Development and validation of a nomogram to predict survival after neoadjuvant chemotherapy in elderly women with triple-negative invasive ductal breast cancer

A SEER population-based study

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ABSTRACT

الأهداف: إنشاء والتحقق من مخطط بياني لتوقع البقاء على قيد الحياة بعد العلاج الكيميائي المساعد لدى النساء المسنات المصابات بسرطان الثدي القنوي الغازي الثلاثي السلبي.

المنهجية: أجرينا فحص للمرضى المسنين الذين تم تشخيصهم بسرطان الثدي القنوي الغازي الثلاثي السلبي خلال الفترة 2019م و 2000م من قاعدة بيانات المراقبة والوبائيات والنتائج النهائية. بناءً على الاستجابة المرضية بعد العلاج الكيميائي المساعد، تم تعيينهم في مجموعة الاستجابة الكاملة أو غير الكاملة. تمت مقارنة الخصائص السريرية المرضية بين المجموعات والبقاء على قيد الحياة الخاص بالمرض والإجمالي. ثم تم توزيعهم عشوائيًا في مجموعة التدريب أو التحقق. تم تطوير مخطط بياني للتنبؤ في مجموعة التدريب والتحقق منه في مجموعة التحقق.

النتائج: تم تضمين ما مجموعه 382 مريضًا، مع 285 مريضًا في مجموعة عدم الاستجابة و 97 مريضًا في مجموعة الاستجابة. بعد مطابقة درجة الميل، أظهر البقاء على قيد الحياة المحدد للمرض فرقًا كبيرًا بين مجموعات الاستجابة وعدم الاستجابة (88.7% مقابل 64.6%، $p<0.001$). شملت مجموعة التدريب 196 مريضًا وشملت مجموعة التحقق 82 مريضًا. تم دمج ما مجموعه 7 متغيرات (العمر والعرق وموقع الورم ومرحلة الورم والعقدة والنقائل والمرحلة الموجزة وتلقي الجراحة والاستجابة للعلاج الكيميائي المساعد) لبناء مخطط تنبؤ بالبقاء على قيد الحياة. كانت مؤشرات C 0.756 في مجموعة التدريب و 0.791 في مجموعة التحقق. في كلتا المجموعتين، أظهر البقاء على قيد الحياة المتوقع تماسكًا مرضيًا مع البقاء الفعلي في تحليل منحنى المعايرة.

الخلاصة: في النساء المسنات المصابات بسرطان الثدي القنوي الغازي السلبي الثلاثي، يمكن أن تشير الاستجابة الكاملة المرضية بعد العلاج الكيميائي المساعد إلى تحسن البقاء على قيد الحياة المحدد للمرض. تم إنشاء مخطط جديد للتنبؤ بالبقاء على قيد الحياة للحصول على أداء مرضي لهؤلاء المرضى

Objectives: To construct and verify a nomogram for post-neoadjuvant chemotherapy survival predication in elderly women with triple-negative invasive ductal breast cancer.

Methods: Elderly patients diagnosed as triple-negative invasive ductal breast cancer between 2019-2000 were screened from surveillance, epidemiology, and end results database. Depending on the post-neoadjuvant chemotherapy pathological response, they were assigned to the complete or non-complete response group. Inter-group clinicopathological characteristics and disease-specific and overall survivals were compared. Then, they were allocated randomly into the training or validation cohort. A prediction nomogram was developed in the training cohort and verified in the validation cohort.

Results: A total of 382 patients were included, with 285 patients in non-response group and 97 patients in response group. After propensity score matching, disease-specific survival showed a significant difference between response and non-response groups (88.7% versus 64.6%, $p<0.001$). The training cohort included 196 patients and the validation cohort included 82 patients. A total of 7 variables (age, race, tumor location, tumor-node-metastasis stage, summary stage, receipt of surgery, and response to neoadjuvant chemotherapy) were integrated to construct a survival prediction nomogram. The C-indexes were 0.756 in the training cohort and 0.791 in the validation cohort. In both cohorts, the predicted survival showed satisfactory coherence with the actual survival in the calibration curve analysis.

Conclusion: In elderly women with triple-negative invasive ductal breast cancer, post-neoadjuvant chemotherapy pathological complete response could indicate improved disease-specific survival. A novel survival prediction nomogram was created to have satisfactory performance in these patients.

Keywords: elderly patients, triple-negative breast cancer, invasive ductal carcinoma, neoadjuvant chemotherapy, nomogram, disease-specific survival

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Breast cancer is a global health concern.[1] Invasive ductal carcinoma represents a common type of breast cancer.[2] Approximately 31% of invasive breast cancers were diagnosed in patients more than 70 years old.[3] In this elderly population, up to 20% of breast cancers were triple-negative breast cancer (TNBC; negative for progesterone receptor, estrogen receptor, and human epidermal growth factor receptor 2).[4] Due to the aggressiveness and poor treatment response of TNBC, affected patients had high risks of cancer recurrence and metastasis and a poor prognosis.[5]

Neoadjuvant chemotherapy is a widely accepted treatment for breast cancer patients, which can effectively shrink the tumor mass, downgrade the cancer stage, improve surgical resectability, and eradicate micrometastases, thereby increasing the overall survival (OS) rate in these patients.[6] In the treatment guidelines published by the European Society of Breast Cancer Specialists and International Society of Geriatric Oncology, neoadjuvant chemotherapy was listed as a treatment option for elderly breast cancer patients.[7] However, the guidelines also stated that the neoadjuvant chemotherapy outcomes of TNBC in this patient population are controversial, and further studies are required. The selection of neoadjuvant chemotherapy should consider each patient's background, comorbidities, and health status.

Several survival prediction nomograms have been developed for breast cancer.[8-10] These nomograms were constructed to estimate patients' outcomes and make evidence-based decisions for individualized treatment. However, there are limited survival prediction analysis data in elderly patients with triple-negative invasive ductal breast cancer. The surveillance, epidemiology, and end results (SEER) database includes data on cancer patient demographics, characteristics, treatment strategies, and follow-up outcomes in the United States. It has been applied to develop different survival prediction models.[11,12] The SEER database gives us an opportunity to analyze the factors associated with treatment outcomes, which could be applied for the survival prediction in elderly patients with triple-negative invasive ductal breast cancer.

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Therefore, we carried out the current study to explore the SEER database and construct and verify a survival prediction nomogram in elderly women undergoing neoadjuvant chemotherapy for triple-negative invasive ductal breast cancer. Our aim was to provide evidence-based data for appropriate treatment selection and care in this patient population.

Methods. The research data were obtained from the SEER. The inclusion criteria were female gender, age ≥70 years, pathological diagnosis of TNBC from 2019-2000, and invasive ductal carcinoma as the histological type (ICD-O-3, 8500/3). Patients with insufficient data were not included in the current study.

The study protocol received the approval from the medical ethics committee of Tianjin People's Hospital, Tianjin, China (2024-B39). All procedures complied with the principles of the Helsinki declaration.

Patient age, race (White, Black, Asian or Pacific Islander, and American Indian/Alaska Native), tumor location (center, lower inner quadrant, upper inner quadrant, lower outer quadrant, upper outer quadrant, axillary tail, overlapping region, and unknown region), SEER summary stage (local involvement, distant metastasis, regional lymph node involvement, direct spread, and direct spread and regional lymph node involvement), tumor-node-metastasis (TNM) stages (I-IV), surgery, response to neoadjuvant chemotherapy, and disease-specific survival (DSS) and OS at the end of 1-, 3-, and 5-year periods were recorded. In addition, the response to neoadjuvant chemotherapy was recorded as pathological complete response (pCR) or non-pathological complete response (non-pCR).

Statistical analysis. The R software (version 4.2.3, R Foundation, Austria) was used for all the statistical analyses and figure creations. Patients were assigned into either the pCR or non-pCR group. After propensity score matching based on clinicopathological characteristics with significant inter-group differences, the independent relationships of pCR with DSS and OS were examined. The statistical significance was set at a p-value of <0.05.

All patients were allocated randomly into the training or validation cohort at a 7-to-3 ratio. The survival prediction nomogram was initially constructed in the training cohort, and then verified in the validation cohort. The area under the curve (AUC) and the concordance index (C-index) were applied to assess the nomogram to predict the survivals, with a higher AUC corresponding to better predictive accuracy. Finally, we examined the accuracy and clinical values of the nomogram by plotting calibration curves.

Results. In the SEER database, 351,485 elderly women with breast cancer were identified between 2019-2000. Of them, 15,609 patients had TNBC, and 12,506 had invasive ductal carcinoma. Finally, our study included 382 elderly women who received neoadjuvant chemotherapy to treat triple-negative invasive ductal carcinoma (Figure 1).

In total, 285 patients were assigned to the non-pCR group and 97 patients were assigned to pCR group. The age distribution, race, tumor location, surgery, and OS rate were comparable between the 2 groups. The SEER summary stage, TNM stage, and DSS significantly differed between these groups (Table 1). After propensity score matching by the SEER summary stage and TNM stage between 2 groups, the pCR group had a higher DSS rate than the non-pCR group (88.7% vs. 64.6%, $p<0.001$, Table 2).

There were 196 patients in the training cohort. The survival prediction nomogram is presented in Figure 2. The C-index was 0.756, suggesting its high accuracy to predict the survival. The 1-, 3-, and 5-year survivals were analyzed by the receiver operating characteristic curves (Figure 3). The AUC for predicting the one-year survival was 0.834 (95% confidence interval [CI]: [0.717-0.947]), AUC for predicting the 3-year survival was 0.796 (95% CI: [0.715-0.843]), and AUC for predicting the 5-year survival was 0.803 (95% CI: [0.731-0.850]). The 1-, 3-, and 5-year calibration curves of DSS exhibited satisfactory coherence between the predicted and actual results (Figure 4A-C).

There were 82 patients included in the validation cohort. The nomogram had a C-index of 0.791. In addition, the predicted and actual results demonstrated satisfactory coherence in the 1-, 3-, and 5-year calibration curves of DSS (Figure 4D-F). These findings suggested that the newly developed prediction nomogram could accurately predict the post-neoadjuvant chemotherapy survival status in elderly women with triple-negative invasive ductal breast cancer.

Discussion. In the clinic practice, TNBC presents as a great challenge because of its aggressive nature

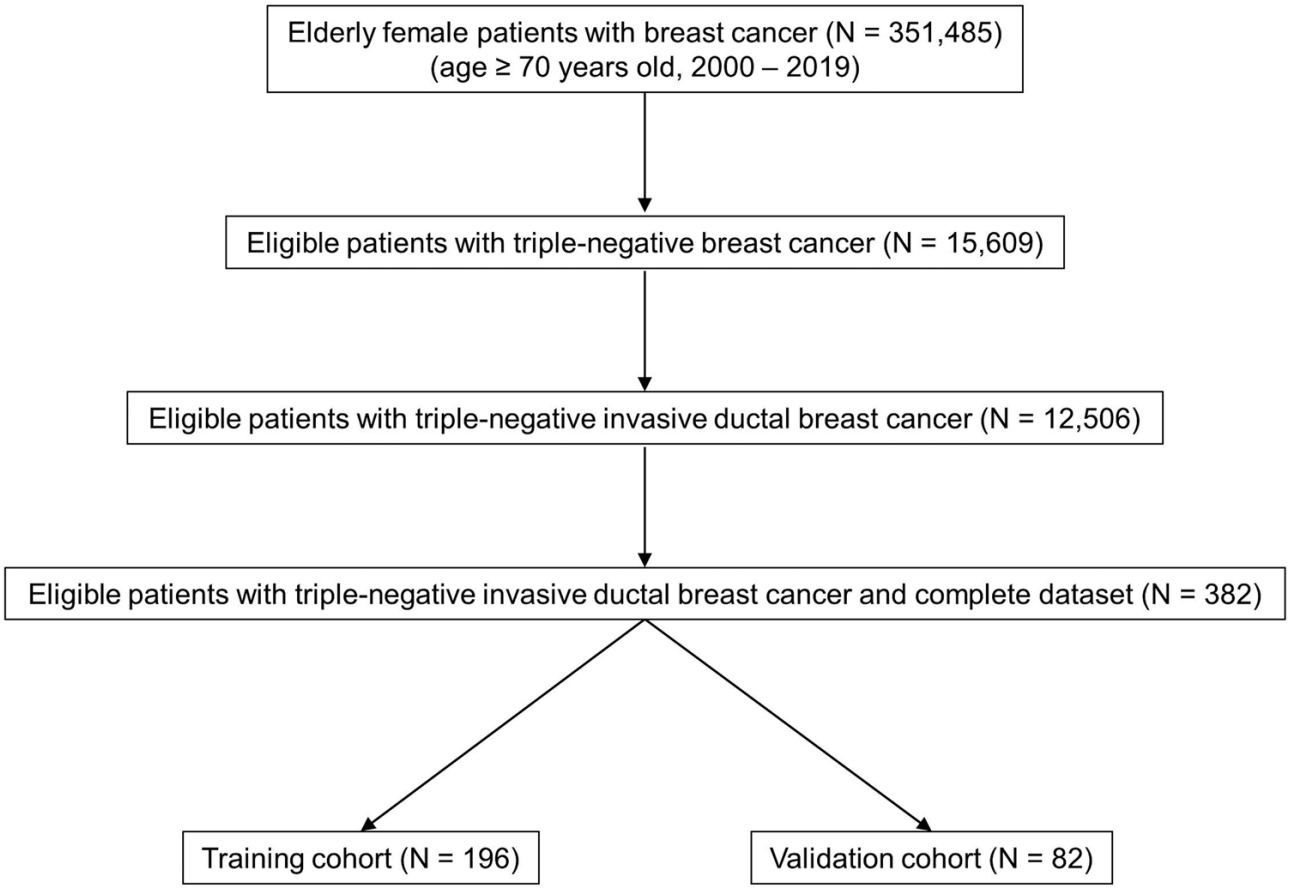

Figure 1 - Patient selection flowchart.

Table 1 - Comparisons of clinicopathological characteristics and survival between the non-pathological complete response and pathological complete response groups of elderly women with triple-negative invasive ductal breast cancer after neoadjuvant chemotherapy.

Characteristics	Non-pathological complete response (n=285)	Pathological complete response (n=97)	*P*-values
Age, years			
70-74	153 (53.7)	55 (56.7)	0.585
75-79	90 (31.6)	28 (28.9)	
80-84	25 (8.8)	11 (11.3)	
≥85	17 (6.0)	3 (3.0)	
Race			
White	197 (69.1)	73 (75.3)	0.751
Black	52 (18.2)	14 (14.4)	
Asian or Pacific Islander	30 (10.5)	9 (9.3)	
American Indian/Alaska Native	6 (2.1)	1 (1.0)	
SEER summary stage			
Local involvement	77 (27.0)	45 (46.4)	0.003
Direct spread	17 (6.0)	5 (5.2)	
Regional lymph node involvement	103 (36.1)	32 (33.0)	
Direct spread and regional lymph node involvement	58 (20.4)	12 (12.4)	
Distant metastasis	30 (10.5)	3 (3.1)	
TNM			
I	26 (9.1)	15 (15.5)	<0.001
II	114 (40.0)	57 (58.8)	
III	118 (41.4)	23 (23.7)	
IV	27 (9.4)	2 (2.1)	
Tumor location			
Center	16 (5.6)	4 (4.1)	0.481
Axillary tail	1 (0.4)	0 (0.0)	
Lower outer quadrant	25 (8.8)	6 (6.2)	
Upper outer quadrant	102 (35.8)	33 (34.0)	
Lower inner quadrant	13 (4.6)	11 (11.3)	
Upper inner quadrant	26 (9.1)	8 (8.2)	
Overlapping region	61 (21.4)	23 (23.7)	
Unknown region	41 (14.4)	12 (12.4)	
Surgery, yes	277 (97.2)	97 (100)	0.209
Disease-specific survival, yes	158 (55.4)	86 (88.7)	<0.001
Overall survival, yes	249 (87.4)	86 (88.7)	0.876

Values are presented as numbers and percentages (%). Statistical tests were either Chi-square test (all categories with % ≥5) or Fisher-Freeman-Halton test (for multiple categorical variables that did not satisfy Chi-square test conditions). SEER: surveillance, epidemiology, and end results, TNM: tumor, node, and metastasis

and poor response to treatment.[5] Because TNBC has no specific molecular target and it is insensitive to endocrine therapy, clinical treatment mainly relies on chemotherapy, although surgical resection and radiation can play a role in certain situations.[13] In this study, we focused on elderly women with triple-negative invasive ductal breast cancer who received the neoadjuvant chemotherapy. We extracted patient information from the SEER database and developed a nomogram that could accurately predict survival in this patient population.

Neoadjuvant chemotherapy is a commonly recommended approach to treat patients with TNBC to relieve clinical symptoms and extend survival. It has been increasingly used in patients with TNBC. Yang et al[14] constructed a nomogram based on the SEER database and showed that chemotherapy significantly reduced the cancer-specific mortality in elderly patients with breast cancer. Yin et al[11] also developed and validated a nomogram to predict survival in locally advanced breast cancer patients derived from the SEER database. This nomogram included age, marital status, tumor grade and type, TNM stage, and treatments (surgery, chemotherapy, and radiotherapy). Chemotherapy improved the survival chance in these patients. Wang et al[15] developed and validated a nomogram to predict breast cancer patient survival after chemoradiotherapy and surgery in SEER database together with the other 2 Chinese cohorts. The nomogram included race, location, positive reginal nodes, TNM stage, subtype, and grade, which showed an accurate performance to predict survivals. In addition, chemotherapy showed no significant negative effects on the cognitive function or quality of life in elderly patients, suggesting that chemotherapy is safe and suitable for elderly patients with breast cancer.[16]

Table 2 - Comparisons of survival after propensity score matching based on clinicopathological characteristics between the non-pathological complete response and pathological complete response groups of elderly women with triple-negative invasive ductal breast cancer after neoadjuvant chemotherapy.

Characteristics	Non-pathological complete response (n=181)	Pathological complete response (n=97)	*P*-values
Age, years			
70-74	104 (57.5)	55 (56.7)	0.638
75-79	53 (29.3)	28 (28.9)	
80-84	14 (7.7)	11 (11.3)	
≥85	10 (5.5)	3 (3.0)	
Race			
White	123 (68.0)	73 (75.3)	0.571
Black	31 (17.1)	14 (14.4)	
Asian or Pacific Islander	21 (11.6)	9 (9.3)	
American Indian/Alaska Native	6 (3.3)	1 (1.0)	
SEER summary stage			
Local involvement	77 (42.5)	45 (46.4)	0.988
Direct spread	10 (5.5)	5 (5.2)	
Regional lymph node involvement	64 (35.4)	32 (33.0)	
Direct spread and regional lymph node involvement	24 (13.3)	12 (12.4)	
Distant metastasis	6 (3.3)	3 (3.1)	
TNM			
I	24 (13.3)	15 (15.5)	0.961
II	107 (59.1)	57 (58.8)	
III	46 (25.4)	23 (23.7)	
IV	4 (2.2)	2 (2.1)	
Tumor location			
Center	8 (4.4)	4 (4.1)	0.643
Axillary tail	1 (0.5)	0 (0.0)	
Lower outer quadrant	20 (11.0)	6 (6.2)	
Upper outer quadrant	67 (37.0)	33 (34.0)	
Lower inner quadrant	11 (6.1)	11 (11.3)	
Upper inner quadrant	16 (8.8)	8 (8.2)	
Overlapping region	42 (23.2)	23 (23.7)	
Unknown region	16 (8.8)	12 (12.4)	
Surgery, yes	176 (97.2)	97 (100)	0.239
Disease-specific survival, yes	117 (64.6)	86 (88.7)	<0.001
Overall survival, yes	155 (85.6)	86 (88.7)	0.601

Values are presented as numbers and percentages (%). Statistical tests were either Chi-square test (all categories with % ≥5) or Fisher-Freeman-Halton test (for multiple categorical variables that did not satisfy Chi-square test conditions). SEER: surveillance, epidemiology, and end results, TNM: tumor, node, and metastasis

However, considering the unique physiological characteristics, underlying comorbidities, and short life expectancy of the elderly population, the accurate selection of appropriate neoadjuvant chemotherapy in elderly patients is highly desired.[17] The medication dosage might be decreased, and treatment-related side effects, such as cardiotoxicity, should be closely monitored. A robust prognostic marker could help clinicians select appropriate neoadjuvant chemotherapy in elderly patients, and such markers have rarely been reported in the literature.

During the breast cancer management, pCR is commonly applied to evaluate treatment responses because of its high prognostic significance.[18-20] In our cohort, 25.4% (97/382) of patients achieved pCR after neoadjuvant chemotherapy, which was lower than the rates reported previously in patients with TNBC over a wide range of ages (40-50%).[21] This could be attributable to the inclusion of elderly patients in our study, as reported previously.[22] Elderly patients commonly have multiple comorbidities, which can complicate their management. Most invasive ductal carcinomas in our study were also in advanced stages, which could have also contributed to the low pCR rate after neoadjuvant chemotherapy.[23]

Our study revealed that elderly patients with TNBC could have significantly improved DSS if they achieved pCR after neoadjuvant chemotherapy. This was consistent with previous findings in other age groups, different breast cancer subtypes, and different stages.[18,24,25] A meta-analysis reported that patients with TNBC and pCR could have a 76% reduced cancer progression and recurrence and an 81% reduced mortality. In addition, patients with TNBC who

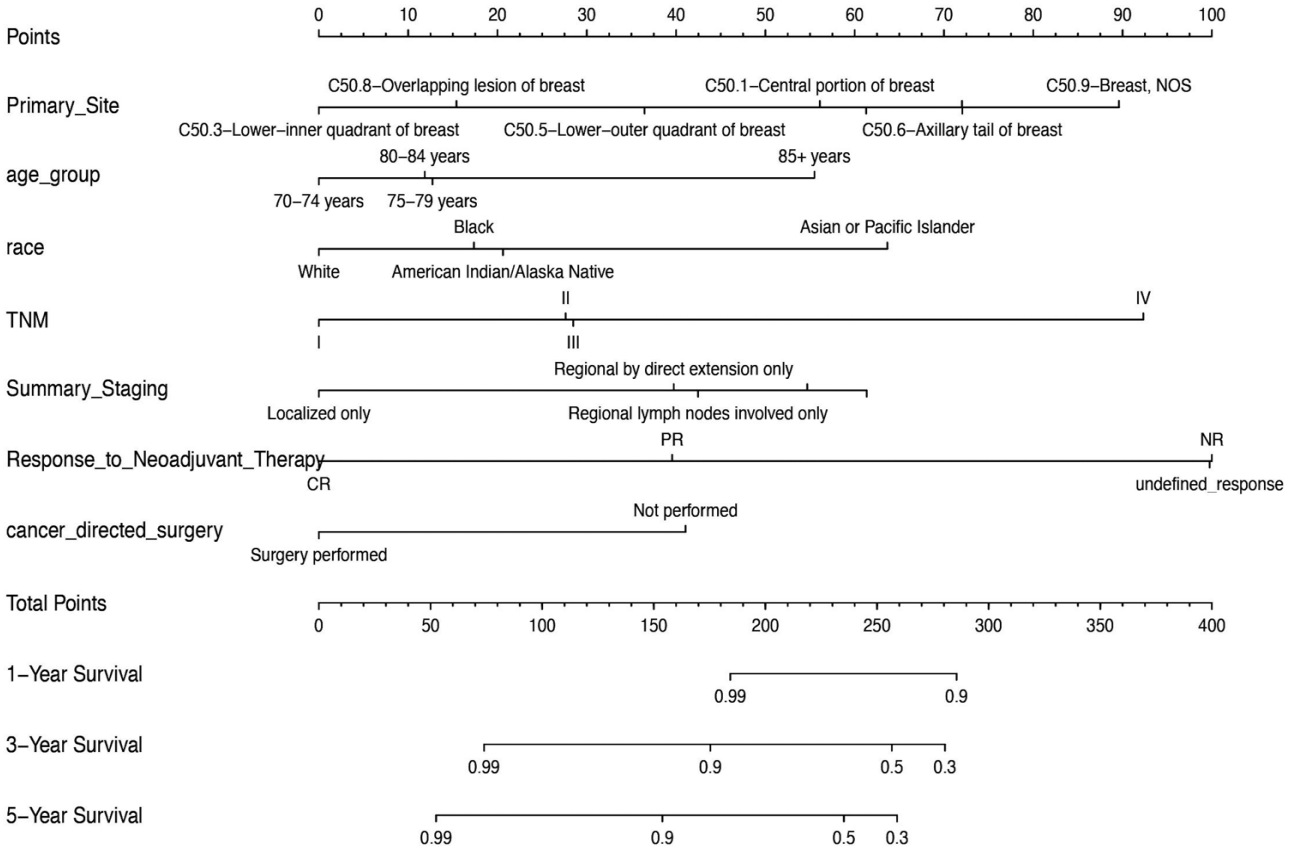

Figure 2 - Nomogram for 1-, 3-, and 5-year disease-specific survival in elderly women with triple-negative invasive ductal breast cancer after neoadjuvant chemotherapy in the training cohort. TNM: tumor, node, and metastasis, NOS: not otherwise specified, CR: complete response, PR: partial response, NR: no response

achieved post-neoadjuvant chemotherapy pCR had a 5-year DSS rate of approximately 90%, versus 57% in those with residual disease.[26] It should be noted that breast cancer patients with post-neoadjuvant chemotherapy pCR could still develop recurrent disease, probably because of residual tumor and the failure of neoadjuvant chemotherapy to eliminate micrometastases.[27] Patients with pCR still require close monitoring and follow-up.[28]

In our study, the SEER summary stage and tumor TNM stage significantly differed between the non-pCR versus pCR groups. The invasiveness of cancer is characterized as localized, regional, or distant. Approximately 67.0% patients in the non-pCR group were found to have local lymph node involvement or distant metastasis, whereas only 48.5% of patients in the pCR group had similar findings. Lymph node involvement and distant metastasis of cancer are associated with poor survival outcomes.[29] The tumor TNM stage is widely used to estimate survival and prognosis.[30] After performing propensity score matching, there was still a significant difference in the DSS between the non-pCR and pCR groups. Therefore, pCR after neoadjuvant chemotherapy could be used to predict DSS in elderly women with triple-negative invasive ductal breast cancer.

A recent SEER research reported survival prediction nomograms for patients with locally advanced breast cancer.[11] The nomograms included different cancer types and grades, as well as treatment strategies, in addition to age, race, gender, and cancer stages. The AUCs of the nomograms for 1-, 3-, and 5-year DSS ranged 0.6-0.9. In our cohort, the AUCs of the developed nomogram were approximately 0.8 when predicting the 1-, 3-, and 5-year survivals, suggesting inadequate discrimination for survival. However, the training cohort had the C-index of 0.756 and the validation cohort had the C-index of 0.791, indicating satisfactory ability of the nomogram to discriminate between survival and death. Further tests on the calibration curves revealed satisfactory coherence between the predicted and actual survival rates in the training and validation cohorts.

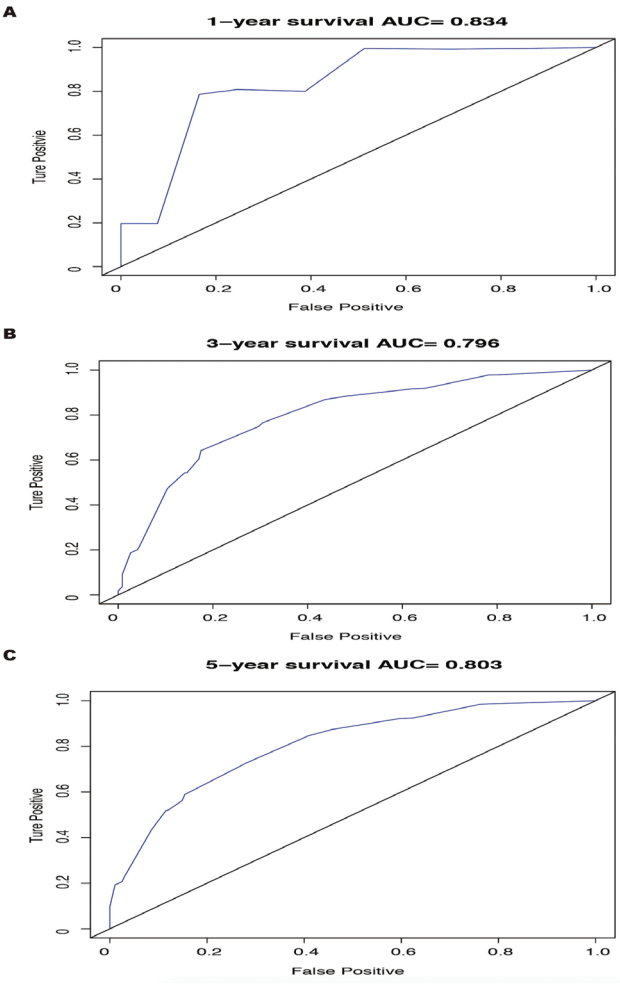

Figure 3 - The receiver operating characteristic (ROC) curves. **A)** one-year survival (the area under the curve was 0.834). **B)** 3-year survival (the area under the curve was 0.796). **C)** 5-year survival (the area under the curve was 0.803) in the training cohort. AUC: area under the curve

In addition, our nomogram model considered several variables that are easily obtained during routine clinical practice. Age is recorded for every patient. The tumor location and stages are evaluated in every patient with cancer before treatment. All of these findings suggested that our newly developed nomogram could have certain utility in clinical practice for predicting post- neoadjuvant chemotherapy survival in elderly women with triple-negative invasive ductal breast cancer. A high score in the nomogram corresponds to a low survival probability and poor prognosis. Patients who are considered to have a low probability of survival should receive additional adjuvant therapy, frequent clinical follow-ups, and early discussion regarding their expected life expectancy and palliative care. Further studies are required to refine this nomogram and improve its accuracy and prediction ability. For example, race and marital status might be considered in the nomogram. Racial disparities are well recognized as a factor in the response to cancer treatment.[31] Approximately 30% of Black women with breast cancer had TNBC.[32] An inadequate socioeconomic status, a lack of healthcare access, and comorbidities also place Black women at high risk for poor prognosis. Marital status was identified to be associated with prognosis in breast cancer patients.[33] Unmarried patients had a higher risk of mortality and lower survival rate than married patients, probably because of the poor social support and unhealthy lifestyle in the former group. A future nomogram including race and marital status might have improved differentiation ability and accuracy for survival prediction.

Study strength & limitations. The SEER database is a well-established authoritative real-world source for cancer statistics that has been used by many researchers for cancer research. The limitations of our study included retrospective data collection using the SEER database, which only includes information on patients in a single country (the United States). Patients in other regions might have different socioeconomical backgrounds or receive cancer treatments. Cancer survival could be impacted by many factors that might not be included in the SEER database. In addition, the elderly patients might die due to other causes, such as cardiovascular disease or infection, which was not reported in the SEER database.

In conclusion, in elderly women with triple-negative invasive ductal breast cancer, post-neoadjuvant chemotherapy pCR could indicate improved DSS. A survival prediction nomogram developed from the SEER database could be applied to assess the outcomes in this patient population. Future investigations are required to improve the accuracy and externally validate this nomogram.

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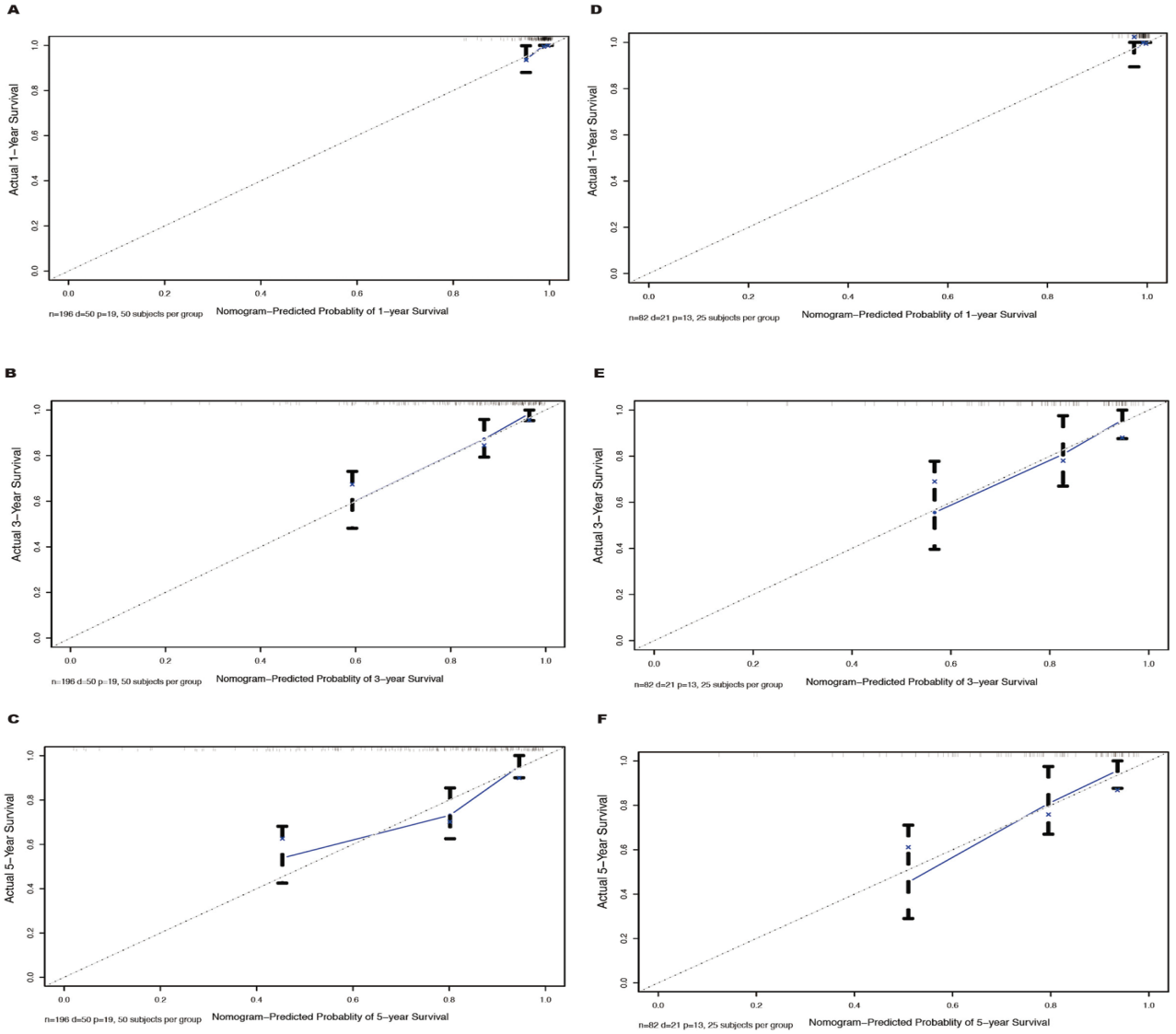

Figure 4 - Calibration curves. **A)** one-year disease-specific survival in the training cohort. **B)** 3-year disease-specific survival in the training cohort. **C)** 5-year disease-specific survival in the training cohort. **D)** one-year disease-specific survival in the validation cohort. **E)** 3-year disease-specific survival in the validation cohort. **F)** 5-year disease-specific survival the validation cohort.

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