Clinical Epidemiology

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ORIGINAL RESEARCH

Prognostic Factors and a Nomogram Predicting Survival in Patients with Breast Ductal Carcinoma in situ with Microinvasion: A Population-Based Study

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Purpose: Ductal carcinoma in situ with microinvasion (DCISM) can be challenging to balance the risks of overtreatment versus undertreatment. We aim to identify prognostic factors in patients with DCISM and construct a nomogram to predict breast cancer-specific survival (BCSS).

Materials and Methods: A retrospective cohort study of women diagnosed with DCISM from 1988 to 2015 who were identified in the Surveillance, Epidemiology and End Results database. Clinical variables and tumor characteristics were evaluated, and Cox proportional-hazards regression was performed. A nomogram was constructed from the multivariate logistic regression to combine all the prognostic factors to predict the prognosis of DCISM patients at 5 years, 10 years, and 15 years.

Results: We identified 5438 total eligible breast cancer patients with a median and max survival time of 78 and 227 months, respectively. Here, patients with poorer survival outcomes were those diagnosed between 1988 and 2001, African-American race, under 40 years of age, higher tumor N stage, progesterone receptor-negative tumor, and received no surgery. The nomogram was constructed by the seven variables and passed the calibration and validation steps. The area under the receiver operating characteristic (ROC) curve (AUC) of both the training set and the validating set (5-year AUC: 0.77 and 0.88, 10-year AUC: 0.75 and 0.73, 15-year AUC: 0.72 and 0.65). Receiving chemotherapy was associated with a better BCSS (hazard ratio, HR=0.45, 95% confidence interval, 95% CI = 0.23–0.89), especially in patients with estrogen receptor (ER) negative, progesterone receptor (PR) negative (HR = 0.35, 95% CI = 0.13–0.97) and ER+PR-/ER-PR+ DCISM (HR = 0.07, 95% CI = 0.01–0.59).

Conclusion: Our current study is the first to construct nomograms of patients with DCISM which could help physicians identify breast cancer patients that more likely to benefit from more intensive treatment and follow-up. Chemotherapy might benefit patients with ER-PR- and ER+PR-/ER-PR+ DCISM.

Keywords: breast cancer, ductal carcinoma in situ, microinvasion, nomogram, survival

Introduction

Ductal carcinoma in situ (DCIS) with microinvasion (DCISM) is a mostly preinvasive breast carcinoma with a small component of invasive disease (presence of one or more foci of stromal invasion, none exceeding 1 mm in size) and presumably has a low but plausible risk of metastasis.[1,2] Tumors with any invasive foci of 1mm or larger in size are defined as invasive carcinoma.[1,2] Microinvasive carcinoma is an uncommon disease, accounting for a mere 1% of all breast cancer diagnoses;[3–5] furthermore, tumor

Received: 16 October 2021
Accepted: 12 November 2021
Published: 30 November 2021

microinvasion is found in association with only approximately 5–10% of DCIS cases.[6–8] Microinvasive cancer is rarely ever seen in the absence of an adjacent in situ lesion.[6] This may be due to difficulty visualizing an isolated 1-mm invasive component, whereas an adjacent in situ lesion will dramatically enhance its detectability. Consequently, microinvasive carcinoma is usually described as "DCIS with microinvasion" despite the presence of DCIS not being necessary. Although DCISM patients account for only a small proportion of total breast cancer cases, the incidence of DCISM continues to increase along with a very significant rise in DCIS as a result of increased detection of breast cancer with the widespread adoption of mammography screening.[9,10]

Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend DCIS treatment and systemic therapy utilization for the majority of DCISM cases, which more closely reflects the therapeutic guidelines for DCIS than for that of invasive carcinoma.[11] However, several years ago it was recommended that patients with microinvasive carcinoma be treated the same as patients with small invasive cancers.[12] While surgery is the standard treatment in DCIS and the majority of invasive carcinomas, additional treatment options vary quite widely between the two entities. Most notably, adjuvant chemotherapy is part of the national treatment guidelines for many invasive breast cancers but is not recommended for DCIS.[13] Given that DCISM is relatively rare compared to pure DCIS and most invasive ductal carcinomas, there exists limited and controversial data regarding its tumor biology and diseases prognosis that serves to guide disease management and patient counseling. Several single-institution retrospective studies have reported clinical features, management, and prognostic implications for DCISM, but yield conflicting results.[14–16] Although DCIS, DCISM, and T1a invasive ductal carcinoma (invasive tumor size >0.1 cm but ≤0.5 cm in greatest dimension was classified as T1a) all have generally excellent prognosis, some population-based studies have revealed that DCISM more closely resembles small invasive carcinoma than pure DCIS and many practitioners are treating it accordingly as such.[17,18] Breast cancer, even with microinvasion, is a very heterogeneous disease characterized by diverse histopathologic and molecular features that are associated with distinct clinical outcomes. As a result, it can be challenging to balance the potential risks of overtreatment versus undertreatment in DCISM.

The American Joint Committee for Cancer (AJCC) staging system is a widely used tool for clinicians to predict disease outcomes and guide therapeutic decision making.[19,20] However, given the many variables that influence the course of cancer, a prognosis based on the AJCC staging system alone is simply insufficient. A precise estimate of DCISM mortality is required to evaluate the clinical implications of this early-stage cancer and guide individualized therapeutic approaches. Nomograms, with the ability to generate an individual probability of a clinical event by integrating biological and clinical variables, help fulfill this requirement and aid in the development of personalized medicine.[21–23] There are currently no studies constructing a nomogram for DCISM female breast cancer. To address this issue, this study aims to establish a comprehensive and reliable prognostic model of DCISM by building a nomogram to better understand the risk factors and prognosis. And by risk regression analysis and propensity score matching method, we aim to deepen the understanding about chemotherapy, radiotherapy and surgery utility in DCISM patients. To obtain a sufficient number of DCISM cases, the Surveillance, Epidemiology and End Results (SEER) cancer database of the National Cancer Institute was used in this study.

Materials and Methods

Source of Data

Study data was obtained from the SEER database of the National Cancer Institute, an open access resource for epidemiologic and survival analyses of various cancers, consisting of a collection of 18 high quality population-based cancer registries with very high estimated completeness of reporting. All data is publicly available and de-identified, and therefore exempted from the review of an Institutional Review Board. SEER database data do not require informed consent.

The SEER*Stat software from the National Cancer Institute (Surveillance Research Program, National Cancer Institute SEER*Stat software, http://www.seer.cancer.gov/seerstat) (Version 8.1.5) was used to identify eligible patients with the following inclusion criteria: female, diagnosed between 1988–2015, pathological diagnosis of breast ductal carcinoma, unilateral breast cancer, stage T1mic (defined as presence of one or more foci of stromal invasion, none exceeding 1 mm in size), one primary site only, and known age at diagnosis. Information regarding the human epidermal growth factor receptor-2 (HER2/neu) status is only available in the SEER database from 2010

onwards; therefore, HER2 variable was not included in the analysis. Patients diagnosed with breast cancer after 2015 were excluded to ensure adequate follow-up time. The pathological diagnosis was based on the primary site and according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3). Breast cancer-specific survival (BCSS) was the primary study outcome of the SEER data, which was calculated as the time period from the date of diagnosis to the date of breast cancer-specific death. The causes of death were categorized as either breast cancer related or non-breast cancer related. Patients who died of non–breast cancer related causes were censored regarding the date of death.

Nomogram Development

The following clinical variables were extracted for the study: year of diagnosis, age, marital status, race, N stage (derived from AJCC stage group 6th edition), primary site, laterality, grade, estrogen receptor (ER) status, progesterone receptor (PR) status, surgery, chemotherapy, radiation. Continuous predictors were tested for linearity and converted to categorical variables if the relationship was determined to be nonlinear. Categorical variables were collapsed over categories, with no significant differences. For nomogram construction and validation, all cases were randomly divided into training (n = 3,806) and validating (n = 1,632) cohorts with a ratio of 7:3.[24] Univariate and multivariate Cox regression were then used to screen for variables that significantly correlated with BCSS in the training group. After backwards step-down validation, predictors that remained in the model were year of diagnosis, age, race, N stage, PR status, surgery, and chemotherapy. The resulting multivariate Cox regression model was used to calculate risk score and build the final nomogram prognostic model.

Model Validation

The validity of the nomogram was tested by discrimination and calibration.[21] The discrimination was estimated by the area under the receiver operating characteristic (ROC) curve (AUC).[25] The theoretical value of the AUC is between 0 and 1; an AUC larger than 0.5 indicates prediction performance better than random chance. Calibration curves were plotted to evaluate the consistency between predicted and actual survival rates at 5, 10, and 15 years.[22] A perfect prediction would result in a 45-degree calibration curve (ie, the identity line).

Other Statistical Methodologies

To account for differences in baseline characteristics across the groups, we matched each patient who received chemotherapy to another patient who did not using the following predetermined factors: year of diagnosis, age, marital status, race, N stage, primary site, laterality, grade, ER status, PR status, surgery, chemotherapy, radiation. Propensity score matching method was utilized and the matching quality was tested. Kaplan–Meier curves, with the corresponding results of Log rank tests, were constructed for breast cancer-specific survival. The same methodology was carried out for patients receiving radiation therapy. All statistical analyses were performed in SPSS (version 24.0; IBM Corp, Armonk, NY, USA) or R environment (version 3.4.0; Vienna, Austria; http://www.R-project.org). All tests were two-sided, and the results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Results

Clinicopathological Characteristics of Patients

Application of the aforementioned inclusion and exclusion criteria resulted in a final study population of 5,438 DCISM cases (Figure 1). These cases were randomly

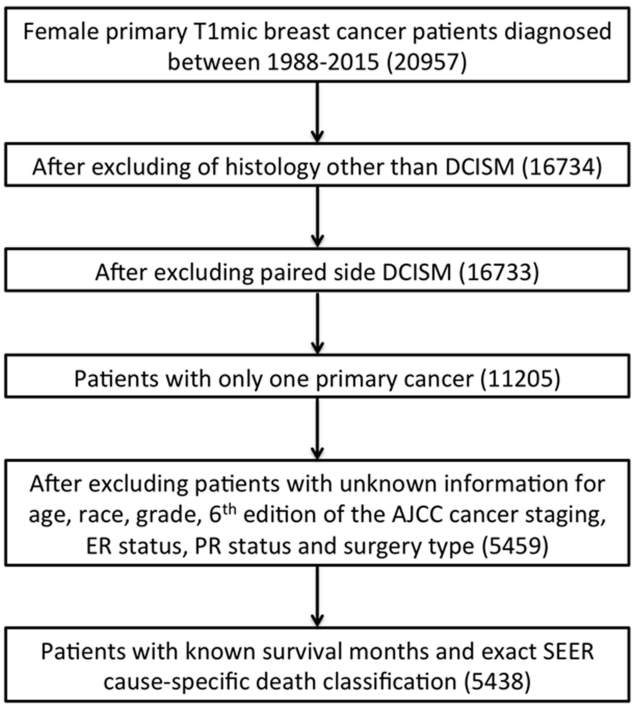

Figure 1 Flowchart of the case selection process in the study.
Abbreviations: DCISM, ductal carcinoma in situ with microinvasion; ER, estrogen receptor; PR, progesterone receptor.

divided into two distinct groups: 3,806 cases were used as the training cohort, while 1,632 cases were used as the validating cohort. The follow-up time ranged from 0 to 227 months (median 78 months) for the training cohort and from 0 to 226 months (median 78 months) for the testing cohort. Patient, disease, and treatment characteristics for the study population are summarized in Table 1. The demographic and clinical variables were similar in the training and validating groups. The majority of patients were diagnosed between 2002–2015, over 40 years of age, Caucasian, tumor grade II–III, ER positive, N0-N1 stage, had undergone surgery and had no chemotherapy.

Building Nomogram Prognostic Model in Training Cohort

In the univariate analysis, each of the following variables significantly increased the BCSS: "diagnosed in 2002–2015", "age between 40 and 70", "married", "Caucasian", "N0 stage", "grade I and II", "PR positive", "received surgery", "no chemotherapy" and "received radiotherapy" (Table 2). According to multivariate analysis, patients diagnosed between 2002–2015 were associated with decreased BCSS compared with patients diagnosed between 1988–2001 (HR=0.56, 95% CI=0.37–0.84). Older age at diagnosis showed association with better BCSS except for the group older than 70 (HR=0.41, 95% CI=0.22–0.78 for age 40–50; HR=0.53, 95% CI=0.30–0.96 for age 51–70; HR=1.40, 95% CI=0.72–2.74 for age over 70). African American patients had worse BCSS than Caucasian at 1.69 times (95% CI=1.06–2.68). More advanced in AJCC N stage corresponded to an increased risk of BCSS (HR=2.69, 95% CI=1.57–4.62 for N1; HR=4.29, 95% CI=1.64–11.19 for N2; HR=9.32, 95% CI=3.23–26.94 for N3). Patients with PR positive breast cancer had a significantly better BCSS than those who with PR negative cancer at 0.503 times (95% CI=0.32–0.80). Receiving surgery, whether lumpectomy or mastectomy, corresponded to significantly better BCSS (HR=0.11, 95% CI=0.04–0.28 for lumpectomy; HR=0.12, 95% CI=0.05–0.28 for mastectomy). Patients who received chemotherapy seemed to have worse BCSS (HR=2.21, 95% CI=1.29–3.76). After stepwise selection via multivariate analysis to further remove potential redundancies, the year of diagnosis, age, race, N stage, PR status, surgery, and chemotherapy were used in the final nomogram model (coefficients summarized in Table 2). The final risk scores for 5-year, 10-year, and 15-year BCSS were calculated by adding up the score of each item using the nomogram depicted in Figure 2. It was demonstrated that surgery contributed the most to prognosis, followed by N stage, age, race, chemotherapy, year of diagnosis, and lastly PR status. Based on this nomogram, some percent of patients would have a 5-year, 10-year or 15-year predicted BCSS under 90%.

Validation and Calibration of the Nomogram

The proposed nomogram was finally validated by discrimination and calibration measures in the independent testing set. The receiver operating characteristic (ROC) curves were plotted both internally and externally in the training and validating sets (Figure 3A and B). In the training set, the AUC for 5-year, 10-year, and 15-year BCSS were 0.77, 0.75 and 0.72, respectively. In the validating set, the AUC for 5-year, 10-year, and 15-year BCSS were 0.88, 0.73 and 0.65, respectively. This confirms the relatively strong prognostic power of the proposed nomogram. A calibration curve at 5 years (Figure 3C), 10 years (Figure 3D) or 15 years (Figure 3E) also showed high consistency between predicted probability and actual proportion of BCSS. The bias-corrected curve as well as the apparent curve were close to the ideal curve which falls along the 45-degree line, demonstrating the robustness of this nomogram. The 5-year, 10-year and 15-year BCSS of the whole study cohort were 98.5%, 96.7% and 95.2%, respectively (Figure 3F). The 5-year, 10-year and 15-year BCSS of the ER+PR+ subgroup were 99.1%, 97.5% and 95.5%, respectively (Figure 3F). The 5-year, 10-year and 15-year BCSS of the single hormone receptor positive (ER+PR- and ER-PR+) subgroup were 97.8%, 95.5% and 94.3%, respectively (Figure 3F). And The 5-year, 10-year and 15-year BCSS of the ER-PR- subgroup were 97.5%, 95.8% and 95%, respectively (Figure 3F).

Statistical Matching for Chemotherapy and Radiotherapy

Chemotherapy and radiotherapy were both commonly applied adjuvant therapies for treatment of breast cancer. Therefore, survival analyses were additionally performed for these two important variables. To ensure that differences in outcome were not attributed to baseline differences in demographic and clinical characteristics across the therapeutic groups, we performed a 1:1 (chemotherapy: no chemotherapy) matched case-control analysis using the propensity score-matching method. We obtained

Table 1 The Individual Characteristics of Variables Involved in the Study

Characteristics	Training Set		Validating Set	
	No. of Patients	%	No. of Patients	%
Year of diagnosis				
1988–2001	391	10.3	183	11.2
2002–2015	3415	89.7	1449	88.8
Age				
<40	201	5.3	71	4.4
40–50	915	24.0	402	24.6
51–70	2048	53.8	863	52.9
>70	642	16.9	296	18.1
Marital status				
Married	1284	33.7	542	33.2
Not married[a]	2357	61.9	1036	63.5
Unknown	165	4.3	54	3.3
Race				
Caucasian	2894	76.0	1231	75.4
African American	445	11.7	188	11.5
American Indian/Alaskan native, or Asian/Pacific Islander	467	12.3	213	13.1
AJCC N stage				
N0	3511	92.2	1527	93.6
N1	248	6.5	94	5.8
N2	32	0.8	7	0.4
N3	15	0.4	4	0.2
Primary site				
Upper-inner quadrant of breast	375	9.9	137	8.4
Lower-inner quadrant of breast	249	6.5	122	7.5
Upper-outer quadrant of breast or axillary tail of breast	1341	35.2	616	37.7
Lower-outer quadrant of breast	268	7.0	106	6.5
Nipple or central portion of breast	217	5.7	106	6.5
Overlapping lesion of breast	1356	35.6	545	33.4
Laterality				
Right-origin of primary	1900	49.9	800	49.0
Left-origin of primary	1906	50.1	832	51.0
Grade				
I	811	21.3	344	21.1
II	1478	38.8	693	42.5
III and undifferentiated	1517	39.9	595	36.5
ER status				
Positive	2685	70.5	1181	72.4
Negative	1121	29.5	451	27.6
PR				
Positive	2177	57.2	971	59.5
Negative	1629	42.8	661	40.5
Surgery				
No surgery	23	0.6	16	1.0
Lumpectomy	2155	56.6	940	57.6
Mastectomy	1628	42.8	676	41.4

(*Continued*)

Table 1 (Continued).

Characteristics	Training Set		Validating Set	
	No. of Patients	%	No. of Patients	%
Chemotherapy				
No	3392	89.1	1499	91.9
Yes	412	10.8	133	8.1
Radiation				
No	1998	52.5	827	50.7
Yes	1808	47.5	805	49.3

Note: [a]Includes divorced, separated, single (never married), and widowed.
Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor.

a group of 726 patients with 363 patients from each chemotherapy group (Figure 4A). Here, we found that chemotherapy was associated with a better BCSS of DCISM (Figure 4A, HR=0.45, 95% CI=0.23–0.89). After stratified by ER and PR status, chemotherapy was not associated with BCSS in patients with ER+PR+ DCISM (Figure 4B, HR=1.66, 95% CI=0.35–7.86). However, benefit with chemotherapy was observed in patients with ER+PR-/ER-PR+ and ER-PR- DCISM (Figure 4C, ER+PR-/ER-PR+, HR=0.07, 95% CI=0.01–0.59; Figure 4D, ER-PR-, HR=0.35, 95% CI=0.13–0.97). Short-term and long term BCSS of patients with different hormone receptor types of DCISM were summarized in Table 3. In ER+PR-/ER-PR+ subgroup, the 5-year BCSS for patients in the chemotherapy and non-chemotherapy groups were 97.8% and 80.1%; the 10-year BCSS were 97.8% and 93.9%; the 15-year BCSS were 97.8% and 73.4%, respectively (Table 3). In ER-PR- subgroup, the 5-year BCSS for patients in the chemotherapy and non-chemotherapy groups were 95.1% and 81.1%; the 10-year BCSS were 89.7% and 81.1%; the 15-year BCSS were 89.7% and 81.1%, respectively (Table 3). The same analysis was performed for radiotherapy with a group of 1,588 patients with 794 patients in each radiotherapy group (Figure 4E). From this, we determined that radiotherapy was not associated with BCSS of DCISM (Figure 4E, HR=0.87, 95% CI=0.49–1.57).

Discussion

Because DCISM constitutes a small minority of cases of breast cancer, it has been difficult to definitively characterize its biological behavior, prognostic factors, and outcomes of multimodality therapy among patients. Previous studies have reported the prognostic implications and clinical management for DCISM, but the therapeutic recommendations proposed in microinvasive breast carcinomas are highly varied and remain controversial.[14–16,26] Recent medical literature shows that current treatment patterns and prognosis of DCISM are comparable to those with small volume invasive ductal carcinoma.[17,18] DCISM breast cancer is a quite heterogeneous disease and could be associated with distinct clinical outcomes. It remains challenging to find a proper, balanced treatment. In this study, a nomogram prognostic model was developed and validated using a large cohort of breast DCISM cases across the United States. Based on routinely available demographic, staging, and treatment information, this nomogram predicts the survival probability for individual DCISM patients and contributes to the development of personalized medicine.

In our present study, we constructed a comprehensive model based on a combination of various risk factors to predict prognosis of breast DCISM. The seven variables include age, race, year of diagnosis, AJCC N stage, PR status, chemotherapy, and surgery were kept in this nomogram after multivariate Cox regression screening and backward stepwise selection; these were all readily available information in the clinical database. Measured by the concordance index, the nomogram passed the discrimination step with an AUC of 0.77, 0.75 and 0.72 (for 5-, 10-, 15-year BCSS, respectively) in the training set and 0.88, 0.73 and 0.65 (for 5-, 10-, 15-year BCSS, respectively) in the validating set, suggesting a decent capability of discerning the breast cancer-specific death event most of the time. As characterized by the confidence intervals in calibration plots, there obviously lies an additional degree of uncertainty in a nomogram estimation. In general, this nomogram model is nevertheless quite reliable and robust in making

Table 2 Univariate and Multivariate Analyses of Breast Cancer-Specific Mortality

Variable	Univariate Analysis	Multivariate Analysis
	HR (95% CI)	HR (95% CI)
Year of diagnosis		
1988–2001	References	References
2002–2015	0.44(0.30,0.65)	0.56(0.37,0.84)
Age		
<40	References	References
40–50	0.35(0.19,0.66)	0.41(0.22,0.78)
51–70	0.35(0.20,0.61)	0.53(0.30,0.96)
>70	0.75(0.41,1.31)	1.40(0.72,2.74)
Marital status		
Not married[a]	References	References
Married	0.67(0.47,0.96)	0.79(0.53,1.16)
Unknown	0.75(0.27,2.03)	0.57(0.20,1.60)
Race		
Caucasian	References	References
African American	2.15(1.40,3.31)	1.69(1.06,2.68)
American Indian/Alaskan native, or Asian/Pacific Islander	0.72(0.38,1.39)	0.75(0.39,1.46)
AJCC N stage		
N0	References	References
N1	5.14(3.42,7.74)	2.69(1.57,4.62)
N2	7.71(3.36,17.66)	4.29(1.64,11.19)
N3	18.86(7.64,46.53)	9.32(3.23,26.94)
Primary site		
Upper-outer quadrant of breast or axillary tail of breast	References	References
Upper-inner quadrant of breast	1.30(0.68,2.50)	1.23(0.63,2.43)
Lower-inner quadrant of breast	0.56(0.20,1.58)	0.62(0.22,1.76)
Lower-outer quadrant of breast	0.84(0.36,1.99)	0.86(0.36,2.06)
Nipple or central portion of breast	1.26(0.59,2.70)	1.10(0.51,2.39)
Overlapping lesion of breast	1.62(1.08,2.45)	1.40(0.92,2.13)
Laterality		
Left-origin of primary	References	References
Right-origin of primary	0.86(0.60,1.22)	0.75(0.52,1.07)
Grade		
I	References	References
II	1.30(0.74,2.27)	1.14(0.64,2.03)
III and undifferentiated	1.77(1.04,3.02)	1.23(0.69,2.20)
ER status		
Negative	References	References
Positive	0.74(0.52,1.06)	1.49(0.92,2.42)
PR		
Negative	References	References
Positive	0.58(0.41,0.83)	0.50(0.32,0.80)

(*Continued*)

Table 2 (Continued).

Variable	Univariate Analysis	Multivariate Analysis
	HR (95% CI)	HR (95% CI)
Surgery		
No surgery	References	References
Lumpectomy	0.06(0.03,0.13)	0.11(0.04,0.28)
Mastectomy	0.11(0.05,0.23)	0.12(0.05,0.28)
Chemotherapy		
No	References	References
Yes	4.47(3.10,6.44)	2.21(1.29,3.76)
Radiation		
No	References	References
Yes	0.66(0.46,0.94)	0.83(0.51,1.36)

Note: [a]Includes divorced, separated, single (never married), and widowed.
Abbreviations: HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.

accurate assessments and predictions but warrants external validation. As is illustrated in the nomogram, there are patients who would have a 5-year, 10-year or 15-year predicted BCSS less than 90%. Clinicians ought to determine more intensive treatment and follow-up strategy if predicted risk is sufficiently high.

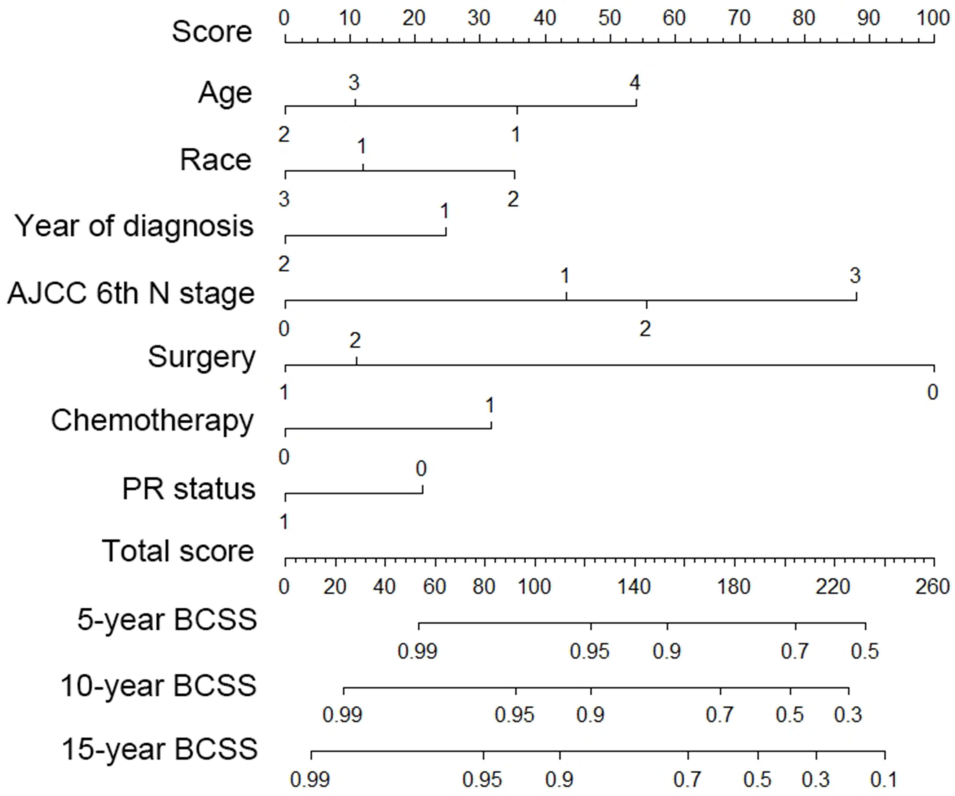

Figure 2 Nomogram to calculate risk score and predict 5-year, 10-year, and 15-year BCSS probability. By summing the points identified on the top scale for each independent variable and drawing a vertical line from the total points scale to the 5-year, 10-year, and 15-year BCSS, the corresponding survival probability can be obtained. Age, 1 = under 40 years, 2 = 41–50 years, 3 = 51–70 years, 4 = over 70 years; Race, 1 = Caucasian, 2 = African American, 3 = American Indian/Alaska Native or Asian/Pacific Islander; Year of diagnosis, 1 = 1988–2001, 2 = 2002–2015; AJCC 6th N stage, 0 = N0 stage, 1 = N1 stage, 2 = N2 stage, 3 = N3 stage; Surgery, 0 = no surgery, 1 = lumpectomy, 2 = mastectomy; Chemotherapy, 0 = no, 1 = yes; PR status, 0 = negative, 1 = positive.
Abbreviations: BCSS, breast cancer-specific survival; PR, progesterone receptor.BCSS, breast cancer-specific survival; PR, progesterone receptor.

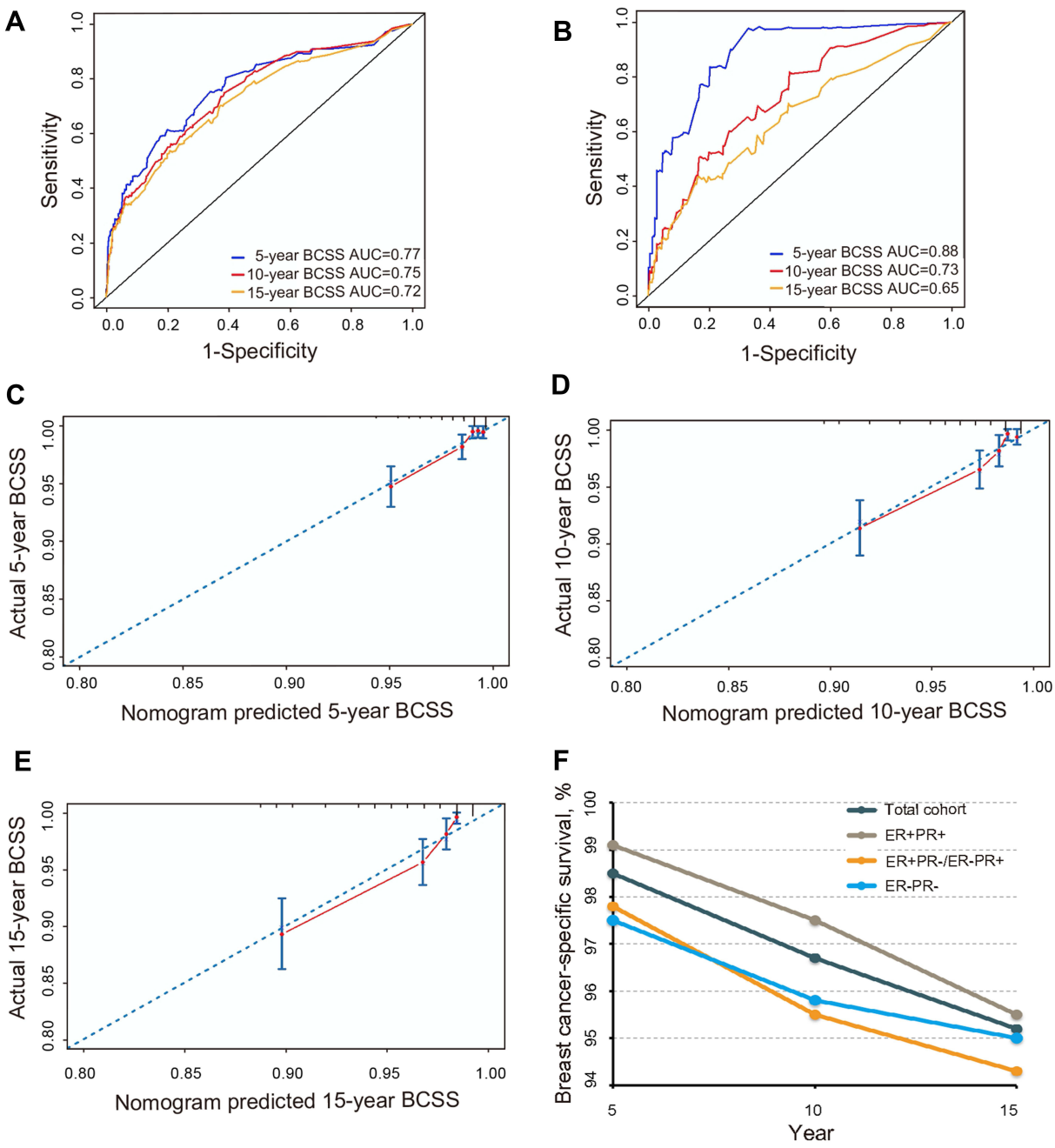

Figure 3 ROC curves and calibration plots for predicting BCSS. ROC curves of the nomogram predicting prognosis in the training set (**A**) and the validating set (**B**). Calibration curves comparing predicted and actual BCSS proportions at 5-year (**C**), 10-year (**D**), and 15-years (**E**), separately. Each point in the plot refers to a group of patients, with the nomogram predicted probability of survival shown on x axis and actual survival proportion shown on y axis. Distributions of predicted survival probabilities are plotted at the top. Error bars represent 95% confidence intervals. (**F**) 5-year, 10-year and 15-year BCSS in patients with each subtype of breast ductal carcinoma in situ with microinvasion.

Abbreviations: AUC, area under the ROC curve; BCSS, breast cancer-specific survival; ER, estrogen receptor; PR, progesterone receptor; ROC, receiver operating characteristic curve.

The prognostic factors described in this study were basically consistent with findings of previous studies. Younger age, lymph node metastasis, multifocality, positive hormone receptor status have all previously been shown to be of significant relevance to the prognosis of DCISM patients.[18,26–28] Diagnostic and therapeutic techniques have been improving over time and influencing prognosis of breast cancer. And the progress against cancer reflects large declines in mortality for breast cancer.[9] Accordingly, patients diagnosed between 2002–2015 in this study had better BCSS than earlier cases did. Despite the increasing proportion of elderly patients with

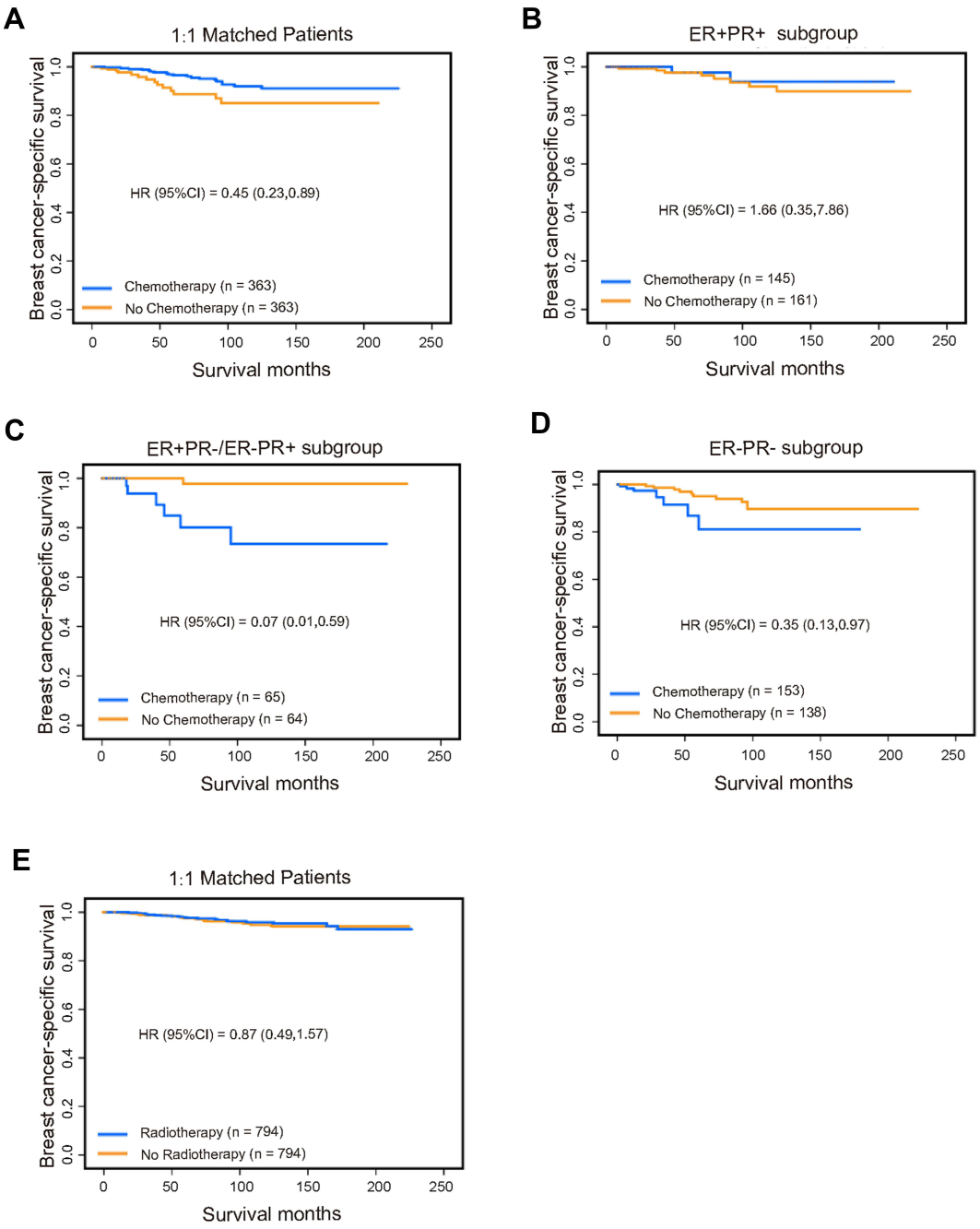

Figure 4 The survival curves for DCISM patients with and without chemotherapy and radiotherapy after 1:1 matching. (**A**) Kaplan-Meier curve depicting the association between chemotherapy and breast DCISM. Kaplan-Meier curve depicting the association between chemotherapy and breast DCISM in ER+PR+ (**B**), ER+PR-/ER-PR+ (**C**) and ER-PR- subgroup (**D**). (**E**) Kaplan-Meier curve depicting the association between radiotherapy and breast DCISM.
Abbreviations: DCISM, ductal carcinoma in situ with microinvasion; ER, estrogen receptor; PR, progesterone receptor.

breast cancer, therapeutic guidelines for elderly patients are inconsistent, leading to challenges for clinicians in managing elderly patients.[29] According to our analysis, patients over 70 showed similar BCSS to those who under 40. From previous publications, clinicians who manage elderly breast cancer patients should consider their comorbidities, functional status, clinical stages, biological characteristics of the cancer, and life expectancy, leading to the under-treatment of elderly patients compared with younger patients.[30,31] Our study result was consistent with previous study that African Americans had a higher risk of death after a breast cancer diagnosis compared with women of other racial groups.[32] Excluding the therapeutic factors, AJCC 6th edition N stage contributes the most to

Table 3 BCSS of Patients with DCISM Between Statistically Matched Chemotherapy and Non-Chemotherapy Groups

Variable	Group	Chemotherapy	Non-Chemotherapy
5-year BCSS	All	95.1%	81.1%
	ER+PR+	97.6%	97.6%
	ER+PR-/ER-PR+	97.8%	80.1%
	ER-PR-	95.1%	81.1%
10-year BCSS	All	89.7%	81.1%
	ER+PR+	91.9%	93.9%
	ER+PR-/ER-PR+	97.8%	93.9%
	ER-PR-	89.7%	81.1%
15-year BCSS	All	89.7%	81.1%
	ER+PR+	90.0%	93.9%
	ER+PR-/ER-PR+	97.8%	73.4%
	ER-PR-	89.7%	81.1%

Abbreviations: BCSS, breast cancer-specific survival; ER, estrogen receptor; PR, progesterone receptor.

the final risk score (Figure 2), with HRs increasing with ascending N stages. The significant contribution of N stage to this nomogram strongly suggests that certain subsets of breast cancer may have an enhanced propensity to metastasize, exhibiting a worse prognosis even when the primary lesion is very small.[33–35] However, the proportion of T1micN2-N3 stage cases (1.07% in this study cohort) was quite low. Despite a large initial study population, substratification by AJCC N stage made the size of N2/N3 subgroup relatively small, yielding a limited statistical power. Consequently, it resulted in wide overlapping CIs and limited ability to detect differences precisely. It is evident from Figure 2 that patients with DCISM treated by lumpectomy had the same or even slightly lower risk scores than those who were treated by mastectomy. Data looking specifically at DCISM is quite limited. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 has shown that stage I and II breast cancer patients who underwent lumpectomy with subsequent radiation had the same rate of survival as those who underwent mastectomies, which is consistent with the multivariate analysis results in our current study.[36] A recent study based on well-matched, contemporary data revealed that breast-conserving therapy was associated with superior overall survival compared to mastectomy for early-stage breast cancer.[37] Undergoing adjuvant chemotherapy in DCISM patients corresponded to a higher risk score according to the nomogram. This might be due to patients at higher risk of relapse being more likely to be selected for chemotherapy. After propensity score matching, patients treated with chemotherapy had better BCSS as expected, supporting the explanation that patients received chemotherapy had higher risk score was due to clinicopathological factors. In ER+PR+ subgroup analysis, we found no significant difference on BCSS between chemotherapy and non-chemotherapy groups. In ER+PR-/ER-PR+ and ER-PR- subgroup, however, BCSS was superior in the chemotherapy group compared with the other group. Study focusing on adjuvant chemotherapy received by DCISM patients is rare. As a small sample sized retrospective study reported, chemotherapy could improve the 5-year disease free survival of ER-/PR- DCISM patients (chemotherapy vs no chemotherapy, 95.8% vs 66.7%).[38] And in our study, the 5-year, 10-year and 15-year BCSS of patients with ER+PR-/ER-PR+ were improved from 80.1%, 93.9% and 73.4% to 97.8%, 97.8% and 97.8%, respectively. Besides, the 5-year, 10-year and 15-year BCSS of patients with ER-PR- were improved from 81.1%, 81.1% and 81.1% to 95.1%, 89.7% and 89.7%, respectively. Although the precision was limited due to small sample size and insufficient events, the study results suggested the potential utility of this prognostic tool to identify candidates for chemotherapy if predicted risk is sufficiently high. Our data showed that patients with ER+PR+ DCISM had best short-term and long-term BCSS, patients with ER-PR- disease had worst short-term BCSS and patients with ER+PR-/ER-PR+ disease had worst long-term survival. From those results we can see that chemotherapy could benefit a certain subgroup of DCISM population with high risk of relapse, especially

ER+PR-/ER-PR+ and ER-PR- subgroup. These results indicated that selecting the best implication of adjuvant chemotherapy for DCISM is important. In addition, there are some plausible explanations for why PR status passed the selection process and was kept in the nomogram while ER status did not. Firstly, our study supported the notion that ER positive, PR negative breast cancer is associated with reduced benefits from endocrine therapy[39] and worse clinical outcomes.[40] Secondly, ER positive breast cancers have a higher distant recurrence risk than triple-negative breast cancer,[41] so these patients are mostly treated with endocrine therapy which would significantly reduce distant recurrence. Due to the lack of information about endocrine therapy, this therapeutic variable was not included during construction of the nomogram, which may have led to ER status being left out of the nomogram. Prognostic implications of applying adjuvant radiotherapy are further shown in Figure 4E. When statistically matched, radiotherapy showed no correlation with prognosis, indicating this adjuvant local-regional treatment might contribute more to local control than to BCSS. From NSABP B-17 and EORTC 10853 trials, radiotherapy reduced the risk of local recurrence instead of distant metastatic rate or overall survival in DCIS patients.[42,43] For invasive breast cancer, however, radiotherapy to the conserved breast halves the rate at which the disease recurs and reduces the breast cancer death rate by about a sixth.[44] In a sense, the significance of radiotherapy for DCISM is closer to DCIS than to invasive breast cancer.

There were several limitations in the study. Firstly, the information regarding the HER2/neu status is only available in the SEER database from 2010 onwards. If cases diagnosed before 2010 were excluded, the sample size would be dramatically reduced and follow-up time insufficient. Therefore, all cases diagnosed between 1988–2015 were enrolled and HER2 status was not included in the construction of the nomogram. Secondly, the SEER database lacks information about endocrine therapy, so this potential confounding factor could not be analyzed. Thirdly, the SEER database lacks information about surgical margin status or number of invasion foci, which might impact analysis. Fourthly, the retrospective nature of our study may have introduced a certain level of bias in our analysis results. Finally, the sequence of treatment was not considered. Because neither recurrence nor progression is recorded in SEER, we had to treat the therapies as baseline variables instead of time-varying covariates. As a result, it was assumed that the exact treatment combination was determined and given at the time point of diagnosis. Since the exact timing of the treatment is not available, relying on this assumption is necessary to incorporate the therapeutic information into the nomogram.

Conclusion

Controversy on DCISM is related to the limited information available on the prognosis of this disease. Our study comprehensively characterized prognostic factors and developed a nomogram prognostic model specifically for DCISM patients. Advanced AJCC N stage, no surgery, under 40 or over 70 years old, African American, diagnosed between 1988–2001, eligible for chemotherapy and PR negative were associated with worse BCSS. Chemotherapy might benefit patients with ER+PR-/ER-PR+ or ER-PR- DCISM. The Individualized risk score calculation method would help clinicians counsel patients more accurately about their prognosis and determine the best treatment strategy.

Abbreviations

DCISM, Ductal carcinoma in situ with microinvasion; DCIS, Ductal carcinoma in situ; BCSS, breast cancer-specific survival; AUC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic; NCCN, National Comprehensive Cancer Network; AJCC, The American Joint Committee for Cancer; SEER, Surveillance, Epidemiology and End Results; HER2/neu, human epidermal growth factor receptor-2; ICD-O-3, International Classification of Disease for Oncology, Third Edition; ER, estrogen receptor; PR, progesterone receptor; NSABP, National Surgical Adjuvant Breast and Bowel Project; HR, hazard ratio; CI, confidence interval.

Data Sharing Statement

The datasets analyzed for this study can be found in the SEER database [http://www.seer.cancer.gov/ seerstat] Further inquiries can be directed to the corresponding author Yi-Zi Zheng.

Ethics Approval and Informed Consent

We obtained permission to access the SEER research data files using the reference number 15223-Nov2019. The data released by the SEER database do not require informed patient consent, and our study was approved by the Ethical Committee of Shenzhen Second People's Hospital. The

methods were performed in accordance with the principles stated in the Declaration of Helsinki.

Acknowledgments

We would like to thank Xian-Ming Wang for providing resources for this study.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Numbers: 81902682, 81902303); Shanghai Sailing Program from Science and Technology Commission of Shanghai Municipality (Grant Number: 19YF1408900); Guangdong Basic and Applied Basic Research Foundation (Grant Number: 2021A1515011122, 2020A151501048); Shenzhen Science and Technology Project (Grant Number: JCYJ20210324103003010, JCYJ20190806170418445, JCYJ20190806164216661); and Clinical Research Project of Shenzhen Second People's Hospital (Grant Number: 20203357028).

Disclosure

The authors report no conflicts of interest in this work.

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