Predictors for Survival and Distribution of 21-Gene Recurrence Score in Patients With Pure Mucinous Breast Cancer: A SEER Population-Based Retrospective Analysis

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Abstract

This study retrospectively analyzed prognostic factors and distribution of the 21-gene recurrence score (RS) in 8048 patients with pure mucinous breast cancer. Molecular phenotype as well as age, race, tumor size, and lymph node status were independent prognostic factors. RS correlated significantly with age, progesterone receptor status, and grade.

Background: Pure mucinous breast cancer (PMBC) is a rare pathologic type of breast cancer, the prognostic factors of which have not been clearly defined. This study aimed to analyze the prognostic markers and distribution of 21-gene recurrence score (RS) in patients with PMBC. **Patients and Methods:** Utilizing the Surveillance, Epidemiology, and End Results (SEER) database, a retrospective analysis of PMBC cases was conducted. Multivariate analyses were used to evaluate the indicators for prognosis and the correlations between RS and traditional clinicopathologic characteristics. Disease was subdivided into 4 molecular phenotypes using estrogen receptor (ER) status and tumor grade. **Results:** Of the 8048 patients, most had ER-positive and node-negative tumors. Multivariate analysis revealed that molecular phenotype as well as age, race, tumor size, and lymph node status was an independent prognostic factor for patients with PMBC ($P < .05$). The 5-year breast cancer−specific survival of patients among different phenotypes was significantly different (97.9% for ER-positive and grade I tumor, 96.9% for ER-positive and grade II-III tumor, 96% for ER-negative and grade I tumor, 90.1% for ER-negative and grade II-III tumors, $P < .001$). The proportions of patients categorized into low, intermediate, and high RS risk group were 64.9%, 31.9%, and 3.2%, respectively. Grade, progesterone receptor status, and age were identified as independent variables associated with RS. **Conclusion:** PMBC had favorable biological features and relatively good prognosis. Molecular phenotype as well as age, race, tumor size, and lymph node status were independent prognostic markers. Furthermore, age, progesterone receptor status, and grade could independently predict RS.

Clinical Breast Cancer, Vol. 19, No. 1, e66-73

Keywords: Mucinous breast cancer, Multigene assay, Prognosis

Introduction

Mucinous breast cancer is a special histologic subtype of invasive breast cancer comprising approximately 1% to 6% of all primary breast cancer.[1-6] Mucinous breast cancer is characterized by having a mucinous component of 50% or more and is histologically classified into to pure mucinous breast cancer (PMBC) and mixed mucinous breast cancer according to quantification of cellularity.[7,8] PMBC consists exclusively of tumor tissue with extracellular mucin production, without an infiltrating ductal epithelial component.[9] Previous studies have shown that PMBC is associated with older age at diagnosis, less node involvement, and better differentiation compared to invasive ductal carcinoma (IDC).[10-12] However, given the relatively low incidence of PMBC, the prognostic value of its clinicopathologic characteristics as well as the molecular phenotype has not been clearly specified to date.

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Submitted: Jun 6, 2018; Revised: Aug 27, 2018; Accepted: Oct 6, 2018; Epub: Oct 13, 2018

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1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2018.10.001

Molecular profiling tests have become promising tools to provide prognosis information during the past decade. According to validation study in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20, Oncotype DX recurrence score (RS) (Genomic Health, Redwood City, CA) is proven to provide additional prognostic information independent of clinicopathologic features and also predicts the likely benefit of chemotherapy for patients with early-stage estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative disease.[13-15] In short, Oncotype DX is both prognostic and predictive, and as a result it has become the only genomic test recommended by the National Comprehensive Cancer Network guidelines; it is widely used in patients with ER-positive, HER2-negative, and node-negative disease.[16] PMBC has favorable features including higher expression of ER, lower incidence of nodal metastasis, and a lower rate of HER2 overexpression,[17-20] which qualifies the main criteria of 21-gene genomic test. However, the utility of the RS in patients with PMBC has not yet been thoroughly evaluated.

This study aimed to assess the prognostic significance of clinicopathologic characteristics, molecular phenotype of PMBC, and RS in PMBC by utilizing data from Surveillance, Epidemiology, and End Results (SEER), a large population-based database.

Patients and Methods

Patient Population

This retrospective study used data derived from SEER database, which contains the available records from 18 population-based cancer registries that together represent 28% of the US population. We used SEER*Stat 8.3.5 software to generate the case list.

Eligible patients were female with a pathologic diagnosis of PMBC, identified on the basis of the International Classification of Diseases for Oncology, Third Revision (ICD-O-3), codes (8480/3) during 2004-2014. We further excluded patients diagnosed from death certificate or autopsy only, having metastatic disease at diagnosis, Tis or T0 stage, unknown T stage or N stage, unknown ER/progesterone receptor (PR) status, and patients without surgery. Hormone receptor status was tested by immunohistochemical analysis. According to the American Society of Clinical Oncology and College of American Pathologists guidelines published in 2010, ER and PR positivity were defined as no less than 1 % stained nuclei.[21] HER2 positivity was defined as HER2 3+ by immunohistochemical or positive on fluorescence in-situ hybridization or chromogenic in-situ hybridization testing. For patients with equivocal (2+) immunohistochemical results who did not undergo a gene-amplification test, HER2 status was considered to be negative.

HER2 status was not recorded until 2010; therefore, patient disease was subdivided into molecular phenotypes using ER status and histologic tumor grade. The 4 molecular phenotypes included the following: ER-positive and grade I tumors, ER-positive and grade II-III tumors, ER-negative and grade I tumors, and ER-negative and grade II-III tumors. Patients with available RS were categorized into low-risk (RS $<$ 18), intermediate-risk (RS 18$\sim$30), and high-risk (RS $>$ 30) groups according to RS cutoffs.

Demographic and clinicopathologic characteristics were collected for each patient. We obtained permission to access the files of SEER

Table 1 Cohort Characteristics of Women Diagnosed With PMBC, 2004-2014

Characteristic	N	%
Age at Diagnosis, y		
$<$65	3448	42.8
$\geq$65	4600	57.2
Race		
White	6295	78.2
Black	801	10.0
Other[a]	952	11.8
AJCC Stage		
I	5220	64.9
II	2533	31.5
III	295	3.7
Tumor size		
$\leq$2 cm	5459	67.8
$>$2 cm	2589	32.2
Nodal Status		
Negative	7287	90.5
Positive	761	9.5
Surgery		
BCS	5431	67.5
Mastectomy	2617	32.5
Grade		
I	4921	61.6
II	2774	34.5
III	353	4.4
ER Status		
Positive	7900	98.2
Negative	148	1.8
PR Status		
Positive	7188	89.3
Negative	860	10.7
HER2 Status		
Positive	197	2.4
Negative	3431	42.6
Unknown	4420	55.0
Molecular Phenotype		
ER positive and grade I	4886	60.7
ER positive and grade II-III	3030	37.6
ER negative and grade I	35	0.4
ER negative and grade II-III	97	1.2
Radiotherapy		
No	3888	48.3
Yes	4160	51.7
Chemotherapy		
No/unknown	6887	85.6
Yes	1161	14.4

Abbreviations: AJCC = American Joint Committee on Cancer; BCS = breast-conserving surgery; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PMBC = pure mucinous breast cancer; PR = progesterone receptor.
[a]Including American Indian, Alaskan Native, Asian, and Pacific Islander.

Table 2 Univariate Analysis of BCSS and OS by Kaplan-Meier Method in 8048 Patients With PMBC

Variable	BCSS		OS	
	χ^2	*P*	χ^2	*P*
Age at diagnosis	17.941	<.001	447.265	<.001
Race	14.298	.003	45.837	<.001
Tumor size	76.426	<.001	53.938	<.001
Nodal status	83.445	<.001	4.617	.032
Grade	30.738	<.001	3.282	.194
Surgery	29.270	<.001	22.088	<.001
Radiotherapy	19.650	<.001	187.433	<.001
Chemotherapy	20.549	<.001	51.691	<.001
ER status	10.150	.001	2.466	.116
PR status	8.898	.003	0.095	.757
HER2 status	3.592	.309	0.696	.857
Molecular phenotype	23.788	<.001	5.164	.160

Abbreviations: BCSS = breast cancer–specific survival; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; OS = overall survival; PR = progesterone receptor.

program custom data with additional treatment fields such as radiotherapy and chemotherapy, so we also collected treatment information. The database documented Oncotype DX score was provided at our request.

Statistical Analysis

The baseline characteristics of the study population were described using frequencies and percentages for all variables. The Pearson chi-square or Fisher exact test, if necessary, was used for comparison across different groups.

Breast cancer–specific survival (BCSS) was defined as the time from diagnosis of PMBC to death caused by breast cancer, with patients who died of other causes or still alive at last follow-up censored. Overall survival (OS) was computed from the time of diagnosis of PMBC to the time of death from any cause or last follow-up, with patients still alive at last follow-up censored. Survival outcomes were estimated by the Kaplan-Meier method and compared by the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by the Cox proportional hazards model to assess the prognostic value of tumor characteristics and molecular subtype. A multivariate logistic regression model was used to assess the factors independently associated with RS distribution. Two-sided $P < .05$ was considered statistically significant. All statistical analyses were performed by Stata 14.0 software (StataCorp, College Station, TX).

Results

Patient Characteristics

We identified 8048 female patients diagnosed with PMBC from 2004 to 2014 in the SEER database. Table 1 outlines the demographic, tumor, and treatment characteristics of the study population.

Among the 8048 patients in our analysis, the median age at diagnosis was 68 years (range, 21-103 years). The majority of patients (78.2%) were white. A total of 67.5% of patients underwent breast-conserving surgery. T1 tumors and node-negative diseases were identified in 67.8% and 90.5% of patients, respectively. The percentage of patients with grade I, II, and III tumors were 61.6%, 34.5%, and 4.4%, respectively.

Most of the patients had ER/PR-positive tumors. Of the 3628 patients (45%) with known HER2 status, only 197 (2.4%) had HER2-positive tumors. With regard to molecular phenotype, the majority of patients (60.7%) had ER-positive and grade I tumor. A total of 3030 patients (37.6%) were diagnosed with ER-positive and grade II-III tumor, while 97 patients (1.2%) had ER-negative and grade II-III tumor. The percentage of patients with ER-negative and grade I tumor was 0.4%.

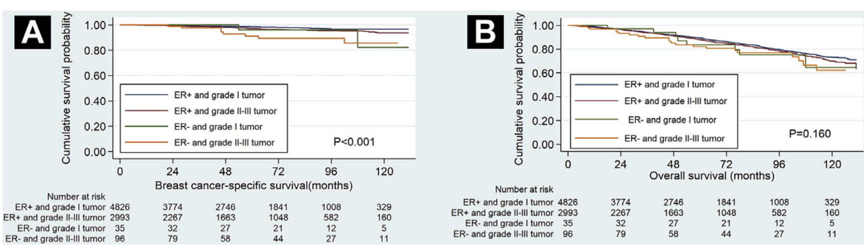
For adjuvant treatment, 14.4% patients were treated with chemotherapy and 51.7% patients received radiotherapy.

Predictors for BCSS in Patients With PMBC

After a median follow-up of 54 months (range, 0-131 months), 178 breast cancer–related deaths were observed out of 8048 cases, and 891 women died of other causes. The Kaplan-Meier survival curves revealed a 5-year BCSS rate of 97.7% and a 5-year OS of 88.6%.

The results of the univariate analyses are provided in Table 2. Factors related to BCSS were age at diagnosis, race, tumor size, nodal status, grade, ER status, PR status, molecular phenotype, and treatment, including surgery, radiotherapy, and chemotherapy. Patients with young age at diagnosis, small tumor size, node-negative

Figure 1 Survival by Molecular Phenotype. (A) Breast Cancer–specific Survival of Different Molecular Phenotypes (Log-rank Test, $P < .001$). (B) Overall Survival of Different Molecular Phenotypes (Log-rank Test, $P = .160$)



Abbreviation: ER = estrogen receptor.

Table 3 Multivariate Analysis of BCSS and OS by Cox Proportional Hazards Models in 8048 Patients With PMBC

Variable	BCSS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Age at Diagnosis, y						
<65	Ref	—	—	Ref	—	—
≥65	3.010	2.073-4.369	<.001	5.010	4.194-5.984	<.001
Race			.002			<.001
White	Ref	—	—	Ref		
Black	1.460	0.964-2.212	.074	0.957	0.776-1.181	.685
Other	0.410	0.208-0.809	.010	0.530	0.405-0.695	<.001
Surgery			.734			
BCS	—	—		Ref	—	—
Mastectomy	—	—		0.822	0.710-0.951	.008
Tumor Size						
≤2 cm	Ref	—	—	Ref	—	—
>2 cm	2.570	1.863-3.545	<.001	1.565	1.367-1.780	<.001
Nodal Status						
Negative	Ref	—	—	Ref	—	—
Positive	2.611	1.801-3.784	<.001	1.509	1.237-1.842	<.001
Molecular Phenotype			.041			.014
ER positive and grade I	Ref	—	—	Ref	—	—
ER positive and grade II-III	1.287	0.942-1.759	.113	1.126	0.992-1.277	.065
ER negative and grade I	2.588	0.629-10.645	.188	1.642	0.816-3.305	.164
ER negative and grade II-III	2.898	1.369-6.135	.005	2.007	1.295-3.111	.002
Radiotherapy						
No	Ref	—	—	Ref	—	—
Yes	0.591	0.433-0.806	.001	0.480	0.415-0.555	<.001
Chemotherapy						.077
No/unknown	Ref	—	—	—	—	—
Yes	1.802	1.178-2.757	.007	—	—	—

Abbreviations: BCS = breast conserving surgery; BCSS = breast cancer—specific survival; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; OS = overall survival; PMBC = pure mucinous breast cancer.

disease, well-differentiated tumor, and ER- or PR-positive tumor had a better prognosis. Poor prognosis was observed in patients who received chemotherapy and in patients not treated with radiotherapy.

Regarding molecular phenotype, the difference in BCSS among the 4 groups was statistically significant ($P < .001$; Figure 1A). The 5-year BCSS of patients with ER-positive and grade I tumor was 97.9%, whereas patients with ER-negative and grade II-III tumor had the worst survival, with a 5-year BCSS of 90.1%. The 5-year BCSS of patients having ER-negative and grade I tumor was 96%, and that of patients having ER-positive and grade II-III tumor was 96.9%.

The multivariate analyses revealed that age at diagnosis, race, tumor size, nodal status, molecular phenotype, radiotherapy, and chemotherapy were all independent prognostic factors for BCSS (Table 3). For molecular phenotype, patients with ER-negative and grade II-III tumors were more likely to die of breast cancer (HR = 2.898; 95% CI, 1.369-6.135; $P = .005$) compared to those with ER-positive and grade I tumor. In contrast, neither patients with ER-positive and grade II-III tumor (HR = 1.287; 95% CI, 0.942-1.759, $P = .113$) nor patients with ER-negative and grade I tumor (HR = 2.588; 95% CI, 0.629-10.645, $P = .188$) had worse BCSS compared to those with ER-positive and grade I tumor.

Predictors for OS in Patients With PMBC

In univariate analyses of OS, no significant difference was observed in subgroups stratified by grade, ER status, PR status, or molecular phenotype ($P > .05$). In multivariate analyses, factors independently associated with OS included age at diagnosis, race, tumor size, nodal status, molecular phenotypes, surgical procedure, and radiotherapy (Table 3). Receipt of chemotherapy failed to predict OS.

Molecular phenotype was an important predictor of OS, with patients with ER-negative and grade II-III tumor having worse OS (HR = 2.007; 95% CI, 1.295-3.111; $P = .002$) compared to those with ER-positive and grade I tumor. Neither patients with ER-positive and grade II-III tumor (HR = 1.126; 95% CI, 0.992-1.277, $P = .065$) nor patients with ER-negative and grade I tumor (HR = 1.642; 95% CI, 0.816-3.305, $P = .164$) had worse OS compared to those with ER-positive and grade I tumor.

Table 4 Distribution of RS Stratified by Clinicopathologic Characteristics

Variable	RS Risk Group			*P*
	Low	Intermediate	High	
All patients	740 (64.9)	364 (31.9)	37 (3.2)	
Age, y				
<60	429 (70)	171 (27.9)	13 (2.1)	<.001
≥60	272 (55.6)	193 (39.5)	24 (4.9)	
Grade				
I	453 (67.7)	203 (3.3)	13 (1.9)	<.001
II	268 (62.3)	147 (34.2)	15 (3.5)	
III	19 (45.2)	14 (33.3)	9 (21.4)	
AJCC Stage				
I	462 (65.7)	219 (31.2)	22 (3.1)	.644
II	271 (63)	144 (33.5)	15 (3.5)	
III	7 (87.5)	1 (12.5)	0	
Tumor Size				
≤2 cm	474 (65.5)	226 (31.2)	24 (3.3)	.803
>2 cm	266 (63.8)	138 (33.1)	13 (3.1)	
Nodal Status				
Negative	711 (64.9)	351 (32)	34 (3.1)	.346
Positive	29 (64.4)	13 (28.9)	3 (6.7)	
ER Status				
Positive	738 (64.9)	363 (31.9)	37 (3.3)	1.000
Negative	2 (66.7)	1 (33.3)	0	
PR Status				
Positive	11 (68.3)	307 (29.5)	23 (2.2)	<.001
Negative	29 (29)	57 (57)	14 (14)	
HER2 Status				
Positive	10 (58.8)	6 (35.3)	1 (5.9)	.026
Negative	434 (68.8)	180 (28.5)	17 (2.7)	
Unknown	296 (60)	364 (31.9)	19 (3.9)	
Subtype				
$HR^{+}HER2-$	434 (68.9)	179 (28.4)	17 (2.7)	.021
$HR^{+}HER2^{+}$	10 (58.8)	6 (35.3)	1 (5.9)	
TNBC	0	1 (100)	0	
Unknown	296 (60)	364 (31.9)	19 (3.9)	
Chemotherapy				
No/unknown	696 (72.4)	255 (26.5)	10 (1.0)	<.001
Yes	44 (24.4)	109 (6.6)	27 (15.0)	
Radiotherapy				
No	275 (65.5)	128 (3.5)	17 (4.0)	.408
Yes	465 (63.0)	236 (31.9)	37 (5.1)	

Data are presented as n (%).
Abbreviations: AJCC = American Joint Committee on Cancer; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; PR = progesterone receptor; RS = recurrence score; TNBC = triple-negative breast cancer.

Utility of 21-Gene RS in PMBC

RS results were available in 1141 patients with PMBC diagnosed from 2004 to 2013. There were 493 cases (43.2%) diagnosed before 2010 with unavailable HER2 status information.

Of the 1141 patients, median RS was 15 (range, 1∼67). There were 740 patients (64.9%) in the low-risk group (RS < 18), 364 patients (31.9%) in the intermediate-risk group (RS 18-30), and 37 patients (3.2%) in the high-risk group (RS > 30) (Table 4).

In univariate analysis, patient characteristics associated with RS included age, grade, PR status, HER2 status, and disease subtype. Multivariate logistic regression indicated that RS varied significantly according to different age, PR status, and grade (Table 5). Compared to grade I, grade III was associated with significantly

Table 5 Multivariate Analysis of Independent Variables Associated With RS

Clinicopathologic Feature	Intermediate vs. Low Risk			High vs. Low Risk		
	P	OR	95% CI	*P*	OR	95% CI
Age, y	<.001			.004		
<60		Ref	—		Ref	—
≥60		1.795	1.379-2.336		2.899	1.399-5.988
PR Status	<.001			<.001		
Positive		Ref	—		Ref	—
Negative		4.184	2.597-6.757		12.346	5.556-27.778
Grade						
I		Ref	—		Ref	—
II	.106	1.252	0.953-1.643	.140	1.805	0.825-3.950
III	.168	1.696	0.800-3.596	<.001	15.420	5.382-44.175

Abbreviations: CI = confidential interval; OR = odds ratio; PR = progesterone receptor; RS = recurrence score.

higher odds of high-risk (odds ratio [OR] = 15.420; 95% CI, 5.382-44.175, $P < .001$) RSs. Patients with PR-negative tumors were more likely to have intermediate-risk (OR = 4.184; 95% CI, 2.597-6.757, $P < .001$) and high-risk (OR = 12.346; 95% CI, 5.556-27.778, $P < .001$) RSs compared to those with PR-positive tumors. In addition, we found that age at diagnosis was another factor associated with RS. Patients diagnosed at older ages had a higher likelihood of having intermediate-risk (OR = 1.795; 95% CI, 1.379-2.336; $P < .001$) and high-risk (OR = 2.899; 95% CI, 1.399-5.988; $P = .004$) RSs compared to young patients.

After a median follow-up of 49 months (range, 0∼131 months), there were only 4 BCSS events and 31 OS events. Because of the relatively small number of events, it is inappropriate to perform survival analysis.

Discussion

PMBC is a rare subtype of breast cancer, with an incidence of 1% to 6% of all primary breast cancers.[1-6] In this large population-based study of 8048 women with PMBC, we aimed to provide deep insight into the prognostic factors of PMBC diagnosed in the last 10 years. Consistent with previous studies,[10,22-27] our data showed that age, race, tumor size, and nodal status were independent prognostic markers in patients with PMBC. However, for the first time, molecular phenotype was revealed to have prognostic value for PMBC in our large population-based series, similar as IDC.

Molecular phenotype was first proposed on the basis of variations in gene expression patterns derived from complementary DNA microarrays[28-30] and has been extensively studied in gene expression profiling and hierarchical cluster analysis.[31-33] The cost of multigene molecular assays has limited its clinical use, but immunohistochemical staining and conventional clinicopathologic factors can be used as surrogate markers for gene expression profiling in invasive breast cancer.[34,35] Moreover, molecular phenotypes beyond the current pathologic-based classification have been endorsed by the 2013 St Gallen Consensus Recommendations,[36] and several research groups have confirmed the prognostic significance of molecular phenotypes in patients with breast cancer.[37,38]

Our study revealed that molecular phenotype has crucial significance as an independent predictor for both OS and, more importantly, BCSS in PMBC patients diagnosed over the last decade. Compared to ER-positive and low-grade group, the risk of breast cancer−specific mortality was nearly 2 times higher in patients with ER-negative and high-grade tumors. Notably, the eighth edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis classification system for breast cancer incorporated biologic factors including tumor grade, expression of hormone receptors and HER2, and multigene assays into the current staging system.[39] According to the biologic factor−based prognostic stage groups for the eighth edition that take into consideration biomarkers, patients with favorable biomarkers such as lower tumor grade and ER-positive disease are more likely to have their disease downgraded compared to anatomic stage defined by conventional AJCC T, N, and M staging. Our analyses are in line with the latest AJCC staging system, which confirmed the prognostic value of molecular phenotype defined by ER status and tumor grade.

To date, to our knowledge, the distribution of the 21-gene RS for PMBC has not been reported in previous studies. This study represents the largest descriptive analysis of RS in a PMBC series. In our population-based study of the SEER database, we observed that the majority of patients had either low-risk (64.9%) or intermediate-risk (31.9%) RS. The percentage of patients with high-risk RS was 3.2%. The distribution pattern of RS in patients with IDC and invasive lobular carcinoma (ILC) has been evaluated in previous studies. A large population-based analysis including more than 30,000 IDC cases indicated that 57%, 35%, and 8% of patients with IDC had low-, intermediate-, and high-risk RS, respectively, based on traditional cutoffs.[40] Of patients with ILC, the percentage of low- and intermediate-risk group were 60%, 38%, and 8% according to another SEER population study.[41] Compared to previous findings on the distribution of RS in IDC and ILC patients, patients with PMBC in our series seem to be associated with having a higher likelihood of having low-risk RS. However, further studies are needed to determine whether the difference on the distribution pattern of RS has statistical significance.

The evaluation of the association between biological features and RS among patients with PMBC that we conducted indicated that PR negativity was a significant independent factor to predict a high-risk RS, as well as age and tumor grade. Similarly, higher tumor grade and negative PR status were also founded to be strong predictors of a high-risk RS in patients diagnosed with IDC and ILC in prior studies.[40,42] Furthermore, younger age was associated with a higher likelihood of a low-risk RS in both PMBC patients and ILC patients,[43] whereas a different result was observed in IDC population, indicating that the elderly were more likely to have a low-risk RS.[40,42]

Specifically, discordance between clinicopathologic factors and RS was also noted in our study. Some patients with favorable clinicopathologic factors were found to display high-risk RS (eg, 3.1% of patients with node-negative diseases had high-risk disease). Although our study found that only a small proportion of mucinous carcinoma (3.2%) was categorized as high-risk RS, the potential for the adverse biology of this subtype may still warrant RS testing. Additionally, because of the small number of events, it is premature to draw any conclusions regarding the prognostic significance of RS at this moment. Further studies are needed to evaluate the prognostic value of RS.

The main strengths of our study included a large, unselected, consecutive population of PMBC patients with detailed knowledge of clinicopathologic variables and RS results. To our knowledge, this study is the first to comprehensively evaluate the prognostic value of molecular phenotype and assess the distribution of RS in such a large population with PMBC. The limitations were the retrospective design of the study, and insufficiency of some specific data, such as HER2 status and Ki-67 expression, which was the result of incomplete records in SEER database. Nonetheless, our findings are of help in providing a better understanding of the prognostic markers and distribution of RS in patients with PMBC.

Conclusion

Our study revealed that larger tumor size and nodal positivity were significantly independent predictors for a worse survival in PMBC. Molecular phenotype, age, and receipt of chemotherapy and radiotherapy were also independent predictors. The distribution of RS varied significantly according to different ages, grades, PR status, HER2 status, and molecular subtype. PR status, age, and tumor grade could independently predict RS.

Clinical Practice Points

- Traditional biological features including age, tumor size, and nodal status are independent prognostic factors in patients with PMBC.
- Molecular phenotype defined by ER status and tumor grade played a vital role as an independent predictor for PMBC. Patients with ER-positive and grade I tumors had a 5-year BCSS of 98.41%, while patients with ER-negative and grade II-III tumors had the worst survival.
- Patients with older age at diagnosis, PR-negative tumors, and poorly differentiated tumors were more likely to have higher RS in PMBC.
- Our study is novel in that it analyzed the distribution of RS in patients with PMBC for the first time.
- Our results contribute to a better understanding of the prognostic significance of biological features and molecular phenotype for patients with PMBC. The findings may be helpful to establish individualized treatment guidance for PMBC.

Acknowledgments

We acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program registries for creating the SEER database. This study was supported by National Natural Science Foundation of China (grant 81572581) and the Technology Innovation Act Plan of Shanghai Municipal Science and Technology Commission (grant 16411966900). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the report.

Disclosure

The authors have stated that they have no conflict of interest.

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