Scientific Research Publishing

International Journal of Clinical Medicine, 2019, 10, 662-678
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Patients with Early-Stage and Estrogen Receptor-Negative Breast Cancers: Young Age Does Link to Poor Outcomes

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How to cite this paper: Xie, Y.Y., Qing, L., Wang, Y., Zhou, Y.T., Qiu, J.J., Yang, Q.R. and Du, Z.G. (2019) Patients with Early-Stage and Estrogen Receptor-Negative Breast Cancers: Young Age Does Link to Poor Outcomes. *International Journal of Clinical Medicine*, **10**, 662-678.
https://doi.org/10.4236/ijcm.2019.1012055

Received: October 21, 2019
Accepted: December 24, 2019
Published: December 27, 2019

Abstract

Purpose: This study aimed to evaluate whether young adult breast cancer patients have poor outcomes independent of established prognostic factors and analyze differences in prognosis between younger and older patients stratified by tumor subtype. **Methods:** Of 10,950 breast cancer patients treated at West China Hospital between 1998 and 2017, 741 younger patients (<35 years) and 3705 older patients (≥35 years) were enrolled in this study after applying exclusion criteria and matching adjusted for the diagnosis year. Breast cancer-specific survival (BCSS) and disease-free survival (DFS) were analyzed between the two groups before and after propensity score matching (PSM) as well as in different subgroups. **Results:** We identified 11 parameters (all $P < 0.05$) that differed between the two groups. Cox regression analysis hazard ratios (HR) for BCSS and DFS in younger patients were 1.604 (95% CI, 1.327 - 1.938; $P < 0.001$) and 1.425 (95% CI, 1.234 - 1.645; $P < 0.001$) with reference to the older group. After balancing the differences in baseline characteristics between the two groups by PSM, the HRs for BCSS and DFS of younger patients decreased; however, the differences remained significant (HR for BCSS = 1.328 [95% CI, 1.038 - 1.698; $P = 0.024$] and HR for DFS = 1.301 [95% CI, 1.077 - 1.572; $P = 0.006$]). When stratified by tumor subtype, younger patients with T1, N0, tumor stage I, G3, estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and Ki67 ≥ 14% had a poor BCSS; in addition, patients with T1, N1, tumor stages I and II, G3, ER-negative, PR-negative, and triple-negative had a poorer DFS than older patients. **Conclusion:** Young age was an independent prognostic factor for BCSS and DFS in breast cancer patients. The increased risk of relapse was most pronounced in early-stage breast cancer, especially in patients with ER-negative disease.

Keywords

Breast Cancer, Young Age, Intrinsic Subtype, Propensity Score Matching, Prognosis

1. Introduction

Breast cancer is the most common cancer in women worldwide [1] [2]. In European and American countries, the majority of breast cancer patients are postmenopausal women [3]. Breast cancers are relatively rare in young adults, representing a small fraction of cases. Annually, about 6% - 7% of all breast cancers are diagnosed in patients under 40 years of age and less than 4% of patients are younger than 35 years [4] [5]. However, in Asian countries, a higher proportion of breast cancer is diagnosed at a young age, with a mean age at diagnosis about 10 years younger than that in western countries [4] [6]. Therefore, patients, doctors, and health departments should attach due attention to the young age at onset of breast cancers.

Young adults with breast cancer represent a group of patients with special management requirements [7] [8]. In a recent study, the risk of death increased by 5% for every one-year reduction in age among patients aged <35 years, whereas there was no significant correlation between the risk of death and age for patients aged 35 - 50 years [9]. However, in terms of prognosis, the majority of investigators reported that poor survival was not attributed to young age but rather that young adult breast cancer patients usually exhibit higher incidences of advanced stages at diagnosis, human epidermal growth factor receptor 2 (HER2)-positive status, ER or PR-negative status, and a higher histological classification grade than those of older patients [10] [11] [12]. Based on these reports, in recent years, nearly all guidelines no longer regard young age at breast cancer onset to be an independent poor prognostic factor [13]. However, other studies reported that younger age may also be associated with other situations, such as gene mutations or gene methylation, which may independently result in poor outcomes [14] [15]. Thus, whether young age remains an independent predictive prognostic factor, after adjusting for breast cancer subtype (ER, PR, and HER2 status) and other known prognostic factors (tumor stage, adjuvant systemic therapy, etc.), has to be determined.

Therefore, our comprehensive evaluation of breast cancer in young women first applied propensity score matching (PSM) to balance the baseline characteristics between younger and older groups to confirm whether young age (<35 years) is an independent risk factor for breast cancer-specific survival (BCSS) and disease-free survival (DFS). We also identified the characteristics of subgroups whose prognosis was most negatively influenced by the early-age onset of breast cancer in order to identify targeted populations of young adult breast cancer patients to receive more effective therapeutic regimens.

2. Methods

2.1. Patients

This retrospective analysis included 10,950 breast cancer patients who underwent surgery between 1998 and 2017 at the Department of Breast Surgery at West China Hospital of Sichuan University. The exclusion criteria included metastatic breast cancer, ductal carcinoma *in situ*, or bilateral breast cancer. We excluded 780 cases, including 375 cases of metastatic breast cancer, 338 cases of ductal carcinoma *in situ* and 67 cases of bilateral breast cancer. After exclusion, 10,170 patients, including 741 younger patients (<35 years) and 9429 older patients (≥35 years), were enrolled in the study. Because there was a stable increase in the proportion of young adult breast cancer patients (from 5.1% in 1998 to 8.2% in 2017), we created a matched cohort after adjusting for diagnosis year (1:5) to decrease the differences in survival due to the development of new therapies over time as well as to the difference in sample size between the two groups. Therefore, patients aged < 35 years at the time of surgery were allocated to the younger group (N = 741), while those aged ≥ 35 years were allocated to the older group (N = 3705) (Figure 1).

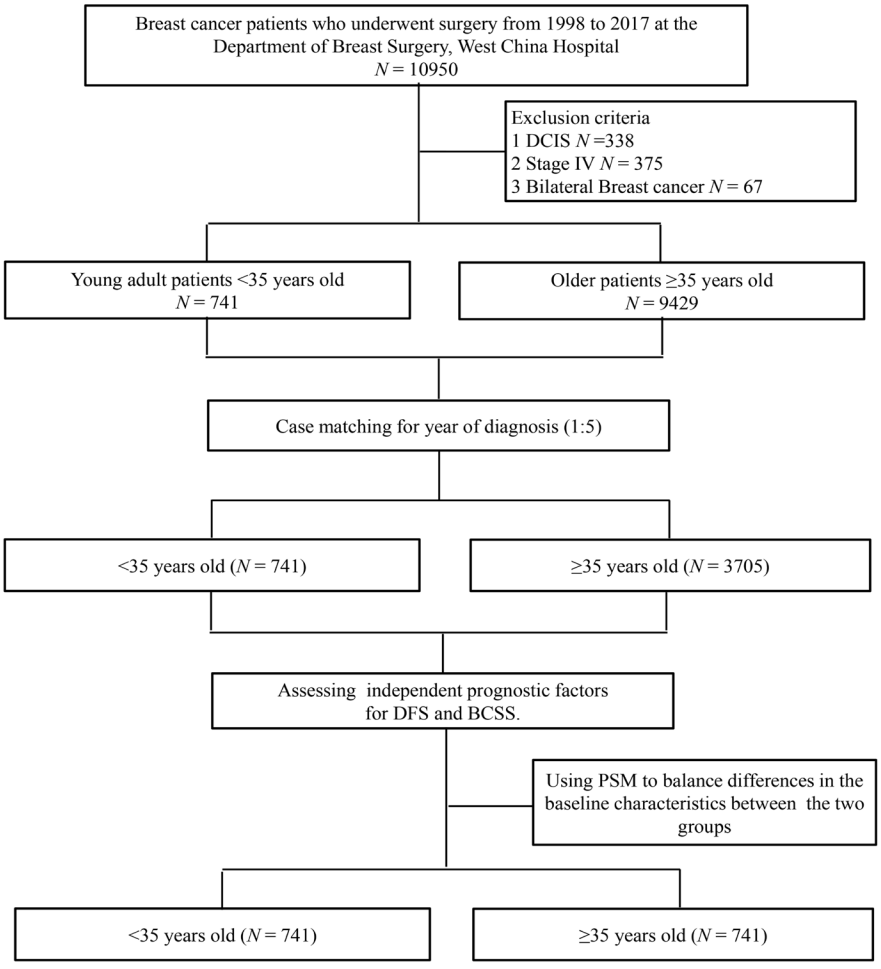

Figure 1. Overview of the study population.

2.2. Tumor Stage, Grade, and Subtypes

Tumor stage was reevaluated using the 8th American Joint Committee on Cancer (AJCC) system [16]. Histologic grade was classified into four groups: well differentiated (G1), moderately differentiated (G2), poorly differentiated and undifferentiated (G3), and unknown. Hormone receptor (HR) status was defined as positive when immunohistochemistry test results for either the ER or PR were positive and as negative when both tests results were negative. HER2 expression was defined as negative when the immunohistochemistry results were negative or 1+ and as positive when the results were 3+. When the results were 2+, we defined the HER2 positivity according to the results of the fluorescent *in situ* hybridization. According to the St. Gallen classification [17], the breast cancers were categorized into four subtypes: luminal A (HR-positive, HER2-negative, Ki-67 < 14%); luminal B (HR-positive, HER2-positiveor Ki-67 ≥ 14%); HER2 (HR-negative and HER2-positive); and triple negative (TN; HR-negative and HER2-negative).

2.3. Endpoint Definitions

The primary endpoints were the incidence of BCSS and DFS. BCSS was defined as the time from the start of treatment to death from breast cancer. Patients who died from causes other than breast cancer are not counted in this measurement. DFS was defined as the length of time from the date of surgery to the appearance of local recurrence, regional metastasis, second primary cancer, distant metastasis, or death.

2.4. Statistical Analysis

The descriptive statistics included means, ranges, standard deviations, and proportions. Categorical data are presented as percentages and differences between proportions were compared using chi-square or Fisher's exact tests. BCSS and DFS in two groups were computed using the Kaplan-Meier method and compared using log-rank tests. Univariate and multivariate analyses using Cox regression models with adjusted hazard ratios (HRs) along with 95% confidence intervals (CIs) were performed to assess the independent prognostic characteristics on DFS or BCSS. PSM was used to balance differences in the baseline characteristics between the younger and older patient groups. The propensity score was calculated using logistic regression including the covariates of T stage, lymph node metastasis, tumor subtype, histologic grade, and ER status. The adjusted cohort was used to validate the effect of age on outcome. Furthermore, we stratified the cases according to tumor characteristics and analyzed the probabilities of BCSS and DFS according to age. The result was presented as a forest plot. All statistical evaluations were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Results with P values < 0.05 were considered statistically significant. This study was reviewed and approved by the Institutional Ethics Committee, West China Hospital of Sichuan University.

3. Results

3.1. Patient Characteristics and the Association with Age at Diagnosis

The cohort of patients adjusted for diagnosis year was classified into younger (<35 years, $N = 741$) and older (≥35 years, $N = 3705$) age groups. The detailed features of the two groups are presented in Table 1. Eleven factors, including T stage, lymph node status, tumor stage, histologic grade, ER status, PR status, HER2 status, Ki-67, tumor subtype, and endocrinotherapy, differed significantly between the two groups. The results of the univariate analysis indicated that tumors in young breast cancer patients were more aggressive than those in older patients.

3.2. Survival Analysis

The median follow-up duration was 83 months (range, 3 - 180 months). In total, 603 (13.6%) patients died of breast cancer and 1126 (25.3%) patients experienced breast cancer recurrence or death. The 15-year BCSS and DFS rates for the younger and older groups were 81.1% and 87.5%, respectively ($P < 0.001$, Figure 2(a)) and 68.2% and 76.0%, respectively ($P < 0.001$, Figure 2(b)).Cox regression analysis showed that the HRs for BCSS and DFS in the younger patients were 1.604 (95% CI, 1.327 - 1.938; $P < 0.001$) and 1.425 (95% CI, 1.234 - 1.645; $P < 0.001$), respectively, with reference to the older group. Thus, the prognosis of younger breast cancer patients was worse than that of older breast cancer patients. However, we cannot conclude that young age is an independent risk factor of BCSS and DFS because the poor outcomes may be due to more aggressive tumors in the younger patients than those in the older patients. In order to discover whether the poor prognosis among young adults with breast cancer was due to age itself, we set the BCSS and DFS as the research endpoints for Cox regression analysis in Table 2. Univariate analysis showed that all factors except for histologic grade, Ki-67, and radiotherapy could predict the BCSS and all factors except for Ki-67, radiotherapy, and chemotherapy could predict the DFS. Furthermore, the multivariate analysis performed using the factors associated with survival outcomes in univariate analysis revealed that age remained an independent factor associated with BCSS ($P < 0.001$) and DFS ($P < 0.001$).

3.3. Survival Analysis According to PSM in the Corrected Cohort

To validate the effect of age on BCSS and DFS, PSM was used to balance the differences in baseline characteristics and generate a corrected cohort. The propensity score was calculated using a logistic regression that included the covariates of all independent risk factors for BCSS and DFS; namely T stage, lymph node status, histologic grade, ER status, and tumor subtype. All covariates were well-balanced between the younger and older groups in the corrected cohort (all P values > 0.260, Table 3). The 15-year BCSS and DFS rates for the younger and older groups were 81.1% and 84.3% ($P = 0.023$, Figure 3(a)) and 68.2% and

Table 1. Clinicopathological characteristics and treatment regiments in younger and older breast cancer patients.

	<35 years N = 741, No. (%)	≥35 years N = 3705, No. (%)	χ^2	P-value
T stage			11.532	0.021
T1	243 (32.8)	1279 (34.5)		
T2	339 (45.7)	1795 (48.4)		
T3	91 (12.3)	399 (10.8)		
T4	55 (7.4)	198 (5.3)		
Unknown	13 (1.8)	34 (0.9)		
Lymph node status			30.096	<0.001
N0	294 (39.7)	1691 (45.6)		
N1	210 (28.3)	1137 (30.7)		
N2	124 (16.7)	535 (14.4)		
N3	113 (15.2)	342 (9.2)		
Tumor stage			26.383	<0.001
1	160 (21.6)	904 (24.4)		
2	314 (42.4)	1,808 (48.8)		
3	260 (35.1)	973 (26.3)		
Unknown	7 (0.9)	20 (0.5)		
Histologic grade			42.810	<0.001
G1	68 (9.2)	535 (14.4)		
G2	256 (34.5)	1553 (41.9)		
G3	383 (51.7)	1470 (39.7)		
Unknown	34 (4.6)	147 (4.0)		
ER status			10.130	0.001
Negative	221 (22.8)	899 (24.3)		
Positive	520 (70.2)	2806 (75.7)		
PR status			4.995	0.025
Negative	225 (30.4)	977 (26.4)		
Positive	516 (69.6)	2728 (73.6)		
HER2 status			8.097	0.017
Negative	361 (48.7)	2016 (54.4)		
Positive	180 (24.3)	790 (21.3)		
Unknown	200 (27)	899 (24.3)		
Ki-67 (%)			8.710	0.013
<14%	277 (37.4)	1503 (40.6)		
≥14%	438 (59.1)	2130 (57.5)		
Unknown	26 (3.5)	72 (1.9)		
Tumor subtype			22.173	<0.001
Luminal A	89 (12.0)	604 (16.3)		
Luminal B	369 (49.8)	1923 (51.9)		

Continued

HER2	58 (7.8)	173 (4.7)		
Triple-negative	103 (13.9)	474 (12.8)		
Unknown	122 (16.5)	531 (14.3)		
Surgery			0.087	0.768
Breast-conserving	97 (13.1)	500 (13.5)		
Mastectomy	644 (86.9)	3205 (86.5)		
Radiotherapy			0.440	0.802
No	599 (80.8)	2,957 (79.8)		
Yes	119 (16.1)	622 (16.8)		
Unknown	23 (3.1)	126 (3.4)		
Chemotherapy			6.622	0.086
No	117 (15.8)	713 (19.2)		
Yes	586 (79.1)	2802 (75.6)		
Unknown	38 (5.1)	190 (5.1)		
Endocrinotherapy			7.101	0.029
No	245 (33.1)	1045 (28.2)		
Yes	485 (65.5)	2604 (70.3)		
Unknown	11 (1.5)	56 (1.5)		

73.3%, respectively (P = 0.006, Figure 3(b)). Cox regression analysis showed that the HRs for BCSS and DFS of the younger patients decreased when compared to those in the unmatched cohort; however, the difference remained statistically significant (HR for BCSS = 1.328 [95% CI, 1.038 - 1.698; P = 0.024] and HR for DFS = 1.301 [95% CI, 1.077 - 1.572; P = 0.006]).

3.4. Subgroup Analysis in the Corrected Cohort

In order to identify the poor outcomes of what kinds of patients were most correlated with young age in this study, subgroup analyses were performed based on all clinicopathological characteristics in the corrected data. The results of BCSS and DFS rates are summarized in Figure 4. Patients in the younger group with T1, N0, tumor stage I, G3, ER-negative, PR-negative, and Ki67 ≥ 14% had a poorer BCSS compared with that in patients in the older group. Similarly, patients in the younger group with T1, N1, tumor stages I and II, G3, ER-negative, PR-negative, and triple-negative tumors had a poorer DFS compared to that in patients in the older group. In general, younger patients with early-stage tumors and ER-negative had a significantly increased incidence of poor outcomes compared to those of older patients.

4. Discussion

Whether young age is an independent risk factor for breast cancer survival is controversial [14] [18] [19] [20]. In this population-based cohort study, we found that young age was highly correlated with progressive tumor characters.

Table 2. Univariate and multivariate Cox regression analysis of all clinical and pathological parameters.

	BCSS				DFSS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	P-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)		<0.001		<0.001		<0.001		<0.001
<35	1.604 (1.327 - 1.938)		1.529 (1.264 - 1.850)		1.425 (1.234 - 1.645)		1.376 (1.191 - 1.589)	
≥35	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T stage		<0.001		<0.001		<0.001		<0.001
T1	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
T2	2.657 (2.106 - 3.352)		2.372 (1.859 - 3.026)		1.574 (1.367 - 1.813)		1.576 (1.368 - 1.816)	
T3	4.922 (3.772 - 6.424)		3.909 (2.858 - 5.348)		2.139 (1.77 - 2.584)		2.121 (1.755 - 2.562)	
T4	3.134 (2.174 - 4.519)		2.483 (1.647 - 3.744)		1.420 (1.076 - 1.872)		1.396 (1.059 - 1.842)	
Unknown	4.129 (2.149 - 7.934)		3.386 (1.744 - 6.576)		1.800 (1.052 - 3.078)		1.770 (1.034 - 3.029)	
Lymph node status		<0.001		0.001		0.003		
N0	1 (ref)				1 (ref)			
N1	1.833 (1.493 - 2.251)		1.451 (1.174 - 1.792)		1.102 (0.958 - 1.268)			
N2	2.514 (2.002 - 3.156)		1.600 (1.238 - 2.068)		1.241 (1.045 - 1.473)			
N3	2.664 (2.08 - 3.411)		1.485 (1.11 - 1.986)		1.383 (1.146 - 1.669)			
Tumor stage		<0.001		0.503		<0.001		
1	1 (ref)				1 (ref)			
2	2.773 (2.067 - 3.72)				1.543 (1.31 - 1.816)			
3	4.576 (3.407 - 6.144)				1.748 (1.469 - 2.081)			
Unknown	3.476 (1.258 - 9.605)				1.149 (0.473 - 2.791)			
Histologic grade		0.177		-		0.001		0.002
G1	1 (ref)				1 (ref)		1 (ref)	
G2	0.997 (0.766 - 1.299)				1.040 (0.855 - 1.264)		1.019 (0.838 - 1.239)	
G3	1.192 (0.921 - 1.542)				1.269 (1.049 - 1.535)		1.232 (1.018 - 1.491)	
Unknown	1.230 (0.795 - 1.901)				1.491 (1.095 - 2.029)		1.497 (1.099 - 2.039)	
ER		<0.001		0.827		0.010		0.029
Positive	1 (ref)				1 (ref)		1 (ref)	
Negative	0.701 (0.591 - 0.831)				0.84 3 (0.74 - 0.959)		0.865 (0.759 - 0.985)	
PR		<0.001		0.782		0.048		
Positive	1 (ref)				1 (ref)			
Negative	0.726 (0.614 - 0.860)				0.879 (0.773 - 0.999)			
HER2		<0.001		0.845		0.011		
Positive	1 (ref)				1 (ref)			
Negative	1.393 (1.144 - 1.695)				1.237 (1.071 - 1.429)			
Unknown	1.366 (1.128 - 1.653)				1.137 (0.986 - 1.31)			
Ki-67(%)		0.258		-		0.783		
<14%	1 (ref)				1 (ref)			
≥14%	1.100 (0.933 - 1.298)				1.009 (0.895 - 1.137)			

Continued

Unknown	0.725 (0.385 - 1.365)			0.870 (0.572 - 1.323)	
Tumor subtype		<0.001	0.001		0.001
Luminal A	1 (ref)		1 (ref)	1 (ref)	
Luminal B	1.266 (0.978 - 1.639)		1.009 (0.777 - 1.311)	1.037 (0.873 - 1.233)	
HER2	2.378 (1.683 - 3.361)		1.462 (1.028 - 2.079)	1.634 (1.26 - 2.12)	
Triple Negative	1.617 (1.185 - 2.207)		1.516 (1.11 - 2.071)	1.038 (0.828 - 1.301)	
Unknown	1.490 (1.099 - 2.021)		0.922 (0.674 - 1.261)	1.187 (0.961 - 1.465)	
Surgery		<0.001	0.377		<0.001
Breast-conserving	1 (ref)			1 (ref)	
Mastectomy	2.101 (1.541 - 2.865)			1.419 (1.171 - 1.720)	
Radiotherapy		0.820	-		0.665
Yes	1 (ref)			1 (ref)	
No	1.047 (0.798 - 1.373)			1.047 (0.897 - 1.222)	
Unknown	0.89 (0.57 - 1.392)			0.895 (0.639 - 1.255)	
Chemotherapy		0.001	0.421		0.264
Yes	1 (ref)			1 (ref)	
No	2.932 (1.655 - 5.194)			1.136 (0.974 - 1.326)	
Unknown	2.695 (1.38 - 5.264)			1.080 (0.807 - 1.445)	
Endocrinotherapy		<0.001	0.478		0.028
No	1 (ref)			1 (ref)	
Yes	0.698 (0.591 - 0.824)			0.858 (0.756 - 0.973)	
Unknown	0.867 (0.445 - 1.688)			1.185 (0.755 - 1.859)	

The survival analysis also indicated that young age (<35 years) at diagnosis was associated with unfavorable clinical outcomes in women with breast cancer in both the unadjusted and adjusted cohorts, especially patients in the early-stage and ER-negative subgroups.

A number of studies have focused on the prognosis of young and old age at diagnosis of breast cancer. Some have reported young age to be an independent risk factor for relapse in operable breast cancer patients [21] [22] [23]; however, others reported that age is not significantly related to mortality from breast cancer when accounting for all prognostic variables [10] [12] [19]. The inconsistent results may be due to differences in the definitions of young age in these studies, such as that under the ages of 30, 35, 40, or even 45 years [8] [24]-[29]. In clinical practice, an optimal cutoff value is needed to define young patients with breast cancer. The Suppression of Ovarian Function Trial (SOFT) showed that ovarian function suppression (OFS) did not provide a significant benefit to the overall study population but did improve disease outcomes in younger patients (<35 years) [30]. After consulting experts and the literature, St Gallen adopted acutoff of 35 years to define the risk categories of breast cancer patients [26]. Therefore, our population-based cohort study used 35 years as the cutoff to

Table 3. Univariate analysis of matched factors between younger and older breast cancer patients in the corrected cohort.

	<35 years N = 741, No. (%)	≥35 years N = 741, No. (%)	χ^2	P-value
T stage			4.521	0.340
T1	243 (32.8)	213 (28.7)		
T2	339 (45.7)	358 (48.3)		
T3	91 (12.3)	107 (14.4)		
T4	55 (7.4)	54 (7.3)		
Unknown	13 (1.8)	9 (1.2)		
Lymph node status			3.134	0.371
N0	294 (39.7)	268 (36.2)		
N1	210 (28.3)	236 (31.8)		
N2	124 (16.7)	131 (17.7)		
N3	113 (15.2)	106 (14.3)		
Tumor stage			2.555	0.465
1	160 (21.6)	137 (18.5)		
2	314 (42.4)	335 (45.2)		
3	260 (35.1)	263 (35.5)		
Unknown	7 (0.9)	6 (0.8)		
Histologic grade			3.976	0.264
G1	68 (9.2)	70 (9.4)		
G2	256 (34.5)	279 (37.7)		
G3	383 (51.7)	348 (47)		
Unknown	34 (4.6)	44 (5.9)		
ER			0.396	0.529
Negative	221 (22.8)	210 (28.3)		
Positive	520 (70.2)	531 (71.7)		
Tumor subtype			5.281	0.260
Luminal A	89 (12.0)	115 (15.5)		
Luminal B	369 (49.8)	348 (47)		
HER2	58 (7.8)	47 (6.3)		
Triple-negative	103 (13.9)	102 (13.8)		
Unknown	122 (16.5)	129 (17.4)		

define young breast cancer patients.

Using this definition, we observed a continuous increase in the proportion of young breast cancer patients (from 5.1% in 1998 to 8.2% in 2017). In the past two decades, the treatment of breast cancer has changed significantly. Thus, relatively more young patients underwent modern therapies and more old patients underwent the old treatments two decades ago. Therefore, we created a matched cohort adjusted for diagnosis year to eliminate the effects of different therapies

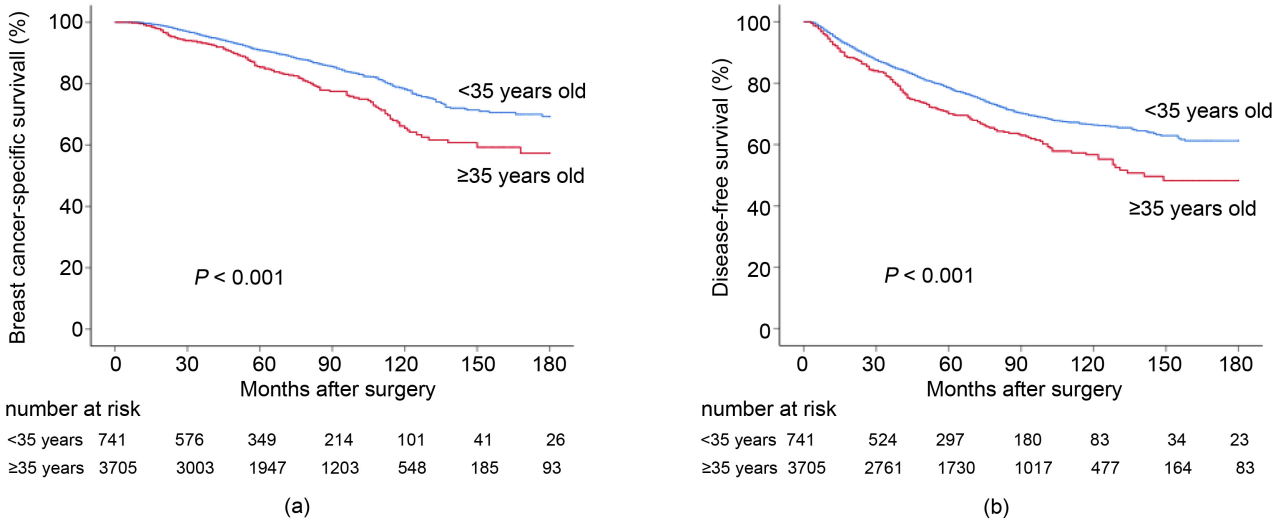

Figure 2. Kaplan-Meier curves showing breast cancer cancer-specific survival (a) and disease disease-free survival (b) with respect to age at diagnosis.

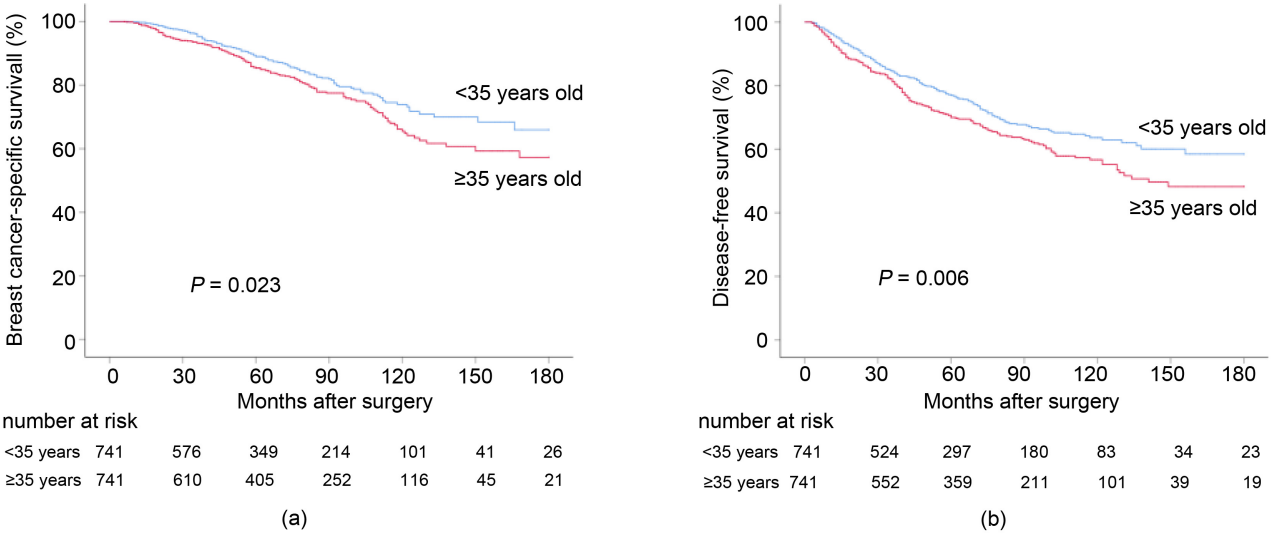

Figure 3. Kaplan-Meier curves showing breast cancer cancer-specific survival (a) and disease disease-free survival (b) with respect to age at diagnosis in the corrected cohort.

in over time. Many previous studies did not match the age at diagnosis of breast cancer, which may also contribute to the inconsistent results.

In this study, young breast cancer patients were more likely to have a higher T grade, proportion of histological grade III, ER and PR-negative status, HER-2 overexpression, TNBC subtype, higher stage, and an increased possibility of lymph node invasion, a finding consistent with other literature [10] [12] [31]. Therefore, it is reasonable that young breast cancer patients had a worse prognosis than that of older patients due to the more aggressive nature of the tumors. However, we cannot conclude that young age is an independent prognostic factor. To elucidate the individual role of young age on survival outcomes, we used PSM to balance differences in baseline characteristics correlated with BCSS or

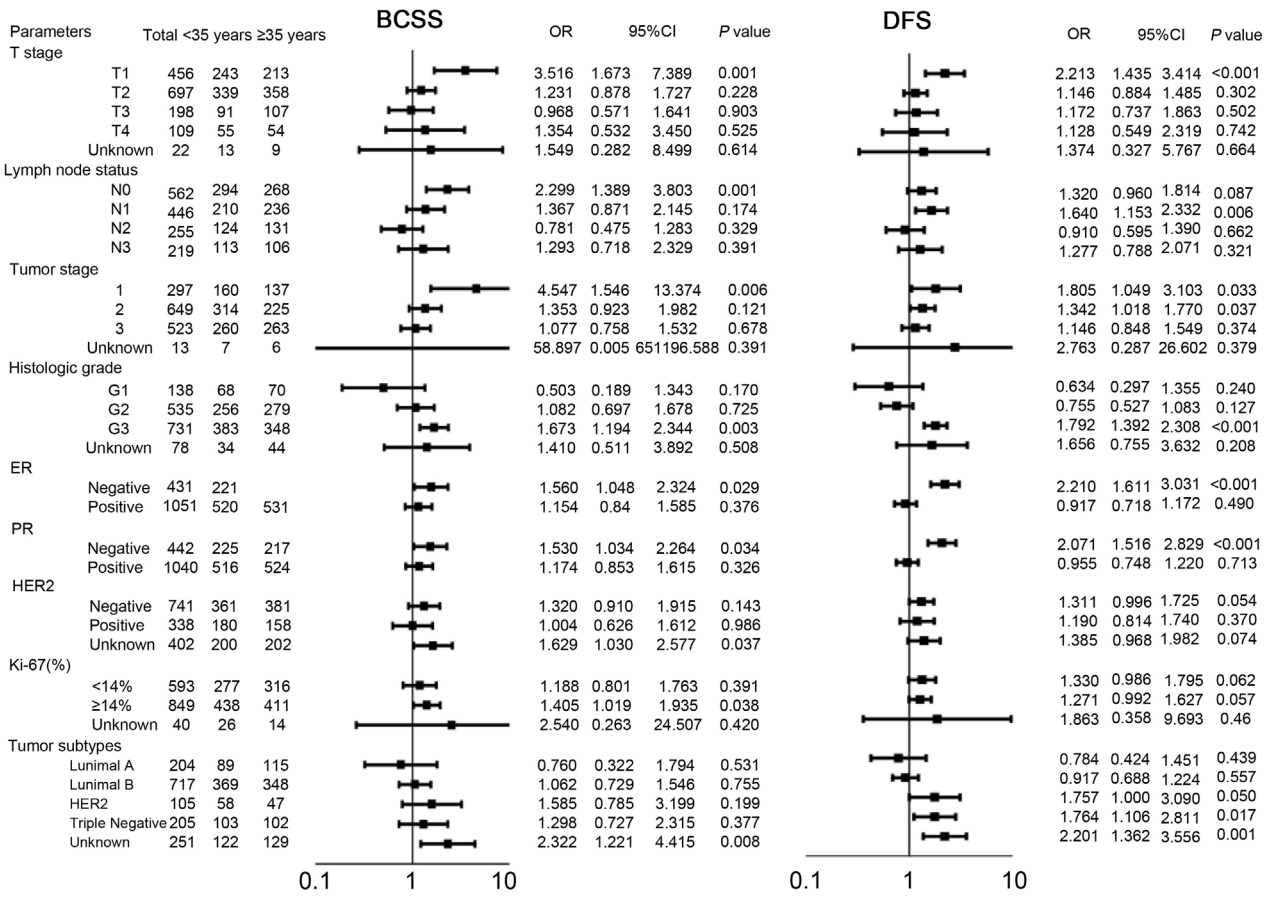

Figure 4. Stratified analysis according to variable and the probability of breast cancer cancer-specific survival analysis and disease disease-free survival according to age.

DFS between the two groups. We found that patients in the younger group had poorer BCSS and DFS compared to those of the patients in the older group. This result showed that, in addition to the aggressive parameters we have already known, other characteristics may also affect the survival of young breast cancer patients. For example, gene expression or molecular biological characteristics in young patients with breast cancer also reportedly contribute to the poor prognosis [32] [33] [34].

As young age at diagnosis of breast cancer appeared to affect patient survival in some way, it remained undetermined if this factor affected all subgroups of breast cancer patients. To answer this question, we performed subgroup analysis and demonstrated that young patients with breast cancer had poorer survival outcomes mainly in the early-stage and ER-negative subgroups. Most of researchers reported that younger patients showed a worse prognosis than that of older patients in ER-positive subgroups [10] [28] [35]. In contrast, just like the other researchers reported [19], our current study showed similar prognosis for younger and older ER-positive patients. The reason for this finding may be due to the fact that up to 73% of ER-positive patients in the younger group underwent adjuvant chemotherapy and more than one-third chose more aggressive

endocrinotherapy such as OFS. Younger patients with ER-negative disease had a worse prognosis, especially those with early-stage disease. One the reason for this observation is that the younger patients, especially those with ER-negative tumors, may have a number of micrometastases [36]. Thus, the results of this study, suggest that younger patients with early-stage and ER-negative breast cancer should undergo more aggressive treatment because traditional treatments may be insufficient.

Our study has several potential limitations. Retrospective analyses always carry a risk of various biases. However, with the use of a large-scale sample size, subgroup analysis, and PSM, our study minimized potential biases and had a high degree of power. Moreover, previous literature mainly analyzed young breast cancer with worse prognosis, rarely indicating whether age was an independent risk factor. Our study not only showed that young age was an independent risk factor for breast cancer but subgroup analysis also revealed that age mainly affected the prognosis of early-stage and ER-negative breast cancers. Although no prospective study has demonstrated young age to be an independent prognostic factor, it should be regarded as a risk predictor for survival. Treatment of breast cancer should consider age in association with other pathological and biological factors so that young breast cancer patients can receive more effective therapeutic regimens.

5. Conclusion

Young age was an independent prognostic factor of BCSS and DFS for breast cancer patients. The excess risk of relapse was most pronounced in early-stage breast cancer, especially in ER-negative tumors.

Conflicts of Interest

The authors do not have any disclosures to report.

Ethical Standards

This study was reviewed and approved by the Institutional Ethics Committee, West China Hospital of Sichuan University.

Financial Support

This study was supported by a grant from the Natural Science Foundation of China (No. 81400652), the supporting projects of the Science and Technology Department, Sichuan Province (2015SZ0236) and the Key Program of the Science and Technology Bureau of Sichuan (No. 2018SZ0052).

Data Availability

The datasets generated during and/or analysed during the current study are not publicly available due our data base runs on a local area network but are available from the corresponding author on reasonable request.

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Abbreviations

BCSS, Breast cancer-specific survival; DFS, Disease-free survival; PSM, Propensity score matching; HR, Hazard ratios; ER, Estrogen receptor; PR, Progesterone receptor.