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Development and validation of a nomogram for predicting taxane-based chemotherapy-induced peripheral neuropathy in patients with breast cancer: a two-center study

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Abstract:

Taxane-based chemotherapy is a standard treatment for breast cancer but is frequently associated with moderate-to-severe chemotherapy-induced peripheral neuropathy (CIPN), which may necessitate dose reductions or treatment discontinuation. Given the limited efficacy of available interventions, early identification of patients at high risk of CIPN is essential. A total of 355 patients with breast cancer receiving taxane-based chemotherapy were enrolled in this two-center study, comprising a training cohort of 243 patients and an external validation cohort of 112 patients. Least absolute shrinkage and selection operator (LASSO) regression and multivariable logistic regression were used to identify independent predictors and develop a nomogram. Model performance was evaluated in terms of discrimination, as measured by the area under the receiver operating characteristic curve (AUC), calibration, assessed using the Brier score, and clinical utility, evaluated by decision curve analysis (DCA). Five independent predictors were identified: history of diabetes, exercise habits, taxane type, body mass index, and age. The nomogram demonstrated good discriminatory performance, with AUCs of 0.835 (95% CI: 0.777–0.887) in the training cohort and 0.832 (95% CI:

0.741–0.911) in the external validation cohort. Calibration was satisfactory, with a Brier score of 0.146 and a calibration slope of 0.95, while DCA demonstrated the model's potential clinical utility. In conclusion, this nomogram provides an effective tool for predicting moderate-to-severe CIPN in patients with breast cancer receiving taxane-based chemotherapy, facilitating early risk stratification and informing personalized prevention and management strategies.

Keywords: Taxane; Chemotherapy-induced peripheral neuropathy; Nomogram; Predictive model; Breast cancer;

1. Introduction:

Taxane-based chemotherapy is a cornerstone of breast cancer treatment. Taxanes are used in the neoadjuvant and adjuvant settings for patients with early-stage operable breast cancer, as well as in the treatment of patients with advanced breast cancer. However, numerous studies have demonstrated that taxane-based chemotherapy is associated with a substantial risk of chemotherapy-induced peripheral neuropathy (CIPN). [1,2] Patients with breast cancer who develop CIPN may experience a range of symptoms affecting the sensory, motor, and autonomic nervous systems, with varying degrees of severity. Despite extensive research, no clearly effective pharmacological interventions are currently available for the treatment of CIPN.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 classifies the severity of CIPN into five grades. Grade 1 is characterized by mild symptoms without functional impairment. In grade 2 or higher,

patients begin to experience limitations in instrumental activities of daily living, such as writing or buttoning actions. Higher grades indicate more severe symptoms, with grade 5 representing death. Mild CIPN may gradually resolve after the completion of chemotherapy. However, moderate-to-severe neuropathy (grade ≥2) may involve more pronounced symptoms and persist for an extended period. The incidence of grade ≥2 CIPN ranges from 18% to 56% and frequently necessitates dose reduction or even treatment discontinuation, thereby adversely affecting patient survival and increasing the risk of recurrence.[1]

Given the substantial symptom burden associated with moderate-to-severe CIPN and the limited treatment options available, early risk identification and proactive management are particularly essential. Therefore, identifying patients at high risk of developing moderate-to-severe CIPN and implementing preventive interventions are of considerable clinical importance. Our study aimed to develop and validate a predictive model for grade ≥2 CIPN in patients with breast cancer receiving taxane-based chemotherapy, thereby providing evidence to inform individualized prevention and management strategies.

2. Material and methods:

2.1 Study Population

Clinical data were collected from 243 patients with breast cancer who received chemotherapy at the Breast Oncology Unit, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, between January 2024 and April 2025. These patients comprised the training cohort for model

development. LASSO regression and multivariable logistic regression were used to identify predictors and construct a nomogram (n=243). An additional 112 patients with breast cancer who received chemotherapy at Renmin Hospital of Wuhan University between April 2025 and December 2025 were included in the external validation cohort to evaluate the model's performance (n=112) (Figure 1). Patients in both cohorts were classified into CIPN and non-CIPN groups according to the occurrence of CIPN.

2.2 Inclusion and Exclusion Criteria

The following inclusion criteria as follows: (1) nonpregnant, nonlactating female patients aged >20 years with a pathologically confirmed diagnosis of any histological subtype of breast cancer; (2) patients with no prior history of chemotherapy who were receiving taxane-based chemotherapy for the first time in an adjuvant or neoadjuvant setting; and (3) a chemotherapy regimen administered every three weeks, with completion of at least two consecutive cycles.

The following exclusion criteria as follows: (1) the presence of pre-existing peripheral neuropathy at baseline, clinical evidence of brain metastases or other severe metastases that may cause disease-related neuropathy, or an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score >2; (2) the concurrent use of other agents clearly associated with CIPN, such as platinum compounds; and (3) the presence of communication or cognitive impairments.

2.3 Assessment of CIPN

The EORTC QLQ-CIPN20 is a commonly used patient-reported outcome measure for assessing CIPN-related clinical symptoms. This scale comprises 20 items evaluating three dimensions, including sensory neuropathy, motor neuropathy, and autonomic neuropathy. In our study, the presence of neuropathy was assessed using the EORTC QLQ-CIPN20, and the severity of symptoms was graded according to the NCI-CTCAE version 5.0. Neuropathy data were obtained through web-based or onsite questionnaires. Each item on the EORTC QLQ-CIPN20 was scored from 1 (not at all) to 4 (very much), and the scores were transformed to a 0–100 scale, with higher scores representing more complaints (item 20 was excluded because all participants were female). A CIPN-positive status was defined as a total scale score ≥1.[3] The time point of CIPN onset was recorded, and severity was further assessed by using the NCI-CTCAE version 5.0, with a focus on the incidence of grade ≥2 CIPN.

2.4 Data Collection

Clinical data were collected from the hospitals' electronic medical record system or via web-based questionnaires, including (1) general characteristics such as age, body mass index (BMI), body surface area (BSA), history of hypertension, history of diabetes and physical activity; (2) treatment-related data such as ECOG-PS score, tumor stage, taxane-containing chemotherapy regimen (including AC-T, TAC, TC, and T), type of taxane (including nab-paclitaxel, liposomal paclitaxel, and docetaxel), occurrence of grade ≥2 nonhematologic adverse events after the first chemotherapy cycle (AE-early), dose reduction after the second cycle (Dose-reduce), number of taxane-containing chemotherapy cycles completed before CIPN onset,

concurrent use of targeted therapy or immunotherapy, and vitamin B6/B12 use; and (3) laboratory parameters such as hemoglobin (Hb), albumin (ALB), total bilirubin (Tbil), γ-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides (TG), total cholesterol (TCh), creatinine clearance (CRcl), and glucose (Glu) levels. Data were collected before CIPN occurred. A total of 456 questionnaires were received. After excluding invalid responses, data from 355 patients were included in the final analysis. All of the cases were rigorously screened according to the inclusion and exclusion criteria, and the data were double-checked before being entered into Microsoft Excel to ensure accuracy.

2.5 Statistical Analysis

Statistical analyses were performed using Python (version 3.13.5). Data management was conducted using pandas (version 2.2.3) and NumPy (version 2.3.5). Baseline comparability between the training cohort (n=243) and validation cohort (n=112), univariate analyses of CIPN risk factors, and other inferential analyses were implemented using SciPy (version 1.17.0) and statsmodels (version 0.14.6). Correlations among variables were evaluated using correlation matrices. To address multicollinearity and reduce model overfitting, Lasso regression was implemented using scikit-learn (version 1.8.0) after predictor standardization, with 10-fold cross-validation used for variable selection. Variables identified via Lasso regression were subsequently entered into multivariate logistic regression, with significant predictors ($P<0.05$) selected for inclusion in the clinical prediction model. The final logistic regression model was fitted using statsmodels, and the nomogram was

generated directly from the fitted model coefficients. Model discrimination was assessed using receiver operating characteristic (ROC) curves and the area under the curve (AUC) in both the training and validation cohorts; 95% confidence intervals for AUCs were estimated using 3,000 stratified bootstrap resamples. Calibration in the external validation cohort was assessed by comparing predicted and observed probabilities across 10 approximately equal-frequency risk groups (m=10), together with a locally weighted (LOWESS) calibration curve. The Brier score, calibration intercept, and calibration slope were calculated to quantify calibration performance. Decision curve analysis was performed to assess clinical utility, with net benefit prevalence-standardized assuming a population prevalence of 0.30 over threshold probabilities from 0.01 to 0.80. Figures were generated using Matplotlib (version 3.10.8). A P value <0.05 was considered to indicate statistical significance.

2.6 Ethics statement

This research was conducted in line with the Declaration of Helsinki (as revised in 2013). Union Hosipital, Tongji Medical College, Huazhong University of Science and Technology Ethics Committee (Ethical Code No: 【2023】 Lun Shen Zi (0562)) and Clinical Research Ethic Committee, Renmin Hospital of Wuhan University (Ethical Code No: WDRY2025-K097) approved the study protocol. All patients provided informed consent.

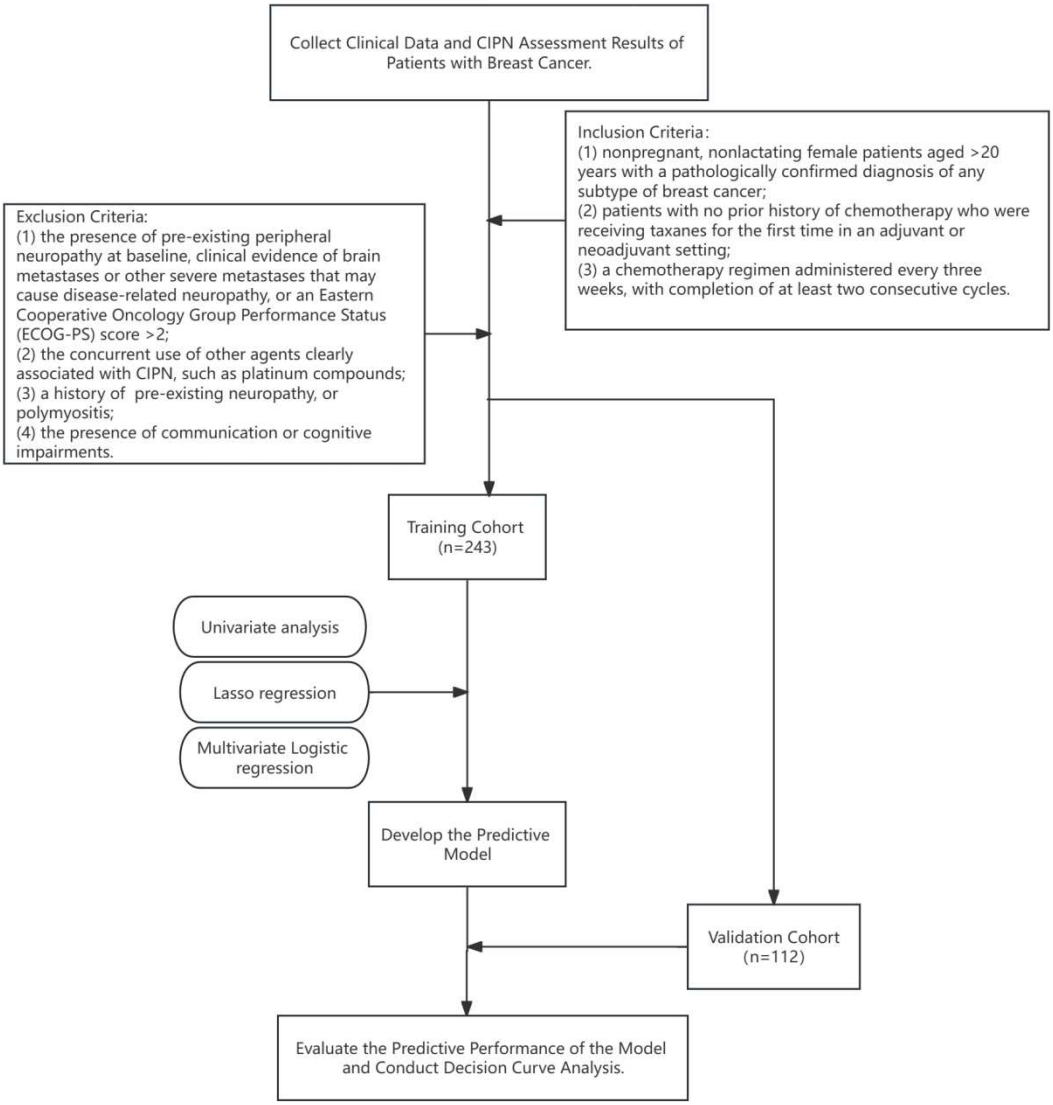


Figure 1. Flow diagram of the Study.

3. Results:

3.1 Comparison of Baseline Characteristics Between the Training and Validation Cohorts

The training cohort comprised 243 patients, including 82 patients (34%) with moderate-to-severe CIPN (grade ≥2). The validation cohort comprised 112 patients, including 41 patients (37%) with moderate-to-severe CIPN. There were no statistically significant differences observed in baseline characteristics between the two cohorts(P >

0.05), except for age, indicating that the cohorts were generally comparable (Table 1).

Table 1. Baseline characteristics of the total cohort and the training and external validation cohorts.

Variable	Total (n=355)	Training cohort (n=243)	External validation (n=112)	P value
Diagnosis, n (%)				0.684
No	232 (65)	161 (66)	71 (63)	
Yes	123 (35)	82 (34)	41 (37)	
Age, Median (Q1,Q3)	48 (42, 57)	49 (43, 57)	48 (39.75, 53.5)	0.031
BMI, Median (Q1,Q3)	21.42 (19.18, 24.39)	21.56 (19.09, 24.33)	21.34 (20, 24.55)	0.498
BSA, Median (Q1,Q3)	1.53 (1.44, 1.64)	1.54 (1.44, 1.65)	1.53 (1.44, 1.64)	0.750
Exercise habits, n (%)				0.926
No	250 (70)	172 (71)	78 (70)	
Yes	105 (30)	71 (29)	34 (30)	
Hypertension, n (%)				0.621
No	294 (83)	198 (81)	96 (86)	
Yes	61 (17)	45 (18)	16 (14)	
Diabetes, n (%)				0.354
No	247 (70)	173 (71)	74 (66)	
<5 years	64 (18)	44 (18)	20 (18)	
≥5years	44 (12)	26 (11)	18 (16)	
ECOG-PS, n (%)				0.443
<2	205 (58)	137 (56)	68 (60)	
2	150 (42)	106 (44)	44 (40)	
TNM stage, n (%)				0.173
1	67 (19)	40 (16)	27 (24)	
2	176 (50)	127 (52)	49 (44)	
3	112 (32)	76 (31)	36 (32)	
Chemotherapy regimen, n (%)				0.967
AC-T	178 (50)	121 (50)	57 (51)	
TAC	106 (30)	72 (30)	34 (30)	
TC	25 (7)	17 (7)	8 (7)	
T	46 (13)	33 (14)	13 (12)	
Taxane categorization, n (%)				0.242
liposomal paclitaxel	167 (47)	109 (45)	58 (52)	

Variable	Total (n=355)	Training cohort (n=243)	External validation (n=112)	P value
nab-paclitaxel	95 (27)	64 (26)	31 (28)	
docetaxel	93 (26)	70 (29)	23 (20)	
Targeted therapy, n (%)				0.836
No	264 (74)	182 (75)	82 (73)	
Yes	91 (26)	61 (25)	30 (27)	
Immunotherapy, n (%)				0.982
No	312 (88)	213 (88)	99 (88)	
Yes	43 (12)	30 (12)	13 (12)	
Vitamin B, n (%)				0.440
No	242 (68)	162 (67)	80 (71)	
Yes	113 (32)	81 (33)	32 (29)	
AE-early, n (%)				0.824
No	176 (50)	119 (49)	57 (51)	
Yes	179 (50)	124 (51)	55 (49)	
Early dose reduction, n (%)				0.623
No	220 (62)	148 (61)	72 (64)	
Yes	135 (38)	95 (39)	40 (36)	
Hb, n (%)				0.954
≤ ULN	210 (59)	143 (59)	67 (60)	
> ULN	145 (41)	100 (41)	45 (40)	
ALB, Median (Q1,Q3)	42.14 (38.77, 46.05)	42.57 (38.94, 46.14)	41.81 (38.28, 45.7)	0.193
Tbil, Median (Q1,Q3)	19.42 (17.22, 21.75)	19.42 (17.13, 21.81)	19.45 (17.34, 21.7)	0.700
AST, n (%)				0.376
≤ 2 × ULN	280 (79)	188 (77)	92 (82)	
> 2 × ULN	75 (21)	55 (23)	20 (18)	
ALT, n (%)				0.176
≤ 2 × ULN	302 (85)	202 (83)	100 (89)	
> 2 × ULN	53 (15)	41 (17)	12 (11)	
GGT, n (%)				0.273
≤ 2 × ULN	291 (82)	195 (80)	96 (86)	
> 2 × ULN	64 (18)	48 (20)	16 (14)	
TG, Median (Q1,Q3)	1.36 (0.99, 1.68)	1.37 (0.98, 1.68)	1.31 (1.01, 1.64)	0.771
TCh, Median (Q1,Q3)	4.81 (4.19, 5.78)	4.84 (4.26, 5.84)	4.69 (3.97, 5.6)	0.107
CRcl, Median (Q1,Q3)	84.94 (70.75, 100.81)	84.86 (70.75, 99.87)	85.13 (71.52, 104.01)	0.563

Variable	Total (n=355)	Training cohort (n=243)	External validation (n=112)	P value
Glu, Median (Q1,Q3)	5.25 (4.39, 6.07)	5.3 (4.44, 6.08)	5.14 (4.2, 5.96)	0.310

Note: Data are presented as n (%) or median (Q1, Q3), as indicated. P values compare the training and external validation cohorts. Abbreviations: BMI, body mass index; BSA, body surface area; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; AE, adverse event; Hb, hemoglobin; ALB, albumin; Tbil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; TG, triglycerides; TCh, total cholesterol; CRcl, creatinine clearance; Glu, glucose; ULN, upper limit of normal.

3.2 Independent Risk Factors for CIPN

Univariate analysis was performed between the CIPN group and non-CIPN group in the training cohort (Table 2). According to the threshold of $P < 0.05$, seven variables showed statistically significant differences: Age; BMI; history of diabetes; Taxane type; AE Early; Dose Reduction Early; Tbil. Subsequently, ROC curves were plotted, and the area under the curve (AUC) was calculated for each variable (Figure 2). Lasso regression was employed to mitigate multicollinearity. Using the lambda.min criterion, 13 characteristic variables were selected from 26 candidate variables: age, type of taxane, history of diabetes, exercise habits, BMI, history of hypertension, AE-early, relative dose intensity, Tbil, TCh, TG, CRcl, and GGT. Using the lambda.1SE criterion, four variables were selected: age, type of taxane, history of diabetes, and exercise habits (Figure 3).

Table 2. Univariate comparison of candidate predictors between the non-CIPN and CIPN groups in the training cohort.

Variable	Total (n=243)	Non-CIPN (n=161)	CIPN (n=82)	P value
Age, Median (Q1,Q3)	49 (43, 57)	47 (42, 55)	52 (47, 60)	<0.001
BMI, Median (Q1,Q3)	21.56 (19.09, 24.33)	20.92 (18.66, 23.69)	22.69 (20.52, 25.8)	<0.001
BSA, Median (Q1,Q3)	1.54 (1.44, 1.65)	1.53 (1.44, 1.65)	1.56 (1.44, 1.64)	0.706
Hypertension, n (%)				0.247
No	198 (81)	135 (84)	63 (77)	

Variable	Total (n=243)	Non-CIPN (n=161)	CIPN (n=82)	P value
Yes	45 (19)	26 (16)	19 (23)	
Diabetes, n (%)				<0.001
No	173 (71)	131 (81)	42 (51)	
<5 years	44 (18)	26 (16)	18 (22)	
≥5years	26 (11)	4 (2)	22 (27)	
ECOG-PS, n (%)				0.116
<2	137 (56)	95 (59)	42 (51)	
2	106 (44)	66 (41)	40 (49)	
TNM stage, n (%)				0.674
1	40 (16)	27 (17)	13 (16)	
2	127 (52)	81 (50)	46 (56)	
3	76 (31)	53 (33)	23 (28)	
Chemotherapy regimen, n (%)				0.862
AC-T	121 (50)	78 (48)	43 (52)	
TAC	72 (30)	50 (31)	22 (27)	
TC	17 (7)	12 (7)	5 (6)	
T	33 (14)	21 (13)	12 (15)	
Taxane categorization, n (%)				<0.001
liposomal paclitaxel	109 (45)	96 (60)	13 (16)	
nab-paclitaxel	64 (26)	31 (19)	33 (40)	
docetaxel	70 (29)	34 (21)	36 (44)	
Targeted therapy, n (%)				0.514
No	182 (75)	118 (73)	64 (78)	
Yes	61 (25)	43 (27)	18 (22)	
Immunotherapy, n (%)				0.877
No	213 (88)	142 (88)	71 (87)	
Yes	30 (12)	19 (12)	11 (13)	
Vitamin B, n (%)				1.000
No	162 (67)	107 (66)	55 (67)	
Yes	81 (33)	54 (34)	27 (33)	
AE-early, n (%)				0.038
No	119 (49)	87 (54)	32 (39)	
Yes	124 (51)	74 (46)	50 (61)	

Variable	Total (n=243)	Non-CIPN (n=161)	CIPN (n=82)	P value
Early dose reduction, n (%)				0.039
No	148 (61)	106 (66)	42 (51)	
Yes	95 (39)	55 (34)	40 (49)	
Hb, n (%)				0.242
≤ ULN	143 (59)	90 (56)	53 (65)	
> ULN	100 (41)	71 (44)	29 (35)	
ALB, Median (Q1,Q3)	42.57 (38.94, 46.14)	42.7 (38.77, 46.56)	42.23 (39.45, 45.64)	0.554
Tbil, Median (Q1,Q3)	19.42 (17.13, 21.81)	19.66 (17.53, 22.08)	18.39 (16.7, 21.36)	0.033
AST, n (%)				0.529
≤ 2 × ULN	188 (77)	127 (79)	61 (74)	
> 2 × ULN	55 (23)	34 (21)	21 (26)	
ALT, n (%)				0.629
≤ 2 × ULN	202 (83)	132 (82)	70 (85)	
> 2 × ULN	41 (17)	29 (18)	12 (15)	
GGT, n (%)				0.109
≤ 2 × ULN	195 (80)	124 (77)	71 (87)	
> 2 × ULN	48 (20)	37 (23)	11 (13)	
TCh, Mean ± SD	5.02 ± 1.14	5.05 ± 1.02	4.95 ± 1.37	0.579
CRcl, Median (Q1,Q3)	84.86 (70.75, 99.87)	84.86 (70.43, 100.06)	84.88 (72.63, 99.6)	0.935
Glu, Median (Q1,Q3)	5.3 (4.44, 6.08)	5.2 (4.4, 6.01)	5.5 (4.72, 6.13)	0.130
TG, Median (Q1,Q3)	1.37 (0.98, 1.68)	1.34 (0.97, 1.56)	1.41 (1.01, 1.74)	0.174

Note: Data are presented as n (%), median (Q1, Q3), or mean ± SD, as indicated. P values are from univariate between-group comparisons in the training cohort. Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; BMI, body mass index; BSA, body surface area; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; AE, adverse event; Hb, hemoglobin; ALB, albumin; Tbil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; TCh, total cholesterol; CRcl, creatinine clearance; Glu, glucose; TG, triglycerides; ULN, upper limit of normal.

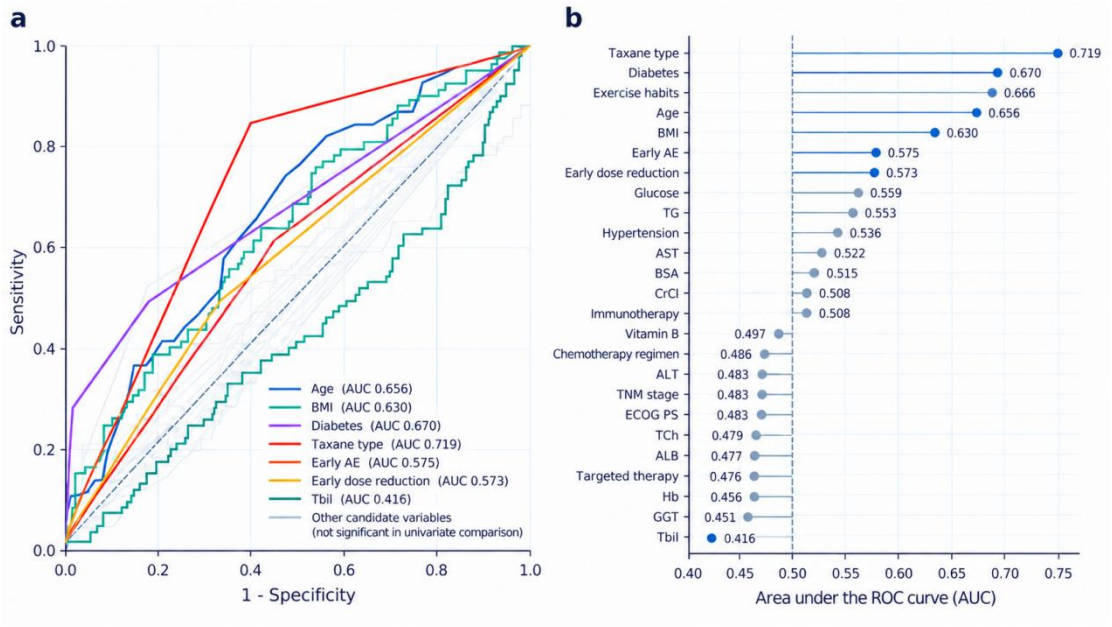


Figure 2. Univariate receiver operating characteristic (ROC) analysis of candidate predictors for moderate-to-severe CIPN. (A) ROC curves for candidate variables in the training cohort. Colored curves highlight variables showing statistically significant differences in the univariate comparison, whereas light-gray curves represent the remaining candidate variables. The diagonal dashed line denotes no discriminative ability. (B) Ranked AUC values for all candidate predictors; the vertical dashed line indicates an AUC of 0.50.

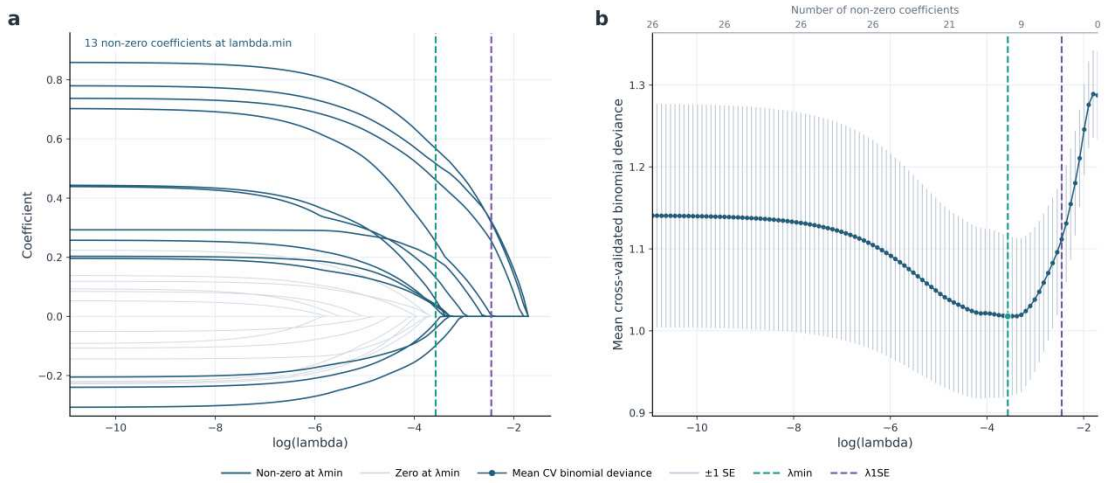


Figure 3. Lasso regression for predictor selection. (A) Coefficient trajectories across log(lambda). Dark-blue curves represent predictors retaining non-zero coefficients at lambda.min, whereas light-gray curves represent predictors shrunk to zero at lambda.min. The green and purple dashed lines indicate lambda.min and lambda.1SE, respectively. (B) Ten-fold cross-validation curve showing the mean cross-validated binomial deviance; vertical light-gray bars represent ±1 standard error. The upper axis shows the number of non-zero coefficients. Thirteen predictors were retained at lambda.min and four predictors at lambda.1SE.

Given the relatively limited number of predictive variables considered in this study and to avoid omitting potentially clinically meaningful predictors while also preventing model overfitting, multivariable logistic regression was subsequently performed. Five independent predictors were identified: history of diabetes, exercise habits, type of taxane, BMI, and age (Table 3).

Table 3. Multivariable logistic regression analysis of independent predictors of moderate-to-severe CIPN.

Variable	OR (95% CI)	P value
BMI	1.75 (1.07–2.85)	0.026
Exercise habits	3.98 (1.94–8.16)	<0.001
Diabetes	7.75 (2.86–20.96)	<0.001
Taxane categorization	6.58 (2.95–14.64)	<0.001
Age	1.84 (1.09–3.10)	0.023

Note: ORs are presented with 95% confidence intervals. For continuous predictors, ORs represent an interquartile-range increase (age: 57 vs 43 years; BMI: 24.33 vs 19.09 kg/m²). For categorical predictors, the reported contrasts are yes vs no for exercise habits, diabetes duration ≥5 years vs no diabetes, and docetaxel vs liposomal paclitaxel for taxane categorization. Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; OR, odds ratio; CI, confidence interval; BMI, body mass index.

3.3 Prediction Model for CIPN in Patients with Breast Cancer Receiving Taxane-based Chemotherapy

A nomogram was constructed to predict CIPN in patients with breast cancer receiving taxane-based chemotherapy (Figure 4), based on the five independent predictive factors identified above. The nomogram model that was constructed by using the five independent predictors demonstrated good discrimination, with AUC values of 0.835 (95% CI: 0.777–0.887) in the training cohort and 0.832 (95% CI: 0.741–0.911) in the validation cohort. External calibration demonstrated agreement between the predicted and observed probabilities, with a Brier score of 0.146, a

calibration intercept of 0.28, and a calibration slope of 0.95. Finally, decision curve analysis was performed to evaluate clinical utility. Across a broad range of probability thresholds, the nomogram provided greater net clinical benefit compared with either the “treat-all” or “treat-none” strategies (Figure 5A–5D).

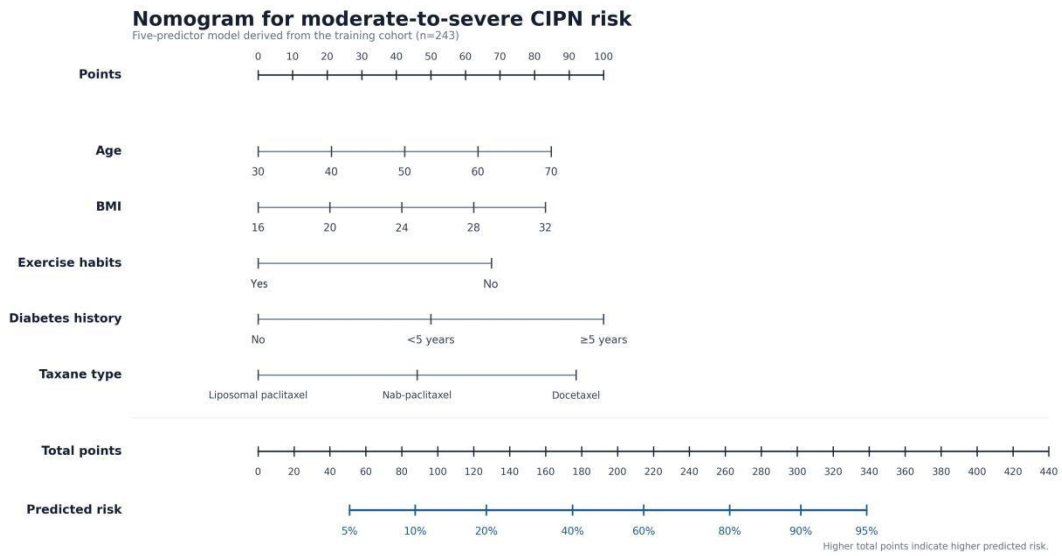


Figure 4. Nomogram for predicting moderate-to-severe CIPN based on the five-predictor logistic regression model comprising age, BMI, exercise habits, diabetes history, and taxane type. Points assigned to each predictor are summed to obtain the total score, which is then mapped to the predicted probability of moderate-to-severe CIPN.

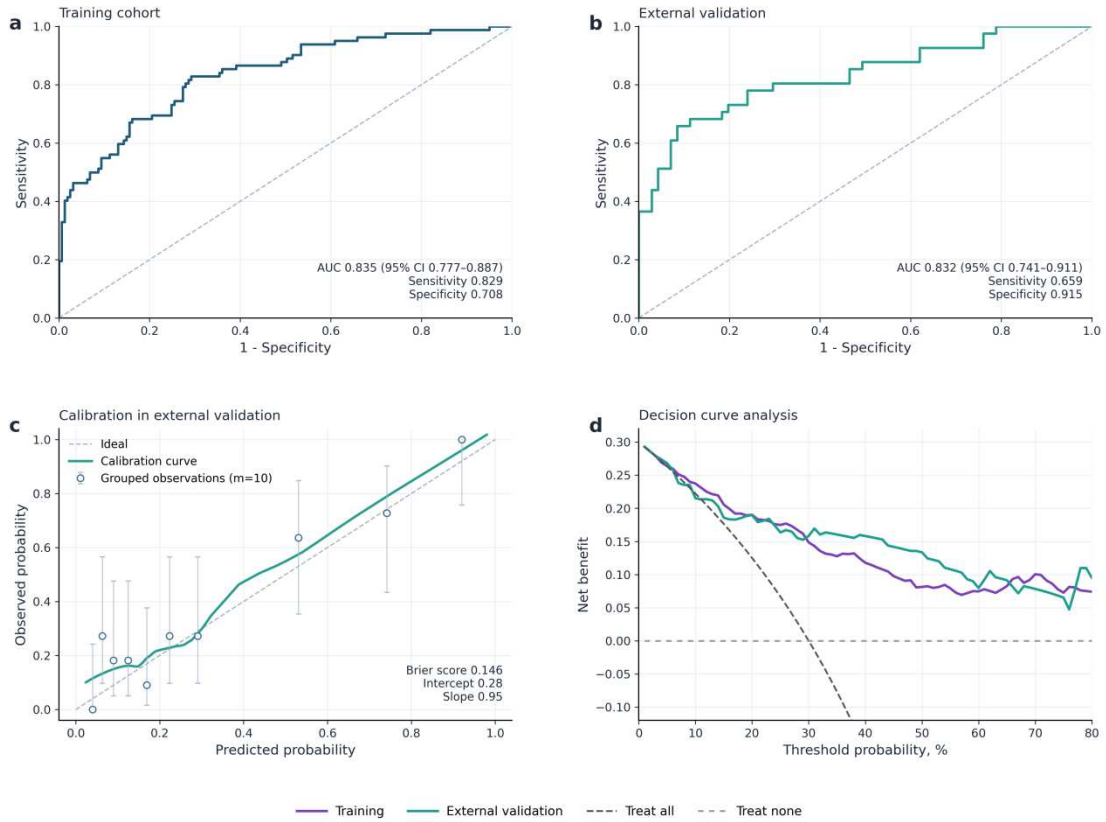


Figure 5. Performance of the final five-predictor model. (A) ROC curve in the training cohort (AUC 0.835, 95% CI 0.777–0.887). (B) ROC curve in the external validation cohort (AUC 0.832, 95% CI 0.741–0.911). (C) Calibration in the external validation cohort, showing the ideal line, LOWESS calibration curve, and observed event rates across 10 approximately equal-frequency risk groups; Brier score = 0.146, calibration intercept = 0.28, and calibration slope = 0.95. (D) Prevalence-standardized decision curve analysis assuming a population prevalence of 0.30. The model net-benefit curves for the training and external validation cohorts are compared with the treat-all and treat-none strategies.

4. Discussion

CIPN is among the most significant dose-limiting adverse reactions associated with chemotherapy for treating breast cancer. Among patients receiving taxane-based chemotherapy, 42% continue to experience CIPN-related symptoms for up to two years after treatment discontinuation, which severely impacts quality of life and adherence to breast cancer treatment.

Using clinical data from two centers, we developed and validated a nomogram to predict taxane-related CIPN. The results showed a sequential increase in CIPN risk across liposomal paclitaxel, docetaxel, and nab-paclitaxel. A history of diabetes lasting more than five years, obesity, older age, and lack of regular exercise were also identified as independent predictors of CIPN.

Several studies have reported differences in the incidence and severity of CIPN associated with different taxanes. Hershman et al. found that the incidence of grade 2–4 neuropathy was significantly higher in patients with breast cancer treated with paclitaxel than in those treated with docetaxel (25% vs. 12%; OR = 2.20; 95% CI, 1.52–3.18; $P < 0.001$).[4] Another prospective cohort study reported that both the overall incidence and severity of CIPN were higher with nab-paclitaxel than with liposomal paclitaxel or docetaxel, whereas no significant differences were observed between the latter two agents. Subgroup analyses further showed greater severity of sensory, motor, and autonomic neuropathy in patients receiving nab-paclitaxel.[3] Similarly, Kida et al. found that patients treated with nab-paclitaxel experienced earlier onset, greater severity, and slower recovery of sensory and motor neuropathy than those receiving conventional paclitaxel.[5]

With respect to the association between diabetes duration and CIPN risk, our study revealed that a history of diabetes exceeding five years was an independent risk factor. Similarly, Hershman et al. reported that compared with nondiabetic patients, patients with breast cancer with comorbid diabetes demonstrated approximately twice the risk of developing grade 2–4 neuropathy after taxane treatment (OR = 2.13; 95% CI: 1.31–

3.46; P = 0.002).[4] The mechanism of diabetes-induced neuropathy may be related to chronic hyperglycemia-induced Schwann cell damage and mitochondrial dysfunction.[6,7] A similar damage mechanism has also been observed in CIPN,[8] which suggests that diabetes and chemotherapy may have a synergistic effect in inducing neuropathy. Furthermore, even with adequate blood glucose control, patients with type 2 diabetes cannot significantly reduce their risk of distal symmetrical polyneuropathy (DSPN).[9] In breast cancer patients with diabetes, the occurrence of CIPN is not significantly associated with blood glucose levels (P = 0.56),[10] which suggests that patients with a diabetes history exceeding five years may warrant close monitoring for CIPN, even when their current blood glucose levels are well controlled.

Furthermore, this study revealed elevated BMI as an independent predictor of CIPN, which is consistent with the findings of previous research. A dose-response meta-analysis demonstrated that for every 5 kg/m² increase in BMI, the risk of CIPN increased by 15% (OR = 1.55; 95% CI: 1.20–1.99).[11] A prospective cohort study of patients with breast cancer (n = 1237) also revealed that overweight (OR = 2.37; 95% CI: 1.19–4.88) and obese (OR = 3.21; 95% CI: 1.52–7.02) patients exhibited a significantly greater risk of CIPN following paclitaxel treatment compared to those with normal weights.[12] The following potential mechanisms may explain these effects: increased absolute chemotherapy dose due to increased body surface area (BSA) in patients with high BMI; the frequent association of obesity with insulin resistance and an elevated risk of type 2 diabetes; and obesity (as a core component of metabolic syndrome) potentially contributing to a chronic low-grade inflammatory state (e.g.,

elevated CRP), which may synergize with chemotherapy to induce neuroinflammation.[13,14]

Advanced age was also identified as an independent risk factor for CIPN. Age-related degenerative changes in the peripheral nervous system may increase susceptibility to neurotoxic agents.[15] Clinical trial data from the Southwest Oncology Group (SWOG) further quantified this association, specifically, among women aged 65 years or older, each one-year increase in age was associated with a 4% increase in the odds of CIPN ($P = 0.006$).[4] Accumulating evidence suggests that exercise not only prevents the occurrence of chemotherapy-induced peripheral neuropathy but also effectively ameliorates its symptoms.[16,17] The underlying mechanisms may be related to the exercise-induced release of neurotrophic factors and the attenuation of inflammatory responses.[18,19]

In our training cohort, 53 of 82 patients with CIPN (64.6%) developed neuropathy within the first two cycles of taxane-based chemotherapy. Although CIPN is commonly considered a cumulative dose-related toxicity, with incidence increasing with treatment duration and cumulative exposure, [20,21] previous studies have also shown that neuropathy can emerge early after treatment initiation. The SWOG S1714 study reported that sensory and motor neuropathy could develop at various time points during paclitaxel treatment.[22] Similarly, a prospective cohort study of 1,234 women with breast cancer found that sensory and motor neuropathy symptoms could appear within the first few weeks of taxane treatment, with onset varying by taxane type.[3] These findings suggest that CIPN development may not be explained solely by cumulative

drug exposure and that early treatment-related factors, potentially including the dose administered per cycle, may also contribute to its onset.

5. Limitations

This study has several limitations. First, psychological factors, such as anxiety and depression, were not systematically assessed, although they may influence CIPN susceptibility. Future studies should incorporate validated psychological scales to account for these potential confounders. Second, only a three-week chemotherapy regimen was included. Existing studies have indicated that weekly paclitaxel treatment may offer superior efficacy and potentially reduced neurotoxicity in early or metastatic breast cancer,[23] thus suggesting that dosing density warrants further investigation. Additionally, factors such as ethnicity, alcohol consumption history, menopausal status, pretreatment hemoglobin levels, and hypoalbuminemia may also serve as potential predictors of CIPN.[24-26] As this was a two-center study with a limited sample size and available clinical data, several potential influencing factors were not included in the analysis. Larger, multicenter prospective studies are needed to validate the model and evaluate additional predictors.

6. Conclusions

We developed and validated a predictive model for CIPN in patients with breast cancer who received taxane-based chemotherapy. For patients with high-risk factors such as long-term diabetes, obesity, or advanced age, the choice of taxane

chemotherapy regimen should carefully balance efficacy against neurotoxicity risk. Taxanes with relatively low neurotoxicity profiles should be prioritized, and enhanced monitoring of neurological function during early chemotherapy is essential. Furthermore, given that CIPN can rapidly develop in the early stages of chemotherapy, clinical attention should be directed toward symptom assessment after the first administration (rather than focusing solely on the cumulative dose). Future large-scale, multicenter prospective studies are needed to further incorporate potential influencing factors, in order to optimize CIPN risk prediction models.

Authors' contributions

Yiling Duan, Mengzhe Zhang collected the data and prepared the figures and tables. Yiling Duan, Mengzhe Zhang, Zhengle Zhang analyzed the data. Yiling Duan, Mengzhe Zhang, Dan Li wrote the paper. Zhongyuan Yin, Qiong Wang provided funding support and supervision.

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Consent for publication

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Conflict of Interest

The authors declare no conflict of interest.

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