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*Original Article*

# Predictive models for breast cancer-related lymphedema after mastectomy

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**Abstract:** Objectives: To establish a nomogram incorporating clinical characteristics to predict the risk of breast cancer-related lymphedema (BCRL). Methods: In this retrospective study, we included 200 consecutive patients with breast cancer undergoing radical mastectomy from January 2022 to December 2023. Of these, 98 patients diagnosed with BCRL were designated as the experimental group, while 102 patients served as the control group. Logistic regression analyses were conducted to explore factors associated with clinical prognosis and to construct and validate a nomogram for predicting the risk of BCRL using R language version 4.1.2. Results: Univariate and multivariate logistic regression analyses identified six independent risk factors: the number of lymph node dissections (95% CI: 1.425-8.956, $P < 0.01$), radiotherapy (95% CI: 1.134-2.341, $P < 0.01$), lack of functional exercise (95% CI: 4.908-19.064, $P = 0.001$), adjuvant and neoadjuvant chemotherapy (95% CI: 1.763-4.287, $P = 0.001$), BMI (95% CI: 1.075-2.897, $P < 0.05$), and hypertension (95% CI: 1.077-2.999, $P < 0.05$). Using these variables, we developed a nomogram to predict the incidence of BCRL. The AUC value for the model was 0.74 (95% CI: 0.675-0.887), indicating acceptable agreement between predicted and observed outcomes. Decision curve analysis demonstrated good positive net benefits for the model. Conclusion: The number of lymph node dissections, radiotherapy, lack of functional exercise, adjuvant and neoadjuvant chemotherapy, BMI, and hypertension are independent risk factors for BCRL. Moreover, the nomogram prediction model showed good predictive performance, high accuracy, and clinical applicability.

**Keywords:** Upper extremity lymphedema, breast cancer, radical mastectomy, nomogram, model construction

## Introduction

Breast cancer is one of the most prevalent malignant tumors among women worldwide. According to the latest statistics from the Centers for Disease Control and Prevention in the United States, breast cancer accounts for 30% of all female cancer cases, ranking first in incidence [1, 2]. In China, the incidence of breast cancer has been rapidly increasing, with rates climbing annually [3, 4]. As medical technology advances, the survival rate of breast cancer patients has also improved. For instance, the breast cancer mortality rate in the United States decreased by 40% from 1989 to 2017 [2], while the 5-year relative survival rate in China is currently 73% [5].

Breast cancer treatment often includes axillary lymph node biopsy, dissection, and radiation therapy, which can lead to secondary lymphedema in the upper limbs [6]. Breast cancer-related lymphedema (BCRL) is a significant complication that affects the quality of life of long-term survivors and is one of the most common postoperative issues [7]. The prevalence of BCRL can reach up to 20% [8, 9], manifesting as limb swelling, pain, and restricted function, which contribute to anxiety, depression, and other negative emotional states in patients [10].

Currently, there is no consensus on the definitive risk factors for BCRL, and research findings are inconsistent. Some suspected risk factors are supported by limited studies, leading to ongoing debate and differing opinions about their significance in BCRL development. Although no reliable method exists to predict lymphedema onset in advance, certain high-

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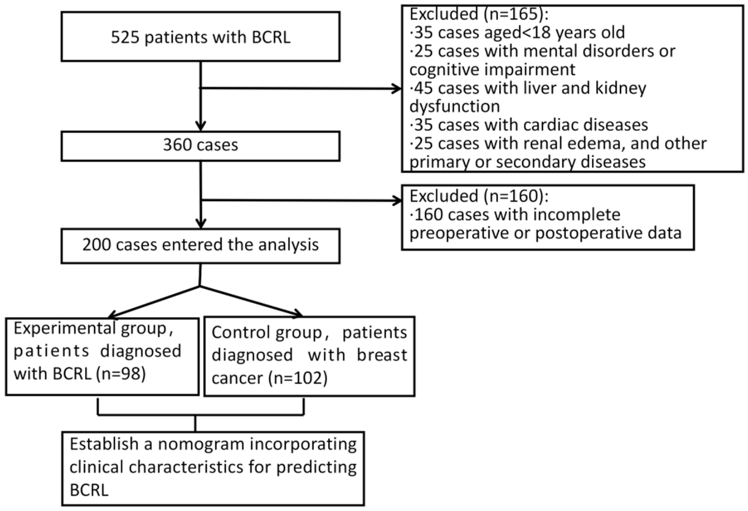


**Figure 1.** Flow diagram detailing the selection of patients included in this study. Note: BCRL: breast cancer-related lymphedema.

risk factors are widely acknowledged, including axillary lymph node dissection (ALND), regional lymph node radiotherapy (RLNR), high body mass index (BMI ≥ 25 kg/m$^2$) at the time of diagnosis, a high number of positive lymph nodes, and tumor capsule invasion [11-13]. The role of age as a risk factor for BCRL is particularly contentious; while some reports suggest that younger survivors are at higher risk [14], others indicate that older age is a significant risk factor [15], or that age is not related to BCRL at all [16]. Thus, further research is necessary to clarify the risk factors for BCRL and to establish a foundation for clinical practice.

The occurrence of BCRL is influenced by multiple postoperative factors. In addition to positive lymph nodes and tumor capsule invasion [11-13], age remains a controversial factor [15, 16]. Predicting the risk of recurrence in individual patients without comprehensive evaluation tools is challenging. Therefore, developing a personalized nomogram prediction model by analyzing BCRL risk factors is crucial for the scientific and effective management of these patients.

This study adopts a retrospective analysis approach to identify independent risk factors for the development of BCRL following breast cancer surgery and to construct a clinical prediction model. The objective is to provide a scientific basis for assessing BCRL risk in postoperative breast cancer patients, enabling the implementation of preventive measures to reduce complications and improve postoperative quality of life.

## Materials and methods

### *Study patients*

We retrospectively collected and analyzed the medical records of 200 postoperative breast cancer patients treated between January 2022 and December 2023 at Shenzhen Maternity and Child Healthcare Hospital. Among them, 98 patients diagnosed with BCRL were designated as the experimental group, while 102 patients without BCRL, who underwent breast cancer surgery during the same period, were randomly selected as the control group. The follow-up period for both groups was 12 months postoperatively. The selection process for patients included in this study is illustrated in **Figure 1**. This study was approved by the Ethics Review Board of Shenzhen Maternity and Child Healthcare Hospital.

Inclusion criteria: ① Pathological biopsy confirming a diagnosis of breast cancer, with patients having undergone standardized surgical treatment according to current breast cancer treatment guidelines (e.g., breast-conserving surgery, modified radical mastectomy, or latissimus dorsi breast reconstruction surgery, as well as receiving sentinel lymph node biopsy (SLNB) or ALND) [17]; ② No mental disorders or cognitive impairment; ③ Patients aged ≥ 18 years without significant hearing or vision impairment or dementia prior to surgery; ④ Complete and standardized medical records, including current and past medical history, laboratory and imaging results.

Exclusion criteria: ① Patients with limb edema caused by cardiac disease, renal edema, or other primary or secondary conditions; ② Patients with liver or kidney dysfunction or other severe organic diseases; ③ Patients with incomplete clinical data.

### *Data collection*

Two researchers (Chunchang Zhong and Hong Xiao) meticulously collected demographic and clinical data from the patients' medical records. The data included age, sex, underlying comorbidities, and clinical presentations.

The primary outcome was the performance of the predictive model, measured by the concordance index (c-index), calibration curve, decision curve analysis (DCA), and area under the receiver operating characteristic (ROC) curve (AUC). The secondary outcome was the collection of clinical data, including surgical treatment details (e.g., whether the breast was removed), the number of lymph nodes removed, the number of lymph nodes with axillary metastasis, patient age, body mass index (BMI), presence of hypertension and diabetes, chemotherapy, use of taxanes, radiation therapy, and other relevant factors. Cut-off values for lymph node quantity, lymph node metastasis quantity, age, and BMI were determined based on the characteristics of BCRL and previous research articles [11-16].

*Statistical analysis*

All statistical analyses were conducted using SPSS v26.0 (SPSS Inc.) and R software v4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Baseline patient, disease, and treatment characteristics were expressed as mean ± SD for continuous variables and frequency (%) for categorical variables. The nomogram, based on multivariate logistic regression analysis, was used to compute the predicted probability of BCRL for each patient. The prognostic performance of the nomogram was evaluated using the concordance index (c-index), calibration curve, DCA, and AUC. A $p$-value < 0.05 was considered statistically significant.

## Results

*Comparison of clinicopathological characteristics*

In our study, there were statistically significant differences between the two groups in terms of breast care, number of lymph node dissections, number of lymph node metastases, age, BMI, hypertension, radiotherapy, pathological staging of breast cancer, complications, functional exercise, and metastasis (all P < 0.05, **Table 1**).

*Multivariate logistic regression analysis*

The results of the multivariate logistic regression analysis indicated that the number of lymph node dissections (95% CI: 1.425-8.956, P < 0.01), radiotherapy (95% CI: 1.134-2.341, P < 0.01), lack of functional exercise (95% CI: 4.908-19.064, P < 0.01), adjuvant and neoadjuvant chemotherapy (95% CI: 1.763-4.287, P < 0.01), BMI (95% CI: 1.075-2.897, P < 0.05), and hypertension (95% CI: 1.077-2.999, P < 0.05) were independent risk factors for BCRL (**Table 2**).

*Development and validation of nomogram*

Based on the results of the multivariate logistic regression analysis, we constructed a nomogram that included these independent risk factors: number of lymph node dissections, radiotherapy, lack of functional exercise, adjuvant and neoadjuvant chemotherapy, BMI, and hypertension (**Figure 2**). The calibration curve (**Figure 3**) in the training set shows that the model's prediction curve closely aligns with the ideal curve, indicating that the model's prediction of BCRL risk is consistent with the actual risk and has high accuracy. Furthermore, the area under the ROC curve was 0.74, suggesting that the model has good predictive performance for BCRL risk (**Figure 4**).

*Clinical utility evaluation and validation*

The DCA curve demonstrated that the nomogram we constructed has high clinical utility for predicting BCRL risk (**Figure 5**).

## Discussion

This study retrospectively analyzed 200 cases of postoperative breast cancer, focusing on the general clinical data and various clinical indicators of the patients to identify independent risk factors for BCRL. The results demonstrated that lymph node dissections, radiotherapy, lack of functional exercise, adjuvant and neoadjuvant chemotherapy, BMI, and hypertension are independent risk factors for the development of BCRL. Using these six identified risk factors, a risk prediction model for BCRL was successfully constructed and subsequently evaluated and validated.

In our study, the incidence rate of BCRL was nearly 50%, which differs from the rates reported in current literature [8]. This discrepancy may be due to several factors: First, variations in the baseline health conditions of the patients included in this study and the type of surgery

**Table 1.** Comparison of clinicopathological characteristics

| Factor | Total number (n = 200) | Experimental group (n = 98) | Control group (n = 102) | χ² | P |
|---|---|---|---|---|---|
| Breast care | | | | 22.13 | < 0.005 |
| Yes | 84 (42.0%) | 26 (26.5%) | 58 (56.9%) | | |
| No | 116 (58.0%) | 72 (73.5%) | 44 (43.1%) | | |
| Number of lymph node dissections | | | | 23.87 | < 0.005 |
| < 10 | 90 (45.0%) | 29 (29.6%) | 61 (59.8%) | | |
| ≥ 10 | 110 (55.0%) | 69 (70.4%) | 41 (40.2%) | | |
| Number of lymph node metastases | | | | 6.78 | < 0.024 |
| < 4 | 137 (68.5%) | 65 (66.3%) | 72 (70.6%) | | |
| ≥ 4 | 63 (31.5%) | 33 (33.7%) | 30 (29.4%) | | |
| Age | | | | 0.01 | 0.007 |
| < 55 | 139 (69.5%) | 65 (66.3%) | 74 (72.6%) | | |
| ≥ 55 | 61 (30.5%) | 33 (33.7%) | 28 (27.5%) | | |
| BMI | | | | 13.78 | 0.047 |
| < 25 | 106 (53.0%) | 40 (40.8%) | 66 (64.7%) | | |
| ≥ 25 | 94 (47.0%) | 58 (59.2%) | 36 (35.3%) | | |
| Hypertension | | | | 6.68 | 0.021 |
| Yes | 56 (28.0%) | 34 (40.8%) | 22 (64.7%) | | |
| No | 144 (72.0%) | 64 (59.2%) | 80 (35.3%) | | |
| Diabetes | | | | - | - |
| Yes | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | |
| No | 200 (100.0%) | 98 (100.0%) | 102 (100.0%) | | |
| Chemotherapy | | | | 0.15 | 2.141 |
| Yes | 146 (73.0%) | 70 (71.4%) | 76 (74.5%) | | |
| No | 54 (27.0%) | 28 (28.6%) | 26 (25.5%) | | |
| Using yew species | | | | 0.87 | 0.476 |
| Yes | 64 (32.0%) | 30 (30.6%) | 34 (33.3%) | | |
| No | 136 (68.0%) | 68 (69.4%) | 68 (66.7%) | | |
| Radiotherapy | | | | 7.26 | 0.037 |
| Yes | 118 (59.0%) | 53 (54.1%) | 65 (63.7%) | | |
| No | 82 (41.0%) | 45 (45.9%) | 37 (36.3%) | | |
| Pathological classification of breast cancer | | | | 6.832 | 0.128 |
| Luminal A | 74 (37.0%) | 34 (34.8%) | 40 (39.2%) | | |
| Luminal B | 54 (27.0%) | 26 (26.5%) | 28 (27.5%) | | |
| Basal like type | 22 (11.0%) | 12 (12.2%) | 10 (9.8%) | | |
| HER2 positive | 50 (25.0%) | 26 (26.5%) | 24 (23.5%) | | |
| Pathological staging of breast cancer | | | | 12.654 | 0.003 |
| Phase I | 52 (26.0%) | 32 (32.7%) | 20 (19.6%) | | |
| Phase II | 96 (48.0%) | 40 (40.8%) | 56 (54.9%) | | |
| Phase III | 52 (26.0%) | 26 (26.5%) | 26 (25.5%) | | |
| Complications | | | | 3.608 | 0.006 |
| Yes | 72 (36.0%) | 30 (30.6%) | 42 (41.2%) | | |
| No | 128 (64.0%) | 68 (69.4%) | 60 (58.8%) | | |
| Functional exercise | | | | 2.012 | 0.002 |
| Yes | 96 (48.0%) | 20 (20.4%) | 76 (74.5%) | | |
| No | 104 (52%) | 78 (80%) | 26 (25.5%) | | |
| Partial execution | 56 (28.0%) | 38 (38.8%) | 18 (17.7%) | | |
| No | 48 (24.0%) | 40 (40.8%) | 8 (7.8%) | | |
| Metastasis | | | | 4.287 | 0.006 |
| Yes | 17 (8.5%) | 8 (8.2%) | 9 (8.8%) | | |
| No | 183 (91.5%) | 90 (91.8%) | 93 (91.2%) | | |

**Table 2.** Multivariate logistic regression analysis

| Factors | Bate | SE | Wald | OR | 95% CI | P |
|---|---|---|---|---|---|---|
| Number of lymph node dissections | 1.234 | 0.459 | 7.445 | 3.541 | 1.425-8.956 | 0.007 |
| Radiotherapy | 0.566 | 0.138 | 6.693 | 1.578 | 1.134-2.341 | 0.009 |
| Lack of functional exercise | 2.238 | 0.667 | 45.872 | 9.876 | 4.908-19.064 | 0.001 |
| Adjuvant and neoadjuvant chemotherapy | 0.984 | 0.238 | 15.872 | 2.876 | 1.763-4.287 | 0.001 |
| Body mass index | 0.667 | 0.276 | 4.986 | 1.765 | 1.075-2.897 | 0.034 |
| Hypertension | 0.456 | 0.254 | 4.587 | 1.748 | 1.077-2.999 | 0.032 |

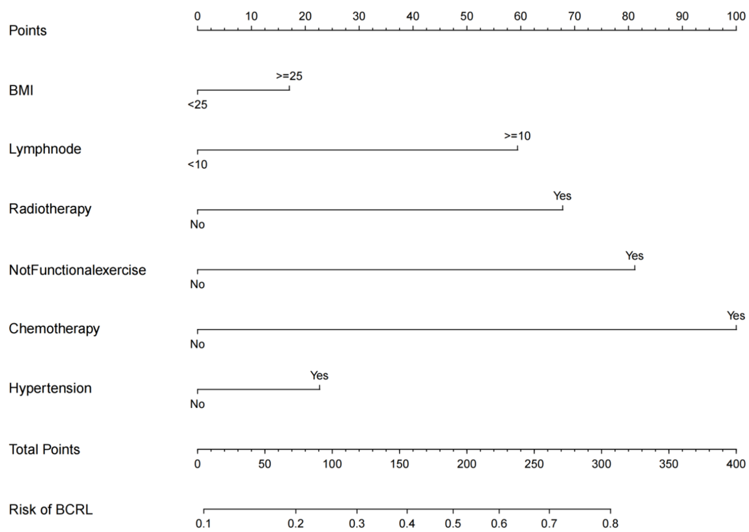


**Figure 2.** Nomogram for predicting BCRL. To use this nomogram, the corresponding position on each variable axis were located first. Then, a line was drawn vertically to the points axis above to obtain the respective points. Finally, the points from all six variables were added up, and a line was drawn from the corresponding position on the total points axis to the predicted value axis to determine the probability of BCRL. Note: BMI: body mass index; BCRL: breast cancer-related lymphedema.

they underwent may have influenced the risk of developing BCRL. Second, as this study is a retrospective analysis, selective bias may have impacted the findings. Lastly, the use of strict and specific diagnostic criteria [17] in this study could have contributed to differences in the reported incidence rate.

Postoperative lymphedema and shoulder joint dysfunction are significant factors affecting the quality of life in patients after breast cancer surgery [18]. Our study found that not engaging in functional exercise is an independent risk factor for BCRL. This finding supports the notion that early postoperative functional exercise can effectively prevent the occurrence of lymphedema. Other studies have also identified postoperative functional exercise as a protective factor against upper limb lymphedema, consistent with our results [19]. Early systematic functional exercise promotes blood circulation in the affected limb, increases lymphatic flow, and reduces the likelihood of edema. Additionally, early functional exercise can soften scar tissue formed after surgery, enhance local mobility, prevent scar contracture compression, and promote functional recovery.

Research has shown that patients often experience negative emotional reactions after surgery, such as emotional distress and reluctance to engage in activities, due to changes in their self-image and incision pain [20]. Functional exercise has been reported to improve emotional well-being and reduce the risk of disease recurrence [21]. Therefore, it is crucial to strengthen patient education and psychological care before and after surgery, encouraging patients to pay attention to lymphedema, increase their motivation to exercise, and improve postoperative limb function while preventing upper limb lymphedema. Clinical healthcare providers should develop appropriate functional exercise plans based on patients' age, surgical method, and pain tolerance, progressing gradually and avoiding overexertion. Teaching patients upper limb exercise methods and monitoring the effects of exercise can improve postoperative limb function and prevent upper limb lymphedema.

The results of this study indicate that hypertension is a risk factor for BCRL. Analysis reveals that hypertensive patients have elevated levels of vasoconstrictors such as vasopressin

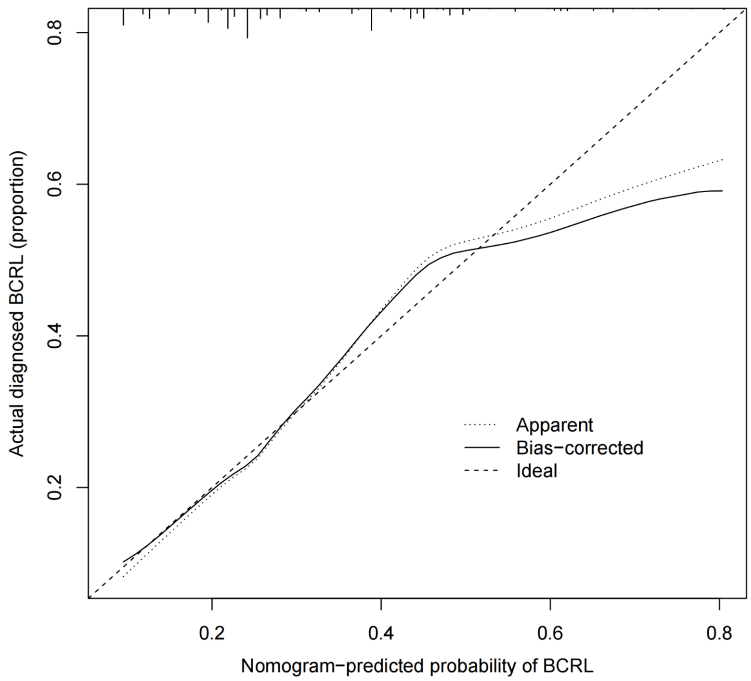


**Figure 3.** Calibration curve of the nomogram. The Ideal line represents a perfect model where predicted probabilities exactly match the actual probabilities. The Apparent line represents the performance of the nomogram model before applying the bootstrap re-sampling method, while the Bias-corrected line shows the model's performance after bootstrap correction. Note: BCRL: breast cancer-related lymphedema.

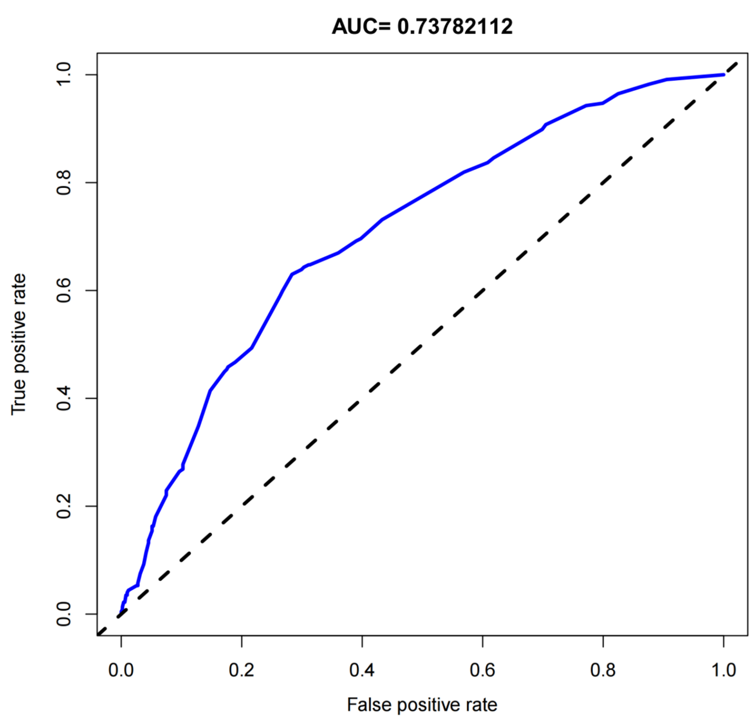


**Figure 4.** ROC curve area. The value of the area under ROC curve (AUC) was 0.73782112 (95% confidence interval of 0.675-0.887).

and neurotransmitters like 5-hydroxytryptamine (5-HT) in their blood and tissue fluid. These neurotransmitters maintain continuous excitation of the sympathetic nervous system, making edema more likely to occur [22]. Long-term regulation of arterial blood pressure primarily occurs through the renal-fluid control system. After breast cancer surgery, extracellular fluid accumulates, increasing circulating blood volume and disrupting the balance between circulating blood volume and vascular capacity, which further elevates arterial blood pressure [23]. Hypertensive patients experience increased fluid entry into tissues through veins, leading to greater tissue fluid formation. Postoperatively, when lymphatic return is restricted and compensation is lost, BCRL may be triggered [24]. Therefore, it is essential to effectively control hypertension in postoperative breast cancer patients through medication or other means. However, calcium channel blockers should be avoided, as they can easily induce upper limb lymphedema after surgery.

This study also identifies the number of lymph node dissections as an independent risk factor for BCRL. Research has shown that when 10 or more lymph nodes are removed during breast cancer surgery, the incidence of upper limb lymphedema increases (OR = 2.16, 95% CI = 1.12-4.17) [25]. Two primary mechanisms are proposed to explain the development of upper limb lymphedema. The first is the early lymphatic obstruction theory, which posits that during axillary lymph node removal, a signifi-

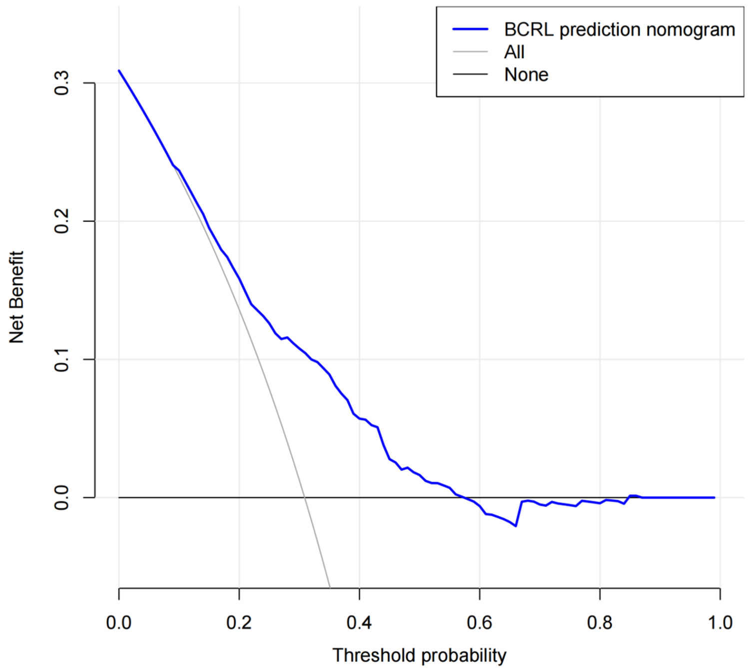


**Figure 5.** Decision curve analysis of the nomogram model. The decision curve indicates that when the threshold probability of BCRL is between 40% and 80%, applying this nomogram would provide a net benefit. Note: BCRL: breast cancer-related lymphedema.

cant number of lymphatic vessels are severed, obstructing the upper limb lymphatic drainage pathway and leading to tissue fluid accumulation and limb swelling [26]. The second theory, lymphatic pump dysfunction, suggests that ALND causes the lymphatic pump to operate under long-term overload, eventually leading to uncompensated upper limb lymphedema [27]. Both mechanisms highlight that surgery damages the lymphatic system, obstructing lymph circulation in the upper limb and causing the accumulation of protein-rich lymph in the interstitial spaces. The increased colloid osmotic pressure in the interstitial spaces initially triggers compensation in the upper limb lymphatic system. However, long-term repeated inflammation and high concentrations of tissue fluid lead to fibrosis of subcutaneous tissues, further obstructing lymph circulation. The residual lymphatic vessels and lymph nodes after surgery eventually reach a state of decompensation, causing lymphatic pump failure, exacerbating lymphedema, and creating a vicious cycle.

This study also found that the incidence of lymphedema was higher in patients who received radiotherapy. RLNR has been recognized as a risk factor for upper limb lymphedema, even in patients who undergo RLNR without ALND, and such patients should be considered at high risk for developing lymphedema [28]. Recent studies have shown that breast cancer patients who receive local or comprehensive lymph node radiotherapy after surgery experience increased disease-free and distant metastasis-free survival rates and reduced breast cancer-related mortality, but no overall survival benefit. Radiotherapy has become an indispensable and important component of breast cancer treatment [29]. However, radiotherapy can cause lymphatic vessel damage and obstruction, leading to the accumulation of protein-rich fluid in the interstitial space, stimulating endothelial cell proliferation, and inducing fibrotic changes. Additionally, radiotherapy can trigger inflammation, such as radiation dermatitis, endothelial cell proliferation, and basal cell damage, which further promote lymphedema occurrence and progression [30]. Based on the results of this study, we believe that increasing the target area and dose of radiotherapy may elevate the risk of upper limb lymphedema in breast cancer patients post-surgery. The "Chinese Anti-Cancer Association Breast Cancer Diagnosis and Treatment Guidelines and Norms (2019 Edition)" recommend postoperative radiotherapy for $T_1$ stage breast cancer with 1-3 lymph node metastases, as evidence suggests it reduces local recurrence rates, recurrence at any site, and breast cancer-related mortality. However, for low-risk subgroups, the benefits and risks of radiotherapy must be carefully balanced [31]. Therefore, we recommend individualizing radiotherapy dose and target area while adhering to radiotherapy indications, assessing risks and benefits, and minimizing the risk of lymphedema.

This study found that as BMI increases, the incidence of upper limb lymphedema also rises.

BMI is already recognized as one of the independent risk factors for upper limb lymphedema following breast cancer surgery, especially when BMI exceeds 30 kg/$m^2$, significantly increasing the risk in obese patients. Currently, over 50% of breast cancer patients are overweight or obese. A 2019 meta-analysis on the risk of BCRL in overweight and obese patients showed that obese patients are at a greater risk of developing BCRL compared to overweight patients [32]. The mechanisms by which obesity promotes BCRL are not yet fully understood. Some studies suggest that lymphatic vessels regulate fluid balance, lipid absorption, and immune responses, and obesity may promote lymphedema, while impaired lymphatic function can lead to fat accumulation and fibrosis [33]. Individuals with a high BMI require more blood circulation and lymphatic system activity to promote fluid flow, leading to lymphatic imbalance and circulatory obstruction. Obesity also causes various cardiovascular issues, such as hypertension and microvascular changes, further increasing circulatory load [34]. Additionally, obesity is more likely to cause fat necrosis, leading to wound infections and poor healing, which reduces the efficiency of the muscle pump in the loose tissue below, separating deep lymphatic channels from excess subcutaneous fat, thereby promoting the occurrence of upper limb lymphedema [35]. Comprehensive decongestive therapy is currently the most commonly used treatment for lymphedema, but obesity reduces the effectiveness of it, and damage to the lymphatic system is not reversed by weight loss.

Our study also suggests that adjuvant and neoadjuvant chemotherapy are potential risk factors for BCRL. In a recent prospective cohort study conducted by Kilbreath and colleagues, arm swelling at 6 and 12 months was associated with adjuvant paclitaxel therapy, and swelling at both time points was an independent risk factor for lymphedema development [36]. Neoadjuvant chemotherapy is used in breast cancer treatment to reduce the size of the primary tumor and any affected lymph nodes, thereby reducing the extent of surgery [37]. Some studies suggest that neoadjuvant chemotherapy may theoretically reduce the incidence of BCRL by reducing the number of positive lymph nodes [38]. On the other hand, neoadjuvant chemotherapy is generally believed to increase the incidence of breast-conserving surgery by reducing the occurrence of lymphedema through downstaging of lymph node involvement [39]. However, there are concerns that changes in lymphatic drainage after neoadjuvant chemotherapy may lead to a high false-negative rate in SLNB. Therefore, caution should be exercised when selecting SLNB for patients after neoadjuvant chemotherapy, especially for clinically lymph node-positive patients. Further research with long-term follow-up data in a large population is needed to determine the risk factors for lymphedema in patients undergoing SLNB after neoadjuvant chemotherapy.

There are limitations to this study. The nomogram lacks sufficient predictive factors to provide absolute predictions. Some known factors may not have been incorporated due to the absence of data or observations, and there may be undisclosed biomarkers. Additionally, this study lacks external data for validation; therefore, future studies with larger sample sizes are needed to further validate these findings.

In conclusion, based on the identified risk factors for BCRL, this study constructed a nomogram prediction model with good predictive performance, high accuracy, and clinical applicability. The model is simple and easy to use in clinical practice, safe and non-invasive for screening, and easily accepted by both doctors and patients. It helps to identify high-risk populations for BCRL early, improving detection rates and reducing complications caused by excessive invasive examinations. This provides an economically effective means of BCRL screening for clinical practice, which is of great medical and social significance.

## Disclosure of conflict of interest

None.

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