

Nomogram for chemotherapy decision-making in patients with small triple-negative breast tumor: A population-based study

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Abstract

Purpose: Small triple-negative breast cancer (TNBC) without lymph node invasion is considered less aggressive. This study aimed to develop nomograms for deciding on the appropriateness of chemotherapy for these patients.

Methods: The data of patients diagnosed with T1abN0M0 TNBC between 2010 and 2016 were extracted from the Surveillance, Epidemiology, and End Results database. Clinicodemographic characteristics were integrated into nomograms for predicting overall survival (OS) and breast cancer-specific survival (BCSS). Nomogram performance was analyzed according to calibration and discrimination. The subpopulation treatment effect pattern plot (STEPP) was further applied to make individualized chemotherapeutic decisions.

Results: Overall, 3133 patients with T1abN0M0 TNBC were evaluated; they were divided equally into the training and validation cohorts. Most tumors were grade III (62.6%) and ductal carcinoma of no special type (88.8%). The median follow-up time was 44.0 months, and 133 patients (4.3%) died by the end of the follow-up. Eight independent prognostic factors, namely, age, race, marital status, tumor size, histology, grade, surgery, and chemotherapy, were identified and used in nomogram construction. The calibration curves showed satisfactory agreement between prediction and observation. The C-indices of the nomograms were significantly higher than those of traditional TNM staging (OS: 0.701 vs 0.503; BCSS: 0.691 vs 0.506). The patients in the training cohort were stratified into two risk groups based on the OS nomogram score cutoff (213), and the groups showed a significant difference in survival, as was further confirmed in the validation cohort. The STEPPs of 5-year OS according to the nomogram score demonstrated distinct patterns of absolute chemotherapeutic effect, with low-risk patients achieving better survival regardless of chemotherapy. In high-risk patients, a significant and consistent chemotherapeutic benefit was observed at the average of 3.7%.

Conclusion: At a cutoff score of ≥ 213 , the nomogram accurately identified TNBC patients likely to receive a survival benefit from chemotherapy.

Background

About 15–20% of newly diagnosed breast cancer cases are triple-negative breast cancer (TNBC). TNBC is characterized by negative expressions of estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) receptors and no amplification of the HER2 gene [1]. Compared with other subtypes, TNBC is often associated with more visceral metastases [2], higher risk of relapse [3], and shorter progression-free survival (PFS) and overall survival (OS) [4-6]. Small TNBC tumors often have good prognosis, especially T1abN0M0 tumors [7, 8]. Hence, the absolute value of adjuvant chemotherapy for patients with T1abN0M0 remains uncertain.

The National Comprehensive Cancer Network Version 3.2020 includes several guidelines for chemotherapy decision-making. For tumors ≤ 0.5 cm (T1a), adjuvant chemotherapy is not necessary,

while it may be generally beneficial for tumors measuring 0.6-1.0 cm (T1b). However, there are limited data for patients aged over 70 years and younger patients unable to tolerate commonly used treatment modalities [9]. The European Society of Medical Oncology recommends adjuvant chemotherapy for all pT1 stage tumors except those with certain low-risk histologic subtypes, such as secretory juvenile, apocrine, and adenoid cystic carcinomas [10]. The hesitation in recommending chemotherapy is because most studies focused on tumors ≥ 1.0 cm and/or with lymph node invasion, excluding patients with early stage tumors [11-15].

Several retrospective studies have evaluated the benefit of adjuvant chemotherapy for TNBC pT1N0M0 patients [9, 16-19]. A study of 264 patients with sub-centimetric TNBC tumors demonstrated improvement in distant-metastasis-free survival (DMFS) with chemotherapy within a median follow-up of 5.5 years. However, such DMFS benefit was not observed in another study of 284 patients with pT1abN0M0 TNBC over a 4-year median follow-up period. In a cohort of 354 consecutive Chinese TNBC patients, those with T1c disease, but not those with T1b disease, had better recurrence-free survival (RFS) after adjuvant chemotherapy with a median follow-up of 3.8 years. A recent real-world study of 4366 newly diagnosed TNBC patients showed that adjuvant chemotherapy was associated with better breast cancer-specific survival (BCSS) and overall survival (OS) in patients with pT1N0M0 tumors compared with their non-chemotherapeutic counterparts, with the chemotherapeutic benefit most evident in pT1c. Apparently, these conflicting findings failed to specify the predictive factors or models to tailor adjuvant chemotherapy for sub-centimetric TNBC tumors.

The present study evaluated data on T1abN0M0 TNBC obtained from a large population from the Surveillance, Epidemiology, and End Results (SEER) database. Nomograms predicting response to chemotherapy were created using multiple clinicopathological factors.

Methods

Study design and population

This study obtained data from the SEER database, which consists of data from 21 population-based cancer registries collected between 1975 and 2016. Data in the SEER database are representative of approximately 34.6% of the total US population. ASCII text version of the data was directly downloaded from the website (<https://seer.cancer.gov>).

We included female patients who had been pathologically diagnosed only with breast cancer in their lifetime. The inclusion criteria were age 18–90 years, TNBC subtype, tumor size ≤ 10 mm (T1a, b), N0M0 disease (American Joint Committee on Cancer [AJCC] 7th Edition), and tumor grade I–III. Patients diagnosed before 2010 were excluded due to the unavailability of data on their HER2 status. The other exclusion criteria were unknown age, histology, surgical treatment, chemotherapy use, or survival status. The patient inclusion flowchart is shown in Supplemental figure 1.

The need for informed consent was waived as data were collected from a publicly accessible source.

Nomogram construction

To establish competing-risks nomograms and validate their usefulness, the patients were equally and randomly divided into the training and validation cohorts. Patients were classified into three major groups based on race/ethnicity: white, black, and others (including American Indian/Alaskan Native and Asian/Pacific Islanders). The “not married” status included single (never married), separated, divorced, unmarried or with domestic partner, and widowed.

Validation and calibration of the nomograms

The nomograms were subjected to 1000 bootstrap resamples for internal validation of the training cohort and of the validation cohort per se. The concordance index (C-index) between predicted probability and response was used to assess the discrimination performance of the nomograms [20]. The value of the C-index theoretically ranges from 0.5 to 1.0, with 0.5 indicating a random chance and 1.0 indicating a perfectly corrected discrimination. Calibration is the capability of a model to make unbiased estimates of outcome. Marginal estimate versus average predictive probability of the models was used to construct calibration curves. The prediction was expected to fall on a 45-degree diagonal line in a well-calibrated model.

Survival stratification based on nomograms

In addition to using C-indices to numerically compare the discrimination capability, we also evaluated the independent discrimination capability of the nomogram. Using 50% as cutoff, we divided the patients in the training cohort into two risk groups according to the OS prediction score. This cutoff score was then applied to the validation cohort, and Kaplan-Meier survival curves were generated.

STEPP method

To investigate absolute treatment effect patterns across the continuum of nomogram scores, the nonparametric sliding-window subpopulation treatment effect pattern plot (STEPP) methodology was applied [21, 22]. STEPP improves precision in a smoothing-by-binning manner by constructing overlapping subpopulations [23].

Statistical analysis

OS was calculated from the date of diagnosis to the date of any-cause death or the last follow-up, whichever came first. BCSS was defined as the time interval from the date of diagnosis to the date of breast cancer death or the last follow-up. Deaths from other causes were regarded as competing risks, and such cases were censored at the date of the last follow-up. The cumulative incidence function was used to assess the probability of death. All univariate prognostic factors were compared using log-rank tests and entered into the multiple analysis via the Cox proportional hazards model. All significant variables, especially those associated with OS or with the cumulative incidences of breast cancer-related death, were adopted in the nomograms. The variables and the point assignment are listed in

Supplemental table 1. All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing. <http://www.r-project.org>). The R package rms was used for modeling and developing the nomograms [24]. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

In total, 3133 patients with pT1abN0M0 TNBC were enrolled in this study. The clinicodemographic patient characteristics are shown in Table 1. The median age was 62 years (range, 24-90 years), and most patients were white (75.9%) and married (59.4%). The median tumor size was 7 mm, and most tumors were classified as grade III (62.6%) and ductal carcinoma of no special type (88.8%). Most patients underwent breast-conserving surgery (BCS, 71.5%), and approximately half the cohort was administered chemotherapy (CT, 49.4%) and radiotherapy (RAD, 59.0%). The median follow-up time was 44.0 months (interquartile range, 26.0–62.0 months). By the end of the last follow-up, 133 patients (4.3%) had died, of which 72 (2.3%) died from breast cancer and 61 (2.0%) died from other causes.

Table 1. Patient characteristics (n=3133)

Characteristics	Total population	Training cohort	Validation cohort
	3133 (100)	1566 (50.0)	1567 (50.0)
Age at diagnosis, years			
18–39	107 (3.4)	55 (3.5)	52 (3.3)
40–49	411 (13.1)	200 (12.8)	211 (13.5)
50–59	813 (25.9)	405 (25.9)	408 (26.0)
60–69	998 (31.9)	499 (31.9)	499 (31.8)
70–79	605 (19.3)	294 (18.8)	311 (19.8)
80–90	199 (6.4)	113 (7.2)	86 (5.5)
Race			
White	2377 (75.9)	1198 (76.5)	1179 (75.2)
Black	518 (16.5)	251 (16.0)	267 (17.0)
Others ^a	225 (7.2)	113 (7.2)	112 (7.1)
Unknown	13 (0.4)	4 (0.3)	9 (0.6)
Marital status at diagnosis			
Not married ^b	1120 (35.7)	567 (36.2)	553 (35.3)
Married	1862 (59.4)	916 (58.5)	946 (60.4)
Unknown	151 (4.8)	83 (5.3)	68 (4.3)
CS tumor size (mm)			
[1,4]	629 (20.1)	317 (20.2)	312 (19.9)
[5,6]	643 (20.5)	319 (20.4)	324 (20.7)
[7,8]	841 (26.8)	419 (26.8)	422 (26.9)
[9,10]	1020 (32.6)	511 (32.6)	509 (32.5)
Histology			
Ductal carcinoma, NST	2781 (88.8)	1386 (88.5)	1395 (89.0)
Other ductal and lobular neoplasms	200 (6.4)	103 (6.6)	97 (6.2)
Others	151 (4.8)	77 (4.9)	74 (4.7)
Grade			
I	184 (5.9)	99 (6.3)	85 (5.4)

II	988 (31.5)	499 (31.9)	489 (31.2)
III	1961 (62.6)	968 (61.8)	993 (63.4)
Surgery of the primary site ^e			
BCS	2240 (71.5)	1121 (71.6)	1119 (71.4)
CPM	140 (4.5)	65 (4.2)	75 (4.8)
Other mastectomies	753 (24.0)	380 (24.3)	373 (23.8)
CT ^f			
No	1585 (50.6)	822 (52.5)	763 (48.7)
Yes	1548 (49.4)	744 (47.5)	804 (51.3)
RAD ^g			
No	1178 (37.6)	594 (37.9)	584 (37.3)
Yes	1848 (59.0)	927 (59.2)	921 (58.8)
Unknown	107 (3.4)	45 (2.9)	62 (4.0)

^aOther races include American Indian/AK Native, Asian/Pacific Islander.

^bNot married includes single (never married), separated, divorced, unmarried or with a domestic partner, and widowed.

Data are presented as no. of patients (%).

Abbreviations: NST, no special type; BCS, breast-conserving surgery; CPM, contralateral prophylactic mastectomy; CT, chemotherapy; RAD, radiation therapy

Overall survival

The results of the univariate and multiple regression analyses in the training cohort based on a Cox proportional-hazards model are presented in Supplemental tables 2 and 3. Several variables, including age (≥ 70 years, hazard ratio, HR = 2.42, $P < 0.001$), surgery (mastectomies other than contralateral prophylactic mastectomy [CPM] HR = 2.00, $P = 0.008$), and chemotherapy (HR = 0.52, $P = 0.016$), showed a significant correlation with OS. All significant factors were then included in multiple regression models, and age (≥ 70 years HR = 1.99, $P = 0.023$), marital status (married HR = 0.64, $P = 0.049$), tumor size (every 1 mm increase: HR = 1.14, $P = 0.024$), and surgery (mastectomies other than CPM HR = 2.43, $P = 0.026$) were identified as independent factors.

Breast cancer-specific survival

The results of univariate and multiple regression analyses of BCSS, along with estimates of probabilities of death resulting from breast cancer, are listed in Supplemental tables 2, 3, and 4. In univariate analysis, surgery (CPM: HR = 3.62, $P = 0.041$; mastectomies other than CPM: HR = 3.07, $P = 0.001$) significantly correlated with BCSS. All factors were then subjected to multiple regression analysis. As expected, surgery remained significantly associated with BCSS (CPM: HR = 9.19, $P = 0.004$; mastectomies other than CPM: HR = 6.23, $P < 0.001$).

Overall, the 3- and 5-year probabilities of death from breast cancer were .02 and .03 (Supplemental table 4). Consistent with regression analyses, surgery remained significantly associated with breast cancer-specific death; CPM had the highest incidence (5-year rate: 0.09), whereas breast-conserving surgery had the lowest incidence (5-year rate: 0.02).

Nomogram validity

Nomograms and their point assignment are presented in Figure 1 and Supplemental table 1. Tumor size, histology, grade, and surgery were included in both nomograms, while age, marital status, and CT were applied solely for OS. In the OS nomogram, surgery (CPM: 78) exhibited the strongest influence, followed by age (66) and tumor size (11 for every 1 mm increase). In contrast, surgery remained the most significant factor influencing BCSS (CPM: 100). By adding all points and locating them on the bottom scales, we could calculate the estimated 3- and 5-year survival probabilities.

Calibration and validation of the nomograms

The calibration plots for the OS and BCSS nomograms in the training cohort and validation cohort are shown in Figure 2 and Supplemental figure 2. Most mean predicted values and their 95% confidence intervals covered the actual survival rate, further indicating concordance between the predicted and observed survival. Harrell's C-indices of the OS and BCSS nomograms were 0.702 [standard error (SE): 0.034] and 0.680 (SE: 0.045), respectively, in the validation cohort. These were similar to those of the training cohort: 0.701 (SE: 0.024) for OS and 0.691 (SE: 0.031) for BCSS. All C-indices were higher than 0.680, indicating that these two nomograms were satisfactorily accurate and suitable for prognosis prediction. In addition, these values significantly exceeded those of the traditional TNM staging system (OS: 0.503 (SE: 0.007), $P < 0.001$; BCSS: 0.506 (SE: 0.011), $P < 0.001$), as indicated by 99.7% of the patients having stage IA disease following the AJCC 7th Edition guidelines.

Application of the nomogram in identifying patients for chemotherapy

To further assess the usefulness of the nomograms in identifying patients who will benefit from adjuvant chemotherapy, we calculated the OS prediction scores for patients in the training cohort. A 50% cutoff was used to divide them into two risk groups (low risk: < 213 ; high risk: ≥ 213). The risk score was significantly associated with survival in both the training cohort (OS: HR= 0.34, 95% CI=0.197-0.863, $P < 0.001$; BCSS: HR= 0.49, 95% CI=0.24-0.99, $P = 0.043$) (Figure 3A and B) and the validation cohort (OS: HR= 0.29, 95% CI=0.15-0.73, $P < 0.001$; BCSS: HR= 0.47, 95% CI=0.23-0.97, $P = 0.040$) (Figures 3C and D). The

high-risk group showed lower 5-year OS (93.06% vs 97.03%) and BCSS (96.98% vs 98.70%) than the low-risk group.

The STEPPs of the 5-year OS according to the nomogram prediction score demonstrated distinct patterns of absolute chemotherapeutic effect (Figure 4). In the low-risk patients, the 5-year OS was 98.0% independent of chemotherapy administration ($P = 0.840$ in the training cohort and $P = 0.900$ in the validation cohort, Figure 4A and C). There was no apparent pattern across the prediction score spectrum, further indicating no clinically relevant improvement in 5-year OS with respect to chemotherapy. For high-risk patients who did not receive chemotherapy, the 5-year OS was 91.8%. A consistent benefit of chemotherapy was evident across the continuum of prediction scores ($P < 0.001$ in both the training and validation cohorts, Figure 4B and D). With the average survival benefit being 3.7%, the pattern of treatment effect according to prediction score distribution was also noticeable. Among subpopulations with the highest prediction score, the smallest absolute improvement of survival from chemotherapy was 2%. Meanwhile, the chemotherapeutic absolute improvement reached 6.5% in subpopulations with approximately 250 points, and patients administered chemotherapy achieved a median 5-year OS of 95% (Figure 4B). Similar chemotherapeutic effects in high-risk patients in the validation cohort were observed (Figure 4D).

To confirm the effect of chemotherapy, we delineated OS and BCSS curves for each prediction score category in both cohorts (Figure 5 and Supplemental figure 3). As expected, chemotherapy did not improve the OS and BCSS (HR = 1.07, $P = 0.911$ for both; all deaths were breast cancer specific) in low-risk patients (Figure 5A and C). In contrast, chemotherapy significantly improved the OS (HR = 2.10, 95% CI = 1.08-8.21, $P = 0.032$) and BCSS (HR = 2.96, 95% CI = 1.23-7.77, $P = 0.028$) in high-risk patients (Figure 5B and D). The association between chemotherapy and survival was further verified in the validation cohort (low-risk group: OS: HR = 0.83, 95% CI = 0.28-2.49, $P = 0.743$; BCSS: HR = 0.64, 95% CI = 0.17-2.49, $P = 0.521$ [Supplemental figure 3A and C]; high-risk group: OS: HR = 1.94, 95% CI = 1.05-3.62, $P = 0.040$; BCSS: HR = 2.71, 95% CI = 1.18-6.17, $P = 0.019$ [Supplemental figure 3B and D]).

We further evaluated the relationship between T1a/b classification and nomogram score categorization. Although T1b patients have generally higher risks than T1a patients (Supplemental table 5, $P < 0.001$), approximately half of them (46.6%) were classified into the low-risk category according to our nomogram score cutoff. This indicated that chemotherapy may not be necessary. However, a significant proportion of pT1a patients (42.0%) were included in the high-risk subgroup. Thus, we subdivided the T1a and T1b patients according to the OS score cutoff (213) and analyzed survival differences associated with chemotherapy (Figure 6, Supplemental figure 4). Patients with a low score did not have an OS benefit from chemotherapy regardless of tumor size (T1a: HR = 1.28, 95% CI = 0.26-6.35, $P = 0.762$; T1 HR = 0.766, 95% CI = 0.29-2.05, $P = 0.595$ [Figure 6A and C]). However, both T1a and T1b high-risk patients showed a significant OS benefit from chemotherapy (T1a: HR = 7.25, 95% CI = 1.01-53.57, $P = 0.050$; T1b: HR = 1.94, 95% CI = 1.18-3.19, $P = 0.009$ [Figure 6B and D]). Similar trends were observed in the BCSS analyses (Supplemental figure 4). Collectively, nomogram score categorization, which combined tumor

size with other clinicopathologic characteristics, could better identify patients who are likely to benefit from chemotherapy compared with the traditional T1a/b classification.

Discussion

Previous studies in untreated sub-centimetric TNBC patients reported a 5-year disease-free survival (DFS) of 80–90%, suggesting that certain pT1ab TNBC patients have a high risk for recurrence and/or metastasis [14, 15]. This highlights the necessity of providing adjuvant chemotherapy for such patients. However, there is no clear guideline on selecting patients with pT1abN0M0 TNBC who are likely to benefit from adjuvant chemotherapy. In this study, we established a novel clinical model to identify patients with pT1abN0M0 TNBC who have high risk of recurrence/metastasis. Those with a higher risk score had significantly worse OS and BCSS and derived a significant survival benefit from adjuvant chemotherapy.

Traditionally, the patients' clinicopathological characteristics (e.g., age; comorbidity; and tumor biology, including tumor grade, histological subtype, lymphatic vessel invasion [LVI], and stromal tumor-infiltrating lymphocytes), are used to evaluate the risk of recurrence/metastasis. The same characteristics are considered in the recommendation for adjuvant chemotherapy. However, it is difficult to accurately determine the risk for each patient. Although gene signature is an alternative tool, it currently cannot aid in determining the need for adjuvant chemotherapy for patients with pT1abN0M0 TNBC because no prospective analysis of available gene assays (e.g., 21-gene assay (Oncotype Dx) and MammaPrint) has included such patients [25, 26]. Hence, it is difficult for physicians to identify the patients with a high metastatic potential based on clinical and biological data alone. Thus, STEPP analysis based on nomogram score was included in the present study. The nomograms showed satisfactory C-indices that significantly exceeded those of the traditional TNM staging system. This proves that in addition to tumor size, a combination of clinicopathologic factors including age, race, marital status, histology, grade, surgery, and chemotherapy could improve the prediction of outcomes for patients with T1abN0M0 tumors. High-risk patients (i.e., those with nomogram scores above 213) were found to have a significant OS and BCSS benefit from chemotherapy.

Tumor size is an important prognostic factor in cancer. It was initially believed that large mammary tumors develop their metastatic capability through an accumulation of gene mutations. However, several studies have shown that certain small tumors also have strong metastatic capability, challenging this theory [27, 28]. The heterogeneity of cancer gives a reasonable explanation for such contradictory findings. It is well-known that TNBC is a heterogeneous disease, exhibiting highly diverse and unsatisfactory outcomes. In this study, 42.0% of pT1a patients were included in the high-risk group, while approximately half of the pT1b patients were categorized into the low-risk group that had better prognosis.

Previous retrospective studies have evaluated the effect of adjuvant chemotherapy on small node-negative breast cancer including TNBC and other subtypes [16-19, 29]. Despite some conflicting findings, these studies unanimously recommended adjuvant chemotherapy for pT1c, partially for pT1b, and never

for pT1a. Better outcome of adjuvant chemotherapy for small breast cancer seems to be associated with the tumor size. In the current study, pT1b patients had generally higher risks than pT1a patients. However, we also found that nearly half of the low-risk pT1b patients did not benefit from adjuvant chemotherapy. Meanwhile, 42.0% of the high-risk pT1a patients had a prognostic benefit from chemotherapy.

This study has some limitations. First, both the training and validation sets were from SEER database because we could not obtain appropriately sized external data. Our findings need to be validated in another external data set incorporating more diverse populations, such as younger patients. Second, to ensure the accuracy of the pathological diagnosis of TNBC, the patients diagnosed before 2010 were excluded in the analysis, resulting in a shorter follow-up time and inability of the model to reflect longer prognosis. Fortunately, the risk of recurrence/metastasis has been verified to be significantly lower in TNBC than in other subtypes, 5 years after surgery. Third, other prognostic factors (e.g., Ki-67 index and LVI) that may have influenced the treatment decision were not reviewed due to lack the information in the database. Fourth, the data on DFS was not obtained due to database restrictions. Despite these limitations, we were able to evaluate the effect of adjuvant chemotherapy in the largest cohort study to date on pT1abN0M0 TNBC. Therefore, our study likely represents the current best available real-world evidence. Other strengths of this study are the detailed clinical and outcome data for BCSS and OS based on nomograms and the STEPP analyses. Our cohort involved 3133 patients with sub-centimetric node-negative TNBC, which allowed us to perform a stratified analysis and validation test. Further, by adopting the STEPP methodology to investigate absolute chemotherapeutic effect across the nomogram score spectrum, our results will be valuable toward an individualized approach to breast cancer treatment, with the nomogram being helpful for the selection of high-risk patients and the accurate recommendation for adjuvant chemotherapy.

Conclusion

We constructed and validated nomograms for prognostic prediction in TNBC patients with pT1abN0M0 stage disease. By applying the STEPP methodology, we identified high-risk patients who could potentially benefit from chemotherapy. Our data can be helpful for balancing the risk–benefit ratio, avoiding unnecessary treatment costs, designing future clinical trials, and increasing patient adherence to the prescribed treatment plan.

List Of Abbreviations

TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2. SEER, the Surveillance, Epidemiology, and End Results database; OS, overall survival; BCSS, breast cancer-specific survival; PFS, progression-free survival; DMFS, distant-metastasis-free survival; DFS, disease-free survival; STEPP, the subpopulation treatment effect pattern plot; C-index, concordance index; SE, standard error; HR, hazard ratio; LVI, lymphatic vessel invasion; BCS, breast-conserving surgery; CPM, contralateral prophylactic mastectomy; CT, chemotherapy; RAD, radiotherapy.

Declarations

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- **Competing interests:** The authors declare that there are no competing interests.
- **Availability of data and materials:** The dataset supporting the conclusions of this article is available in the Surveillance, Epidemiology, and End Results (SEER) database, [<https://seer.cancer.gov>].
- **Code availability:** Not applicable.
- **Authors' contributions:** Conception and design: Z.H. Tao, X.C. Hu. Development of methodology: X.Y. Chen, Y.L. Shao, X. Liu. Analysis and interpretation of data: X.Y. Chen, Y.L. Shao, Z.H. Tao, X. Liu. Writing, review and revision of the manuscript: X.Y. Chen, Y.L. Shao, X. Liu, Z.H. Tao, X.C. Hu, J. Zhang, W.X Zhi.
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Supplementary Material

Supplementary Material is not provided in this version.

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Figures

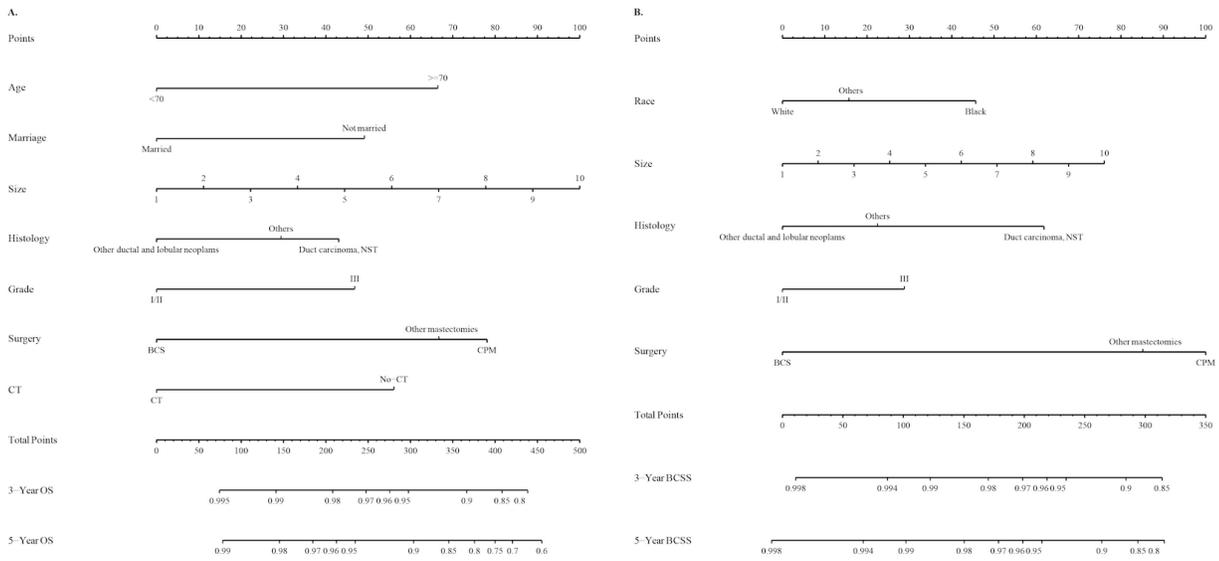


Figure 1

Nomograms for predicting 3- and 5-year survival probabilities in T1abN0M0 TNBC. (A) OS, (B) BCSS. We drew a vertical line from the variable value to the “Points” axis to determine the point for each variable. After adding up all points, the total points are added to the bottom scales to identify the 3- and 5-year survival probabilities. OS, Overall survival; BCSS, breast cancer-specific survival; NST, no special type; BCS, breast-conserving surgery; CPM, contralateral prophylactic mastectomy; CT, chemotherapy

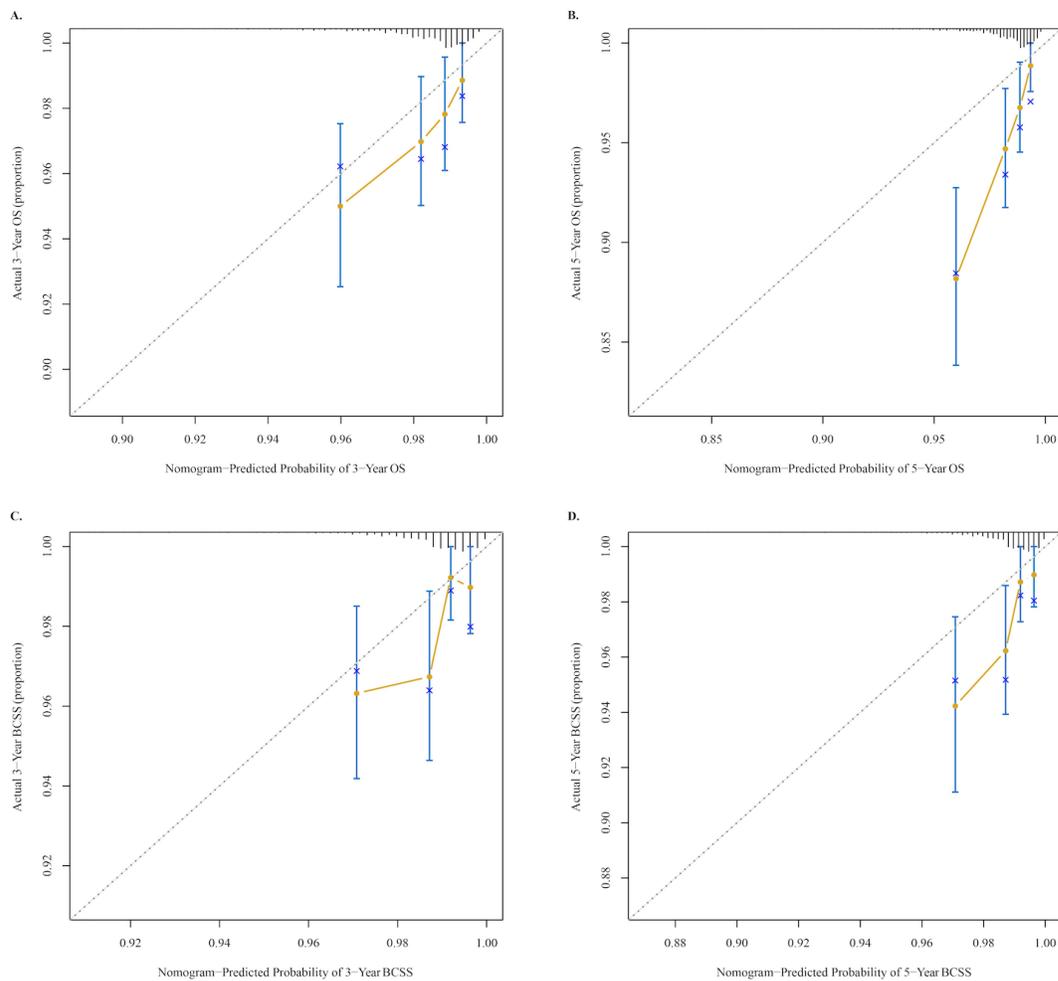


Figure 2

Calibration curves for predicting survival in the training cohort. The (A) 3-year and (B) 5-year OS and the (C) 3-year and (D) 5-year BCSS. Nomogram-predicted probability of survival is plotted on the x-axis, while actual survival is on the y-axis. Vertical bars indicate 95% CIs measured using the Kaplan-Meier method. Orange dots indicate the mean predicted value. The dashed 45-degree diagonal lines through the origin point represent the perfect calibration model. OS, overall survival; BCSS, breast cancer-specific survival; CI, confidence interval

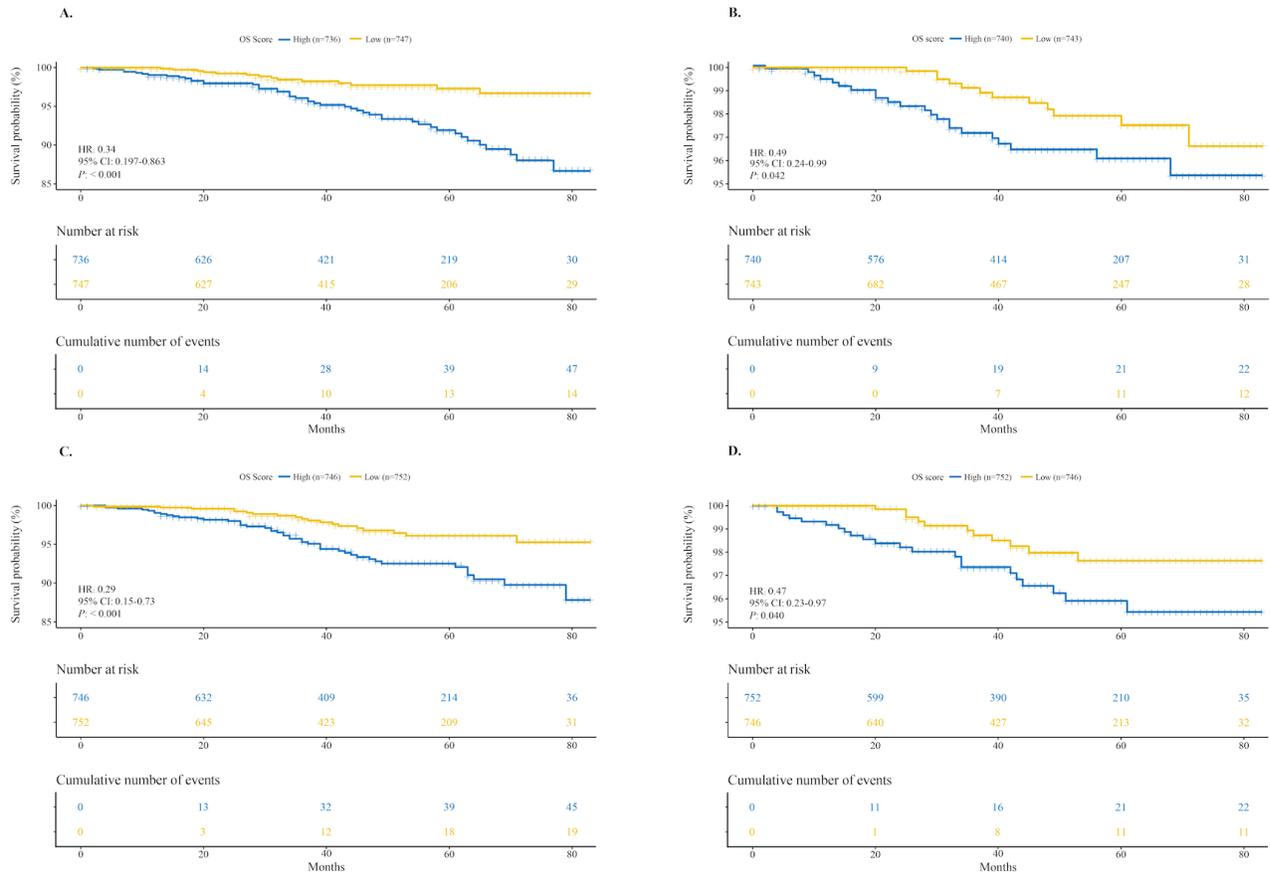


Figure 3

Comparison of OS by nomogram risk stratification. The (A) OS and (B) BCSS of the training cohort and the (C) OS and (D) BCSS of the validation cohort. OS, overall survival; BCSS, breast cancer-specific survival

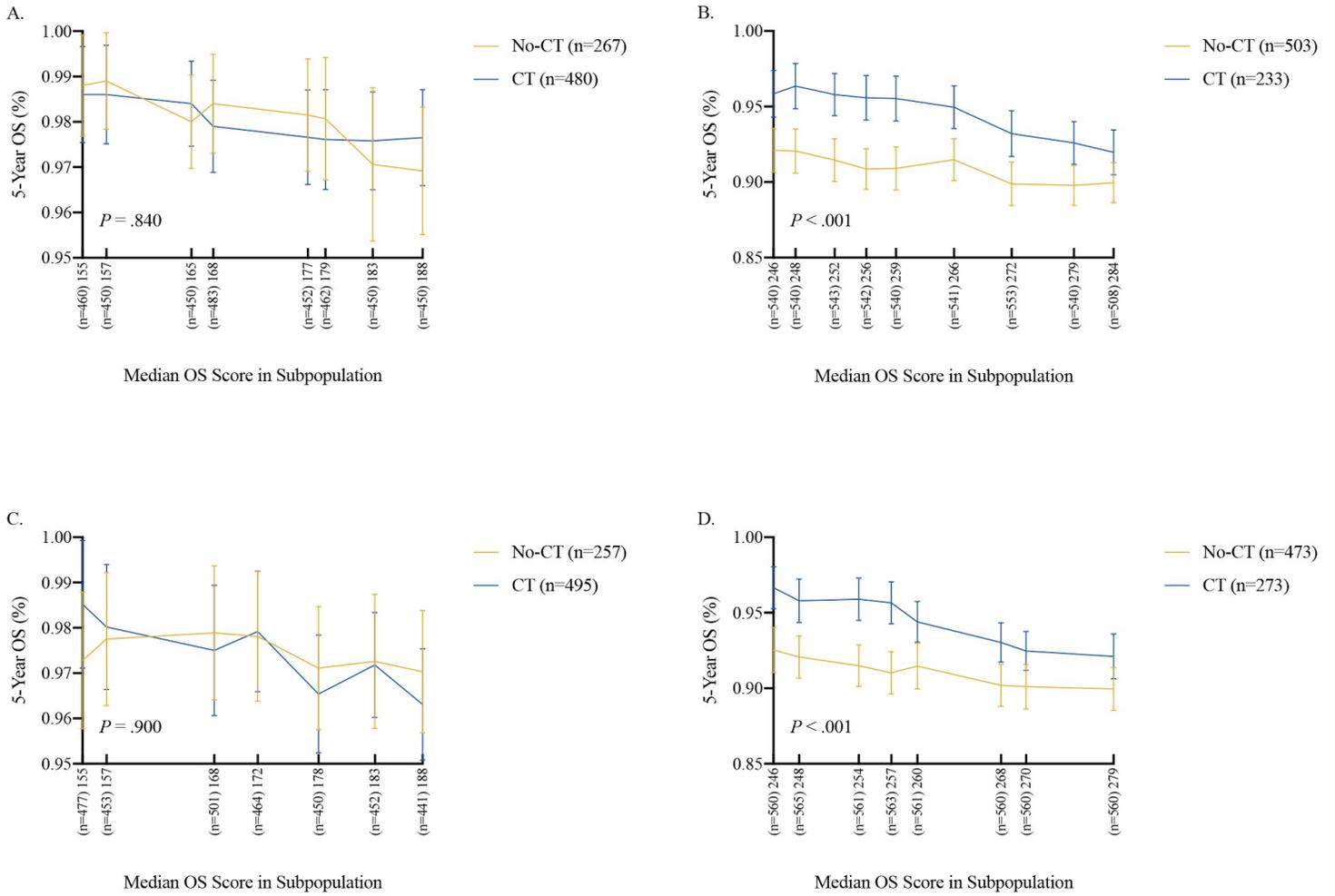


Figure 4

STEPP of 5-year OS defined by chemotherapy. The (A) low-risk and (B) high-risk patients in the training cohort and the (C) low-risk and (D) high-risk patients in the validation cohort. STEPP, the subpopulation treatment effect pattern plot; OS, overall survival; CT, chemotherapy.

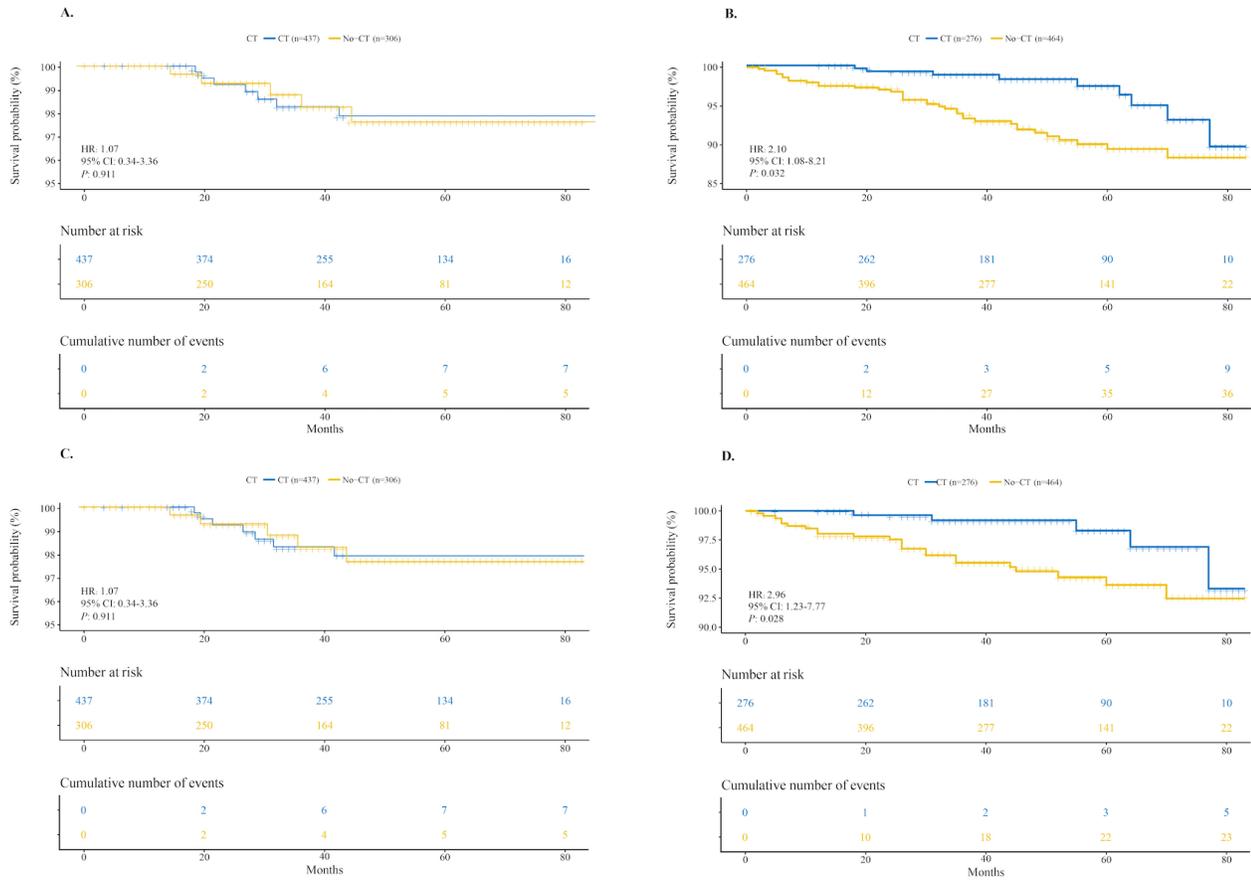


Figure 5

Comparison of survival by chemotherapy status in the training cohort. OS of the (A) low-risk and (B) high-risk patients and the BCSS of the (C) low-risk and (D) high-risk patients. OS, overall survival; BCSS, breast cancer-specific survival; CT, chemotherapy

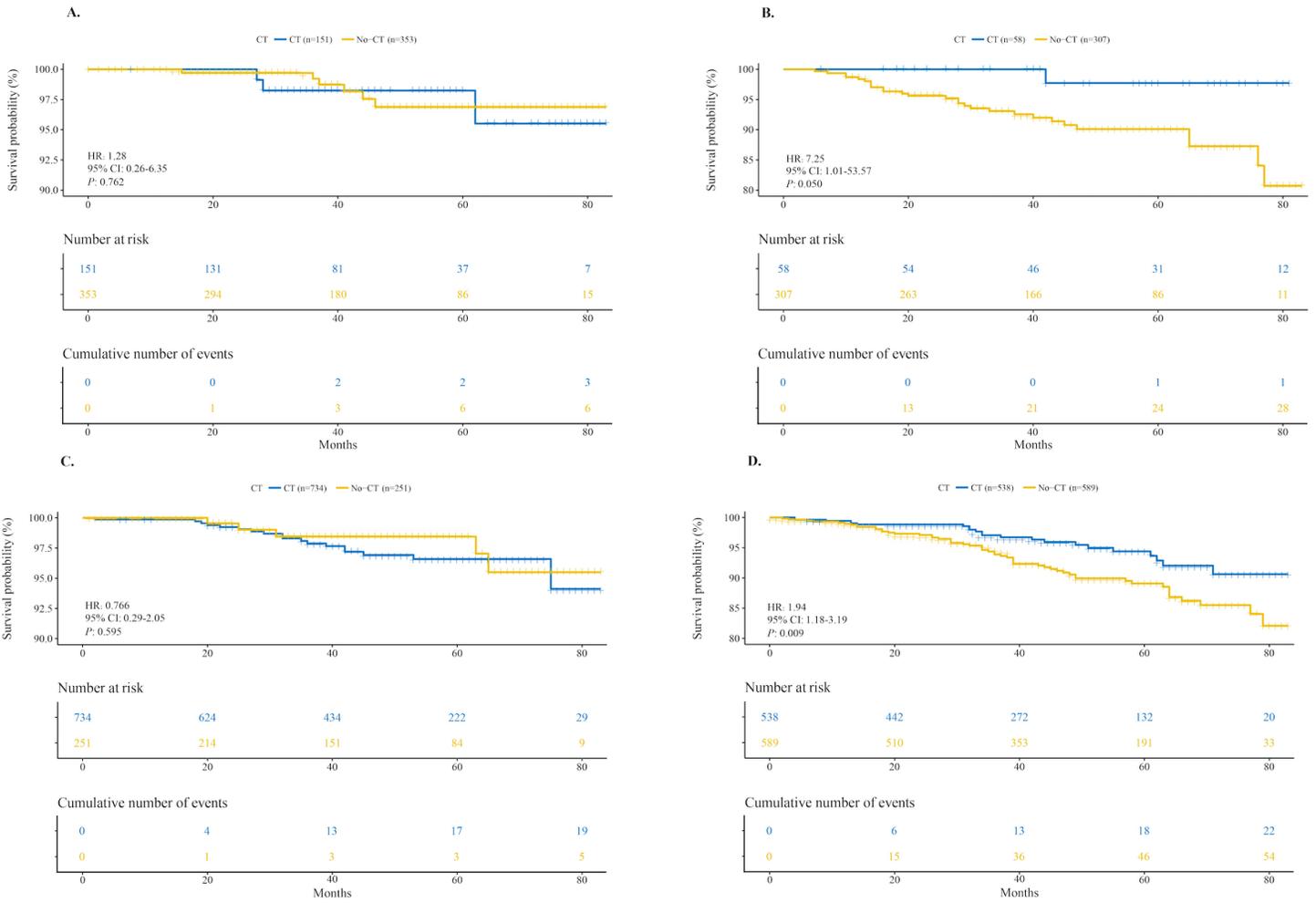


Figure 6

Comparison of OS by chemotherapy status in the nomogram score subgroups of pT1a/b. The (A) low-risk and (B) high-risk pT1a patients and the (C) low-risk and (D) high-risk pT1b patients. OS, overall survival; CT, chemotherapy