Original Article

Comparison of the prognosis of medullary breast carcinoma and invasive ductal carcinoma: a SEER-based study

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Background: Medullary breast carcinoma (MBC) is a rare type of breast cancer. Our study aimed to compare the differences in clinical characteristics and prognosis between MBC and invasive ductal carcinoma (IDC), and to further develop and validate nomograms to predict overall survival (OS) and cancer-specific survival (CSS) in MBC patients.

Methods: A total of 179,613 patients from the Surveillance, Epidemiology and End Results (SEER) database from 2010 to 2015, including 596 MBC patients, were analyzed using the Kaplan-Meier method and propensity score matching (PSM) to compare patients' OS and CSS. Cox proportional hazard regression model was used to determine independent prognostic factors for OS and CSS in MBC patients. Nomograms were constructed based on Cox regression analysis whereas receiver operating characteristic (ROC) curves and calibration curves were used to evaluate the predictive accuracy.

Results: There were significant differences in the clinical characteristics between MBC and IDC. According to the logrank test, MBC had better OS and CSS than IDC before and after PSM. Cox multivariate analysis showed that age, race, tumor size, lymph node (LN), and radiation therapy were independent prognostic factors for OS, whereas age, tumor size, American Joint Committee on Cancer (AJCC) stage, laterality, type of surgery, and chemotherapy were independent prognostic factors for CSS. Nomograms of OS and CSS were constructed based on independent prognostic factors.

Conclusions: MBC had better OS and CSS than IDC. Nomograms based on clinicopathological features were sufficiently accurate in predicting the OS and CSS for MBC patients, which can effectively predict the survival risk of MBC patients and guide clinicians to provide more effective treatment measures.

Keywords: Medullary breast carcinoma (MBC); invasive ductal carcinoma (IDC); overall survival (OS); cancer-specific survival (CSS); nomogram

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Introduction

Medullary breast carcinoma (MBC) is a distinctive type of invasive breast cancer, accounting for less than 5% of all cases of this malignancy (1). Research has demonstrated that immunohistochemical staining of patients with MBC reveals a greater prevalence of triple-negative status, which is characterized by negativity for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (2). It is well known that both triple negative breast cancer (TNBC) and invasive breast cancer are linked to a poorer prognosis. Nonetheless, some studies have indicated that patients diagnosed with MBC had a favorable prognosis (3-7), whereas other studies have demonstrated that the prognosis for MBC was not dissimilar to that of invasive ductal carcinoma (IDC) (8,9). Hence, a consistent consensus has yet to be reached regarding the discernible distinctions in clinical characteristics and prognostic profiles between MBC and IDC.

Recent research suggested that MBC was not a strictly pathological diagnosis, but a heterogeneous, spectrum-based group of lesions (10). It is imperative to ascertain the prognostic factors of MBC in order to facilitate the provision of more targeted and tailored treatment options to patients. Park *et al.* noted that overall survival (OS) and disease-free survival (DFS) were poorer in MBC patients with lymph node (LN) metastases, whereas no discernible difference was identified in terms of tumor size, hormone receptor status, or treatment modalities (8). Wang *et al.* utilized the Cox proportional hazards model as a means of evaluating the prognostic factors associated with cancer-specific survival (CSS) and OS among patients with MBC (1). Owing to the limited sample size and the presence of confounding factors, the prognostic factors pertaining specifically to MBC patients remained relatively unclear. The nomogram, which is regarded as a reliable tool based on multivariate regression analysis, encompasses the integration of numerous predictors to construct models that can accurately predict the prognostic outcomes for various cancers (11,12).

Given the controversial prognostic factors for MBC patients, the aim of our research was to identify disparities in clinical characteristics and prognosis between MBC and IDC by using the Surveillance, Epidemiology and End Results (SEER) database, and to further build and validate nomograms based on clinicopathological features for MBC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-858/rc).

Highlight box

Key findings

- Medullary breast carcinoma (MBC) exhibited better overall survival and cancer-specific survival than invasive ductal carcinoma (IDC). Moreover, laterality and type of surgery were found to be independent prognostic factors for MBC. The development and validation of the nomogram for predicting the prognosis of MBC would be highly desirable.

What is known and what is new?

- MBC has a better prognosis than IDC.
- Construction and validation of nomograms for MBC are needed.

What is the implication, and what should change now?

- Clinicians can offer tailored treatments to patients by utilizing prognostic factors, but larger sample sizes will be required in the future to confirm and refine the accuracy of the nomogram.

Methods

Patients

We utilized SEER *Stat version 8.4.0.1 (https://seer.cancer.gov/seerstat/) to obtain 179,613 patients diagnosed between 2010 and 2015 who satisfied the following inclusion criteria: female, pathologically confirmed IDC (8500/3: IDC-NOS) or MBC (8510/3: MBC-NOS, 8512/3: MBC with lymphoid stroma, 8513/3: atypical MBC), histological grades I–IV, American Joint Committee on Cancer (AJCC) stages I–IV, with breast conserving surgery (BCS) or mastectomy, ER, PR, HER2 statuses known. We excluded patients who had not undergone surgery or with incomplete information, as well as those with no record of radiotherapy and chemotherapy. As information on radiotherapy, chemotherapy, and HER2 was not available in the SEER database until 2010, we excluded patients before 2010. Additionally, due to the different versions of staging after 2015 and our desire to ensure a sufficiently long follow-up period, we also excluded those who diagnosed with breast cancer after 2015. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The demographic and clinical features of the 2 histological patient groups were compared using chi-squared test. Survival curves were generated via the Kaplan-Meier

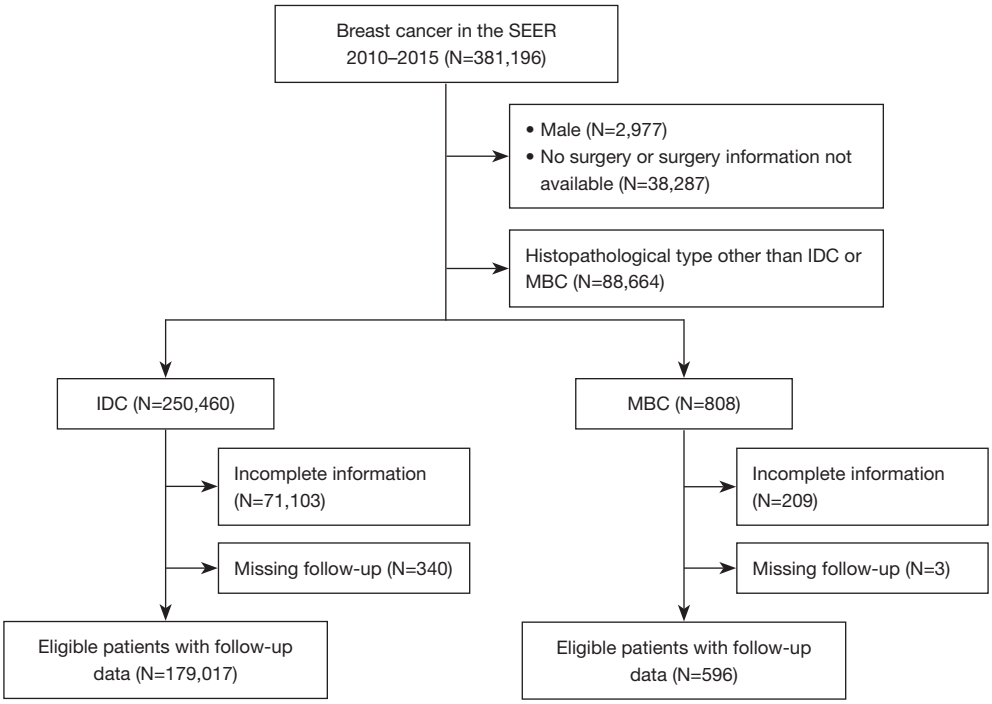

Figure 1 Flowchart of the study. SEER, Surveillance, Epidemiology and End Results; IDC, invasive ductal carcinoma; MBC, medullary breast carcinoma.

method, with disparities in CSS and OS evaluated utilizing the log-rank test. Moreover, we opted to employ a propensity score matching (PSM) technique in order to pair each MBC patient with an IDC patient who best aligned with pertinent variables. Cox proportional models were utilized to undertake univariate analysis, thereby enabling the identification of hazard ratios (HRs) for all potential risk factors, along with corresponding 95% confidence intervals (CIs). In addition, multivariate analysis was implemented to identify all independent prognostic factors. Nomograms were constructed to enable the prediction of 1-, 3-, and 5-year OS and CSS, with the predictive ability of these models evaluated via receiver operating characteristic (ROC) curve analysis. Ultimately, the calibration curve was implemented to assess agreement between predicted prognosis and actual prognosis. The aforementioned analytical procedures were performed using the software SPSS (IBM Corp., Armonk, NY, 25.0) and R (version 4.2.2; http://www.r-project.org) with bilateral P values <0.05 considered statistically significant.

The limitations of the statistical methods

Certainly, the aforementioned statistical methods also have limitations. Firstly, PSM is based on matching observed data of known variables, but there may be unobserved important variables that can influence the comparison of outcomes. Although PSM is used to control confounding variables, residual confounding factors may still exist, which can lead to erroneous positive or negative results, limiting the generalizability of the study findings. Secondly, the nomogram has limited applicability and cannot cover all possible scenarios and target variables. Each nomogram is developed based on specific samples or populations, and its applicability may be limited to the characteristics and scope of the samples used.

Results

Demographic and clinical characteristics of patients

After data filtering, 179,613 patients met our inclusion criteria, including 596 (0.33%) MBC and 179,017 (99.67%) IDC (*Figure 1*). *Table 1* presents a synopsis of demographic and clinical features in patients with distinct histological types. There were significant differences among age, marital status, race, grade, AJCC stage, radiation and chemotherapy experience, LN, ER, PR, HER2 status, and tumor size.

Table 1 Characteristics of patients with MBC and IDC

Variables	IDC (n=179,017), n (%)	MBC (n=596), n (%)	Total (n=179,613), n (%)	P value
Age (year)				<0.001
≤70	136,190 (76.1)	518 (86.9)	136,708 (76.1)	
>70	42,827 (23.9)	78 (13.1)	42,905 (23.9)	
Marital status				0.025
Married	106,741 (59.6)	328 (55.0)	107,069 (59.6)	
Not married[a]	72,276 (40.4)	268 (45.0)	72,544 (40.4)	
Race				<0.001
Black	19,290 (10.8)	138 (23.2)	19,428 (10.8)	
White	141,669 (79.1)	410 (68.8)	142,079 (79.1)	
Other[b]	18,058 (10.1)	48 (8.0)	18,106 (10.1)	
Grade				<0.001
I/II	113,658 (63.5)	32 (5.4)	113,690 (63.3)	
III/IV	65,359 (36.5)	564 (94.6)	65,923 (36.7)	
Laterality				0.649
Left	90,432 (50.5)	295 (49.5)	90,727 (50.5)	
Right	88,585 (49.5)	301 (50.5)	88,886 (49.5)	
AJCC stage				<0.001
I	97,849 (54.7)	237 (39.8)	98,086 (54.6)	
II	60,901 (34.0)	317 (53.2)	61,218 (34.1)	
III/IV	20,267 (11.3)	42 (7.0)	20,309 (11.3)	
Surgery				0.377
BCS	99,490 (55.6)	320 (53.7)	99,810 (55.6)	
Mastectomy	79,527 (44.4)	276 (46.3)	79,803 (44.4)	
Radiation				<0.001
Beam radiation	101,348 (56.6)	293 (49.2)	101,641 (56.6)	
None/unknow	77,669 (43.4)	303 (50.8)	77,972 (43.4)	
Chemotherapy				<0.001
Yes	79,308 (44.3)	448 (75.2)	79,756 (44.4)	
None/unknow	99,709 (55.7)	148 (24.8)	99,857 (55.6)	
LN				<0.001
Positive	53,556 (29.9)	119 (20.0)	53,675 (29.9)	
Negative	125,461 (70.1)	477 (80.0)	125,938 (70.1)	
ER				<0.001
Positive	145,659 (81.4)	201 (33.7)	145,860 (81.2)	
Negative	33,358 (18.6)	395 (66.3)	33,753 (18.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	IDC (n=179,017), n (%)	MBC (n=596), n (%)	Total (n=179,613), n (%)	P value
PR				<0.001
Positive	127,985 (71.5)	106 (17.8)	128,091 (71.3)	
Negative	51,032 (28.5)	490 (82.2)	51,522 (28.7)	
HER2				0.001
Positive	28,789 (16.1)	66 (11.1)	28,855 (16.1)	
Negative	150,228 (83.9)	530 (88.9)	150,758 (83.9)	
Tumor size				<0.001
<2 cm	107,455 (60.0)	228 (38.3)	107,683 (60.0)	
2–5 cm	62,132 (34.7)	335 (56.2)	62,467 (34.8)	
>5 cm	9,430 (5.3)	33 (5.5)	9,463 (5.2)	

[a], not married includes divorced, separated, single (never married), unmarried, or domestic partner and widowed. [b], other includes American Indian/Alaskan native, and Asian/Pacific Islander. MBC, medullary breast carcinoma; IDC, invasive ductal carcinoma; AJCC, American Joint Committee on Cancer; BCS, breast conserving surgery; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Patients with MBC demonstrated a younger age (86.9% *vs.* 76.1%, P<0.001), a higher proportion of Black race (23.2% *vs.* 10.8%, P<0.001), more unmarried (45.0% *vs.* 40.4%, P=0.025), higher ER negative (66.3% *vs.* 18.6%, P<0.001), PR negative (82.2% *vs.* 28.5%, P<0.001), and HER2 negative (88.9% *vs.* 83.9%, P=0.001) rates, higher LN negative (80.0% *vs.* 70.1%, P<0.001) rate, and less experience of chemotherapy (24.8% *vs.* 55.7%, P<0.001) and radiation (49.2% *vs.* 56.6%, P<0.001) than those with IDC. Moreover, compared to IDC, MBC had larger tumor size (more tumors ≥2 and ≤5 cm in size, 56.2% *vs.* 34.7%, P<0.001). Additionally, patients with MBC were likely to have a significantly higher grade (grade III and IV, 94.6% *vs.* 36.5%, P<0.001) and a higher proportion of the AJCC stage of II (53.2% *vs.* 34.0%, P<0.001) than those with IDC. No statistically significant differences were observed in other characteristics, including laterality and surgical type, between the 2 histological types.

Survival comparison between patients with MBC and IDC

Comparisons of OS and CSS of the 2 histological types were conducted separately through Kaplan-Meier analysis (*Figure 2*). As shown in *Figure 2*, MBC patients exhibited superior OS (P=0.0025) and CSS (P=0.0098) to IDC patients. To account for any potential bias or confounding factors, PSM was employed to facilitate a 1:1 matched case-control analysis (*Figure 3*). After matching, we had a total of 1,192 patients, including 596 patients for each histological type. There was no significant difference in clinical characteristics between IDC and MBC (*Table 2*). However, we found that these 2 histological types had a similar outcome for OS and CSS (*Figure 4*, P=0.0073 and P<0.0001 for OS and CSS, respectively).

The construction and validation of the nomograms of MBC

MBC patients were randomly allocated into training and validation groups, with a ratio of 7:3 (*Table 3*). After performing univariate analysis of variables for MBC patients in the training set, seven variables, including age (HR: 4.6, 95% CI: 2.48–8.53, P<0.001), AJCC stage (III/IV) (HR: 5.76, 95% CI: 2.6–12.74, P<0.001), chemotherapy (HR: 0.38, 95% CI: 0.21–0.69, P=0.002), radiotherapy (HR: 2.44, 95% CI: 1.28–4.67, P=0.007), LN (HR: 3.16, 95% CI: 1.74–5.75, P<0.001), type of surgery (HR: 2.05, 95% CI: 1.11–3.79, P=0.022), and tumor size (>5 cm) (HR: 5.11, 95% CI: 2.2–11.84, P<0.001), were found to be correlated with OS in MBC (*Table 4*). Meanwhile, age (HR: 3.88, 95% CI: 1.58–9.51, P=0.003), AJCC stage (III/IV) (HR: 4.88, 95% CI: 1.69–14.08, P=0.003), chemotherapy (HR: 0.28, 95% CI: 0.12–0.66, P=0.003), laterality (HR: 0.36, 95% CI: 0.14–0.91, P=0.031), LN (HR: 2.89, 95% CI: 1.24–6.77, P=0.014), type of surgery (HR: 4.59, 95% CI: 1.69–12.43,

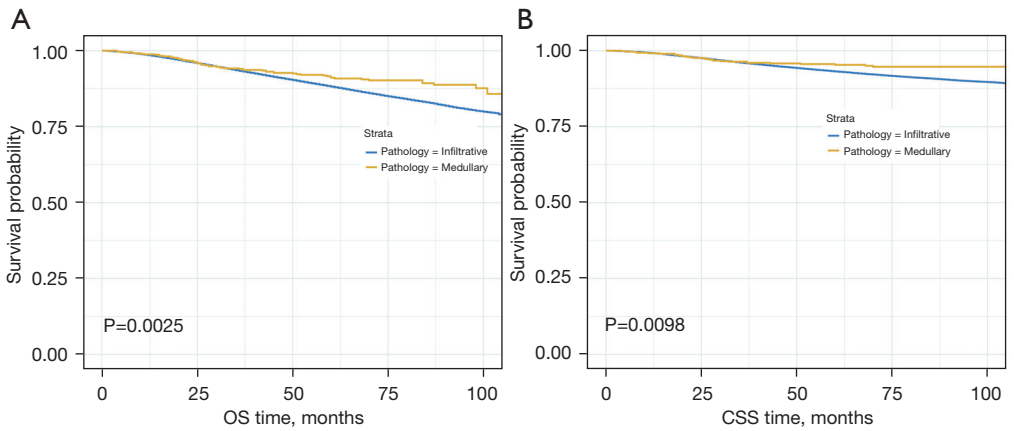

Figure 2 Kaplan-Meier plot and log-rank test compared OS (A) and CSS (B) by histology for all patients, MBC vs. IDC. OS, overall survival; CSS, cancer-specific survival; MBC, medullary breast carcinoma; IDC, invasive ductal carcinoma.

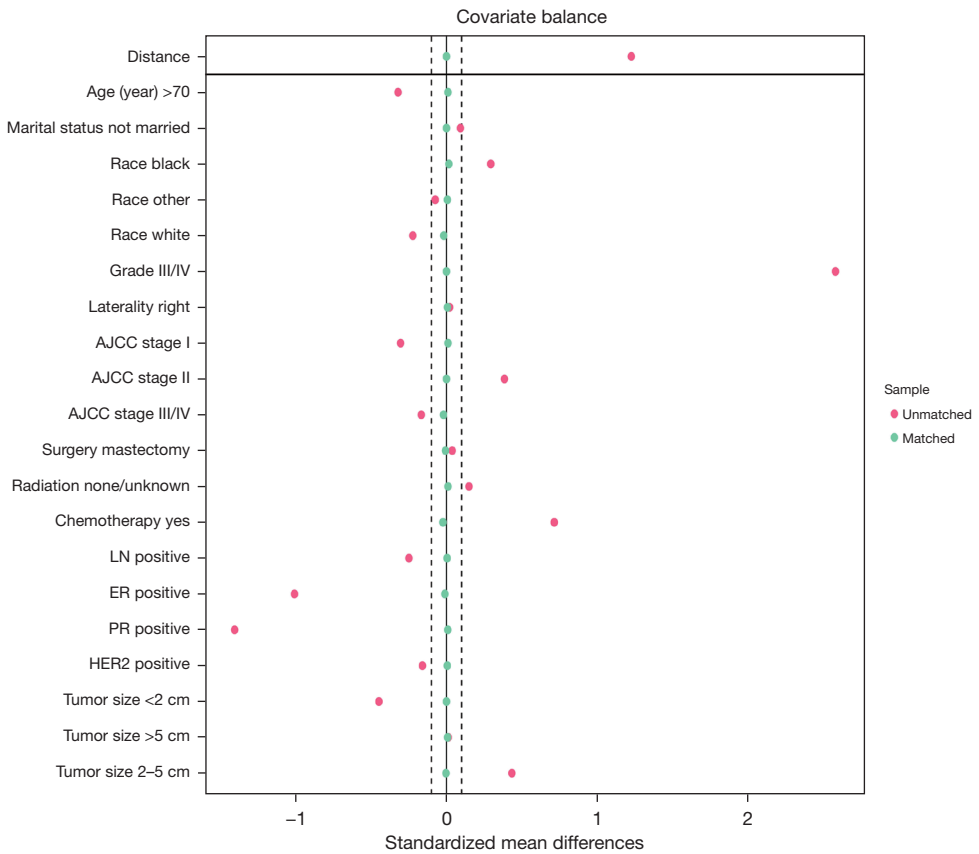

Figure 3 Standardized differences between MBC and IDC. MBC, medullary breast carcinoma; IDC, invasive ductal carcinoma; AJCC, American Joint Committee on Cancer; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 2 Characteristics of patients with medullary breast carcinoma and invasive ductal carcinoma in 1:1 matched group

Variables	IDC (n=596), n (%)	MBC (n=596), n (%)	Total (n=1,192), n (%)	P value
Age (year)				0.931
≤70	520 (87.2)	518 (86.9)	1,038 (87.1)	
>70	76 (12.8)	78 (13.1)	154 (12.9)	
Marital status				>0.99
Married	328 (55.0)	328 (55.0)	656 (55.0)	
Not married[a]	268 (45.0)	268 (45.0)	536 (45.0)	
Race				0.951
Black	134 (22.5)	138 (23.2)	272 (22.8)	
White	415 (69.6)	410 (68.8)	825 (69.2)	
Other[b]	47 (7.9)	48 (8.1)	95 (8.0)	
Grade				1.000
I/II	32 (5.4)	32 (5.4)	64 (5.4)	
III/IV	564 (94.6)	564 (94.6)	1,128 (94.6)	
Laterality				0.954
Left	297 (49.8)	295 (49.5)	592 (49.7)	
Right	299 (50.2)	301 (50.5)	600 (50.3)	
AJCC stage				0.941
I	234 (39.3)	237 (39.8)	471 (39.5)	
II	317 (53.2)	317 (53.2)	634 (53.2)	
III/IV	45 (7.6)	42 (7.0)	87 (7.3)	
Surgery				0.954
BCS	318 (53.4)	320 (53.7)	638 (53.5)	
Mastectomy	278 (46.6)	276 (46.3)	554 (46.5)	
Radiation				0.908
Beam radiation	296 (49.7)	293 (49.2)	589 (49.4)	
None/unknown	300 (50.3)	303 (50.8)	603 (50.6)	
Chemotherapy				0.736
Yes	454 (76.2)	448 (75.2)	902 (75.7)	
None/unknown	142 (23.8)	148 (24.8)	290 (24.3)	
LN				>0.99
Positive	118 (19.8)	119 (20.0)	237 (19.9)	
Negative	478 (80.2)	477 (80.0)	955 (80.1)	
ER				0.903
Positive	204 (34.2)	201 (33.7)	405 (34.0)	
Negative	392 (65.8)	395 (66.3)	787 (66.0)	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	IDC (n=596), n (%)	MBC (n=596), n (%)	Total (n=1,192), n (%)	P value
PR				0.939
Positive	104 (17.4)	106 (17.8)	210 (17.6)	
Negative	492 (82.6)	490 (82.2)	982 (82.4)	
HER2				>0.99
Positive	65 (10.9)	66 (11.1)	131 (11.0)	
Negative	531 (89.1)	530 (88.9)	1,061 (89.0)	
Tumor size				0.992
<2 cm	228 (38.3)	228 (38.3)	456 (38.3)	
2–5 cm	336 (56.4)	335 (56.2)	671 (56.3)	
>5 cm	32 (5.4)	33 (5.5)	65 (5.5)	

[a], not married includes divorced, separated, single (never married), unmarried, or domestic partner and widowed. [b], other includes American Indian/Alaskan native, and Asian/Pacific Islander. IDC, invasive ductal carcinoma; MBC, medullary breast carcinoma; AJCC, American Joint Committee on Cancer; BCS, breast conserving surgery; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

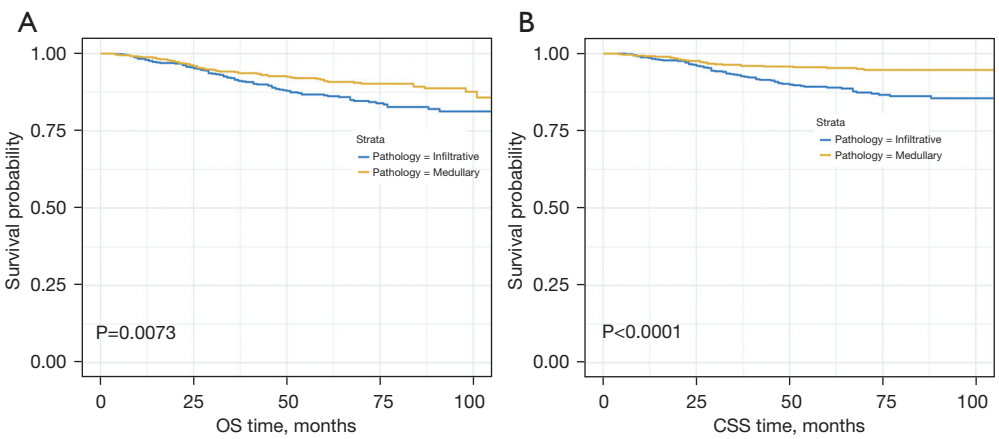

Figure 4 Kaplan-Meier plot and log-rank test compared OS (A) and CSS (B) by histology for 1:1 matched group, MBC vs. IDC. MBC, medullary breast carcinoma; IDC, invasive ductal carcinoma; OS, overall survival; CSS, cancer-specific survival.

P=0.003), and tumor size (>5 cm) (HR: 7.12, 95% CI: 2.17–23.37, P=0.001) were correlated with CSS in MBC patients (*Table 5*). A subsequent multivariate analysis demonstrated that age (HR: 4.59, 95% CI: 2.32–9.06, P<0.001), race (other) (HR: 0.25, 95% CI: 0.07–0.95, P=0.042), radiotherapy (HR: 3.1, 95% CI: 1.38–6.98, P=0.006), LN (HR: 2.42, 95% CI: 1.05–5.55, P=0.037), and tumor size (>5 cm) (HR: 4.21, 95% CI: 1.12–15.83, P=0.033) were independent prognostic factors for OS (*Table 4*). In addition, multivariate analysis demonstrated that age (HR: 3.89, 95% CI: 1.49–10.19, P=0.006), AJCC stage (II) (HR: 0.23, 95% CI: 0.05–0.95, P=0.042), chemotherapy (HR: 0.33, 95% CI: 0.13–0.86, P=0.024), laterality (HR: 0.2, 95% CI: 0.07–0.56, P=0.002), type of surgery (HR: 5.69, 95% CI: 1.63–19.87, P=0.006), and tumor size (>5 cm) (HR: 8.44, 95% CI: 1.33–53.49, P=0.024) were independent prognostic factors of CSS of MBC patients (*Table 5*). Nomograms estimating the 1-, 3-, and 5-year OS and CSS of MBC patients were created based on independent prognostic factors. *Figure 5A*,*5B* present the nomograms for predicting the OS and CSS in

Table 3 Characteristics of the training and validation cohorts

Variables	Total (n=596)	Training set (n=417)	Validation set (n=179)	P value
Age (year)				0.415
≤70	518 (86.9)	366 (87.8)	152 (84.9)	
>70	78 (13.1)	51 (12.2)	27 (15.1)	
Marital status				0.859
Married	328 (55.0)	228 (54.7)	100 (55.9)	
Not married[a]	268 (45.0)	189 (45.3)	79 (44.1)	
Race				0.170
Black	138 (23.2)	96 (23.0)	42 (23.4)	
White	410 (68.8)	293 (70.3)	117 (65.4)	
Other[b]	48 (8.0)	28 (6.7)	20 (11.2)	
Grade				0.403
I/II	32 (5.4)	25 (6.0)	7 (3.9)	
III/IV	564 (94.6)	392 (94.0)	172 (96.1)	
Laterality				0.158
Left	295 (49.5)	198 (47.5)	97 (54.2)	
Right	301 (50.5)	219 (52.5)	82 (45.8)	
AJCC stage				0.421
I	237 (39.8)	159 (38.1)	78 (43.6)	
II	317 (53.2)	229 (54.9)	88 (49.2)	
III/IV	42 (7.0)	29 (7.0)	13 (7.2)	
Surgery				0.334
BCS	320 (53.7)	218 (52.3)	102 (57.0)	
Mastectomy	276 (46.3)	199 (47.7)	77 (43.0)	
Radiation				0.655
Beam radiation	293 (49.2)	208 (49.9)	85 (47.5)	
None/unknow	303 (50.8)	209 (50.1)	94 (52.5)	
Chemotherapy				0.096
Yes	448 (75.2)	322 (77.2)	126 (70.4)	
None/unknow	148 (24.8)	95 (22.8)	53 (29.6)	
LN				0.782
Positive	119 (20.0)	85 (20.4)	34 (19.0)	
Negative	477 (80.0)	332 (79.6)	145 (81.0)	
ER				0.687
Positive	201 (33.7)	138 (33.1)	63 (35.2)	
Negative	395 (66.3)	279 (66.9)	116 (64.8)	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Total (n=596)	Training set (n=417)	Validation set (n=179)	P value
PR				0.877
Positive	106 (17.8)	73 (17.5)	33 (18.4)	
Negative	490 (82.2)	344 (82.5)	146 (81.6)	
HER2				0.344
Positive	66 (11.1)	50 (12.0)	16 (8.9)	
Negative	530 (88.9)	367 (88.0)	163 (91.1)	
Tumor size				0.788
<2 cm	228 (38.3)	156 (37.4)	72 (40.2)	
2–5 cm	335 (56.2)	237 (56.8)	98 (54.8)	
>5 cm	33 (5.5)	24 (5.8)	9 (5.0)	

[a], not married includes divorced, separated, single (never married), unmarried, or domestic partner and widowed. [b], other includes American Indian/Alaskan native, and Asian/Pacific Islander. AJCC, American Joint Committee on Cancer; BCS, breast conserving surgery; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 4 Univariate and multivariate analyses of variables associated with OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (year)				
≤70	Reference			
>70	4.6 (2.48–8.53)	<0.001	4.59 (2.32–9.06)	<0.001
Marital status				
Married	Reference			
Not married[a]	1.48 (0.82–2.68)	0.194		
Race				
Black	Reference			
White	0.55 (0.29–1.04)	0.066	0.5 (0.25–0.99)	0.047
Other[b]	0.66 (0.19–2.28)	0.512	0.25 (0.07–0.95)	0.042
Grade				
I/II	Reference			
III/IV	0.79 (0.25–2.57)	0.699		
Laterality				
Left	Reference			
Right	0.76 (0.42–1.37)	0.357		

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
AJCC stage				
I	Reference			
II	0.88 (0.44–1.76)	0.715	0.76 (0.27–2.14)	0.598
III/IV	5.76 (2.6–12.74)	<0.001	2.31 (0.48–11.12)	0.295
Surgery				
BCS	Reference			
Mastectomy	2.05 (1.11–3.79)	0.022	0.96 (0.45–2.05)	0.916
Radiation				
Beam radiation	Reference			
None/unknown	2.44 (1.28–4.67)	0.007	3.1 (1.38–6.98)	0.006
Chemotherapy				
None/unknown	Reference			
Yes	0.38 (0.21–0.69)	0.002	0.63 (0.32–1.26)	0.193
LN				
Negative	Reference			
Positive	3.16 (1.74–5.75)	<0.001	2.42 (1.05–5.55)	0.037
ER				
Negative	Reference			
Positive	0.74 (0.38–1.44)	0.380		
PR				
Negative	Reference			
Positive	0.9 (0.4–2.02)	0.796		
HER2				
Negative	Reference			
Positive	1.18 (0.5–2.79)	0.706		
Tumor size				
<2 cm	Reference			
2–5 cm	0.92 (0.47–1.81)	0.804	0.84 (0.3–2.33)	0.740
>5 cm	5.11 (2.2–11.84)	<0.001	4.21 (1.12–15.83)	0.033

[a], not married includes divorced, separated, single (never married), unmarried, or domestic partner and widowed. [b], other includes American Indian/Alaskan native, and Asian/Pacific Islander. OS, overall survival; AJCC, American Joint Committee on Cancer; BCS, breast conserving surgery; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval.

Table 5 Univariate and multivariate analyses of variables associated with CSS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (year)				
≤70	Reference			
>70	3.88 (1.58–9.51)	0.003	3.89 (1.49–10.19)	0.006
Marital status				
Married	Reference			
Not married[a]	1.03 (0.45–2.39)	0.944		
Race				
Black	Reference			
White	0.69 (0.28–1.72)	0.428		
Other[b]	0.41 (0.05–3.36)	0.409		
Grade				
I/II	Reference			
III/IV	1.13 (0.15–8.41)	0.905		
Laterality				
Left	Reference			
Right	0.36 (0.14–0.91)	0.031	0.2 (0.07–0.56)	0.002
AJCC stage				
I	Reference			
II	0.68 (0.26–1.81)	0.44	0.23 (0.05–0.95)	0.042
III/IV	4.88 (1.69–14.08)	0.003	0.8 (0.11–5.8)	0.822
Surgery				
BCS	Reference			
Mastectomy	4.59 (1.69–12.43)	0.003	5.69 (1.63–19.87)	0.006
Radiation				
Beam radiation	Reference			
None/unknown	2.18 (0.89–5.34)	0.089	1.1 (0.33–3.6)	0.881
Chemotherapy				
None/unknown	Reference			
Yes	0.28 (0.12–0.66)	0.003	0.33 (0.13–0.86)	0.024
LN				
Negative	Reference			
Positive	2.89 (1.24–6.77)	0.014	2.45 (0.73–8.18)	0.145
ER				
Negative	Reference			
Positive	0.55 (0.2–1.49)	0.238		

Table 5 (*continued*)

Table 5 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
PR				
Negative	Reference			
Positive	0.5 (0.12–2.12)	0.345		
HER2				
Negative	Reference			
Positive	1.77 (0.6–5.22)	0.304		
Tumor size				
<2 cm	Reference			
2–5 cm	1.19 (0.44–3.23)	0.727	2.16 (0.52–8.88)	0.287
>5 cm	7.12 (2.17–23.37)	0.001	8.44 (1.33–53.49)	0.024

[a], not married includes divorced, separated, single (never married), unmarried, or domestic partner and widowed. [b], other includes American Indian/Alaskan native, and Asian/Pacific Islander. CSS, cancer-specific survival; AJCC, American Joint Committee on Cancer; BCS, breast conserving surgery; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval.

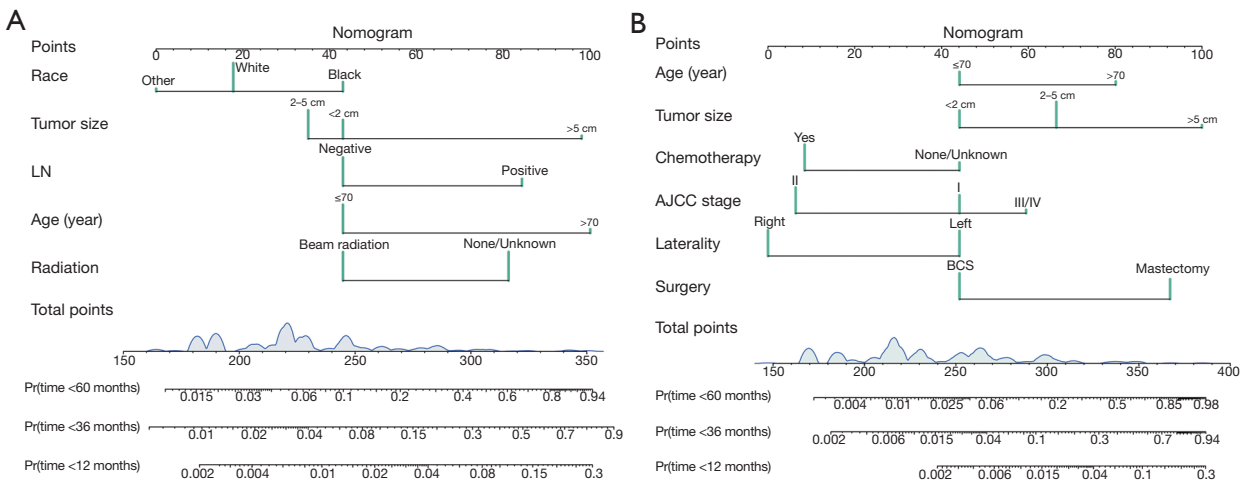

Figure 5 Nomograms for predicting the 1-, 3-, and 5-year (A) OS and (B) CSS of MBC. OS, overall survival; CSS, cancer-specific survival; MBC, medullary breast carcinoma; LN, lymph node; AJCC, American Joint Committee on Cancer; BCS, breast conserving surgery.

MBC patients. The ROC curve reflected the sensitivity and accuracy of the nomograms when the same threshold or different thresholds were selected. The ROC curves for the training and validation sets of MBC patients' OS and CSS were plotted, as depicted in *Figure 6*. As we can see, the concordance index (C-index) of the nomograms for the 1-, 3-, and 5-year OS were 0.852, 0.826, and 0.791, respectively, in the training set, whereas the C-index for the 1-, 3-, and 5-year CSS were 0.845, 0.786, and 0.795, respectively. In the validation set, the C-index was 0.803, 0.806, and 0.846 for the 1-, 3-, and 5-year OS, respectively, and 0.712, 0.754, 0.765 for the 1-, 3-, and 5-year CSS, respectively. The calibration plots demonstrated good correspondence between the predicted outcomes generated

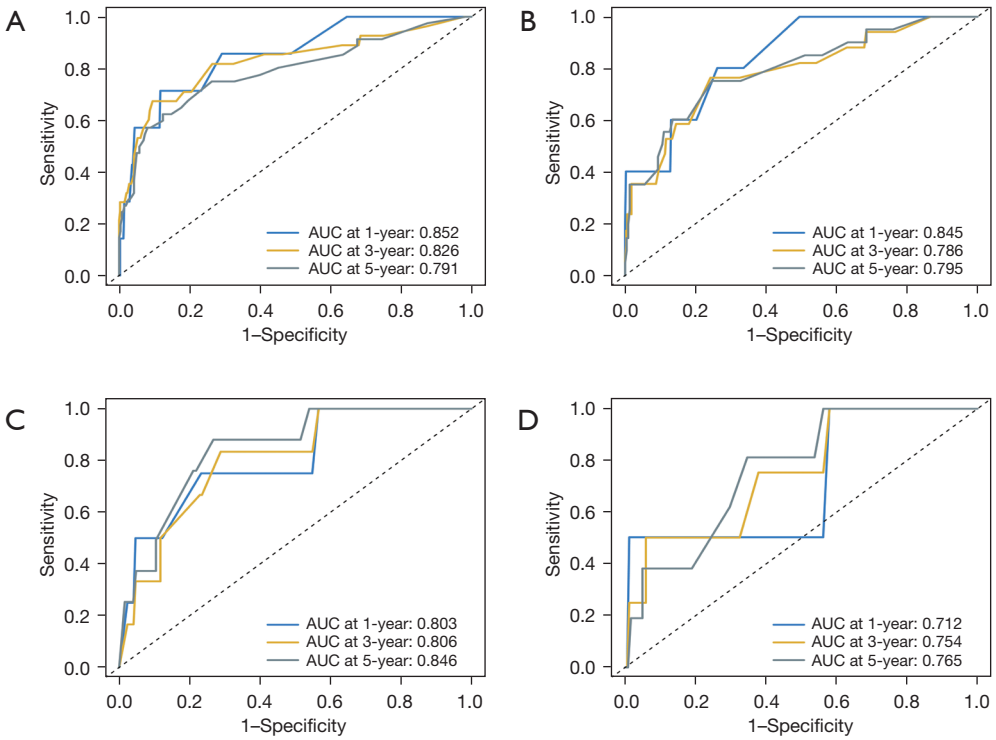

Figure 6 The ROC curves for predicting the survival of MBC patients. The OS (A) and CSS (B) in the training cohort at 1-, 3-, and 5-year after diagnosis, and the OS (C) and CSS (D) in the validation cohort at 1-, 3-, and 5-year after diagnosis. ROC, receiver operating characteristic; MBC, medullary breast carcinoma; OS, overall survival; CSS, cancer-specific survival; AUC, area under the curve.

by the nomograms and the observed outcomes of MBC, for both sets, across the 1-, 3-, and 5-year timepoints (*Figure* 7).

Discussion

Given that MBC is a comparatively uncommon type of breast cancer observed in clinical practice, the SEER database was utilized for comparing the differences in prognosis between MBC and IDC and constructing nomograms to predict OS and CSS in MBC patients. Our study showed that MBC patients were younger, had a higher grade, larger tumor size, and higher ER, PR, HER2 negative rates compared to IDC patients. These results were partially identical to those of previous studies. For example, Dai *et al.* noted that MBC patients exhibited higher stage, higher grade, and larger tumor size compared to patients with IDC (13). Park *et al.* concluded that MBC presented with rare LN metastases, negative ER and PR, nuclear pleomorphism, and high tumor grade (8). In addition, Wang *et al.* demonstrated that, in comparison to the IDCs, the MBCs were younger and presented with more advanced tumor stage, higher grade level, larger tumor size, and a greater proportion of TNBC (1). Nevertheless, in the study by Zangouri *et al.*, although the MBC patients were younger, there was no statistically significant difference in age compared to IDC; this may be due to its insufficient sample size, with ethnic differences also having an effect (14). Moreover, MBC patients in China exhibited less aggressive characteristics such as lower stage, smaller size of tumor, and a lesser proportion of LN metastases (3).

Our present study indicated that both OS and CSS were superior in the MBC cohort when compared to the IDC cohort, both before and after controlling for confounding factors. IDCs were more aggressive than MBCs, which was similar to the findings of several previous studies (15-18). In a previous study, there was no notable difference in OS between IDC and specific histological types, whereas after PSM, the MBC group had better OS than IDC, which might be explained by the greater difference in prognosis of patients with different specific histological types (19).

Despite existing research having identified risk factors that impact the prognosis of MBC patients, to date,

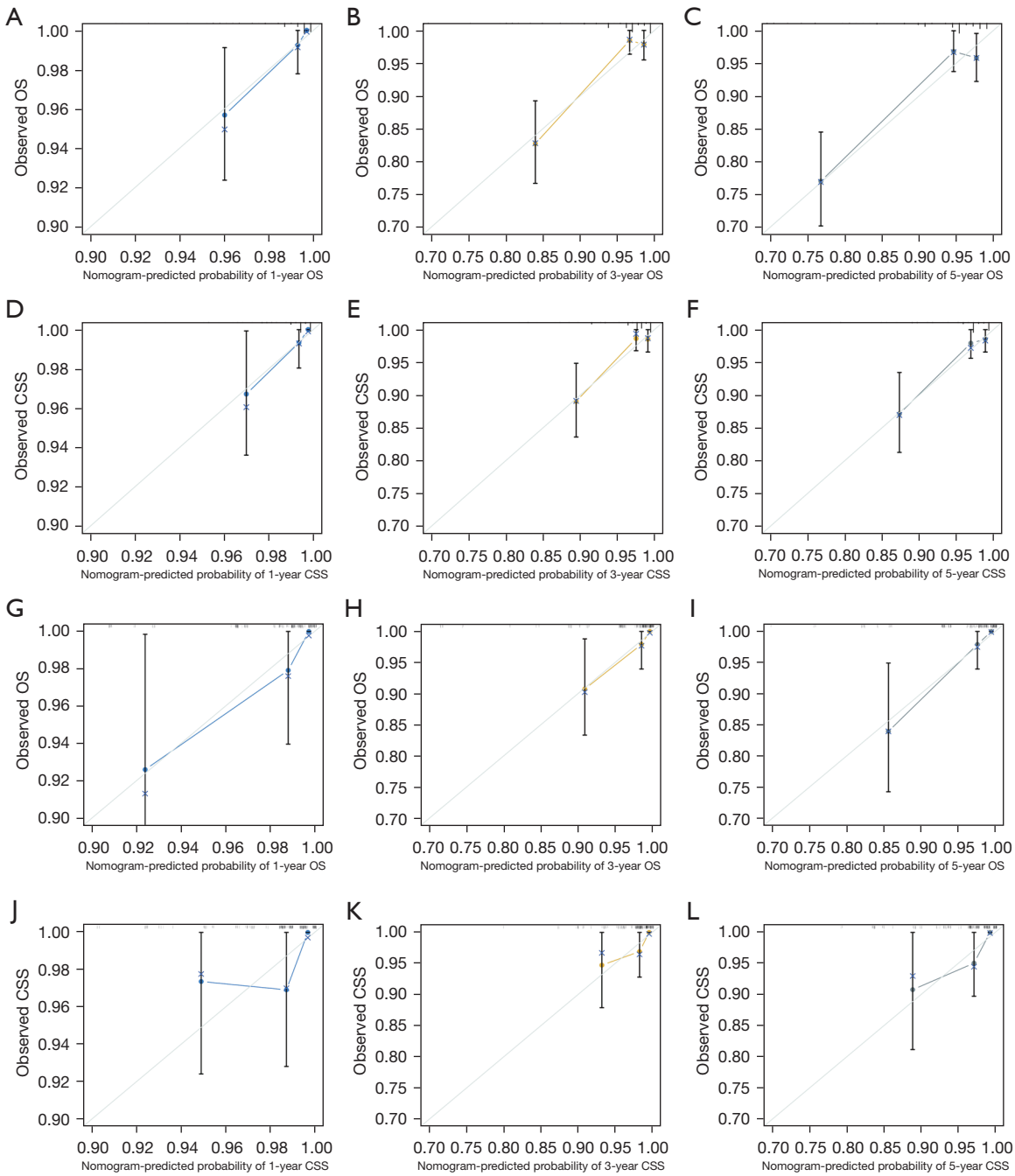

Figure 7 The calibration curves for predicting the survival of MBC patients. The OS (A-C) and CSS (D-F) in the training cohort at 1-, 3-, and 5-year after diagnosis, and the OS (G-I) and CSS (J-L) in the validation cohort at 1-, 3-, and 5-year after diagnosis. MBC, medullary breast carcinoma; OS, overall survival; CSS, cancer-specific survival.

nomograms have yet to be constructed for the purpose of predicting both OS and CSS in MBC patients. Nomograms can be used to calculate the probability of producing a clinical event by integrating various clinical variables, which have been found to be superior to the tumor-node-metastasis (TNM) staging system (20-22). As observed by Dai *et al.*, race appeared to be a significant factor in the prognosis of MBC patients, with Asian populations

exhibiting more favorable outcomes, whereas African Americans tended to have poorer prognoses (13). Our study also confirmed this, with Black patients having a worse prognosis than Whites. MBC patients were younger than IDC (7), which was also confirmed by our findings: younger patients in MBC showed better CSS and OS. A number of factors were discovered to be significantly linked to OS in MBC, including age, marital status, stage, breast cancer subtype, tumor size, and radiotherapy (1). Our study observed a correlation between AJCC stage and the OS of MBC patients, although after conducting a Cox multivariate analysis, AJCC stage was no longer identified as an independent prognostic factor for OS. However, AJCC stage was an independent prognostic factor for CSS. Furthermore, ER and PR positivity have often been considered good prognostic factors for breast cancer, as endocrine therapy might benefit patients (23). Conversely, our study showed that ER and PR status were not associated with the prognosis of MBC patients. Both chemotherapy and radiotherapy are indispensable to the therapeutic regimen for managing invasive breast cancer. Lim *et al.* concluded by multivariate analysis that chemotherapy significantly improved OS (P=0.007) and CSS (P=0.009), but the effect of chemotherapy was limited in patients with larger tumors (>2 cm) (24). Aihara *et al.* concluded that the risk of death in MBC patients with ER and HER2 negativity was approximately half that of IDC patients and that postoperative chemotherapy reduced mortality and recurrence rates (25). However, another study disclosed that neither radiotherapy nor chemotherapy showed any notable association with the prognosis of patients with MBC (13). Our study found that radiotherapy improved patients' OS and chemotherapy improved patients' CSS, which might be related to the higher proportion of patients with severe conditions in our cohort, such as patients with larger tumor size and higher grade. A meta-analysis demonstrated that patients who underwent BCS exhibited better OS compared to mastectomy (26). Our study showed that patients with MBC who underwent BCS had better CSS compared to mastectomy. In addition to the independent prognostic factors mentioned above, we found that tumor size, LN, and laterality were also independent prognostic factors. The calibration curve and ROC curve both evinced the high predictive accuracy of the nomograms, which effectively forecasted 1-, 3-, and 5-year OS and CSS for MBC.

There were some limitations in our study. Firstly, as the SEER database did not provide information on HER2 and radiochemotherapy until 2010, this could potentially have resulted in inadequate follow-up time for our selected patients. Secondly, in our study, we exclusively considered patients with complete information on all variables and excluded those with incomplete data, which might have influenced the generalizability of our findings by introducing selection bias and limiting the sample size. Thirdly, due to the absence of specific information on endocrinology, targeted therapy, and chemotherapy regimens in the SEER database, we were unable to generate more comprehensive treatment plans for patients. Lastly, the utilization of the same database for both creating and validating nomograms may have introduced selection bias; utilizing data from diverse clinical cohorts would be recommended for validation purposes to make the nomograms more reliable.

Conclusions

Our study revealed noticeable differences between MBC and IDC, including younger age, higher stage and grade, lower rates of LN metastasis, larger tumor size, and higher prevalence of ER, PR, and HER2 negativity in MBC patients. Nevertheless, MBC patients had a comparatively better prognosis with respect to both OS and CSS. Our research identified age, race, tumor size, LN, and radiation therapy as independent prognostic factors for OS, whereas age, tumor size, AJCC stage, laterality, type of surgery, and chemotherapy were deemed independent prognostic factors for CSS. We observed no association between ER, PR, or HER2 status, as well as marital status, and the prognosis of MBC. The nomogram that we developed functioned effectively as a predictive tool for survival risk in MBC patients, thereby providing healthcare professionals with practical guidance for treatment options.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-858/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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