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A comparative clinicopathological and survival analysis of synchronous bilateral breast cancers

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Summary. Objective. The present study aimed to explore the clinicopathological characteristics, potential heterogeneity and prognostic factors in synchronous bilateral breast cancer (SBBC).

Methods. We performed a retrospective review and paired comparison of the clinicopathological characteristics of 114 patients with SBBC in the Peking Union Medical College Hospital from January 2008 to September 2019. The prognostic significance of triple negativity status and coexistence ductal carcinoma in situ (DCIS) with bilateral invasive ductal carcinomas of no special type (IDC-NST) was analyzed in SBBC.

Results. Most bilateral lesions on both sides were of IDC-NST, grade 2, luminal subtype, and stage I. Although most lesions were concordant between the left and right side, discordances were observed in histological type (25 cases, 21.9%), histological grade (31 cases, 27.2%), pTNM (61 cases, 53.5%), molecular subtypes (20 cases, 17.5%), and immunohistochemical staining of ER (18 cases, 15.8%), PR (26 cases, 22.8%), and HER2 (12 cases, 10.5%). Moreover, there was no significant difference in disease-free survival (DFS) and overall survival (OS) between IDC-NST with coexisting DCIS on both sides and IDC-NST with coexisting DCIS on one side or pure IDC-NST. SBBC with triple negativity on both sides exhibited a significantly shorter DFS and OS when compared with triple negativity on one side or non-triple negativity on both sides ($p<0.001$), and remained an independent prognostic factor by multivariate analysis.

Conclusions. A considerable proportion of discordance in clinicopathological characteristics is observed in SBBC, supporting the necessity of comprehensive pathological examination including immunohistochemical testing on both sides in clinical practice. Moreover, SBBC with triple negativity on both sides is a prognostic for poor survival.

Key words: Bilateral breast cancer, Synchronous, Ductal carcinoma in situ (DCIS), Triple-negative breast cancer (TNBC), Prognosis

Introduction

Breast cancer is the most common malignancy and the leading cause of cancer-related mortality in women (Bray et al., 2018). Patients with single-sided breast cancer have a high risk of developing contralateral breast cancer as their life expectancy has increased with improvements in breast cancer screening and treatment methods. Recently, a study demonstrated the incidence of synchronous bilateral breast cancer (SBBC) newly diagnosed has increased (Sakai et al., 2019). Moreover, studies with large sample sizes suggested an inferior prognosis of SBBC as compared with unilateral breast cancer (Hartman et al., 2007; Jobsen et al., 2015; Pan et al., 2019).

Nowadays, the selection of endocrine and targeted therapies in breast cancer is based on the hormonal status and human epidermal receptor 2 (HER2) expression. For patients with SBBC, it is vital to evaluate the lesions on both sides. However, few studies

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Abbreviations. BBC, Bilateral breast cancer; SBBC, Synchronous bilateral breast cancer; MBBC, Metachronous bilateral breast cancer; IDC-NST, Invasive ductal carcinomas of no special type; ILC, Invasive lobular carcinoma; NEC, Neuroendocrine carcinoma; DCIS, Ductal carcinoma in situ; HER2, Human epidermal receptor 2; ER, Oestrogen receptor; PR, Progesterone receptor; TNBC, Triple-negative breast cancer; UTNBC, Unilateral triple-negative breast cancer; IHC, Immunohistochemistry; pTNM, Pathological tumour-node-metastasis; DFS, Disease-free survival; OS, Overall survival

have investigated the clinicopathological concordance of bilateral breast cancer (BBC) lesions (Huo et al., 2011; Huang et al., 2020; Huber et al., 2020; Kim et al., 2020), and some researchers concluded that the occurrence of two-side lesions in SBBC may develop independently (Song et al., 2015; Fountzilas et al., 2016). Therefore, it is necessary to further investigate the concordance between SBBC cases.

Invasive ductal carcinomas of no special type (IDC-NST) are the most prevalent histological type of all breast cancers, and often coexist with ductal carcinoma in situ (DCIS) (IDC-NST+DCIS). Some previous studies have reported that patients with IDC-NST + DCIS exhibit significantly longer survival than those with pure IDC-NST in unilateral breast cancer (Carabias-Meseguer et al., 2013; Dieterich et al., 2014; Goh et al., 2019; Kole et al., 2019). However, relevant research is lacking in SBBC. Triple-negative breast cancer (TNBC), which is defined as negative oestrogen receptor (ER) and progesterone receptor (PR) expression and HER2 non-overexpression, is a special subtype with high aggressive clinical behavior and poor prognosis (Foulkes et al., 2010). Regretfully, the effect of TNBC on patient survival in SBBC has been poorly illustrated.

This study reviewed the clinicopathological characteristics and survival of SBBC. We analyzed the concordance between left- and right-sided lesions in SBBC, explored the prognostic significance of coexistence DCIS with bilateral IDC-NST and different triple negativity status in SBBC.

Materials and methods

Patient enrollment and clinical data collection

The study was conducted in patients with breast cancer diagnosed and treated at the Peking Union Medical College Hospital between January 2008 and September 2019. According to the interval between two onsets, BBC can be classified into synchronous bilateral breast cancer (SBBC, interval ≤6 months) and metachronous bilateral breast cancer (MBBC, interval >6 months) (Newman et al., 2001; Baretta et al., 2015; Qiu et al., 2019; Pak et al., 2021). Patients with both left and right invasive breast cancer with an interval of no more than 6 months between the two onsets were included in the study, with no evidence of distant metastasis in the study. Patients without invasive lesions on both sides were excluded. Simultaneously, another cohort comprising patients diagnosed with unilateral triple-negative breast cancer (UTNBC) by immunohistochemistry (IHC) was recruited. A total of 114 patients with SBBC and 306 patients with UTNBC were included in our study. The present study was approved by the institutional review board with written informed consent from each patient.

Clinicopathological data collection

Clinical data such as age, sex, family history, date of diagnosis, pathological characteristics, recurrence, and survival were gathered from patient medical records and pathology information system. Patients with first- or second-degree relatives with breast cancer were considered to have a positive family history of breast cancer.

Pathological data, such as histological type, histological grade, molecular subtypes, and pathological tumour-node-metastasis staging (pTNM), were obtained by two independent pathologists, and a consensus was reached with the use of a third pathologist, in case of disagreement. Tumour stage was determined based on the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system for breast cancer (Giuliano et al., 2017). The histological type was classified according to the fifth edition of the World Health Organization classification of breast cancer (2019) (WHO Classification of Tumours Editorial Board, 2019). The histological grading was based on the Elston-Ellis system (Elston and Ellis, 1991). The molecular subtyping was based on the 2013 St. Gallen consensus (Untch et al., 2013).

IHC detection was performed on 4 μm FFPE slides for ER (H15308; Roche; Switzerland), PR (H19496; Roche; Switzerland), HER2 (H22187; Roche; Switzerland) and Ki-67 (ZM-0166; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.; China) expression. Operating steps were followed the manufacturer's instructions. For cases with HER2(2+), the PathVysion HER2 DNA Probe Kit (Abbott, USA) was used for fluorescence in situ hybridization detection. ER and PR positivity were defined as the proportion of tumour cells with positive staining ≥1%. The HER2 status was determined based on the ASCO/CAP guidelines for HER2 (2018) (Wolff et al., 2018). Patients with HER2 (3+) assessed through IHC or her2/neu amplification using fluorescence in situ hybridisation were regarded as HER2 positive. Ki-67 index was counted positive nuclei among hotspots.

Follow-ups were accomplished through telephone and medical record reviews. Disease-free survival (DFS) was defined as the time from the date of diagnosis of the second tumour until the date of local or distant recurrence or the last follow-up. Overall survival (OS) was measured from the date of diagnosis of the second tumour to the date of death from any cause or the last follow-up. For the purpose of survival analysis in SBBC, the worst tumour characteristics were used. The worse tumour was defined by the lesion of the largest diameter, and if similar size, then by axillary lymph node metastases.

Statistical analysis

All data were analysed using SPSS software (version 26.0; IBM, California, USA). Kaplan-Meier method was used to plot survival curves, and the log-rank test was used to calculate statistical significance, where a P value of <0.05 was considered statistically significant.

Multivariate analysis was performed using Cox proportional hazards regression analysis.

Results

Clinicopathological characteristics of SBBC

Of the 11131 screened patients with breast cancer, 267 (2.4%) were diagnosed with BBC. 114 (1.0%) patients with SBBC were included in this study. The clinicopathological characteristics of 114 patients with SBBC are summarized in Table 1. The median age of patients with SBBC was 54 years-old (range 29-88), with only 1 (0.9%) male patient. A family history of breast cancer was observed in 12.3% of the patients. The lesions on both sides were predominantly invasive ductal carcinomas of no special type (IDC-NST), grade 2, Luminal subtype, and pTNM stage I.

Table 1. Summary of clinicopathological characteristics of synchronous bilateral breast cancer.

Characteristic	SBBC (%)	
Age (median, range)	54.0(29-88)	
Sex		
female	113(99.1)	
male	1(0.9)	
Family History		
Breast cancer	14(12.3)	
None	100(87.7)	
	Left (%)	Right (%)
Histological type		
IDC-NST	96(84.2)	95(83.3)
ILC	4(3.5)	8(7.0)
Others	14(12.3)	11(9.6)
Grade		
1	11(9.6)	16(14.0)
2	72(63.2)	67(58.8)
3	31(28.1)	31(27.2)
Molecular subtypes		
Luminal A	36(31.6)	40(35.1)
Luminal B	52(45.6)	53(46.5)
HER2 positive	7(6.1)	5(4.4)
Triple-negative	19(16.7)	16(14.0)
pTNM stage		
I	56(49.1)	58(50.9)
II	32(28.1)	30(26.3)
III	26(22.8)	26(22.8)
Tumour size		
T1	78(68.4)	82(71.9)
T2	31(27.2)	29(25.4)
T3	5(4.4)	3(2.6)
Lymph node		
N0	68(59.6)	69(60.5)
N1	22(19.3)	20(17.5)
N2	14(12.3)	12(10.5)
N3	10(8.8)	13(11.4)

SBBC, synchronous bilateral breast cancer; IDC-NST, invasive ductal carcinomas of no special type; ILC, invasive lobular carcinoma; pTNM, pathological tumour-node-metastasis.

Paired comparison of clinicopathological characteristics between left- and right-sided lesions in SBBC

A paired comparison of clinicopathological characteristics between the left- and right-sided SBBC lesions is presented in Table 2. The histological types were divided into IDC-NST, invasive lobular carcinoma (ILC), and others. A total of 89 (78.1%) concordant cases were observed in terms of histological types, of which two-sided IDC-NST (72.8%) played a dominant

Table 2. Paired comparison of clinicopathological characteristics between left- and right-sided lesions in SBBC.

Characteristics	No. of patients (%)	Concordance (%)
Histological type		89(78.1)
IDC-NST/IDC-NST	83(72.8)	
ILC/ILC	2(1.8)	
Other/Others †	4(3.5)	
IDC-NST/ILC	8(7.0)	
IDC-NST/Others	17(14.9)	
ILC/Others	0(0.0)	
Histological grade		83(72.8)
1/1	5(4.4)	
2/2	57(50.0)	
3/3	21(18.4)	
1/2	11(9.6)	
1/3	6(5.3)	
2/3	14(12.3)	
pTNM stage		53(46.5)
I/I	33(28.9)	
II/II	8(7.0)	
III/III	12(10.5)	
I/II	33(28.9)	
I/III	15(13.2)	
II/III	13(11.4)	
Molecular types		94(82.4)
Luminal/ Luminal	81(71.0)	
HER2 positive/HER2 positive	1(0.9)	
Triple-negative/Triple-negative	12(10.5)	
Luminal/HER2 positive	9(7.9)	
Luminal/Triple-negative	10(8.8)	
HER2 positive/Triple-negative	1(0.9)	
ER		96(84.2)
+/+	80(70.2)	
-/-	16(14.0)	
+/-	18(15.8)	
PR		88(77.2)
+/+	68(59.6)	
-/-	20(17.5)	
+/-	26(22.8)	
HER2		102(89.5)
+/+	3(2.6)	
-/-	99(86.8)	
+/-	12(10.5)	

SBBC, synchronous bilateral breast cancer; IDC-NST, invasive ductal carcinomas of no special type; ILC, invasive lobular carcinoma; ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal receptor; pTNM, pathological tumour-node metastasis.
†Other histological subtype comprised mucinous/mucinous, mucinous/mucinous, mixed (IDC-NST + ILC) /mixed (IDC-NST + ILC), neuroendocrine/ neuroendocrine.

role. Other histologically concordant cases included 2 (1.8%) cases of mucinous carcinoma, 1 (0.9%) case of neuroendocrine carcinoma (NEC), and 1 (0.9%) case of the mixed histological type (IDC-NST+ILC). The concordance rates of ER, PR, and HER2 were 84.2%, 77.2%, and 89.5%, respectively. ER and PR were mostly concordantly positive, whereas HER2 was concordantly negative. Most cases with a concordant pTNM stage were at stage I.

A discordance in histological type, histological grade, pathological stage, ER, PR, and HER2 status was observed in 25 (21.9%), 31 (27.2%), 61 (53.5%), 18 (15.8%), 26 (22.8%), and 12 (10.5%) patients, respectively. The representative staining images in SBBC cases with discordant histology and IHC results are given in Figs. 1, 2. All of the 25 patients with discordant histological types had IDC-NST on one side. Contralateral lesions were mainly micropapillary carcinomas (9/25) or lobular carcinomas (8/25). Another 2 (2/25) patients had mucinous carcinoma on the contralateral side.

Comparison of clinicopathological characteristics and prognosis between IDC-NST with and without coexisting DCIS in SBBC

The bilateral IDC-NST cases were divided into three subtypes, pure IDC-NST on both sides (IDC-NST/IDC-NST), bilateral IDC-NST with coexisting DCIS on one side (IDC-NST/IDC-NST+DCIS), and bilateral IDC-NST with coexisting DCIS on both sides (IDC-NST+DCIS/IDC-NST+DCIS). We analyzed the

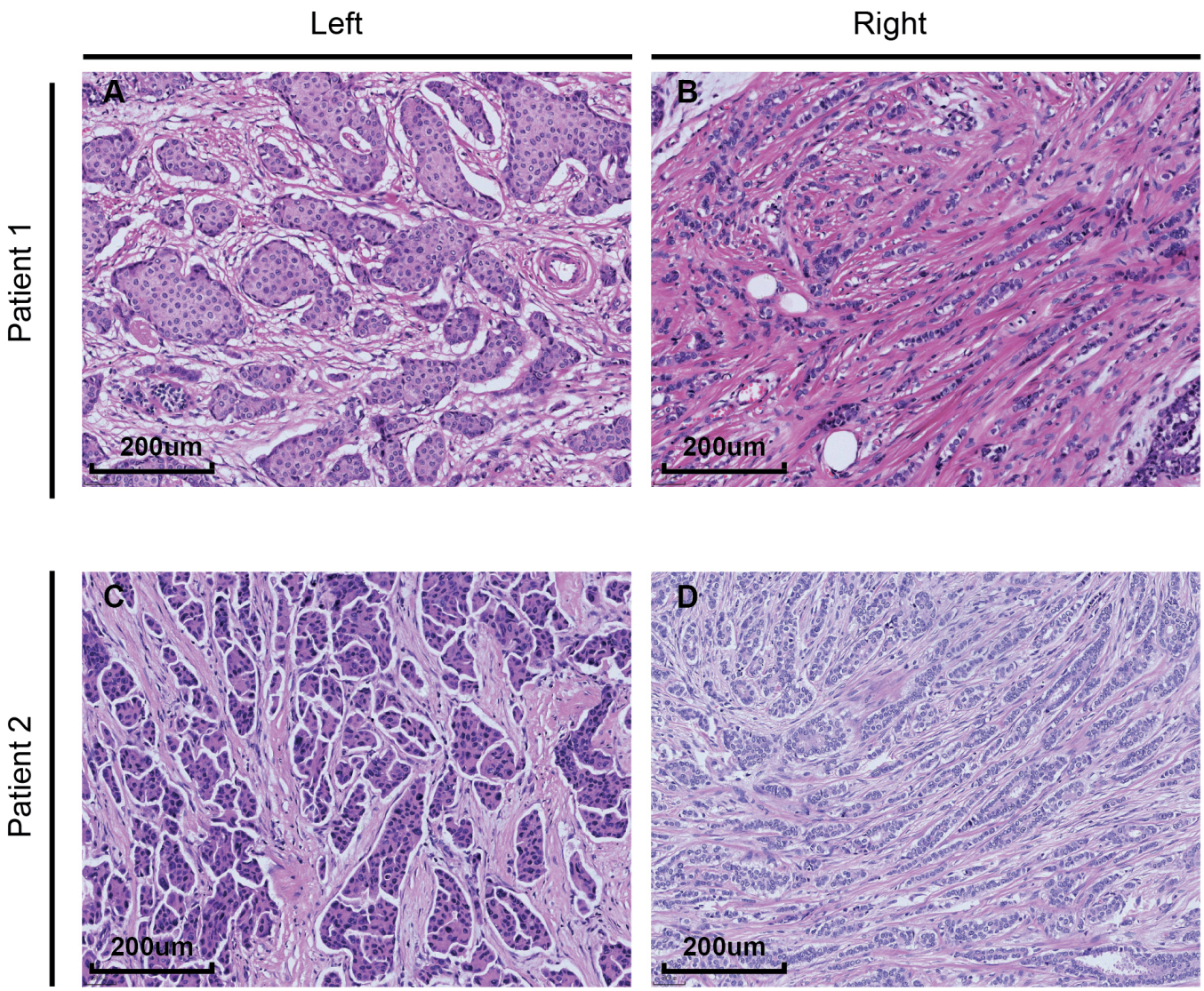

Fig. 1. A-D. Representative H&E image of the left- and right-sided lesions in two SBBC cases with discordant histology. Patient 1: IDC-NST **(A)**; Invasive lobular carcinoma **(B)**. Patient 2: Invasive micropapillary carcinoma **(C)**; IDC-NST **(D)**. x 200.

correlation of the clinicocharacteristics in three subtypes and found that patients with IDC-NST/IDC-NST exhibited a significantly higher histological grade compared with the other two subtypes ($p<0.05$), whereas no significant differences in age, family history, pTNM and molecular types were observed (Table 3). Moreover, patients bearing IDC-NST/IDC-NST+DCIS and IDC-NST+DCIS/IDC-NST+DCIS exhibited a slightly better prognosis than those with IDC-NST/IDC-NST. However, no statistically significant difference of DFS and OS was observed among the three subtypes (Fig. 3).

Comparison of prognosis between SBBC subgroups with different triple negativity status and UTNBC

To further explore the prognostic significance of triple negativity status in SBBC, we classified the SBBC cases into three subtypes: SBBC with triple negativity on both sides (TNBC/TNB), SBBC with triple negativity on one side (TNBC/non-TNBC), SBBC with non-triple

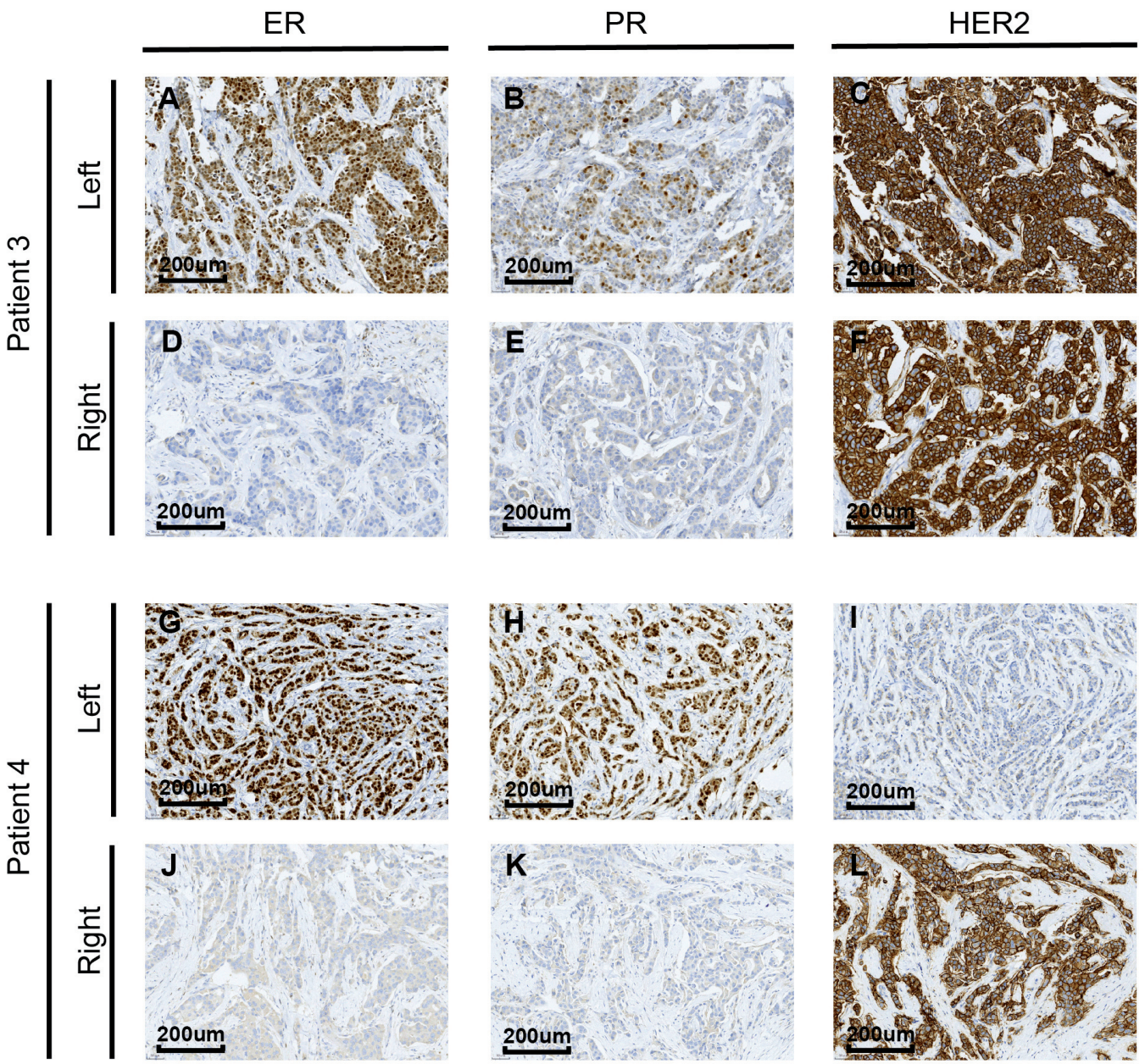

Fig. 2. Representative immunohistochemistry (IHC) staining images in SBBC cases with discordant IHC results. ER (left column), PR (middle column), and HER2 (right column) stainin for the left- and right-sided lesions in patient 3 **(A-F)** and patient 4 **(G-L)**. x 200.

negativity on both sides (non-TNBC/non-TNBC). An additional unilateral-TNBC (UTNBC) cohort with 306 randomly enrolled cases was included as a control cohort. Through comparing clinicopathological characteristics among the four groups, we observed that patients with bilateral TNBC had more advanced stages and higher grades than others (Table 4). Next, we investigated the prognostic significance of triple negativity status. Patients with TNBC/TNBC exhibited a significantly shorter DFS and OS when compared with the other three groups ($p<0.001$) (Table 5, 6, Figure 4). Moreover, pTNM stage was also a significant prognostic factor for poor DFS and OS. Further multivariate analysis revealed that bilateral TNBC was an independent adverse prognostic factor for DFS and OS ($p<0.001$) (Tables 5, 6).

Discussion

In the present study, we investigated the clinicopathological characteristics and prognosis of SBBC, based on a relatively large-scale single-centre Chinese cohort.

The median age of diagnoses of this cohort was 54 years, which is consistent with existing Chinese SBBC studies (Liang et al., 2013; Chen et al., 2014, 2015). Only 1 (0.9%) patient in our cohort was male, comparable to the reported less than 1% in all breast cancers and 0.5%-2.5% quota in SBBCs, respectively (Korde et al., 2010; Nwashilli and Ugiagbe, 2015; Lehrberg and Bensenhaver, 2020). Fourteen (12.3%) patients had a family history of breast cancer, slightly higher than that in the literature, which was less than 10% in the Chinese population (Shi et al., 2012; Chen et al., 2015; Huang et al., 2020). However, it was lower than the reported percentile in foreign populations (Beckmann et al., 2011; Ozturk et al., 2018). The difference might be explained by the selection of the study population; yet other confounding factors, such as an incomplete collection of family histories, cannot be excluded.

Although most SBBC cases exhibited concordant

Table 3. Comparison of clinicopathological characteristics between bilateral IDC-NST with and without coexisting DCIS.

Characteristic	IDC-NST/ IDC-NST (n=43)	IDC-NST/ IDC-NST+DCIS (n=29)	IDC-NST+DCIS/ IDC-NST+ DCIS (n=11)	p-value
Age (mean ± SD)	54.2±14.4	55.9±12.9	46.4±11.5	0.110
Family History				0.524
Yes	7(16.3)	2(6.9)	1(9.1)	
No	36(83.7)	27(93.1)	10(90.9)	
Grade				0.012
1&2	22(51.2)	24(82.8)	9(81.8)	
3	21(48.8)	5(17.2)	2(18.2)	
pTNM stage				0.372
I	11(25.6)	11(37.9)	4(36.4)	
II	12(27.9)	11(37.9)	4(36.4)	
III	20(46.5)	7(24.1)	3(27.3)	
Tumour size				0.368
T1	19(44.2)	18(62.1)	7(63.6)	
T2	21(48.8)	8(27.6)	4(36.4)	
T3	3(7.0)	3(10.3)	0(0.0)	
Lymph node				0.953
Positive	25(58.1)	16(55.2)	6(54.5)	
Negative	18(41.9)	13(44.8)	5(45.5)	
Molecular types				0.358
TNBC	10(23.3	3(10.3)	1(9.1)	
Non-TNBC	33(76.7)	26(89.7)	10(90.9)	

IDC-NST, invasive ductal carcinomas of no special type; DCIS, ductal carcinoma in situ; IDC-NST/IDC-NST, pure IDC-NST on both sides; IDC-NST/IDC-NST+DCIS, bilateral IDC-NST with coexisting DCIS on one side; IDC-NST+DCIS/IDC-NST+DCIS, bilateral IDC-NST coexisting DCIS on both sides; TNBC, triple-negative breast cancer; pTNM, pathological tumour-node-metastasis.

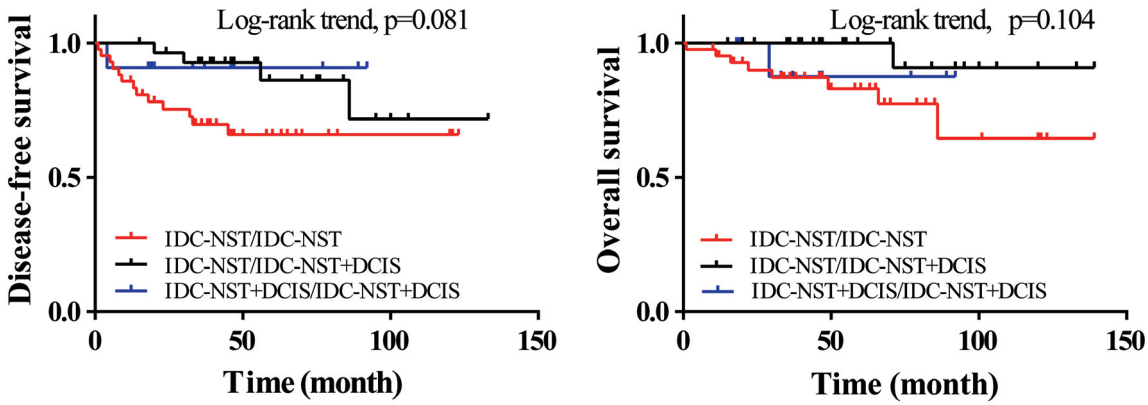

Fig. 3. Kaplan-Meier survival curves for DFS **(A)** and OS **(B)** of bilateral IDC-NST patients with or without coexisting DCIS. IDC-NST, invasive ductal carcinomas of no special type; DCIS, ductal carcinoma in situ; IDC-NST/IDC-NST, pure IDC-NST on both sides; IDC-NST/IDC-NST+DCIS, bilateral IDC-NST with coexisting DCIS on one side; IDC-NST+DCIS/IDC-NST+DCIS, bilateral IDC-NST coexisting DCIS on both sides; DFS, disease-free survival; OS, overall survival.

Table 4. Clinicopathological characteristics of unilateral TNBC and SBBC patients with different triple negativity status.

Characteristic	UTNBC (n=306)	TNBC/non-TNBC (n=11)	TNBC/TNBC (n=12)	non-TNBC/non-TNBC (n=91)	p value
Age (mean ± SD)	49.2±11.4	58.5±15.6	43.0±10.1	55.8±13.5	0.000
Family History					0.121
Yes	16(5.2)	2(18.2)	1(8.3)	11(12.1)	
No	285(93.1)	9(81.8)	11(91.7)	80(87.9)	
Unknown	5(1.6)	0(0.0)	0(0.0)	0(0.0)	
Grade					<0.001
1&2	89(29.1)	8(72.7)	1(8.3)	70(76.9)	
3	217(70.9)	3(27.3)	11(91.7)	21(23.1)	
pTNM stage					0.046
I	104(34.0)	4(36.4)	2(16.7)	26(28.6)	
II	137(44.8)	5(45.5)	3(25.0)	34(37.4)	
III	65(21.2)	2(18.2)	7(58.3)	31(34.1)	
Tumour size					0.719
T1	149(48.7)	7(63.6)	5(41.7)	46(50.5)	
T2	141(46.1)	3(27.3)	6(50.5)	39(42.9)	
T3	16(5.2)	1(9.1)	1(8.3)	6(6.6)	
Lymph node					0.050
Positive	127(41.5)	4(36.4)	8(66.8)	50(54.9)	
Negative	179(58.5)	7(63.6)	4(33.3)	41(45.1)	

SBBC, synchronous bilateral breast cancer; UTNBC, unilateral triple-negative breast cancer; TNBC/TNBC, SBBC with triple negativity on both sides; TNBC/non-TNBC, SBBC with triple negativity on one side; non-TNBC/non-TNBC, SBBC with non-triple negativity on both sides; pTNM, pathological tumour-node-metastasis.

Table 5. Analysis for overall survival of patients with triple negativity status in SBBC and UBC.

	Univariate analysis		Multivariate analysis		
	HR	P	HR	[HR 95% CI]	P
Age					
≤40	1.0(reference)		-	-	-
>40	0.874	0.631	-	-	-
Family history					
No	1.0(reference)		-	-	-
Yes	0.389	0.189	-	-	-
Triple negativity status		<0.001			<0.001
TNBC/non-TNBC	1 (reference)		1 (reference)		
TNBC/TNBC	10.276	0.029	9.122	[1.095,76.027]	0.041
UTNBC	1.606	0.639	1.771	[0.243,12.880]	0.573
non-TNBC/non-TNBC	0.461	0.488	0.425	[0.047,3.822]	0.446
Grade					
1&2	1 (reference)		-	-	-
3	1.299	0.306	-	-	-
pTNM stage		<0.001			0.041
I	1.0(reference)		1.0(reference)		
II	1.452	0.279	1.518	[0.564,4.086]	0. 409
III	4.128	<0.001	3.492	[1.035,11.777]	0.044
Tumor size		0.001			0.114
T1	1 (reference)		1 (reference)		
T2	1.273	0.350	0.851	[0.445,1.628]	0.626
T3	4.104	<0.001	1.974	[0.827,4.711]	0.125
Lymph node					
negative	1 (reference)		1 (reference)		
positive	2.460	<0.001	1.162	[0.516,2.615]	0.717

SBBC, synchronous bilateral breast cancer; UBC, unilateral breast cancer; TNBC, triple-negative breast cancer; UTNBC, unilateral triple-negative breast cancer; TNBC/TNBC, SBBC with triple negativity on both sides; TNBC/non-TNBC, SBBC with triple negativity on one side; non-TNBC/non-TNBC, SBBC with non-triple negativity on both sides; pTNM, pathological tumour-node-metastasis; HR, hazardous ratio; CI, confidential interval.

clinicopathological characteristics between bilateral lesions, a proportion of these cases demonstrated discordant ER (18 cases, 15.8%), PR (26 cases, 22.8%), and HER 2 (12 cases, 10.5%) status. Studies on the discordance rate of HER2 status between bilateral lesions were relatively lacking. However, the previously reported discordance rates of the ER and PR status between bilateral lesions were 9.3-27% and 19-35.1%, respectively, which were similar to our findings (Baker et al., 2013; Baretta et al., 2015; Padmanabhan et al., 2015; Huang et al., 2020; Huber et al., 2020). Further, in a cohort study of the Chinese population, when using 12 months as the time interval, Huang et al. (2020) reported that the discordance rate of the ER status was 22.1%. In this study, we defined the interval as 6 months as did most previous studies (Newman et al., 2001; Baretta et al., 2015; Qiu et al., 2019; Pak et al., 2021). As such, the discordance rate of the clinicopathological characteristics might be associated with the time interval between the diagnoses of bilateral lesions (Huo et al., 2011). Additionally, the independent origins of bilateral lesions in SBBC based on somatic genomic profiles were reported in recent studies (Song et al., 2015; Fountzilas et al., 2016). The discordance of histological type, grade and molecular subtypes observed in our study potentially indicated the independent origins of

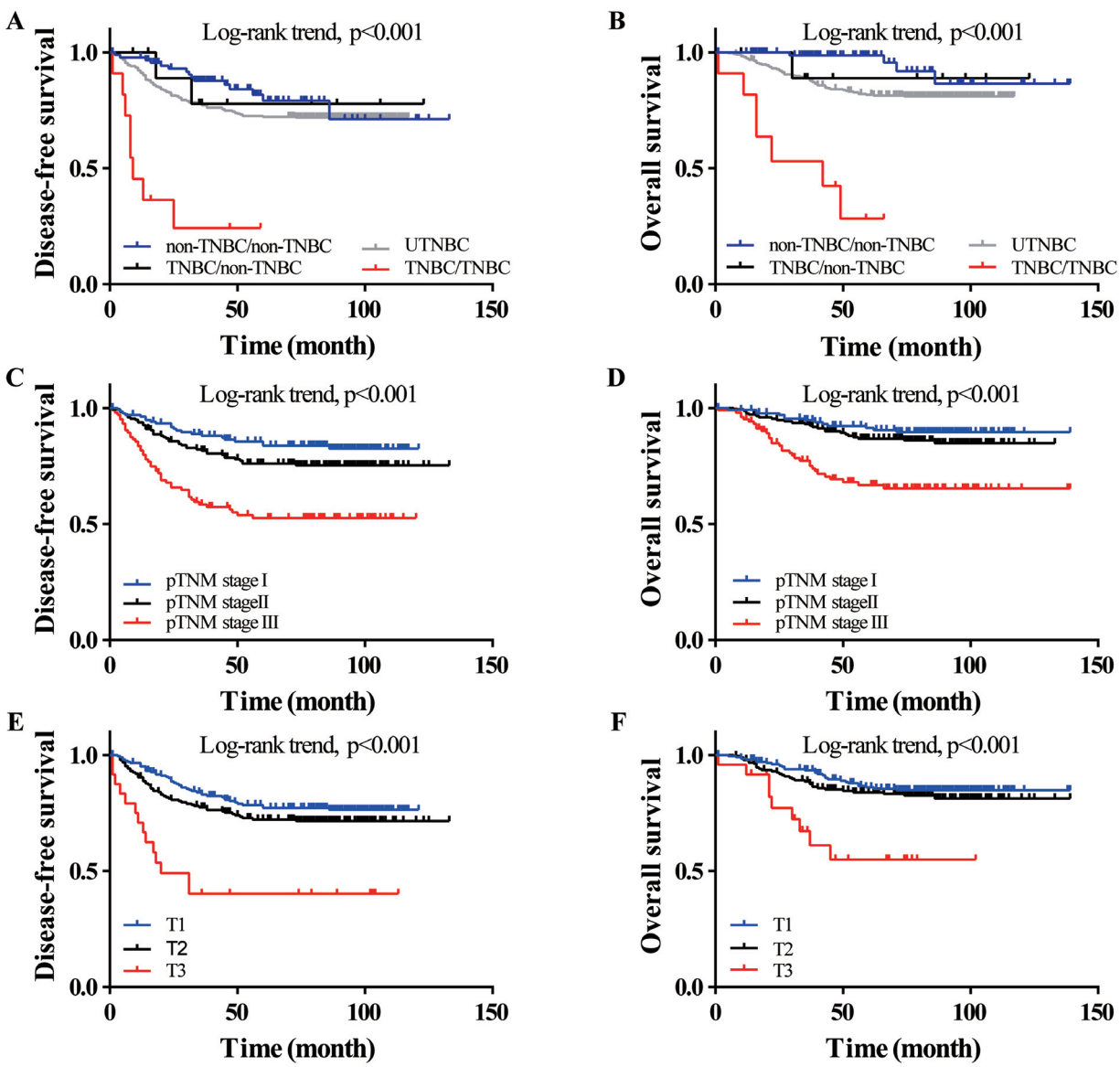

Fig. 4. Kaplan-Meier survival curves of DFS and OS. A-B, DFS **(A)** and OS **(B)** curves for patients with different triple negativity status; **C, D.** DFS **(C)** and OS **(D)** curves for patients according to pTNM stages; **E, F.** DFS **(E)** and OS **(F)** curves for patients according to tumour size.

bilateral breast tumours in a proportion of SBBCs. To avoid treatment options deviated by differences in IHC and molecular features, the necessity of comprehensive pathological examination for bilateral lesions of SBBC was further emphasised.

Furthermore, we found that the micropapillary component occurred in 7.9% of SBBC cases, and no bilateral micropapillary carcinoma was observed in SBBC patients. Micropapillary carcinoma, associated with early lymph node metastasis, is a rare subtype of breast cancer. Yang et al. (2016) reported that the prevalence of micropapillary carcinoma in invasive breast cancer was approximately 4.8%-6.2%. The present cohort exhibited a higher prevalence of micropapillary carcinoma than a previous study in a Polish cohort (Senkus et al., 2013) which reported 1 case (2%) in 61 SBBCs. The discrepancy might result from the bias introduced by the small sample size or ethnic differences. Based on current statistics, it would be difficult to conclude the relative risk of micropapillary histology in SBBC, and further study is warranted.

Coexisting DCIS and IDC-NST account for 21.3% to 76.9% of breast cancer (Carabias-Meseguer et al., 2013; Chen et al., 2019). It is widely accepted that unilateral IDC-NST patients with or without DCIS exhibit different clinicopathological features. Unilateral IDC-NST patients with coexisting DCIS were younger and typically of lower grade than those without coexisting DCIS (Chen et al., 2019; Goh et al., 2019; Lopez Gordo et al., 2019). Similarly, our data showed that DCIS coexistence on both sides was observed in about half of our bilateral IDC-NST cases, which were of significantly lower grade. Some previous studies have revealed the association between a favorable prognosis and coexisting DCIS in unilateral IDC-NST (Carabias-Meseguer et al., 2013; Dieterich et al., 2014; Goh et al., 2019; Kole et al., 2019), although some results did not reach statistical significance (Chagpar et al., 2009; Wong et al., 2010). In our study, no significant difference of survival was found between bilateral IDC-NST patients with or without coexisting DCIS, though there remained a trend towards worse OS in bilateral IDC-NST patients without coexisting DCIS. It may be a result of the limited sample size and relatively favorable overall survival of IDC-NST. Further exploration in a larger cohort would be needed.

The incidence of TNBC was approximately 4.0%-19.0% in SBBC in most studies (Padmanabhan et al., 2015; Mruthyunjayappa et al., 2019; Kim et al., 2020). In our cohort, TNBC occurred in 20.2% of cases. It has

Table 6. Analysis for disease-free survival of patients with triple negativity status in SBBC and UBC.

	Univariate analysis		Multivariate analysis		
	HR	P	HR	[HR 95% CI]	P
Age					
≤40	1.0(reference)		-	-	-
>40	0.781	0.252	-	-	-
Family history					
No	1.0(reference)		-	-	-
Yes	1.054	0.886	-	-	-
Triple negativity status		<0.001			<0.001
TNBC/non-TNBC	1 (reference)		1 (reference)		
TNBC/TNBC	8.342	0.007	8.361	[1.728,40.455]	0.008
UTNBC	1.334	0.687	1.445	[0.354,5.901]	0.608
non-TNBC/non-TNBC	0.855	0.835	0.748	[0.178,3.448]	0.748
Grade					
1&2	1 (reference)		-	-	-
3	1.111	0.591	-	-	-
pTNM stage		<0.001			0.003
I	1.0(reference)		1.0(reference)		
II	1.545	0.098	2.124	[0.990,4.557]	0.053
III	3.664	<0.001	4.717	[1.833,12.140]	0.001
Tumor size		<0.001			0.020
T1	1 (reference)		1 (reference)		
T2	1.320	0.173	0.779	[0.457,1.328]	0.358
T3	4.184	<0.001	1.930	[0.961,3.874]	0.064
Lymph node					
negative	1 (reference)		1 (reference)		
positive	1.905	0.001	0.791	[0.427,1.464]	0.456

SBBC, synchronous bilateral breast cancer; UBC, unilateral breast cancer; TNBC, triple-negative breast cancer; UTNBC, unilateral triple-negative breast cancer; TNBC/TNBC, SBBC with triple negativity on both sides; TNBC/non-TNBC, SBBC with triple negativity on one side; non-TNBC/non-TNBC, SBBC with non-triple negativity on both sides; pTNM, pathological tumour-node-metastasis; HR, hazardous ratio; CI, confidential interval.

been reported that 10.4%-13.5% of breast cancers were TNBC in Chinese patients (Li et al., 2013). Our findings indicated that TNBC was more frequent in SBBC than in unilateral breast cancer. The prognostic value of triple negativity status in SBBC patients had been rarely reported. Existing evidence has shown that patients with bilateral ER-positive tumours have the best prognoses, followed by those with ER discordant tumours, whereas the prognoses for patients with bilateral ER-negative tumours were the worst (Baretta et al., 2015). However, they did not further separate TNBC from ER-negative breast cancers in their analyses. We further analysed the impact on patient survival of triple negativity in SBBC. In the current study, the DFS and OS for patients with bilateral TNBC were significantly worse than the other groups, whereas no significant difference between patients of TNBC/non-TNBC, non-TNBC/non-TNBC and unilateral TNBC was noticed. In contrast to our finding, a recent study reported that bilaterally different molecular subtypes were related to poor survival of SBBC patients (Ding et al., 2021). A possible explanation for the discrepancy may be ascribed to the higher proportions of bilateral TNBC (10.5% vs. 3.6%) in our study. While we could not preclude the effect of small sample size, our findings have suggested that patients with unilateral TNBC, TNBC/non-TNBC, and non-TNBC/non-TNBC SBBC could have a more favorable prognosis compared to the bilateral TNBCs. Further characterization of such association using a larger cohort is therefore warranted. Also, the underlying mechanism needs to be further explored.

In conclusion, the bilateral lesions in SBBCs may show discordance in clinicopathological characteristics, emphasizing the need to conduct comprehensive pathological examination including IHC testing for both sides in the pathological routines. Moreover, triple negativity on both sides in SBBC constitutes a poor prognosticator for the disease, whereas SBBC with triple negativity on one side has a relatively favorable prognosis. In further studies, it would be interesting to determine the mechanisms that drive distinct genotypes and phenotypes of bilateral breast cancers with the same hereditary and environmental background.

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Availability of data and materials. The datasets used and analysed during the current study are available by emailing the corresponding author Zhiyong Liang on reasonable request.

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