

# Strong adverse effect of epidermal growth factor receptor 2 overexpression on prognosis of patients with invasive lobular breast cancer: a comparative study with invasive ductal breast cancer in Chinese population

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**Abstract** The data on the outcome of breast invasive lobular carcinoma (ILC) are conflicting. In addition, the prognostic effect of molecular subtypes on ILC remains unclear. In this study, the clinicopathological and prognostic data between 269 ILC and 816 invasive ductal carcinoma (IDC) cases in a Chinese population were extensively compared, with a median follow-up time of 7.8 years. Compared with the IDC group, ILC tumors had more lymph node invasion, hormonal receptor positivity, and human epidermal growth factor receptor 2 (HER2) negativity. ILC patients showed overall survival (OS) and recurrence/metastasis-free survival (RFS) rates similar to those of IDC patients but exhibited worse disease-free survival (DFS) rate because of the higher rate of contralateral breast cancer (BC). Further analysis showed that

OS, RFS, and DFS were similar between ILC and IDC patients in the subgroups of luminal A and triple-negative BC with HER2 negativity but were worse in ILC patients than those in IDC patients in the subgroups of luminal B and HER2 overexpression with positive HER2 expression. Multivariate analysis indicated HER2 positivity as an independent risk factor for OS, RFS, and DFS of ILC patients, which increased the risk in the ILC group than that in IDC group. The interaction of HER2 and ILC was also defined as an independent risk factor for OS, RFS, and DFS of the entire population. In conclusion, overexpression of HER2 exhibited stronger negative effect on the prognosis of ILC patients than that in IDC patients, suggesting that treatment targeting HER2 is crucial for this BC subgroup.

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## Introduction

Breast cancer is a heterogeneous entity with different subtypes displaying distinct morphology. The World Health Organization has classified 31 distinct entities of this malignancy [1, 2]. Understanding the distinct biological and prognostic features of the different subtypes of breast cancer would be an essential strategy for the selection of treatment that minimizes side effects without reducing efficacy [1, 3, 4]. Among all the varieties of invasive breast cancer, invasive ductal carcinoma (IDC) accounts for approximately 60 to 75 %, while invasive lobular carcinoma (ILC) is the second most common histologic subtype [5, 6].

Collective studies have confirmed the unique clinical, pathological, and biological characteristics of ILC among breast tumors [7]. The most outstanding features distinct from IDC are elevated expressions of estrogen receptor (ER) and progesterone receptor (PR). ILC is responsive to estrogen, which is related to hormone replacement therapy (HRT) in postmenopausal patients, leading to increased ILC incidence [8]. In contrast to the continuous elevation in breast cancer incidence with increasing age in Western countries, the incidence of breast cancer in China increases rapidly before menopause and decreases afterward [9, 10]. Whether estrogen plays a unique role in breast tumorigenesis in Chinese women remains unclear. Although breast cancer is usually positive to hormone receptor (HR), ILC in Chinese patients may present distinct features from the data in Western reports. However, such information in China remains limited to date.

ILC is also more often negative than IDC to human epidermal growth factor receptor 2 (HER2), with lower histologic grade and decreased proliferation markers [11]; these features are favorable to prognosis. Meanwhile, ILC presents larger tumors and higher nodal stage than those of IDC, which are adverse to prognosis [11]. Notably, almost all ILC tumors are negative to E-cadherin [12, 13]. Loss of E-cadherin fundamentally occurs in epithelial–mesenchymal transition, a key event during cancer metastasis [14]. Consistent with the paradoxical biological features, contradictory data in the literature compared the outcomes of ILC patients with those of women with IDC [2, 11].

Over the last decade, the molecular subtypes generated by microarray-based gene expression studies have elucidated the breast cancer heterogeneity differently [15–18]. In clinical practice, immunohistochemistry (IHC) is commonly used for detection of breast cancer. Breast cancers are classified into the following four groups based on the expression of ER, PR, and HER2 as detected by IHC: luminal A (ER- or PR-positive, HER2-negative), luminal B (ER- or PR-positive, HER2-positive), HER2-overexpressing (ER- and PR-negative, HER2-positive), and triple-negative breast cancer (TNBC: ER, PR, and HER2 are all negative) [6]. This classification contributes to the treatment guidelines for breast cancer and shows great prognostic significance [15]. However, the cases in these studies were overwhelmingly IDC. The efficiency of the classification in ILC remains unclear, and the outcomes of ILC compared with those of IDC under the same molecular subtypes remain unknown.

In this study, we attempted to establish the clinicopathological characteristics of ILC compared with those of IDC in Chinese. Based on a large database with long-term follow-up, we aimed to explain the difference of outcomes between ILC and IDC patients, particularly for those under the same subtypes, as defined by ER, PR, and HER2 expressions.

## Materials and methods

### Patients

A total of 10,132 primary breast cancer patients underwent surgeries in the Tianjin Medical University Cancer Institute and Hospital between January 1, 1997 and December 31, 2005. Every patient in the study accepted the informed consent, and the study was approved by the ethics committee of Tianjin Medical University Cancer Institute and Hospital. Around 280 cases were diagnosed with pure ILC, which accounted for 2.8 % of all the breast cancer patients. A total of 7463 cases were diagnosed with IDC without any other invasive tumors, which accounted for 73.7 % in this patient cohort. Cases were excluded if they met the following exclusion criteria: mixed ILC/IDC or other types of breast cancer, patients had previous or bilateral breast malignancy, or standard four to six cycles of neoadjuvant chemotherapy or endocrine therapy were applied. Finally, we enrolled 269 ILC cases, while 816 IDC cases were enrolled as the control group by systematic sampling with the interval of nine cases. All patients were female, and their medical records were reviewed for personal history, clinical findings, histopathological features, treatment, and postoperative follow-up records. The family history of malignant tumors, including breast cancer, was defined with at least one second-degree relative that had the disease.

### Clinicopathological assessment

Tumors were classified histologically as ILC or IDC based on the criteria described by the World Health Organization. Clinical and pathological staging was performed in accordance with the sixth edition of the American Joint Committee on Cancer TNM classification principle [19]. Patients with stage IV diseases usually received systemic therapy instead of surgery and excluded in this study. Histologic grade of tumor was based on the criteria of Elston and Ellis [20].

ER and PR positivity was defined as at least 15 % nucleus staining by IHC. HER2 expression was assessed by IHC or fluorescence in situ hybridization (FISH). HER2 was considered positive if the IHC score was +++ and negative if the score was 0 or + based on staining intensity. If the score was ++, further assay with FISH was performed. For subgroup analysis, the IHC classifications were as follows: luminal A, ER- or PR-positive, and HER2-negative; luminal B, ER- or PR-positive, and HER2-positive; HER2-overexpressing, ER- and PR-negative, but HER2-positive; TNBC, ER, PR, and HER2 were all negative.

### Statistical analysis

Differences in the characteristics were analyzed by chi-square test for distribution and Mann–Whitney *U* test for the means

between groups. To investigate the difference of outcomes between ILC and IDC, we conducted extensive survival analysis using the primary endpoints of overall survival (OS), recurrence/metastasis-free survival (RFS), and disease-free survival (DFS). OS was defined as the length of time from the first diagnosis of primary breast cancer to death from any cause. RFS was defined as the length of time from the initial diagnosis to local recurrence or distant metastasis. Considering ILC was at high risk for bilateral breast cancer [11], we defined DFS as the length of time from the initial diagnosis to any relapse (including local recurrence and metastasis), appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. Local recurrence included the reappearance of tumor in the operative area, as well as in the ipsilateral axillary and supraclavicular lymph nodes. Distant metastasis included the recurrence after surgery in any distant organ aside from the above-mentioned local sites. Contralateral breast cancer referred to the primary breast cancer of the contralateral breast diagnosed after surgery of the initial breast cancer. Kaplan–Meier product limit method was used to obtain the survival curves; log-rank test was performed to investigate the difference in survival between groups. Multivariate Cox proportional-hazards regression analysis was used to assess the independent prognostic significance of various pathological features on each of the previous outcomes. SPSS 16.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Values of  $p < 0.05$  were considered statistically significant.

## Results

### Comparison of clinical/pathological characteristics between ILCs and IDCs

Table 1 summarizes the personal features and clinical findings. ILC occurred more often in people aged  $>50$  years [2, 11]; however, an opposite result was obtained in our patient cohort. Compared with IDC, ILC patients were seemingly younger at initial diagnosis (49.82 vs 51.51,  $p=0.103$ ). Significantly, more patients were diagnosed before age 50 in the ILC group (62.8 vs 55.5 %,  $p=0.036$ ). ILC patients were more often diagnosed at premenstrual status (60.0 vs 57.7 %,  $p=0.407$ ), but the difference was insignificant. The proportion of positive malignant tumor family history was much higher in ILC patients than that in IDC patients (30.9 vs 19.6 %,  $p=0.0001$ ).

Almost all the patients underwent axillary lymph node dissection, except for six cases with early stage IDC because of severe systemic diseases that were unsafe for general anesthesia. Other patients received mastectomy or breast-conserving

**Table 1** Clinical characteristics of invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC)

Clinical parameter	No. of patients (%)		P value
	ILC	IDC	
Mean age (years)	49.82±0.587	51.51±0.608	0.103
Age group			0.036*
≤50	169 (62.8 %)	453 (55.5 %)	
>50	100 (37.2 %)	363 (44.5 %)	
Mean age of menarche	14.89±0.125	14.87±0.067	0.711
Menopausal status			0.407
Premenopausal	163 (60.6 %)	471 (57.7 %)	
Postmenopausal	106 (39.4 %)	345 (42.3 %)	
Mean age of menopause	49.75±0.395	49.16±0.221	0.132
Malignancy family history			0.0001*
Negative	186 (69.1 %)	656 (80.4 %)	
Positive	83 (30.9 %)	160 (19.6 %)	
Breast cancer family history			0.113
Negative	251 (93.3 %)	781 (95.7 %)	
Positive	18 (6.7 %)	35 (4.3 %)	
Clinical stage			0.244
I	41 (15.2 %)	123 (15.1 %)	
II	171 (63.6 %)	556 (68.1 %)	
III	57 (21.2 %)	137 (16.8 %)	
Operative type			0.013*
Breast conservation	7 (2.6 %)	54 (6.6 %)	
Mastectomy	262 (97.4 %)	762 (93.4 %)	
Radiotherapy			0.192
Negative	171 (63.6 %)	554 (67.9 %)	
Positive	98 (36.4 %)	262 (32.1 %)	
Endocrine therapy			0.020*
Negative	98 (43.4 %)	425 (52.1 %)	
Positive	128 (56.6 %)	391 (47.9 %)	
Chemotherapy			0.053
Negative	22 (8.2 %)	68 (8.3 %)	
CMF	133 (49.4 %)	445 (54.5 %)	
Antracycline	59 (21.9 %)	198 (24.3 %)	
Taxanes	53 (19.7 %)	101 (12.4 %)	
Others	2 (0.7 %)	4 (0.5 %)	

surgery (BCS), along with axillary lymph node dissection. The proportions of BCS were very low in both ILC and IDC patients in our study. The ILC group showed even lower BCS rate than the IDC group (2.6 vs 6.6 %,  $p=0.013$ ). Patients who underwent BCS and those with high risk of local relapse (tumor size  $>5$  cm or positive lymph nodes  $>3$ ) received radiotherapy. Adjuvant systemic therapies included four to six cycles of chemotherapy and endocrine therapy based on pathological features. None of the patients were treated with Herceptin targeting HER2 amplification in our cohort

for economic reasons. No significant differences existed in postoperative therapies between the ILC and IDC groups ( $p>0.05$ ). However, more ILC patients received endocrine therapy because of much HR positivity. The therapeutic data are summarized in Table 1.

Table 2 shows the pathological characteristics. The mean diameters of tumors within the two groups were

**Table 2** Pathological characteristics of invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC)

Pathological parameter	No. of patients (%)		P value
	ILC	IDC	
Mean diameter of tumor (cm)	2.65±0.091	2.54±0.043	0.409
Tumor size group			0.531
≤5 cm	255 (94.8 %)	781 (95.7 %)	
>5 cm	14 (5.2 %)	35 (4.3 %)	
Lymph node invasion			0.006*
Negative	106 (39.6 %)	399 (49.3 %)	
Positive	162 (60.4 %)	411 (50.7 %)	
Nodal status			0.011*
0	106 (39.6 %)	399 (49.3 %)	
1–3	74 (27.6 %)	184 (22.7 %)	
4–9	31 (11.6 %)	105 (13.0 %)	
≥10	57 (21.3 %)	122 (15.1 %)	
Pathological stage			0.276
I	59 (21.9 %)	201 (24.8 %)	
II	116 (43.1 %)	367 (45.3 %)	
III	94 (34.9 %)	242 (29.9 %)	
Histologic grade			<0.0001*
I	12 (18.2 %)	38 (5.5 %)	
II	49 (74.2 %)	548 (80.0 %)	
III	5 (7.6 %)	99 (14.5 %)	
ER			0.027*
Negative	74 (28.8 %)	293 (36.3 %)	
Positive	183 (71.2 %)	514 (63.7 %)	
PR			0.004*
Negative	95 (37.0 %)	381 (47.2 %)	
Positive	162 (63.0 %)	26 (52.8 %)	
HR			0.005*
Negative	47 (8.3 %)	217 (26.9 %)	
Positive	210 (81.7 %)	590 (73.1 %)	
HER2			0.001*
Negative	198 (87.6 %)	622 (77.9 %)	
Positive	28 (12.4 %)	176 (22.1 %)	
Molecular subtype			0.005*
Luminal A	167 (73.9 %)	496 (62.2 %)	
Luminal B	16 (7.1 %)	86 (10.8 %)	
HER2 overexpression	12 (5.3 %)	90 (11.3 %)	
TNBC	31 (13.7 %)	126 (15.8 %)	

similar, although an insignificantly higher rate of tumor size >5 cm was observed in ILC patients (5.2 vs 4.3 %,  $p=0.531$ ). Significantly more patients in the ILC group had lymph node invasion (60.4 vs 50.7 %,  $p=0.006$ ) and advanced nodal stage ( $p=0.011$ ). However, no significant difference existed in the pathological stage distribution. Histologic grading system may not be suitable for the entire ILC assessment [21]; we found only 66 cases with histologic grading information in the ILC group. We also observed more cases with grade I and fewer cases with grade III in ILC than in IDC ( $p<0.0001$ ). We used a stricter standard for the definition of ER and PR positivity than that of other studies [6, 22], in which 15 % nucleus staining was the dividing line. However, we still found significantly higher proportion of ER-positive (71.2 vs 63.7 %,  $p=0.027$ ) and PR-positive (63.0 vs 52.8 %,  $p=0.004$ ) tumors in the ILC group than in the IDC group. We also obtained a much lower rate of HER2-positive expression in ILC patients as previously reported (12.4 vs 22.1 %,  $p=0.001$ ). Given the different HR and HER2 statuses, significant difference was found in the distribution of subgroups as determined according to HR and HER2 expression, in which more luminal A and fewer luminal B, HER2 overexpression, and TNBC cases were observed in the ILC group ( $p=0.005$ ).

#### Comparison of outcome between ILC and IDC patients

The median follow-up time of our cohort was 93.02 months (ranging from 7 to 197 months): 91.53 months for the ILC group with ten missing cases and 93.68 months for the IDC group with eight missing cases.

No significant differences existed in the total rate of local recurrence (6.9 vs 7.2 %,  $p=0.867$ ) and distant metastasis (21.9 vs 16.9 %,  $p=0.068$ ) between the ILC and IDC groups, although the first recurrence sites in the ILC group differed from those in the IDC group. Very few patients were diagnosed with secondary tumor in organs other than the breast in both ILC and IDC groups (0.8 vs 0.4 %,  $p=0.407$ ). We also found a significantly higher rate of contralateral primary breast cancer that occurred after operation of the initial breast cancer in ILC patients than in IDC patients (3.5 vs 1.3 %,  $p=0.027$ ). The follow-up data are summarized in Table 3.

We used three primary endpoints, namely, OS, RFS, and DFS, to assess the patient outcomes. DFS differs from RFS mainly for the secondary cancer, specifically contralateral breast cancer. The 5-year and 10-year OS of ILC were 88.4 and 80.8 %, while those of IDC were 87.8 and 84.9 %, respectively (log-rank  $p=0.560$ ). The 5-year and 10-year RFS of ILC (78.3 and 70.9 %) did not differ from that of IDC (80.4 and 77.1 %) (log rank  $p=0.205$ ). However, worse 5-year and 10-year DFS were noted in the ILC group than those in

**Table 3** Overall distribution of invasive lobular and invasive ductal according to event

Event	No. of patients (%)		P value
	ILC	IDC	
Local recurrence			0.867
Negative	242 (93.1 %)	757 (92.8 %)	
Positive	18 (6.9 %)	59 (7.2 %)	
First local recurrence site			0.020*
Skin of operative area	17 (94.4 %)	35 (59.3 %)	
Ipsilateral axillary lymph node	0 (0 %)	2 (3.4 %)	
Ipsilateral supraclavicular lymph node	1 (5.6 %)	22 (37.3 %)	
Distant metastasis			0.068
Negative	209 (78.1 %)	678 (83.1 %)	
Positive	57 (21.9 %)	138 (16.9 %)	
First distant metastasis site			0.310
Bone	25 (44.6 %)	57 (41.3 %)	
Lung/pleura	12 (21.4 %)	49 (28.3 %)	
Liver	8 (14.3 %)	25 (18.1 %)	
CNS	4 (7.1 %)	8 (5.8 %)	
Ovary	2 (3.6 %)	1 (0.7 %)	
Gastrointestinal tract	2 (3.6 %)	1 (0.7 %)	
Contralateral breast	1 (1.8 %)	6 (4.3 %)	
Other	2 (3.6 %)	1 (0.7 %)	
Contralateral primary breast cancer			0.027*
Negative	250 (96.5 %)	805 (98.7 %)	
Positive	9 (3.5 %)	11 (1.3 %)	
Second nonbreast malignancy			0.407
Negative	258 (99.2 %)	813 (99.6 %)	
Positive	2 (0.8 %)	3 (0.4 %)	

the IDC group (75.2 and 64.9 % vs 78.9 and 75.0 %, log-rank  $p=0.039$ ). These findings may be attributed to the higher rate of contralateral breast cancer in ILC patients. The survival curves are shown in Fig. 1.

When adjuvant systemic therapies were included in the analysis, ILC and IDC patients who received adjuvant chemotherapy and endocrine therapy yielded similar OS and RFS (log-rank  $p>0.05$ ). However, worse DFS remained in ILC patients (log-rank  $p<0.05$ ). These data are also illustrated in Fig. 1.

Subsequently, we grouped the patients by molecular subtype according to ER, PR, and HER2 expressions and compared the outcomes between ILC and IDC extensively (Fig. 2). Interestingly, similar OS, RFS, and DFS were found between the ILC and IDC groups (log-rank  $p>0.05$ ) for the patients in the subgroup of luminal A and TNBC. However, for the patients in the subgroup of luminal B and HER2 overexpression, the ILC prognosis

was significantly worse than that of IDC (log-rank  $p<0.05$ ). Thus, we speculated a stronger negative effect of HER2 expression on ILC prognosis than that of IDC and divided our patients into HER2-positive and HER2-negative groups. As speculated, the prognosis of ILC patients in the HER2-negative group was similar to that of IDC patients (log-rank  $p>0.05$ ), whereas in the HER2-positive group, worse OS, RFS, and DFS were found in the ILC patients (log-rank  $p<0.05$ ). Systemic treatment did not reduce the disparity of outcome, as evidenced by the HER2-positive ILC patients who received chemotherapy and endocrine therapy, but still exhibited worse OS, RFS, and DFS than those of IDC patients under the same situation ( $p<0.05$ ). These data are depicted in Fig. 3.

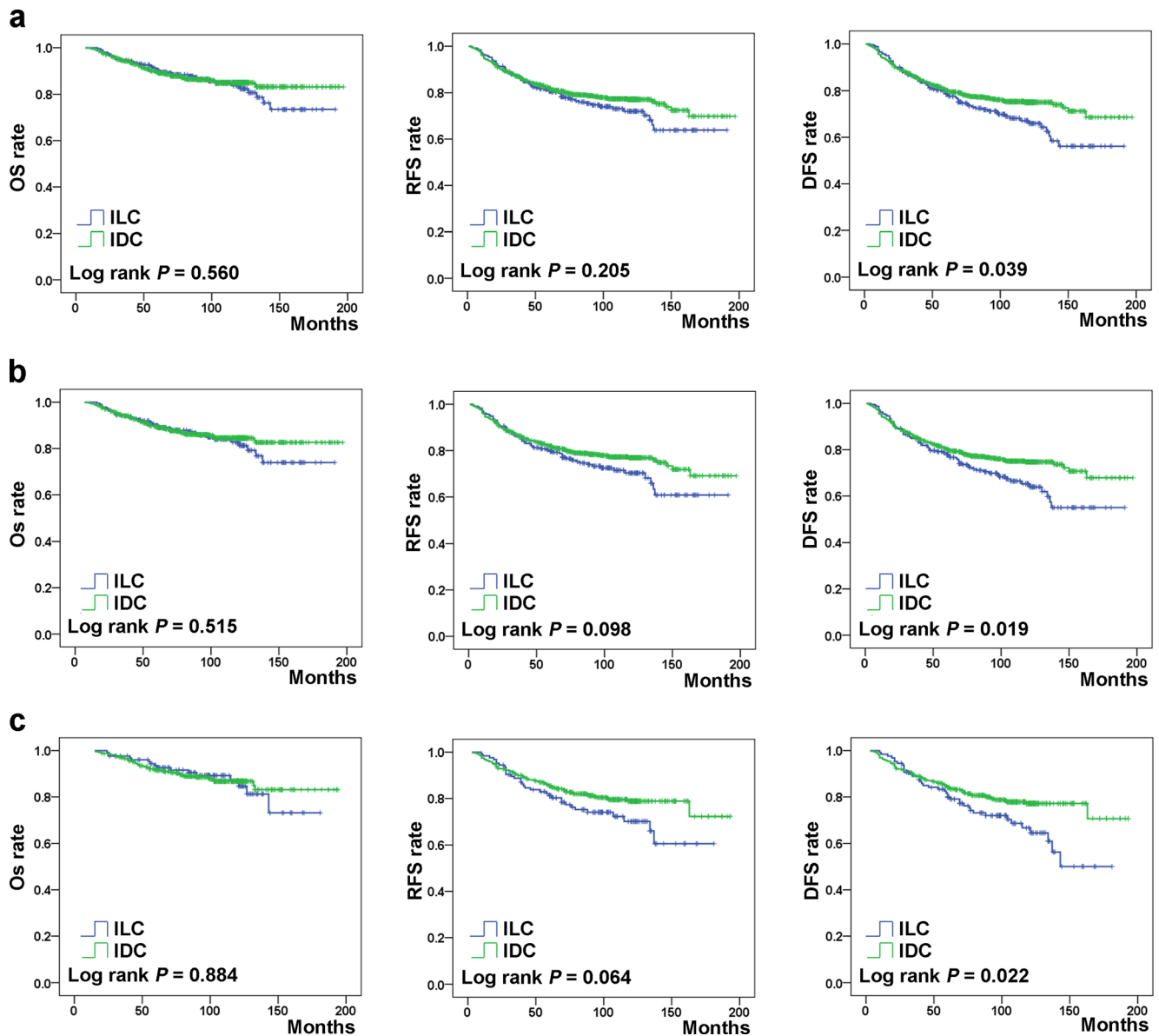
#### Risk factors of outcome analyzed by univariate and multivariate analysis

Table 4 summarizes the results of univariate analysis of OS, RFS, and DFS for ILCs, IDCs, and the whole population. To observe the effect of HER2 on the ILC outcome, we added a new variant, which is the interaction of HER2 and ILC (HER2×ILC) for the whole population (ILCs+IDCs). The patients with ILC and HER2 positivity were defined as 1, and other patients were defined as 0. As speculated, HER2 positivity and HER×ILC both worsen the OS, RFS, and DFS of the whole population.

Multivariate analysis was performed to determine the independent prognostic factors; the significant variables determined by univariate analysis were included. Given that most of the ILC cases were not accessed by histologic grading, we excluded the variant histologic grading to maintain the relative integrity of the data. Lymph node invasion and HER2 positivity were revealed as the two independent risk factors of OS, RFS, and DFS for ILC patients (Table 5). For IDC patients, lymph node invasion was the independent risk factor of OS, RFS, and DFS. Although HER2 positivity was also an independent risk factor for OS of IDC patients, the relative risk of 2.320 was much lower than the 4.814 for OS in the ILC group. For the whole population, the interaction of ILC and HER2 was confirmed to be the independent risk factor of OS, RFS, and DFS. These results suggest that HER2 overexpression may cause more aggressive ILCs and has stronger adverse effect on the prognosis in ILC patients.

#### Discussion

Breast cancer is the most common malignancy and the leading cause of death from cancer among females worldwide, including China [9, 23, 24]. Although the majority of breast cancer is



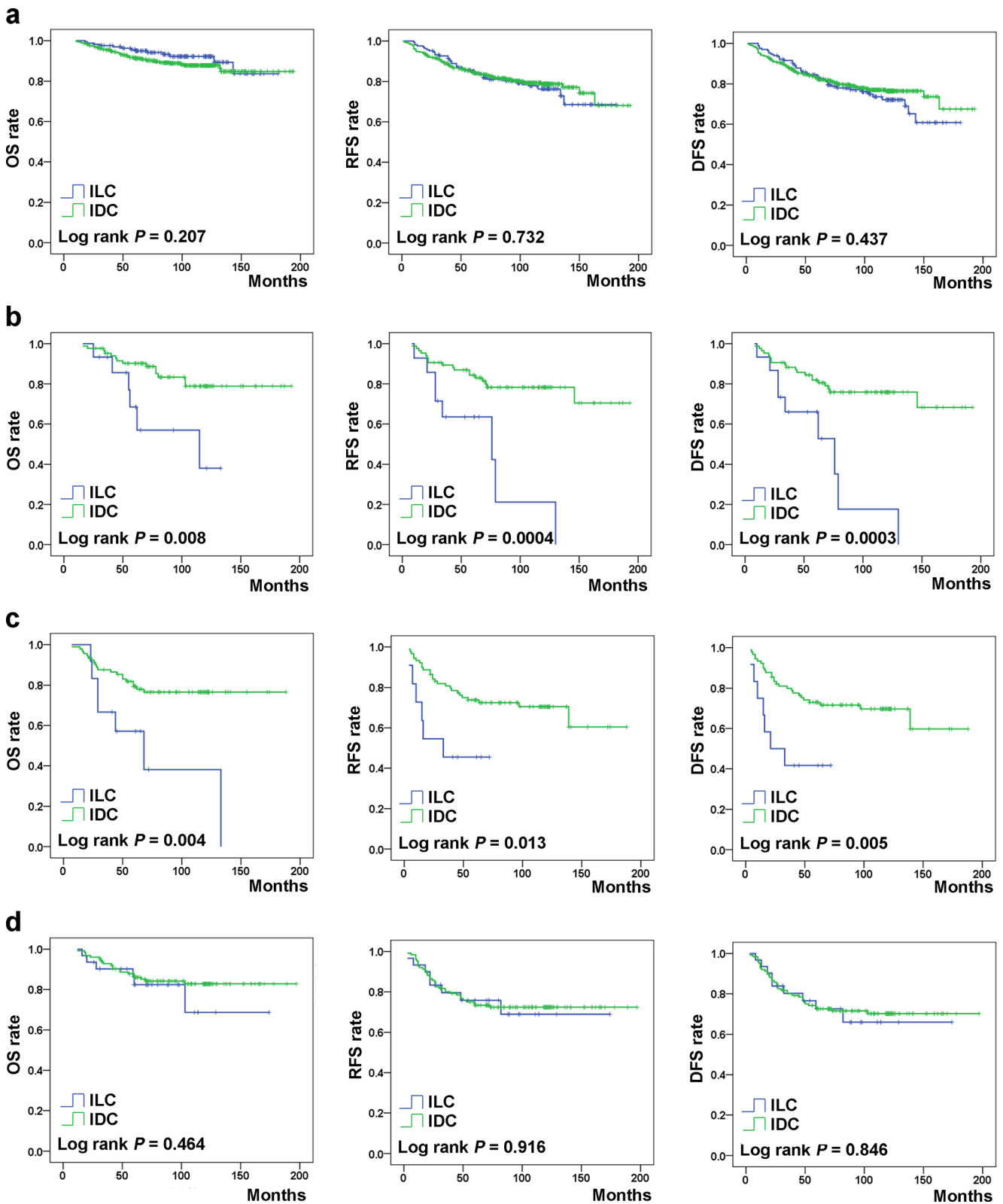
**Fig. 1** Comparison of overall outcome between ILC and IDC patients. Overall survival (OS), recurrence/metastasis-free survival (RFS), and disease-free survival (DFS) according to histologic types in all patients

(a), patients who received adjuvant chemotherapy (b), and patients who received adjuvant endocrine therapy (c)

IDC, the incidence of ILC as the second most common subtype has increased even more significantly in the past two decades [11, 25]. ILC has been contributing 5 to 15 % of all breast cancers in Western countries [2, 11, 21, 26]. According to the reports from Korea and Japan, the incidence of ILC in East Asia is low (1 to 4 %) [6, 27–29], but the data from China remain limited. In our cohort, primary breast cancer patients who underwent surgery were included, and ILC without any other invasive tumor represented 2.8 %, which is similar to that in East Asian countries.

In Western countries, ILC occurs more often in older women, particularly in women aged >50 years [8, 30, 31]. HRTs were considered the main cause of ILC increase,

which indicates that ILC is more sensitive to female hormones [8, 32]. However, the use of HRT was not as popular in China. We also obtained opposite results, in which more ILC patients were younger than 50 and premenopausal compared with IDC patients. The incidence of ILC may be reduced by attenuation of hormones with increasing age. We suggest that ILC development may be more dependent on female hormones in Chinese women, although the exact role of these hormones is unclear. Moreover, we explored the effect of cancer family history on ILC for the first time. We found a significantly higher rate of malignant tumor family history in the ILC group than that in the IDC group. The familial aggregation of cancer may provide evidence of

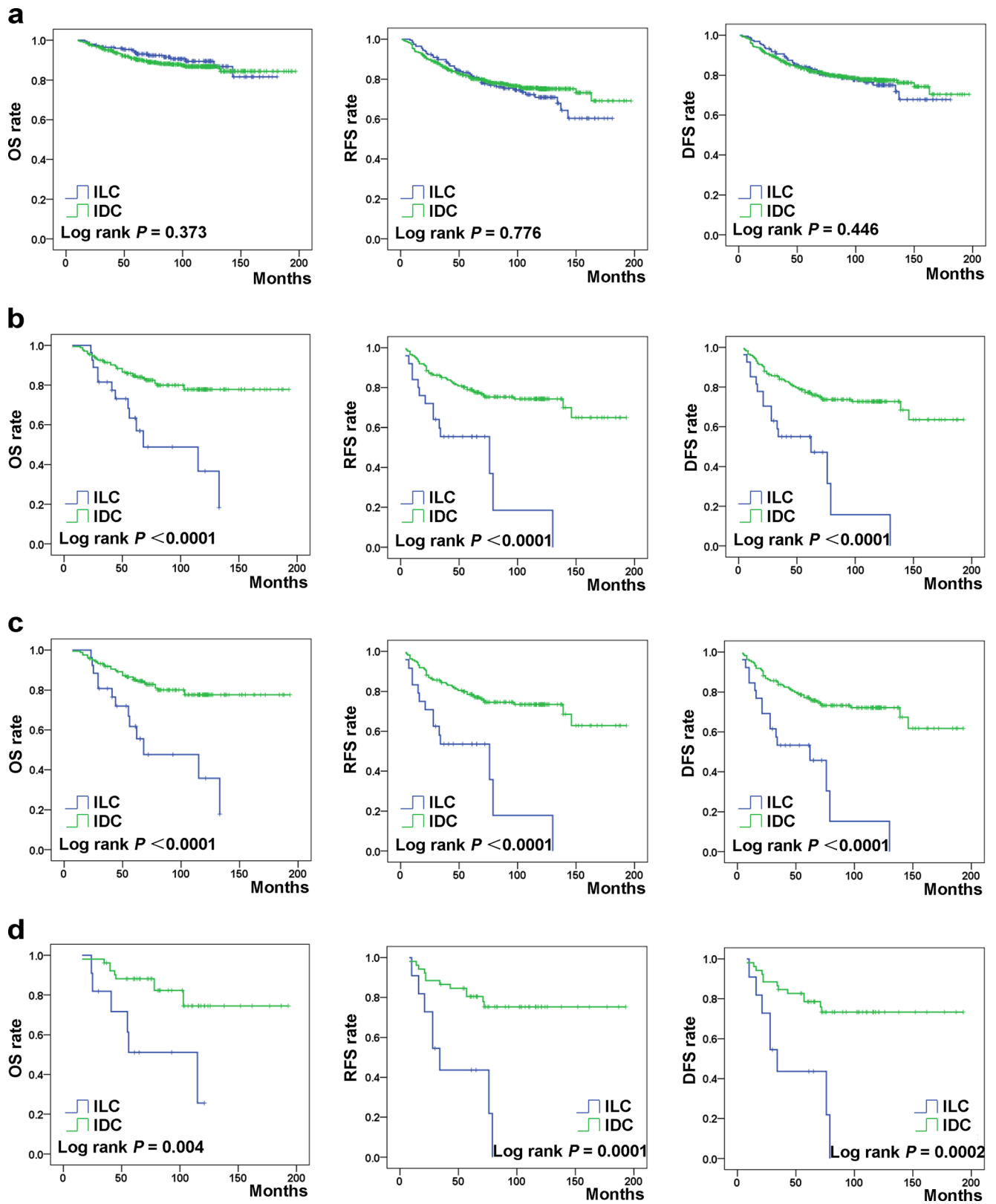


**Fig. 2** Comparison of outcome between ILC and IDC patients within a matched molecular subtype. Overall survival (OS), recurrence/metastasis-free survival (RFS), and disease-free survival (DFS) according

to histologic types in luminal A group (a), luminal B group (b), HER2-overexpression group (c), and TNBC group (d)

the genomic background of ILC occurrence. ILC is more likely present as multifocal and is treated less often with

BCS [11, 21]. The BCS rate is still low in China for the educational and economic reasons. Thus, in our cohort,



**Fig. 3** Comparison of outcome between ILC and IDC patients within a matched HER2 status. Overall survival (OS), recurrence/metastasis-free survival (RFS), and disease-free survival (DFS) according to histologic types in HER2-negative group (a) and HER2-positive group (b); OS,

RFS, and DFS according to histologic types in HER2-positive patients who received adjuvant chemotherapy (c) and HER2-positive patients who received adjuvant endocrine therapy (d)



**Table 4** Univariate analysis of overall survival (OS), recurrence/metastasis-free survival (RFS), and disease-free survival (DFS)

Variable	<i>P</i> value for OS	<i>P</i> value for RFS	<i>P</i> value for DFS
For ILC			
Age>50	0.544	0.970	0.864
Postmenopausal	0.806	0.379	0.483
Positive malignancy family history	0.239	0.622	0.645
Positive breast cancer family history	0.071	0.531	0.844
BCS	0.290	0.916	0.889
Chemotherapy	0.356	0.054	0.080
Endocrine therapy	0.261	0.267	0.482
Radiotherapy	0.747	0.112	0.124
Tumor size (>5 cm)	0.001*	0.049*	0.049*
Lymph node positive	0.005*	<0.0001*	<0.0001*
ER positive	0.004*	0.035*	0.018*
PR positive	<0.0001*	0.0003*	0.0002*
HER2 positive	<0.0001*	<0.0001*	<0.0001*
For IDC			
Age>50	0.879	0.783	0.931
Postmenopausal	0.902	0.277	0.271
Positive malignancy family history	0.611	0.238	0.178
Positive breast cancer family history	0.095	0.391	0.541
BCS	0.125	0.430	0.422
Chemotherapy	0.410	0.589	0.521
Endocrine therapy	0.117	0.052	0.057
Radiotherapy	0.051	0.067	0.053
Tumor size (>5 cm)	0.049*	<0.0001*	0.0003*
Lymph node positive	<0.0001*	<0.0001*	<0.0001*
ER positive	0.048*	0.009*	0.015*
PR positive	0.011*	<0.0001*	<0.0001*
HER2 positive	0.0008*	0.024*	0.029*
For ILC+IDC			
Histological type (ILC)	0.560	0.039*	0.205
Age>50	0.853	0.796	0.669
Postmenopausal	0.916	0.262	0.172
Positive malignancy family history	0.290	0.505	0.556
Positive breast cancer family history	0.634	0.349	0.597
BCS	0.058	0.288	0.386
Chemotherapy	0.268	0.150	0.134
Endocrine therapy	0.074	0.084	0.135
Radiotherapy	0.052	0.054	0.058
Tumor size (>5 cm)	0.024*	<0.0001*	0.0003*
Lymph node positive	<0.0001*	<0.0001*	<0.0001*
ER positive	0.003*	0.003*	0.002*
PR positive	<0.0001*	0.0002*	<0.0001*
HER2 positive	<0.0001*	0.016*	0.012*
HER2×ILC positive	<0.0001*	<0.0001*	<0.0001*

the proportions of BCS were very low in both ILC and IDC patients, and an even lower BCS rate was found in the ILC group.

Largely in consonance with other studies, our data suggest distinct pathological characteristics of ILC from those of IDC. ILC tends to be present with larger tumor and higher nodal stage [6, 21, 33], partly caused by the linear growth pattern of ILC tumors, which is not easily detected by mammography [34]. Similar to a previous report [35], we found a significantly higher rate of lymph node invasion and nodal stage III in the ILC group. The use of histologic grading in ILC has been controversial, primarily because of the absence of any tubule formation in ILC, and tubule formation was one of the criteria of histologic grading [36]; a population-based study also reported much higher incidence of unknown grade in ILC than that in IDC [21]. In our cohort, only 66 ILC cases showed histologic grading information; however, limited data in the ILC group showed a much higher rate of grade I and much lower rate of grade III than those in the IDC group; these findings agreed with previous reports [6, 21]. Distinctive features of IHC results in the ILC group were confirmed in the present study as reported in collective studies [2, 6, 11, 21]. Although a stricter standard for definition of ER and PR positivity was used, we still found a significantly higher proportion of ER and PR in ILC tumors than that in IDC tumors. FISH was performed to determine the overexpression of HER2 in HER2 ++ tumors as detected by IHC, and the rate of HER2 positivity was 12.4 % in the ILC group, which was significantly lower than that in the IDC group, higher than that in Western reports [22], and similar to the rate in another Chinese cohort [37].

ILC is more often bilateral than IDC [11, 37]. In our present series with a median follow-up of 7.8 years, significantly more incidence of contralateral breast cancer occurred after the initial breast cancer in the ILC group. Furthermore, the most frequent site of first recurrence of ILC was different from that of IDC group. ILC spread less frequently to the lungs and pleura and targeted the ovaries and gastrointestinal tract instead, which agreed with the previous study [26].

Data regarding the specific prognosis of patients with ILC in the literature are conflicting, whereas more recent studies agree with a similar prognosis to that of IDC [2]. Based on Chinese population with long-term follow-up, our study found similar OS and RFS between the ILC and IDC groups. However, the DFS was worse in ILC patients, which may be attributed to the significantly higher rate of contralateral breast cancer in ILC. Evidence suggests lower pCR rate after neoadjuvant chemotherapy in ILC patients than that in IDC patients [38, 39]. However, the effectiveness of adjuvant chemotherapy in ILC is unclear, and no clear prognostic benefit from endocrine therapy in ILC patients has been determined [11]. In our cohort, the results suggest that the efficiency of

**Table 5** Multivariate analysis of overall survival (OS), recurrence/metastasis-free survival (RFS), and disease-free survival (DFS)

Variable	OS		RFS		DFS	
	HR (95 % CI)	<i>P</i> value	HR (95 % CI)	<i>P</i> value	HR (95 % CI)	<i>P</i> value
For ILC						
Tumor size (>5 cm)	1.431 (0.587–3.490)	0.431	1.324 (0.518–3.380)	0.558	1.009 (0.304–3.293)	0.859
Lymph node positive	3.382 (1.182–9.113)	0.023*	2.972 (1.600–5.524)	0.001*	3.230 (1.628–6.408)	0.001*
ER positive	0.720 (0.335–1.550)	0.402	0.711 (0.422–1.196)	0.199	0.709 (0.404–1.245)	0.231
PR positive	0.477 (0.215–1.057)	0.068	0.502 (0.300–0.838)	0.008*	0.438 (0.252–0.763)	0.005*
HER2 positive	4.814 (2.097–11.050)	0.0002*	2.513 (1.357–4.655)	0.003*	2.584 (1.338–4.992)	0.004*
For IDC						
Tumor size (>5 cm)	0.936 (0.408–2.148)	0.877	1.718 (1.022–2.888)	0.041*	1.844 (1.095–3.107)	0.021*
Lymph node positive	3.134 (2.031–4.836)	<0.0001*	3.542 (2.525–4.967)	<0.0001*	3.846 (2.682–5.516)	<0.0001*
ER positive	0.901 (0.677–1.333)	0.828	0.862 (0.630–1.179)	0.353	0.848 (0.613–1.174)	0.320
PR positive	0.480 (0.291–0.645)	0.053	0.574 (0.417–0.788)	0.035*	0.527 (0.378–0.736)	0.056
HER2 positive	2.320 (1.264–4.557)	0.026*	1.112 (0.418–3.235)	0.680	1.129 (0.506–3.303)	0.450
For ILC+IDC						
Tumor size (>5 cm)	1.330 (0.713–2.981)	0.370	1.613 (1.002–2.597)	0.049*	1.590 (1.012–2.500)	0.044*
Lymph node positive	2.868 (1.939–4.244)	<0.0001*	3.766 (2.734–5.187)	<0.0001*	3.478 (2.583–4.684)	<0.0001*
ER positive	0.945 (0.659–1.355)	0.759	0.834 (0.629–1.105)	0.206	0.849 (0.649–1.110)	0.231
PR positive	0.524 (0.309–0.689)	0.153	0.508 (0.381–0.676)	0.003*	0.562 (0.429–0.735)	0.008*
HER2 positive	1.347 (0.895–2.029)	<0.0001*	1.218 (0.656–3.336)	0.048*	1.242 (0.689–3.713)	0.091
HER2×ILC	2.355 (1.209–4.587)	0.012*	2.671 (1.426–5.001)	0.002*	2.570 (1.427–4.628)	0.002*

chemotherapy and endocrine therapy is not better in ILC patients than that in IDC patients and is even worse in reducing the rate of contralateral breast cancer.

Over the last decade, the molecular subtypes generated by complementary DNA microarrays have served as base guidelines for systemic therapy decision and prognostic evaluation of breast cancer. Most correlations between molecular signatures and patient outcomes were derived from studies based on IDC. ILCs also differ from grade and molecular subtype-matched IDCs in the expression of various genes, although no differences existed among the histologic subtypes of ILC [40], which confirmed the unique biological behavior of ILC from IDC. Thus, the actual effect of ILC on the outcome would require comparison of the matched molecular classes of IDC but has drawn little attention. In the present study, we compared the outcomes of ILC and IDC patients according to molecular subtypes as determined by IHC. Interestingly, the OS, RFS, and DFS were similar between the subgroups of luminal A and TNBC, which were HER2-negative. In contrast with the subgroups of luminal B and HER2 overexpression with positive HER2 expression, the OS, RFS, and DFS were worse in ILC patients than those in IDC patients. Further analysis found HER2-positive ILCs had worse outcome than HER2-positive IDCs; however, ILCs and IDCs had similar outcome in HER2-negative subgroup. Multivariate analysis also determined that in the whole

population including ILCs and IDCs, the interaction of HER2 positivity and histologic type ILC was an independent risk factor for OS, RFS, and DFS. These results indicate that the subgroup of ILCs with HER2 positivity have worse outcome, though patients with ILC have similar outcome to IDC patients. HER2 overexpression may cause ILCs to be more aggressive. Therefore, HER2 overexpression exhibited stronger negative effect on prognosis than that in the IDC group, despite the lower rate in ILC patients. Unfortunately, no patients in our cohort received anti-HER2 treatment of trastuzumab because of its expensive cost that is not covered by medical insurance in China. The efficiency of trastuzumab could not be observed in the present study. However, the data confirmed the adverse effect of HER2 on outcome, and anti-HER2 treatment should be recommended.

In conclusion, our data based on a Chinese population show that despite the favorable biological features, ILC patients show no benefit of outcome compared with the IDC patients. Remarkably, ILCs with HER2 positivity have worse outcome, and the interaction of HER2 and ILC was defined as the independent risk factor for the outcome of the whole population. These results suggest that HER2 overexpression has stronger adverse effect on the prognosis in ILC patients than that in IDC patients, which suggests that a treatment targeting HER2 is crucial for this subgroup of breast cancer.

**Conflicts of interest** None

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