

Correlation Between Clinical-Pathologic Factors and Long-Term Follow-Up in Young Breast Cancer Patients

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Abstract

OBJECTIVE: Diagnosis of breast cancer in young patients (≤ 35) correlates with a worse prognosis compared to their older counterparts (>35). The aim of this study is to evaluate the relevance of clinical-pathologic factors and prognosis in young (≤ 35) breast cancer patients. **METHODS:** One hundred thirty-two patients of operable breast cancer who were younger than 35 are analyzed in this study. They were treated in our hospital between January 2006 and December 2012. Patients are classified into four molecular subtypes based on the immunohistochemical profiles of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. Clinical and pathologic factors have been combined to define a specific classification of three risk levels to evaluate the prognosis of these young women. **RESULTS:** Patients whose ages are less than 30 have poorer prognosis than patients whose ages are between 31 and 35. The status of lymph nodes post-surgery seems to be the only factor related to patient age in young patients. The patients in level of ER + or PR + and HER2 –/+ status have the worst prognosis in hormone receptor–positive breast cancer. Group 3 in risk factor grouping has the poorer prognosis than the other two groups. **CONCLUSIONS:** Patient age and axillary lymph nodes post-surgery are the independent and significant predictors of distant disease-free survival, local recurrence-free survival, and overall survival. The absence of PR relates to poor prognosis. The risk factor grouping provides a useful index to evaluate the risk of young breast cancer to identify subgroups of patients with a better prognosis.

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Introduction

Breast cancer is uncommon in young women and correlates with a less favorable prognosis; still it is the most frequent cancer in women under 40. Around 6.6% of all breast cancer cases are diagnosed in women less than 40 years old, 2.4% in women less than 35, and 0.65% in women less than 30 [1,2]. However, in China, the proportion of patients in the age group of less than 35 was reported much higher [3].

On the basis of various prospective and retrospective studies, age is an independent prognostic factor with worse survival; however, this issue is now considered controversial. A great number of reports showed that young breast cancer patients have more aggressive features, such as biologically more ER negative [4–7], higher histologic grade, and more triple-negative subtype [8,9]. Yet other studies have attributed the inferior outcome of young age to the more advanced presentation at diagnosis, including higher rates of axillary lymph node positivity and

larger tumor size [10–13]. Others have postulated that the effect of differential gene expression between different age groups might play a role [6,14]. However, all the above studies demonstrated that young breast cancer patients have early recurrence with shorter disease-free survival and overall survival (OS) compared with older patients.

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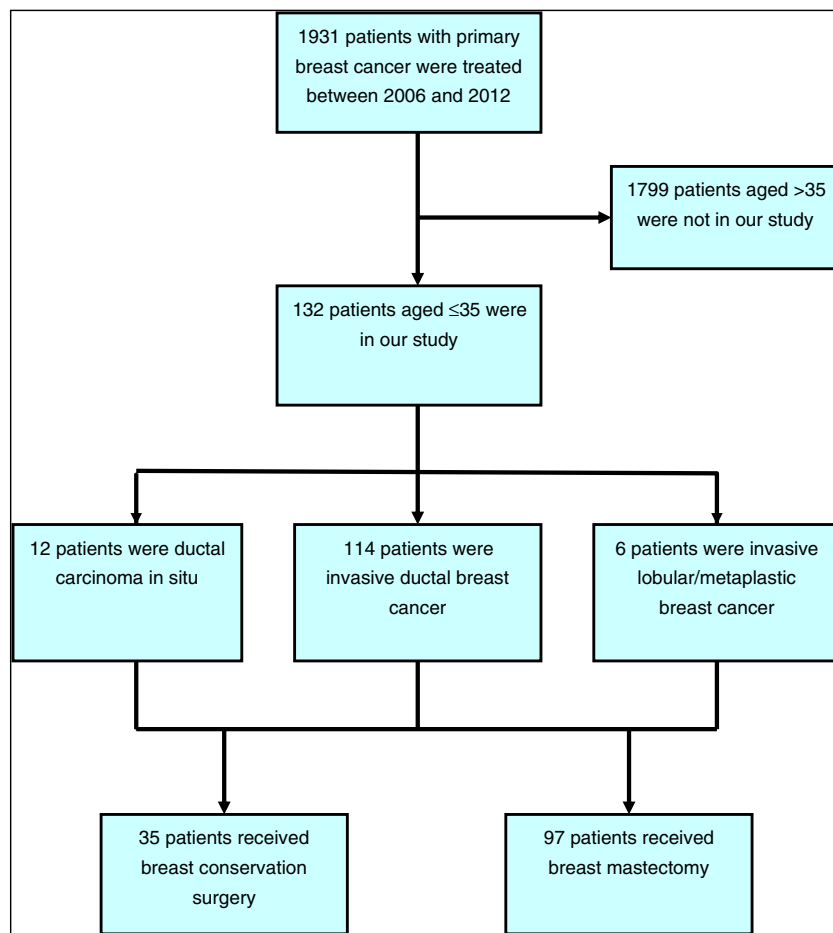


Figure 1. Patient selection, pathologic diagnosis, and surgical procedure.

Other than triple-negative and HER2-enriched subtypes, hormone receptor-positive breast cancer is also the main subtype in young patients. In this study, we divided hormone receptor-positive breast cancer and invasive ductal carcinomas into different risk levels to evaluate the prognosis of young patients.

Materials and Methods

Patients

This study was approved by the institutional review board (IRB) of Harbin Medical University. One thousand nine hundred thirty-one patients who were initially diagnosed with breast cancer between 2006 and 2012 by surgical resection were retrieved from the Second Affiliated Hospital, Harbin Medical University. Among those patients, a total of 132 patients younger than age 35 was included in this analysis. The patient selection process, pathologic diagnosis, and surgical procedure are shown in Figure 1. Tumor size and lymph nodes were assessed using the seventh edition of the American Joint Committee on Cancer staging manual [15].

Molecular Subtypes and Treatment

Immunohistochemical assay was used to test for the expression of ER, PR, HER2, and Ki-67. The cutoff value for ER positivity was defined as $\geq 10\%$ of tumor cells with nuclear staining; PR positivity was defined as $\geq 20\%$ of tumor cells with nuclear staining. The immunohistochemical staining for HER2 was scored as 0, 1+, 2+, or

3+ according to standard criteria [16]. Scores of 0 and 1+ were considered negative and 3+ was considered HER2-positive. When a score of 2+ was found, additional fluorescence in situ hybridization (FISH) testing was done to establish HER2 gene amplification status. A positive result was defined as an HER2 gene/chromosome 17 ratio of larger than 2.0. The Ki-67 positive was defined as $\geq 14\%$, and negative was defined as $< 14\%$ [17]. The subtype was proposed to separate luminal A (ER+, PR+, HER2-, Ki-67 $< 14\%$), luminal B (ER+ or PR+, HER2-; ER+, PR+, HER2-, Ki-67 $\geq 14\%$; ER+/PR+, HER2+), HER2-enriched (ER-, PR-, HER2+), and triple-negative (ER-, PR-, HER2-) [18].

Nineteen patients who were hormone receptor positive and Ki-67 $< 14\%$ in post-surgery cancers only received 5 years of adjuvant endocrine therapy, whereas hormone receptor positive and Ki-67 $\geq 14\%$ received adjuvant/neoadjuvant chemotherapy and endocrine therapy. Patients who were positive for axillary lymph node following surgery ($n \geq 3$) and patients who received breast conservation surgery received radiation therapy, whereas patients positive for axillary lymph node following surgery ($n \geq 3$) and patients who received breast conservation surgery received radiation therapy.

Classification of Hormone Receptor-Positive Breast Cancer

Although there have been more triple-negative and HER2-enriched subtypes, hormone receptor-positive breast cancer is still the main subtype in young patients. ER+ and/or PR+ breast cancer is a highly heterogeneous disease comprising different histology, gene expression

Table 1. Clinical-Pathologic Characteristics and Outcome

	Total	Local Relapse	Distant Relapse	Died of Disease	LRFS			DDFS			OS		
	N (%)	N (%)	N (%)	N (%)	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI
Patient age													
≤30	43 (32.58)	25 (46.30)	21 (46.67)	19 (59.38)	.0004	0.37	0.22-0.64	.0030	0.41	0.23-0.74	.0002	0.26	0.13-0.53
31-35	89 (67.42)	29 (53.70)	24 (53.33)	13 (40.63)									
ER status													
+	89 (67.42)	36 (66.67)	24 (53.33)	17 (53.13)	.7804	0.92	0.52-1.63	.0161	0.49	0.27-0.88	.0460	0.49	0.24-0.99
-	43 (32.58)	18 (33.33)	21 (46.67)	15 (46.88)									
PR status													
+	86 (65.15)	33 (61.11)	20 (44.44)	16 (50.00)	.0677	0.60	0.34-1.04	<.0001	0.29	0.16-0.52	.0050	0.37	0.18-0.74
-	46 (34.85)	21 (38.89)	25 (55.56)	16 (50.00)									
HER2 status													
+	37 (28.03)	22 (40.74)	22 (48.89)	17 (53.13)	.0113	2.02	1.17-3.48	.0007	2.77	1.54-4.98	.0040	2.79	1.39-5.60
-	91 (68.94)	32 (59.26)	23 (51.11)	15 (46.88)									
NA	4 (3.03)	0 (0.00)	0 (0.00)	0 (0.00)									
Diagnosis													
DCIS	12 (9.09)	0 (0.00)	0 (0.00)	0 (0.00)	.0808	1.95	0.92-4.11	.1000	1.95	0.88-4.34	.1140	2.22	0.83-5.97
IDC	114 (86.36)	52 (96.30)	43 (95.56)	30 (93.75)									
Other	6 (4.55)	2 (3.70)	2 (4.44)	2 (6.25)									
Tumor grade													
1	9 (6.82)	2 (3.70)	1 (2.22)	1 (3.13)	<.0001	3.97	2.28-6.91	<.0001	4.03	2.26-7.19	<.0001	4.59	2.28-9.25
2	74 (56.06)	27 (50.00)	21 (46.67)	11 (34.38)									
3	31 (23.48)	23 (42.59)	21 (46.67)	18 (56.25)									
NA	18 (13.64)	2 (3.70)	2 (4.44)	2 (6.25)									
Tumor size													
T1	35 (26.52)	4 (7.41)	6 (13.33)	3 (9.38)	<.0001	4.53	2.96-6.92	<.0001	2.86	1.94-4.22	<.0001	3.14	2.00-4.93
T2	73 (55.30)	29 (53.70)	20 (44.44)	15 (46.88)									
T3	21 (15.91)	18 (33.33)	16 (35.56)	11 (34.38)									
T4	3 (2.27)	3 (5.56)	3 (6.67)	3 (9.38)									
Lymph nodes post-surgery													
pN0	65 (49.24)	11 (20.37)	9 (20.00)	5 (15.63)	<.0001	2.87	2.20-3.79	<.0001	2.71	2.04-3.59	<.0001	2.79	2.00-3.90
pN1	31 (23.48)	12 (22.22)	9 (20.00)	6 (18.75)									
pN2	18 (13.64)	13 (24.07)	11 (24.44)	5 (15.63)									
pN3	18 (13.64)	18 (33.33)	16 (35.56)	16 (50.00)									
Ki-67 status													
+	84 (63.64)	40 (74.07)	38 (84.44)	26 (81.25)	.0243	2.04	1.10-3.78	.0015	3.71	1.65-8.32	.0069	3.90	1.45-10.466
-	44 (33.33)	14 (25.93)	7 (15.56)	6 (18.75)									
NA	4 (3.03)	0 (0.00)	0 (0.00)	0 (0.00)									
Molecular subtype													
Luminal A	8 (6.06)	2 (3.70)	5 (11.11)	2 (6.25)	.4532	1.11	0.85-1.45	.0035	1.51	1.14-1.98	.0157	1.52	1.08-2.13
Luminal B	27 (20.45)	6 (11.11)	1 (2.22)	0 (0.00)									
HER2-enriched	66 (50.00)	39 (72.22)	30 (66.67)	24 (75.00)									
Triple-negative	10 (7.58)	0 (0.00)	0 (0.00)	0 (0.00)									
NA	21 (15.91)	7 (12.96)	9 (20.00)	6 (18.75)									

Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma.

profiles, and mutational patterns, with very varied clinical courses and responses to systemic treatment [19–22]. However, despite ongoing international efforts to improve Ki-67 testing, including recommendations on pre-analytical and analytical issues, interpretation, and scoring [23], a recent Ki-67 reproducibility study involving experienced pathologists showed significant interobserver variability [24]. In our study, we divided hormone receptor-positive breast cancer into three levels regardless of the status of Ki-67 to evaluate the prognosis of young patients: level 1—ER+, PR+, HER2-; level 2—ER+, PR+, HER2+; level 3—ER+ or PR+, HER2-/+ . Patients with level 2 and level 3 tumors received more chemotherapy than the level 1 subgroup. The level 1 subgroup was treated with less chemotherapy and more endocrine therapy than the other subgroups.

Definition of Important Risk Factors

According to the important risk factors (ER, PR, HER2, and Ki-67 status, tumor grade, and lymph nodes post-surgery), 114 patients were divided into three groups. Group 1's score is from 1 to 4, group 2's score is from 5 to 6, and group 3's score is from 7 to 10. Tumors in the three different groups were calculated as immunohistochemical results

(ER-, PR-, HER2+, and Ki-67+, one point each) + tumor grade (grade 1 tumor equals one point, and so on) + lymph nodes post-surgery (score: 0 for no positive node, 1 for 1-3 nodes, 2 for 4-9 nodes, and 3 for ≥10 nodes). Groups 1, 2, and 3 were categorized as low risk, medium risk, and high risk, respectively.

Statistical Analysis

The study comprised two parts: the univariate and the multivariate analyses. In the univariate section, the studied factors were analyzed through the time-to-event endpoints. Distant disease-free survival (DDFS) was defined as the time interval between surgery and the first documented distant relapse, death, or last follow-up. Local recurrence-free survival (LRFS) was defined as the time interval between surgery and the first documented local recurrence, death, or last follow-up. OS was defined as the time between surgery and death or last follow-up, which ever occurred first. For both endpoints, the median survival time were estimated for all variables (patient age, ER status, PR status, HER2 status, tumor grade, tumor size, lymph nodes post-surgery, Ki-67 status, molecular subtype, hormone receptor-positive grouping, and risk grouping). The median follow-up is summarized by its median and interquartile range.

Table 2. Clinical-Pathologic Characteristics and Patient Age

	Total	≤30	31-35	χ^2	P	Median Survival Time (Months)		
	N (%)	N (%)	N (%)			LRFS	DDFS	OS
ER status								
+	89 (67.42)	30 (69.77)	59 (66.29)	0.1594	.6897	81	>99	92
-	43 (32.58)	13 (30.23)	30 (33.71)			78	66	85
PR status								
+	86 (65.15)	26 (60.47)	60 (67.42)	0.6169	.4322	83	>99	>99
-	46 (34.85)	17 (39.53)	29 (32.58)			59	49	92
HER2 status								
+	37 (28.03)	14 (32.56)	23 (25.84)	2.4198	.2982	56	54	89
-	91 (68.94)	29 (67.44)	62 (69.66)			83	>99	>99
NA	4 (3.03)	0 (0.00)	4 (4.49)			>80	>80	>80
Diagnosis								
DCIS	12 (9.09)	3 (6.98)	9 (10.11)	1.1437	.5645	>85	>85	>85
IDC	114 (86.36)	37 (86.05)	77 (86.52)			78	>99	92
Others	6 (4.55)	3 (6.98)	3 (3.37)			>72	>72	>72
Tumor grade								
1	9 (6.82)	2 (4.65)	7 (7.87)	5.0097	.1711	>81	>83	>83
2	74 (56.06)	20 (46.51)	54 (60.67)			87	>99	>99
3	31 (23.48)	15 (34.88)	16 (17.98)			37	49	61
NA	18 (13.64)	6 (13.95)	12 (13.48)			>85	>85	>85
Size of IC								
T1	35 (26.52)	11 (25.58)	24 (26.97)	6.7839	.0791	>99	>99	>99
T2	73 (55.30)	19 (44.19)	54 (60.67)			78	>98	92
T3	21 (15.91)	11 (25.58)	10 (11.24)			33	39	63
T4	3 (2.27)	2 (4.65)	1 (1.12)			24	37	46
Lymph nodes post-surgery								
pN0	65 (49.24)	23 (53.49)	42 (47.19)	12.0924	.0071	>96	>96	>96
pN1	31 (23.48)	7 (16.28)	24 (26.97)			83	>99	92
pN2	18 (13.64)	2 (4.65)	16 (17.98)			47	56	79
pN3	18 (13.64)	11 (25.58)	7 (7.87)			26	33	46
Ki-67 of IC								
+	84 (63.64)	32 (74.42)	52 (58.43)	-	.1229	75	67	89
-	44 (33.33)	11 (25.58)	33 (37.08)			>99	>99	>99
NA	4 (3.03)	0 (0.00)	4 (4.49)			>80	>80	>80
Molecular subtype								
Luminal A	8 (6.06)	1 (2.33)	7 (7.87)	7.4842	.1124	>99	>99	>99
Luminal B	27 (20.45)	6 (13.95)	21 (23.60)			73	75	89
HER2-enriched	66 (50.00)	27 (62.79)	39 (43.82)			>96	47	>96
Triple-negative	10 (7.58)	1 (2.33)	9 (10.11)			>86	76	>86
NA	21 (15.91)	8 (18.60)	13 (14.61)			>85	>85	>85

Abbreviation: IC, invasive carcinoma.

LRFS, DDFS, and OS were the outcomes of interest in the prognosis analyses. Survival rates were estimated using the Kaplan-Meier product limit method. Differences between survival curves were tested using the log rank test. LRFS, DDFS, and OS interrelated predictors were analyzed by Cox proportional hazards regression with univariate and multiple regression models. Multivariate logistic regression analysis was used to test the association of patient age, ER status, PR status, HER2 status, tumor grade, tumor size, lymph nodes post-surgery, Ki-67 status, molecular subtype, hormone receptor-positive grouping, and risk grouping to survival. The multiple Cox proportional hazards models were also used to estimate the crude hazard ratios (HR) along with their corresponding 95% confidence intervals (CIs). The Fisher exact test was used to assess the relationship between the different age groups and the clinical and pathologic factors. Statistical analyses were performed using SAS (version 9.2), and GraphPad Prism 5 was used for drawing survival rates. All P values < .05 were considered statistically significant.

Results

Clinical-Pathologic Factors Predict Outcome and Clinical-Pathologic Factors and Patient Age

We reported data of 132 patients who were initially diagnosed with breast cancer. The clinical and pathologic characteristics of the study

population are summarized in Table 1. The median age of patients was 32. The median follow-up time was 67 months, with 32 deaths, 45 distant metastases, and 54 local recurrences. Median survival time of all predictors is shown in Table 6. Patient age, HER2 status, tumor grade, tumor size, lymph nodes post-surgery, and Ki-67 status were associated with LRFS; patient age, ER status, PR status, HER2 status, tumor grade, tumor size, lymph nodes post-surgery, Ki-67 status, and molecular subtype were associated with DDFS and OS. In Table 2, compared with women aged 31 to 35, women younger than 30 years old had more positive lymph nodes post-surgery (P = .0071). Hence, in our study, other clinical pathologic factors were not correlated with patient age in young women except lymph nodes post-surgery.

In our study, patient age (≤35) was an independent predictor of patient’s prognosis both in univariate and multivariate analyses (Figure 2, A–C, and Tables 1 and 5). Patients younger than 30 have poorer prognosis compared to patients of age between 31 and 35.

Hormone Receptor-Positive Breast Cancer and Outcome

Among the classification schemes evaluated, three levels of hormone receptor-positive breast cancer predicted LRFS, DDFS, and OS in our cohort (Figure 3, A–C, and Table 3). The level of ER, PR, and HER2 status was associated with LRFS (P < .0001, HR: 2.17, 95% CI: 1.58-2.98), DDFS (P < .0001, HR: 2.29, 95% CI: 1.84-4.23), and OS

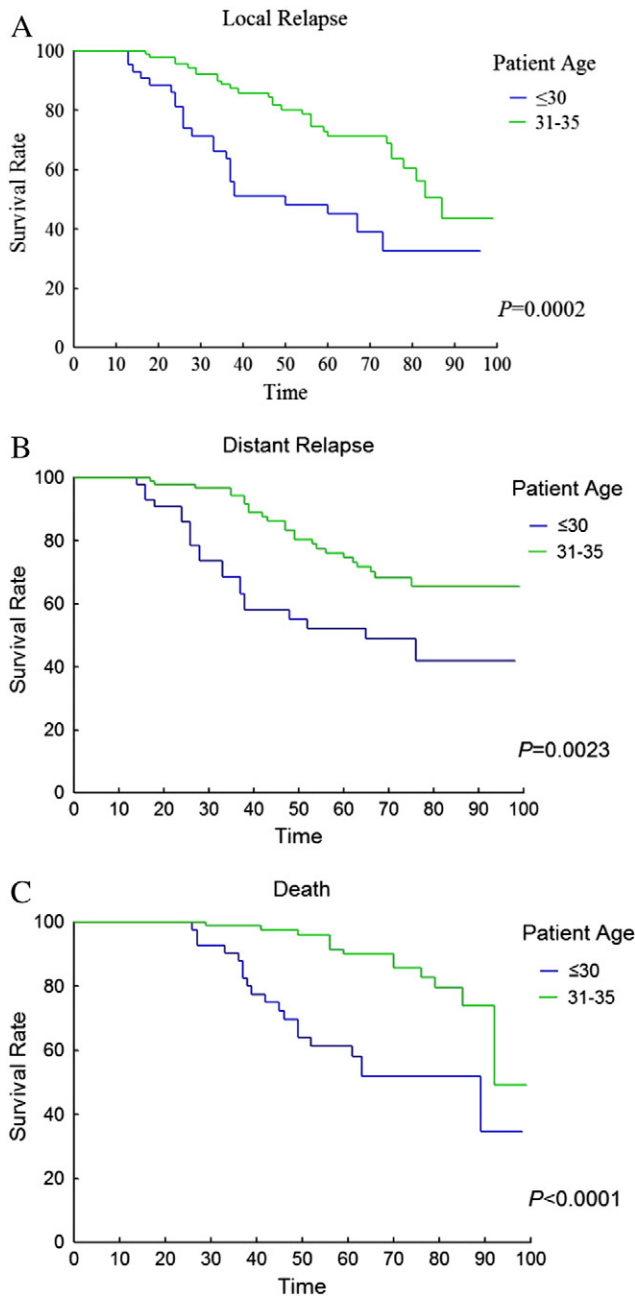


Figure 2. Patient age with outcome. (A) Patient age in relation to LRFS by Kaplan-Meier survival analysis. Median survival time: patients ≤ 30 years old, 50 months; patients 31 to 35 years old, 87 months. (B) Patient age in relation to DDFS by Kaplan-Meier survival analysis. Median survival time: patients ≤ 30 years old, 65 months; patients 31 to 35 years old, >99 months. (C) Patient age in relation to OS by Kaplan-Meier survival analysis. Median survival time: patients ≤ 30 years old, 89 months; patients 31 to 35 years old, 92 months.

($P < .0001$, HR: 2.95, 95% CI: 1.80-4.85). It identified the subset of carcinoma patients in young women with best prognosis (ER+, PR+, HER2-), and it also identified the group of carcinoma patients who have the worst prognosis (ER+ or PR+, HER2-/+) in hormone receptor-positive breast cancer. The level of hormone receptor-positive breast cancer is a significant independent predictor of LRFS, DDFS, and OS.

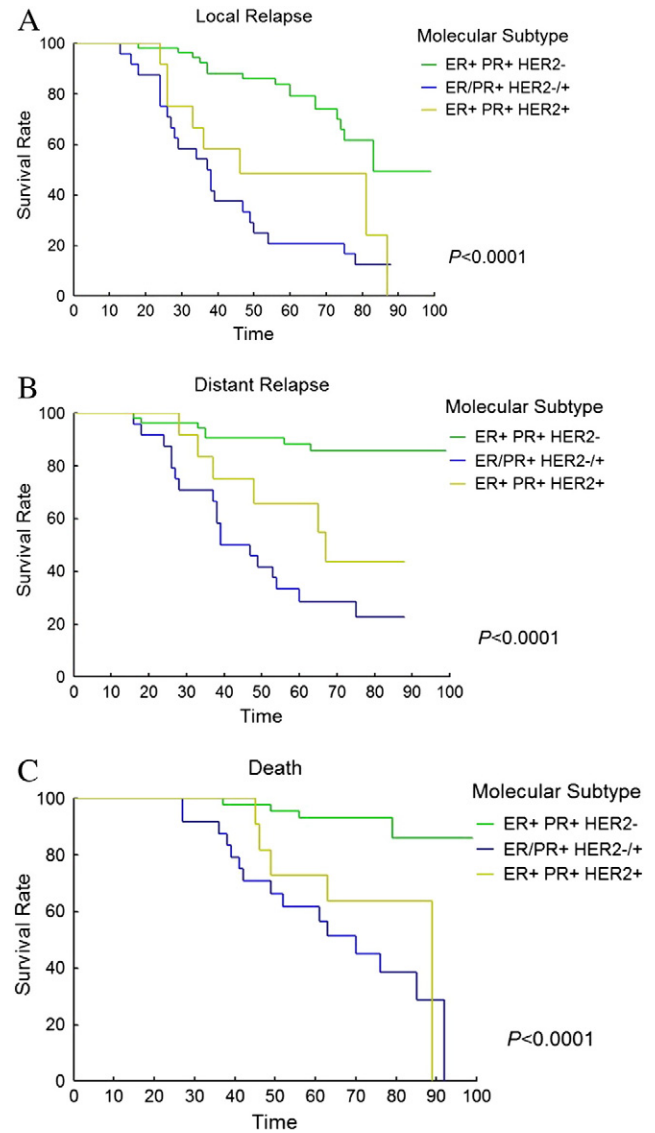


Figure 3. ER, PR, and HER2 status with outcome. (A) ER, PR, and HER2 status in relation to LRFS by Kaplan-Meier survival analysis. Median survival time: level 1 with 83 months; level 2 with 46 months; level 3 with 37.5 months. (B) ER, PR, and HER2 status in relation to DDFS by Kaplan-Meier survival analysis. Median survival time: level 1 with >99 months; level 2 with 67 months; level 3 with 43 months. (C) ER, PR, and HER2 status in relation to OS by Kaplan-Meier survival analysis. Median survival time: level 1 with >99 months; level 2 with 89 months; level 3 with 70 months.

Different Risk Groupings Predict Survival

This classification proposed the important risk factors resulting in significantly different LRFS, DDFS, and OS values (all $P < .0001$). The patients in group 3 were considered to have the worst LRFS, worst DDFS, and worst OS in our cohort (Figure 4, A-C, and Table 4). All of 19 patients in group 3 had distant metastases, and 17 of them with local recurrences have died. Hence, the risk grouping is considered a significant independent predictor of LRFS, DDFS, and OS.

Multivariate Analysis for Predicting Survival

In our study, a multivariate analysis was undertaken to determine which factors were independent or significant predictors of patient's survival using the Cox proportional hazards regression model. The

Table 3. ER, PR, and HER2 Status with Outcome

ER,PR, and HER2 Status	Total	Local Relapse	Distant Relapse	Died of Disease	LRFS			DDFS			OS		
	N (%)	N (%)	N (%)	N (%)	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI
ER+, PR+, HER2-	55 (60.44)	16 (35.56)	7 (22.58)	4 (16.67)	<.0001	2.17	1.57-2.98	<.0001	2.79	1.84-4.23	<.0001	2.95	1.80-4.85
ER+, PR+, HER2+	12 (13.19)	8 (17.78)	6 (19.35)	5 (20.83)									
ER+/PR+, HER2 -/+	24 (26.37)	21 (46.67)	18 (58.06)	15 (62.50)									

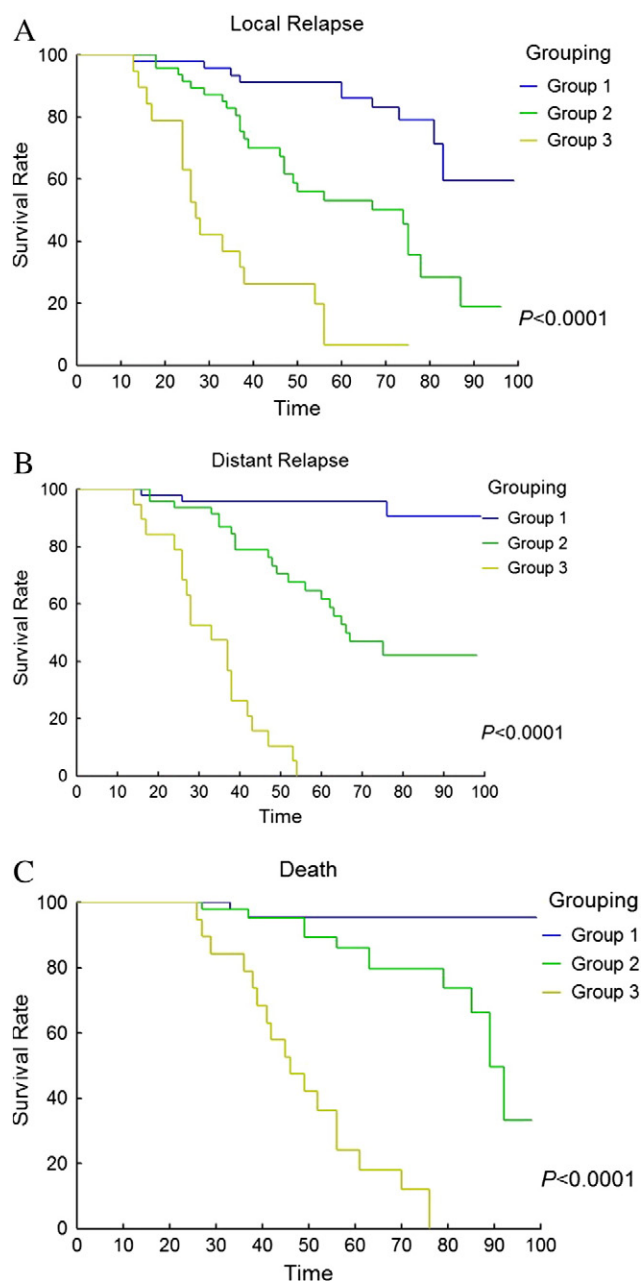


Figure 4. Risk factor grouping with outcome. (A) Risk grouping in relation to LRFS by Kaplan-Meier survival analysis. Median survival time: group 1 with >99 months; group 2 with 74 months; group 3 with 27 months. (B) Risk grouping in relation to DDFS by Kaplan-Meier survival analysis. Median survival time: group 1 with >99 months; group 2 with 67 months; group 3 with 33 months. (C) Risk grouping in relation to OS by Kaplan-Meier survival analysis. Median survival time: group 1 with >99 months; group 2 with 89 months; group 3 with 46 months.

factors for the statistical analysis were given as follows: patient age, tumor size, diagnosis, tumor grade, lymph nodes, ER, PR, HER2, Ki-67 status, molecular subtypes, hormone receptor-positive breast cancer grouping, and risk groups.

The results of interrelated predictor analysis of DDFS, LRFS, and OS are shown in Table 5. Patient age, lymph nodes, PR status, molecular subtypes, and risk groups were the interrelated predictors of DDFS in young patients. Patient age, lymph nodes, PR status, and tumor size were the interrelated predictors of LRFS in young patients. Patient age, lymph nodes, PR status, Ki-67 status, and tumor size were the interrelated predictors of OS in young patients. It can be seen that PR+ as well as patients at the age older than 30 were interrelated predictors of better DDFS, LRFS, and OS. The increasing grade of lymph nodes, risk groups, and molecular subtype were influence predictors of worse DDFS. The increasing grade of lymph nodes and tumor size were interrelated predictors of worse LRFS. The increasing grade of lymph nodes, tumor size, and Ki-67+ were interrelated predictors of worse OS.

Discussion

On the basis of the various prospective and retrospective studies performed in the last two decades, it has been generally accepted that young age (≤ 35) at diagnosis correlates with a worse clinical outcome compared to their older counterparts (> 35). However, few studies had paid attention to the fact that the difference between clinical and pathologic factors in young patients (≤ 35) might have different prognoses. In our study, we choose some clinical and pathologic factors that may affect the prognosis of young breast cancer patients in univariate and multivariate analyses. Patient age, HER2 status, tumor grade, tumor size, lymph nodes post-surgery, and Ki-67 status were associated with LRFS; patient age, ER status, PR status, HER2 status, tumor grade, tumor size, lymph nodes post-surgery, Ki-67 status, and molecular subtype were associated with DDFS and OS. Patient age of 31 to 35 years and ER+ and PR+ were associated with better prognosis; other factors were associated with worse prognosis (Tables 1 and 6).

Patient age for this cohort was statistically significant for DDFS, LRFS, and OS in both univariate and multivariate analyses (Tables 1 and 5). Patients whose ages are less than 30 have poorer prognosis compared with patients of ages between 31 and 35. We also show the correlation between patient age and clinicopathologic factors. The results have shown that patients younger than 35 only related to the status of lymph nodes post-surgery. In other words, patients younger than 30 are related with more axillary lymph node positivity compared with patients of age between 31 and 35 (Table 2).

Our study confirmed that the number of positive lymph nodes after surgery is a very important parameter for the long-term outcome. The number of involved lymph nodes is relevant to long-term outcome (Tables 1 and 5). More positive lymph nodes after surgery correlated with worse DDFS, LRFS, and OS by Kaplan-Meier and Cox regression analyses. At the same time, the status of lymph nodes post-surgery was the only related factor to patient age in young

Table 4. Risk Factors Grouping with Outcome

Grouping	Total	Local Relapse	Distant Relapse	Died of Disease	LRFS	DDFS			OS				
	N (%)	N (%)	N (%)	N (%)	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI
Group 1	48 (42.10)	10 (19.23)	3 (6.98)	2 (6.67)	<.0001	3.67	2.45-5.50	<.0001	7.90	4.57-13.65	<.0001	7.95	4.08-15.48
Group 2	47 (41.23)	25 (48.08)	21 (48.84)	11 (36.67)									
Group 3	19 (16.67)	17 (32.69)	19 (44.19)	17 (56.67)									

women. Hence, more axillary lymph node positivity in patients younger than 30 years is one of the reasons of the poorer outcome in patients younger than 30 compared to patients of age between 31 and 35 (Figure 2, A–C, and Table 2).

It is well established that there are at least four main subtypes of breast cancer based on different patterns of gene expression, and they have a considerable impact on prognosis [19,20]. Many studies have confirmed the increasing proportion of ER/PR negativity, HER2-enriched subtype, and high grade in young women with breast cancer [6]. Although there have been more triple-negative and HER2-enriched subtypes, hormone receptor-positive breast cancer remains to be the major subtype among young patients. Luminal A tends to have the best prognosis; the HER2-enriched and the triple-negative tumors both confer worse prognosis [19]. In our study, level 1 (ER+, PR+, HER2-) in hormone receptor-positive breast cancer has better prognosis compared with other levels (triple-positive and ER+ or PR+, HER2-/+). The patients in level 3 have the worst prognosis in hormone receptor-positive breast cancer (Table 3), and the median survival time was shorter than triple-negative and HER2-enriched subtypes in LRFS, DDFS, and OS (Figure 3, A–C, and Tables 2 and 6).

The absence of PR may be a marker of aberrant growth factor signaling and, consequently, one mechanism for anti-estrogen resistance [25,26]. ER+/PR- tumors as defined by RNA profiling represent a distinct subset of breast cancer with aggressive features and poor outcome despite being clinically ER+ [27]. The results of the recent study indicate that PR is an important prognostic factor to properly define subgroups with different prognoses within the hormone receptor-positive subtype, irrespective of HER2 overexpression or amplification. The prognostic and predictive values of PR have been, for a long time, ascribed to the dependence of PR expression on ER activity, with the absence of PR reflecting a nonfunctional ER and resistance to hormonal therapy [25,28,29]. In our cohort, PR+ was considered as a better prognosis factor both in univariate and multivariate analyses except in LRFS univariate analysis. The result showed that the absence of PR related to poorer

prognosis, and PR status was a statistically significant prognosis factor in long-term follow-up.

In this article, we focused on prognostic factors and survival. Several prognostic factors have been identified in invasive breast cancer. As we observed in our works and in studies of others, ER, PR, HER2, Ki-67 status, tumor grade, and lymph nodes post-surgery were the significant prognostic factors. Indeed, the most powerful prognostic factor was axillary lymph nodes post-surgery. In addition, we focused on tumor grading, finding that survival was worse in patients with poorly differentiated tumors (grades II and III) compared with that of patients with well-differentiated grade I tumors. Globally, other four factors with axillary lymph nodes post-surgery and tumor grade have been combined to create a single prognostic parameter. This combination classification has been divided into three groups. As shown in Table 4, the risk of local recurrence has increased 3.67 times; the risk of distant relapse has

Table 6. Median Survival Time of All Predictors

		Median Survival (Months)		
		LRFS	DDFS	OS
Patient age	≤30	50	65	89
	31-35	87	>99	92
ER status	+	81	>99	92
	-	78	66	85
PR status	+	83	>99	>99
	-	59	49	92
HER2 status	+	56	54	89
	-	83	>99	>99
Diagnosis	NA	>80	>80	>80
	DCIS	>85	>85	>85
	IDC	78	>99	92
	Other	>72	>72	>72
Tumor grade	1	>81	>83	>83
	2	87	>99	>99
	3	37	49	61
	NA	>85	>85	>85
Size of IC	T1	>99	>99	>99
	T2	78	>98	92
	T3	33	39	63
	T4	24	37	46
Lymph nodes post-surgery	pN0	>96	>96	>96
	pN1	83	>99	92
	pN2	47	56	79
	pN3	26	33	46
Ki-67 of IC	+	75	67	89
	-	>99	>99	>99
Molecular subtype	NA	>80	>80	>80
	Luminal A	>99	>99	>99
	Luminal B	73	75	89
	HER2-enriched	>96	47	>96
ER, PR, and HER2 status	Triple-negative	>86	76	>86
	NA	>85	>85	>85
	ER and PR+, HER2-	83	>99	>99
	ER/PR+, HER2-/+	37.5	43	70
Grouping	ER and PR+, HER2+	46	67	89
	Group 1	>99	>99	>99
	Group 2	74	67	89
	Group 3	27	33	46

Table 5. Outcome in Multivariate Analysis

Outcome	Influence Factor	β	P	HR	95% CI	
					Lower Limit	Upper Limit
DDFS	Patient age	-0.97	.0325	0.38	0.18	0.92
	PR status	-1.44	.0020	0.24	0.10	0.59
	Lymph nodes post-surgery	0.89	.0034	2.42	1.34	4.38
	Molecular subtype	2.32	.0392	10.13	1.12	91.47
LRFS	Grouping	1.01	.0295	2.74	1.11	6.78
	Patient age	-1.12	.0014	0.33	0.16	0.65
	PR status	-1.42	.0002	0.24	0.11	0.51
	Tumor size	1.33	<.0001	3.78	2.14	6.68
OS	Lymph nodes post-surgery	0.75	<.0001	2.12	1.49	3.02
	Patient age	-1.81	.0004	0.16	0.06	0.45
	PR status	-1.89	.0006	0.15	0.05	0.44
	Tumor size	0.78	.0312	2.18	1.07	4.44
	Lymph nodes post-surgery	0.76	.0015	2.13	1.34	3.40
	Ki-67 status	1.78	.0120	5.94	1.48	23.82

increased 7.90 times; the risk of death has increased 7.95 times (Figure 4, A–C, and Table 4); and the median survival time in level 3 was shorter than level 1 and level 2 in LRFS, DDFS, and OS (Table 6). This classification of important risk factors resulting in significantly different LRFS, DDFS, and OS (all $P < .0001$) should help us in the selection of subgroups of patients for further adjuvant treatment.

Conclusions

In conclusion, this study shows that patient age in young women and axillary lymph nodes post-surgery are the independent and significant predictors in DDFS, LRFS, and OS. The absence of PR related to poorer prognosis, and PR status was a statistically significant prognosis factor in long-term follow-up. The risk factor grouping provided evidence for prognostic significance and appears to be applicable to invasive breast cancer. This classification may offer a useful index to evaluate the risk of young breast cancer to identify subgroups of patients with better prognosis.

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