

Construction and Validation of a Model for Predicting Severe Chemotherapy-Induced Peripheral Neuropathy in Pediatric Cancer Patients Based on Patient-Reported Outcomes

Chunlei He

Department of Hematology and Oncology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Jiwen Sun

Department of Nursing, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Mengxue He

Department of Nursing, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Haishan Ruan

Department of Hematology and Oncology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Xiaoxue Wei

Department of Hematology and Oncology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Kangjia Zhao

Department of Hematology and Oncology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Geng Lin

Department of Hematology and Oncology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Huimin Qian

Department of Hematology and Oncology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Nanping Shen

shennanping@scmc.com.cn

Department of Nursing, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Research Article

Keywords: pediatric hematology, pediatric oncology, patient-reported outcomes, chemotherapy-induced peripheral neuropathy, nomogram, predictive model

Posted Date: September 29th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10677085/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Severe chemotherapy-induced peripheral neuropathy (CIPN) significantly compromises quality of life in pediatric oncology patients and often necessitates chemotherapy dose reduction, treatment discontinuation, or leads to life-threatening outcomes. Early detection and intervention are critical to halting CIPN progression and improving clinical outcomes. In this study, we developed and internally validated a predictive nomogram for severe CIPN in pediatric oncology patients by integrating treatment-related risk factors and patient-reported outcomes.

Methods

A prospective study was conducted from January 2024 to October 2025 at a tertiary hospital in Shanghai. 342 pediatric cancer patients receiving vincristine-containing regimens were consecutively enrolled. A logistic regression framework identified independent determinants of severe CIPN, and a nomogram was constructed. The predictive model was evaluated via the area under the receiver operating characteristic curve (AUC), the Brier score, the calibration curve and the Hosmer-Lemeshow test.

Results

Severe CIPN occurred in 15.5% of participants. The nomogram was created with the independent predictive factors including CIPN history, cumulative dose, and mean scores of patient-reported "numbness/tingling in the hands/feet" and "limb weakness". The AUC of the proposed model demonstrated acceptable discriminatory ability. The Brier score was 0.108. The calibration curve showed good consistency between the predicted and actual probabilities. The Hosmer-Lemeshow test indicated that the predictive model was well-calibrated. A concordance index quantifying predictive ranking ability was derived from internal validation.

Conclusion

The nomogram can identify pediatric cancer patients with vincristine-containing regimens at high risk for severe CIPN and may be a rapid visual tool for nurses. This model incorporates patient-reported outcomes to help nurses identify children with cancers who are at high risk for severe CIPN and allow timely preventive action.

1 Background

Childhood and adolescent cancers represent a significant global health burden,¹ particularly in China, where the overall incidence is increasing.² Chemotherapy serves as a cornerstone of pediatric cancer treatment but is frequently associated with chemotherapy-induced peripheral neuropathy (CIPN), which is a common, dose-limiting adverse effect related to chemotherapeutic agents.³ Among pediatric cancer patients, the incidence of CIPN can exceed 90%.⁴ Vincristine, which is a chemotherapeutic agent that is commonly used for treating childhood cancer,⁵ is a major causative factor for CIPN. It primarily affects sensory nerves but can also involve motor and autonomic nerve damage.⁶ Although its initial symptoms may be mild, CIPN can progressively worsen with continued treatment,⁷ leading to significant functional impairment (e.g., the loss of fine motor control⁸ and abnormal gait patterns⁹). This further increases the risk of falls¹⁰ and causes multidimensional quality-of-life deterioration (including anxiety, depression, etc.).¹¹ According to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0,¹² CIPN with a grade

≥ 2 is defined as severe CIPN,¹³ manifesting as limitations in age-appropriate instrumental daily living activities, with an incidence ranging from 17.5% to 46.7%.^{14–16} Severe CIPN often necessitates chemotherapy dose reductions, delays, or discontinuation, directly compromising the efficacy of treatments.¹⁷ Consequently, the early identification of pediatric patients who are at high risk for progression to severe CIPN is critical for implementing timely interventions, informing treatment modifications, and improving patient prognoses.

The established risk factors for CIPN in pediatric patients include demographic (e.g., age and sex), genetic, nutritional, and clinical characteristics (including underlying diagnoses and preexisting neuropathy) as well as treatment-related variables (such as doses, treatment durations, and concomitant agents).^{4,5,16} A growing body of adult CIPN prediction research has identified clinical risk factors, genetic markers, and hematological biomarkers^{18,19} that may provide insights for pediatric risk stratification. Although biomarkers such as genetic variants offer greater precision, the cost-prohibitive nature of these predictive methods limits their clinical adoption. Furthermore, the existing models²⁰ focus primarily on predicting the occurrence of CIPN rather than the severity of CIPN, thus underutilizing early clinical presentations—particularly patient-reported symptoms. Studies involving adults have demonstrated that the early symptoms of sensory neuropathy in the hands or feet captured by the Patient-reported Outcomes Common Terminology Criteria Adverse Events (PRO-CTCAE) may serve as significant precursors for predicting the severity of later neuropathy.²¹ Nevertheless, systematically capturing and quantifying these early subjective experiences in children and effectively integrating them into prediction models remains an unresolved research challenge. In recent years, increasing research has leveraged the Pediatric Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (Ped-PRO-CTCAE) for early toxicity monitoring.^{22–24} These studies indicate that the Ped-PRO-CTCAE can more sensitively detect disease progression trends by capturing early subtle symptoms, enabling the prediction of severe treatment-related toxicities in pediatric cancer patients.^{22–24} Notably, Zhao et al²⁴ incorporated comprehensive Ped-PRO-CTCAE symptom scores, performed symptom screening, and combined clinically accessible variables to develop a model for predicting severe cytokine release syndrome, which yielded promising results.

This study was aimed at developing a risk prediction model for severe CIPN in pediatric cancer patients. First, we prospectively collected and systematically analyzed patient-reported subjective symptoms during chemotherapy phases via the Ped-PRO-CTCAE, integrating these symptoms with readily available clinical variables to ensure the accessibility of the model. Second, we employed the final model as an intuitive nomogram to enhance its clinical utility. This tool was developed to enable the early detection of at-risk patients, supporting the prompt implementation of preventive measures or closer clinical surveillance. Ultimately, this strategy is aimed at reducing the incidence of severe CIPN, maintain the continuity of chemical treatments, and improving the quality of life experienced by children.

2 Methods

2.1 Aim and Design

This prospective study sought to identify the predictors of severe CIPN in pediatric cancer patients undergoing vincristine-containing regimens and to develop and validate a corresponding predictive model. The model is intended to identify high-risk patients, facilitate timely interventions, and enhance symptom management processes.

2.2 Participants

This study was conducted in the Department of Pediatric Hematology-Oncology at a tertiary hospital in Shanghai between January 2024 and October 2025. The inclusion criteria were as follows: (1) presence of hematologic malignancies or solid tumors receiving vincristine-containing chemotherapy regimens, (2) ages between 5 and 18 years, (3) demonstrated self-reporting capabilities, and (4) written informed consent obtained from legal guardians, with additional assent

provided by children aged ≥ 8 years. The exclusion criteria were as follows: (1) diagnoses of central nervous system tumors, (2) preexisting severe CIPN, and (3) end-of-life care statuses (life expectancy ≤ 6 weeks).

2.3 Sample Size Calculation

Sample size estimation was based on an empirical formula for multifactor logistic regression, which stipulates that the sample size for the lesser category of the outcome variable should be at least 10 times the number of independent variables²⁵. Given four key independent variables and a literature-reported severe CIPN prevalence of 17.5–46.7%,^{14–16} this yielded an estimated sample size of 86–229 cases. Consecutive sampling was employed, enrolling eligible children throughout the treatment period until the target sample size was achieved.

2.4 Procedure

The relevant information was extracted from the electronic medical records system of the hospital. Two researchers independently verified the critical variables (including the treatment duration and drug dosages) to ensure the accuracy and consistency of the data. The literature indicates that approximately 13% of patients develop sensory abnormalities within the first week following vincristine administration.²⁶ To capture early manifestations of neurotoxicity, children self-reported relevant Ped-PRO-CTCAE items within 7 days following vincristine-containing chemotherapy sessions. Paper-based questionnaires were administered in person, with assistance from researchers or guardians when necessary to ensure the completeness and accuracy of the data. From day 8 postchemotherapy until the initiation of the next cycle, clinicians assessed and graded CIPN according to the NCI-CTCAE v5.0 criteria, with all evaluations formally documented. The duration of a cycle varied according to the specific treatment regimen, typically spanning 21 to 28 days.²⁷

2.5 Outcomes

The primary outcome of this study was the occurrence of severe CIPN. Severe CIPN was defined per the NCI-CTCAE (version 5.0) as grade ≥ 2 in either the "peripheral sensory neuropathy" or "peripheral motor neuropathy" domain. NCI-CTCAE version 5.0 grades adverse events as follows: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe or disabling), Grade 4 (life-threatening), and Grade 5 (death). Grade-2 CIPN specifically denotes limitations in age-appropriate instrumental daily living activities, which are manifested as impaired fine motor skills (e.g., buttoning shirts, writing/drawing, or using utensils) or gait abnormalities, without a complete loss of the ability to perform these tasks.

2.6 Sociodemographic and Clinical Characteristics

The following three domains were informed by a comprehensive literature review and expert consultation. First, the patient characteristics included their age, sex, and body mass index (BMI). Second, the disease information included cancer type and CIPN histories. Third, the treatment parameters included cumulative dose of vincristine.

2.7 Chinese Version of the Ped-PRO-CTCAE

This study utilized the Chinese version of the Ped-PRO-CTCAE. This Chinese adaptation was translated by our research team and formally authorized by both the original research team at the National Cancer Institute and relevant domestic field experts²⁸. Prior validation studies demonstrated its good acceptability and measurement stability.^{22,24,28} The Ped-PRO-CTCAE includes 62 symptomatic adverse events, and all technical terms are explained in language that children can understand, making it child-friendly.²⁹ For example, "peripheral sensory neuropathy" is described as "numbness/tingling in the hands/feet", while "generalized muscle weakness" is described as "limb weakness", which can be ascertained directly from patient reports. These examples illustrate how specific clinical diagnoses can be translated into straightforward, lay descriptions that are based directly on patient-reported symptoms. Each symptomatic adverse event corresponds to 1 to 3 questions designed to assess its frequency, severity, and/or degree of interference with daily activities.²⁸ All the items employ a 7-day recall period and feature 4-point Likert scale response options (scored from 0 to 3). The scale was self-administered by the pediatric patients. Higher scores indicate greater severity for the corresponding symptomatic

adverse events. The scale demonstrated excellent reliability, with Cronbach's α coefficients of 0.923²² and 0.860 in the present study, indicating strong internal consistency.

2.8 Ethical Considerations

All the participants were children. Written informed consent was obtained from all participants, including legal guardians, prior to their enrollment. Children aged 8 years or older additionally provided assent using age-appropriate forms. The study adhered to the principles of the Declaration of Helsinki on Ethics. This prospective study was approved by the Institutional Review Board of the tertiary hospital in Shanghai (SCMCIRB-K2023220-1).

2.9 Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation or median (interquartile range), whereas categorical variables are presented as counts (percentages). The appropriate statistical test for between-group comparisons was selected based on the distribution of the data. Normally distributed continuous variables were analyzed with the independent samples t-test, non-normally distributed continuous variables with the Mann-Whitney U test, and categorical variables with the Pearson chi-square test.

This study employed logistic regression to screen the potential predictive indicators. In accordance with previous studies,^{22,24} the mean value of the three dimensions of the Ped-PRO-CTCAE (frequency, severity, and/or degree of interference with daily activities) was used as the symptom score for the present research, and the number of symptoms was added to the univariate analysis. Additionally, for each symptom item within the Ped-PRO-CTCAE, Cohen's d effect size was calculated. Symptom items with moderate effect size ($d > 0.5$),³⁰ along with the variables that were significant ($P < 0.05$) in the univariate analysis and were established as risk factors, were subsequently included in the multivariate logistic regression analysis.

The independent determinants of severe CIPN were identified using a stepwise logistic regression analysis, and a risk prediction model was subsequently developed. The model was visualized via a nomogram. The discrimination ability of the model was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC), with an AUC > 0.7 indicating good discrimination performance. Calibration was assessed using the Hosmer-Lemeshow test, where a P value > 0.05 signified a good fit, and the Brier score, with values closer to 0 indicating better accuracy. The nomogram model was internally validated using the bootstrap resampling method to evaluate its stability and generalizability.

Statistical analyses were conducted using SPSS software (version 25.0). The prediction model was constructed and validated using R software (version 4.4.1). A significance level of $\alpha = 0.05$ was applied for all the statistical tests, with $P < 0.05$ considered statistically significant.

3 Results

3.1 Characteristics of Severe CIPN

This study enrolled 342 pediatric cancer patients (no shedding), with a male predominance ($n = 250$, 73.1%). The age of the patients ranged from 5 to 17 years, with a median of 10.17 ± 3.17 years. Their BMI values varied between 10.87 and 36.68, yielding a median of 16.42 (interquartile range: 14.48–19.75). Cancer type included acute lymphoblastic leukemia (31.3%), lymphoma (36.0%), and other malignancies (32.7%). The cumulative dose of vincristine administered ranged from 0.94 to 36.00 mg, with a median of 7.06 (3.96–13.59) mg. Most (86.0%) patients had no CIPN history. Severe CIPN developed in 53 patients (15.5%); the remaining 289 (84.5%) did not. Among the severe CIPN patients, 51 (14.9%) experienced Grade 2 CIPN, while 2 (0.6%) had Grade 3. One statistically significant predictor was found in the comparative analysis: CIPN history ($P < 0.05$). (Table 1).

TABEL 1. Univariate Analysis of the Demographic and Clinical Characteristics of the Groups With and Without Severe CIPN				
Variable	Severe CIPN Group (n = 53)	Non-severe CIPN Group (n = 289)	Statistic	P
Gender, n (%)			0.179 ^a	0.738
Male	40 (75.5)	210 (72.7)		
Female	13 (24.5)	79 (27.3)		
Age (yrs), M ± SD	10.66 ± 3.25	10.08 ± 3.16	-1.215 ^b	0.225
BMI, M (P25, P75)	16.65 (14.61, 19.43)	16.31 (14.41, 20.06)	-0.242 ^c	0.810
Cancer type, n (%)			4.946 ^a	0.084
Acute lymphoblastic leukemia	10 (18.9)	98 (33.9)		
Lymphoma	24 (45.3)	99 (34.3)		
Other ^d	19 (35.8)	92 (31.8)		
Cumulative dose (mg), M (P25, P75)	5.94 (4.00, 11.07)	7.89 (3.87, 13.87)	-0.877 ^c	0.382
CIPN history, n (%)			13.565 ^a	<0.001
Yes	16 (30.2)	32 (11.1)		
No	37 (69.8)	257 (88.9)		
Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy.				
^a Pearson χ^2 ; ^b Independent samples t-test; ^c Mann-Whitney U test; ^d Including Langerhans cell hyperplasia, Ewing's sarcoma, hepatoblastoma, and renal malignancies.				
The bold indicates differences that were statistically significant ($P < .05$).				

3.2 Differences in the Occurrence of Severe CIPN-Related Symptoms Based on the Ped-PRO-CTCAE

Eight symptoms showed significant intergroup differences ($P < 0.05$), with patient-reported "numbness/tingling in the hands/feet" and "limb weakness" exhibiting moderate effect sizes (Cohen's $d > 0.5$) (Table 2).

Table 2
Univariate Analysis of the Ped-PRO-CTCAE in Groups With and Without Severe CIPN ($P < .05$)

Variable	Severe CIPN Group (n = 53) (mean $\pm$ SD)	Without Severe CIPN Group (n = 289) (mean $\pm$ SD)	P	Cohen d
Fatigue	0.340 $\pm$ 0.526	0.178 $\pm$ 0.451	0.040	0.329
Anorexia	1.151 $\pm$ 1.045	0.792 $\pm$ 0.957	0.014	0.358
Numbness/tingling in the hands/feet	0.311 $\pm$ 0.565	0.043 $\pm$ 0.169	0.001	0.642
Limb weakness	0.409 $\pm$ 0.594	0.128 $\pm$ 0.353	0.001	0.574
Urinary frequency	2.793 $\pm$ 6.545	0.874 $\pm$ 3.434	0.042	0.367
Urinary urgency	2.651 $\pm$ 6.594	0.780 $\pm$ 3.438	0.049	0.356
Nosebleed	0.025 $\pm$ 0.089	0.067 $\pm$ 0.265	0.036	0.211
Dry skin	0.377 $\pm$ 0.489	0.183 $\pm$ 0.388	0.008	0.439
Abbreviations: Ped-PRO-CTCAE, Pediatric Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; CIPN, chemotherapy-induced peripheral neuropathy.				
The bold indicate differences that were statistically significant ($P < .05$ or Cohen $d > 0.5$).				

3.3 Results of the Logistic Regression Analysis

Utilizing backward likelihood ratio (LR) selection, we identified the predictors of severe CIPN in pediatric cancer patients undergoing vincristine-containing regimens. Multivariate logistic regression included cumulative dose, CIPN history, and mean scores of patient-reported "numbness/tingling in the hands/feet" and "limb weakness" as independent variables (Table 3).

Table 3
Multivariate Logistic Regression Analysis of Severe CIPN-Related Risk Factors

Variable	B	S.E.	Wald	P	OR (95% CI)
Constant	-2.431	0.554	19.272	<.001	0.088 (-)
Age	0.056	0.051	1.234	0.267	1.058 (0.958–1.168)
Cumulative Dose (mg)	-0.065	0.029	4.985	0.026	0.937 (0.885–0.992)
CIPN history					
With	1.186	0.406	8.556	0.003	3.276 (1.479–7.254)
Without					1.000 (Reference)
Mean score of patient-reported "numbness/tingling in the hands/feet"	1.892	0.517	13.393	<.001	6.632 (2.408–18.269)
Mean score of patient-reported "limb weakness"	0.988	0.333	8.828	.003	2.686 (1.400–5.154)
Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy.					
The bold indicates differences that were statistically significant ($P < .05$).					

3.4 Construction and Internal Validation of the Nomogram Model

Utilizing the multivariate logistic regression equation described above, we developed and presented a nomogram for severe CIPN risk prediction (Fig. 1). In this nomogram, each predictor is assigned points ranging from 0 to 100. The total score (range: 0-220) is calculated by summing the points assigned to each predictor. A perpendicular line drawn from the total points axis to the probability axis indicates the predicted probability of severe CIPN occurring at the intersection point (Fig. 1).

The model demonstrated excellent discrimination capability, with an AUC of 0.750 (95% confidence interval [CI]: 0.670–0.829; $P < 0.001$), significantly exceeding the 0.7 threshold (Fig. 2). The diagnostic performance yielded a sensitivity of 60.4%, a specificity of 81.7%, and a corresponding Youden's index of 0.420. Hosmer-Lemeshow testing indicated a good calibration effect ($\chi^2 = 10.134$, $P = 0.256$), confirming the effective extraction of information from the data and an appropriate model fit. An overall Brier score of 0.108 was observed, reflecting excellent calibration of the predictive model.

An internal validation was performed using bootstrap resampling with 1000 iterations to assess the performance of the model. The mean bootstrap concordance index (C-index) of 0.733 (95% CI: 0.668–0.829) indicated acceptable discrimination. The calibration curves demonstrated strong agreement between the predicted and observed outcomes (Fig. 3). Hosmer-Lemeshow testing further confirmed an adequate level of fit ($\chi^2 = 9.655$, $P = 0.290$). The bootstrap-corrected Brier score was 0.114, indicating good overall predictive accuracy of the model.

4 Discussion

To our knowledge, this represents the first study regarding the development and validation of a CIPN prediction model for Chinese pediatric oncology patients receiving vincristine-containing regimens. Four significant predictors, including CIPN history, the cumulative dose and the mean scores of patient-reported "numbness/tingling in the hands/feet" and "limb weakness" were identified. The model demonstrated good calibration and discrimination capabilities. The resulting nomogram could assist nurses in identifying patients who are at high risk for severe CIPN during chemotherapy.

In this study, severe CIPN occurred in 15.5% of the pediatric cancer patients, which was higher than the previous retrospective finding at our center (5.8%)³¹ but lower than the 17.5–46.7% range reported in prior prospective studies.^{14–16} This discrepancy may reflect the heterogeneity exhibited by treatment protocols. Although existing evidence indicates that CIPN is worse in lymphoma patients than in those with acute lymphoblastic leukemia (ALL),⁸ our analysis revealed no significant intergroup differences in terms of severe CIPN occurrence. Furthermore, clinicians have implemented prophylactic vincristine dose reductions (by one-third to one-half) when coadministering azole antifungals such as posaconazole,³² which may partially account for our lower incidence of severe CIPN. The early identification of high-risk patients and the implementation of personalized preventive interventions should be prioritized in clinical practice to mitigate CIPN progression.

Our study identified CIPN history and the cumulative dose as independent predictors of severe CIPN. We observed significantly elevated severe CIPN risk in patients with CIPN history, which was consistent with established findings stating that a neuropathic history predisposes patients to motor neuropathy.³³ This finding aligns with CIPN pathophysiology, in which preexisting neural damage caused by the microtubule disruption mechanism of vincristine⁵ may lower the threshold for symptom exacerbation during retreatment. Additionally, an age-related decrease in neuronal repair capacity³⁴ may increase the severity of CIPN. Therefore, rigorous assessments of neurotoxic risk factors and individualized treatment planning schemes are essential for mitigating severe CIPN. Paradoxically, lower cumulative vincristine doses conferred greater severe CIPN risk, which was consistent with the report of Eker et al regarding early-

onset CIPN at lower doses in children < 7 years,³⁵ yet this contradicted the conventional dose-toxicity correlation.^{4,5} This may reflect dosing frequency variability and individual susceptibility. Li et al³⁶ demonstrated rapid CIPN progression with increased vincristine dose intensity (treatment frequency) during ALL induction.³⁷ Molassiotis et al further suggested a time-dependent CIPN development process,³³ noting symptom improvement despite cumulative dose increases when the dosing intervals lengthened.³⁶ Thus, both cumulative exposure and administration frequency require clinical consideration. Genetic variations also critically influence the susceptibility of patients to CIPN.^{38,39} Differential vincristine sensitivity explains the early emergence of neurotoxicity, particularly in patients who are homozygous for the CEP72 TT genotype.³⁸ Future research should elucidate the molecular mechanisms involved in precision treatment strategies.

The mean scores of patient-reported "numbness/tingling in the hands/feet" and "limb weakness" were significant predictors of severe CIPN in our study. Similarly, the symptom defined per PRO-CTCAE as "numbness/tingling in the hands/feet"²¹ can emerge at lower cumulative chemotherapy doses, typically progressing distally to proximally.⁴⁰ Wang et al⁴¹ further established that prechemotherapy touch sensation deficits significantly predict CIPN progression. These findings corroborate our observation that numbness/tingling in the hands/feet is a sensitive early warning indicator for severe CIPN risk. Therefore, this patient reported symptom item serves as a critical early warning indicator for severe CIPN risk, as it can be used to sensitively detect neurofunctional changes.²¹ Additionally, "limb weakness" predicts severe cytokine release syndrome after CAR-T-cell therapy in pediatric B-cell malignancies, as reported by Zhao et al.²⁴ Our study revealed a high incidence of "limb weakness" (23.40%), which was consistent with Toftthagen's interview-based findings.⁴² This symptom increases the risk of falling through impaired balance.⁴³ Mounting evidence^{44,45} supports the use of exercise interventions for mitigating the symptoms and progression of CIPN. The recognition of patient-reported "numbness/tingling in the hands/feet" and "limb weakness" is thus imperative. Timely assessments and interventions can improve patient prognoses and their quality of life. Future research should explore multimodal intervention strategies for optimizing the CIPN management process.

Severe CIPN significantly reduces patient quality of life and affects treatment outcomes,¹⁷ but the early identification of high-risk CIPN remains unresolved, which is a challenge that is particularly acute in pediatric patients. Compared with the existing CIPN prediction tools, our model demonstrates superior discriminative performance. Wiranata et al²⁰ developed a decision tree model to predict CIPN in breast cancer patients using demographic and inflammatory biomarkers (the baseline C-reactive protein, neutrophil-to-lymphocyte ratio, BMI, and marital status), yielding a model AUC of 0.705. In contrast, Li et al⁴⁶ incorporated both clinical parameters (chemotherapy regimen, cycle count, and vitamin D deficiency) and symptom burden (fatigue levels) in their model for breast cancer survivors, achieving greater discriminatory power, with development and validation AUCs of 0.866 and 0.848, respectively. The superior performance of Li et al's model suggests that including patient-reported symptom variables significantly enhances the predictive efficacy achieved in oncology outcome research. In line with this, the present model, which achieved an AUC of 0.750, may derive its predictive value particularly from the inclusion of key early symptoms of severe CIPN, with a stronger focus on hand and foot involvement.

5 Conclusion

We developed and validated a model for predicting severe CIPN in a pediatric population of oncology patients. The model incorporates four factors: CIPN history, cumulative dose, the mean scores of patient-reported "numbness/tingling in the hands/feet" and "limb weakness". The nomogram constructed in this study was well differentiated and calibrated, providing a quicker and more visual assessment tool with which healthcare professionals can identify the risk of developing severe CIPN.

This study has several limitations. First, while this study was conducted at East China's largest pediatric hematology oncology center with a representative sample, its single-center design warrants future prospective multicenter studies with larger cohorts. Second, the model requires external validations to confirm its generalizability beyond the current cohort. Finally, given the complexity of combining drugs for peripheral neuropathy, further research could be conducted in the future.

Abbreviations

CIPN chemotherapy-induced peripheral neuropathy

AUC area under the receiver operating characteristic curve

NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events

PRO-CTCAE Patient-reported Outcomes Common Terminology Criteria Adverse Events

Ped-PRO-CTCAE Pediatric Patient-Reported Outcomes Common Terminology Criteria for Adverse Events

BMI body mass index

ROC receiver operating characteristic

LR likelihood ratio

CI confidence interval

ALL acute lymphoblastic leukemia

Declarations

Ethics approval and consent to participate

The study adhered to the principles of the Declaration of Helsinki on Ethics. This prospective study was approved by the Institutional Review Board of the tertiary hospital in Shanghai (SCMCIRB-K2023220-1).

Consent for publication

Not applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

C.H. and J.S. are co-first author.

Funding

This study was supported by Shanghai Hospital Development Center Foundation (2023SKMR-23); 2024 Shanghai Jiao Tong University School of Nursing “Nursing + X” Interdisciplinary Research Foundation (HLXKGDD2024); Shanghai Jiao Tong University China Hospital Development Research Institute Foundation (CHDI-2025-A-16); Shanghai Jiao Tong University School of Medicine: Nursing Development Program (SJTUHLXK2023, SJTUHLXK2024); Shanghai Hospital Association Hospital Management Research Youth Project (Q2025043); Clinical Research Plan of SHDC (No.SHDC2023CRS010).

Authors' contributions

C.L.H. and J.W.S. designed the study, analyze the data and wrote the manuscript. K.J.Z., G.L. and H.M.Q. collected the data and verified the study materials and data. M.X.H., H.S.R. and X.X.W. reviewed the manuscript and contributed to manuscript polishing and language revision. N.P.S. contributed to the conceptualization and design of the study, critically reviewed the manuscript, and revised it for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the Clinical Research Center, Shanghai Jiao Tong University School of Medicine for their expert statistical support.

References

1. The global burden of childhood and adolescent cancer. in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol* Sep. 2019;20(9):1211–25.
2. Ni X, Li Z, Li X, et al. Socioeconomic inequalities in cancer incidence and access to health services among children and adolescents in China: a cross-sectional study. *Lancet* Sep. 2022;24(10357):1020–32. 10.1016/s0140-6736(22)01541-0.
3. [Chinese expert consensus on the diagnosis. and treatment of chemotherapy-induced peripheral neuropathy (2022 edition)]. *Zhonghua Zhong Liu Za Zhi* Sep. 2022;23(9):928–34. 10.3760/cma.j.cn112152-20220213-00099.
4. Tay N, Laakso EL, Schweitzer D, Endersby R, Vetter I, Starobova H. Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. *Front Mol Biosci*. 2022;9:1015746. 10.3389/fmolb.2022.1015746.
5. Triarico S, Romano A, Attinà G, et al. Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. *Int J Mol Sci* Apr. 2021;16(8). 10.3390/ijms22084112.
6. Maihöfner C, Diel I, Tesch H, Quandel T, Baron R. Chemotherapy-induced peripheral neuropathy (CIPN): current therapies and topical treatment option with high-concentration capsaicin. *Support Care Cancer* Aug. 2021;29(8):4223–38. 10.1007/s00520-021-06042-x.
7. Beijers AJ, Mols F, Tjan-Heijnen VC, Faber CG, van de Poll-Franse LV, Vreugdenhil G. Peripheral neuropathy in colorectal cancer survivors: the influence of oxaliplatin administration. Results from the population-based PROFILES registry. *Acta Oncol* Apr. 2015;54(4):463–9. 10.3109/0284186x.2014.980912.

8. Gilchrist LS, Tanner LR. Short-Term Recovery of Balance Control: Association With Chemotherapy-Induced Peripheral Neuropathy in Pediatric Oncology. *Pediatr Phys Ther Apr.* 2018;30(2):119–24. 10.1097/pep.0000000000000484.
9. Winters-Stone KM, Horak F, Jacobs PG, et al. Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. *J Clin Oncol Aug.* 2017;10(23):2604–12. 10.1200/jco.2016.71.3552.
10. Kolb NA, Smith AG, Singleton JR, et al. The Association of Chemotherapy-Induced Peripheral Neuropathy Symptoms and the Risk of Falling. *JAMA Neurol Jul.* 2016;1(7):860–6. 10.1001/jamaneurol.2016.0383.
11. McNeish BL, Richardson JK, Whitney DG. Chemotherapy-induced peripheral neuropathy onset is associated with early risk of depression and anxiety in breast cancer survivors. *Eur J Cancer Care (Engl) Nov.* 2022;31(6):e13648. 10.1111/ecc.13648.
12. Hertz DL, Childs DS, Park SB, et al. Patient-centric decision framework for treatment alterations in patients with Chemotherapy-induced Peripheral Neuropathy (CIPN). *Cancer Treat Rev Sep.* 2021;99:102241. 10.1016/j.ctrv.2021.102241.
13. Lustberg Me L, Ce SL. *Diagnosis, Management and Emerging Strategies for Chemotherapy-Induced Neuropathy A MASCC Book.* 1st ed. 2021. ed. Cham: Springer International Publishing : Imprint: Springer; 2021.
14. Kishi S, Cheng C, French D, et al. Ancestry and pharmacogenetics of antileukemic drug toxicity. *Blood May.* 2007;15(10):4151–7. 10.1182/blood-2006-10-054528.
15. Lombardi AJ, Sutton ME, Tiao GM, Geller JI. Vincristine-associated neurological morbidity in the treatment of hepatoblastoma. *J Pediatr Hematol Oncol May.* 2015;37(4):e258–63. 10.1097/mpb.0000000000000321.
16. Li C, Jin J, Huang J, et al. [A cohort study of vincristine-induced peripheral neuropathy in children]. *Zhongguo Dang Dai Er Ke Za Zhi May.* 2023;15(5):470–5. 10.7499/j.issn.1008-8830.2212032. 0000000000000000.
17. Schneider BP, Hershman DL, Loprinzi C. Symptoms: Chemotherapy-Induced Peripheral Neuropathy. *Adv Exp Med Biol.* 2015;862:77–87. 10.1007/978-3-319-16366-6_6.
18. Yildirim N, Cengiz M. Predictive clinical factors of chronic peripheral neuropathy induced by oxaliplatin. *Support Care Cancer Oct.* 2020;28(10):4781–8. 10.1007/s00520-020-05319-x.
19. Bloomingdale P, Mager DE. Machine Learning Models for the Prediction of Chemotherapy-Induced Peripheral Neuropathy. *Pharm Res Jan.* 2019;7(2):35. 10.1007/s11095-018-2562-7.
20. Wiranata JA, Astari YK, Ucche M, et al. Predictive Factors of Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer: A Decision Tree Model Approach. *JCO Glob Oncol Nov.* 2024;10:e2400160. 10.1200/go.24.00160.
21. Tan AC, McCrary JM, Park SB, Trinh T, Goldstein D. Chemotherapy-induced peripheral neuropathy-patient-reported outcomes compared with NCI-CTCAE grade. *Support Care Cancer Dec.* 2019;27(12):4771–7. 10.1007/s00520-019-04781-6.
22. Li Y, Shen N, Sun J, He M, Ran H, Zhao K. Construction of a Risk Predictive Model for Febrile Neutropenia in Children with Tumors Chemotherapy Based on Patient-reported Tool. 00000000000000000000000000000000. *Military Nurs.* 2022;39(12):26–9. 2097 – 1826(2022)39:12 < 26:Jyzwbg > 2.0.Tx;2-z.
23. Sharma MR, Mehrotra S, Gray E, et al. Personalized Management of Chemotherapy-Induced Peripheral Neuropathy Based on a Patient Reported Outcome: CALGB 40502 (Alliance). *J Clin Pharmacol Apr.* 2020;60(4):444–52. 10.1002/jcph.1559.
24. Zhao K, Sun J, He M, Ruan H, Lin G, Shen N. A Predictive Model of Severe Cytokine Release Syndrome After Coadministration of CD19- and CD22-Chimeric Antigen Receptor T-Cell Therapy in Children With B-Cell Hematological Malignancies Based on Patient-Reported Outcomes. *Cancer Nurs Jan-Feb.* 2025;01(1):3–11. 10.1097/ncc.0000000000001275.
25. van Smeden M, Moons KG, de Groot JA, et al. Sample size for binary logistic prediction models: Beyond events per variable criteria. *Stat Methods Med Res Aug.* 2019;28(8):2455–74. 10.1177/0962280218784726.

26. Arzanian MT, Mehdizadeh M, Zamani GR. VINCRISTINE INDUCED NEUROTOXICITY: STUDY OF 75 CASES. *Iran J child Neurol.* 2009;3(2):39–44.
27. Nygren P. What is cancer chemotherapy? *Acta Oncol.* 2001;40(2–3):166–74. 10.1080/02841860151116204.
28. Shen N, Ruan H, Sun J, et al. Translation Into Simplified Chinese and Cultural Validation of the Pediatric Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events Using Cognitive Interviewing. *Cancer Nurs Jan-Feb.* 2023;01(1):E31–40. 10.1097/ncc.0000000000001090.
29. Reeve BB, Withycombe JS, Baker JN, et al. The first step to integrating the child's voice in adverse event reporting in oncology trials: a content validation study among pediatric oncology clinicians. *Pediatr Blood Cancer Jul.* 2013;60(7):1231–6. 10.1002/pbc.24463.
30. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* Rev ed. ed. Academic; 2013.
31. Yuan Y, Wu J, Shen A, Jiang H, Zhang S. Epidemiology and Risk Factors of Vincristine-induced Peripheral Neuropathy in Children. *Chin J Pharmacoepidemiology.* 2022;31(11):720–4.
32. Yuan Y, Hu W, Chen C, et al. Pharmacokinetic, Pharmacodynamic and Pharmacogenetic Studies Related to Vincristine-Induced Peripheral Neuropathy in Chinese Pediatric ALL Patients. *Clin Pharmacol Ther Feb.* 2025;117(2):454–64. 10.1002/cpt.3462.
33. Molassiotis A, Cheng HL, Leung KT, et al. Risk factors for chemotherapy-induced peripheral neuropathy in patients receiving taxane- and platinum-based chemotherapy. *Brain Behav Jun.* 2019;9(6):e01312. 10.1002/brb3.1312.
34. Reid DA, Reed PJ, Schlachetzki JCM, et al. Incorporation of a nucleoside analog maps genome repair sites in postmitotic human neurons. *Science Apr 2.* 2021;372(6537):91–4. 10.1126/science.abb9032.
35. Eker N, Ozturk G. Vincristine-Induced Peripheral Neuropathy in Children With Malignancy and the Effect of Missed Doses on Treatment Success. *Cureus Sep.* 2023;15(9):e46063. 10.7759/cureus.46063.
36. Li T, Kandula T, Cohn RJ, Kiernan MC, Park SB, Farrar MA. Prospective assessment of vincristine-induced peripheral neuropathy in paediatric acute lymphoblastic leukemia. *Clin Neurophysiol Oct.* 2023;154:157–68. 10.1016/j.clinph.2023.08.002.
37. Lavoie Smith EM, Li L, Hutchinson RJ, et al. Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. *Cancer Nurs Sep-Oct.* 2013;36(5):E49–60. 10.1097/NCC.0b013e318299ad23.
38. Diouf B, Crews KR, Lew G, et al. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. *Jama Feb.* 2015;24(8):815–23. 10.1001/jama.2015.0894.
39. Li GZ, Hu YH, Li DY, et al. Vincristine-induced peripheral neuropathy: A mini-review. *Neurotoxicology Dec.* 2020;81:161–71. 10.1016/j.neuro.2020.10.004.
40. Boyette-Davis JA, Cata JP, Driver LC, et al. Persistent chemoneuropathy in patients receiving the plant alkaloids paclitaxel and vincristine. *Cancer Chemother Pharmacol Mar.* 2013;71(3):619–26. 10.1007/s00280-012-2047-z.
41. Wang XS, Shi Q, Dougherty PM, et al. Prechemotherapy Touch Sensation Deficits Predict Oxaliplatin-Induced Neuropathy in Patients with Colorectal Cancer. *Oncology.* 2016;90(3):127–35. 10.1159/000443377.
42. Tofthagen C. Patient perceptions associated with chemotherapy-induced peripheral neuropathy. *Clin J Oncol Nurs Jun.* 2010;14(3):E22–8. 10.1188/10.Cjon.E22-e28.
43. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. *Support Care Cancer Mar.* 2012;20(3):583–9. 10.1007/s00520-011-1127-7.
44. Dhawan S, Andrews R, Kumar L, Wadhwa S, Shukla G. A Randomized Controlled Trial to Assess the Effectiveness of Muscle Strengthening and Balancing Exercises on Chemotherapy-Induced Peripheral Neuropathic Pain and Quality of Life Among Cancer Patients. *Cancer Nurs Jul/Aug.* 2020;43(4):269–80. 10.1097/ncc.0000000000000693.
45. Zimmer P, Trebing S, Timmers-Trebing U, et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer

patients: a randomized controlled trial. Support Care Cancer Feb. 2018;26(2):615–24. 10.1007/s00520-017-3875-5.

46. Li RL, Li J, Liu JE, Bai LX, Liu J, Li C. Construction and Validation of a Predictive Model for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Survivors Receiving Taxane-Based Chemotherapy: A Multicenter Cross-sectional Study. Cancer Nurs May. 2025;27. 10.1097/ncc.0000000000001516.

Figures

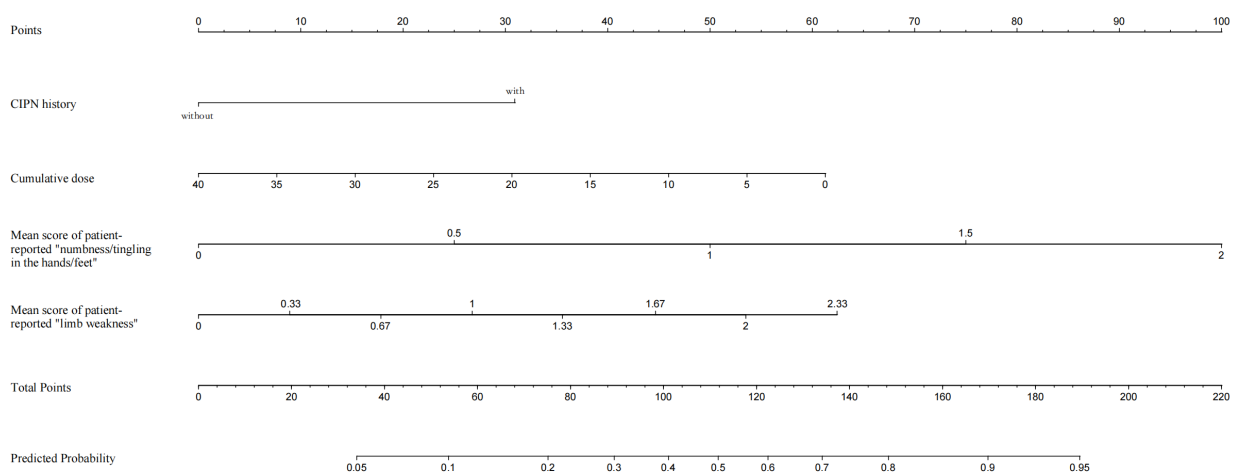


Figure 1

Nomogram for Predicting the Risk of Severe Chemotherapy-Induced Peripheral Neuropathy

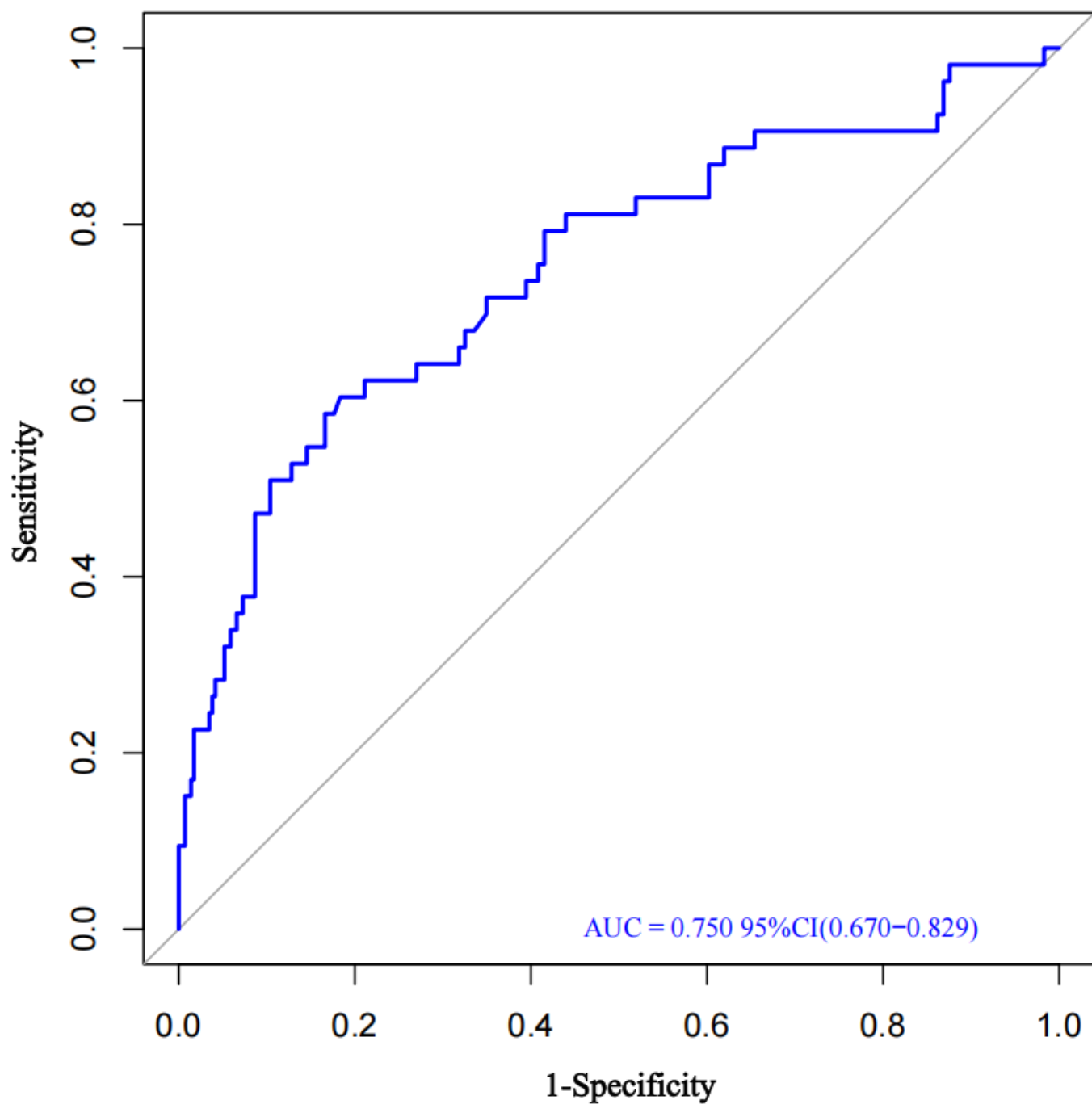


Figure 2

Discrimination Ability of the Risk Prediction Model for Determining Severe Chemotherapy-Induced Peripheral Neuropathy (ROC Curve)

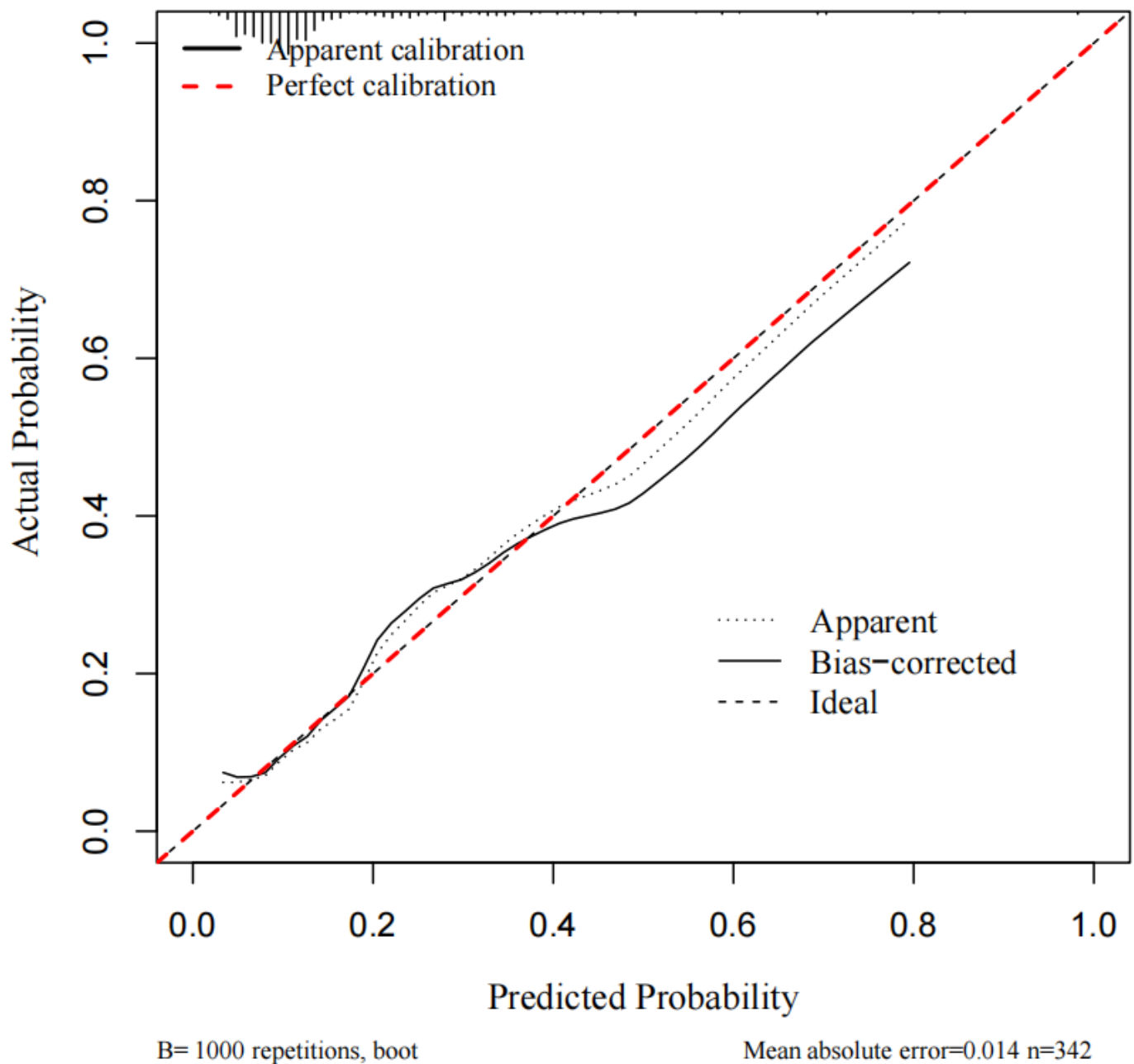


Figure 3

Internal Validation Calibration Curve Produced by the Risk Prediction Model for Severe Chemotherapy-Induced Peripheral Neuropathy

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TABEL1UnivariateAnalysisoftheDemographicandClinicalCharacteristicsoftheGroupsWithandWithoutSevereCIPN.docx](#)

- [TABLE3MultivariateLogisticRegressionAnalysisofSevereCIPNRelatedRiskFactors.docx](#)
- [TABLE2UnivariateAnalysisofthePedPROCTCAEinGroupsWithandWithoutSevereCIPN.docx](#)