A web-based prediction model for early death in patients with metastatic Triple-Negative Breast Cancer: a SEER database analysis

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Research Article

Keywords: Triple-negative breast cancer (TNBC), nomogram, predictive model, early death

Posted Date: April 21st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2832406/v1

Abstract

Background Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the absence of expression of estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER-2). This subtype of breast cancer is known for its high aggressiveness, high metastatic potential, a tendency for recurrence, and poor prognosis. Patients with metastatic TNBC (mTNBC) have a poorer prognosis and a higher likelihood of early death (survival time ≤3 months). Therefore, the development of effective individualized survival prediction tools, such as prediction nomograms and web-based survival calculators, is of great importance for predicting the probability of early death in patients with metastatic TNBC.

Methods: Patients diagnosed with mTNBC in the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015 were included in the model construction. Univariate and multivariate logistic regression analysis was performed to identify risk factors associated with early death in patients with mTNBC, and predictive prognostic nomograms were constructed. The accuracy of the nomograms was verified using receiver operating characteristic (ROC) curves, and GiViTi Calibration belt plots were used to evaluate the model consistency. The clinical applicability of the nomograms was evaluated using decision curve analysis (DCA). Based on the predictive prognostic nomograms, a network survival rate calculator was developed for individualized survival prediction in patients with mTNBC.

Results: A total of 2,230 patients diagnosed with mTNBC were included in the SEER database for this study. After strict exclusion criteria, 1,428 patients were found to be eligible for the study. All the patients were randomly divided into a training cohort and a validation cohort in a ratio of7:3. Independent risk factors for mTNBC, including age, tumor size, brain metastasis, liver metastasis, surgery, and chemotherapy, were identified and integrated to construct the prediction nomogram and survival calculator. Results of ROC curves, calibration curves, and DCA curves from the training and validation cohort confirmed that the developed nomogram and web-based survival calculator in this study could accurately predict the probability of early death in patients with mTNBC.

Conclusion: In this study, we developed a reliable prediction nomogram and web-based survival calculator for predicting the probability of early death in patients with mTNBC. These tools can assist clinical physicians in identifying high-risk patients and developing personalized treatment plans as early as possible.

1 Introduction

Breast cancer is the most prevalent malignancy among women, with breast cancer-specific deaths accounting for approximately 15% of cancer-related deaths in 2018[1]. Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the absence of expression of estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER-2) [2]. Epidemiological data indicate that TNBC primarily affects young premenopausal women under the age

of 40, representing approximately 10–20% of all breast cancer cases [3, 4]. This subtype of breast cancer is known for its aggressive biology, early onset of metastatic disease, visceral metastases, rapid disease progression, short response time to available therapies, and poor survival outcomes [5]. Chemotherapy is the primary treatment for patients with TNBC[6].

Due to the absence of ER, PR, and HER2 expression, TNBC is highly aggressive, and has a worse prognosis than other subtypes of breast cancer, representing a mortality rate of 40% within the first five years of diagnosis [5]. Furthermore, approximately 46% of patients with TNBC develop distant metastases [7] occurring within the third year of diagnosis [8]. These metastases commonly involve the brain and visceral organs. 40% of metastases are occurred in the lung, which is one of the most common sites of distant metastasis. The mortality rate of distant metastasis is higher than that of carcinoma in situ [9]. The median survival time (MST) following metastasis is only 13.3 months, and the postoperative recurrence rate is as high as 25%. The MST of patients with metastatic TNBC is 1-1.5 years [10], and the mortality rate of these patients could gradually decrease with the advancement of treatments. However, the survival rate for these patients remains suboptimal [11–15].

Currently, the American Joint Committee on Cancer (AJCC) TNM staging system is a widely accepted tool for predicting the survival of breast cancer patients. However, its predictive value is limited when applied to patients with metastatic disease. To date, there have been no comprehensive studies using predictive models to determine the incidence of early death in patients with metastatic triple-negative breast cancer (mTNBC). Therefore, it is crucial to identify a new method for predicting the probability of early death in mTNBC patients. There is an urgent need for a simple and accurate model for assessing these patients' risk of early death. Recent studies have shown that the nomogram is a convenient and accurate tool to assess the prognosis of cancer patients [16, 17]. Nomograms could combine important factors to quantify the probability of patients experiencing a certain clinical event, such as survival or recurrence rates. Therefore, nomograms have become a useful clinical tool for facilitating decision-making and risk stratification. However, there is a lack of studies on nomograms for predicting early death in patients with mTNBC [16], and little is known about the risk factors for early death in this patient population.

In light of this, there is a need to construct a nomogram for predicting early death in patients with mTNBC in order to better assess the survival and prognosis of these patients. Since a manual calculation may limit the nomogram's usefulness in clinical practice, a network calculator based on prognostic nomograms can improve the accuracy and usability of disease survival prediction when compared with prognostic nomograms alone. This study explores the risk factors of early death in patients with mTNBC using the Surveillance, Epidemiology, and End Results (SEER) database, and constructs a nomogram and a network survival calculator. These tools not only assist clinicians in identifying high-risk patients but also guide treatment decision-making and monitoring. Furthermore, these tools can help formulating timely individualized treatment plans, ultimately extending life expectancy, improving patients' quality of life, and reducing the economic burden on society and families.

2 Materials And Methods

SEER database (https://seer.cancer.gov/) is the National Cancer Institute's open public database containing cancer incidence and survival data from 17 established cancer registries across the United States accounts. The present authors obtained authorization from the National Cancer Institute (USA) to access research data on cancer patients (reference number: 17461-November 2020) from the SEER database. Using the data from the SEER database does not require informed consent from patients, as cancer is a reportable disease in every state of the United States. This study adheres to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical guidelines.

2.1 Patient Cohorts

Data of patients with mTNBC for this present study were extracted from the SEER*Stat (version 8.4.0.1) database during the period of 2010 to 2015. Inclusion criteria for the study were as follows: (1) patients were diagnosed with triple-negative breast cancer; (2) patients had demographic information including age, marital status, and race; (3) patients had clinical and pathological information including primary tumor site, stage, histological type, TNM, and tumor size. Exclusion criteria for the study were as follows: (1) patients with unknown survival time; (2) patients with unknown race; (3) patients with no identified primary tumor or unknown tumor site, size, degree of infiltration, stage, or lymph node metastasis; (4) patients with unknown marital status; (5) patients under 18 years of age. The study aimed to investigate the probability of early death in patients with mTNBC and to construct a predictive prognostic nomogram and a network survival rate calculator.

2.2 Data Collection

Figure 1 illustrates the screening process of patients in this study. Taking into account the aggressive nature of mTNBC and previous research, early death was defined as death within three months of initial diagnosis. All-cause early death was defined as death from any cause (such as hypertension, diabetes mellitus, coronary artery disease, traffic accidents, etc.) within three months of the patient's initial diagnosis with mTNBC [18, 19]. Survival time was calculated from the date of the first histological or cytological diagnosis with mTNBC.

Finally, this study included 1428 patients with mTNBC, among which 275 patients were died within three months of their initial diagnosis. The patient population was randomly divided into a training cohort (accounting for 70%) and a validation cohort (accounting for 30%). The prediction model was constructed using patients from the training cohort and subsequently validated using the corresponding patients in the validation cohort.

The baseline characteristics of patients, including age, gender, race, marital status, and tumor characteristics such as tumor location, size, histological grade, AJCC 7th TNM stage, and presence of bone, brain, liver, and lung metastasis, were collected for analysis. Additionally, the information on the treatment received, including surgery, radiotherapy, and chemotherapy, were also collected for analysis. The patient's age was classified into four groups: $\leq$49 years,50–59 years,60–69 years, $\geq$ 70 years. While

the tumor size was reclassified as < 50, 50–100 and > 100 mm. Race was divided into white, black or others. Histological type was grouped as 8500(invasive ductal carcinoma ,ICD-O-3, code 8500/3) or others. Treatments and metastasis sites were grouped as “yes” or “no/unknown.” Laterality was grouped into left, right.

2.3 Statistical Analysis

Categorical data were described using numbers and percentages (N, %), and chi-square tests were employed to compare subgroups. Statistical analysis was conducted using SPSS 24.0 and R software (version 4.1.0; http://www.r-project.org/). P value of < 0.05 (two-tailed) was considered statistically significant. Patients with mTNBC were randomly divided into training and validation cohorts, and the distribution of variables was compared using either Pearson's chi-square test or Fisher's exact test.

In the training cohort, univariate logistic analysis was employed to identify risk factors associated with mTNBC. Variables with P < 0.05 in the univariate analysis were subsequently included in the multivariate logistic analysis using the "Forward LR" method in SPSS 24.0 to determine independent risk factors for early mortality in patients with mTNBC [20]. Furthermore, a prognostic nomogram was developed using the "replot" package based on these independent risk factors, and various methods were employed to evaluate its performance in the training and validation cohorts. A concordance index (C-index) was generated to measure prediction accuracy and discriminatory ability, while receiver operating characteristic (ROC) curves were plotted, and the area under the time-dependent receiver operating characteristic curve (AUC) was calculated to validate prediction accuracy.[21, 22] Typically, the C-index and AUC values range from 0 to 1. When both the C-index and AUC values are greater than 0.7, it could be considered as reasonable estimates. Moreover, the higher values reveal the greater predictive power. GiViTi Calibration belts were also constructed to a confidence interval around the calibration curve. The red line is perfect calibration line between the predicted probability and observed. The light and dark gray calibration bands represent the 80% and 95% confidence levels for this predictive model, respectively [23]. If the red line is included in the calibration band, the model fits well when the P-value > 0.05. Decision curve analyses (DCAs) were performed to assess the clinical applicability and the benefit of the nomogram [24]. This study aimed to develop a prognostic nomogram and a web-based survival calculator that can dynamically predict the early mortality probability of mTNBC through a population-based retrospective cohort study using the SEER database data.

3 Results

3.1 Baseline Characteristics of the Study Population

A total of 2,230 patients diagnosed with mTNBC were included in this study from the SEER database. After the strict exclusion criteria, 1,428 patients were found to meet the study requirements. As shown in Table 1, 19.3% (275/1428) of mTNBC patients died within three months of diagnosis. The majority of mTNBC patients were the white race (70.2%), and bone metastases were the most common type (41.1%) compared to the liver (27.2%), brain (10.9%), and lung (39.8%) metastases. Most patients with mTNBC

received chemotherapy (77.2%), while only a minority chose radiotherapy (35.1%). The probability of morbidity in the left breast (52.6%) was higher than that in the right breast (47.4%). The early mortality rate in whites (71.3%) was higher than that in other racial groups. Treatments including surgery and chemotherapy could significantly decrease premature mortality in mTNBC patients.

Table 1
Baseline clinical characteristics of mTNBC patients.

Clinical Characteristics	No (N = 1153)	Yes (N = 275)	Overall(N = 1428)
Age			
< 49 years	299 (25.9%)	32 (11.6%)	331 (23.2%)
50–59 years	321 (27.8%)	50 (18.2%)	371 (26.0%)
60–69 years	286 (24.8%)	74 (26.9%)	360 (25.2%)
70 + years	247 (21.4%)	119 (43.3%)	366 (25.6%)
Race recode			
Black	265 (23.0%)	65 (23.6%)	330 (23.1%)
Other	82 (7.1%)	14 (5.1%)	96 (6.7%)
White	806 (69.9%)	196 (71.3%)	1002 (70.2%)
Grade			
Grade I	11 (1.0%)	2 (0.7%)	13 (0.9%)
Grade II	187 (16.2%)	52 (18.9%)	239 (16.7%)
Grade III	934 (81.0%)	215 (78.2%)	1149 (80.5%)
Grade IV	21 (1.8%)	6 (2.2%)	27 (1.9%)
AJCC T 7th			
T1	146 (12.7%)	41 (14.9%)	187 (13.1%)
T2	384 (33.3%)	78 (28.4%)	462 (32.4%)
T3	237 (20.6%)	51 (18.5%)	288 (20.2%)
T4	386 (33.5%)	105 (38.2%)	491 (34.4%)
AJCC N 7th			
N0	242 (21.0%)	86 (31.3%)	328 (23.0%)
N1	527 (45.7%)	118 (42.9%)	645 (45.2%)
N2	134 (11.6%)	26 (9.5%)	160 (11.2%)
N3	250 (21.7%)	45 (16.4%)	295 (20.7%)
Histologic			

Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated. 8500: invasive ductal carcinoma (ICD-O-3, code 8500/3)

Clinical Characteristics	No (N = 1153)	Yes (N = 275)	Overall(N = 1428)
Age			
8500	946 (82.0%)	215 (78.2%)	1161 (81.3%)
Other	207 (18.0%)	60 (21.8%)	267 (18.7%)
Marital status			
Married	559 (48.5%)	91 (33.1%)	650 (45.5%)
Never married	252 (21.9%)	61 (22.2%)	313 (21.9%)
Other	342 (29.7%)	123 (44.7%)	465 (32.6%)
Sequence number			
More primaries	253 (21.9%)	58 (21.1%)	311 (21.8%)
One primary only	900 (78.1%)	217 (78.9%)	1117 (78.2%)
Chemotherapy			
No	152 (13.2%)	174 (63.3%)	326 (22.8%)
Yes	1001 (86.8%)	101 (36.7%)	1102 (77.2%)
Radiotherapy			
No	715 (62.0%)	212 (77.1%)	927 (64.9%)
Yes	438 (38.0%)	63 (22.9%)	501 (35.1%)
Surgery			
No	509 (44.1%)	211 (76.7%)	720 (50.4%)
Yes	644 (55.9%)	64 (23.3%)	708 (49.6%)
Tumor size			
< 50 mm	619 (53.7%)	132 (48.0%)	751 (52.6%)
> 100 mm	155 (13.4%)	54 (19.6%)	209 (14.6%)
50–100 mm	379 (32.9%)	89 (32.4%)	468 (32.8%)
Bone metastasis			
No/Unknown	697 (60.5%)	144 (52.4%)	841 (58.9%)
Yes	456 (39.5%)	131 (47.6%)	587 (41.1%)

Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated. 8500: invasive ductal carcinoma (ICD-O-3, code 8500/3)

Clinical Characteristics	No (N = 1153)	Yes (N = 275)	Overall(N = 1428)
Age			
Brain metastasis			
No/Unknown	1052 (91.2%)	221 (80.4%)	1273 (89.1%)
Yes	101 (8.8%)	54 (19.6%)	155 (10.9%)
Lung metastasis			
No/Unknown	717 (62.2%)	142 (51.6%)	859 (60.2%)
Yes	436 (37.8%)	133 (48.4%)	569 (39.8%)
Liver metastasis			
No/Unknown	883 (76.6%)	156 (56.7%)	1039 (72.8%)
Yes	270 (23.4%)	119 (43.3%)	389 (27.2%)
Laterality			
Left	616 (53.4%)	135 (49.1%)	751 (52.6%)
Right	537 (46.6%)	140 (50.9%)	677 (47.4%)
Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated. 8500: invasive ductal carcinoma (ICD-O-3, code 8500/3)			

As shown in Table 2, Patients were randomly divided via a 7:3 ratio into two cohorts: a training cohort (n = 999) for nomogram building, and a validation cohort (n = 429) for model validation. There were no significant differences between the training and validation cohorts in terms of age, gender, marital status, race, tumor laterality, histological type, grading stage, TN stage (AJCC 7th edition), tumor size, surgery, radiotherapy, chemotherapy, tumor sequence number, brain metastases, liver metastases, and lung metastases. Therefore, the training and validation cohorts could be used for the follow-up study.

Table 2
Demographic information of patients with mTNBC in training and validation cohorts.

Clinical Characteristics	Training(N = 999)	Validation(N = 429)	Overall(N = 1428)	χ2	P-value
Age				0.13571	0.9872
< 49 years	232 (23.2%)	99 (23.1%)	331 (23.2%)		
50–59 years	257 (25.7%)	114 (26.6%)	371 (26.0%)		
60–69 years	252 (25.2%)	108 (25.2%)	360 (25.2%)		
70 + years	258 (25.8%)	108 (25.2%)	366 (25.6%)		
Race recode				0.072292	0.9645
Black	232 (23.2%)	98 (22.8%)	330 (23.1%)		
Other	68 (6.8%)	28 (6.5%)	96 (6.7%)		
White	699 (70.0%)	303 (70.6%)	1002 (70.2%)		
Grade				0.0063	0.9999
Grade I	9 (0.9%)	4 (0.9%)	13 (0.9%)		
Grade II	167 (16.7%)	72 (16.8%)	239 (16.7%)		
Grade III	804 (80.5%)	345 (80.4%)	1149 (80.5%)		
Grade IV	19 (1.9%)	8 (1.9%)	27 (1.9%)		
AJCC T 7th				0.9999	0.8013
T1	134 (13.4%)	53 (12.4%)	187 (13.1%)		
T2	321 (32.1%)	141 (32.9%)	462 (32.4%)		
T3	196 (19.6%)	92 (21.4%)	288 (20.2%)		
T4	348 (34.8%)	143 (33.3%)	491 (34.4%)		
AJCC N 7th				0.7998	0.8495
N0	227 (22.7%)	101 (23.5%)	328 (23.0%)		
N1	457 (45.7%)	188 (43.8%)	645 (45.2%)		
N2	108 (10.8%)	52 (12.1%)	160 (11.2%)		
N3	207 (20.7%)	88 (20.5%)	295 (20.7%)		
Histologic				0.6128	0.4337

Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated.8500: invasive ductal carcinoma (ICD-O-3, code 8500/3)

Clinical Characteristics	Training(N = 999)	Validation(N = 429)	Overall(N = 1428)	χ2	P-value
8500	818 (81.9%)	343 (80.0%)	1161 (81.3%)		
Others	181 (18.1%)	86 (20.0%)	267 (18.7%)		
Marital status				2.0127	0.3656
Married	465 (46.5%)	185 (43.1%)	650 (45.5%)		
Never married	210 (21.0%)	103 (24.0%)	313 (21.9%)		
Others	324 (32.4%)	141 (32.9%)	465 (32.6%)		
Sequence number				0.5026	0.4783
More primaries	212 (21.2%)	99 (23.1%)	311 (21.8%)		
One primary only	787 (78.8%)	330 (76.9%)	1117 (78.2%)		
Chemotherapy				0.1242	0.7245
No	225 (22.5%)	101 (23.5%)	326 (22.8%)		
Yes	774 (77.5%)	328 (76.5%)	1102 (77.2%)		
Radiotherapy				2.4765	0.1156
No	635 (63.6%)	292 (68.1%)	927 (64.9%)		
Yes	364 (36.4%)	137 (31.9%)	501 (35.1%)		
Surgery				0.2348	0.6280
No	499 (50.0%)	221 (51.5%)	720 (50.4%)		
Yes	500 (50.1%)	208 (48.5%)	708 (49.6%)		
Tumor size				3.7536	0.1531
< 50 mm	524 (52.5%)	227 (52.9%)	751 (52.6%)		
> 100 mm	136 (13.6%)	73 (17.0%)	209 (14.6%)		
50–100 mm	339 (33.9%)	129 (30.1%)	468 (32.8%)		
Bone metastasis				12.514	0.0004
No/Unknown	619 (62.0%)	222 (51.7%)	841 (58.9%)		
Yes	380 (38.0%)	207 (48.3%)	587 (41.1%)		
Brain metastasis				0.2966	0.5860

Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated.8500: invasive ductal carcinoma (ICD-O-3, code 8500/3)

Clinical Characteristics	Training(N = 999)	Validation(N = 429)	Overall(N = 1428)	χ2	P-value
No/Unknown	894 (89.5%)	379 (88.3%)	1273 (89.1%)		
Yes	105 (10.5%)	50 (11.7%)	155 (10.9%)		
Lung metastasis				0.1644	0.6851
No/Unknown	597 (59.8%)	262 (61.1%)	859 (60.2%)		
Yes	402 (40.2%)	167 (38.9%)	569 (39.8%)		
Liver metastasis				0.7404	0.3895
No/Unknown	734 (73.5%)	305 (71.1%)	1039 (72.8%)		
Yes	265 (26.5%)	124 (28.9%)	389 (27.2%)		
Survival Status				3.5574	0.0592
No	820 (82.1%)	333 (77.6%)	1153 (80.7%)		
Yes	179 (17.9%)	96 (22.4%)	275 (19.3%)		
Laterality				0.4627	0.4963
Left	519 (52.0%)	232 (54.1%)	751 (52.6%)		
Right	480 (48.0%)	197 (45.9%)	677 (47.4%)		

Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated.8500: invasive ductal carcinoma (ICD-O-3, code 8500/3)

3.2 Factors Influencing Early Death in Patients with mTNBC

In this study, 275 eligible patients with mTNBC were included to investigate the factors associated with early mortality. The chi-square and Fisher's exact tests revealed that there were no significant differences between the training and validation cohorts for all variables. Subsequently, univariate and multivariate logistic regression analyses were conducted to identify influential factors. The results of the univariate logistic analysis revealed that age at diagnosis, marital status, tumor size, lymph node stage, brain metastasis, lung metastasis, liver metastasis, breast surgery, chemotherapy, and radiotherapy were potentially influential factors (Table 3). In order to further investigate the effect of metastatic pattern on survival, we included the number of metastatic organs in the logistic model, considering the interaction between metastatic site and number of metastatic organs. In the multivariate logistic analysis, age at diagnosis, tumor size, brain metastasis, liver metastasis, breast surgery, and chemotherapy were identified as independent prognostic factors for early mortality in patients with mTNBC (Table 3). The results indicated that older age at diagnosis ($p < 0.001$), larger primary tumor size ($p < 0.05$), the presence of brain metastasis ($p = 0.009$) and liver metastasis ($p < 0.001$), not receiving surgery ($p < 0.001$), and not

receiving chemotherapy ($p < 0.001$) were independent factors associated with early death in patients with mTNBC.

Table 3
The univariate and multivariate logistic analysis of risk factors for early death from mTNBC.

Clinical	Univariable			Multivariable		
Characteristics	**OR**	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Age						
< 49 years						
50–59 years	1.988	1.189–3.415	0.0313*	1.790	0.979–3.354	0.1183*
60–69 years	3.095	1.900-5.213	0.0002*	2.544	1.416–4.711	0.0103*
70 + years	6.402	4.037–10.571	< 0.0001*	4.373	2.414–8.181	< 0.0001*
Race recode						
Black						
Others	0.616	0.310–1.145	0.2200			
White	0.871	0.638–1.202	0.4760			
Grade						
Grade I						
Grade II	2.198	0.492–22.296	0.4646			
Grade III	1.643	0.378–16.466	0.6409			
Grade IV	2.857	0.501–32.034	0.3743			
AJCC T 7th						
T1						
T2	0.766	0.493–1.207	0.3270			
T3	1.014	0.634–1.636	0.9600			
T4	1.078	0.709–1.668	0.7710			
AJCC N 7th						
N0						
N1	0.609	0.439–0.846	0.0126*			
N2	0.531	0.312–0.873	0.0422*			

Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated. 8500: invasive ductal carcinoma (ICD-O-3, code 8500/3); *p < 0.05

Clinical	Univariable			Multivariable		
Characteristics	**OR**	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Age						
N3	0.537	0.355–0.805	0.0125*			
Histologic						
8500						
Others	1.223	0.865–1.706	0.3280			
Marital status						
Married						
Never married	1.253	0.855–1.818	0.3243			
Others	2.054	1.513–2.795	0.0001*			
Sequence number						
More primaries						
One primary only	1.085	0.780–1.533	0.6890			
Chemotherapy						
No						
Yes	0.083	0.060–0.112	< 0.0001*	0.093	0.063–0.134	< 0.0001*
Radiotherapy						
No						
Yes	0.457	0.331–0.622	< 0.0001*			
Surgery						
No						
Yes	0.225	0.162–0.307	< 0.0001*	0.201	0.133–0.297	< 0.0001*
Tumor size						
< 50 mm						
> 100 mm	1.658	1.118–2.429	0.0315*	2.279	1.395–3.709	0.0054*

Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated. 8500: invasive ductal carcinoma (ICD-O-3, code 8500/3); *p < 0.05

Clinical	Univariable			Multivariable		
Characteristics	**OR**	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Age						
50–100 mm	1.278	0.944–1.726	0.1791	1.594	1.080–2.357	0.0487*
Bone metastasis						
No/Unknown						
Yes	1.183	0.896–1.559	0.3150			
Brain metastasis						
No/Unknown						
Yes	2.111	1.430–3.074	0.0013*	2.264	1.343–3.809	0.0097*
Lung metastasis						
No/Unknown						
Yes	1.646	1.253–2.163	0.0027*			
Liver metastasis						
No/Unknown						
Yes	2.391	1.798–3.174	< 0.0001*	3.137	2.174–4.55	< 0.0001*
Laterality						
Left						
Right	1.055	0.804–1.385	0.7420			
Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated. 8500: invasive ductal carcinoma (ICD-O-3, code 8500/3); *p < 0.05						

3.3 Construction a predictive Nomograms

Based on these six prognostic factors verified in Table 3, a predictive nomogram model was developed to assess the risk of early mortality in mTNBC (Fig. 2). This model can select the subcategories of each predictor variable based on individual characteristics and calculate the specific points by drawing a vertical line on the upper point axis. The total number of points is obtained by summing the points corresponding to all predictors.

3.4 Validation of the nomogram

Figures 3A and 3B depict the ROC curves of the nomograms for early death patients with mTNBC in the training and validation cohorts. The AUC value for the training cohort was 0.878 (95% CI 0.850-0.9045), and the AUC value for the validation cohort was 0.857 (95% CI 0.815–0.899), indicating the good predictive performance of the nomograms. In Fig. 4, the x-axis of the calibration curve represents the predicted probability of early death, and the y-axis represents the actual probability of early death. Figures 4A and 4B show that the GIVITI calibration curve does not cross the 95% CI area along the 45-degree line ($P > 0.05$), indicating the good fitting of the nomograms. The discrimination ability of the nomograms was evaluated using the DCA method. Figures 5A and 5B show that the favorable threshold probability of the nomograms ranged from 0.0–83% in the training cohort analysis of early death, while the validation cohort analysis of early death ranged from 5.0–83%. The DCA results demonstrated that the nomograms have a wide range of threshold probabilities, displaying a promising potential to get superior net benefits.

3.5 Clinical application

Based on this model, a dynamic web-based calculator was developed to facilitate the application of this nomogram. The calculator can predict the probability of early mortality in patients with mTNBC by inputting patient-specific clinical characteristics through the website https://kevinpan.shinyapps.io/DynNom-Breast, along with its 95% CI.

For example, for a patient with mTNBC aged 55 years with a primary tumor diameter of 60 mm and diagnosed with liver metastasis, the probability of early mortality following surgical treatment is 37.40% (Fig. 6A, 6B). However, if the patient receives chemotherapy in addition to surgery, the probability of early mortality is reduced to 5.11% (Fig. 6C, 6D). This example highlights the effectiveness of chemotherapy in reducing the risk of early mortality in mTNBC patients, which is helpful to quickly make effective clinical recommendations.

4 Discussion

TNBC is a highly aggressive tumor that is prone to distant metastasis [25]. mTNBC is particularly malignant and often results in early death. In this study, we employed a large sample with comprehensive clinical information from the SEER database to construct a predictive nomogram model and a web-based dynamic calculator for the probability predicting of early mortality in patients with mTNBC. The performance of this model was evaluated using ROC, calibration, and DCA curves. The results demonstrated the model's good performance in predicting early mortality in mTNBC patients. This model can provide guidance for clinical treatment and may assist clinicians in making treatment decisions and monitoring disease progression.

Although the prognosis for patients with mTNBC is poor, early detection is crucial for patients to receive appropriate treatment [26]. Therefore, identifying risk factors for mTNBC is important to guide clinical treatment. Several prognostic factors and biomarkers have been identified, including age, tumor size, linc-

ZNF469-3, and miR-629-3p [27–30]. However, to our knowledge, there is no study to construct a nomogram model for predicting the risk of early death in mTNBC patients. Therefore, the risk of early death in this patient population cannot be quantified. Our results showed that age and tumor size were independent predictors of early death in patients with mTNBC, consistent with previous findings.

In addition, our findings showed that patients without brain and liver metastases had a better prognosis after undergoing surgery and chemotherapy. We constructed an early death prognostic nomogram based on six independent prognostic factors, which can be useful in identifying high-risk patients. We found that patients with distant metastases had a lower survival rate, which is consistent with the findings of Wang *et al*[31]. Moreover, different sites of metastasis also affect the survival of mTNBC patients. The prognosis of mTNBC patients with brain and liver metastases was much worse than that with lung and bone metastases. Some studies have also reported that patients with visceral metastases have a worse prognosis than those with bone metastases [32]. Typically, treating patients with advanced diseases should focus on improving survival. Previous studies have also shown that chemotherapy and surgery significantly improve the prognosis of patients with mTNBC [33]. This is consistent with our findings that surgery and chemotherapy favor the survival of patients with mTNBC, as demonstrated by our prognostic nomogram.

At present, chemotherapy is still the standard treatment for patients with mTNBC [34]. The change of the chemotherapy scheme not only improves the prognosis but also provides more treatment options. The National Comprehensive Cancer Network (NCCN) guidelines recommend a combination regimen based on paclitaxel, anthracyclines, cyclophosphamide, cisplatin, and fluorouracil for treating mTNBC [7]. A phase III randomized clinical trial investigated the efficacy and safety of cisplatin in combination with nab-paclitaxel (AP) or gemcitabine (GP) as first-line treatment for mTNBC, showing that patients receiving AP had a more prolonged progression-free survival (PFS) than those treated with the GP regimen (9.8 months *vs* 7.4 months) [35]. Furthermore, previous studies have demonstrated that patients can benefit from surgery despite metastasis to distant organs[36, 37]. Recently, immunotherapy and targeted therapies have emerged as new treatment modalities for mTNBC, potentially improving patient life expectancy and quality of life. The KEYNOTE-355 trial investigated the efficacy and safety of adding immunotherapy (pembrolizumab) to chemotherapy scheme in 847 cases of advanced TNBC. In patients overexpressed programmed death ligand (PD-L1), the survival treated with the combination of pembrolizumab was significantly higher than that treated with chemotherapy alone. Additionally, previous studies have shown that novel targeted therapies may be promising for patients with TNBC. Therefore, the risk factors identifying of early death may help to identify high-risk patients and establish a specific monitoring program.

Our study has several limitations. Firstly, the information collected in the SEER database pertains to the disease at the initial diagnosis, which means that cases of mTNBC occurring later cannot be included. Secondly, the SEER database does not currently collect information on other metastatic sites, such as distant lymph nodes, pleura, peritoneum, or skin. Thirdly, this is a retrospective study with a large sample size, which may result in selection bias. Furthermore, we could not consider the influence of other clinical

factors and biomarkers, such as targeted therapies, postoperative complications, gene expression, and chromosomal alterations, which excluded in the database. Finally, the SEER database does not provide detailed information on chemotherapy and radiotherapy regimens, which may have a differential impact on survival or life quality in patients with mTNBC.

5 Conclusion

This study identified age, tumor size, liver metastases, brain metastases, surgery, and chemotherapy as independent risk factors affecting early death in patients with mTNBC. These findings will help determine individualized therapy and ensure appropriate management of mTNBC patients. A web-based survival calculator, which utilizes these risk factors to predict the risk of early death in mTNBC, may aid clinicians in developing better clinical management and treatment strategies.

Abbreviations

AUC Area under the curve

TNBC Triple-negative breast cancer

ER Estrogen receptor

PR Progesterone receptor

HER-2 Human epidermal growth factor receptor 2

ROC Receiver operating characteristic

MTNBC Metastatic Triple-negative breast cancer

SEER Surveillance, Epidemiology, and End Results

AJCC American Joint Committee on Cancer

CI Confidence interval

NCCN National Comprehensive Cancer Network

Declarations

Ethics approval and consent to participate Since data released by the SEER database was publicly available, ethics approval and informed patient consent was not required for this study.

Consent for publication Not applicable.

Availability of data and materials All data generated or analyzed during this study are included in this published article.

Competing interests The authors declare that they have no conflicts of interest to disclose and has no financial relationships with any biomedical companies.

Funding Not applicable.

Authors' contributions The study's design and main manuscript text were created by LBC. PWK and RSY supplied the research subjects or participants and conducted the data analysis. The manuscript was revised by PWK and ZLX. The article's submission was reviewed and approved by all authors. All authors are also responsible for the manuscript content.

Acknowledgements Thanks to the anonymous peer-reviewers for their careful reading of our manuscript and their many insightful comments and suggestions.

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Figures

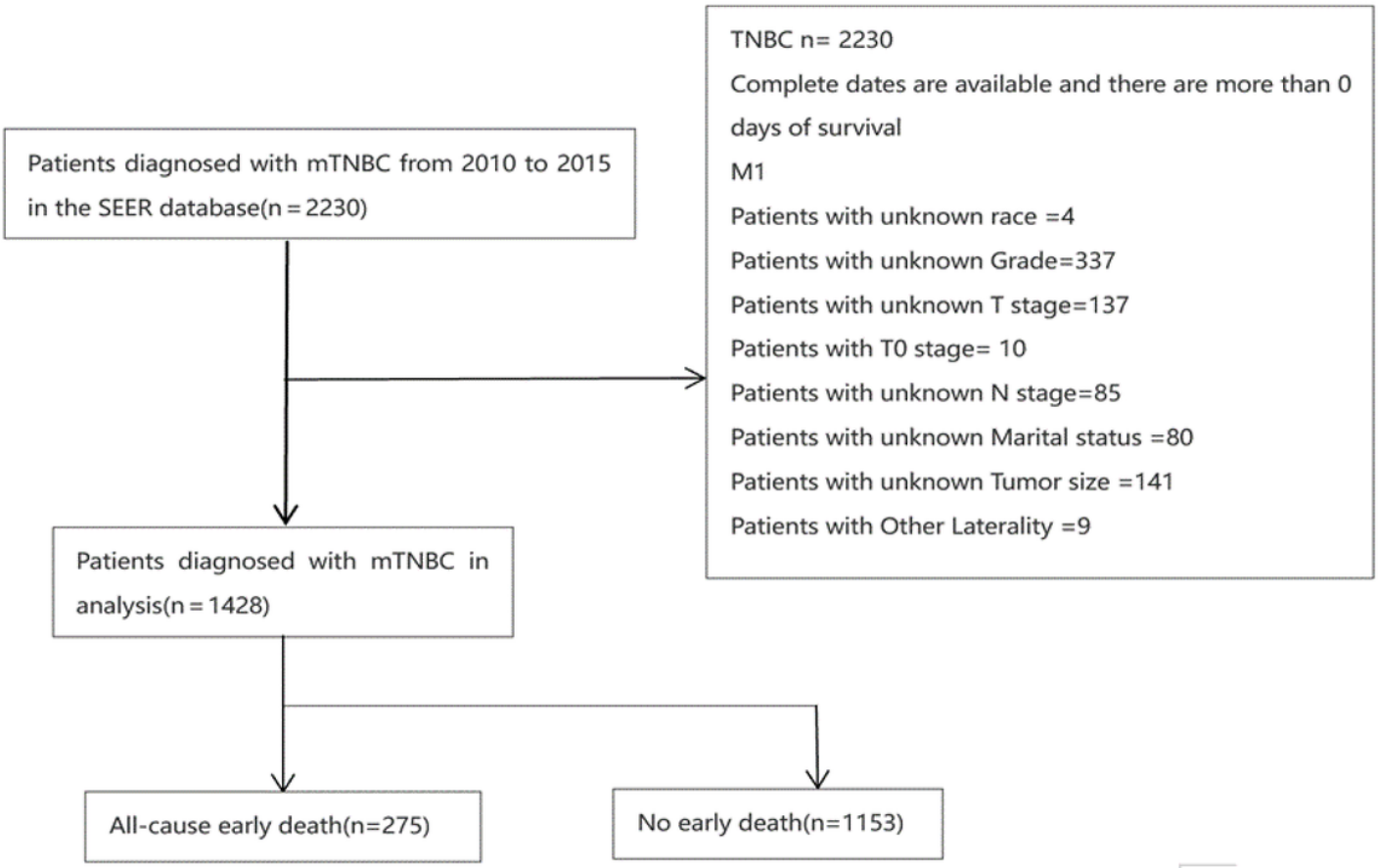


Figure 1

Flowchart for selection procedure of patients with mTNBC

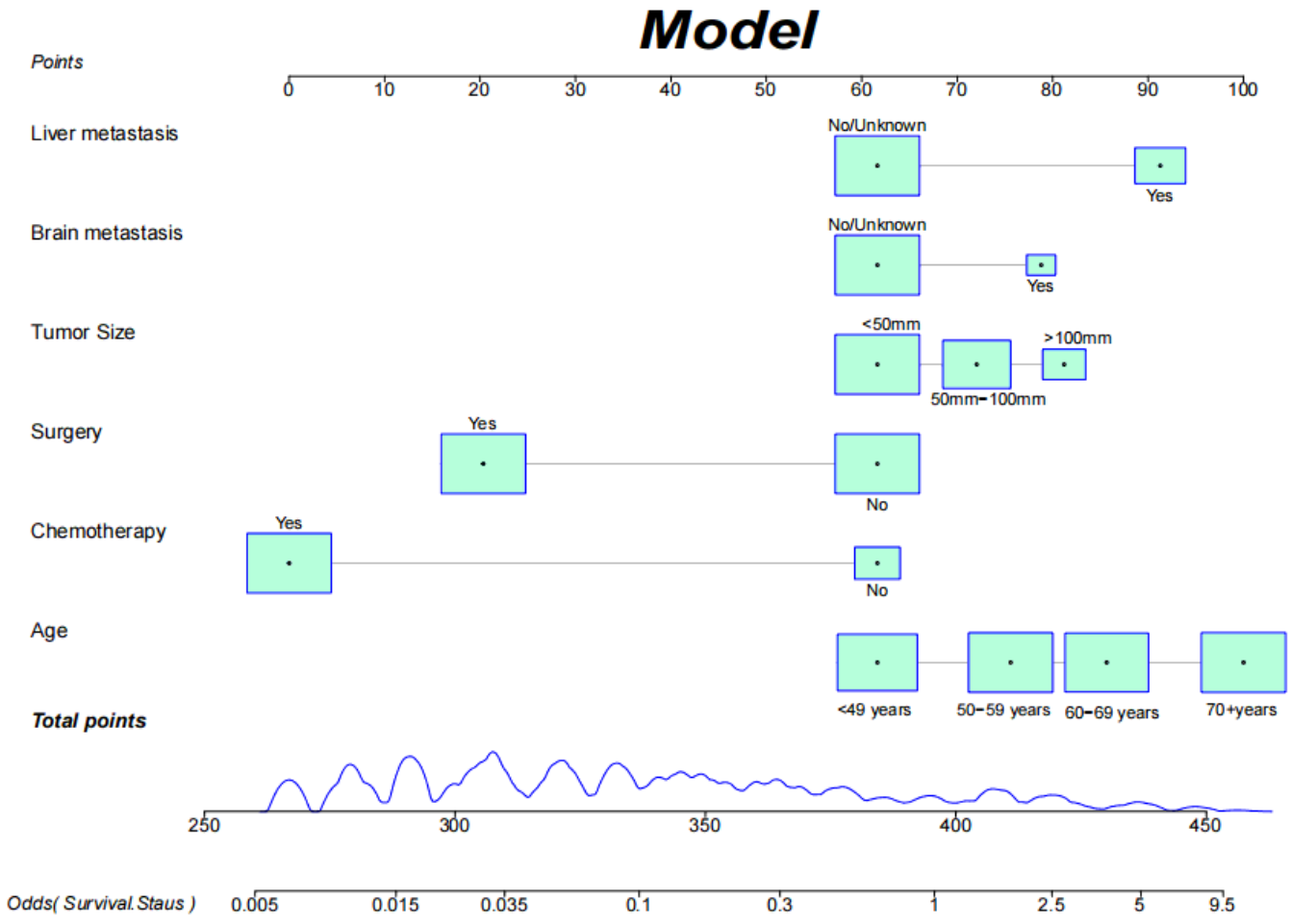


Figure 2

A predictive prognostic nomogram for predicting early death in patients with mTNBC.

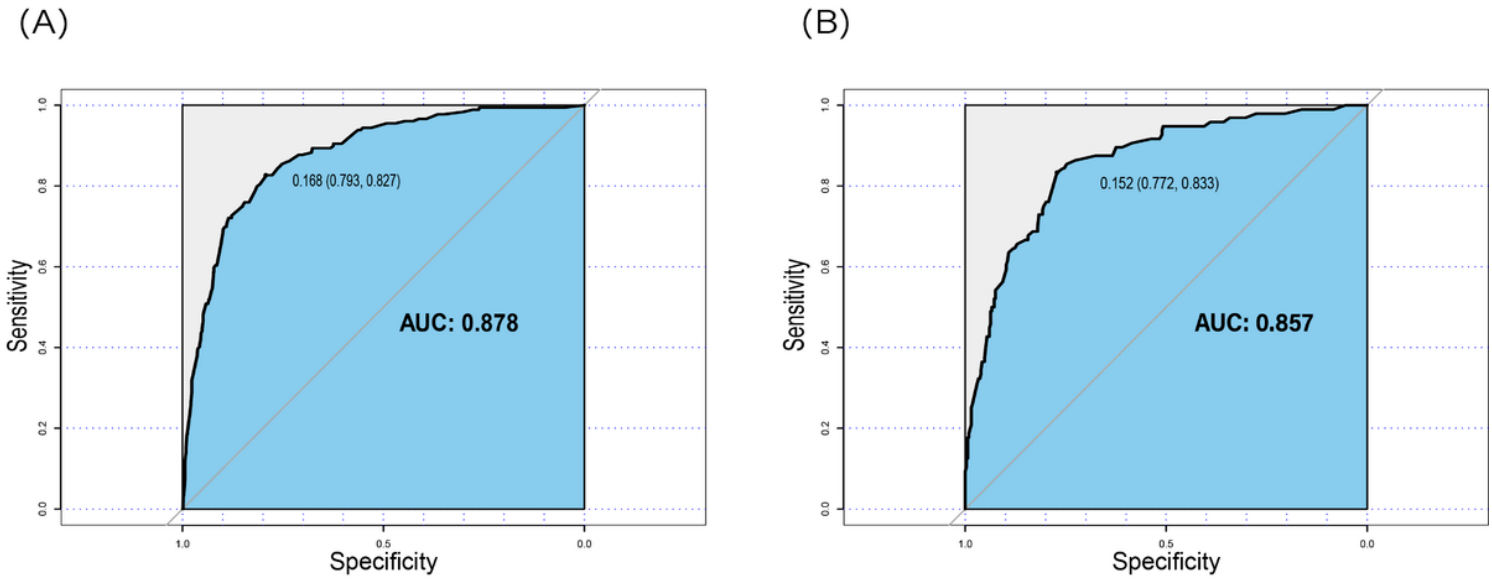


Figure 3

ROC curves for the nomogram. (A) The ROC curve for the training cohort early death nomogram in the SEER database; (B)ROC curve for the validation cohort early death nomogram in the SEER database.

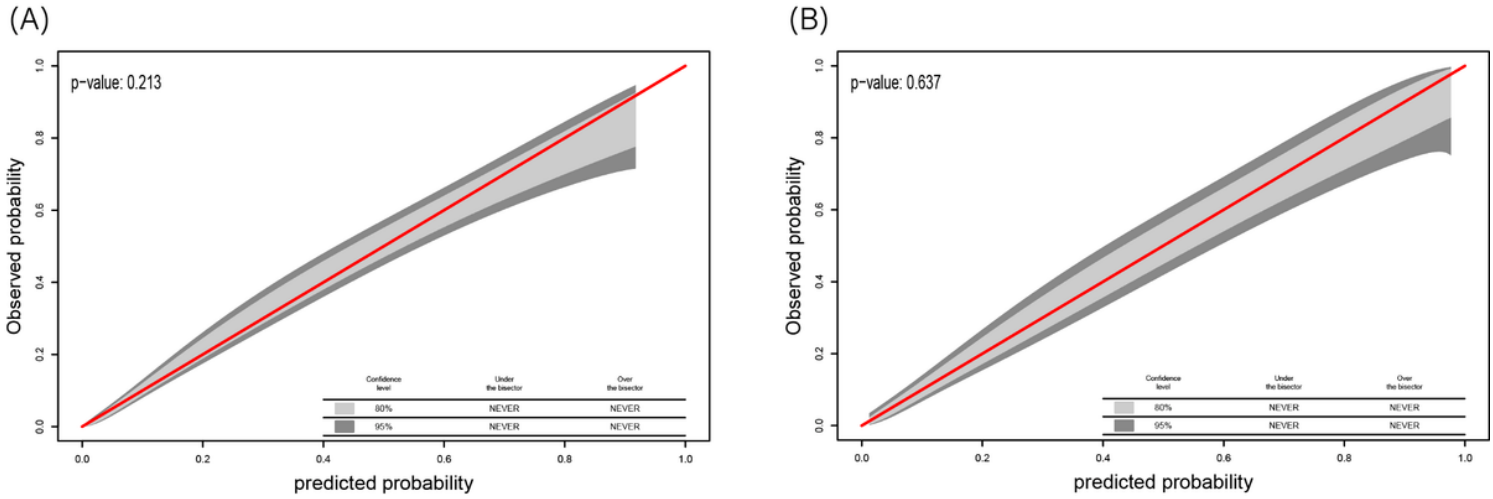


Figure 4

GIVITI Calibration belt plots for the nomogram of (A) training cohort early death in the SEER database; (B) validation cohort early death in the SEER database.

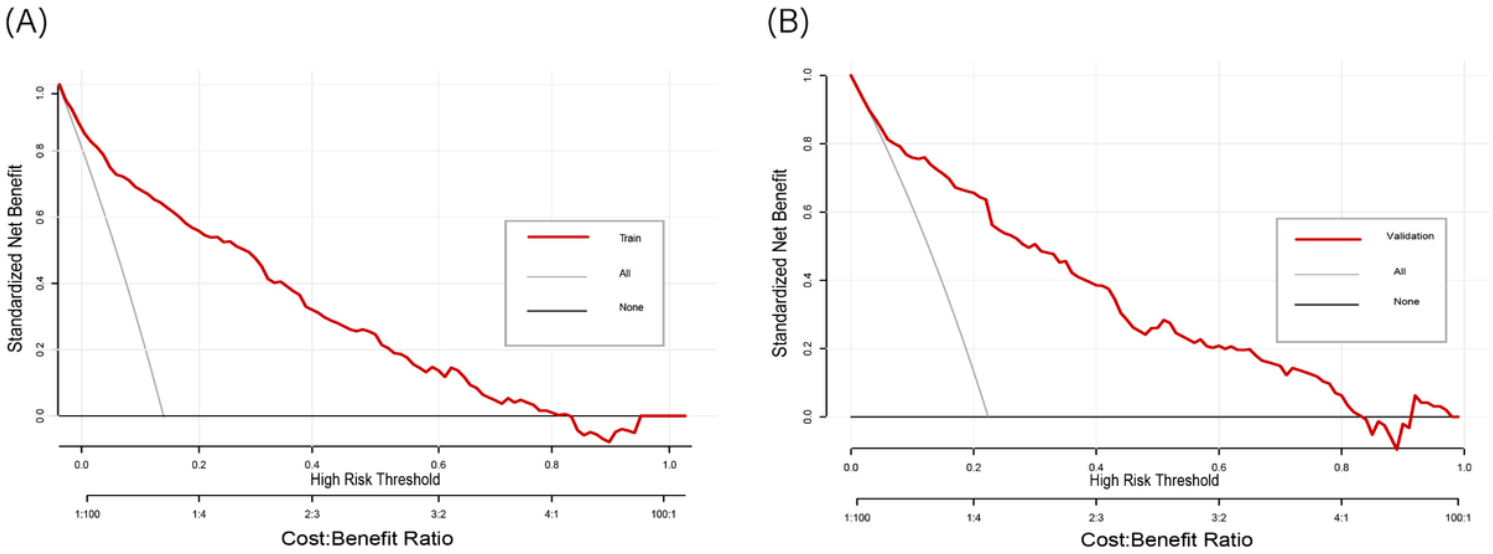
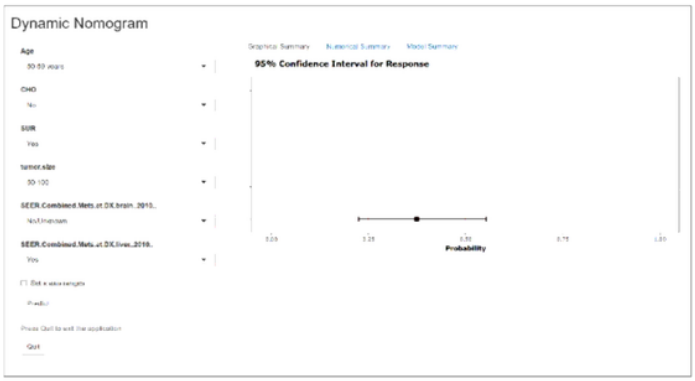


Figure 5

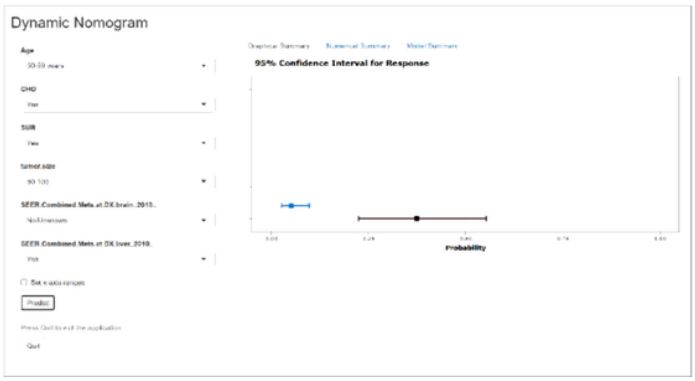
DCA curves for the nomogram of (A) training cohort early death and (B) validation cohort early death in the SEER database.

(A)



(B)

(C)



(D)

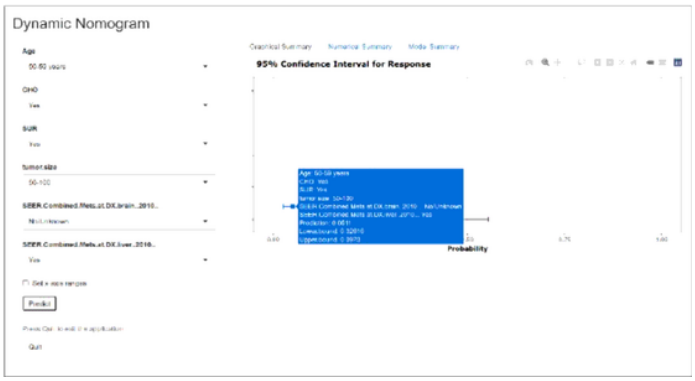


Figure 6

Probability of early postoperative death in a 55-year-old mTNBC patient with a primary tumor of 60 mm with liver metastases (A, B). Probability of early death after postoperative chemotherapy treatment in a 55-year-old mTNBC patient with a primary tumor of 60 mm with liver metastases (C, D).