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Association of molecular subtype concordance and survival outcome in synchronous and metachronous bilateral breast cancer

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ABSTRACT

Background: The aim of this study was to analyze the association of molecular subtype concordance and disease outcome in patients with synchronous bilateral breast cancer (SBBC) and metachronous breast cancer (MBBC).

Patients and methods: Patients diagnosed with SBBC or MBBC in the Surveillance, Epidemiology, and End Results (SEER) database or Comprehensive Breast Health Center (CBHC) Ruijin Hospital, Shanghai were retrospectively reviewed and included. Clinicopathologic features, molecular subtype status concordance, and prognosis were compared in patients with SBBC and MBBC. Other prognostic factors for breast cancer-specific survival (BCSS) and overall survival (OS) were also identified for bilateral breast cancer patients.

Results: Totally, 3395 and 115 patients were included from the SEER and Ruijin CBHC cohorts. Molecular subtype concordance rate was higher in the SBBC group compared to MBBC in both SEER cohort (75.8% vs 57.7%, $p < 0.001$) and Ruijin CBHC cohort (76.2% vs 45.2%, $p = 0.002$). Survival analyses indicated that SBBC was related to worse BCSS than MBBC ($p = 0.015$). Molecular subtype discordance was related to worse BCSS (hazard ratio (HR), 1.64, 95% confidential interval (CI), 1.18–2.27, $p = 0.003$) and OS (HR, 1.59, 95% CI, 1.24–2.04, $p < 0.001$) in the SBBC group, but not for the MBBC group ($p = 0.650$ for BCSS, $p = 0.669$ for OS).

Conclusions: Molecular subtype concordance rate was higher in the SBBC group than MBBC group. Patients with discordant molecular subtype was associated with worse disease outcome in the SBBC patients, but not in MBBC, which deserves further clinical evaluation.

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1. Introduction

Breast cancer is the most commonly diagnosed malignancy in women, which accounts for 30% of all female cancers [1]. The constantly increasing incidence of breast cancer, gradually improved diagnosis and treatment together with the longer life expectancy have contributed to an increase in the number of women at risk for bilateral breast cancer (BBC), which is reported to account for 1.4%–11.8% of all breast cancer [2–6]. Therefore, it is necessary to analyze biological features and identify prognostic factors for BBC to better guide clinicians to make therapeutic decisions.

Based on the interval time between the diagnosis of first and second tumor, BBC can be classified into metachronous bilateral breast cancer (MBBC) and synchronous bilateral breast cancer (SBBC) [7–9]. However, the concordance of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, and molecular subtype within tumor pairs has not been well described and compared between SBBC and MBBC yet. The prognostic value of biomarker discordance has been studied in neoadjuvant setting and metastatic breast cancer. For example, the positive-to-negative change in ER status after neoadjuvant chemotherapy was associated with poor prognosis [10]. Other studies reported that the discordant-ER status between primary and recurrent tumors related to worse survival outcomes [11,12]. Furthermore, in bilateral breast cancer setting, Baretta et al. found that discordance in the hormone-receptor status was an independent predictor of survival outcomes for bilateral breast

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cancer [13]. Molecular subtype has been proved to be a significant prognostic factor for early breast cancer and was routinely used to guide treatment decision [14,15]. Therefore, whether discordant molecular subtype within bilateral breast cancer has impact on the prognosis of SBBC and MBBC was well worth to be investigated.

The objective of this study is to describe the clinicopathologic features of SBBC and MBBC in both first and second tumor, to compare the concordance rates of clinicopathological factors and molecular subtype within tumor pairs, and to evaluate their prognostic significance on survival outcomes among patients with SBBC and MBBC.

2. Methods

2.1. Study population

This retrospective, population-based study consisted of two cohorts. One cohort derived data from Surveillance, Epidemiology, and End Results Database (SEER). Another cohort comprised selected patients operated at a single Asian institution from January 2009 to December 2019, namely Comprehensive Breast Health Center (CBHC) at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. Clinical characteristics and follow-up information of patients in the Ruijin CHBC cohort were retrieved from the Shanghai Jiaotong University Breast Cancer Database (SJTU-BCDB), which was a multicenter breast cancer specific database based on Chinese population. In this SJTU-BCDB, patients' demographic and clinical information were fully recorded, including adjuvant systemic therapy and recurrence data, which were not well recorded in the SEER database. Patients recorded in the SJTU-BCDB were followed by outpatient visit or call every 3 months for the first 2 years after surgery, every 6 months between the 3rd and 5th years, then annually every year until death.

Patients meeting the following criteria were eligible: 1) female; 2) diagnosed with bilateral breast cancer; 3) pathologically confirmed invasive ductal breast cancer; 4) received surgery. In SEER cohort, the invasive ductal breast cancer was identified based on the International Classification of Diseases for Oncology, Third Revision (ICD-O-3), codes (8500/3). Because the human epidermal growth factor receptor 2 (HER2) status was not routinely recorded before 2010 in SEER database, the SEER cohort was restricted to patients diagnosed from 2010 to 2016, while the Ruijin CBHC cohort included patients diagnosed from January 2009 to December 2019. Patients with metastasis at diagnosis, locally advanced cancer, diagnosed with third or more primaries cancer, or having locoregional or distant recurrence before the diagnosis of contralateral breast cancer were not included. Patients were also excluded if pathologists specifically had described the one side as likely being a metastasis from the contralateral breast.

2.2. Clinicopathological features and follow up

Demographic, clinicopathologic, treatment and follow-up information were extracted from the databases for individual patient. Patients were then divided into MBBC group and SBBC group according to the interval time between diagnosis of their first and second tumors. There was no consensus on the interval time criteria to separate SBBC from MBBC. Among different definitions of synchronicity used in previous studies, the 6-month interval criteria were relatively more commonly used [13,16–24]. Moreover, in our study, we used 3 months, 6 months or 12 months as the interval time to define MBBC and SBBC, respectively. We found there were significant BCSS differences between MBBC and SBBC when the 6-month or 12-month category was used, but not for 3-month category (Supplement figure1). Besides, compared to 12-month category, the 6-month category was more commonly used in the previous published studies. Therefore, we chose 6-month as the interval time to separate SBBC from MBBC in our current study. The bilateral breast cancer was classified as MBBC if the second tumor was diagnosed more than 6 months after the first tumor, while SBBC were defined as bilateral tumors diagnosed within 6 months.

Breast cancer-specific survival (BCSS) was calculated from the date of initial diagnosis to the date of death caused by breast cancer. Overall survival (OS) was measured as the time from initial diagnosis to the death of any cause.

2.3. Molecular subtype classification

The immunohistochemistry (IHC) testing was used to determine the status of hormone receptor (HR). ER and PR positivity were defined as no less than 1% stained nuclei according to the American Society of Clinical Oncology/college of American pathologists (ASCO/CAP) guideline recommendations [25]. HER2 status was considered as positive if there was gene amplification confirmed by fluorescence in situ hybridization (FISH) or 3+ score tested by IHC.

Molecular subtype classification was based on HR and HER2 status determined by IHC or FISH. Tumors were divided into four molecular subtypes: HR+/HER2-, HR+/HER2+, HR-/HER2+, and triple-negative breast cancer (TNBC).

2.4. Statistical analysis

Pearson Chi-square test, or Fisher's exact test if necessary, was used to compare the categorical variables between the SBBC and MBBC. Survival outcomes of different groups were estimated by Kaplan-Meier curves and compared by log-rank test. In multivariate analyses, cox proportional hazards models were conducted to evaluate the association between survival outcomes and potential prognostic factors based on hazard ratios (HRs) and 95% confidential interval (CI). For all statistical analyses, a p value of less than 0.05 was defined as statistically significant. All data analyses were performed using SPSS version 26.0 (SPSS, Chicago, Illinois, USA) and R version 3.6.2 (R Foundation for Statistical Computing).

3. Results

3.1. Patient and tumor characteristics

A total of 3395 patients with BBC were identified in the SEER cohort, with 2542 (74.9%) patients diagnosed with SBBC and 853(25.1%) patients diagnosed with MBBC (Fig. 1). The median age was 63.0 years, ranging from 22 to 96. The median interval time between two tumors was 0 months (range, 0–5 months) in SBBC group and 22.3 months (range, 6.0–70.9) in the MBBC group. In the Ruijin CHBC cohort, 115 patients with BBC were analyzed and the percentage of SBBC and MBBC was 73.0% and 27%, respectively. The median age was 58.0 years (range, 26–86). The median interval time between tumor pairs was 0.2 months (range, 0–4.4 months) in the SBBC group and 20.7 months (range, 6.7–44.1 months) in the MBBC group. Demographic and clinicopathologic features of both cohorts were summarized in Supplement Table1 and treatment information was listed in Supplement Table2.

As for receptor status, SBBC had a higher rate of ER-positive tumors (first tumor, 88.4% vs 80.8%; second tumor, 88.5% vs

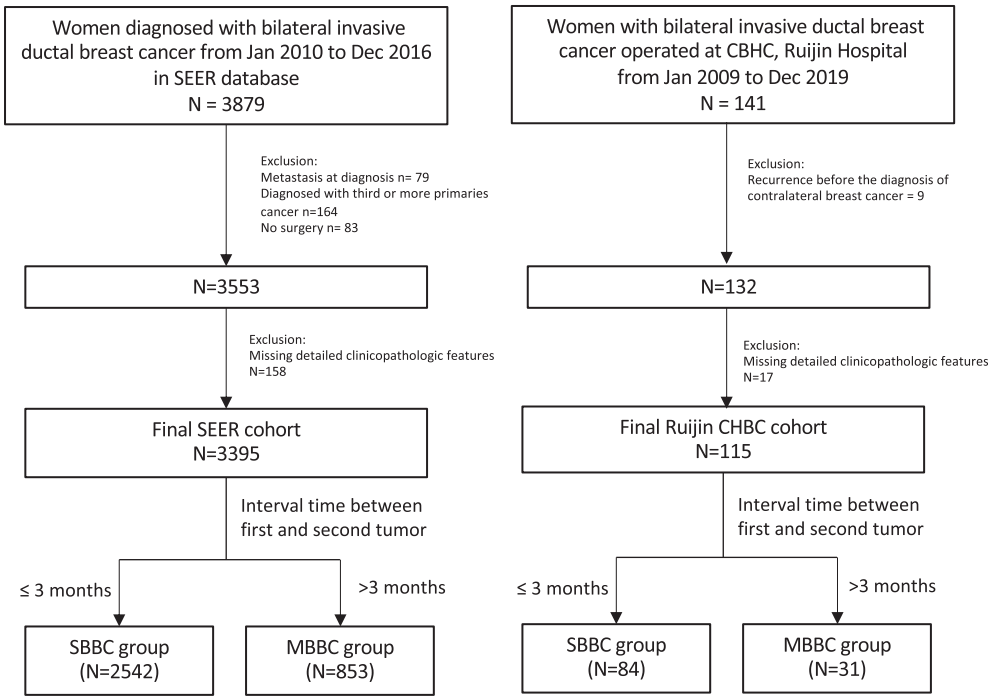

Fig. 1. Flow chart for selection of the study cohorts. Abbreviations: SEER, Surveillance, Epidemiology, and End Results; CBHC, Comprehensive Breast Health Center; SBBC, synchronous bilateral breast cancer, MBBC, metachronous bilateral breast cancer.

77.4%) and PR-positive tumors (first tumor, 79.7% vs 70.2%; second tumor, 79.9% vs 62.0%) than MBBC (all $p < 0.001$), which was also observed in the CBHC cohort. Regarding molecular subtype distribution, in the Ruijin CHBC cohort, HR-positive and HER2-negative tumors were more likely to be identified in the first (77.4% vs 54.8%) and second tumor (78.6% vs 48.4%) of SBBC compared to MBBC, while the percentage of TNBC was significantly higher in the first (16.1% vs 11.9%) and second (25.8% vs 9.5%) tumor of MBBC compared to SBBC (all $p < 0.05$), which were consistent with the results in the SEER cohort.

3.2. Concordance of clinicopathological factors between bilateral breast cancer

Concordance of clinicopathologic characteristics between the first tumor and second tumor were further analyzed and compared between SBBC and MBBC groups (Table 1).

In the SEER cohort, there was a higher percentage of ER-discordant tumors (28.7% vs 14.2%), PR-discordant tumors (41.5% vs 23.4%) and HER2-discordant tumors (23.0% vs 14.6%) in the MBBC group than the SBBC group (all $p < 0.001$). Similarly, in the CBHC cohort, SBBC was also significantly related to higher concordance in ER status (81.0% vs 54.8%, $p = 0.001$), PR status (78.6% vs 48.4%, $p = 0.001$) and HER2 status (86.9% vs 58.1%, $p = 0.002$) compared to MBBC.

Regarding molecular subtype status, SBBC was more likely to have concordant molecular subtype compared to MBBC in the SEER cohort (75.8% vs 57.7% $p < 0.001$) and in the CBHC cohort (76.2% vs 45.2%, $p = 0.002$). In the SBBC group, the percentage of patients with concordant HR+/HER2-tumors, HR+/HER2+ tumors, HR-/HER2+ tumors and TNBC were 70.3%, 1.8%, 0.4% and 3.3% in the SEER cohort, 67.9%, 1.2%, 3.6% and 3.6% in the CBHC cohort. Whereas in the MBBC group, concordant HR+/HER2-tumors, HR+/HER2+ tumors, HR-/HER2+ tumors and TNBC accounts for 52.1%, 1.2%, 0.4% and 4.1% in the SEER cohort, 29.0%, 0%, 3.2% and 12.9% in the CBHC cohort, respectively.

3.3. Survival outcomes of SBBC and MBBC

With a median follow-up of 46 (range, 0–83) months, a total of 218 BCSS events and 420 OS events were observed in the SEER cohort. After a median follow-up of 56 (range, 2–124) months, 6 deaths were observed in CBHC cohort, with 5 breast-cancer related deaths and 1 patient died of other cause. Due to the relatively low incidence of events, patients in the CBHC cohort were not included in the survival analyses.

In the SEER cohort, SBBC had significantly poorer BCSS than MBBC ($p = 0.015$, Fig. 2A) but no statistical difference was observed in OS between two groups ($p = 0.300$, Fig. 2B). Multivariate analyses, adjusted by age, race, tumor size, nodal status, and concordance of molecular subtype, showed that SBBC was independently associated with worse BCSS (HRs, 1.53; 95% CI, 1.10–2.11; $p = 0.010$) but not OS ($p = 0.842$) compared to MBBC.

Furthermore, subgroup analyses showed that among patients with concordant molecular subtype within tumor pairs, there were no statistically significant differences in terms of BCSS ($p = 0.300$) or OS ($p = 0.690$) between SBBC and MBBC groups (Supplement figure3). However, among patients with discordant molecular subtypes within the tumor pairs, SBBC was significantly related to poorer BCSS ($p < 0.001$) and poor OS ($p = 0.022$) than MBBC (Supplement figure3).

3.4. Prognostic value of molecular subtype concordance

In overall patients, concordance in molecular subtype was associated with better BCSS (5-year BCSS, 93.01% vs 89.12%, $p = 0.003$, Fig. 3A) and OS (5-year OS, 86.00% vs 81.01%, $p < 0.001$, Fig. 3B).

In the SBBC group, patients with discordant molecular subtypes had significantly poorer BCSS (5-year BCSS, 84.27% vs 92.91%,

Table 1
Concordance of clinicopathologic characteristics between first tumor and second tumor in bilateral breast cancer.

Characteristics	SEER cohort			Ruijin CBHC cohort		
	SBBC, n = 2542	MBBC, n = 853	P	SBBC, n = 84	MBBC , n = 31	P
Surgical procedure			<0.001			0.291
Concordant	2215(87.1)	524(61.4)		76(90.5)	25(83.3)	
Discordant	327(12.9)	329(38.6)		8(9.5)	5(16.7)	
Tumor size			0.090			0.019
Both ≤ 2 cm	1276(50.2)	443(51.9)		84(100.0)	29(93.5)	
Both >2 cm	308(12.1)	80(9.4)		0	2(6.5)	
Discordant	958(37.7)	330(38.7)		0	0	
Node status			0.020			0.300
Both positive	211(8.3)	48(5.6)		11(13.1)	1(3.2)	
Both negative	1450(57.0)	519(60.8)		43(51.2)	17(54.8)	
Discordant	881(34.7)	286(33.6)		30(35.7)	13(41.9)	
Stage			0.760			0.341
Concordant	1135(44.6)	386(45.3)		35(41.7)	16(51.6)	
Discordant	1407(55.4)	467(54.7)		49(58.3)	15(48.4)	
Grade			<0.001			0.193
Concordant	1248(49.1)	343(40.2)		52(61.9)	15(48.4)	
Discordant	1249(50.9)	510(59.8)		32(38.1)	16(51.6)	
ER status			<0.001			0.001
Both positive	2068(81.4)	552(64.7)		61(72.6)	11(35.5)	
Both negative	113(4.4)	56(6.6)		7(8.3)	6(19.4)	
Discordant	361(14.2)	245(28.7)		16(19.0)	14(45.2)	
PR status			<0.001			0.001
Both positive	1730(68.1)	387(45.4)		52(61.9)	8(25.8)	
Both negative	216(8.5)	112(13.1)		14(16.7)	7(22.6)	
Discordant	596(23.4)	354(41.5)		18(21.4)	16(51.6)	
HER2 status			<0.001			0.002
Both Positive	76(3.0)	22(2.6)		4(4.8)	2(6.5)	
Both Negative	2096(82.5)	635(74.4)		69(82.1)	16(51.6)	
Discordant	370(14.6)	196(23.0)		11(13.1)	13(41.9)	
Molecular subtype			<0.001			0.002
Concordant	1928(75.8)	492(57.7)		64(76.2)	14(45.2)	
Discordant	614(24.2)	361(42.3)		20(23.8)	17(54.8)	

Abbreviations: SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer; ER, estrogen receptor; PR, progestogen receptor; HER2, human epidermal growth factor receptor type 2.

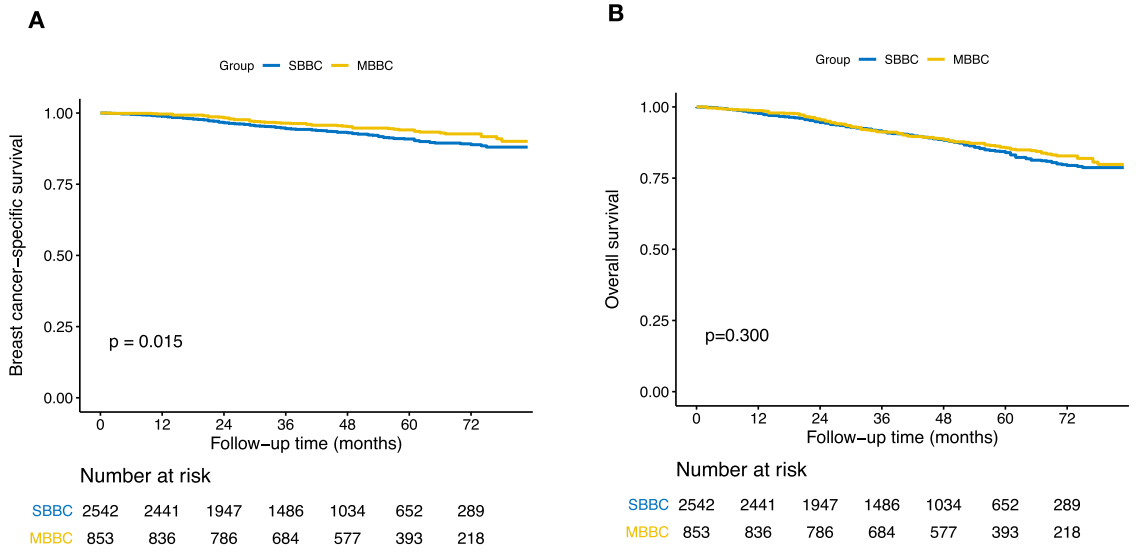

Fig. 2. Breast cancer-specific survival (A) and overall survival(B) of the SBBC group and the MBBC group in overall patients. Abbreviations: SBBC, synchronous bilateral breast cancer, MBBC, metachronous bilateral breast cancer.

p < 0.001, Fig. 4A, Table 2) and OS (5-year OS,77.31% vs 86.04%, p < 0.001, Fig. 4B, Supplement Table3) compared to those with concordant molecular subtype. Multivariate analyses demonstrated that discordance of molecular subtype was an independent worse prognostic factor for BCSS (HRs, 1.64; 95% CI, 1.18–2.27; p = 0.003, Table 3) and OS (HRs, 1.59; 95%CI, 1.24–2.04; p < 0.001, Supplement Table4) in the SBBC group. Besides, age(p = 0.001), race (p = 0.001), tumor size(p < 0.001) and node status (p = 0.045) were also identified as independent predictors for BCSS (Table 3). Similar results were observed for OS (Supplement Table4).

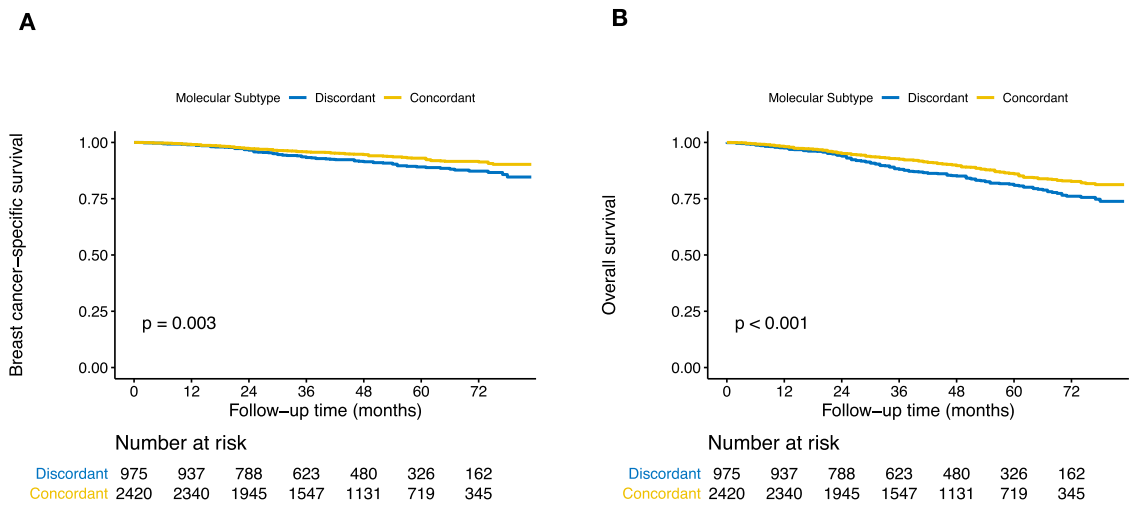

Fig. 3. Breast cancer-specific survival (A) and overall survival(B) of concordant molecular subtype group and discordant molecular subtype group in overall patients.

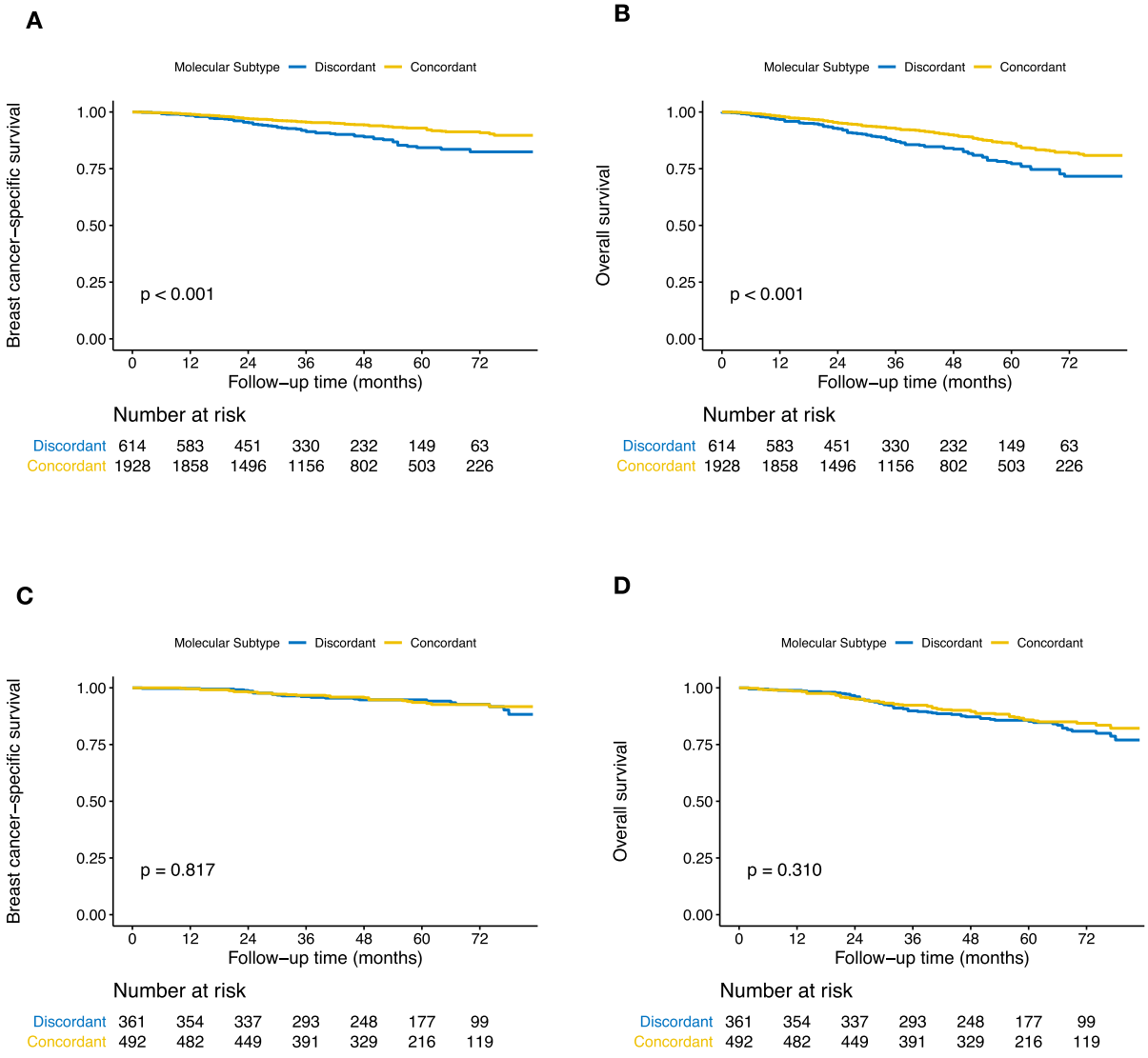

Fig. 4. Survival curves of patients with concordant molecular subtype and patients with discordant molecular subtype in the SBBC group (A, B) and MBBC group (C, D). Abbreviations: SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer.

Table 2
Univariate analysis for breast-cancer-specific survival in patients with bilateral breast cancer.

Factor	SBBC(N = 2542)			MBBC(N = 853)		
	Event, n (%)	5y BCSS	P	Event, n (%)	5y BCSS	P
Age at first diagnosis			0.001			0.074
≤65	82(5.7)	92.16		23(5.0)	95.18	
>65	85(7.7)	88.85		28(7.1)	92.35	
Race			<0.001			0.186
White	129(6.1)	91.37		37(5.7)	94.16	
Black	28(13.6)	84.62		9(8.0)	92.25	
Asian or Pacific Islander	9(4.3)	92.40		3(4.0)	95.11	
American Indian/Alaska Native	1(5.3)	93.75		2(13.3)	71.43	
Tumor size			<0.001			<0.001
Both≤2cm	39(3.1)	96.68		14(3.2)	96.31	
Both>2 cm	50(16.2)	75.70		12(15.0)	85.91	
Discordant	78(8.1)	88.87		25(7.6)	93.15	
Node status			<0.001			<0.001
Both positive	28(13.3)	81.22		9(18.8)	81.68	
Both negative	63(4.3)	93.86		18(3.5)	95.73	
Discordant	76(8.6)	88.55		24(8.4)	93.35	
Stage			<0.001			0.017
Concordant	47(4.1)	94.46		15(3.9)	95.47	
Discordant	120(8.5)	88.04		36(7.7)	92.93	
Grade			0.211			0.459
Concordant	75(6.0)	91.97		23(6.7)	93.78	
Discordant	92(7.1)	89.77		28(5.5)	94.25	
ER status			<0.001			<0.001
Both positive	100(4.8)	93.38		21(3.8)	95.77	
Both negative	25(22.1)	72.92		12(21.4)	78.46	
Discordant	42(11.6)	82.28		18(7.3)	94.03	
PR status			<0.001			<0.001
Both positive	66(3.8)	94.72		12(3.1)	96.78	
Both negative	43(19.9)	76.64		18(16.1)	85.37	
Discordant	58(9.7)	85.35		21(5.9)	94.09	
HER2 status			0.033			0.655
Both Positive	9(11.8)	85.13		2(9.1)	90.43	
Both Negative	126(6.0)	92.12		39(6.1)	93.85	
Discordant	32(8.6)	84.47		10(5.1)	95.24	
Molecular subtype			<0.001			0.817
Concordant	106(5.5)	92.91		28(5.7)	94.71	
Discordant	61(9.9)	84.27		23(6.4)	93.56	

Abbreviations: SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer; BCSS, breast cancer-specific survival; ER, estrogen receptor; PR, progestogen receptor; HER2, human epidermal growth factor receptor type 2.

Conversely, in the MBBC group, no significantly differences between the concordant and discordant molecular subtype group were observed in terms of BCSS ($p = 0.817$, Fig. 4C) or OS ($p = 0.310$, Fig. 4D). Whereas, age ($p = 0.008$), tumor size ($p = 0.010$) and node status ($p = 0.012$) were independent prognostic factors for BCSS in the MBBC group (Table 3). Similar results were observed for OS (Supplement Table4).

The prognostic value of molecular subtype concordance was also evaluated among patients with different molecular subtype. In the SBBC group, molecular subtype concordance was significantly related to better BCSS (5-year BCSS, 94.06% vs 86.22%; $p = 0.019$) and OS (5-year OS, 86.78% vs 77.59%, $p = 0.003$) among patients with HR+/HER2-breast cancer as the first tumor, whereas it was not a prognostic factor for patients with HR+/HER2+ breast cancer ($p = 0.496$ for BCSS, $p = 0.317$ for OS), HR-/HER2+ breast cancer ($p = 0.106$ for BCSS, $p = 0.275$ for OS) or TNBC ($p = 0.391$ for BCSS, $p = 0.952$ for OS) as the first tumor (supplement figure3). Differently, in the MBBC group, molecular subtype concordance was not associated with BCSS($p = 0.461$) but related to worse OS (5-year OS, 60.00% vs 89.65%; $p = 0.034$) among patients with HR+/HER2+ breast cancer as the first tumor. Among patients having HR+/HER2-breast cancer, HR-/HER2+ breast cancer or TNBC as the first tumor in the MBBC group, molecular subtype concordance could not either predict BCSS or OS (all $p > 0.05$, supplement figure4.

4. Discussion

In this large population-based retrospective study, we compared the clinicopathologic characteristics, ER, PR, HER2, and molecular subtype concordance within tumor pairs between patients with SBBC and MBBC. Particularly, molecular subtype concordance rate was found much higher in the SBBC group than the MBBC group. Moreover, survival outcomes and prognostic factors were also evaluated in SBBC and MBBC groups. Our results indicated that discordance of molecular subtype within bilateral breast cancer was associated with worse prognosis for SBBC but not for MBBC.

In line with previously published data [13,26–28], our analyses indicated that the discordant rates of ER, PR and HER2 status in MBBC were higher than those in SBBC. Bilateral tumors that developed simultaneously are more likely to have identical hormonal and environmental influences during tumorigenesis compared to metachronous tumors, which could possibly be part of the reasons for the stronger biomarker similarity in the SBBC group observed in our study. Another possible reason for the higher biological concordance in the SBBC group may be that synchronous tumors were mainly treatment-naïve while patients with MBBC may have received systemic treatment such as endocrine therapy and chemotherapy for the primary tumor, which may influence the biomarker status of the subsequent tumor and weaken the ER concordance between primary and contralateral tumors, as suggested in previous studies [29,30].

Table 3
Multivariate analyses for breast cancer specific survival among patients with bilateral breast cancer.

Variables	SBBC(n = 2542)		MBBC (n = 853)	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at first diagnosis				
<65	Ref		Ref	
>65	1.71(1.25–2.33)	0.001	2.21(1.23–3.99)	0.008
Race		0.007		0.133
White	Ref		Ref	
Black	1.97(1.30–2.98)	0.001	1.45(0.68–3.10)	0.334
Asian or Pacific Islander	0.71(0.36–1.41)	0.334	0.66(0.20–2.16)	0.495
American Indian/Alaska Native	0.73(0.10–5.26)	0.757	4.57(1.06–19.83)	0.042
Tumor size		<0.001		0.010
Both≤2cm	Ref		Ref	
Both>2 cm	4.34(3.71–6.93)	<0.001	3.96(1.62–9.65)	0.002
Discordant	2.23(1.40–3.56)	0.001	2.28(1.02–5.11)	0.045
Node status		0.106		0.012
Both positive	Ref		Ref	
Both negative	0.61(0.37–0.99)	0.045	0.26(0.11–0.64)	0.003
Discordant	0.82(0.51–1.32)	0.406	0.52(0.23–1.19)	0.188
Stage				
Concordant	Ref		Ref	
Discordant	1.10(0.69–1.76)	0.684	0.99(0.44–2.24)	0.977
Grade				
Concordant	Ref		Ref	
Discordant	1.13(0.83–1.54)	0.439	0.76(0.43–1.32)	0.325
Molecular subtype				
Concordant	Ref		Ref	
Discordant	1.64(1.18–2.27)	0.003	1.14(0.65–2.00)	0.650

Abbreviations: SBBC, synchronous bilateral breast cancer; MBBC, metachronous bilateral breast cancer; HR, hazard ratio, CI, confidential interval.

Our results also found a higher concordant rate of molecular subtype within bilateral tumors in the SBBC group compared with the MBBC group, which was not reported previously. Different from previous studies that mainly focused on the heterogeneity of ER and PR status, our study incorporated HER2 status and analyzed the molecular subtype heterogeneity of bilateral breast cancers in a large population-based cohort for the first time. Moreover, our study included two different cohorts. The SEER cohort was based on US-population while the Ruijin CHBC cohort was based on Chinese population, which has different ethnic background with different BRCA mutation rate of 5.5% in breast cancer patients [31]. According to our analyses, tumor characteristics were similar in both cohorts, indicating ethnic background may not influence the clinicopathological features of bilateral breast cancer. Molecular subtype status analysis also found these two cohorts had similar concordance rates. Additionally, SBBC was more likely to have concordant molecular subtype compared to MBBC both in the SEER cohort (75.8% vs 57.7% $p < 0.001$) and in the CBHC cohort (76.2% vs 45.2%, $p = 0.002$), which could provide more robust data supporting that SBBC had a higher concordant rate in molecular subtype than patients in the MBBC group.

Age was an important factor for bilateral breast cancer, but previous studies showed different results regarding age at diagnosis between SBBC and MBBC. Some studies found that patients with MBBC had younger age at diagnosis compared to SBBC patients [32,33], while some studies showed similar age between patients with SBBC and MBBC [34,35]. In our study, the percentage of patients younger than 65 at diagnosis was similar between SBBC and MBBC group in the SEER cohort (56.4% vs 53.8%, $p = 0.185$), but the percentage was higher in the MBBC group than the SBBC group in the CBHC cohort (96.8% vs 64.3%, $p < 0.001$). The discordant results may be caused by the different ethnic background between the two cohorts. The germline BRCA (gBRCA) mutations was found to be associated with bilateral breast cancer and earlier onset of breast cancer. In our study, the information about gBRCA mutations of patients were lacking in both cohorts. However, in the CHBC cohort, there was a higher percentage of patients younger than 65 at diagnosis in the MBBC group than the SBBC group (96.8% vs 64.3%, $p < 0.001$), as well as a higher percentage of patients with family history of breast cancer and/or ovarian cancer in the MBBC group than the SBBC group (12.9% vs 6%, $p = 0.219$). Although the difference in family history was not statistically significant, it might imply that the younger age at diagnosis of MBBC may be associated with gBRCA mutation, which deserved further investigation.

Previous studies have yielded controversial results when comparing the survival outcomes of SBBC and MBBC. Some reported that SBBC was associated with worse prognosis [3,4,33,34,36,37], while others stated that SBBC had similar, or even better prognosis compared to MBBC [21,27,35,38]. The conflicting results could be explained by two main reasons. First of all, the interval time to distinguish MBBC from SBBC varied among previous series, while it was evidenced that the interval time between bilateral tumors may influence the prognosis of bilateral breast cancer [8,39]. Secondly, many previous studies failed to conduct multivariate analyses due to limited sample size. According to our analyses based on a large population, SBBC was related to a higher breast cancer-related mortality compared with its metachronous counterpart. Multivariate analyses adjusted by demographic and tumor characteristics further validated our finding. One explanation for this finding would be that patients with two simultaneous cancers may suffer from heavier overall tumor burden and the combined effect of two cancers may lead to excess mortality and inferior prognosis [23,40].

In this retrospective study with large populations, we evaluated the prognostic significance of molecular subtype concordance for SBBC and MBBC. Our results suggested that the discordance of molecular subtype within bilateral breast cancer was associated with worse prognosis for SBBC but not for MBBC. This disparity in prognostic significance of molecular subtype discordance within tumor pairs remained distinct in multivariate analyses. Besides leading to possible different therapeutic response of bilateral tumors, discrepancies in molecular subtype between SBBC tumor

pairs may also indicated more tumor mutation burden in this subset of patients [41], which might contribute to their worse prognosis as well. Further investigation was needed to explore the underlying mechanism of this finding. Furthermore, our study also investigated the prognostic value of molecular subtype concordance in subgroups stratified by different molecular subtype. For SBBC group, discordant molecular subtype was associated with worse BCSS and OS only among patients with HR+/HER2-tumor as first diagnosis. The possible reason might be limited sample size in other subgroups.

Instead of evaluating the prognostic value of molecular concordance in bilateral tumors, some studies utilized different methods to analyze the prognosis of bilateral breast cancer. For example, a study aimed to evaluate the excess mortality of SBBC compared to unilateral breast cancer have applied three different ways to define the characteristics of SBBC and perform adjustments, namely the characteristics of the worst tumor, the worst disease characteristics regardless of side, and the characteristics of both tumors. the characteristics of the worst tumor, (ii) the worst disease characteristics regardless of side, and the (iii) characteristics of both tumors [42]. This indicated that the analyses based on the "worst" type of tumor pairs might be helpful. Accordingly, we performed survival analyses based on the molecular subtype determined by the worst type (ER+/HER2- > ER+/HER2+ > ER-/HER2+ > TNBC). In our cohort, the percentage of patients with ER+/HER2-, ER+/HER2+, ER-/HER2+, and TNBC as the worst molecular subtype was 70.3%, 11.8%, 4.4%, and 13.5% in the SBBC group, which was 52.1%, 14.0%, 7.6%, and 26.4% in the MBBC group. The worst molecular subtype was associated with inferior BCSS and OS in the overall patients (both $p < 0.001$, Supplement figure 4A 4B). Similarly, in the SBBC group, the worst molecular subtype had the worst BCSS and OS (both $p < 0.001$, Supplement Fig. 4C and 4D). While in the MBBC group, worst molecular subtype was related with BCSS ($p < 0.001$, Supplement Fig. 4E) and a trend of worse OS ($p = 0.091$, Supplement figure 4F). Detailed above survival outcomes were listed in the Supplement Table 5.The results indicated that the worst molecular subtype of bilateral cancers can also provide prognosis information for clinicians to guide their treatment decisions.

The strengths of our study were as follows. Firstly, this population-based study included the largest cohort to evaluate the receptor status and molecular subtype concordance between bilateral breast cancer. This study also excluded patients who had distant relapse concurrently or before the diagnosis of contralateral breast cancer. Additionally, different from previous studies evaluating the prognostic value of clinicopathological features of unilateral tumor in BBC [21,27,38], our study combined the characteristics of bilateral cancers to identify prognostic indicators for SBBC and MBBC. Moreover, the large population-based cohort enables multivariate analyses to identify independent prognostic factors for SBBC and MBBC, while few studies have conducted due to the relatively small sample size of BBC. Last but not least, prognostic value of molecular subtype concordance for SBBC and MBBC was evaluated for the first time in our study. Our investigation of molecular subtype in bilateral breast cancer may shed light on the understanding of biological relationships between the bilateral tumors and has implications in cancer treatment, which was of high scientific value.

Undeniably, limitations existed in our study. On the one hand, there was inherent bias in retrospective study. On the other hand, treatment information regarding chemotherapy regimen and receipt of endocrine therapy and target therapy was insufficient in SEER database. Moreover, it was worth noting that our analyses included only invasive ductal breast cancer. Therefore, the conclusions might not apply to lobular carcinomas, for the reason that lobular tumors can present as synchronous multicentric/multifocal neoplasms and retain a prognosis likely different from ductal types. Another limitation was that it is hard to completely excluded contralateral metastatic tumors in current diagnosis routine, because there are no uniform clinical criteria that allow discriminating between the contralateral metastatic breast cancer and primary bilateral breast cancer. Some pathological features could be used to help define a contralateral breast cancer as independent or suspected metastasis of the primary, such as different/identical histological type/histological grading, presence/absence of an in situ component, different/identical bioprofiles, or the presence/absence of distant metastasis. However, some of the criteria are not considered fully reliable, due to the tumor heterogeneity, evolution of metastases and some inherent ambiguities regarding histological type and/or IHC [43–45]. In the CBHC cohort, comprehensive evaluations were carried out to distinguish a second primary tumor from metastasis. To begin with, all patients would receive locoregional staging with bilateral mammography, ultrasound ± breast MRI. Secondly, detailed pathological examination was conducted to evaluate the histological grading, pathological types, and molecular biomarker status for both tumors. Moreover, systemic staging was routinely carried out by chest CT scan, abdominal ultrasound or CT scan, in order to exclude patients with synchronous metastatic disease. Bilateral tumors sharing different clinical and histological patterns were recognized as two primary tumors. Whereas, contralateral tumors with identical pathological types and molecular status need more cautious evaluations to define it as a primary tumor or metastasis, such as referring to bilateral breast imaging and systemic staging, or conducting multidisciplinary discussion by pathologists, radiologists and surgeons if necessary. The application of novel molecular techniques was expected to provide more reliable discrimination in the future.

In conclusion, our study found that SBBC had a higher concordant rate of ER, PR, HER2, and molecular subtype status within bilateral breast cancer compared with MBBC. SBBC was associated with poor BCSS compared to MBBC, which may due to the discordance of molecular subtypes within the tumor pairs in SBBC, deserving further clinical validation.

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Declaration of competing interest

The authors declare no conflict of interest.

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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.2021.03.005.

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