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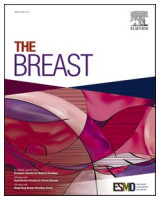

Analysis of factors influencing chemotherapy-induced peripheral neuropathy in breast cancer patients using a random forest model

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ABSTRACT

Objective: This study aimed to analyze the factors influencing chemotherapy-induced peripheral neuropathy (CIPN) in breast cancer patients, identify modifiable factors, and provide a theoretical basis for targeted interventions.

Methods: A total of 542 patients with breast cancer who were hospitalized for chemotherapy in multiple hospitals from September 2022 to September 2023 were selected as the study objects. Data were collected using questionnaires covering demographic characteristics, disease-related information, lifestyle, and psychological status. Lasso-logistic regression was employed to identify influencing factors, and a random forest model was used to rank the importance of variables.

Results: Lasso-logistic regression analysis identified age, BMI, cumulative chemotherapy dose, hypertension, physical activity level, and depression as significant factors associated with CIPN ($P < 0.05$). The variable importance ranking from the random forest model was as follows: age, BMI, cumulative chemotherapy dose, physical activity, hypertension, and depression.

Conclusion: Early identification of high-risk CIPN patients is crucial for guiding clinical nursing practices. These findings provide a foundation for the management and intervention of CIPN in breast cancer patients.

1. Introduction

According to the latest data released by the International Agency for Research on Cancer (IARC) in 2022, breast cancer accounts for 11.6 % of all newly diagnosed cancers worldwide, making it the most common cancer among women globally [1]. Chemotherapy is a crucial approach for the treatment of breast cancer. According to the 2023 CSCO Breast Cancer Diagnosis and Treatment Guidelines, taxanes are recommended as the first-line foundational therapy for breast cancer [2]. However, chemotherapy-induced peripheral neuropathy (CIPN) is a characteristic dose-limiting side effect of taxane-based drugs, with an incidence as high as 70 % [3]. Even six months or several years after completing chemotherapy, some patients continue to suffer from CIPN [4].

CIPN primarily causes sensory, motor, and autonomic nerve dysfunction. Common symptoms of sensory nerve damage include numbness, pain, and sensory loss in the hands and feet [5]. Motor nerve damage often manifests as gait instability, difficulty maintaining balance, or impaired fine motor skills, while autonomic nerve dysfunction may result in symptoms such as constipation or diarrhea, abnormal sweating, and orthostatic dizziness. When CIPN reaches grade 3 or higher, dose reductions or even discontinuation of chemotherapy are typically required, which can hinder the continuation of antitumor treatment and compromise therapeutic efficacy [6].

This study employs a Lasso regression model to identify factors influencing CIPN and uses a random forest algorithm to rank the importance of these factors. The goal is to provide clinical insights for identifying modifiable risk factors and to inform potential interventions.

2. Materials and methods

2.1. Study subjects

This study selected 542 breast cancer patients receiving breast surgery chemotherapy in multiple hospitals from September 2022 to September 2023 as the study object.

Inclusion criteria: (1) Age ≥18 years; (2) Diagnosis of breast cancer

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meeting the criteria outlined in the *2024 Chinese Anti-Cancer Association Guidelines and Standards for Breast Cancer Diagnosis and Treatment* [7]; (3) The enrolled patients received a chemotherapy regimen of albumin-bound paclitaxel (250 mg/m^2, every 21 days) as neoadjuvant therapy; (4) Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) from grade 1 to 5; (5) Willingness to participate in the study and provision of informed consent; (6) Patients had the ability to hear, speak, read, and write and were able to independently complete the questionnaire.

Exclusion criteria: (1) Metastases in other organs; (2) Peripheral neuropathy caused by infection, toxicity, radiotherapy, or severe diabetes; (3) Neuropathy resulting from electrolyte imbalances or other systemic diseases; (4) Severe cardiovascular or pulmonary diseases or other malignancies; (5) Recurrent breast cancer patients with a history of chemotherapy before recurrence. (6) Breast cancer patients receiving platinum-based chemotherapy in combination. This study was approved by the hospital ethics committee (Ethics No.: RMYY-LLKS-2022-055).

2.2. Research program

This study designated the 21st day after the patient's final chemotherapy session as the study time point. Baseline and relevant data of breast cancer patients with chemotherapy-induced peripheral neuropathy (CIPN) were recorded. General patient information was collected through face-to-face interviews, and relevant laboratory parameters were reviewed in the electronic medical record system. Two trained nursing graduate students administered the questionnaires. After obtaining informed consent, the purpose and significance of the study were explained to participants using standardized instructions. The investigators accompanied patients during the completion of the questionnaire, addressing any questions that arose. A total of 562 patients met the inclusion criteria, provided informed consent, and completed the survey. However, due to various reasons, 20 cases were excluded from the analysis. The participant flow diagram is available in (Supplementary Fig. S1).

2.3. Study instruments

2.3.1. General information questionnaire

A self-designed questionnaire was developed based on a literature review to collect demographic and disease-related data. Demographic data included gender, age, marital status, BMI, education level, and household income. Disease-related data included TNM staging, cumulative chemotherapy dose, medical history, and family history of cancer.

2.3.2. Frailty assessment

The FRAIL scale, developed in 2008 by the International Academy on Nutrition and Aging based on Fried's frailty phenotype [8], was used to assess frailty. Jing et al. [9]localized the scale to the Chinese population, achieving a Cronbach's α coefficient of 0.705, indicating good reliability and validity. The scale consists of five items: meeting three or more criteria indicates frailty, one to two indicates pre-frailty, and zero indicates non-frailty.

2.3.3. Social Support Rating Scale (SSRS)

The SSRS, developed by Xiao Shuiyuan based on international scales [10], measures objective support, subjective support, and the utilization of social support. The scale comprises 10 items, with a total score ranging from 12 to 66; higher scores indicate higher levels of social support. The SSRS has demonstrated good reliability and validity, with a Cronbach's α coefficient of 0.90.

2.3.4. Hospital Anxiety and Dpression Scale (HADS)

The HADS, developed by Zigmond and Snaith in 1983 [11], includes 14 items, with seven assessing anxiety and seven assessing depression. The scale has demonstrated good reliability and validity, with a Cronbach's α coefficient of 0.879 and a test-retest reliability of 0.945, indicating excellent stability. Scores for anxiety and depression are categorized as 0–7 (normal), 8–10 (mild symptoms), and 11–21 (severe symptoms).

2.3.5. International Physical Ativity Questionnaire (IPAQ)

The IPAQ, developed by the International Physical Activity Questionnaire Group in 1997 [12], is a reliable and valid tool for assessing physical activity. It includes three components: walking, moderate-intensity activity, and vigorous-intensity activity, with seven items in total. Each activity is assigned a corresponding metabolic equivalent (MET) value.

2.3.6. Lifestyle assessment

The Health-Promoting Lifestyle Profile II (HPLP-II) was used to evaluate lifestyle. The scale includes six dimensions and 52 items, scored on a 4-point Likert scale, with higher scores indicating a healthier lifestyle. The Cronbach's α coefficient for the overall scale is 0.93, and for individual dimensions, it ranges from 0.69 to 0.87 [13].

2.4. Peripheral neuropathy assessment

Peripheral neuropathy (CIPN) in both groups was assessed using NCI-CTCAE 5.0 (National Cancer Institute Common Terminology Criteria for Adverse Events). This grading system classifies peripheral sensory and motor neuropathy into four levels based on symptom severity:

Grade 1: Asymptomatic or mild sensory abnormalities limited to clinical or diagnostic observations, requiring no intervention. Grade 2: Moderate symptoms that restrict complex daily activities (e.g., household chores, shopping). Grade 3: Severe symptoms that limit basic daily activities (e.g., self-care) and require assistive devices. Grade 4: Life-threatening symptoms requiring urgent intervention. This assessment framework categorizes neuropathy into four grades according to symptom severity. Grade 5: Due to the adverse event resulting in death [14].

2.5. Operational definitions

Smoking and Alcohol Consumption: A smoking history was defined as consuming at least one cigarette per day for more than one year. Individuals who had completely quit smoking for two or more years were considered former smokers. Regardless of the type of alcohol, a history of alcohol consumption was defined as an average intake of alcohol at least once per week.

2.6. Statistical analysis

Statistical analysis was conducted using SPSS 26.0. Univariate analysis was performed using the chi-square test. Variable selection was performed using the glmnet function in R Studio, selecting the λ value corresponding to the minimum cross-validated error to retain variables with non-zero coefficients. The selected variables were included in a binary logistic regression analysis, with a significance level of $\alpha = 0.05$. The importance of variables was ranked using the Random Forest algorithm in R Studio.

3. Results

3.1. Univariate analysis of CIPN in breast cancer patients undergoing chemotherapy

A univariate analysis was conducted using the presence or absence of CIPN as the dependent variable. The results indicated significant differences in CIPN occurrence among breast cancer patients based on age, presence of a fixed caregiver, history of hypertension, BMI, cumulative

chemotherapy dose, levels of social support, anxiety, depression, physical activity, and adherence to a healthy lifestyle ($P < 0.05$). Detailed results are presented in Table 1.

3.2. Identification of factors influencing CIPN in breast cancer patients undergoing chemotherapy

3.2.1. Variable selection

Lasso regression analysis was performed in R Studio using the glmnet function on 10 variables identified as statistically significant in the univariate analysis. As shown in Figs. 1 and 2, the vertical dashed line on the left represents lambda.min, while the line on the right represents lambda.1se. When the lambda (λ) value was 0.0452, the model achieved the minimum error, corresponding to eight influencing factors. Consequently, the top eight variables—age, BMI, cumulative chemotherapy dose, hypertension, physical activity, depression, social support, and adherence to a healthy lifestyle—were included in the multivariate stepwise regression analysis.

Table 1
Univariate analysis of factors associated with CIPN in breast cancer patients receiving chemotherapy.

Item	Category	No CIPN Group (n = 270)	CIPN Group (n = 272)	t/Z/χ^2	*P*-value
Age (years)	18–44	139(51.5)	43(15.8)	103.621	<0.001
	45–59	114(42.2)	138(50.7)		
	60-	17(6.3)	91(33.5)		
TNM Stage	I	26(9.6)	39(14.3)	5.041	0.08
	II	138(51.1)	116(42.6)		
	III	106(39.3)	117(43.0)		
Surgical Method	Breast-conserving surgery	103(38.1)	87(32.0)	7.109	0.069
	Modified radical mastectomy	77(28.5)	74(27.2)		
Surgical Method	Simple mastectomy	76(28.1)	103(37.9)		
	Others (implants)	14(5.2)	8(2.9)		
Presence of a Fixed Caregiver	No	153(56.7)	182(66.9)	6.025	0.014
	Yes	117(43.3)	90(33.1)		
Educational Level	Primary school or below	54(20.0)	69(25.4)	3.841	0.279
	Junior high school	108(40.0)	111(40.8)		
	High school or vocational school	74(27.4)	68(25.0)		
	College or above	34(12.6)	24(8.8)		
Marital Status	Married	243(90.0)	236(86.8)	1.582	0.453
	Divorced	18(6.7)	22(8.1)		
	Widowed	9(3.3)	14(5.1)		
Smoking History	No	270(100.0)	269(98.9)	1.326	0.250
	Yes	0(0.0)	3(1.1)		
Alcohol Consumption History	No	268(99.3)	268(98.5)	0.161	0.688
	Yes	2(0.7)	4(1.5)		
Medical Insurance Type	Urban resident insurance	181(67.0)	194(71.3)	1.177	0.555
	Employee insurance	88(32.6)	77(28.3)		
	Other (insurance)	1(0.4)	1(0.4)		
Family Income (RMB/month)	<3000	37(13.7)	53(19.5)	5.577	0.134
	3000–4999	85(31.5)	80(29.4)		
	5000–7999	73(27.0)	81(29.8)		
	≥8000	75(27.8)	58(21.3)		
History of Hypertension	No	218(80.7)	142(52.2)	49.466	<0.001
	Yes	52(19.3)	130(47.8)		
Family History of Cancer	No	244(90.4)	239(87.9)	0.875	0.350
	Yes	26(9.6)	33(12.1)		
Body Mass Index (BMI)	<18.5	35(13.0)	7(2.6)	33.869	<0.001
	18.5~	122(45.2)	100(36.8)		
	25~	101(37.4)	134(49.3)		
	≥30	12(4.4)	31(11.4)		
Cumulative Dose of Chemotherapy (mg)	≤900	161(59.6)	100(36.8)	28.374	<0.001
	>900	109(40.4)	172(63.2)		
Frailty	Non-frail	98(36.3)	108(39.7)	5.824	0.054
	Pre-frail	152(56.3)	130(47.8)		
	Frail	20(7.4)	34(12.5)		
Infusion Time of Chemotherapy (min)	≤30	135(50.0)	133(48.9)	0.066	0.797
	>30	135(50.0)	139(51.1)		
Social Support	Low	46(17.0)	80(29.4)	17.063	<0.001
	Moderate	91(33.7)	100(36.8)		
	High	133(49.3)	92(33.8)		
Anxiety	No symptoms	146(54.1)	91(33.5)	24.467	<0.001
	Suspected	70(25.9)	113(41.5)		
	Confirmed	54(20.0)	68(25.0)		
Depression	No symptoms	177(65.6)	104(38.2)	66.656	<0.001
	Suspected	89(33.0)	112(41.2)		
	Confirmed	4(1.5)	56(20.6)		
Physical Activity	Low	25(9.3)	79(29.0)	53.480	<0.001
Physical Activity	Moderate	158(58.5)	161(59.2)		
	High	87(32.2)	32(11.8)		
Healthy Lifestyle	Low	35(13.0)	39(14.3)	15.503	<0.001
	Moderate	183(67.8)	212(77.9)		
	High	52(19.3)	21(7.7)		

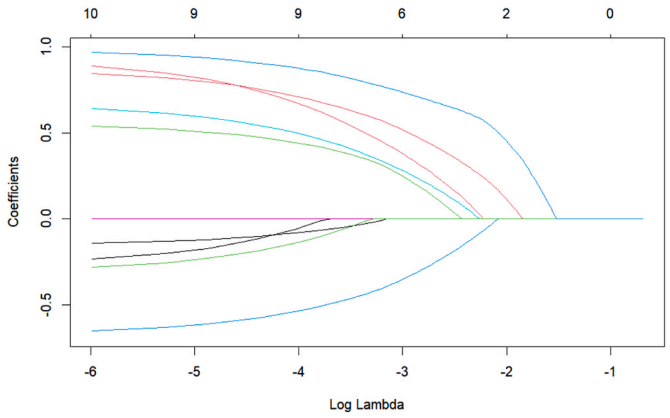

Fig. 1. Feature selection based on LASSO analysis.

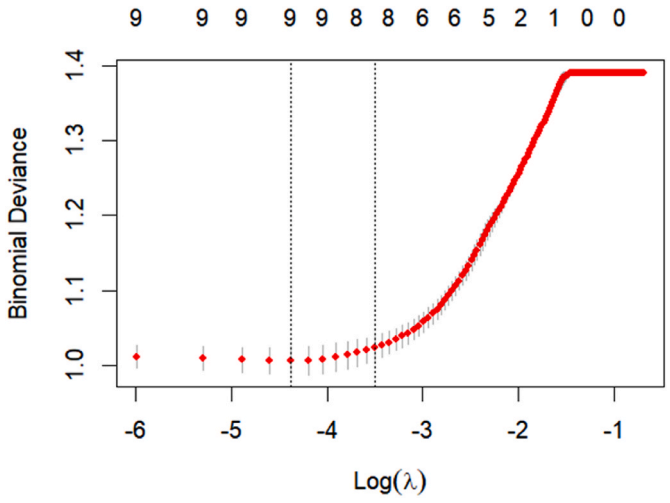

Fig. 2. LASSO regression with cross-validation.

3.3. Multivariate analysis of factors influencing CIPN in breast cancer patients undergoing chemotherapy

Multivariate stepwise regression analysis was conducted using the presence or absence of CIPN as the dependent variable and the statistically significant variables identified through Lasso regression as independent variables. The results indicated that age, BMI, cumulative chemotherapy dose, hypertension, physical activity level, and depression were the primary factors influencing the occurrence of CIPN (Table 2).

3.3.1. Ranking of variable importance

Using the presence or absence of CIPN as the dependent variable, variables identified as statistically significant in the binary logistic regression analysis were incorporated into a Random Forest model. The analysis was conducted using the Random Forest package in R Studio. The details of variable coding and assignment for the model are available in (Supplementary Table S1). The importance ranking of variables, in descending order, was as follows: age, BMI, cumulative chemotherapy dose, physical activity, hypertension, and depression(Fig. 3).

4. Discussion

The findings of this study indicate that age, body mass index (BMI), cumulative chemotherapy dose, physical activity, hypertension, and depression are major factors influencing the occurrence of chemotherapy-induced peripheral neuropathy (CIPN) in breast cancer patients.

Age emerged as the most critical factor associated with CIPN caused by taxane-based chemotherapy agents. As age increases, natural neurodegeneration, including the fragility of nerve fibers and myelin sheaths, combined with diminished metabolic and excretory functions, prolongs the retention of chemotherapeutic agents in the body, thereby elevating the risk of neurotoxicity [15–17]. Multiple studies have shown a positive correlation between age and CIPN severity. In particular, patients receiving paclitaxel and oxaliplatin exhibit a 4 % annual increase in neuropathy risk [15–17]. These findings underscore the importance of tailoring chemotherapy protocols for older patients. Personalized treatment plans that balance efficacy and safety are crucial, alongside vigilant monitoring and timely adjustments to mitigate neurotoxic risks. Preventive and therapeutic interventions, such as nerve-protective agents, could further minimize the burden of CIPN in

Table 2
Multivariate analysis of factors associated with CIPN in breast cancer patients receiving chemotherapy.

Factor	Category	B	S.E.	Wald	*P*-value	OR	95 % CI
Constant	–	−3.097	0.800	14.975	0.000	0.045	–
Hypertension	–	0.861	0.250	11.856	0.001	2.365	1.449–3.859
Cumulative Dose of Chemotherapy (mg)	–	0.572	0.231	6.131	0.013	1.771	1.127–2.785
BMI				16.920	0.001		3.654–15.450
	18.5~	1.309	0.567	5.338	0.021	3.703	
	25~	1.760	0.562	9.794	0.002	5.810	
	≥30	2.469	0.682	13.106	0.000	11.811	
Physical Activity	Low level	–	–	13.144	0.001	–	–
	Moderate level	−0.697	0.303	5.276	0.002	0.498	0.275–0.903
	High level	−1.368	0.377	13.144	0.000	0.255	0.121–0.533
Social Support	Low level	–	–	1.296	0.523	–	–
	Moderate level	0.038	0.298	0.016	0.898	1.039	0.580–1.862
	High level	−0.245	0.302	0.659	0.417	0.782	0.433–1.415
Depression	No symptoms	–	–	22.662	0.000	–	–
	Suspected	0.497	0.232	4.603	0.032	1.644	1.044–2.588
	Confirmed	2.691	0.589	20.849	0.000	14.745	4.645–46.802
Healthy Lifestyle	Low level	–	–	5.607	0.061	–	–
	Moderate level	0.061	0.331	0.034	0.853	1.063	0.556–2.033
	High level	−0.778	0.457	2.893	0.089	0.459	0.187–1.126
Age	18–44 years	–	–	32.926	0.000	–	–
	45–59 years	1.072	0.257	17.410	0.000	2.922	1.766–4.835
	60- years	2.017	0.368	30.070	0.000	7.514	3.654–15.450

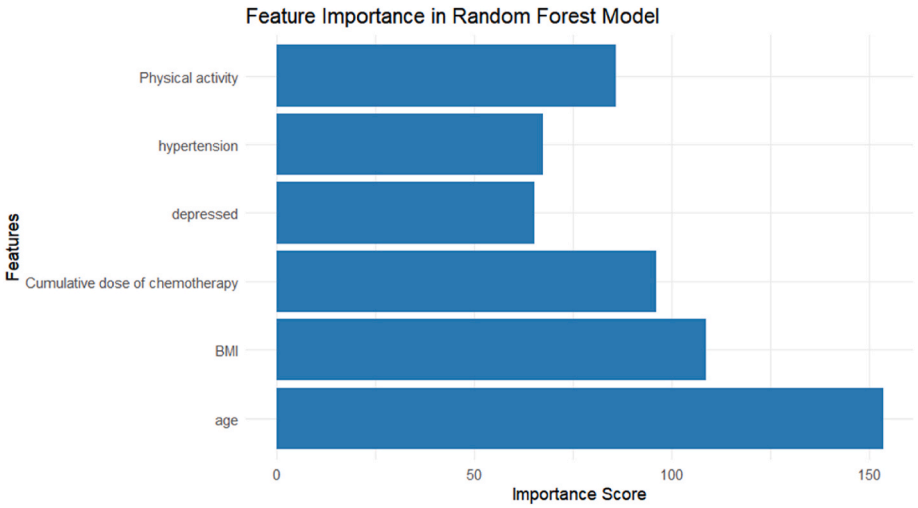

Fig. 3. Importance ranking of factors influencing peripheral neuropathy in breast cancer.

elderly patients.

BMI was identified as the second most significant factor. Elevated BMI is linked to a higher risk of CIPN, potentially due to increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which contribute to neuronal damage and exacerbate neuropathic symptoms. Obesity may alter the pharmacokinetics of chemotherapeutic agents, leading to their accumulation in adipose tissues, particularly for lipophilic drugs like paclitaxel, thereby increasing their neurotoxic effects [4]. Research by Bao T et al. reported that obese patients are 1.94 times more likely to develop CIPN compared to those with normal BMI [18]. Clinicians should emphasize the importance of maintaining a healthy weight through dietary guidance and physical activity to reduce CIPN risk. Nutritional counseling and lifestyle interventions tailored to obese patients could significantly mitigate this risk.

Cumulative chemotherapy dose ranked third among influencing factors. This study confirmed that the risk of CIPN increases significantly with higher cumulative doses of taxane-based chemotherapeutic agents. These drugs induce neuronal damage through mechanisms such as DNA synthesis inhibition, microtubule destabilization, and mitochondrial dysfunction [19]. For example, Guo Q et al. demonstrated a significant rise in CIPN risk when cumulative paclitaxel exposure exceeded 1500 mg/m^2 [20]. Therefore, personalized dosing regimens that minimize cumulative exposure without compromising therapeutic efficacy are essential. Adjunctive therapies, such as neuroprotective agents or physical therapies, should also be integrated into treatment plans to alleviate CIPN symptoms and enhance quality of life.

Physical activity was identified as the fourth critical factor inversely correlated with CIPN occurrence. Regular moderate-intensity activities, such as walking, yoga, or stretching, improve blood circulation, enhance oxygen delivery to nerve tissues, and promote neuronal metabolism [21]. Physical activity also strengthens the antioxidant defense system, reduces oxidative stress, and modulates inflammatory pathways by lowering levels of pro-inflammatory cytokines such as TNF-α and IL-6 [22]. Furthermore, physical activity stimulates the release of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which support nerve repair and regeneration. Studies have shown that patients engaging in moderate-to-vigorous activity experience lower CIPN rates and improved quality of life, including better physical functioning and social interactions [23,24]. Encouraging patients to adopt regular physical activity from the early stages of chemotherapy could significantly mitigate CIPN symptoms and enhance overall well-being.

Hypertension and depression were also significant factors. Hypertension contributes to CIPN by causing endothelial dysfunction and reducing blood flow to nerve tissues, impairing oxygen and nutrient delivery. Chronic hypertension may lead to microvascular damage, exacerbating structural and functional nerve fiber injury, particularly in elderly patients [4]. Depression, a common psychological comorbidity, may aggravate CIPN by altering pain perception thresholds and interfering with neuronal repair processes. Neurotransmitter imbalances, particularly reductions in serotonin and norepinephrine levels, are implicated in heightened nerve damage and diminished repair capacity [25]. Furthermore, depression is associated with increased systemic inflammation, evidenced by elevated levels of pro-inflammatory cytokines [18]. Effective hypertension management through lifestyle modifications and pharmacotherapy, coupled with timely psychological interventions such as cognitive-behavioral therapy, could mitigate the dual impact of these comorbidities on CIPN.

In summary, This study highlights age, BMI, cumulative chemotherapy dose, physical activity, hypertension, and depression as key factors influencing CIPN occurrence in breast cancer patients. Comprehensive management of these modifiable factors can effectively reduce CIPN risk and improve quality of life. Future research should focus on large-scale, longitudinal studies to explore CIPN progression and develop evidence-based strategies for prevention and intervention.

5. Summary

This study utilized random forest modeling and binary logistic regression analysis to identify critical factors influencing CIPN from demographic, clinical, and lifestyle data. The findings provide valuable insights for healthcare professionals to identify high-risk individuals and implement interventions to reduce CIPN incidence or severity. Further large-scale studies and extended follow-ups are necessary to deepen understanding and inform prevention and intervention strategies for CIPN in chemotherapy patients.

6. Limitations

The current study exclusively enrolled participants of Asian descent; hence, the findings may not be fully generalizable to other racial or ethnic groups. Future research should broaden the sample scope to include individuals from diverse backgrounds, thereby validating the universality and applicability of the current observations. Additionally, large-scale studies with extended follow-up periods will be conducted to further investigate the incidence and progression of chemotherapy-induced peripheral neuropathy (CIPN).

CRediT authorship contribution statement

Huiqian Xu: Conceptualization, Data curation, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Hong Li:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Yijing Fan:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Yaqi Wang:** Writing – review & editing, Supervision, Software, Investigation, Data curation, Conceptualization. **Zeyuan Li:** Validation, Software, Methodology, Investigation, Formal analysis. **Lizhi Zhou:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition. **Xijun Hao:** Visualization, Supervision, Methodology, Investigation, Formal analysis.

Patient consent statement

All patients participating in this study provided written informed consent. The consent forms detailed the study's purpose, procedures, potential risks, and measures to protect their rights and confidentiality. Participants' personal information was kept confidential throughout the study.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Ethics Committee of Tangshan People's Hospital (Approval No. RMYY-LLKS-2022-055). All participants were informed of the study's purpose and provided written informed consent prior to participation. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Conflict of interest statement

All authors declare no conflicts of interest that could influence the interpretation of the results of this research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2025.104457.

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