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Original article

Nomogram for predicting the overall survival of patients with inflammatory breast cancer: A SEER-based study

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ABSTRACT

Objectives: Inflammatory breast cancer (IBC) is a rare malignancy that is a unique biologic subtype of breast cancer. A nomogram to predict the overall survival (OS) of IBC patients is lacking. The aim of the study was to construct and validate a nomogram to predict the OS of IBC patients based on the Surveillance, Epidemiology, and End Results (SEER) Program.

Methods: Patients diagnosed with IBC between 2010 and 2016 were selected from the SEER database. Univariate and multivariate Cox regression analyses were used to identify independent prognostic factors. A nomogram was constructed to predict the 1-, 3- and 5-year OS of these patients. The nomogram was internally and externally validated by Harrell's C-indexes and calibration plots.

Results: Patients were randomly divided into a training set (n = 2464) and a validation set (n = 1052). The training set was used to establish a nomogram. Multivariate analysis identified that race, age at diagnosis, breast cancer subtype, grade, N stage, M stage, radiation, chemotherapy, and surgery were significant prognostic factors for the OS. The internally and externally validated Harrell's C-indexes were 0.763 and 0.786, respectively. The calibration plots for predictions of the 1-, 3-, and 5-year OS were in excellent agreement.

Conclusions: A nomogram was constructed to predict the OS for IBC patients based on the SEER database and to provide accurate and individualised survival predictions.

1. Introduction

Inflammatory breast cancer (IBC) is undoubtedly a unique biologic subtype of breast cancer with poor prognosis, which accounts for 1–5% of all breast cancer and comprises 7.0% of all breast cancer-specific mortality [1]. IBC is a clinicopathological entity that combines the clinical presentation of breast carcinoma with specific features of inflammation and pathological evidence [2]. According to the TNM classification, IBC is classified as T4d (a category reserved for IBC) for its aggressive biological behaviour. With great efforts to improve survival, including advancements in surgical technique, targeted therapy, radiotherapy and chemotherapy and improvements in supportive treatment, the prognosis of IBC has increased [3]. However, patients with IBC still have dismal outcomes, with a 5-year overall survival rate of less than 55% and a median survival of 2.9–3.8 years [1,4–6].

Due to the limited incidence, complex treatment, and high mortality, randomized prospective controlled trials specifically in the IBC patient population are still limited. In our review of the literature, we found only several enrolling IBC-focused clinical trials, which were rarely reported [7]. Owing to the rarity of the disease and the scarcity of data, the published literature for predicting the overall survival (OS) of IBC tumours has seldom been reported. Therefore, a more accurate method for predicting individualised survival of IBC patients is required, and a nomogram is a good method for this purpose.

In this study, we analysed the clinicopathological features and prognostic factors of IBC based on the Surveillance, Epidemiology, and End Results (SEER) Program, a well-constructed database from multiple institutions in the United States. We further established

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and validated a nomogram of IBC patients based on the results of the survival analysis to better predict the prognosis of patients.

2. Patients and methods

The SEER database from National Cancer Institute is the most authoritative source of information on cancer incidence and survival in the United States (https://seer.cancer.gov/). SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the U.S. population. Data for this study were identified from the SEER.

2.1. Study population

Data about the population consisted of all women with a diagnosis of IBC and were extracted from the SEER 18 Regs (1975–2016 varying) using the SEER*Stat software (version 8.3.5; Surveillance Research Program, NCI, Bethesda, MD). The specific criteria for the SEER*Stat software to identify patients with IBC were as follows: (1) "Breast" was limited to Site and Morphology (TNM 7/CS v0204 + Schema); (2) Derived TNM classification, AJCC 7th edition (2010–2015) was limited to "T4d", and SEER Combined T (2016+) was limited to "cT4d" and "pT4d"; and (3) Histology type (ICD-O-3) ranged from 8500 to 8549. We limited our research to between 2010 and 2016 because the AJCC TNM staging system 7th edition was published in 2010, and SEER started collecting breast cancer subtype in 2010.

2.2. Variables

For each case, the following information from SEER was obtained: race, age at diagnosis, marital status, breast cancer subtype, grade, N stage (AJCC, 7th ed.), M stage (AJCC, 7th ed.), radiation, chemotherapy, surgery, survival months, and vital status. In addition, cases were excluded from the study if they had incomplete information on any of these characteristics. Patients who survived less than one month were also excluded. Because IBC often has diffuse erythema and oedema, without an underlying palpable mass, tumour size was not analysed in the current study. The value of age at diagnosis was transformed into small categorical variables by X-tile software to fit the Cox PH regression and linear assumption (Fig. S1). In the race category, "Other" was defined as American Indian/Alaska Native or Asian/Pacific Islander. Overall survival was defined as the time from diagnosis to death from any cause or to the time of the last follow-up. The cutoff date of follow-up time was December 31, 2016.

2.3. Construction of the nomogram

The eligible patients were randomly divided into a training set (n = 2464) and a validation set (n = 1052). A training set was used to establish a nomogram. Univariate and multivariate Cox regression analyses were used to identify the prognostic value of the factors. The independent factors were used to build the nomogram for the OS by using the package of *rms* in R version 3.5.1 [8].

Table 1
Clinicopathological characteristics of training and validation sets.

Characteristic	Training set (n = 2464)	Validation set (n = 1052)	P-value
Race			0.429
White	1883 (76.4%)	820 (77.9%)	
Black	390 (15.8%)	163 (15.5%)	
Other	191 (7.8%)	69 (6.6%)	
Age at diagnosis			0.753
≤59	1399 (56.8%)	593 (56.4%)	
60–74	755 (30.6%)	317 (30.1%)	
≥75	310 (12.6%)	142 (13.5%)	
Marital status			0.641
No	1246 (50.6%)	541 (51.4%)	
Yes	1218 (49.4%)	511 (48.6%)	
Breast cancer subtype			0.923
Luminal A	1002 (40.7%)	416 (39.5%)	
Luminal B	472 (19.2%)	209 (19.9%)	
HER2 enriched	408 (16.6%)	174 (16.5%)	
Triple Negative	582 (23.6%)	253 (24.0%)	
Grade			0.711
I + II	838 (34.0%)	351 (33.4%)	
III + IV	1626 (66.0%)	701 (66.6%)	
N stage			0.240
N0	324 (13.1%)	127 (12.1%)	
N1	1113 (45.2%)	493 (46.9%)	
N2	460 (18.7%)	215 (20.4%)	
N3	567 (23.0%)	217 (20.6%)	
M stage			0.277
M0	1621 (65.8%)	712 (67.7%)	
M1	843 (34.2%)	340 (32.3%)	
Radiation			0.297
No/Unknown	1173 (47.6%)	521 (49.5%)	
Yes	1291 (52.4%)	531 (50.5%)	
Chemotherapy			0.799
No/Unknown	350 (14.2%)	146 (13.9%)	
Yes	2114 (85.8%)	906 (86.1%)	
Surgery			0.813
No/Unknown	805 (32.7%)	348 (33.1%)	
Yes	1659 (67.3%)	704 (66.9%)	

2.4. Validation of the nomogram

The nomogram was internally validated in the training set and externally validated in the validation set. The Harrell's C-index was used to evaluate the discrimination of the nomogram. A higher C-index indicates more accurate prognostic predictions [9]. The C-index shows relatively good discriminative ability between 0.71 and 0.90, while the C-index >0.90 shows better accuracy. The calibration plot was also used to evaluate the nomogram performance. In a perfectly calibrated model, the predictions should fall at a diagonal 45° line in the calibration plot [10].

2.5. Statistical analysis

The clinical and pathological characteristics of the training and validation sets were compared using the chi-square or Fisher exact tests as appropriate. Cumulative survival curves for each patient variable were calculated using the Kaplan-Meier method. The prognostic value of the factors was identified through univariate and multivariate Cox regression analyses. P values were two-sided, and values of <0.05 were considered statistically significant. The optimal cut-off value for age at diagnosis was calculated using X-tile 3.6.1 (Yale University, New Haven, CT, USA). Univariate and multivariate Cox analyses were performed using SPSS 24.0 software (IBM Corp, Armonk, NY, USA). A nomogram was constructed and validated by R software version 3.5.1 (http://www.R-project.org). The R package included *survival* and *rms*.

3. Results

3.1. Clinicopathological characteristics of the training and validation sets

A total of 4843 female IBC cases were eligible during 2010–2016 in the SEER database for our study population. Of these, 1327 patients were excluded because they had incomplete information; the remaining 3516 patients were included in our analyses. The eligible patients were randomly divided into a training set (n = 2464) and a validation set (n = 1052). The clinicopathological characteristics of training and validation sets are shown in Table 1.

3.2. Survival analysis in the training set

The median OS of the 2464 IBC patients in the training set was 43 (95% CI: 40–50) months, and the 1-, 3-, and 5-year OS rates were 82.33% (95% CI: 80.76–83.93%), 55.20% (95% CI: 52.94–57.55%), and 42.91% (95% CI: 40.34–45.63%), respectively (Fig. 1). A total of 1021 patients in the training set died during the follow-up period.

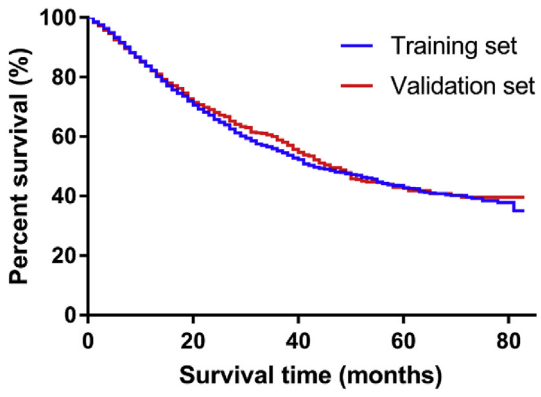

Fig. 1. Survival analysis of patients with IBC in the training and validation sets.

3.3. Independent prognostic factors in the training set and construction of the nomogram

A training set was used to establish the nomogram. Table 2 shows univariate and multivariate analyses of potential predictors for the OS. Race, age at diagnosis, marital status, breast cancer subtype, grade, N stage, M stage, radiation, chemotherapy, and surgery were significantly associated as risk factors for the OS in the univariate analysis. Therefore, these significant risk factors were included in the multivariate analysis. Multivariate analysis identified that race, age at diagnosis, breast cancer subtype, grade, N stage, M stage, radiation, chemotherapy, and surgery were independently able to predict survival (Table 2). The independent factors were used to build the nomogram for 1-, 3-, and 5-year OS (Fig. 2).

3.4. Nomogram validation

The nomogram was validated internally using the training set. The Harrell's C-index, which indicates discrimination ability, was 0.763 in the training set. Similarly, the Harrell's C-index was 0.786 in the external validation set. These findings indicate that the nomogram can accurately predict the OS. The internal and external calibration plots were also used to evaluate the nomogram performance. As shown in Fig. 3, the calibration plots for predictions for the 1-, 3-, and 5-year OS in both the training and validation sets were in excellent agreement.

Table 2
Risk factors for OS according to the Cox proportional hazards regression model.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Race				
White	1		1	
Black	1.63 (1.40, 1.89)	<0.001	1.27 (1.08, 1.49)	0.003
Other	0.88 (0.68, 1.13)	0.322	0.97 (0.75, 1.25)	0.794
Age at diagnosis				
≤59	1		1	
60–74	1.37 (1.19, 1.57)	<0.001	1.27 (1.10, 1.46)	0.001
≥75	2.23 (1.88, 2.64)	<0.001	1.77 (1.47, 2.13)	<0.001
Marital status				
No	1		1	
Yes	0.70 (0.62, 0.80)	<0.001	0.92 (0.81, 1.04)	0.180
Breast cancer subtype				
Luminal A	1		1	
Luminal B	0.64 (0.53, 0.78)	<0.001	0.81 (0.66, 0.99)	0.042
HER2 enriched	0.75 (0.62, 0.92)	0.005	0.96 (0.78, 1.18)	0.689
Triple Negative	1.96 (1.70, 2.26)	<0.001	2.65 (2.26, 3.10)	<0.001
Grade				
I + II	1		1	
III + IV	1.33 (1.16, 1.52)	<0.001	1.25 (1.08, 1.44)	0.002
N stage				
N0	1		1	
N1	1.10 (0.90, 1.34)	0.366	1.04 (0.85, 1.28)	0.700
N2	1.14 (0.91, 1.43)	0.261	1.25 (0.99, 1.58)	0.059
N3	1.50 (1.21, 1.86)	<0.001	1.44 (1.15, 1.79)	0.001
M stage				
M0	1		1	
M1	2.55 (2.25, 2.88)	<0.001	2.01 (1.74, 2.31)	<0.001
Radiation				
No/Unknown	1		1	
Yes	0.48 (0.42, 0.54)	<0.001	0.78 (0.68, 0.90)	0.001
Chemotherapy				
No/Unknown	1		1	
Yes	0.37 (0.32, 0.43)	<0.001	0.53 (0.45, 0.64)	<0.001
Surgery				
No/Unknown	1		1	
Yes	0.34 (0.30, 0.39)	<0.001	0.55 (0.47, 0.65)	<0.001

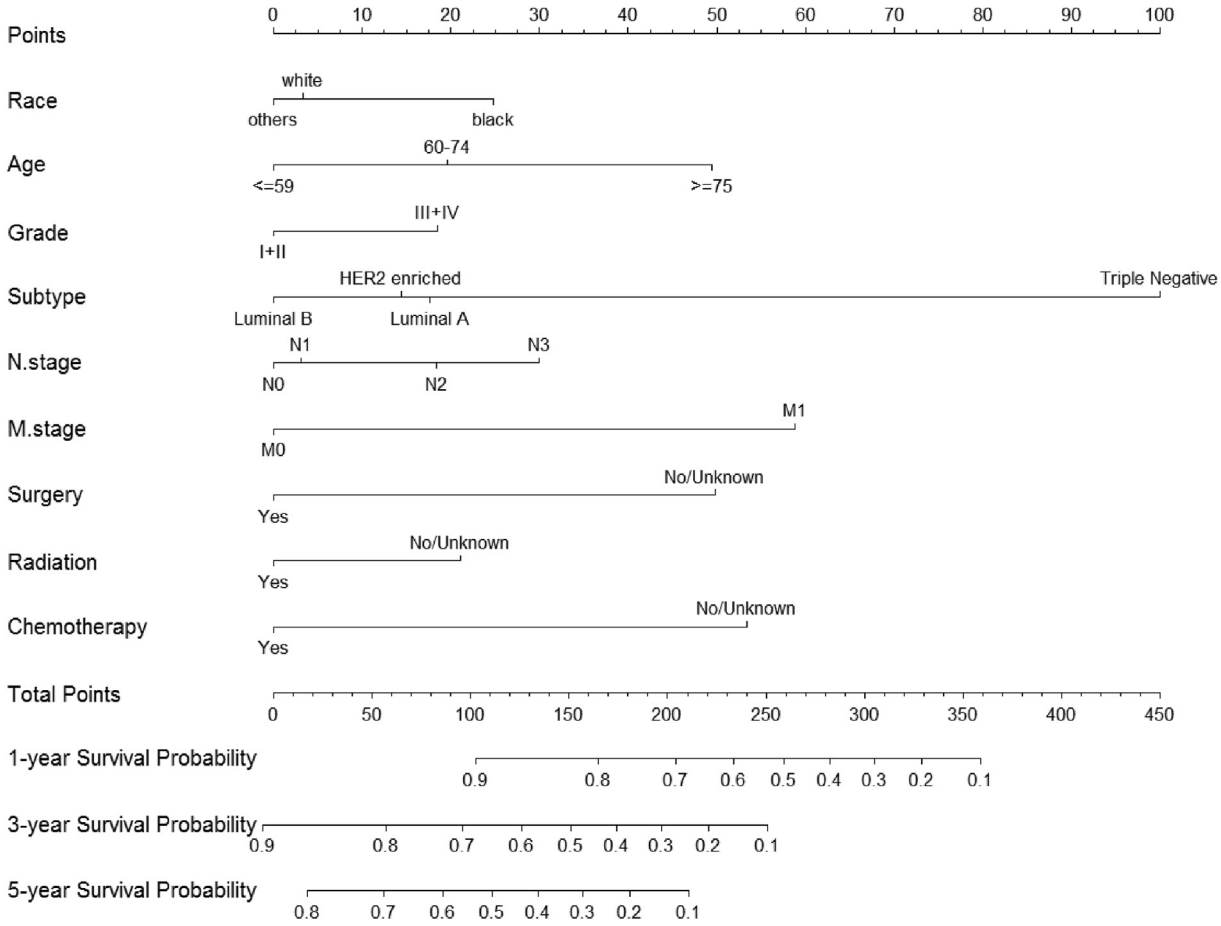

Fig. 2. Nomogram to predict 1-, 3-, and 5-year OS of IBC patients. **Notes:** Vertical line between each variable and points scale can be drawn to acquire points of each variable. Predicted survival rate was calculated according to the total points by drawing a vertical line from Total Points scale to overall survival scale.

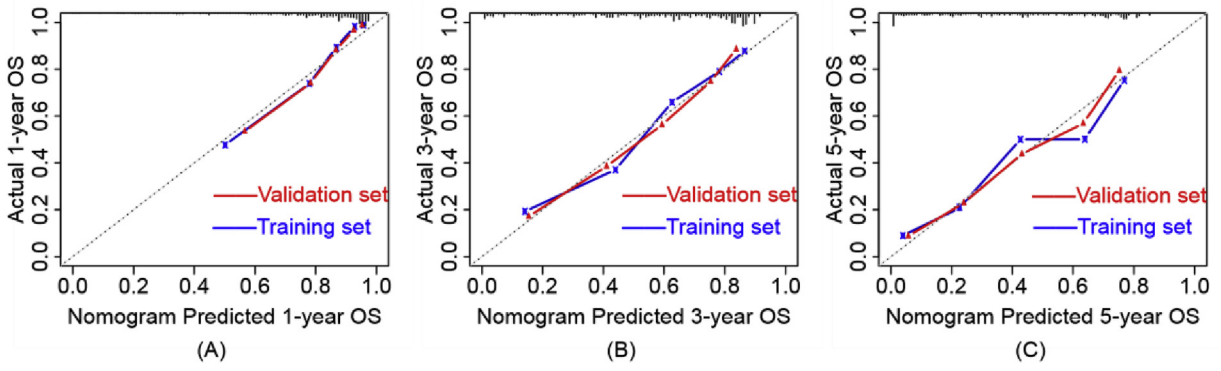

Fig. 3. Calibration plots for predictions for the 1-(A), 3-(B), and 5-year OS(C). The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis. The predictions fall at a diagonal 45° line in the calibration plot indicate higher prediction accuracy.

4. Discussion

The TNM staging system is the most common method to predict the prognosis of patients. However, considerable survival differences have been observed even in patients at the same stage of IBC and non-IBC [11,12]. Because of its rarity, few data on the clinicopathological characteristics and prognosis of IBC are available. Nomograms have been shown to be more accurate than the TNM staging system for predicting prognosis for the majority of cancer types [8,10]. In the current study, a large cohort of IBC patients from the SEER database was analysed to study this highly aggressive disease. We developed a nomogram derived from the Cox regression model to predict the 1-, 3-, and 5-year OS of patients with IBC. The nomogram showed good discrimination and good performance

in both internal and external validation.

In this study, race directly confirmed the independent prognostic role in IBC patients. Accumulated evidence suggests that black women with IBC have a poorer survival rate than white women with IBC [13–15]. This result might be due to the higher incidence of triple-negative breast cancer observed in black American women [16]. A growing body of evidence has shown that married patients have lower mortality than unmarried patients in non-IBC [17–19]. However, studies on the association specific to IBC are limited. Our results demonstrated that marital status does not influence the survival outcomes of patients with IBC. Age was proven to be an important prognostic factor for IBC by Ahmed et al. [20]. To obtain the best cut-points for age at diagnosis, we used X-tile software for data stratification. Our results also showed that age at diagnosis has prognostic value in IBC.

As shown in the nomogram that we presented, breast cancer subtype and histological grade had strong prognostic associations with the OS. Recent research has suggested that the molecular subtype has significant prognostic effects on the OS of IBC [21,22]. Our research showed that approximately 24% of IBC cases are triple-negative breast cancers, which have worse outcomes than other breast cancer subtypes. Our research also showed that the majority of IBC patients have histological grade 3 tumours, and a small minority of IBC patients have grade 1 tumours. Tumour size is an important independent predictor of outcomes in IBC. However, many IBC patients have diffuse erythema and oedema and lack a palpable lump; in fact, this is the typical presentation in IBC patients [2]. Therefore, tumour size was not analysed in the current study.

Presently, treatment strategies and prognostic predictions for IBC patients are based on the TNM staging system. Wecsler et al. [23] demonstrated that positive nodal status is an adverse prognostic factor of IBC. This study also showed that the N stage had a strong prognostic association with the OS.

The therapeutic approach of IBC was multidisciplinary, including systemic therapy and local treatment with surgery and radiotherapy. Multidisciplinary approaches have improved local disease control, but long-term prognoses remain poor [24]. In the present study, radiotherapy, chemotherapy, and surgery were independently able to predict survival and were in agreement with previous studies [25]. Our study showed that the 1-, 3-, and 5-year OS rates were 82.79%, 56.59%, and 44.12%, respectively. However, continued improvements in local and systemic therapies still needs to be developed for the treatment of IBC.

Although the nomogram showed good discrimination and good performance, our study still has several limitations. First, 1327 (27.40%) of the 4843 patients were excluded due to missing data, which might result in selection bias. Second, the SEER database does not provide more information about systemic therapy, such as targeted therapy records, chemotherapy regimens, and endocrine therapy. Third, details about other prognostic factors, such as the expression of Ki-67 and the 21-gene recurrence score, are lacking. Information regarding locoregional recurrence was also not available. Fourth, this nomogram was based on a retrospective set, and further validation in prospective clinical trials is needed. Despite these limitations, our prognostic nomogram is an important and effective model for providing accurate and individualised survival prediction in IBC patients.

5. Conclusions

The present study identified race, age at diagnosis, breast cancer subtype, grade, N stage, M stage, radiation, chemotherapy, and surgery as independent prognostic factors for the OS of IBC patients. These independent factors were used to build the nomogram prognosis evaluation model for IBC patients. This nomogram accurately and reliable predicted the 1-, 3- and 5-year OS of IBC patients.

Ethical statement

This SEER analysis was approved by the Institutional Ethnic Committee of the Nanhai Hospital Affiliated to Southern Medical University. Data extracted from the SEER database do not require individual informed consent. The patient data in this study was anonymously managed in all stages, including stages of data cleaning and statistical analyses. This study was conducted in accordance with the Declaration of Helsinki.

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Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.05.015.

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