



Nomograms for Estimating Cause-Specific Death Rates of Patients With Inflammatory Breast Cancer: A Competing-Risks Analysis

Technology in Cancer Research & Treatment
 Volume 20: 1-12
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 DOI: 10.1177/15330338211016371
journals.sagepub.com/home/tct


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Abstract

Purpose: Inflammatory breast cancer (IBC) is a rare, aggressive and special subtype of primary breast cancer. We aimed to establish competing-risks nomograms to predict the IBC-specific death (BCSD) and other-cause-specific death (OCSD) of IBC patients. **Methods:** We extracted data on primary IBC patients from the SEER (Surveillance, Epidemiology, and End Results) database by applying specific inclusion and exclusion criteria. Cumulative incidence function (CIF) was used to calculate the cumulative incidence rates and Gray's test was used to evaluate the difference between groups. Fine-Gray proportional sub-distribution hazard method was applied to identify the independent predictors. We then established nomograms to predict the 1-, 3-, and 5-year cumulative incidence rates of BCSD and OCSD based on the results. The calibration curves and concordance index (C-index) were adopted to validate the nomograms. **Results:** We enrolled 1699 eligible IBC patients eventually. In general, the 1-, 3-, and 5-years cumulative incidence rates of BCSD were 15.3%, 41.0%, and 50.7%, respectively, while those of OCSD were 3.0%, 5.1%, and 7.4%. The following 9 variables were independent predictive factors for BCSD: race, lymph node ratio (LNR), AJCC M stage, histological grade, ER (estrogen receptor) status, PR (progesterone receptor) status, HER-2 (human epidermal growth factor-like receptor 2) status, surgery status, and radiotherapy status. Meanwhile, age, ER, PR and chemotherapy status could predict OCSD independently. These factors were integrated for the construction of the competing-risks nomograms. The results of calibration curves and C-indexes indicated the nomograms had good performance. **Conclusions:** Based on the SEER database, we established the first competing-risks nomograms to predict BCSD and OCSD of IBC patients. The good performance indicated that they could be incorporated in clinical practice to provide references for clinicians to make individualized treatment strategies.

Keywords

inflammatory breast cancer, competing-risks analysis, SEER, cause-specific death, nomogram

Received: January 18, 2021; Revised: April 14, 2021; Accepted: April 19, 2021.

Introduction

Inflammatory breast cancer (IBC) is an aggressive subtype of primary breast cancer. While it has a low incidence, reportedly representing 2%-6% of newly diagnosed breast cancers in the US, it also accounts for 10% of all breast cancer-related deaths.^{1,2} IBC is clinically characterized by extensive breast sclerosis, erythema, edema, and fever, accompanied by breast pain involving more than one-third of the breast and usually without palpable lumps.^{3,4} Although IBC appears as an inflammatory change in the skin, it is not really inflammatory, instead being caused by tumor emboli blocking the dermal lymphatic vessels of the breast.¹ Compared with other subtypes of breast cancer, women diagnosed with IBC tend to have a worse long-

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term survival due to rapid disease progression and early distant spread.^{1,4}

The triple therapy of new adjuvant chemotherapy, modified radical mastectomy, and postmastectomy radiotherapy is currently widely adopted to treat IBC. There is also a targeted therapy applied to HER-2(+) patients, mainly involving trastuzumab, and an endocrine therapy for patients with positivity for the estrogen receptor (ER) or progesterone receptor (PR).^{5,6} Treatment strategies are often based on the assessment of the patient's prognosis, and accurate assessment of the prognosis can reduce inappropriate treatment. The American Joint Committee on Cancer (AJCC) classification is commonly used to predict the prognosis of IBC patients. However, it is just based on the 3 predictors of tumor size or the extent of invasion (T), nodal involvement (N) and distant metastasis (M). The neglect of other important prognostic factors often leads to the deviation of the predicted value. Unlike the AJCC classification, nomogram incorporates as many prognostic factors as possible, such as age, race, histological grade and molecular types, hence the prediction by it is more accurate.⁷ Many studies have shown nomogram to be superior to the AJCC classification.^{7,8}

Traditional survival analysis involves using the Kaplan-Meier method to estimate the cumulative incidence, the log-rank test to compare cumulative incidence curves, and the Cox model to evaluate the effects of covariates.⁹ The Kaplan-Meier method is only applicable to estimate the cumulative incidence of single outcome.¹⁰ However, there are often multiple outcomes in medical research which are in a competitive relationship, that is, the occurrence of one outcome will prevent or greatly change the probability of occurrence of other outcomes, such as patients who die from heart disease can not subsequently die of cancer.¹¹ At these circumstances, if the Kaplan-Meier method is adopted to analyze one specific outcome (interesting event), other outcomes (competing event) will be treated as censored, which violates the important assumption underlying the Kaplan-Meier method that the survival prospects are the same in censored patients and in those who continue to be followed until the event of interest occurs. Thus, the cumulative incidence of the interesting event will be overestimate, and the results of the study will be biased. Although combining multiple outcomes into one and then using the Kaplan-Meier method will not lead to competing risks bias, it is impossible to analyze the effect of covariates on the cumulative incidence rates of specific outcomes.¹² In order to analyze the specific outcome in the case of coexistence of multiple outcomes, Fine and Gray proposed the competing risks model.^{7,11-13} However, as far as we know, competing-risks nomograms for IBC patients have not been reported yet.

This study applied a competing-risks analysis to IBC patients with the aims of (1) more-accurately identifying independent predictors of IBC-specific death (BCSD) and other-cause-specific death (OCSD) and (2) establishing nomograms which provide references for clinicians to make individualized treatment strategies.

Methods

Data Source

The SEER database was created in 1973 by the National Cancer Institute of the US National Institutes of Health with the aim of reducing the cancer burden. This database contains information on cancer incidence, prevalence, and mortality as well as other relevant evidence-based medical findings across various US states covering a period of decades.¹⁴ Now the number of registries has expanded to 18, covering approximately 34.6% of the US population.¹⁵ It is one of the most-authoritative large cancer databases in the US, and some of the data are freely available to the public. We used the SEER*Stat software (version 8.3.6) to extract data from the SEER database on patients with IBC. The subdatabase used was "Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying)." The end date of follow-up for this version of subdatabase was December 31, 2016.

Screening of Patients

We applied the third revision of the International Classification of Diseases for Oncology (ICD-O-3) criteria to identify IBC patients. The following inclusion criteria were applied: (a) with primary site of breast (ICD-O-3 codes C50.1–50.9), (b) with histological type of IBC (ICD-O-3 code 8530/3), (c) diagnosed between January 1, 2004 and December 31, 2015 (since the sixth edition of the AJCC staging system was published in 2004), and (d) female patients (male patients were excluded since they had different characters from female patients). The exclusion criteria were as follows: (a) unknown race or marital status, (b) unknown AJCC M stage, histological grade, number of lymph nodes examined, number of positive lymph nodes, or laterality, or bilaterally origin, (c) survival time less than 1 month, (d) follow-up involving autopsy or death certificate only.

Selection of Variables

The demographic variables selected comprised the age at diagnosis, race, and marital status. The clinical pathological data comprised laterality, lymph node ratio (LNR), histological grade, AJCC M stage, ER status, PR status, HER-2 status, and multiple primary status. The treatment information was related to chemotherapy, radiotherapy, and surgery. Finally, the outcome indicators were the cause of death (COD) and survival time.

LNR was calculated as the number of positive lymph nodes divided by the number of lymph nodes examined. The optimal cutoff points determined by X-tile software divided LNR into the following 3 stages: I (0-0.40), II (0.41-0.95), III (0.96 -1). Age was classified according to recognized cutoff values and was divided into 5 categories: 20–39, 40–49, 50–59, 60–74, and ≥ 75 years.^{16,17} For the categorical variables, race had 3 categories (white, black, and others), marital status had 3 categories (married, unmarried, and separated), laterality was

classified into left and right, histological grade was divided into 3 categories (I, II, and III/IV), AJCC M stage was divided into 2 categories (M0 and M1), ER, PR, and HER-2 statuses were divided into 3 categories (positive, negative, and others, including unknown), radiation, chemotherapy, and surgery statuses were classified into yes and no/unknown. Multiple primary status corresponded to the variable “Sequence number” in the SEER database, and all values other than “one primary only” (which was classified as “no”) were classified as “yes.”¹⁸

The outcome indicator COD was divided into alive, BCSD, and OCSD. BCSD was defined as having died from IBC, and OCSD was defined as having died from other causes. There was a competitive relationship between BCSD and OCSD.

Construction of the Nomograms

The IBC patients selected from the SEER database were randomly divided at a ratio of 7:3 into a training set and a validation set. The training set was used to establish nomograms, and the validation set was used for external validation. Differences of composition ratio of each variable between the training and validation sets were evaluated with X^2 tests. The cumulative incidence function (CIF) was used to calculate the cumulative incidence of BCSD and OCSD at 1-, 3-, 5-year in patient groups with different characteristic, and Gray’s test was used to compare differences between groups of each variable.¹⁹ We also plotted Nelson-Aalen curves for variables which were statistically significant on Gray’ test. Fine-Gray proportional subdistribution hazard function was applied to analyze the effects of covariates (which were statistically significant on Gray’ test) and to identify independent predictors for BCSD and OCSD. Compared with the cause-specific hazard function (another commonly used competing risks analysis method), there is a one-to-one relationship with the cumulative incidence rate for the subdistribution hazard function, so it is more suitable to evaluate the prognosis.²⁰ The subdistribution hazard ratio (sdHR) and 95% confidence interval (95% CI) were also calculated for each independent predictor. Based on the results, we constructed nomograms to predict the cumulative incidence rates of BCSD and OCSD at 1, 3, and 5 years after the diagnosis.

Validation of the Nomograms

We used Harrell’s concordance index (C-index) and calibration curve for internal validation in the training set and for external validation in the validation set. The C-index was calculated to evaluate the discrimination ability of the model. The C-index varies from 0.5 to 1.0, with 0.5 indicating that the prediction is completely random and the model has no discrimination ability, while 1.0 shows that the model has the ability to provide exact discrimination. It is generally considered that C-indexes of 0.5–0.7, 0.71–0.90, and 0.91–1.0 indicate that a model has low, moderate, and high discrimination abilities, respectively. The calibration curve describes the degree of consistency between predicted and observed risks, and is used to evaluate

the prediction accuracy of a model. In a perfectly calibrated model the points will fall on a 45-degree diagonal line.²¹

Statistical Analysis

MS Excel 2016 was used to collate the data and analyze the baseline characteristics of the cases. All of the variables are presented as frequencies and proportions except survival months. Survival months was presented as median and range. SAS software (version 9.4) was employed for the univariate and multivariate analyses. R software (version 4.0.0) was used to establish and validate the nomograms using the R packages *survsim*, *mstate*, *rms*, *cmprsk*, *riskRegression*, *pec*, and *foreign*. All P values were 2-sided, and those <0.05 were considered statistically significant.

Results

Baseline Characteristics

We enrolled 1699 eligible IBC patients eventually and randomly divided 1189 of them to the training set and 510 to the validation set. The baseline characteristics of them are listed in Table 1. All variables were similar distributed between the training set and validation set. The largest proportions of the patients were diagnosed at an age of 50–59 years (29.7%), white (79.3%), married (51.9%), LNR stage I (58.4%), histological grade III/IV (72.3%), AJCC stage M0 (73.0%), PR(–) (58.6%), and a single primary site (77.9%), and had received chemotherapy (85.5%) and surgery (75.5%). Because the HER-2 status has only been recorded in the SEER database since 2010, many of the patients lacked HER-2 information and so were classified as others. The median follow-up was 33 months (Range, 1–155 months). At the end of the follow-up, 1,091 (64.2%) patients had died: 916 (53.9%) from IBC and 175 (10.3%) from other causes.

Univariate Analysis

Table 2 presents the estimated 1-, 3-, and 5-year cumulative incidence rates of BCSD and OCSD for patients with different characteristics. And on the whole, these were 15.3%, 41.0%, and 50.7%, respectively, for BCSD, and 3.0%, 5.1%, and 7.4% for OCSD. Gray’s test indicated that all factors other than age, laterality, and multiple primary status were related to BCSD, while age, marital status, ER status, PR status, chemotherapy, and radiotherapy were potentially correlated with OCSD. The Nelson-Aalen curves of all potential prognostic factors are shown in Figure 1, A–K for BCSD and L–Q for OCSD.

Multivariate Analysis

All potential prognostic factors were included in the Fine-Gray proportional subdistribution hazard analysis; the results are presented in Table 3. Race, number of positive lymph nodes, histological grade, AJCC M stage, and ER, PR, HER-2, radiation, and surgery statuses were independent predictors for

Table 1. Demographic and Clinicopathological Characteristics of the Included Inflammatory Breast Cancer Patients.

Variables	Total (%)	Training set (%)	Validation set (%)	P-value
N	1699	1189	510	
Age				0.523
20-39	170 (10.0)	109 (9.2)	61 (12.0)	
40-49	306 (18.0)	218 (18.3)	88 (17.3)	
50-59	504 (29.7)	355 (29.9)	149 (29.2)	
60-74	467 (27.5)	328 (27.6)	139 (27.3)	
≥75	252 (14.8)	179 (15.1)	73 (14.3)	
Race				0.465
White	1348 (79.3)	950 (79.9)	398 (78.0)	
Black	252 (14.8)	175 (14.7)	77 (15.1)	
Other	99 (5.8)	64 (5.4)	35 (6.9)	
Marital status				0.676
Married	882 (51.9)	625 (52.6)	257 (50.4)	
Unmarried	318 (18.7)	222 (18.7)	96 (18.8)	
Separated	499 (29.4)	342 (28.8)	157 (30.8)	
Laterality				> 0.999
Left	855 (50.3)	598 (50.3)	257 (50.4)	
Right	844 (49.7)	591 (49.7)	253 (49.6)	
LNR				0.261
I	992 (58.4)	692 (58.2)	300 (58.8)	
II	343 (20.2)	251 (21.1)	92 (18.0)	
III	364 (21.4)	246 (20.7)	118 (23.1)	
Grade				0.186
I	29 (1.7)	23 (1.9)	6 (1.2)	
II	441 (26.0)	320 (26.9)	121 (23.7)	
III/IV	1229 (72.3)	846 (71.2)	383 (75.1)	
M stage				0.423
M0	1240 (73.0)	875 (73.6)	365 (71.6)	
M1	459 (27.0)	314 (26.4)	145 (28.4)	
ER				0.470
Positive	821 (48.3)	573 (48.2)	248 (48.6)	
Negative	803 (47.3)	568 (47.8)	235 (46.1)	
Other	75 (4.4)	48 (4.0)	27 (5.3)	
PR				0.814
Positive	606 (35.7)	419 (35.2)	187 (36.7)	
Negative	996 (58.6)	703 (59.1)	293 (57.5)	
Other	97 (5.7)	67 (5.6)	30 (5.9)	
HER2				0.271
Positive	214 (12.6)	145 (12.2)	69 (13.5)	
Negative	374 (22.0)	252 (21.2)	122 (23.9)	
Other	1111 (65.4)	792 (66.6)	319 (62.5)	
Multiple primary				0.367
No	1324 (77.9)	919 (77.3)	405 (79.4)	
Yes	375 (22.1)	270 (22.7)	105 (20.6)	
Chemotherapy				0.340
NO/Unknown	247 (14.5)	166 (14.0)	81 (15.9)	
Yes	1452 (85.5)	1023 (86.0)	429 (84.1)	
Radiation				0.763
NO/Unknown	845 (49.7)	588 (49.5)	257 (50.4)	
Yes	854 (50.3)	601 (50.5)	253 (49.6)	
Surgery				0.569
NO/Unknown	416 (24.5)	286 (24.1)	130 (25.5)	
Yes	1283 (75.5)	903 (75.9)	380 (74.5)	
COD				0.631
Alive	608 (35.8)	434 (36.5)	174 (34.1)	
BCSD	916 (53.9)	635 (53.4)	281 (55.1)	
OCSD	175 (10.3)	120 (10.1)	55 (10.8)	

(continued)

Table I. (continued)

Variables	Total (%)	Training set (%)	Validation set (%)	P-value
Survival Months				
Median (Range)	33 (1-155)	33 (1-155)	32 (1-154)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor-like receptor 2; BCSD, inflammatory breast cancer-specific death; OCSD, other-cause-specific death.

BCSD. Black patients are 1.563 times (95%CI, 1.257 -1.944) more likely to have BCSD than white patients. Patients with more advanced LNR stage have higher risk of BCSD (stage II vs stage I: sdHR = 1.562, 95%CI 1.271 -1.920; stage III vs stage I: sdHR = 1.654, 95%CI 1.344-2.035). Grade III/IV had a higher incidence of BCSD than grade I (grade III/IV vs grade I: sdHR = 2.879, 95%CI 1.146-7.233), however, there was no significant difference between grade II and grade I. The risk of BCSD of patients with distant metastasis was 2.163 times (95%CI 1.773-2.639) as those with non-with distant metastasis. ER(+), PR(+), HER-2(+), received radiotherapy and received surgery were protective factors for patients. (ER(-) vs ER(+): sdHR = 1.428, 95%CI 1.133 -1.799; PR(-) vs PR(+): sdHR = 1.561, 95%CI 1.226 -1.987; HER(-) vs HER(+): sdHR = 2.130, 95%CI 1.471-3.084; had radiotherapy vs no radiotherapy: sdHR = 0.779, 95%CI 0.651-0.933; had surgery vs no surgery: sdHR = 0.449, 95%CI 0.356-0.566). After adjustment by multivariate regression, marital status and chemotherapy lost their predictive value for BCSD. When it came to OCSD, age and the ER, PR and chemotherapy statuses were independent predictors.

Nomograms Construction

Based on the results of the analysis of Fine-Gray proportional subdistribution hazard function, we established the nomograms for predicting the 1-, 3-, and 5-year cumulative incidence rates of BCSD and OCSD, which are shown in Figure 2A and 2B, respectively. The scores for the prognostic factors are indicated at the upper part of the nomogram. Adding all scores of individual items of a patient, we can obtain a total score. By drawing a vertical line from it, there will be 3 points of intersection with the bottom lines. The corresponding rates were the 1-, 3-, and 5-year cumulative incidence rates of BCSD or OCSD of the patient.[8]

Nomograms Validation

We validated the nomograms both internally and externally. For BCSD, the C-indexes for 1, 3, and 5 years were 0.822, 0.750, and 0.733 in the internal validation cohort, and 0.784, 0.737, and 0.722 in the external validation cohort; the corresponding values for OCSD were 0.763, 0.692, 0.714, 0.743, 0.745, and 0.742, respectively. These results indicated that both

Table 2. Cumulative Incidence Function Analysis of Cause-Specific Death Rates in Patients with Inflammatory Breast Cancer.

Variables	BCSD (%)				OCSD (%)			
	1-Year	3-Year	5-Year	P-value	1-Year	3-Year	5-Year	P-value
Total	15.3	41.0	50.7		3.0	5.1	7.4	
Age				0.623				<0.001
20-39	9.3	38.3	49.9		0.0	3.1	4.2	
40-49	12.0	40.2	51.2		1.4	1.9	2.4	
50-59	13.9	38.0	46.8		1.1	2.9	3.6	
60-74	17.1	42.3	53.3		4.3	6.2	8.4	
≥75	22.3	47.4	53.3		8.4	12.7	20.5	
Race				<0.001				0.759
White	13.7	37.4	47.1		3.1	5.1	7.3	
Black	26.9	62.3	70.1		2.3	4.1	7.3	
Other	6.3	35.1	50.1		4.7	8.1	8.1	
Marital status				<0.001				0.027
Married	9.8	35.5	46.0		2.3	4.3	6.2	
Unmarried	20.3	47.8	54.8		3.2	4.6	7.4	
Separated	22.0	46.6	56.4		4.4	6.9	9.4	
Laterality				0.765				0.524
Left	14.9	42.7	50.4		2.9	4.5	6.3	
Right	15.6	39.3	50.9		3.2	5.8	8.4	
LNR				<0.001				0.216
I	16.0	37.9	46.8		3.2	5.1	7.3	
II	8.0	36.4	46.6		3.6	6.0	9.0	
III	20.8	54.4	65.8		2.0	4.2	5.8	
Grade				<0.001				0.196
I	4.3	8.9	8.9		0.0	0.0	5.1	
II	11.3	34.8	44.8		2.8	5.3	8.0	
III/IV	17.1	44.3	54.0		3.2	5.2	7.2	
M stage				<0.001				0.123
M0	9.9	33.2	42.7		2.8	5.0	7.8	
M1	30.4	63.3	73.5		3.8	5.6	6.0	
ER				<0.001				0.035
Positive	9.8	27.6	40.4		3.9	5.8	9.1	
Negative	20.1	52.6	59.4		2.5	4.7	5.9	
Other	23.6	61.8	68.7		0.0	2.2	4.5	
PR				<0.001				0.016
Positive	7.9	26.4	37.9		3.4	5.7	9.0	
Negative	19.1	48.6	57.3		2.9	4.7	6.0	
Other	21.3	53.2	61.4		3.1	6.3	11.1	
HER2				<0.001				0.461
Positive	7.7	29.2	35.9		1.4	2.3	4.9	
Negative	18.0	46.3	59.6		2.8	5.6	7.0	
Other	15.8	41.3	50.5		3.4	5.5	7.8	
Multiple primary				0.467				0.280
No	15.4	40.4	49.9		3.0	5.1	7.1	
Yes	14.8	43.0	53.2		3.3	5.3	8.2	
Chemotherapy				0.002				<0.001
NO/Unknown	29.2	51.0	56.4		11.0	16.4	21.8	
Yes	13.1	39.4	49.8		1.8	3.3	5.1	
Radiation				<0.001				0.036
NO/Unknown	22.6	50.0	59.3		4.5	6.7	8.6	
Yes	8.2	32.4	42.5		1.7	3.6	6.2	
Surgery				<0.001				0.439
NO/Unknown	40.9	66.4	77.1		4.9	7.1	7.7	
Yes	7.2	33.3	43.2		2.4	4.6	7.2	

Abbreviations: BCSD, inflammatory breast cancer-specific death; OCSD, other-cause-specific death; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor-like receptor 2.

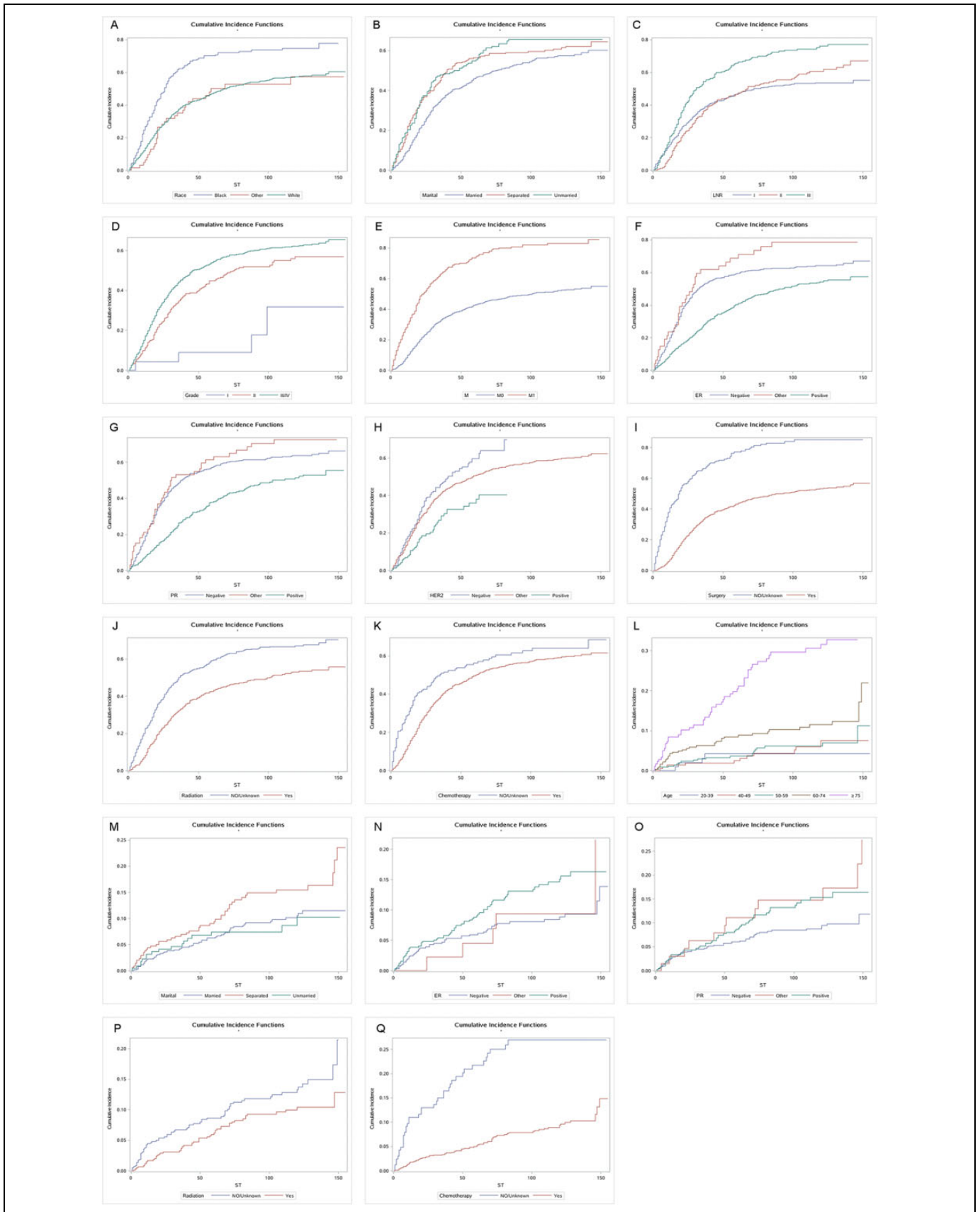


Figure 1. Nelson-Aalen curves for each characteristic. (A)-(K) for BCSD, (L)-(Q) for OCSD.

Table 3. Fine-Gray Regression Analysis for BCSD and OCSD in Patients With Inflammatory Breast Cancer.

Variables	BCSD				OCSD			
	Coefficient	sdHR	95%CI	P-value	Coefficient	sdHR	95%CI	P-value
Age								
20-39	–	–	–	–	Reference			
40-49	–	–	–	–	0.226	1.253	0.398-3.948	0.700
50-59	–	–	–	–	0.295	1.343	0.455-3.969	0.593
60-74	–	–	–	–	0.885	2.424	0.857-6.859	0.095
≥75	–	–	–	–	1.796	6.024	2.129-17.048	<0.001
Race								
White	Reference				–	–	–	–
Black	0.447	1.563	1.257 -1.944	<0.001	–	–	–	–
Other	-0.201	0.818	0.544 -1.229	0.334	–	–	–	–
LNR								
I	Reference				–	–	–	–
II	0.446	1.562	1.271 -1.920	<0.001	–	–	–	–
III	0.503	1.654	1.344-2.035	<0.001	–	–	–	–
Grade								
I	Reference				–	–	–	–
II	0.908	2.480	0.980-6.277	0.055	–	–	–	–
III/IV	1.057	2.879	1.146-7.233	0.025	–	–	–	–
M stage								
M0	Reference				–	–	–	–
M1	0.772	2.163	1.773-2.639	<0.001	–	–	–	–
ER								
Positive	Reference				Reference			
Negative	0.356	1.428	1.133 -1.799	0.003	-0.170	0.843	0.521 -1.364	0.488
Other	0.356	1.427	0.747-2.729	0.282	-1.549	0.212	0.069-0.656	0.007
PR								
Positive	Reference				Reference			
Negative	0.445	1.561	1.226 -1.987	<0.001	-0.241	0.786	0.489 -1.261	0.317
Other	0.386	1.471	0.833-2.600	0.184	1.137	3.118	1.494-6.508	0.002
HER2								
Positive	Reference				–	–	–	–
Negative	0.756	2.130	1.471-3.084	<0.001	–	–	–	–
Other	0.791	2.205	1.580-3.078	<0.001	–	–	–	–
Chemotherapy								
NO/Unknown	–	–	–	–	Reference			
Yes	–	–	–	–	-0.636	0.530	0.353-0.794	0.002
Radiation								
NO/Unknown	Reference				–	–	–	–
Yes	-0.250	0.779	0.651-0.933	0.007	–	–	–	–
Surgery								
NO/Unknown	Reference				–	–	–	–
Yes	-0.801	0.449	0.356-0.566	<0.001	–	–	–	–

Abbreviations: BCSD, inflammatory breast cancer-specific death; OCSD, other-cause-specific death; sHR, subdistribution hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor-like receptor.

models exhibited good discrimination ability. The calibration curves for the internal and external validation cohorts of BCSD and OCSD are shown in Figure 3. The prediction results from the nomograms were in good agreement with the actual observed values, indicating that the models can provide relatively accurate predictions.

Discussion

IBC has a low incidence and accounts for a small proportion of primary breast cancers. Many of the previous studies on the

prognosis of IBC have been limited to small, single-center samples. And the lack of representation of these samples often leads to poor extrapolation of research conclusions. The prognostic value of many factors is therefore controversial. In contrast, the large SEER database contains high-quality surveillance data from numerous regions across the US, and can provide clinicians with valuable information about tumors and a broad pathway for studying rare malignant tumors.²² The present study extracted information on a relatively large sample of 1,699 female IBC patients from the SEER database, making the results more reliable than the previous studies.

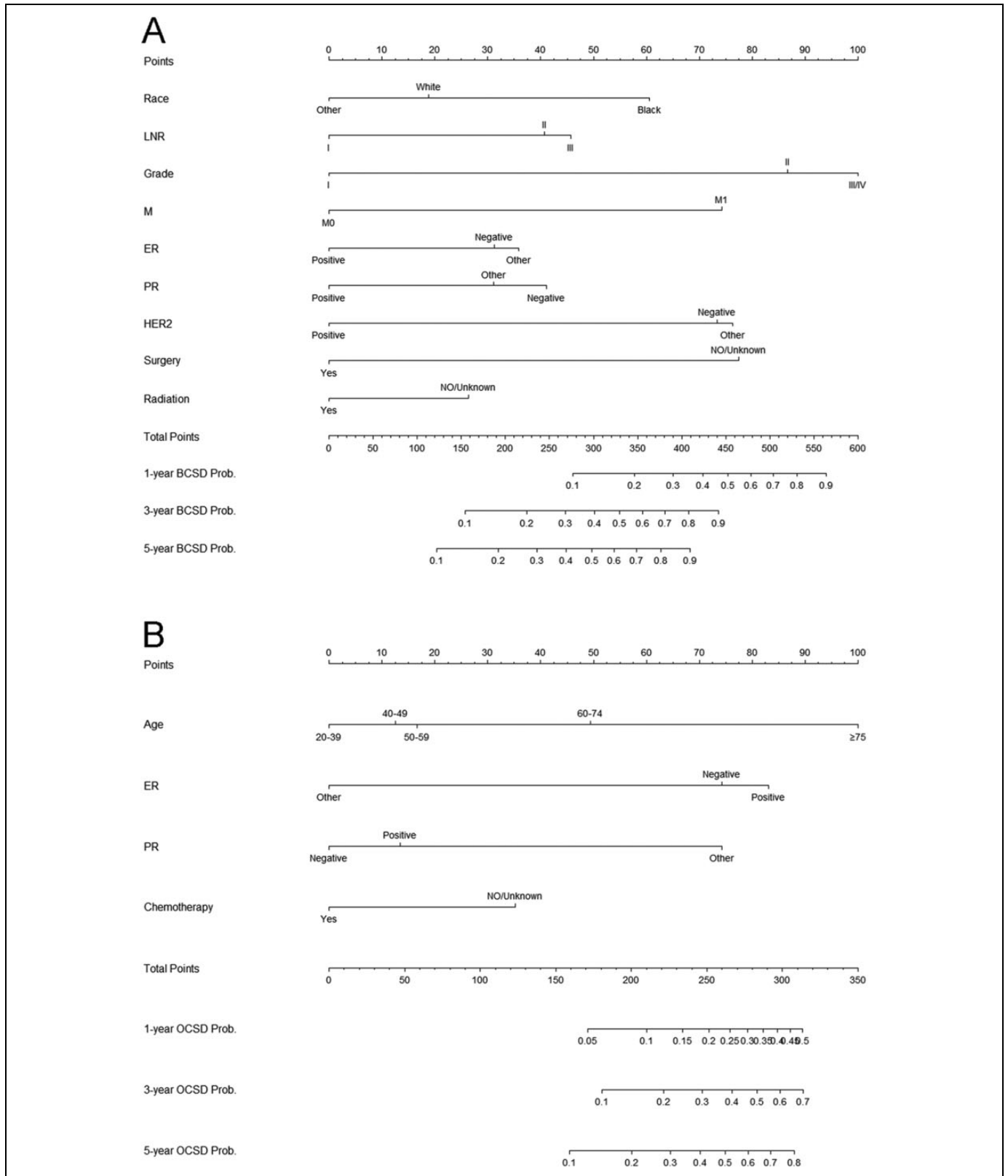


Figure 2. Competing-risks nomograms for predicting 1-, 3- and 5-year cumulative incidence probabilities for BCSD and OCSD in patients with inflammatory breast cancer. (A) BCSD; (B) OCSD.

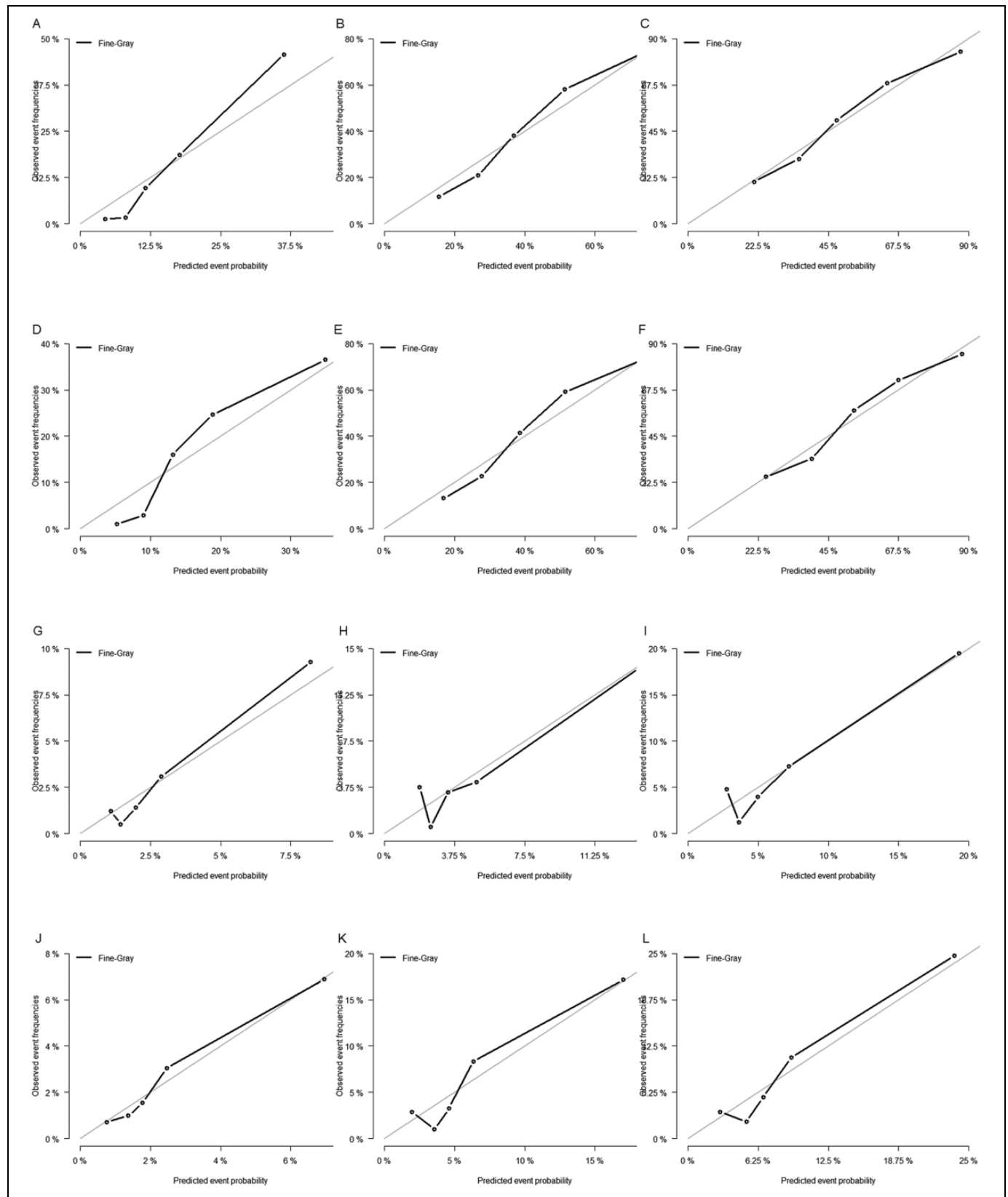


Figure 3. Calibration curves for 1-, 3- and 5-year prediction. (A)-(F) for BCSD; (A)1-year, (B) 3-year, (C)5-year for internal validation; (D) 1-year, (E) 3-year, (F)5-year for external validation. (G)-(L) for OCSD; (G) 1-year, (H) 3-year, (I) 5-year for internal validation; (J) 1-year, (K) 3-year, (L)5-year for external validation.

At the end of the follow-up, 916 (53.9%) had died from IBC and 175 (10.3%) had died from other causes. OCS D accounted for a relatively large proportion of deaths. In Kaplan-Meier method, the OCS D would be regarded as censored when analyzing BCSD, therefore the cumulative incidence of BCSD would be significantly overestimated.[18] By contrast, the $CIF_k(t)=Pr(T\leq t, D=k)$ which represents the probability of the k event before time t and other types of events, can provide unbiased estimate.[13] Although there have been some reports of predictors associated with the cause-specific death of IBC, all of them were based on Kaplan-Meier method and Cox proportional hazard model. In the present study, we adopted the competing risks analysis method (CIF, Gray's test and Fine-Gray proportional subdistribution hazard model), which will make the prediction more accurate.

Age is considered a prognostic factor in many chronic diseases, and being older is associated with significant decline in physical function. Some studies of the overall survival of IBC patients have found age to be a prognostic factor.^{23,24} However, the present study found that age was a predictor for OCS D but not for BCSD, Which suggested that age could significantly affect overall survival only because it affected OCS D. One possible explanation for the high incidence of OCS D in older patients was the high prevalence of comorbidities in these patients. And the fact that high incidence of OCS D hindered the incidence of BCSD in the higher age groups might explain the insignificance difference in the risk of BCSD in different age groups.⁸ This indicated that providing older IBC patients with treatment for IBC alone might not yield much benefit, and the treatment for comorbidities should also be taken seriously. Moreover, race was found to be an independent predictor of BCSD, which was consistent with the findings of previous studies.[6, 15, 16] In this study, the risk of BCSD was 1.563 times (95%CI, 1.257 -1.944) in black patients as in white patients. This might be due to the worse overall economic status and access to health care of blacks. In addition, Rizzo *et al* found that the expression rate of cancer-related gene BP1 was significantly higher in blacks than in whites, and that mutation or overexpression of the tumor suppressor gene p53 was also more common in blacks.²⁵ Yan-ling Liu *et al* thought that unmarried patients were more likely to have BCSD than married patients (unmarried vs married: HR = 1.188, 95%CI 1.033 -1.367). However, their research was based on the Kaplan-Meier method, which would lead to competing risks bias. In our study, after adjustment of the multivariate analysis, marital status was no longer significantly associated to BCSD. This might be because marital status is only an indirect prognostic factor for BCSD.

Multiple primary tumors refer to 2 or more primary malignant tumors occurring simultaneously or successively in one or more organs of the same host.¹⁸ A study of tracheal cancer found that this variable was strongly associated with tumor-specific death.¹⁸ We have not seen any previous study on IBC analyzed this variable, and only Jieqiong Liu *et al* mentioned the effect of comorbidity on the prognosis of IBC.²⁶ However, in our study this variable was not significant at any levels of the

analyses of BCSD and OCS D. ER (+) and PR (+) have been considered as protective factors for the prognosis of IBC in most previous studies,^{3,6,24,27} which is also supported by the present study. HER-2 is a proto-oncogene located on chromosome 17 that is overexpressed in approximately 30% of breast cancers and is associated with a more-aggressive breast cancer phenotype.²⁸ There is considerable debate on the protective significance of the HER-2 status^{15,16,23,25} And the present study suggested that HER-2(+) patients were less likely to have BCSD. This might be because ER (+), PR (+) and HER-2 (+) provide patients with broader therapeutic approaches. It is commonly believed that hormone therapy is an effective therapy for hormone-receptor-positive patients, and targeted therapy is important for HER-2-positive patients.^{1,29} Histological grade, AJCC M stage, radiotherapy and surgery were recognized prognostic factors for IBC,^{1,15,23,30} our study showed the same results. And from the nomogram, these factors explained the largest part of survival variation. In many other cancer related studies, LNR was an important prognostic factor.^{31,32} Our study also found that LNR has prognostic value for IBC patients, and the higher the LNR stage, the worse the prognosis. The predictive value of radiotherapy is controversial, with some studies suggesting that it can not reduce the risk of BCSD.²⁸ However, in our study, patients receiving radiotherapy had lower incidence of BCSD, which suggested radiotherapy is an effective treatment for IBC patients.

Based on the results of Fine-Gray proportional hazard analysis, we established nomograms to predict the cumulative incidence rates of BCSD and OCS D at 1, 3, and 5 years after diagnosis. They were, as we know, the first competing risks nomograms for IBC. The C-indexes and the calibration curves showed that both of them exhibited good discrimination ability and prediction accuracy. Because the prognostic characteristics of IBC are very different from those of other subtypes of breast cancer, our specific nomograms for IBC patients can provide more accurate estimate than the AJCC system which is applicable for all subtypes of breast cancer. Moreover, the establishment of our nomograms were based on competing risks analysis. Although most prognostic factors have been mentioned in previous studies, the prognostic effects of the same prognostic factors are different in the Fine-Gray model and the traditional Cox model. And the Fine-Gray model can make the assessment more accurate by considering the competing risks. The 2 nomograms contain a wide range of clinical risk factors that are readily available for collection from historical records. This is also one of the reasons they are superior to the AJCC system. And as we described in the results section, they were also easy to use. In the future, clinicians can use them to evaluate the prognosis of IBC patient more accurately and accordingly apply individualized treatments while also intuitively explain the disease status and the benefits of treatments to the patients.

IBC is a rare subtype of primary breast cancer. The utilization of the high-quality relatively large sample data and competing risks analysis made the results of the present study more

reliable. However, this study was still subject to some limitations. Firstly, the SEER database is not comprehensive, with important potential prognostic variables not recorded, such as BMI, reproductive status, levels of Ki-67, and type of chemotherapy. Thus, not all prognostic factors were included in our nomograms, and the prediction results were not completely accurate and could only be used as a reference. Secondly, many cases were excluded due to incomplete information, which might lead to selection bias. Thirdly, the values were missing for some variables (e.g., HER-2 status), and classifying them as “others” might lead to information bias. Fourthly, OCS D refers to death from causes other than IBC, including cardiovascular disease, respiratory disease, diabetes, etc. In other words, OCS D, as a competing risk event, still contains many competing events. However, due to the small sample size of each event, it is almost impossible to analyze them individually, so in this study we only treated them as a whole, which made interpretation of the OCS D nomogram difficult. Fifthly, the present study is based on historical data, so the nomograms still require be validated externally by prospective cohort before being applied to clinical practice.

Conclusion

In conclusion, we have performed a competing-risks analysis in IBC patients based on the SEER database, and established the first nomograms to predict the 1-, 3-, and 5-year cumulative incidence rates of BCSD and OCS D. The good performance of the nomograms indicates that clinicians can incorporate them in their clinical practice.

Ethical approval & Informed consent

All procedures performed in the present study were in accordance with the principles outlined in the 1964 Helsinki Declaration and its later amendments. Institutional review board approval and informed consent were not required in current study because SEER research data is publicly available and all patient data are de-identified.

Author contribution

Fengshuo Xu and Jin Yang contributed equally to this work.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


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Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was supported by The National Social Science Foundation of China (grant/award no. 16BGL183).

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