent (%)	IDC (n = 260) No	Percent (%)	P
Age					0.718
< 60 years	32	61.5	153	58.8	
≥60 years	20	38.5	107	41.2	
Race					0.689
Black	12	23.1	55	21.2	
White	36	69.2	190	73.1	
Other	4	7.7	15	5.8	
Grade					0.928
II	1	1.9	9	3.5	
III	48	92.3	231	88.8	
IV	3	5.8	20	7.7	
Laterality					0.541
Left	25	48.1	111	42.7	
Right	27	51.9	149	57.3	
Marital status					0.880
Married	26	50	134	51.5	
Unmarried	26	50	126	48.5	
Stage					0.676
I	6	11.5	32	12.3	
II	33	63.5	162	62.3	
III	9	17.3	55	21.2	
IV	4	7.7	11	4.2	
T stage					0.400
T1	8	15.4	40	15.4	
T2	21	40.4	114	43.8	
T3	17	32.7	59	22.7	
T4	6	11.5	47	18.1	
N stage					0.184
N0	40	76.9	195	75.0	
N1	7	13.5	52	20.0	
N2	3	5.8	11	4.2	
N3	2	3.8	2	0.8	
Metastasis					0.288
M0	48	92.3	249	95.8	
M1	4	7.7	11	4.2	
Molecular subtype					0.920
HR + HER2-	11	21.2	55	21.2	
HR-HER2+	2	3.8	19	7.3	
HR + HER2+	2	3.8	12	4.6	
Triple negative	37	71.2	174	66.9	
Surgery					1.000
No surgery	1	1.9	9	3.5	
breast-conserving surgery	11	21.2	54	20.8	
Mastectomy	40	76.9	197	75.8	
Radiation					0.748
Yes	16	30.8	89	34.2	
No/unknown	36	69.2	171	65.8	
Chemotherapy					1.000
Yes	39	75	194	74.6	
No/unknown	13	25	66	25.4	

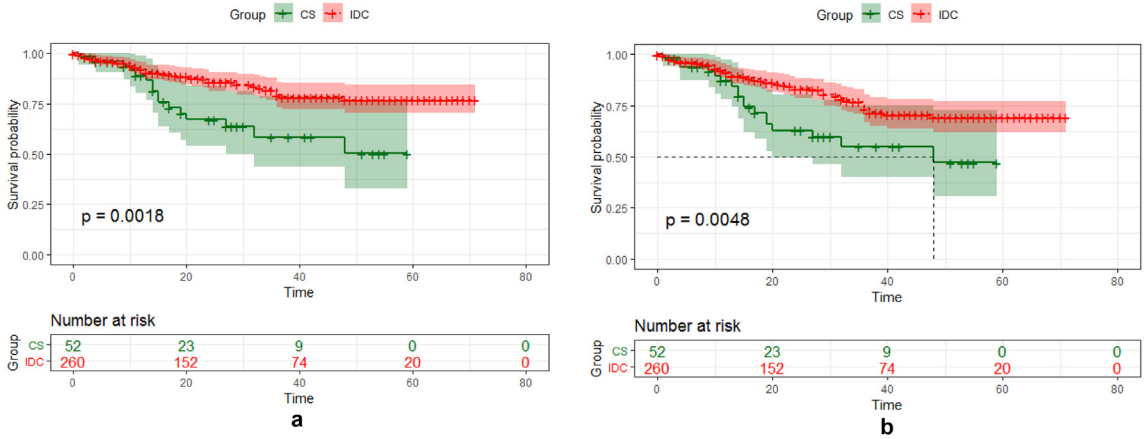

Fig. 3. The comparison of survival in the 1:5 matching group conducted between carcinosarcoma (CS) and invasive ductal carcinoma (IDC). (a) breast cancer cause-specific survival (BCSS); (b) overall survival (OS).

Table 3
Baseline characteristics of patients with carcinosarcoma-TNBC (CS-TNBC) and invasive ductal carcinoma-TNBC (IDC-TNBC) subgroup in 1:5 matched group.

Characteristics	CS-TNBC (n = 37) No	Percent (%)	IDC-TNBC (n = 185) No	Percent (%)	P
Age					1.000
< 60 years	21	56.8	108	58.4	
≥60 years	16	43.2	77	41.6	
Race					0.704
Black	6	16.2	26	14.1	
White	28	75.7	134	72.4	
Other	3	8.1	25	13.5	
Grade					1.000
I	0	0	1	0.5	
II	1	2.7	6	3.2	
III	33	89.2	164	88.6	
IV	3	8.1	14	7.6	
Laterality					0.856
Left	17	45.9	79	42.7	
Right	20	54.1	106	57.3	
Marital status					1.000
Married	20	54.1	98	53.0	
Unmarried	17	45.9	87	47.0	
Stage					0.820
I	4	10.8	20	10.8	
II	25	67.6	120	64.9	
III	6	16.2	39	21.1	
IV	2	5.4	6	3.2	
T stage					0.583
T1	5	13.5	22	11.9	
T2	14	37.8	73	39.5	
T3	15	40.5	60	32.4	
T4	3	8.1	30	16.2	
N stage					0.808
N0	31	83.8	144	77.8	
N1	3	8.1	27	14.6	
N2	2	5.4	8	4.3	
N3	1	2.7	6	3.2	
Metastasis					0.623
M0	35	94.6	179	96.8	
M1	2	5.4	6	3.2	
Surgery					1.000
No surgery	1	2.7	7	3.8	
breast-conserving surgery	9	24.3	44	23.8	
Mastectomy	27	73.0	134	72.4	
Radiation					1.000
Yes	14	37.8	71	38.4	
No/unknown	23	62.2	114	61.6	
Chemotherapy					1.000
Yes	29	78.4	148	80	
No/unknown	8	21.6	37	20	

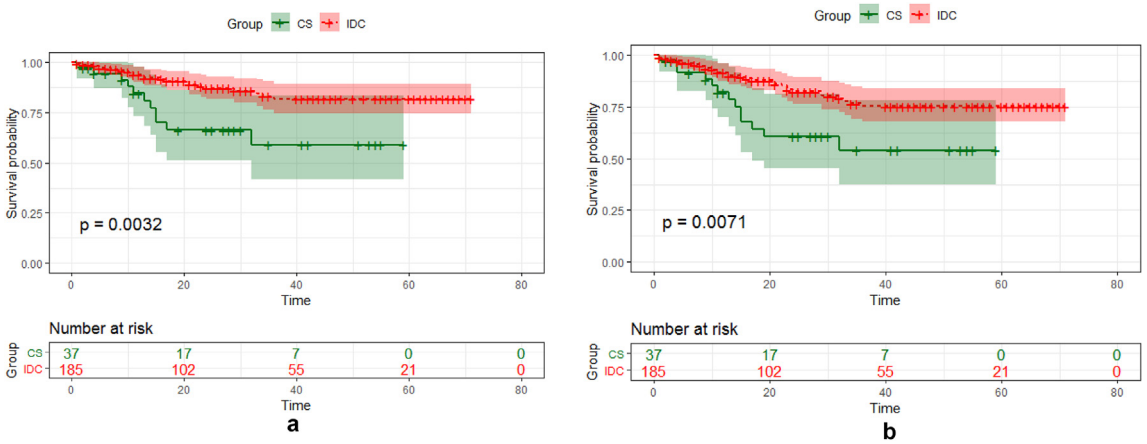

Fig. 4. The comparison of survival in the 1:5 matching group conducted between carcinosarcoma-TNBC (CS-TNBC) and invasive ductal carcinoma-TNBC (IDC-TNBC). (a) breast cancer cause-specific survival (BCSS); (b) overall survival (OS).

Table 4
Prognostic factors for breast cancer caused-specific survival (BCSS) and overall survival (OS) in breast carcinosarcoma by univariate analyses.

Parameter	BCSS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Age				
< 60 years	1		1	
≥60 years	2.263 (0.935–5.474)	0.070	1.999 (0.880–4.542)	0.098
Race				
Black	1		1	
White	1.407 (0.466–4.249)	0.545	1.593 (0.535–4.744)	0.403
Other	1.285 (0.140–11.753)	0.824	2.419 (0.432–13.548)	0.315
Laterality				
Left	1		1	
Right	0.718 (0.296–1.745)	0.465	0.969 (0.425–2.208)	0.941
Marital status				
Married	1		1	
Unmarried	2.362 (0.856–6.514)	0.097	2.227 (0.876–5.661)	0.093
Unknown	0	0.986	0	0.985
Grade				
IV	1		1	
II	0	0.982	0	0.984
III	0.310 (0.069–1.387)	0.125	0.246 (0.070–0.859)	0.028
Unknown	0.449 (0.073–2.774)	0.389	0.314 (0.062–1.601)	0.163
Stage				
I-II	1		1	
III-IV	3.041 (1.230–7.515)	0.016	3.973 (1.714–9.209)	0.001
T stage				
T1-T2	1		1	
T3-T4	3.392 (1.262–9.115)	0.015	4.091 (1.571–10.652)	0.004
Unknown	63.01 (5.130–773.970)	0.001	48.659 (4.502–525.919)	0.001
N stage				
N0	1		1	
N1–N3	1.329 (0.477–3.706)	0.586	1.859 (0.748–4.623)	0.182
Unknown	0	0.990	73.170 (4.503–1189.004)	0.003
Metastasis				
M0	1		1	
M1	10.733 (3.017–38.180)	0.000	7.647 (2.284–25.603)	0.001
Molecular subtype				
Non-triple negative	1		1	
Triple negative	0.858 (0.325–2.261)	0.756	0.986 (0.382–2.545)	0.977
Unknown	6.516 (0.652–65.132)	0.111	10.759 (1.806–64.103)	0.009
Surgery				
No surgery	1		1	
breast-conserving surgery	1 (0.004–281.607)	1.000	1 (0.010–103.820)	1.000
Mastectomy	1 (0.004–269.101)	1.000	1 (0.010–98.900)	1.000
Radiation				
Yes	1		1	
No/unknown	1.283 (0.491–3.349)	0.611	1.240 (0.509–3.024)	0.636
Chemotherapy				
Yes	1		1	
No/unknown	1.998 (0.795–5.020)	0.141	1.954 (0.826–4.620)	0.127

through the National Cancer Database. In that study, comorbidity index, insurance status, clinical T stage, surgical margin status, and treatment modality were associated with the greatest OS. In Mei et al.'s [12] study of 25 operable breast carcinosarcomas, they showed that treatment modality was the only prognostic factor through multivariate COX regression. Through univariate COX regression analysis, we have also identified several potential prognostic factors for breast carcinosarcoma, such as stage, tumor size, distant metastasis, and grade. Due to the small sample size, we did not subject these factors for further multivariate analysis. With the expansion of the SEER database, more comprehensive and accurate information on prognostic factors for breast carcinosarcoma can be determined.

The present study had several limitations. First, some bias may occur due to the small sample size. For example, we observed that the unknown N stage (P = 0.003, HR = 73.170) and molecular subtype (P = 0.009, HR = 10.759) also correlated with poor OS. Second, the record pattern of the SEER database may potentially affect the analyses. For example, for some patients, the records were not clear on the use of chemotherapy and radiotherapy, but they may actually have received one of these treatments. This bias may underestimate the treatment effect. Therefore, a further expanded study is warranted to verify our findings.

In conclusion, we showed that breast carcinosarcoma has distinct clinicopathological features. Breast carcinosarcoma uniformly showed a significantly worse clinical outcome than IDC for both the whole group and the TNBC subgroup.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.11.008.

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