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Original Article

Survival estimates based on molecular subtype and age in patients with early node-negative breast cancer

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Abstract: Purpose: To evaluate the prognosis for T1mic, T1a, and T1b breast cancer patients with node-negative by age and tumor molecular subtype. Methods: A total of 885 patients diagnosed with pT1mic, a, bN0 breast cancer were included. Clinicopathologic characteristics were compared using the Chi-square test. Survival outcomes were estimated using the Kaplan-Meier method. Cox regression model was used to determine association of breast cancer subtypes and age with other variables. Results: The median age at diagnosis was 53 years. The median follow-up was 81 months. Worse survival in the HER2 positive and Triple Negative subtype (P<0.0001) and patients with aged 40 years or younger (P<0.0001) were found. Triple-negative associated with a reduced risk of DFS (P<0.0001) and OS (P<0.0001) compared with Luminal A subtype, and patients with HER2 positive subtype had a reduced risk of OS (P=0.019). Patients with 40-years old or younger had 2.50 (P<0.0001) times greater risk of worse DFS compared to patients with aged older than 50 years. Moreover, the nomogram could more accurately predict LRR in small invasive breast cancer. Conclusions: Patients with T1mic, T1a, and T1b breast cancer are at higher risk of relapse and death if with younger age, HER2 positive, and Triple negative subtype.

Keywords: Small invasive breast cancer, node negative, molecular subtype, age, prognosis

Introduction

With the development of screening strategies, the frequency of small breast cancers (BCs) has increased overtime [1]. Small invasive BCs with tumor size less than or equal to 1 cm with node-negative (pT1mic, a, bN0) are curable with less than 10% likelihood of recurrence, even in the absence of systemic adjuvant treatment [2, 3]. It was generally acknowledged that most of these tumors do not require adjuvant systemic therapy [4, 5]. However, features which might indicate increased risk of relapse in such patients include peritumoural vascular invasion [6], the presence of high grade and/or high proliferation indexes [7, 8], HER2 positive status and hormone receptor (HR) negative status [9]. Finally, age should also be taken into consideration due to its different prognosis significance compared to older premenopausal breast cancer patients [10]. Some retrospective studies showed that patients aged younger than 35 years have a significantly higher rate of recurrence [11], distant failure, and overall mortality [12].

Breast cancer is a heterogeneous disease and gene expression studies have identified its molecularly distinct subtypes with prognostic implications across multiple treatment settings [13]. These subtypes include Luminal A, Luminal B, HER2-positive, and Triple-negative which were identified by immunohistochemical evaluation of estrogen receptor (ER), progesterone receptor (PR), HER2 status and Ki67 index. Moreover, molecular subtyping has been shown to predict recurrence and survival in breast cancer [14, 15]. Whether this classification for tumors less than 1 cm might be useful in order to accurately predict outcome in clinical practice is a hypothesis that has not been tested. As this patient population continues to increase, it will be important to identify factors that increase recurrence risk in order to guide management

recommendations. Given all of the above known data, including age at diagnosis and emerging data about receptor status, we sought to evaluate outcome differences in Chinese breast cancer patients with T1mic, T1a, and T1b with node-negative according to molecular subtype and age.

Materials and methods

Study population

A retrospective consecutive study was conducted on 8358 patients with breast cancer at the Cancer Hospital of Tianjin Medical University, China, from January 1, 2003 to December 31, 2008. The breast lesions were thoroughly sampled for pathological examination. From this cohort, we included those patients who meet all of the following criteria: (1) patients with pathologic tumor size less than or equal to 1 cm with node-negative, (2) ER, PR, Her-2, Ki67, p53 information were all complete, (3) patients who have sufficient data to allow for the estimation of a hazard ratio (HR) with 95% confidence intervals (95% CI), (4) completed follow-up date during the study period. The major exclusion criteria were as follows: (1) bilateral primary breast cancer, (2) patients who received neoadjuvant chemotherapy, (3) patients who have severe accompanying disease, (4) male patients. A total of 885 patients formed the study population.

The study was performed according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital.

Molecular subtype evaluation

Based on 2013 St Galen Consensus, subtypes of breast cancer (Luminal A, Luminal B-HER2-negative, Luminal B-HER2-positive, HER2 positive, and Triple-negative) were defined by ER, PR, Ki67, and HER2 status [16]: Luminal A (ER+ and PR≥20%, HER2-, Ki67<20%); Luminal B which including Luminal B-HER2-negative like (ER+ and PR-/<20%, HER2-, Ki67≥20%), and Luminal B-HER2-positive like (ER+ and HER2+, any PR and Ki67); HER2 positive (nonluminal: HER2+, ER- and PR-); Triple-negative (basal-like: HER2-, ER- and PR-).

Follow-up study and study endpoints

Follow-up data were obtained via medical records, making telephone calls and study questionnaire every 3 months for the first 2 years, every 6 months for the third through fifth years, and annually after 5 years. The primary endpoints were disease-free survival (DFS) and overall survival (OS). Locoregional relapse (LRR) was defined as recurrent breast cancer in the ipsilateral chest wall, skin, axilla, internal mammary, or supraclavicular lymph nodes. All other sites of recurrence were coded as distant metastases (DM). DFS was defined as the length of time before any evidence of LRR, DM, or death from breast cancer (DFBC) by the end of follow-up. OS was determined as the time from surgery until the date of DFBC or was censored at the date of last follow-up. The last follow-up date was defined as the last breast cancer evaluation by a physician or a mammogram.

Statistical methods

The Chi-square test for trend was used to assess the association between variables. Cumulative incidence and survival plots were drawn using the Kaplan-Meier method. The log-rank test was used to assess the difference between strata. A forward stepwise Cox regression model was used to assess the impact of various clinical and histopathological characteristics of the tumor on survival.

All *P*-values were two-sided, and *P*-values <0.05 were considered to be statistically significant. All analyses were conducted using SPSS, version 19.0.

Nomogram development

The Cox proportional hazards regression model was used to construct the nomogram. The model performance was quantified with respect to discrimination and calibration. Discrimination (i.e., whether the relative ranking of individual predictions is in the correct order) was quantified using the concordance index (c-index). The c-index ranges from 0 to 1, with 1 indicating perfect concordance, 0.5 indicating no better concordance than chance, and 0 indicating perfect discordance.

Table 1. Clinicopathologic characteristics according to four molecular subtype

	All N	Luminal A N (%)	Luminal B-HER2-negative N (%)	Luminal B-HER2-positive N (%)	HER2 positive N (%)	Triple negative N (%)	*P* value
All	885	321 (100)	289 (100)	106 (100)	81 (100)	88 (100)	
Tumor size							
pT1mic	37	12 (3.7)	6 (2.1)	4 (3.8)	6 (7.4)	9 (10.2)	0.012*
pT1a	237	80 (24.9)	73 (25.3)	32 (30.2)	29 (35.8)	23 (26.1)	
pT1b	611	229 (71.3)	210 (72.7)	70 (66.0)	46 (56.8)	56 (63.6)	
Age							
≤40	101	45 (14.0)	16 (5.5)	18 (17.0)	9 (11.1)	13 (14.8)	<0.0001*
41-49	216	112 (34.9)	37 (12.8)	30 (28.3)	22 (27.2)	15 (17.0)	
≥50	568	164 (51.1)	236 (81.7)	58 (54.7)	50 (61.7)	60 (68.2)	
Tumor grade							
G1	422	177 (55.1)	126 (43.6)	56 (52.8)	31 (38.3)	32 (36.4)	<0.0001*
G2	335	109 (34.0)	148 (51.2)	41 (38.7)	21 (25.9)	16 (18.2)	
G3	128	35 (10.9)	15 (5.2)	9 (8.5)	29 (35.8)	40 (45.5)	
LVI							
Absent	842	309 (96.3)	272 (94.1)	103 (97.2)	77 (95.1)	81 (92.0)	0.367
Present	43	12 (3.7)	17 (5.9)	3 (2.8)	4 (4.9)	7 (8.0)	
Histology							
Ductal	773	276 (86.0)	260 (90.0)	93 (87.7)	71 (87.7)	73 (83.0)	0.421
Other	112	45 (14.0)	29 (10.0)	13 (12.3)	10 (12.3)	15 (17.0)	
Endocrine therapy							
Yes	695	309 (96.3)	282 (97.6)	104 (98.1)	0 (0.0)	0 (0.0)	<0.0001*
No	190	12 (3.7)	7 (2.4)	2 (1.9)	81 (100.0)	88 (100.0)	
Radiotherapy							
Yes	54	18 (5.6)	5 (1.7)	8 (7.5)	14 (17.3)	9 (10.2)	<0.0001*
No	831	303 (94.4)	284 (98.3)	98 (92.5)	67 (82.7)	79 (89.8)	
Chemotherapy							
Yes	85	15 (4.7)	15 (5.2)	5 (4.7)	19 (23.5)	31 (35.2)	<0.0001*
No	800	306 (95.3)	274 (94.8)	101 (95.3)	62 (76.5)	57 (64.8)	

LVI: lymphovascular invasion. *Statistically significant.

Results

Patient characteristics

Patients and tumor characteristics according to molecular subtype are shown in **Table 1**. Of the 885 patients, 321 (36.3%) patients had Luminal A tumors, 289 (32.7%) patients had Luminal B-HER2-negative tumors, 106 (12.0%) patients had Luminal B-HER2-positive tumors, 81 (9.2%) patients had HER2-positive tumors, and 88 (9.9%) patients had Triple negative tumors. Patients with Triple negative tumors tended to be younger (≤40 years) and have a higher nuclear grade. About the histology type, 773 cases were ductal cancer and 112 cases were other types of breast cancer (including lobular carcinoma, mucinous carcinoma, etc.) (**Figure 1**). Regarding to therapy, only 3.7%, 2.4% and 1.9% of patients with Luminal A, Luminal B-HER2-negative tumors and Luminal B-HER2-positive tumors respectively, did not receive any hormonal treatment. Finally, 95.3%, 94.8% and 95.3% of patients with Luminal A, Luminal B-HER2-negative tumors and Luminal B-HER2-positive tumors did not receive adjuvant chemotherapy; 17.3% and 10.2% of patients with HER2 positive and Triple Negative tumors received radiotherapy.

Patients and tumor characteristics according to patient's age are shown in **Table 2**. The median age at diagnosis was 53 years (range, 24-88). Patients were divided into the following age

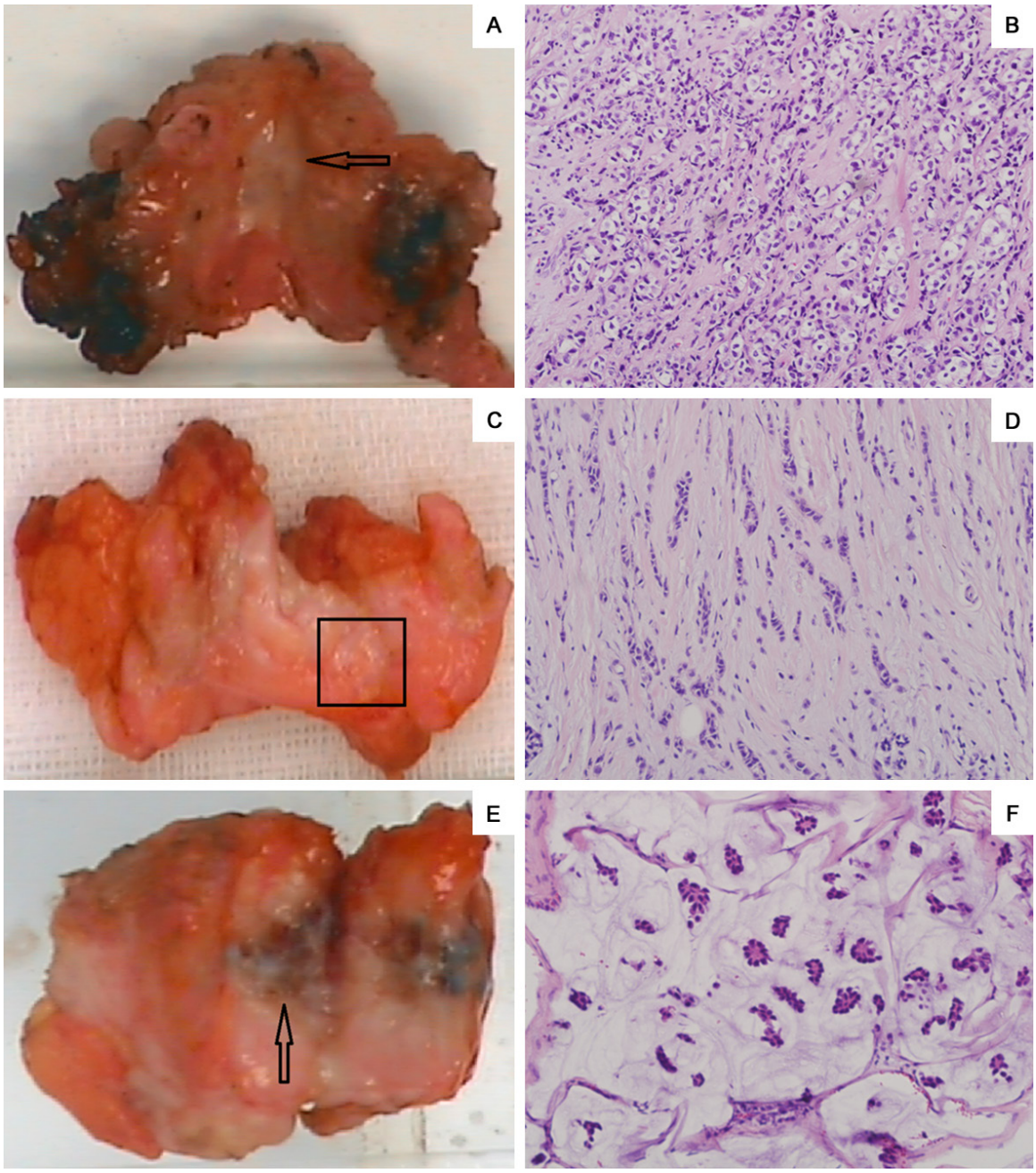

Figure 1. Morphological changes of the breast carcinoma. A. Macroscopic findings. Invasive ductal carcinoma of the breast (Tumor size 0.7×0.5×0.5 cm); B. Microscopic findings. Invasive ductal carcinoma of the breast. HE staining; magnification ×200; C. Macroscopic findings. Invasive lobular carcinoma of the breast (Tumor size 0.5×0.5×0.5 cm); D. Microscopic findings. Invasive lobular carcinoma of the breast. HE staining; magnification ×200; E. Macroscopic findings. Mucoid carcinoma of the breast (Tumor size 1.0×0.9×0.9 cm); F. Microscopic findings. Mucoid carcinoma of the breast. HE staining; magnification ×200.

groups: 101 (11.4%) patients were 40 years old or younger, 216 (24.4%) patients were between 41 and 49 years old, and 568 (64.2%) patients were equal or older than 50 years. Patients with 40-years-old or younger were more frequent in T1mic tumors compared to older patients (P=0.006).

In our study, the median follow-up was 81 months (range 2-139 months). To explore the difference in rates of recurrence and death caused by molecular subtype and age, an analysis, presented in **Tables 3** and **4**, was undertaken among patients experienced local recurrence, distant metastasis or death during the

Table 2. Clinicopathologic characteristics according to patients age

Characteristics	≤40	41-49	≥50	*P* value
	N (%)	N (%)	N (%)	
All	101 (100.0)	216 (100.0)	568 (100.0)	
Tumor size				
pT1mic	5 (5.0)	6 (2.8)	26 (4.6)	0.006*
pT1a	24 (23.8)	40 (18.5)	173 (30.5)	
pT1b	72 (71.3)	170 (78.7)	369 (65.0)	
Tumor grade				
G1	44 (43.6)	98 (45.4)	280 (49.3)	0.203
G2	35 (34.7)	88 (40.7)	212 (37.3)	
G3	22 (21.8)	30 (13.9)	76 (13.4)	
LVI				
Absent	99 (98.0)	205 (94.9)	538 (94.7)	0.358
Present	2 (2.0)	11 (5.1)	30 (5.3)	
Histology				
Ductal	86 (85.1)	188 (87.0)	499 (87.9)	0.744
Other	15 (14.9)	28 (13.0)	69 (12.1)	
Endocrine therapy				
Yes	69 (68.3)	159 (73.6)	400 (70.4)	0.560
No	32 (31.7)	57 (26.4)	168 (29.6)	
Radiotherapy				
Yes	11 (10.9)	25 (11.6)	55 (9.7)	0.722
No	90 (89.1)	191 (88.4)	513 (90.3)	
Chemotherapy				
Yes	14 (13.9)	35 (16.2)	76 (13.4)	0.596
No	87 (86.1)	181 (83.8)	492 (86.6)	

LVI: lymphovascular invasion. *Statistically significant.

Table 3. Frequency of recurrence and death among patients with poor prognosis by molecular subtype

Molecular subtypes	Patients NO.	LRR		DM		DFBC	
		NO.	%	NO.	%	NO.	%
Luminal A	23	12	52.2	12	52.2	5	21.7
Luminal B-HER2-negative	26	13	50.0	13	50.0	7	26.9
Luminal B-HER2-positive	12	8	66.7	4	33.3	6	50.0
HER2 positive	18	10	55.6	12	66.7	11	61.1
Triple negative	37	18	48.6	30	81.1	25	46.6
Total	116	*P* value		*P* value		*P* value	
		0.766		0.037*		0.034*	

LRR: Loco-regional relapse; DM: Distant metastasis; DFBC: death from breast cancer. *Statistically significant.

follow-up interval, respectively. As shown in **Table 3**, higher rates of DM were demonstrated among 'HER2 positive' (66.7%) and 'Triple negative' (81.1%) breast cancer. In addition, DFBC were higher in 'Luminal B-HER2-positive' (50.0%) and 'HER2 positive' (61.1%) breast cancer. There was no significant difference among subtypes in rates of LRR (*P*=0.766). As shown in **Table 4**, LRR rates were higher in patients with 40 years old or younger (82.4%). There was no significant difference among age in rates of DM (*P*=0.291) and DFBC (*P*= 0.929).

The 5-year DFS and 5-year OS estimate for the entire population was 91.6% (95% confidence interval [CI]: 89.6-93.4%) and 93.0% (95% CI: 91.2-94.6%), respectively. As shown in **Table 5**, when studying DFS estimates by breast cancer subtype and age, patients 40-years old or younger had the worst outcomes in Luminal B-HER2-positive (66.7%) and HER2 positive (55.6%) breast cancer. For OS, patients ≤40 years had the worst outcomes in Triple negative breast cancer (*P*=0.037).

Figure 2 shows the incidence of disease-free survival (DFS) and overall survival (OS) curves according to molecular subtype and patients' age. Decreased rate of DFS were observed in the HER2 positive and Triple Negative subtype (*P*<0.0001) and patients with aged 40 years or younger (*P*<0.0001). Decreased rate of OS were observed in the HER2 positive and Triple Negative subtype (*P*<0.0001), while no statistical significant difference was found in the influence of patients age on OS (*P*=0.316).

Univariate analysis for DFS revealed that molecular subtype have prognostic significance (*P*<0.0001) along with age (*P*< 0.0001), tumor grade (*P*=0.045) and LVI (*P*= 0.045). For OS, molecular subtype have prognostic significance (*P*<0.0001) along with LVI (*P*=0.047). As shown in **Table 6**, we performed a multivariate analysis including significant clin-

Table 4. Frequency of recurrence and death among patients with poor prognosis by patients' age

Age (years)	Patients NO.	LRR		DM		DFBC	
		NO.	%	NO.	%	NO.	%
≤40	17	14	82.4	9	52.9	9	52.9
41-49	33	21	63.6	16	48.5	12	36.4
≥50	66	26	39.4	46	69.7	33	50.0
Total	116	*P* value		*P* value		*P* value	
		0.040*		0.291		0.929	

LRR: Loco-regional relapse; DM: Distant metastasis; DFBC: death from breast cancer.
*Statistically significant.

Table 5. DFS and OS according to breast cancer molecular subtype and patients' age

Molecular subtype	Age (years)	DFS N (%)	*P* value	OS N (%)	*P* value
Luminal A	≤40	41 (91.1)		42 (93.3)	
	41-49	100 (89.3)		101 (90.2)	
	≥50	157 (95.7)	0.080	158 (96.3)	0.079
Luminal B-HER2-negative	≤40	14 (87.5)		15 (93.8)	
	41-49	31 (83.8)		32 (86.5)	
	≥50	218 (92.4)	0.177	224 (94.9)	0.157
Luminal B-HER2-positive	≤40	12 (66.7)		15 (83.3)	
	41-49	23 (76.7)		27 (90.0)	
	≥50	55 (94.8)	0.042*	56 (96.6)	0.419
HER2 positive	≤40	5 (55.6)		6 (66.7)	
	41-49	17 (77.3)		20 (90.9)	
	≥50	41 (82.0)	0.031*	45 (90.0)	0.125
Triple negative	≤40	8 (61.5)		8 (61.5)	
	41-49	11 (73.3)		11 (73.3)	
	≥50	32 (53.3)	0.268	51 (85.0)	0.037*

*Statistically significant.

ical and biological features at univariate analysis. Triple-negative patients associated with a statistical significant reduced risk of DFS (*P*<0.0001) and OS (*P*<0.0001) compared with Luminal A subtype, and patients with HER2 positive subtype had a reduced risk of OS (*P*=0.019). While no difference was found between Luminal B-HER2-negative, Luminal B-HER2-positive, and Luminal A subtypes for any of the outcomes analyzed. Patients with 40-years old or younger had 2.50 (*P*<0.0001) times greater risk of worse DFS compared to patients older than 50 years. Patients with aged between 41 and 49 years old had 1.65 (*P*=0.022) times greater risk of worse DFS compared to patients older than 50 years.

To predict the survival of T1mic, T1a, and T1b with node-negative breast cancer patients, prognostic nomogram was depicted by Cox regression model analysis using all the significant independent indicators for DFS (**Figure 3**). The nomogram was able to predict the probability of recurrence patients within 3 or 5 years. The C-index of the nomogram for LRR prediction was 0.70.

Discussion

There is a paucity of data guiding clinicians' management on patients who present with small, node-negative breast cancer (BC). In this retrospective study of 885 patients with pT1mic, a, bN0, both age at diagnosis and molecular subtype were significantly associated with patients' survival or prognosis. Patients with younger age, HER2 positive, and Triple negative subtype correlated with worse survival. These findings could have significant implications in treatment options.

It was reported that younger patients have a more aggressive presentation of disease at diagnosis, which is associated with a worse prognoses than those of older patients [17, 18]. A limited number of studies evaluated the age in patients with small size breast cancer. Our data showed that younger patients (≤40-years old) had a worse prognosis when compared with older patients; this is consistent with historical data. Recently, Kwon et al [19] evaluated the outcome of 378 Korean BC patients with small tumors. Data showed that age younger than 35 years was significantly associated with a higher rate of recurrence (HR 4.91; 95% CI= 1.01-23.76; *P*=0.048). Similar to our study, Cancello et al [20] explored survival rates by

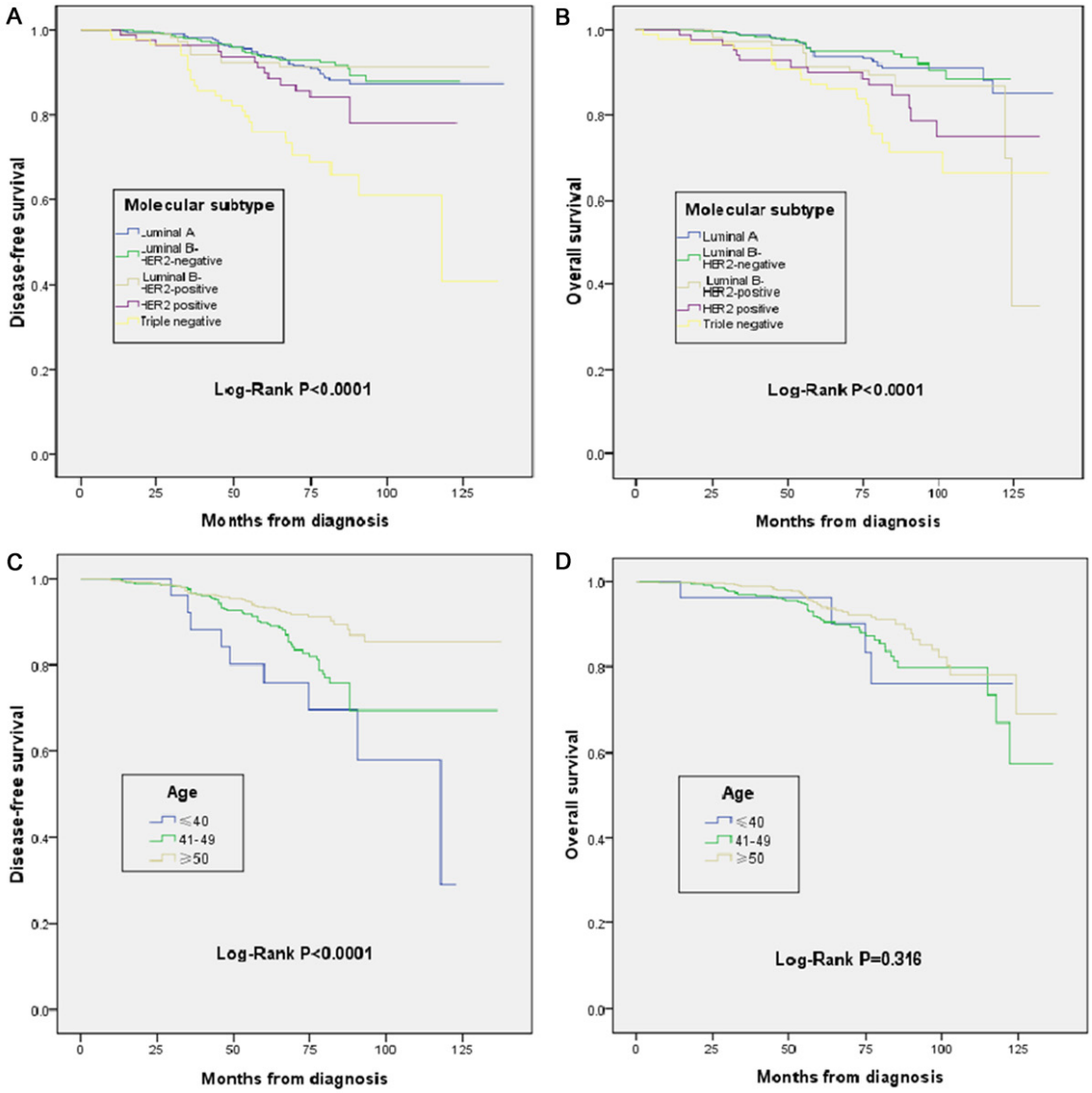

Figure 2. Survival analyses based on molecular subtyping and patients' age. A. Kaplan-Meier curves for disease-free survival by molecular subtype. B. Kaplan-Meier curves for overall survival by molecular subtype. C. Kaplan-Meier curves for disease-free survival by patients' age. D. Kaplan-Meier curves for overall survival by patients' ageS.

age according to four molecular subtypes; very young patients (age less than 35) with HER2-positive, Triple Negative or Luminal B breast cancer had a worse prognosis when compared to older patients.

For all we know that molecular subtypes of BC in combination with clinicopathologic features may provide more information for determining refined estimates of survival and treatment management [21]. Several large trials have demonstrated that trastuzumab combined with adjuvant chemotherapy regimens can improve both disease-free survival and overall survival in patients who had HER2-positive disease [22]. While most of these trials consistently excluded patients with node-negative tumors that were 1 cm or smaller [23-26]. Kwon et al [11] performed a retrospective analysis of patients with node-negative T1mic, T1a, and T1b invasive ductal carcinoma, patients with triple negative disease were identified to be the highest risk group of recurrence. Data from literature [4, 9, 27] are consistent with our findings that HER2 positive and Triple Negative phenotypes were associated with a significant-

Table 6. Multivariate analysis of factors associated with DFS and OS

Factors	DFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Molecular subtype				
Luminal A	1.00		1.00	
Luminal B	0.98 (0.83, 1.16)	0.502	0.84 (0.47, 1.50)	0.555
HER2-negative				
Luminal B	0.85 (0.41, 1.76)	0.657	1.64 (0.87, 3.13)	0.129
HER2-positive				
HER2 positive	1.73 (0.93, 3.21)	0.085	2.16 (1.14, 4.10)	0.019*
Triple negative	3.84 (2.33, 6.32)	<0.0001*	3.44 (1.98, 5.98)	<0.0001*
Age				
≥50	1.00		1.00	
≤40	2.50 (1.54, 4.06)	<0.0001*	1.44 (0.80, 2.58)	0.226
41-49	1.65 (1.08, 2.53)	0.022*	1.31 (0.84, 2.06)	0.238
LVI				
Absent	1.00		1.00	
Present	1.98 (0.96, 3.92)	0.058	1.97 (0.99, 3.92)	0.052

DFS: Disease-free survival; OS: Overall survival; LVI: lymphovascular invasion. *statistically significant.

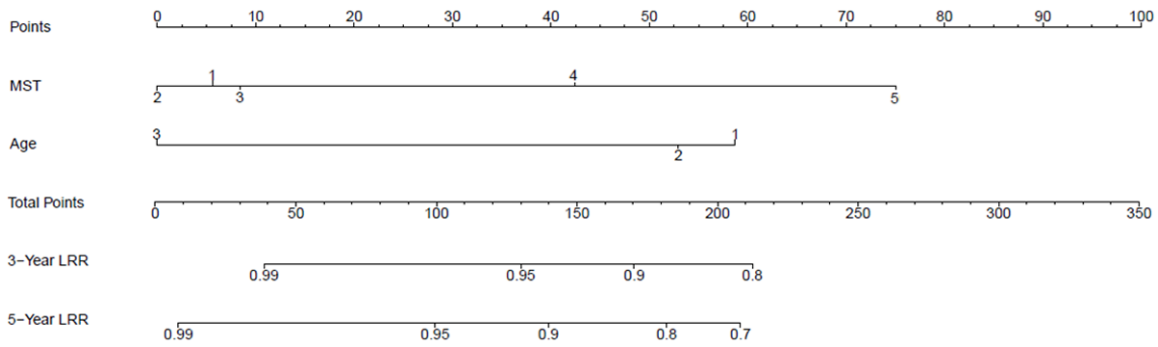

Figure 3. Postoperative nomogram with significant clinicopathologic characteristics predicted the probability of locoregional relapse (LRR). To use the nomogram, the value attributed to an individual patient is located on each variable axis, and a line is drawn upwards to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis, and a line is then drawn downwards to the survival axis to determine the 3-year and 5-year LRR likelihood.

ly more aggressive clinical presentation in early-stage breast cancer. Gonzalez-Angulo et al [28] showed that small invasive breast cancer patients who had HER2 positive subtype had 3.89 times (95% CI: 2.56-10.14; *P*=0.0001) risk of recurrence and 2.84 times (95% CI: 0.99-8.14; *P*=0.053) risk of distant recurrence compared with patients who had hormone receptor positive breast cancer. These data suggest that even in very early-stage disease, Triple Negative and HER2-positive patients might benefit from chemotherapy, anti-HER2 therapy, or more aggressive locoregional therapy.

Some nomograms have been developed in various cancers, and the nomograms have shown to be more accurate than the conventional staging systems for predicting prognosis in cancers [29]. The present study attempted to establish a predictive nomogram to predict the probability of patients who will recur within 3-year and 5-year based on clinicopathological factors. The nomogram performed well in predicting DFS, and the prediction was supported by c-index (0.70). The results supported that the nomograms could better predict prognosis in T1mic, T1a, and T1b with node-negative breast cancer patients.

In conclusion, the present study confirms that the prognosis of patients with node negative small breast cancer depended on variable features. Although patients with these cancers have a low risk of recurrence and death, certain subgroups showed notably higher recurrence risk, such as younger age, Triple Negative subtype, and HER2-positive subtype patients. Thus, despite small tumor in size, biologically more aggressive characteristics should be considered for future clinical trials to prospectively evaluate treatment options in women with small but high-risk tumors.

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Disclosure of conflict of interest

None.

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