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Prognosis of Invasive Micropapillary Carcinoma of the Breast Analyzed by Using the SEER Database

Lang Qin[1], Chuanbo Xie[2], Kaitao Yuan[3], Tiantian Zhen[4], Ying Lin[1*] and Nan Shao[1*]

[1]Breast Disease Center, The First Affiliated Hospital, Sun Yat-sen University, No.58 Zhongshan 2nd Road, Guangzhou 510080, China

[2]Cancer Prevention Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou 510080, China

[3]Center of Gastrointestinal Surgery, The First Affiliated Hospital, Sun Yat-sen University, No.58 Zhongshan 2nd road, Guangzhou 510080, China

[4]Department of Pathology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China

[*]Corresponding author:

Nan Shao and Ying Lin,
Breast Disease Center, The First Affiliated Hospital, Sun Yat-sen University, No.58 Zhongshan 2nd Road, Guangzhou 510080, China,
Tel: 8620-87755766 ext. 8198,
E-mail: shaon@mail.sysu.edu.cn and linying3@mail.sysu.edu.cn

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1. Abstract

1.1. Background: Invasive micropapillary carcinoma (IMPC) is a rare type of breast cancer with high frequency of regional lymph node metastasis. However, the prognosis of IMPC has remained controversial for decades. We aimed to compare the differences of prognosis between IMPC and Invasive ductal carcinoma(IDC) of the breast by utilizing Surveillance, Epidemiology, and End Results (SEER) database.

1.2. Material and Methods: Patients diagnosed with IMPC and IDC between 1 January 2010 and 31 December 2016 from the SEER database were retrieved. Propensity score matching was used to match the two groups at a 1:1 ratio. Breast cancer-specific survival (BCSS) and overall survival (OS) rates were compared between IMPC and IDC using Kaplan-Meier estimates, Log-rank tests, univariate and multivariate Cox proportional hazard models. Stratification analyses on breast subtype were also performed.

1.3. Results: A total of 921 patients with IMPC and 173, 621 patients with IDC were included in the present retrospective study. IMPC had more regional node metastasis than IDC (48.97% vs. 31.41%, $p<0.05$). IMPC had a better prognosis than IDC as shown by both the BCSS ($p<0.01$) and OS ($p=0.03$) but shared the same prognosis after PSM. IMPC had a better OS ($p=0.04$) and less distant metastasis ($p=0.04$) in the HR+/HER2- breast subtype than IDC.

1.4. Conclusion: IMPC had more axillary lymph nodes metastasis than IDC. Despite aggressive regional invasion, IMPC had a similar outcome compared with IDC in the BCSS and OS after PSM. Furthermore, IMPC had a better overall survival rate and less distant metastasis than IDC in the HR+/HER2- group.

2. Introduction

Invasive micropapillary carcinoma (IMPC) of the breast was first noted in 1980, defined as a pathological subtype by Siriaunkgul and Tavasol in 1993 [1], and listed in the World Health Organization (WHO) tumor histologic classification in 2003 [2]. IMPC accounts for approximately 6% of all invasive breast cancers [3]. The pathology of IMPC is characterized by tufts of cells arranged in pseudopapillary structures devoid of fibrovascular cores and surrounded by empty, clear spaces lined by delicate strands of fibrocollagenous stroma [4], with EMA and MUC-1 expressed on the basal surface of the cells [5]. In addition, IMPC is known for its high propensity for lymphatic vessel invasion and regional lymph node metastasis [1,3,6], which might cause a worse prognosis than

invasive ductal carcinoma (IDC). Previous studies demonstrated that there was no difference in the prognosis of IMPC and IDC [7-11]. In contrast, another study found that IMPC had a better prognosis than IDC despite its highly aggressive clinical presentation [12]. In a recent meta-analysis, IMPC exhibited a similar, even favorable, overall survival rate but a shorter relapse-free survival rate than IDC [13]. There was no consensus on IMPC prognosis and treatment worldwide to date. In this retrospective study, we analyzed the survival rate of IMPC and IDC by using the Surveillance, Epidemiology, and End Results (SEER) database.

3. Materials and Methods

3.1. Data source and Patient Selection

Data were retrieved from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 18 registry database released in April 2019 by the v8.3.8 SEER*Stat program. The ICD-O-3 (International Classification of Diseases for Oncology Version 3) codes of IMPC and IDC were 8507 and 8500/3, respectively. Since HER2 (human epidermal growth receptor 2) status records were available after 2010 in the SEER database, we chose IMPC and IDC patients diagnosed between 1 January 2010 and 31 December 2016. Search criteria were restricted to patients who were female, had confirmed histology of invasive carcinoma and whose tumor was a primary occurrence. Exclusion criteria including bilateral breast cancer, autopsy or death certification reports, unknown American Joint Committee on Cancer (AJCC) TNM stage (7th edition), unknown estrogen receptor (ER)/progesterone receptor (PR)/HER2 status, unknown pathological grade or surgery type and stage IV disease.

3.2. Propensity Score Matching

To avoid bias and balance the basic characteristics for the analysis, we performed 1:1 propensity score matching (PSM). PSM variables were selected as follows: age, histologic grade, T stage, N stage, ER, PR, and HER2 status.

3.3. Statistical Analysis

The primary outcomes were the breast cancer-specific survival (BCSS) and overall survival (OS) rates. The BCSS rate was defined as the time from disease occurrence to the date of death due to breast cancer and the OS rate was defined as the time from disease occurrence to the date of death due to any cause.

Univariate and multivariate Cox proportional hazards models were generated to assess the unadjusted and adjusted odds ratios (ORs) with 95% CIs (confidence intervals) of the various characteristics of IMPC patients. To confirm the difference in regional node metastasis, Mann-Whitney tests were conducted for positive lymph nodes depending on T stage. All analyses were performed via SPSS statistical software, version 25.0 (Armonk, NY, IBM Crop). A two-sided $p < 0.05$ was considered to indicate statistical significance.

4. Results

4.1. Characteristics of IMPC and IDC

Based on the inclusion and exclusion criteria, 921 patients with IMPC and 173,621 patients with IDC were included (Figure 1). Compared to the IDC, the IMPC had more advanced stage and more nodal metastasis (stage III: 22.37% vs. 11.26%, T3/T4 stage: 11.40% vs. 7.37%, nodal metastasis: 48.97% vs. 31.41%). As for nodal metastasis, IMPC metastasized more than IDC at any T stage ($p<0.05$) (Figure 2). In terms of subtype, the IMPC had a higher proportion of ER-positive (91.21% vs. 80.77%, $p<0.01$) and PR-positive (81.76% vs. 70.97%, $p<0.01$), and the triple-negative subtype accounted for only 4.0% of IMPC patients. In addition, a higher percentage of IMPC patients received chemotherapy (52.55% vs. 44.87%, $p<0.01$) and radiation therapy (61.13% vs. 55.12%, $p<0.01$). The types of surgery distributed similarly between the two histological types ($p=0.13$). A complete 1:1 matched case-control study by the propensity score match (PSM) method was performed. A total of 917 IMPC patients were completely matched to another 917 IDC patients (Table 1). In PSM cohort, compared to IDC, IMPC group were treated with similar type of surgery ($p=0.68$), chemotherapy ($p=0.58$) and radiation ($p=0.10$).

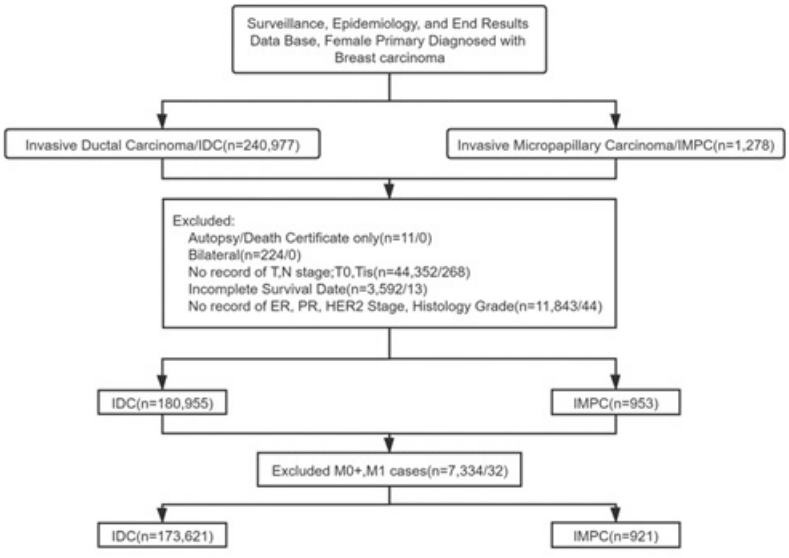

Figure 1: Flow chart of selecting records of patients with SEER database.

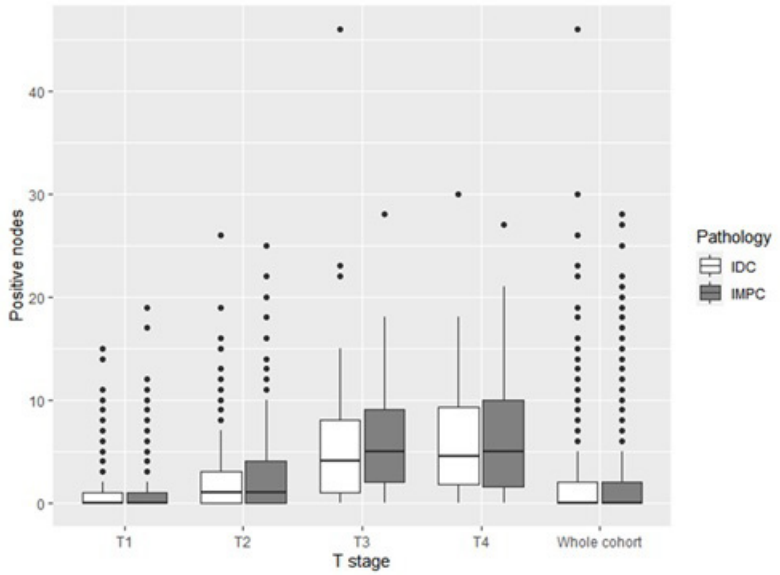

Figure 2: Comparison of positive nodes in different T stages.

Table 1: Characteristics of IMPC and IDC in the whole/PSM cohort.

	Whole cohort				PSM cohort			
Characteristics	Total n=174,317	IDC n=173,396	IMPC n=921	p	Total n=1,834	IDC n=917	IMPC n=917	p
Age				0.12				>0.99
>50	47,283 (27.12%)	47,054 (27.14%)	229 (24.86%)		452 (24.65%)	226 (24.65%)	226 (24.65%)	
≤50	127,034 (72.88%)	126,342 (72.86%)	692 (75.14%)		1,382 (75.35%)	691 (75.35%)	691 (75.35%)	
Tumor Stage				<0.01				>0.99
T1	107,631 (61.74%)	107,117 (61.78%)	514 (55.81%)		1,028 (56.05%)	514 (56.05%)	514 (56.05%)	
T2	53,801 (30.86%)	53,499 (30.85%)	302 (32.79%)		604 (32.93%)	302 (32.93%)	302 (32.93%)	
T3	8,528 (4.89%)	8,451 (4.87%)	77 (8.36%)		148 (8.07%)	74 (8.07%)	74 (8.07%)	
T4	4,357 (2.50%)	4,329 (2.50%)	28 (3.04%)		54 (2.94%)	27 (2.94%)	27 (2.94%)	
Nodal Stage				<0.01				>0.99
N0	119,396 (68.49%)	118,926 (68.59%)	470 (51.03%)		940 (51.25%)	470 (51.25%)	470 (51.25%)	
N1	41,621 (23.88%)	41,335 (23.84%)	286 (31.05%)		568 (30.97%)	284 (30.97%)	284 (30.97%)	
N2	8,887 (5.10%)	8,785 (5.07%)	102 (11.07%)		202 (11.01%)	101 (11.01%)	101 (11.01%)	
N3	4,413 (2.53%)	4,350 (2.51%)	63 (6.84%)		124 (6.76%)	62 (6.76%)	62 (6.76%)	
AJCC Stage				<0.01				0.99
I	92,507 (53.07%)	92,117 (53.13%)	390 (42.35%)		783 (42.69%)	393 (42.86%)	390 (42.53%)	
II	62,077 (35.61%)	61,752 (35.61%)	325 (35.29%)		647 (35.28%)	322 (35.11%)	325 (35.44%)	
III	19,733 (11.32%)	19,527 (11.26%)	206 (22.37%)		404 (22.03%)	202 (22.03%)	202 (22.03%)	
Histologic Grade				<0.01				>0.99
I	36,402 (20.88%)	36,342 (20.96%)	60 (6.51%)		116 (6.32%)	58 (6.32%)	58 (6.32%)	
II	72,630 (41.67%)	72,088 (41.57%)	542 (58.85%)		1,082 (59.00%)	541 (59.00%)	541 (59.00%)	
III and IV	65,285 (37.45%)	64,966 (37.47%)	319 (34.64%)		636 (34.68%)	318 (34.68%)	318 (34.68%)	
ER Status				<0.01				>0.99
Negative	33,417 (19.17%)	33,336 (19.23%)	81 (8.79%)		160 (8.72%)	80 (8.72%)	80 (8.72%)	
Positive	140,900 (80.83%)	140,060 (80.77%)	840 (91.21%)		1,674 (91.28%)	837 (91.28%)	837 (91.28%)	
PR Status				<0.01				>0.99
Negative	50,498 (28.97%)	50,330 (29.03%)	168 (18.24%)		330 (17.99%)	165 (17.99%)	165 (17.99%)	
Positive	123,819 (71.03%)	123,066 (70.97%)	753 (81.76%)		1,504 (82.01%)	752 (82.01%)	752 (82.01%)	
HER2 Status				<0.01				>0.99
Negative	144,939 (83.15%)	144,222 (83.17%)	717 (77.85%)		1,434 (78.19%)	165 (17.99%)	165 (17.99%)	
Positive	29,378 (16.85%)	29,174 (16.83%)	204 (22.15%)		400 (21.81%)	752 (82.01%)	752 (82.01%)	
Breast Subtype				<0.01				>0.99
HR+/HER2-	122,538 (70.30%)	121,858 (70.28%)	680 (73.83%)		1,360 (74.15%)	680 (74.15%)	680 (74.15%)	
HR+/HER2+	20,471 (11.74%)	20,308 (11.71%)	163 (17.70%)		320 (17.45%)	160 (17.45%)	160 (17.45%)	
HR-/HER2+	8,907 (5.11%)	8,866 (5.11%)	41 (4.45%)		80 (4.36%)	40 (4.36%)	40 (4.36%)	
Triple negative	22,401 (12.85%)	22,364 (12.90%)	37 (4.02%)		74 (4.03%)	37 (4.03%)	37 (4.03%)	
Type of Surgery				0.13				0.68
No surgery performed	6,631 (3.80%)	6,603 (3.81%)	28 (3.04%)		58 (3.16%)	30 (3.27%)	28 (3.05%)	

BCS	104,465 (59.93%)	103,932 (59.94%)	533 (57.87%)		1,082 (59.00%)	549 (59.87%)	533 (58.12%)	
Mastectomy	63,221 (36.27%)	62,861 (36.25%)	360 (39.09%)		694 (37.84%)	338 (36.86%)	356 (38.82%)	
Chemotherapy				<0.01				0.58
None/ Unknown	96,035 (55.09%)	95,598 (55.13%)	437 (47.45%)		884 (48.20%)	448 (48.85%)	436 (47.55%)	
Yes	78,282 (44.91%)	77,798 (44.87%)	484 (52.55%)		950 (51.80%)	469 (51.15%)	481 (52.45%)	
Radiation therapy				<0.01				0.1
None/Unknown	78,171 (44.84%)	77,813 (44.88%)	358 (38.87%)		680 (37.08%)	323 (35.22%)	357 (38.93%)	
Yes	96,146 (55.16%)	95,583 (55.12%)	563 (61.13%)		1,154 (62.92%)	594 (64.78%)	560 (61.07%)	

4.2. Overall Survival and Breast Cancer-Specific Survival

The median length of follow-up was 40 months for the IDC group and 32 months for the IMPC group. Overall, patients with IMPC had better survival outcomes than IDC patients as revealed by both the BCSS (HR=0.57, 95% CI: 0.41-0.78, p<0.01) and OS (HR=0.74, 95% CI: 0.58-0.94, p=0.03). However, after PSM, patients with IMPC and IDC had similar BCSS (HR=0.88, 95% CI: 0.54-1.45, p=0.62) and OS (HR=0.86, 95% CI: 0.62-1.20, p=0.45) rates (Figure 3). In the long-term survival comparison with the PSM group, IMPC patients had better OS rates from the 3rd to 5th years and better BCSS rates at the 4th and 5th years after diagnosis(p<0.05). Further stratification analysis showed a better 5-year BCSS (HR=0.36, 95%CI: 0.18-0.72, p<0.01) and OS (HR=0.35, 95%CI: 0.22-0.55, p<0.01) rate in the HR+/HER2- subtype (Table 2). We conducted both univariate and multiple Cox regression models for the PSM cohort (Table 3). In the univariate model, IMPC was not an independent factor for either OS (p=0.36) or BCSS (p=0.62), which was confirmed in the multivariate model (OS p=0.24, BCSS p=0.41).

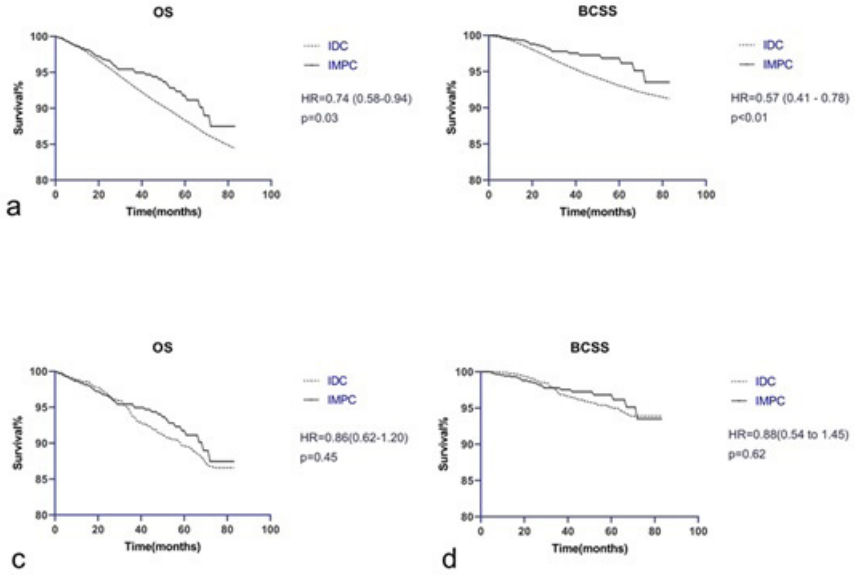

Figure 3: Kaplan-Meier survival curves of the OS and BCSS rates of the whole/PSM cohort. (a-b. OS and BCSS rate of whole cohort. b-c. OS and BCSS rate of PSM cohort.).

Table 2: Long-term survival comparison and subtype subset analysis of IMPC and IDC in the PSM group

	BCSS				OS			
	Survival rates		HR(95% CI)	p	Survival rates		HR(95% CI)	p
	IMPC	IDC			IMPC	IDC		
Year of survival								
1 year survival	99.5	99.9	5.02(0.59-43.07)	0.1	98.4	98.7	1.25(0.58-2.69)	0.56
2 year survival	96.9	97.1	1.04(0.61-1.78)	0.89	96.9	97.1	1.04(0.61-1.78)	0.89
3 year survival	98.3	97.1	0.59(0.31-1.09)	0.09	96.2	93.9	0.61(0.40-0.94)	0.02
4 year survival	98	96.2	0.51(0.28-0.90)	0.02	95.6	91.7	0.51(0.34-0.75)	<0.01
5 year survival	97.9	95.5	0.45(0.26-0.79)	<0.01	95.1	90.2	0.47(0.33-0.69)	<0.01
1 year survival correlation								
HR+/HER2-	99.6	99.9	3.01(0.31-29.0)	0.32	98.8	98.5	1.25(0.58-2.69)	0.64
HR+/HER2+	100	100	1.00(1.00-1.00)	>0.99	98.1	98.8	0.80(0.31-2.03)	0.65
HR-/HER2+	97.5	100	1.03(0.98-1.08)	0.31	95,0	100	1.51(0.25-9.16)	0.15
Triple negative	97.3	100	1.03(0.97-1.08)	0.31	94.6	100	1.06(0.98-1.14)	0.15

3 year survival correlation								
HR+/HER2-	98.5	97.1	0.49(0.23-1.06)	0.07	96.9	93.4	0.45(0.27-0.76)	<0.01
HR+/HER2+	98.8	98.8	1.00(0.14-7.19)	>0.99	95.6	96.9	1.42(0.44-4.57)	0.56
HR-/HER2+	97.5	97.5	1.00(0.06-16.56)	>0.99	95	97.5	2.05(0.18-23.59)	0.56
Triple negative	91.9	89.2	0.73(0.15-3.51)	0.69	86.5	86.5	1.00(0.26-3.79)	>0.99
5 year survival correlation								
HR+/HER2-	98.4	95.6	0.36(0.18-0.72)	<0.01	96.2	89.7	0.35(0.22-0.55)	<0.01
HR+/HER2+	98.8	98.1	0.66(0.11-4.02)	0.65	94.4	95	1.13(0.43-3.01)	0.8
HR-/HER2+	97.5	97.5	1.00(0.06-16.56)	>0.99	92.5	92.5	1.00(0.19-5.28)	>0.99
Triple negative	86.5	81.1	0.67(0.19-2.34)	0.53	81.1	75.7	0.73(0.24-2.21)	0.57

Table 3: Univariate and multivariate Cox proportional hazard models of overall survival (OS) and breast cancer-specific survival (BCSS) rates in the propensity score matched analysis

	Univariate				**Multivariate**			
	BCSS		OS		BCSS		OS	
	HR(95% CI)	p	HR(95% CI)	p	HR(95% CI)	p	HR(95% CI)	p
Pathological type IMPC vs. IDC	0.88(0.52-1.47)	0.62	0.85(0.60-1.21)	0.36	0.81(0.48-1.35)	0.41	0.81(0.57-1.15)	0.24
Age >50 vs. ≤50	1.48(0.81-2.70)	0.12	3.18(1.87-5.41)	<0.01	2.51(1.32-4.79)	0.01	3.52(2.02-6.13)	<0.01
Stage I & II vs. III	6.28(3.9-10.10)	<0.01	2.69(1.95-3.71)	<0.01	7.37(4.17-13.01)	<0.01	2.34(1.86-2.94)	<0.01
Grade I & II vs. III	2.37(1.49-3.79)	<0.01	1.43(1.04-1.95)	0.03	2.09(1.26-3.44)	<0.01	1.45(1.09-1.94)	0.02
Subtype								
HR+/HER2-	ref.	0.01	ref.	<0.01	ref.	<0.01	ref.	<0.01
HR+/HER2+	0.47(0.19-1.18)		0.70(0.42-1.16)	0.16	0.32(0.12-0.8)	0.02	0.70(0.41-1.18)	0.18
HR-/HER2+	1.05(0.33-3.37)		1.22(0.60-2.50)	0.58	1.03(0.32-3.37)	0.96	1.71(0.82-3.58)	0.16
HR-/HER2-	4.72(2.52-8.86)		2.90(1.74-4.83)	<0.01	3.73(1.89-7.34)	<0.01	3.14(1.83-5.40)	<0.01
Surgery Mast. vs. BCS	2.77(1.30-5.90)	0.03	3.26(1.89-5.60)	<0.01	1.50(0.67-3.33)	0.32	0.59(0.32-1.11)	0.1
Chemotherapy Yes vs. No	1.71(1.05-2.78)	<0.01	0.65(0.47-0.89)	0.01	0.98(0.56-1.71)	0.93	0.48(0.33-0.70)	<0.01
Radiation therapy Yes vs. No	0.37(0.23-0.59)	<0.01	0.34(0.25-0.47)	<0.01	0.33(0.2-0.57)	<0.01	0.32(0.22-0.46)	<0.01

*Mast.= mastectomy

4.3. HR+/HER2- Invasive Micropapillary Carcinoma Had Better Long-Term Survival Outcomes

91.5% of the IMPC and 82% of the IDC were luminal type (HR+, Her2-/+) (p<0.01, Mann-Whitney U-test) respectively. Therefore, it is necessary to confirm weather higher propotions of luminal subtype influence IMPC prognosis. In the PSM cohort, we performed a subgroup analysis based on breast subtype. The OS rate of IMPC was significantly better than that of IDC for the HR+/HER2- type (HR=0.65, 95% CI: 0.44-0.98, p=0.04) but the BCSS rate was similar (HR=1.31, 95% CI: 0.68-2.52, p=0.19). (Figure 4) In the HR+/HER2- subtype, IMPC and IDC patients received similar treatments, including surgery (p=0.27), chemotherapy (p=0.99), and radiotherapy (p=0.28) (Mann-Whitney U-test). Univariate and multivariate Cox regression models were performed in the HR+/HER2- subset, and IMPC was an independent prognostic factor for OS (Table 4).

Table 4: Univariate and multivariate Cox proportional hazard models of overall survival (OS) and breast cancer-specific survival (BCSS) rates in the HR+/HER2- subset in the propensity score matched analysis.

	Univariate				**Multivariate**			
	BCSS		OS		BCSS		OS	
	HR(95% CI)	p	HR(95% CI)	p	HR(95% CI)	p	HR(95% CI)	p
Pathological type IMPC vs. IDC	0.68(0.35-1.29)	0.24	0.63(0.41-0.97)	0.04	0.59(0.31-1.12)	0.1	0.58(0.38-0.90)	0.01
Age >50 vs. ≤50	1.15(0.58-2.30)	0.69	2.72(1.46-5.05)	<0.01	1.90(0.90-4.01)	0.09	2.83(1.47-5.43)	<0.01
Stage I & II vs. III	6.43(3.68-11.21)	<0.01	2.53(1.72-3.71)	<0.01	5.42(2.82-10.45)	<0.01	3.47(2.20-5.48)	<0.01
Grade I & II vs. III	2.86(1.65-4.96)	<0.01	1.60(1.10-2.32)	0.01	2.54(1.43-4.49)	<0.01	1.74(1.19-2.55)	0.01
Surgery Mast vs. BCS	4.59(2.08-10.11)	<0.01	3.99(2.17-7.36)	<0.01	2.91(1.26-6.74)	0.01	2.32(1.24-4.37)	0.01
Chemotherapy Yes vs. No	2.00(1.14-3.50)	0.02	0.73(0.50-1.06)	0.1	1.24(0.64-2.40)	0.53	0.62(0.40-0.97)	0.04
Radiation therapy Yes vs. No	0.34(0.20-0.59)	<0.01	0.33(0.23-0.47)	<0.01	0.34(0.18-0.64)	<0.01	0.32(0.21-0.49)	<0.01

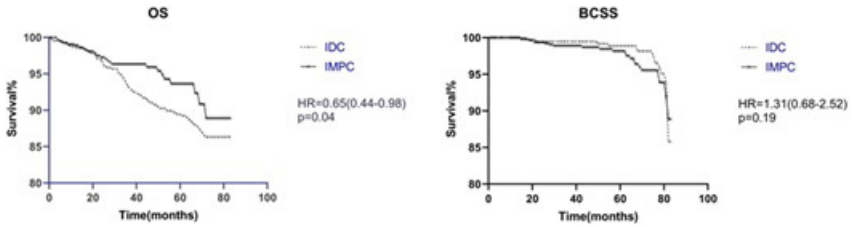

Figure 4: Kaplan-Meier survival curves of the OS and BCSS rates of HR+/HER2- in the PSM cohort.

5. Discussion

Our data were collected from the latest SEER database (November 2019 submission). In this large, population-based cohort, we included more patients than a previous study and incorporated records of HER2 status entered after 2010. Over 49% of patients with IMPC had axillary lymph node involvement, while only 31% of IDC patients had regional metastasis. We observed that IMPC had a better survival than IDC in OS and BCSS in whole cohort, but not significant in PSM cohort, even IMPC had more axillary lymph node metastasis. Furthermore, IMPC metastasized more than IDC at any T stage ($p<0.05$). In the whole cohort, IMPC was associated with a better outcome than IDC, but similar after PSM; however, IMPC patients had better survival outcomes at 4 and 5 years after diagnosis ($p<0.05$). Additional univariate and multivariate Cox regression models revealed that IMPC was not an independent factor for prognosis ($p>0.05$). Stratification analysis indicated a better OS outcome of HR+/HER2- subtype IMPC (HR=0.65, p=0.04). In addition, a comparison of the distant metastasis rate was performed, and we found IMPC had less M1 patients than IDC after PSM (p=0.01) but similar in whole cohort (p=0.22). In stratified analysis, only HR+/HER2- subtype IMPC metastasized less than IDC in distant location (Supplement Table 1). IMPC patients exhibited more lymph node metastasis than IDC patients but similar survival outcomes to IDC patients, which was similar to the previous studies [7,8,11]. However, IMPC patients had a better survival tendency, especially at 4 and 5 years after diagnosis. The prognosis of IMPC remains controversial. Chen and Fan et al. (2008) reported that IMPC is a more aggressive tumor with a poorer prognosis [14]. Ga Young Yoon et al. (2019) discovered worse recurrence-free survival (RFS) rates for IMPC than IDC [15]. However, Chen and Paulino et al. (2014) discovered that IMPC had better DSS and OS rates than IDC [16]. Chen and Wu et al. (2017) found that IMPC and IDC patients had comparable OS and BCSS rates before and after propensity score matching [17]. In addition, Hao et al. (2018) found no differences in OS and DFS rates between IMPC and IDC patients [18]. Some of the above studies applied propensity score matching to the whole cohort; however, few achieved a good balance of the basic characteristics, which might have affected the outcome of the comparison. Our study included 173,396 IDC and 921 IMPC patients and achieved perfect matches for age, AJCC stage, grade, and HR HER2 status after PSM. Although no differences were observed in treatment ($p>0.05$), IMPC patients tended to have better outcomes. We persumed that advanced therapy might be applied causing a better outcome. In the PSM cohort, IMPC patients received higher rates of radiation therapy and mastectomy surgery, which could influence the long-term survival rate. Unlike the findings reported in other studies, we unexpectedly observed that HR+/HER2- IMPC patients had a better long-term survival rates than IDC patients. A previous study indicated that the prevalence of the HR+ type is high in IMPC [19] and that the TNBC subtype is associated with worse prognosis[20]. In our research, 91.5% of IMPC patients were HR+/HER2- type which had the best prognosis among all breast cancer subtypes. Combined with the finding that the HR+/HER2- type was associated with favorable OS rates in the PSM cohort, we could assume that IMPC had a better prognosis due to a higher proportion of the HR+/HER2- subtype. The IMPC distant metastasis rate was similar to that of IDC in whole cohort, but less in PSM cohort. Deman F et al. found a low rate of distant recurrences of stage I-III IMPCs treated with primary surgery, despite a high proportion of grade 3 tumors and lymph node involvement [21], but the study only included 105 IMPC patients. Tang et al. found that IMPC had a higher rate of distant metastasis [22], but this study included more triple-negative subtypes of IMPC (IMPC:IDC 21.8% vs 1.4%, $p<0.01$), while TNBC metastasized more than other subtypes. Kaya C et al. discovered that between two groups divided by IMPC component ratio (≤75% and >75%), no differences in distant metastasis were found [23]. We propose that despite its aggressive lymph invasion ability, IMPC lacked traits for distant metastasis, and the mechanism within still needs to be studied. There were some flaws within our study. We collected data from over 921 IMPC patients from the SEER database, but a series of clinical characteristics were absent, such as chemotherapy regimens, hormone therapy, target treatment, menopausal status, etc. Therefore, selection bias is inevitable.

Supplement Table 1: Comparison of distant metastasis rate

	Whole cohort				PSM cohort			
	All	M0	M1	p	All	M0	M1	p
Overall				0.22				0.01
IDC	180,955	173,643(95.96%)	7,312(4.041		953	900(94.44%)	53(5.56%)	
IMPC	953	922(96.75%)	31(3.25%)		953	922(96.75%)	31(3.25%)	
HR+/HER2-				0.53				0.04
IDC	125,952	122,000 (70.26%)	3,952 (54.05%)		699	665 (73.89%)	34 (64.15%)	
IMPC	699	680 (73.75%)	19 (61.29%)		699	680 (73.75%)	19 (61.29%)	
HR+/HER2+				0.22				0.05
IDC	21,746	20,349 (11.72%)	1,397 (19.11%)		171	155 (17.22%)	16 (30.19%)	
IMPC	171	164 (17.79%)	7 (22.58%)		171	164 (17.79%)	7 (22.58%)	
HR-/HER2+				0.41				>0.99
IDC	9,666	8,886 (5.12%)	780 (10.67%)		43	41 (4.56%)	2 (3.77%)	
IMPC	43	41 (4.45%)	2 (6.45%)		43	41 (4.45%)	2 (6.45%)	
HR-/HER2-				0.47				0.31
IDC	23,591	22,408 (12.90%)	1,183 (16.18%)		40	39 (4.33%)	1 (1.89%)	
IMPC	40	37 (4.01%)	3 (9.68%)		40	37 (4.01%)	3 (9.68%)	

6. Conclusion

In summary, IMPC metastasized to more axillary lymph nodes than IDC but the distant metastasis rate was similar. Despite aggressive regional invasion, IMPC had a similar overall survival and breast cancer specific survival outcome to IDC. However, HR+/HER2- IMPC had a better overall survival rate than IDC.

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