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Original Article

Nomogram for predicting survival in triple-negative breast cancer patients with histology of infiltrating duct carcinoma: a population-based study

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Abstract: Triple-negative breast cancer (TNBC) represents around 15%-20% of newly diagnosed breast cancer and is more aggressive than other breast cancer sub-types. Infiltrating duct carcinoma (IDC) is the most common type of TNBC. Nomogram is a valuable tool for prognosis prediction by integrating different biological and clinical variables. The purpose of current study was to evaluate the prognostic value of clinical factors of TNBC patients with IDC histology type and construct nomograms for their outcome prediction. The cohort was selected from Surveillance, Epidemiology, and End Results (SEER) program. Univariate and multivariate analyses were performed using Cox proportional hazards regression model to evaluate the prognostic value of involved variables. Nomogram was constructed from the multivariate logistic regression model to combine all the prognostic factors to predict the 1-year and 3-year prognosis of TNBC patients with histology of IDC. Internal validation of nomogram was tested by discrimination and calibration. We identified 14,538 patients with the median and max survival time was 28 months and 59 months, respectively. There were 1,592 deaths, accounting for 10.9% of the cohort. Multivariate analyses showed that grade, tumor stage, tumor size, regional nodes positive, marital status, experience of radiotherapy or chemotherapy were independent prognostic factors of IDC of TNBC. Eleven variables were combined to construct 1-year and 3-year nomograms. It was revealed that the C-index of the nomograms was 0.763 and the calibration curves showed good agreement between the nomogram prediction and actual observation. Current study was the first one to construct nomograms of TNBC patients with IDC histology, which could help physicians to identify patients at high risk for intensive treatment or follow-up.

Keywords: Triple-negative breast cancer, infiltrating duct carcinoma, nomograms, prognosis

Introduction

Breast cancer (BC) is the most common cancer and the leading cause of deaths of all cancers in females [1]. The triple-negative breast cancer (TNBC) sub-type is defined by immunohistochemical methods, which shows estrogen receptor (ER)-negative, progesterone receptor (PR)-negative and human epidermal growth factor receptor 2 (HER2)-negative [2]. It represents around 15%-20% of newly diagnosed breast cancer [2] and is associated with young age (<40 years), advanced disease and early recurrence [3-5]. Generally, it is more aggressive than other breast cancer sub-types [6].

TNM staging system is a common tool used to predict the outcomes of cancer patients by evaluated the tumor size or location (T), regional lymph node involvement (N), and distant metastases (M) [7]. However, TNM staging system might not enough for encompassing the tumor biology and predicting outcomes of BC, especially for TNBC [8]. Furthermore, other clinical factors such as age, race, tumor location, grade, adjuvant treatments and molecular background could also influence the prognosis of TNBC patients. Nomogram is a valuable pictorial tool to incorporate biological and clinical variables to determine a prognostic model that generates a probability of clinical outcomes for a particular individual [9]. Nomograms have been shown to compare favorably to the traditional TNM staging systems in many cancers [10, 11].

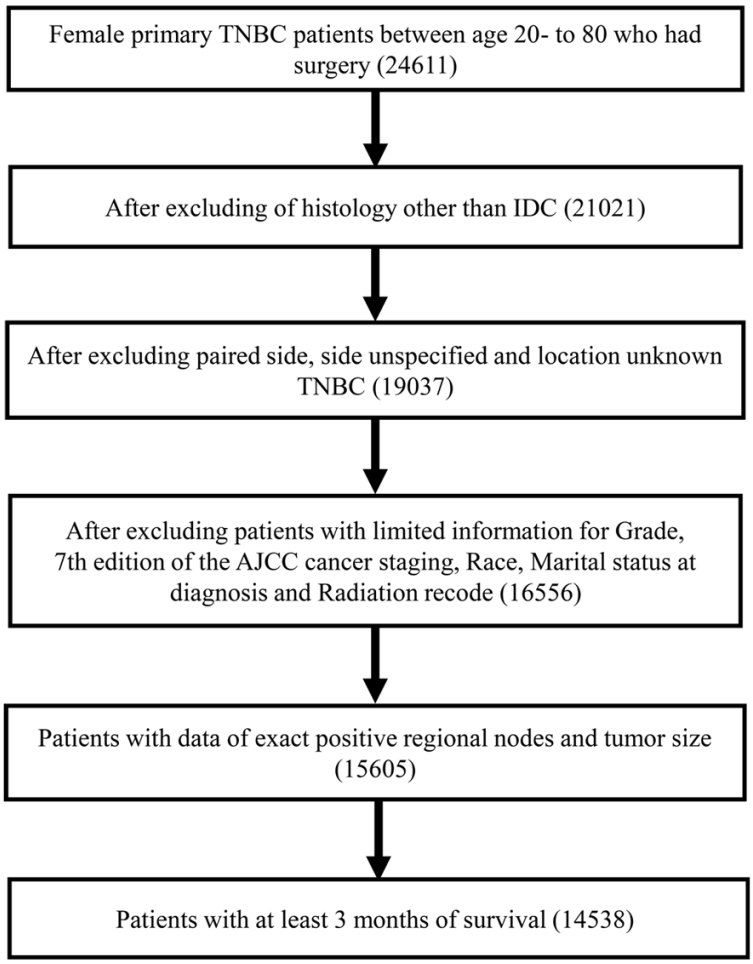

Figure 1. Flowchart of selection process in this study.

Different histology subtype exhibits distinguish prognosis of TNBC [12]. Infiltrating duct carcinoma (IDC) (ICD-O-3 Histology/behavior-8500/3) is the most common type of TNBC, accounting for almost 90% of TNBC [12]. Therefore, the prediction of IDC type of TNBC is relative important, especially for early diagnosed patients suitable for radical operation. There are currently no studies to construct nomograms for IDC of female TNBC. The aim of current study was to evaluate the prognostic value of clinical factors of TNBC patients with IDC histology type and construct nomograms for their outcome prediction.

Patients and methods

Patient screening

Current cohort was selected from 18 registries of Surveillance, Epidemiology, and End Results (SEER) program. As HER2 status was registered since 2010 in SEER database, we included patients diagnosed equal to or after 2010. The follow inclusion criteria was used for data screening: (1) it should be female primary TNBC patients diagnosed between age 20 to 79 who had surgery; (2) the histology type of patients should be IDC (ICD-O-3 Histology/behavior-8500/3); (3) it should be unilateral invasive ductal carcinoma with specific location; (4) it should include clinicopathological information for the age at diagnosis, race, laterality, tumor location, grade, tumor size, 7th American Joint Committee on Cancer (AJCC) tumor stage, number of positive regional nodes, marital status, and if the patients had radiotherapy or chemotherapy; (5) The survival time should over 3 months, and the vital status should be recoded for survival analyses. Any patients did not meet the above criteria or lack of information for certain clinicopathological information would be excluded.

Study variables and endpoints

We extracted the following variables from the selected cohorts that included the age at diagnosis, race (Caucasian, African American, American Indian/Alaska Native, Asian or Pacific Islander), laterality (right or left side), tumor location (nipple, central portion of breast, upper-inner quadrant of breast, lower-inner quadrant of breast, upper-outer quadrant of breast, lower-outer quadrant of breast, axillary tail of breast, overlapping lesion of breast), grade (well-differentiated, moderately differentiated, poorly differentiated, undifferentiated or anaplastic), tumor size, 7th AJCC tumor stage, number of positive regional nodes, marital status, and radiotherapy or chemotherapy experience. The 7th AJCC tumor stage was roughly considered as I, II, III, IV. The widowed or single (never married or having a domestic partner) or divorced or separated patients was classified

Table 1. The characteristic of each involved variables

Characteristics	No. of patients	%
Age		
20-29	174	1.20%
30-39	1199	8.25%
40-49	3035	20.88%
50-59	4185	28.79%
60-69	3792	26.08%
70-79	2153	14.81%
Race		
White	10525	72.40%
Black	2942	20.24%
American Indian/Alaska Native	90	0.62%
Asian or Pacific Islander	981	6.75%
Laterality		
Right-origin of primary	7115	48.94%
Left-origin of primary	7423	51.06%
Location		
Nipple	25	0.17%
Central portion of breast	475	3.27%
Upper-inner quadrant of breast	2167	14.91%
Lower-inner quadrant of breast	945	6.50%
Upper-outer quadrant of breast	6222	42.80%
Lower-outer quadrant of breast	1137	7.82%
Axillary tail of breast	113	0.78%
Overlapping lesion of breast	3454	23.76%
Grade		
Well differentiated; Grade I	211	1.45%
Moderately differentiated; Grade II	2269	15.61%
Poorly differentiated; Grade III	11960	82.27%
Undifferentiated; anaplastic; Grade IV	98	0.67%
Tumor size		
≤1 cm	2372	16.32%
≤2 cm	4761	32.75%
≤3 cm	3722	25.60%
≤4 cm	1803	12.40%
≤5 cm	823	5.66%
>5 cm	1057	7.27%
Tumor stage		
I	5922	40.73%
II	6539	44.98%
III	1830	12.59%
IV	247	1.70%
Positive regional nodes number		
≥10	397	2.73%
0	10396	71.51%
1-3	2892	19.89%
4-9	853	5.87%
Marital status		

as unmarried. The value of age at diagnosis, tumor size and number of positive regional nodes were transformed into small categorical variables to fit the linear assumption. Both overall survival and breast cancer specific survival were used as endpoints.

Statistical analyses

Univariate and multivariate analyses were performed using Cox proportional hazards regression model to evaluate the prognostic value of involved variables. Hazard ratio (HR) and 95% confidence index (95% CI) were calculated. The Kaplan-Meier method was used to draw the survival curve. Nomogram was constructed from the multivariate logistic regression model to combine all the prognostic factors to predict the 1-year and 3-year prognosis of TNBC patients with histology of IDC.

The internal validation of nomogram was tested by discrimination and calibration [9]. The discrimination was estimated by Concordance index (C-index). C-index ranges from 0.5-1.0, with 0.5 indicates the outcomes is completely random and 1.0 indicates the perfect discrimination. Calibration assesses how close the nomogram estimated risk is to the observed risk, which was depicted by a calibration plot. Bootstrap analyses with 1,000 resamples were used for these analyses. Statistical matching was performed by coarsened Exact Matching (CEM), which is able to achieve lower levels of imbalance, model dependence, and bias than Propensity Score matching [13, 14]. All the statistical analyses were performed using R version 3.4.2. A *p*-value less than 0.05 was considered statistically significant.

Results

Clinicopathologic characteristics of patients

As shown in **Figure 1**, there were 14,538 patients involved in our prognostic analyses. The clinical features were listed in **Table 1**. The mean age of the cohort was 56.03 ± 12.01 years. The median and max survival time was 28 months and 59 months, respectively. There were 1,592

Married	8737	60.10%
Unmarried	5801	39.90%
Radiotherapy		
No	6373	43.84%
Yes	8165	56.16%
Chemotherapy		
No	2875	19.78%
Yes	11663	80.22%

deaths, accounting for 10.9% of the cohort. The majority of patients were diagnosed with the grade of poorly differentiated, tumor size less than 3 cm, stage I-II, no positive regional node, and had radiotherapy or chemotherapy.

Independent risk factors associated with overall survival in this cohort

Univariate and multivariate Cox proportional hazards model were applied to assess the prognostic value of the 11 variables. When using univariate survival analysis, variables included race, grade, tumor stage, tumor size, regional nodes status, marital status and radiotherapy were found to be significantly correlated with OS (p value <0.05, **Table 2**). Multivariate analysis was further used to confirm independently prognostic factors of OS. In addition to variables identified significant in univariate model, chemotherapy was also found to be associated with better OS (HR = 0.703, p value <0.001, **Table 2**). Old patients (70-79 years) led to bad prognosis (HR = 1.886, p value = 0.007, **Table 2**) and Asian or Pacific Islander had better prognosis compared with Caucasian (HR = 0.627, p value <0.001, **Table 2**).

Nomogram development and validation

We involved 6,468 patients with enough follow-up time to build nomogram. Nomogram was constructed based on the result of multivariate analyses. A weighted total score calculated from each variable was used to estimate the 1-year and 3-year overall survival prediction (**Figure 2**). Internally validation was done by discrimination and calibration method. C-index was calculated as 0.763, which indicated relative good discrimination of the nomogram. The calibration plots showed good correlation between observed OS and nomogram predicted OS (**Figure 3**).

Statistical matching for radiotherapy and chemotherapy

Statistical matching methods could lower the differences between groups on confounding variables and made cancer observation studies in somehow be considered as a quasi-experimental study [15]. Radiotherapy and chemotherapy were the most used adjuvant therapy for TNBC. We additionally performed CEM for these two important variables. The mean difference between treated group and control group of all variables was eliminated into zero after matching (data not shown). The histograms after CEM were much more similar than the left side ones without matching (**Figure 4**), indicating that our matching was successful. The univariate analysis was performed for the new matched data, and we found both radiotherapy and chemotherapy were associated with better prognosis of IDC-TNBC (**Figure 5**).

Discussion

There was a study constructed a nomogram for predicting TNBC prognosis [16]. However, this study was based on limited cases (247 patients from single center) and variables (4 variables). Our study included 14,538 female patients from SEER database and involved total of 11 variables. Each variable was evaluated for its prognostic value by cox regression model. We found that grade, tumor stage, tumor size, regional nodes positive, marital status, experience of radiotherapy or chemotherapy were significantly associated with the prognosis of IDC of TNBC by multivariate analyses. The nomogram was constructed to predict the 1-year and 3-year overall survival for IDC of female TNBC The discrimination and calibration of nomogram indicated our nomogram was valuable. The variables of this nomogram were easy to be obtained, allowing feasible translation into clinical use in the near future.

There is a SEER-based study for elderly TNBC patients, which displayed elevated early mortality within the first two years of diagnosis compared to the younger individuals [17]. Our updated study showed similar result that aged TNBC patients with IDC type presented worse prognosis compared with young patients.

African American BC patients exhibit lower breast cancer incidence and higher mortality

Table 2. Univariate and multivariate analyses of overall survival in current cohort

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age				
20-29	References		References	
30-39	1.024 (0.642, 1.633)	0.922	1.398 (0.873, 2.240)	0.163
40-49	0.840 (0.534, 1.319)	0.448	1.187 (0.752, 1.874)	0.461
50-59	0.758 (0.484, 1.187)	0.226	1.158 (0.735, 1.823)	0.528
60-69	0.832 (0.531, 1.305)	0.424	1.419 (0.900, 2.236)	0.132
70-79	1.199 (0.763, 1.885)	0.431	1.886 (1.190, 2.990)	0.007
Race				
Caucasian	References		References	
African American	1.316 (1.174, 1.475)	<0.001	1.112 (0.988, 1.252)	0.078
American Indian/Alaska Native	1.338 (0.739, 2.424)	0.336	1.098 (0.605, 1.992)	0.759
Asian or Pacific Islander	0.603 (0.468, 0.777)	<0.001	0.627 (0.485, 0.809)	<0.001
Laterality				
Right-origin of primary	References			
Left-origin of primary	1.062 (0.963, 1.172)	0.229	1.067 (0.966, 1.179)	0.199
Location				
Nipple	References		References	
Central portion of breast	0.778 (0.339, 1.786)	0.553	0.503 (0.218, 1.161)	0.107
Upper-inner quadrant of breast	0.479 (0.213, 1.079)	0.076	0.601 (0.266, 1.358)	0.221
Lower-inner quadrant of breast	0.530 (0.233, 1.207)	0.131	0.613 (0.268, 1.400)	0.245
Upper-outer quadrant of breast	0.525 (0.235, 1.172)	0.116	0.453 (0.202, 1.017)	0.055
Lower-outer quadrant of breast	0.488 (0.215, 1.111)	0.087	0.453 (0.198, 1.033)	0.060
Axillary tail of breast	0.589 (0.226, 1.532)	0.278	0.467 (0.179, 1.220)	0.120
Overlapping lesion of breast	0.601 (0.269, 1.347)	0.216	0.552 (0.245, 1.240)	0.150
Grade				
Well differentiated; Grade I	References		References	
Moderately differentiated; Grade II	2.873 (1.352, 6.104)	0.006	2.164 (1.016, 4.608)	0.045
Poorly differentiated; Grade III	3.795 (1.806, 7.976)	<0.001	2.369 (1.123, 4.997)	0.024
Undifferentiated; anaplastic; Grade IV	4.719 (1.942, 11.472)	0.001	2.747 (1.125, 6.704)	0.026
Tumor stage				
I	References		References	
II	2.525 (2.176, 2.931)	<0.001	1.807 (1.454, 2.245)	<0.001
III	8.906 (7.651, 10.366)	<0.001	2.899 (2.219, 3.788)	<0.001
IV	28.919 (23.556, 35.502)	<0.001	10.448 (7.799, 13.995)	<0.001
Tumor size				
≤1 cm	References		References	
≤2 cm	2.058 (1.636, 2.589)	<0.001	1.624 (1.281, 2.059)	<0.001
≤3 cm	2.707 (2.152, 3.403)	<0.001	1.395 (1.061, 1.835)	0.017
≤4 cm	4.368 (3.450, 5.530)	<0.001	2.003 (1.517, 2.644)	<0.001
≤5 cm	5.491 (4.237, 7.116)	<0.001	2.277 (1.689, 3.070)	<0.001
>5 cm	9.281 (7.351, 11.718)	<0.001	2.734 (2.063, 3.622)	<0.001
Regional nodes positive				
0	References		References	
1-3	2.863 (2.542, 3.224)	<0.001	1.926 (1.677, 2.212)	<0.001
4-9	6.192 (5.378, 7.128)	<0.001	4.686 (3.765, 5.833)	<0.001
≥10	11.596 (9.897, 13.588)	<0.001	2.891 (2.343, 3.568)	<0.001

Marital status				
Married	References		References	
Unmarried	1.542 (1.398, 1.701)	<0.001	1.303 (1.177, 1.443)	<0.001
Radiotherapy				
No	References		References	
Yes	0.829 (0.751, 0.914)	<0.001	0.782 (0.704, 0.868)	<0.001
Chemotherapy				
No	References		References	
Yes	1.074 (0.948, 1.216)	0.261	0.703 (0.611, 0.808)	<0.001

Notes: Significant results were bolded. Abbreviations: HR, hazard ratio; 95% CI, 95% confidence index.

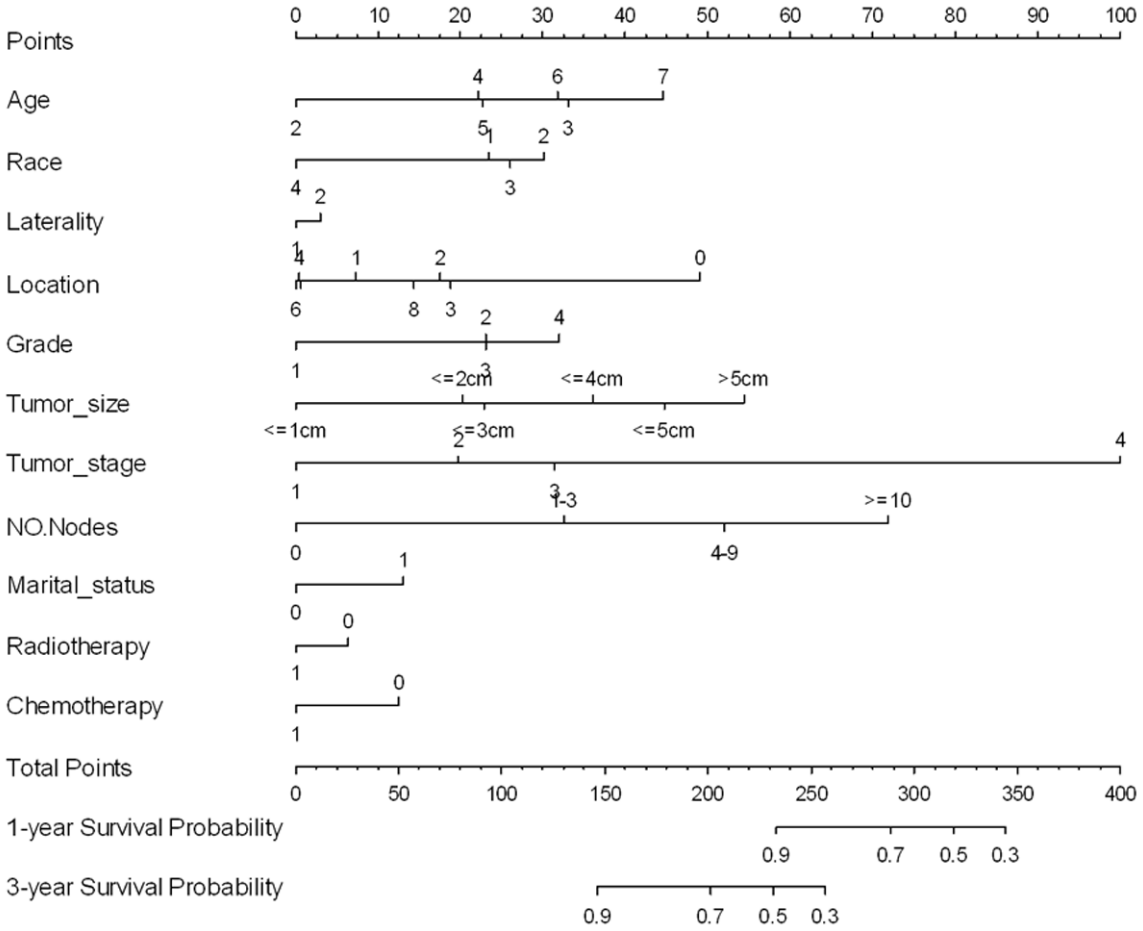

Figure 2. Nomogram for predicting 1- and 3-year OS of IDC type of TNBC. The nomogram is used by summing the points identified on the top scale for each independent variable and drawing a vertical line from the total points scale to the 1- and 3-year OS to obtain the probability of survival. The total points projected to the bottom scale indicate the % probability of the 1- and 3-year survival. Age: 2 = 20-29 years, 3 = 30-39 years, 4 = 40-49 years, 5 = 50-59 years, 6 = 60-69 years and 7 = 70-79 years; Race: 1 = Caucasian, 2 = African American, 3 = American Indian/Alaska Native and 4 = Asian or Pacific Islander; Laterality: 1 = Right-origin of primary and 2 = Left-origin of primary; Location, 0 = Nipple, 1 = central portion of the breast, 2 = upper-inner quadrant of the breast, 3 = lower-inner quadrant of the breast, 4 = upper-outer quadrant of the breast, 5 = lower-outer quadrant of breast, 6 = Axillary tail of breast and 8 = Overlapping lesion of breast; Grade: 1 = Well differentiated; Grade I, 2 = Moderately differentiated; Grade II, 3 = Poorly differentiated; Grade III, 4 = Undifferentiated; anaplastic; Grade IV; Tumor stage, 1 = I stage, 2 = II stage, 3 = III stage and 4 = IV stage; NO. Nodes, the number of positive regional lymph nodes; Marital status: 0 = married; 1 = widowed or single (never married or having a domestic partner) or divorced or separated; Radiotherapy, 1 = beam radiation or combination of beam with implants or isotopes or radiation with method or source not specified or radioactive implants or radioisotopes and 0 = none/unknown or refused; Chemotherapy, 1 = yes and 0 = none/unknown.

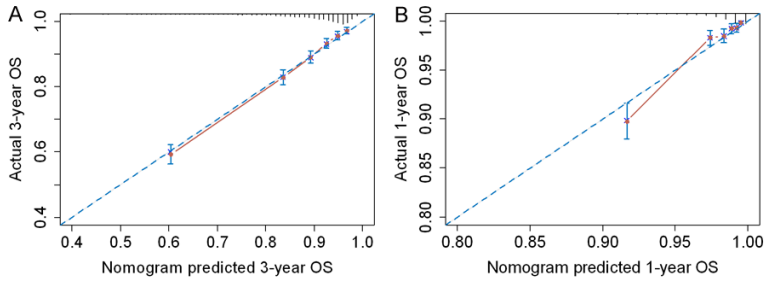

Figure 3. Nomogram model calibration curves. A. 1-years calibration curves; B. 3-years calibration curves; The x-axis shows the nomogram predicted probability, and the y-axis gives the actual survival as estimated by the Kaplan-Meier method. The blue circle overlaps the light blue line indicating near perfect calibration.

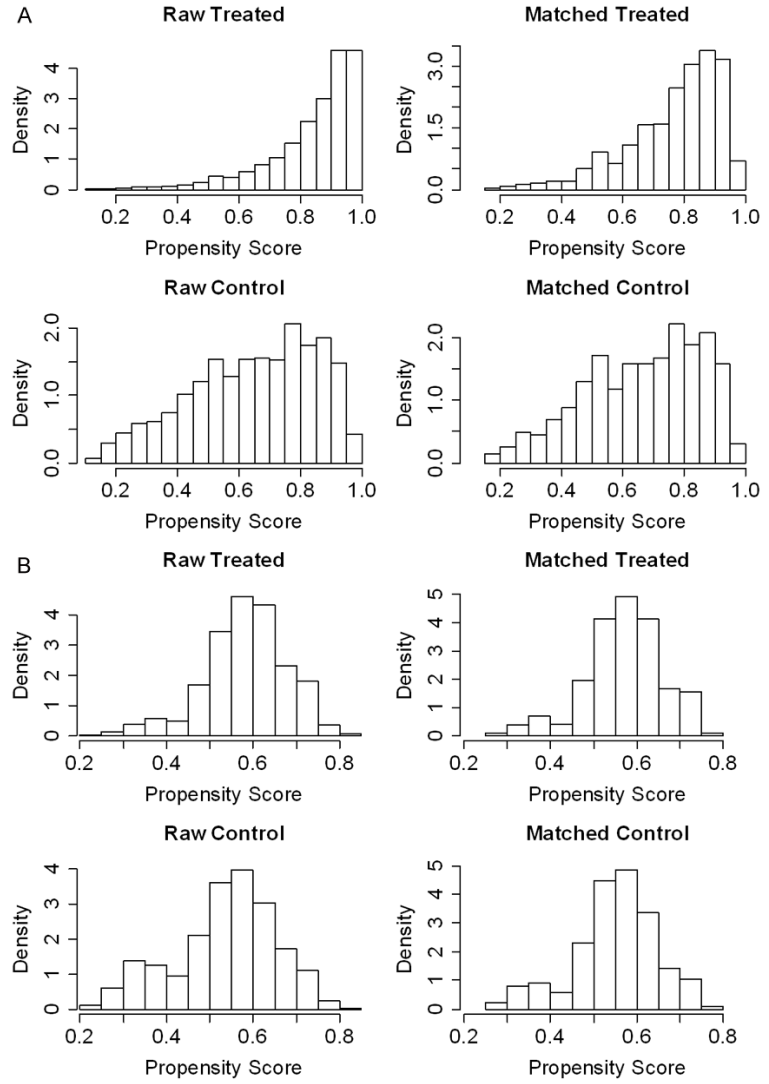

Figure 4. The histogram of raw data and matched data for radiotherapy and chemotherapy. A. Histogram of raw data and matched data for radiotherapy; B. Histogram of raw data and matched data for chemotherapy; The histograms before matching was on the left while the histograms after matching was on the right. The similarity between treated and control group was correlated with the success of matching.

than Caucasian patients [18, 19]. It might be a result of higher incidence of TNBC observed in African American women [20, 21]. However, there were studies showed African American TNBC patients presented no different prognosis with Caucasians [22, 23]. Our study also found there was no significant difference between African American and Caucasian women. Furthermore, we found races from Asian or Pacific Islander exhibited a better prognosis. However, the cohort from Asian or Pacific Islander was relative small (981, 6.75% of all patients).

Marital status was associated with cancer incidence [24] and outcome [25]. Unmarried patients were at higher risk of metastatic cancer, and shorter survival [25]. Consistently, our study also showed unmarried patients was associated with a worse prognosis of TNBC.

TNBC patients presented with more *BRCA1/2* mutations [26], which might cause radiosensitivity due to deficient DNA damage repair. Adjuvant radiation significantly improved the survival of TNBC with lumpectomy surgery but not the patients underwent simple mastectomy or modified radical mastectomy [27, 28]. Postmastectomy radiotherapy (PMRT) was found to improve locoregional recurrence-free survival (LRFS) and disease-free survival (DFS) in TNBC patients with T1-T2 Disease [29]. Nevertheless, the using of radiotherapy was encouraged in TNBC [30]. Chemotherapy is currently the only systemic treatment to improve TNBC outcomes. The response of TNBC to neoadju-

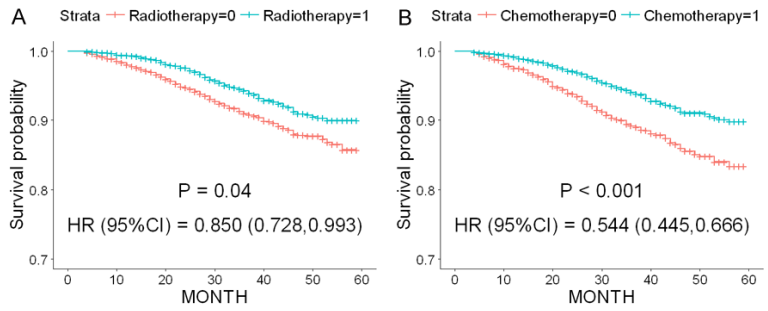

Figure 5. The survival curve of association between radiotherapy or chemotherapy and IDC type of TNBC after CEM. A. Survival curve of association between radiotherapy and IDC type of TNBC; B. Survival curve of association between chemotherapy and IDC type of TNBC; Radiotherapy, 1 = beam radiation or combination of beam with implants or isotopes or radiation with method or source not specified or radioactive implants or radioisotopes and 0 = none/unknown or refused; Chemotherapy, 1 = yes and 0 = none/unknown.

vant chemotherapy was relative good [31, 32]. However, treatment options are limited and the responses generally lack durability in metastatic TNBC. Multivariate Cox proportional hazards model and CEM-based analysis both showed either the radiotherapy or chemotherapy was significantly associated with improved survival of TNBC patients in this cohort. To be noted, the current data of radiotherapy and chemotherapy from SEER had potential bias because many factors involved in determining the course of treatment will not be captured in the registry data.

There were some limitations in our study. Firstly, although 11 variables were involved, there are still many variables that SEER does not included, such as the chemotherapy regiments, blood tests and molecular test information. Second, selection bias might exist as we only included patients with complete information of involved variables. Third, duo to the limited of the number of patients, we only involved TNBC patients with histology of IDC. Other types of TNBC, such as metaplastic carcinoma, medullary carcinoma, invasive lobular carcinoma, apocrine carcinoma and adenoid cystic carcinoma were not involved. Fourth, our nomogram was based on retrospective cohort, which presented relative low level of clinical evidence, further validation in prospective clinical trials is needed.

Conclusion

In conclusion, our study was the first one to construct a nomogram for female TNBC patients with IDC type. The nomogram was well validated. It could help clinicians identify patients at high risk of overall mortality within 1 or 3 years.

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Disclosure of conflict of interest

None.

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