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ORIGINAL RESEARCH

Development and Validation of Upper Limb Lymphedema in Patients After Breast Cancer Surgery Using a Practicable Machine Learning Model: A Retrospective Cohort Study

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Objective: Upper limb lymphedema is one of the most common adverse events related to surgery owing to the large gap between guideline implementation and the intended clinical outcomes. However, the monitoring of limb lymphedema remains challenging because of vague clinical presentations. This study aimed to develop and validate practical predictive models for upper limb lymphedema through machine learning.

Methods: We retrospectively collected clinical data to develop models for early risk prediction of upper limb lymphedema based on a single-center electronic health record data from patients who underwent breast cancer surgery from June 2021 through June 2023. For prediction model building, 70% and 30% of the data were randomly split into training and testing sets, respectively. We then developed an upper limb lymphedema prediction model using machine learning algorithms, which included random forest model (RFM), generalized logistic regression model (GLRM), and artificial neural network model (ANNM). For evaluating the model's performance, we used the area under the receiver operating characteristic curve (AUROC), calibration curve to compare different models. The potential clinical usefulness of the best model at the best threshold was assessed through a net benefit approach using a decision curve analysis (DCA).

Results: Of the 3201 patients screened for eligibility, 3160 participants were recruited for the prediction model. Among these, Body Mass Index (BMI), hypertension, TNM, lesion site, level of lymph node dissection(LNMD), treatment, and nurse were independent risk factors for upper limb lymphedema and were listed as candidate variables of ML-based prediction models. The RFM algorithm, in combination with seven candidate variables, demonstrated the highest prediction efficiency in both the training and internal verification sets, with an area under the curve (AUC) of 0.894 and 0.889 and a 95% confidence interval (CI) of 0.839–0.949 and 0.834–0.944, respectively. The other two types of prediction models had prediction efficiencies between AUCs of 0.731 and 0.819 and 95% CIs of 0.674–0.789 and 0.762–0.876, respectively.

Conclusion: The interpretable predictive model helps physicians more accurately predict the upper limb lymphedema risk in patients undergoing breast cancer surgery. Especially for the RFM, this newly established machine learning-based model has shown good predictive ability for distinguishing high risk of upper limb lymphedema, which could facilitate future clinical decisions, hospital management, and improve outcomes.

Keywords: upper limb lymphedema, breast cancer surgery, machine learning, risk, prediction

Introduction

According to the 2020 global cancer disease burden data report, the number of new cases of breast cancer has become the malignant tumor with the highest new incidence rate in the world.[1,2] Surgery, as one of the important

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means of clinical treatment of breast cancer, can effectively improve the prognosis of patients.[3] However, with the prolongation of the survival period, more attention has been paid to the quality of life of breast cancer patients after surgery, especially the complications caused by surgery cannot be ignored. Upper limb lymphedema is the most common complication of breast cancer patients after surgery. The incidence rate reported in the past is about 15% to 30%, and with the development of breast cancer, its risk will also increase.[4,5] Previous studies have shown that long-term upper limb edema in patients can seriously affect their limb shape and daily labor activity, as well as increase the risk of lymphangitis.[6,7] Therefore, it is necessary to achieve personalized prediction of the risk of early postoperative lymphedema in patients and early prevention of postoperative upper limb lymphedema.

At present, there is no effective prediction method for upper limb lymphedema in clinical practice. Common methods include circumference measurement, water displacement, infrared analysis, bioelectrical impedance, and subjective symptom evaluation.[8,9] However, considering the unsatisfactory clinical promotion and practicality, there is an urgent need to optimize warning strategies. Many research groups have attempted to address issues such as difficulty in early prediction of limb lymphedema using electronic health records (EHR) data, but so far, there is a clear need for interpretable and actionable predictive tools to be applied in clinical practice, but no model has explained the operability and clinical utility of specific predictions.[10] Fortunately, machine learning methods have shown significant performance in medicine, especially in using advanced clinical practice algorithms to construct disease diagnosis and prognosis prediction models, highlighting their unparalleled advantages.[11] This also means that they will play an important guiding role in joint decision-making between doctors and patients.

In view of this, in this study, we will explore the risk of upper limb lymphedema after breast cancer surgery based on machine learning algorithms and build an effective prediction model, in order to provide guidance for clinical prevention and individualized prevention and treatment of upper limb lymphedema.

Materials and Methods

Study Population

The clinical data of patients diagnosed with breast malignant diseases who need to be hospitalized for surgery from January 2021 to June 2023 were retrospectively analyzed, and candidate clinical variables were screened to construct the prediction model. The inclusion criteria was as follows: 1) Patients who meet the diagnosis of breast cancer and are confirmed by postoperative pathology; 2) Patients aged ≥18 years and under 70 years old; 3) Patients who meet the surgical indications and need breast cancer surgery; 4) Patients with complete clinical follow-up data. Exclusion criteria: 1) Patients who received other anti-tumor treatments before admission; 2) Patients with significant organ dysfunction or tumors in other parts of the body; 3) Patients with combined symptoms of malnutrition, cardiogenic, and nephrogenic edema; 4) Patients with a history of significant upper limb trauma or surgery; 5) Pregnant or lactating patients.

Considering that each independent variable of the machine learning prediction model needs to meet at least 5 to 10 patients, and that there may be 10% to 20% of samples that do not meet the requirements during the data collection process, the sample size required for this study is calculated according to the following formula: 20 × ten × (1+0.2) ×0.13 (incidence rate). Finally, a total of 3201 patients were included in the study, and 3160 eligible patients were randomly divided into training set (70%) and test set (30%).

Diagnostic Criteria for Postoperative Limb Lymphedema

Diagnostic criteria and follow-up methods for upper limb lymphedema are as follows: Patients have discomfort such as heaviness, soreness, and swelling in their upper limbs, and the difference in circumference between the affected wrist joint, ulna olecranon, and healthy side is ≥ 2cm in any part of the upper limb.[12] At the same time, we also follow-up patients for six months or more through WeChat, telephone communication, and outpatient follow-up to record the occurrence of upper limb lymphedema in patients.

Postoperative Nursing Strategies

General nursing are as follows: for the postoperative nursing of patients with breast cancer, we advocate that patients stay in bed after surgery (that is, no more than 8 hours a day), and pay attention to keeping patients' skin clean and lifting patients' limbs (that is, 25–30cm from the heart plane). In addition, the patient's postoperative limb warmth, skin color, skin temperature, etc. are monitored, and the circumference of different planes of the affected limb is monitored and recorded daily. In terms of patient clothing, it is recommended that patients wash their affected limbs with warm water and move gently. And after the surgery, adhere to daily skin massage (stop if there is any damage) 2–4 times, and if there is intermittent inflation and contraction pump, twice a day, 30–60 minutes per time. Dietary care: Instruct patients to have a low salt, low-fat, and high protein diet after surgery. Medication treatment nursing: When patients receive medication to clear circulation after surgery, the infusion rate should be controlled at 40 drops/min to avoid discomfort such as dizziness, headache, and palpitations.[4,13]

Data Source and Predictor Variables Collection

We collect the general information of the research subjects through the hospital medical record system, including gender, age, height, weight, and underlying diseases, and so on. For the variable with missing value (usually refers to that the missing value of the variable is less than 10%), the mean value of the variable shall be filled. If ≥10% of the given variables are missing, this value is excluded from the variable screening of the final model. Similarly, for missing values that meet the interpolation requirements, this study adopted unit feature interpolation, that is, missing values can be interpolated using the constant values provided, or using the statistical data of each column where the missing values are located (average value, median value or the most frequently occurring value).

Machine Learning Explainable Tool

We used three machine learning algorithms: generalized logistic regression model (GLRM), random forest model (RFM), and artificial neural network model (ANNM).[11,14] As an extension of the linear model, the generalized linear model establishes the relationship between the mathematical expectation value of the response variable and the prediction variable of the linear combination through the connection function, so it is a development of the linear model when studying the non-normal distribution of the response value and the simple and direct linear transformation of the nonlinear model. The random forest algorithm consists of a multitude of decision trees comprising multiple true or false conditions using input variables. The deep neural network comprises layers of interconnected artificial neurons. An artificial neuron is designed based on the biological neuron itself and receives multiple inputs multiplied by weights and outputs the sum of the inputs. The sum of the decisions made by the decision trees is used for the final classification.

Statistical Analysis

All statistical analysis and calculations were performed using R software and Python (version 3.8.0; Python Software Foundation). The categorical variables are expressed as total numbers and percentages, and the $\chi 2$ test or Fisher exact test (expected frequency <10) is used to compare the differences between groups (that is, limb lymphedema group and non-limb lymphedema group). The continuous variables are expressed as median and inter-quartile range(IQR), and the Wilcoxon rank sum test is used when comparing the two groups. Statistical significance was defined as a two-tailed P-value of < 0.05.

Results

Patient Characteristics

Among 3201 patients who underwent breast cancer surgery in our hospital during the past three years, a total of 3160 patients diagnosed were included in the final cohort for this study. The patient screening process is shown in Figure 1. The data set was randomly divided into two parts: 70% (n=2212) of the data were used for model training, and 30% (n=948) of the data were used

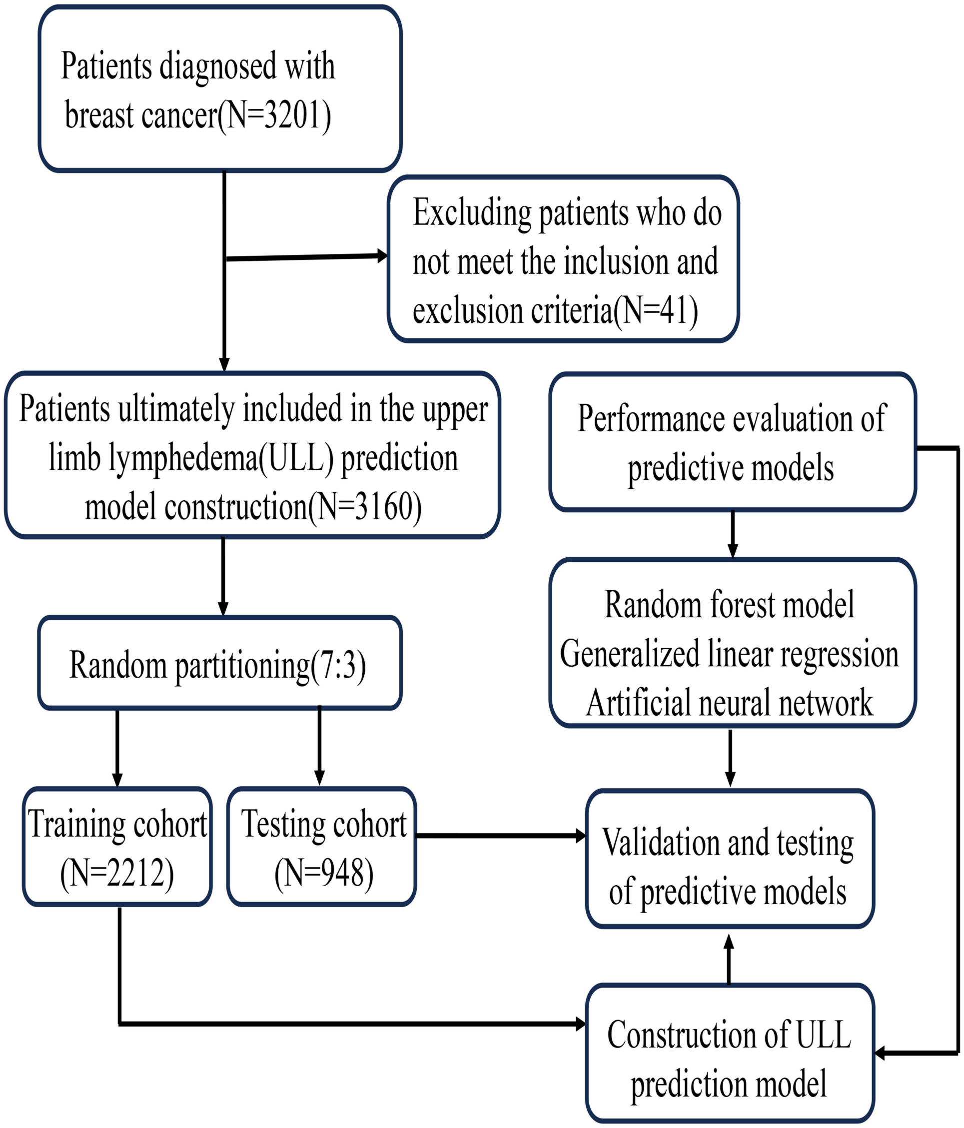

Figure 1 Patient selection and prediction model construction process.

for model validation. We found that Body Mass Index (BMI), hypertension, Tumor Node Metastasis (TNM), lesion site, level of lymph node dissection(LNMD), treatment, and nurse showed significant statistical differences (P values less than 0.05) in the inter-group comparison, suggesting that they may become candidate variables for upper limb lymphedema. Table 1 and Supplementary Table 1 showed the comparisons of predictor variables between limb lymphedema group and non-limb lymphedema group after breast cancer surgery.

Predictor Variables Selection

The LASSO regularization process resulted in potential predictors on the basis of patients in the training data set, which were used for model developing. As the included candidate variables were inevitably biased and had a non-normal distribution, we added penalty terms to the loss function (ie, optimization goal) during the training and parameter-solving processes. This allowed the size of the coefficient to be considered. By setting a reduction coefficient (penalty coefficient), the coefficient of features with less impact was reduced to zero, retaining only important features, which is known as LASSO regression. Specifically, cross-validation was performed on all candidate parameters, and a dashed line was drawn at the optimal parameter (ie, nine for non-zero parameters) to indicate the best-fitted LASSO regression

Table 1 Patient Baseline Characteristics

Variables	Overall (N=3160)	Yes (N=410)	No (N=2750)	P-Value
Sex (%)				
Male	1602 (50.7)	227 (55.4)	1375 (50.0)	0.048
Female	1558 (49.3)	183 (44.6)	1375 (50.0)	
Age (median [IQR]), year	43.00 [30.00, 56.00]	43.00 [30.00, 56.00]	43.00 [30.00, 56.00]	0.599
BMI (median [IQR]), kg/m2	22.30 [20.90, 23.80]	28.30 [26.40, 30.17]	22.00 [20.70, 23.20]	<0.001
Diabetes (%)				
Yes	1518 (48.0)	204 (49.8)	1314 (47.8)	0.488
No	1642 (52.0)	206 (50.2)	1436 (52.2)	
Hypertension (%)				
Yes	1246 (39.4)	279 (68.0)	967 (35.2)	<0.001
No	1914 (60.6)	131 (32.0)	1783 (64.8)	
TNM (%)				
I–II	1957 (61.9)	149 (36.3)	1808 (65.7)	<0.001
IIIa	1203 (38.1)	261 (63.7)	942 (34.3)	
Site (%)				
Unilateral	1953 (61.8)	133 (32.4)	1820 (66.2)	<0.001
Bilateral	1207 (38.2)	277 (67.6)	930 (33.8)	
Pathology (%)				
Invasive ductal carcinoma	1094 (34.6)	137 (33.4)	957 (34.8)	0.829
Infiltrating lobular carcinoma	1059 (33.5)	142 (34.6)	917 (33.3)	
Others	1007 (31.9)	131 (32.0)	876 (31.9)	
Tumor diameter (%), cm				
≥2	1576 (49.9)	210 (51.2)	1366 (49.7)	0.595
<2	1584 (50.1)	200 (48.8)	1384 (50.3)	
Differentiation (%)				
Medium to high	1052 (33.3)	128 (31.2)	924 (33.6)	0.493
Low	1065 (33.7)	137 (33.4)	928 (33.7)	
Undifferentiated	1043 (33.0)	145 (35.4)	898 (32.7)	
Surgery (%)				
Resection	777 (24.6)	102 (24.9)	675 (24.5)	0.182
Curative	825 (26.1)	96 (23.4)	729 (26.5)	
Extended radical	775 (24.5)	94 (22.9)	681 (24.8)	
Modified radical	783 (24.8)	118 (28.8)	665 (24.2)	
LNMD (%)				
I–II	2046 (64.7)	151 (36.8)	1895 (68.9)	<0.001
III	1114 (35.3)	259 (63.2)	855 (31.1)	
NLM (median [IQR])	14.00 [13.00, 15.00]	14.00 [13.00, 15.00]	14.00 [13.00, 15.00]	0.918
Treatment (%)				
Yes	1265 (40.0)	279 (68.0)	986 (35.9)	<0.001
No	1895 (60.0)	131 (32.0)	1764 (64.1)	
Nurse (%)				
Yes	1924 (60.9)	147 (35.9)	1777 (64.6)	<0.001
No	1236 (39.1)	263 (64.1)	973 (35.4)	

Abbreviations: IQR, interquartile range; BMI, Body mass index; LNMD, Level of lymph node dissection; NLM, Number of lymph nodes cleaned.

model. In the subsequent prediction model analysis, the optimal lambda value selected was substituted into the LASSO coefficient curve containing candidate variables, that was BMI, hypertension, TNM, lesion site, LNMD, treatment, and nurse. As shown in Figure 2, these variables were used to predict the risk propensity of limb lymphedema.

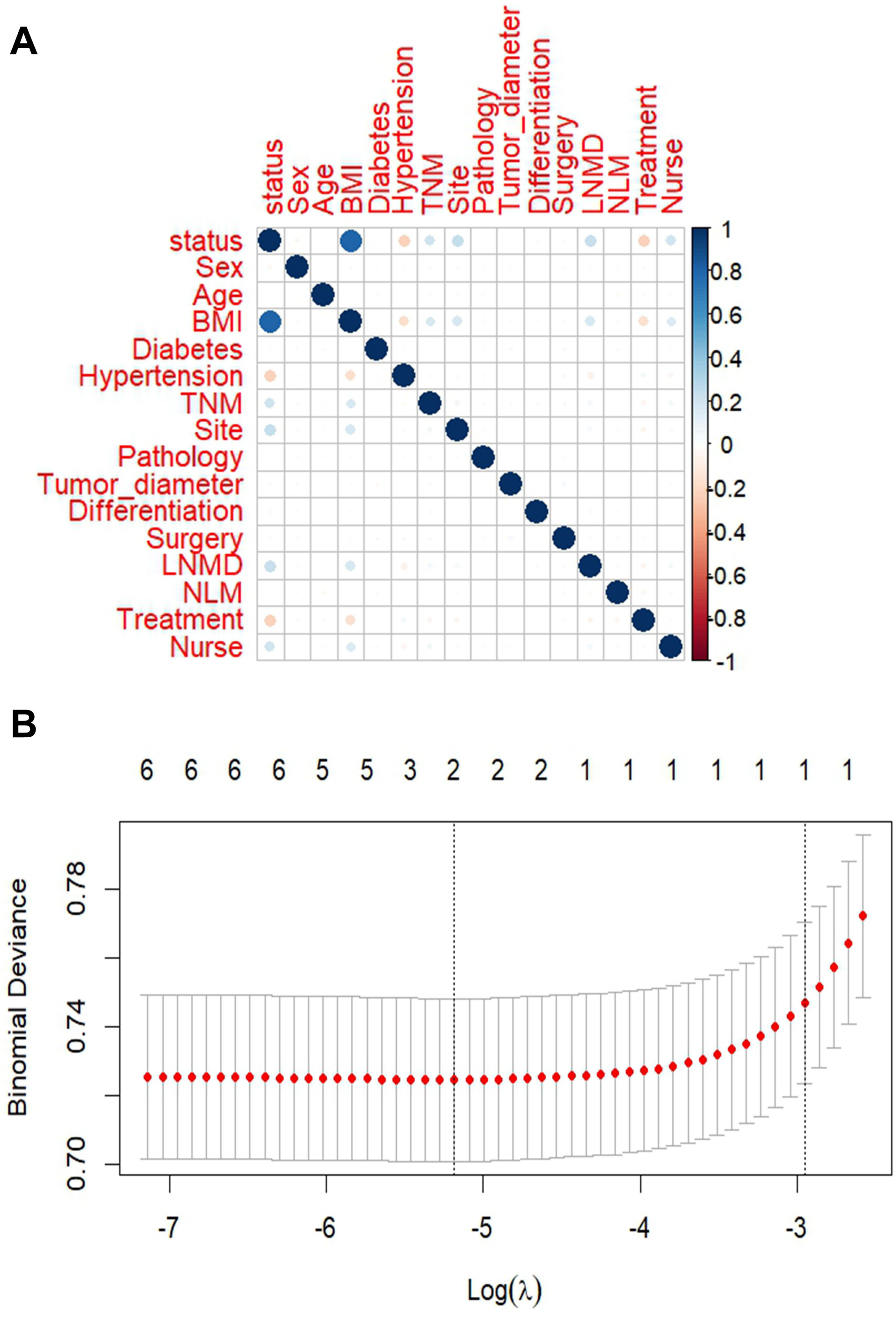

Figure 2 Selection of upper limb lymphedema candidate predictive variables based on LASSO regression (**A**) Spearman correlation analysis; (**B**) LASSO regression analysis.

Model Building Based-on Machine Learning Algorithms

As shown in Table 2, we conducted a multivariate logistic regression analysis on all included candidate variables and found that seven variables were independent risk factors for limb lymphedema, including BMI, hypertension, TNM, lesion site, LNMD, treatment, and nurse. Based on the Akaike information criterion, we developed a predictive model for limb lymphedema and a nomogram (Figure 3). The nomogram shows the overall variables included in the prediction model on the left side, and each variable is assigned a scale value. The total score can be obtained by assigning scores to

Table 2 Selection of Upper Limb Lymphedema Predictive Variables Based on Logistic Regression

Variables	Univariate			Multivariate		
	OR	95% CI	P-Value	OR	95% CI	P-Value
Sex (%)						
Male	1.00					
Female	0.87	0.23–1.23	>0.05			
Age (median [IQR]), year	1.25	0.56–2.26	>0.05			
BMI (median [IQR]), kg/m2	1.18	0.56–2.28	<0.05	1.12	0.41–2.21	<0.05
Diabetes (%)						
Yes	1.00					
No	0.75	0.13–4.15	>0.05			
Hypertension (%)						
Yes	1.00					
No	0.87	0.21–2.28	<0.05	0.79	0.12–1.54	<0.05
TNM (%)						
I–II	1.00					
IIIa	2.15	1.08–3.76	<0.05	2.04	0.99–3.41	<0.05
Site (%)						
Unilateral	1.00					
Bilateral	1.85	0.74–2.71	<0.05	1.58	0.46–2.64	<0.05
Pathology (%)						
Invasive ductal carcinoma	1.00					
Infiltrating lobular carcinoma	0.56	0.11–1.25	>0.05			
Others	0.72	0.24–2.72	>0.05			
Tumor diameter (%), cm						
≥2	1.00					
<2	0.78	0.13–1.27	>0.05			
Differentiation (%)						
Medium to high	1.00					
Low	1.23	0.16–2.85	>0.05			
Undifferentiated	0.99	0.16–2.07	>0.05			
Surgery (%)						
Resection	1.00					
Curative	0.72	0.12–1.45	>0.05			
Extended radical	0.83	0.31–2.47	>0.05			
Modified radical	0.75	0.13–2.26	>0.05			
LNMD (%)						
I–II	1.00					
III	2.23	0.35–4.16	<0.05	2.02	0.56–3.98	<0.05
NLM (median [IQR])	0.83	0.11–1.59	>0.05			
Treatment (%)						
Yes	1.00					
No	0.91	0.53–1.89	<0.05	0.88	0.34–1.78	<0.05
Nurse (%)						
Yes	1.00					
No	0.77	0.21–2.87	<0.05	0.67	0.17–2.76	<0.05

Abbreviations: OR, Odd ratios; 95% CI, 95% confidence interval; BMI, Body mass index; LNMD, Level of lymph node dissection; NLM, Number of lymph nodes cleaned.

each variable for the included patients. Finally, the probability of limb lymphedema in patients can be evaluated based on the corresponding risk scale value of the total score. Moreover, the C-index value, which was verified internally by the bootstrap method, was 0.751, indicating good clinical applicability.

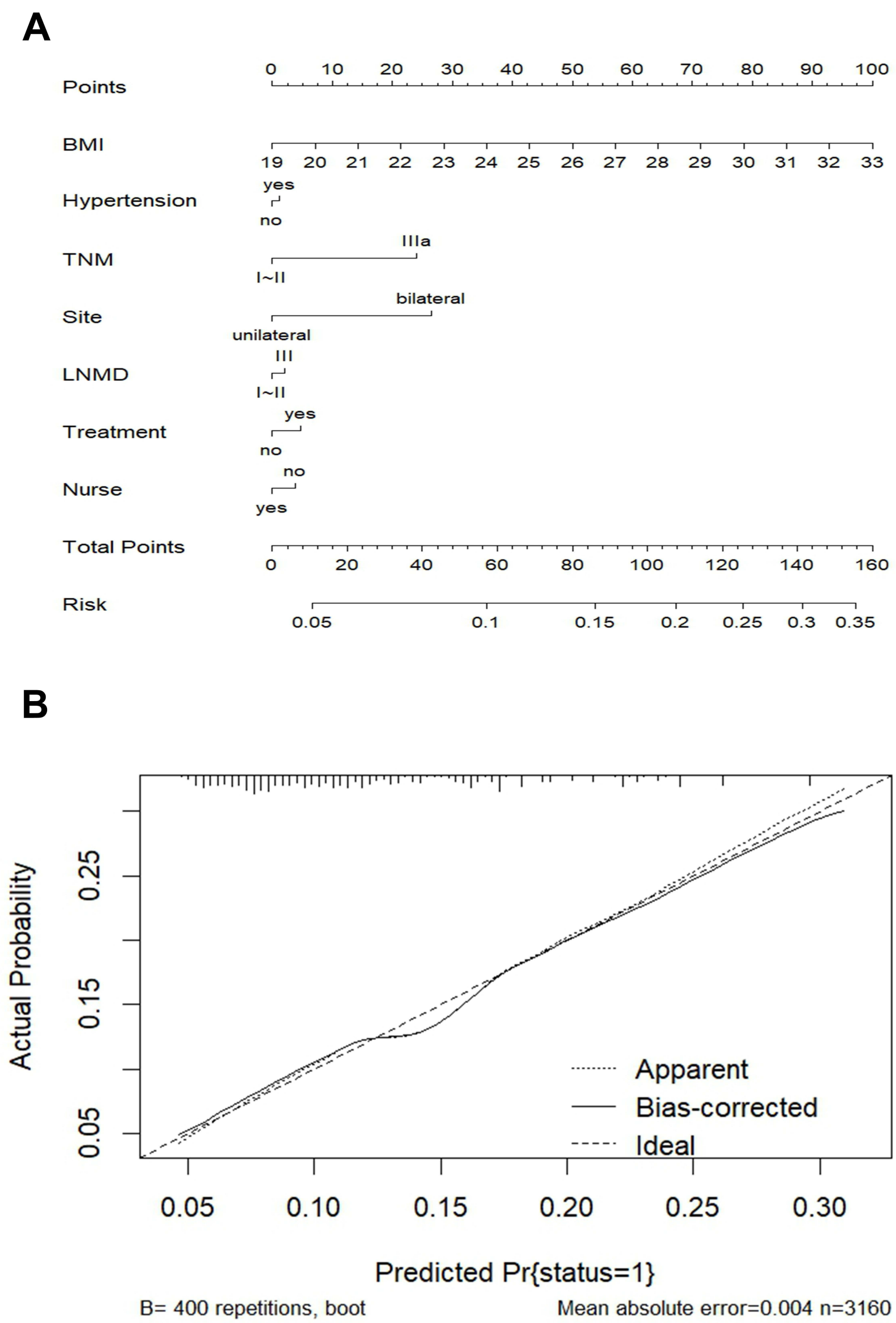

Figure 3 Nomogram visual prediction model for predicting upper limb lymphedema (**A**) Nomogram; (**B**) Calibration curve.

RFM and ANNM are the most widely used machine learning algorithms in various fields, including healthcare. In this study, three supervised learning algorithms were used to develop the limb lymphedema model. As shown in Supplementary Table 2, top-ranking weight values in the RFM prediction model were obtained for BMI, hypertension, TNM, lesion site, LNMD, treatment, and nurse, indicating their potential as candidate variables for RFM-based prediction of limb lymphedema (Figure 4). Consequently, in BMI, hypertension, TNM, lesion site, LNMD, treatment, and nurse also served as candidate variables for predicting limb lymphedema, and their assignments in the two different algorithm prediction models were inconsistent.

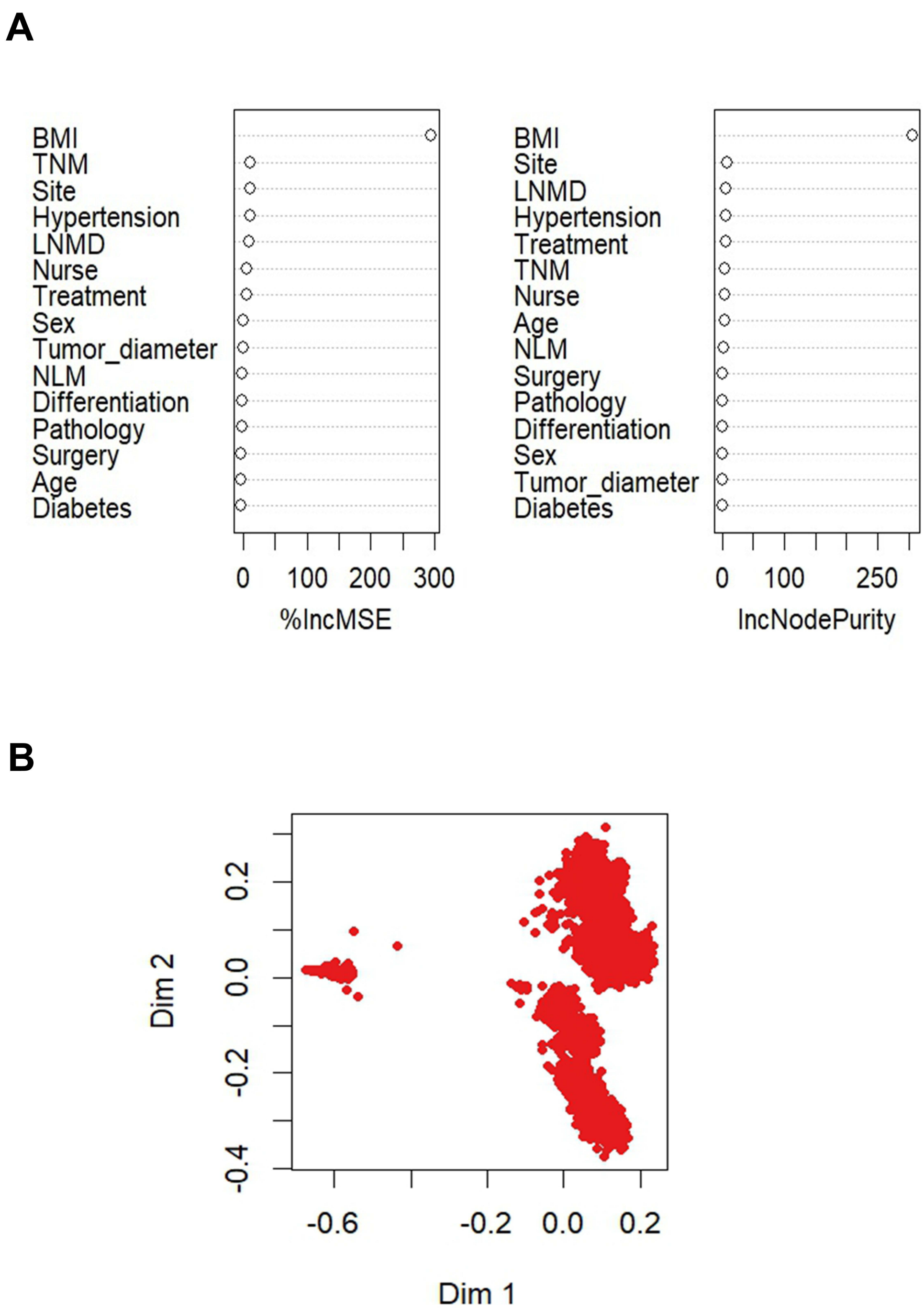

Figure 4 Random forest prediction model for predicting upper limb lymphedema (**A**). The random forest prediction model based on machine learning algorithms; (**B**) Predictive performance detection of models.
Notes: The red dots represent patients with upper limb lymphedema, and the blue dots represent patients without upper limb lymphedema.

Evaluation of Prediction Model Performance

The receiver operating characteristic (ROC) curves were drawn to evaluate the predictive efficacy of each risk factor and the nomogram model. The ROC curve showed that the RFM model had higher predictive efficacy in both training and verification sets than the ANNM model, with AUCs of 0.894 and 0.889 and a 95% confidence interval (CI) of 0.839–0.949 and 0.834–0.944, respectively, compared to the AUCs of 0.819 and 0.807 and 95% CIs of 0.762–0.876 and 0.750–0.864, respectively, for the ANNM model (Figure 4 and Supplementary Figure 1). The predictive performance of preoperative clinical indicators for limb lymphedema was provided in Table 3. The prediction efficiency of the limb

Table 3 Evaluation of Predictive Performance of Upper Limb Lymphedema Prediction Model Based on ROC

Prediction model	Training Set				International Set			
	AUC	95% CI	PPV	NPV	AUC	95% CI	PPV	NPV
RFM	0.894	0.839–0.949	0.979	0.996	0.889	0.834–0.944	0.927	0.995
GLRM	0.788	0.731–0.845	0.962	0.994	0.731	0.674–0.789	0.853	0.989
ANNM	0.819	0.762–0.876	0.893	0.984	0.807	0.750–0.864	0.775	0.977

Abbreviations: Annotations: AUC, Area under the curve; 95% CI, 95% confidence interval; PPV, Positive predictive value; NPV, negative predictive value; RFM, Random forest model; GLRM, Generalized linear regression; ANNM, artificial neural network model.

lymphedema prediction model developed by a machine learning-based algorithm was better than that of the GLRM. Furthermore, Figure 5 shows the DCA curve, with the abscissa indicating the threshold probability and the ordinate indicating the net benefit. The black horizontal line indicates a net benefit of zero, indicating that all patients were free of limb lymphedema. The gray diagonal line represents a scenario where all patients had a limb lymphedema and received treatment. DCA addresses the practical needs for clinical decision-making by incorporating patient or decision-maker preferences in the analysis. The DCA curve shows that the nomogram is more effective in predicting limb lymphedema than administering all or non- limb lymphedema.

Explanation of RFM Model with the SHAP Method

The SHAP algorithm was used to obtain the importance of each predictor variable to the outcome predicted by the RFM model. After developing three predictive models for limb lymphedema based on candidate predictive factors, we evaluated the optimal predictive performance of the RFM model. To further evaluate the differentiation efficiency of RFM, we used the clinical influence curve to assess the "classification accuracy" in the training set and internal verification set. As shown in Supplementary Figure 2, RFM effectively distinguished patients with limb lymphedema from those without limb lymphedema, which was consistent with the results of the postoperative examination. Our study suggested that RFM is a reliable tool for the preoperative evaluation of limb lymphedema in patients and may become a powerful guiding tool for determining postoperative prevention of limb lymphedema. This also demonstrated that RFM is suitable for the preoperative assessment of the risk stratification of limb lymphedema.

Discussion

Upper limb lymphedema is a common complication of breast cancer patients after surgery. Breast cancer surgery can damage upper limb lymph tissue, cause distal lymphatic obstruction, thus blocking upper limb lymphatic return.[15,16] A large amount of protein-rich lymph fluid accumulates in the tissue gap, promoting the deposition and proliferation of collagen in the body's connective tissue, leading to upper limb edema, and even can develop into upper limb lymphangitis or cellulitis.[17] In this study, we obtained the potential risk of upper limb lymphedema after breast cancer surgery based on cross-sectional survey, and built a prediction model of lymphedema through advanced algorithms, which has a very important guiding significance for clinical medical staff to assist in decision-making, especially to help identify the risk of upper limb lymphedema early, so as to effectively reduce the incidence of postoperative lymphedema and improve the quality of life of patients.

The results of this study show that obesity, hypertension, TNM stage, bilateral breast lesions, axillary lymph node dissection level III, postoperative radiotherapy and chemotherapy, and nursing strategies are independent risk factors for upper limb lymphedema after breast cancer surgery. Previous studies have shown that patients with high BMI, due to the presence of excessive adipose tissue in the body, can have their skin overly stretched and reduce muscle contraction ability, leading to poor lymphatic drainage and increased risk of fat liquefaction and necrosis, ultimately leading to lymphatic vessel obstruction and lymphangitis.[18,19] In addition, hypertension patients may be due to high risk factors that hypertension promotes the entry of body lymph into the tissue gap, as well as the occurrence of water and sodium retention, which increases the fluid in the blood vessels, thereby increasing the risk of upper limb lymphedema.[20]

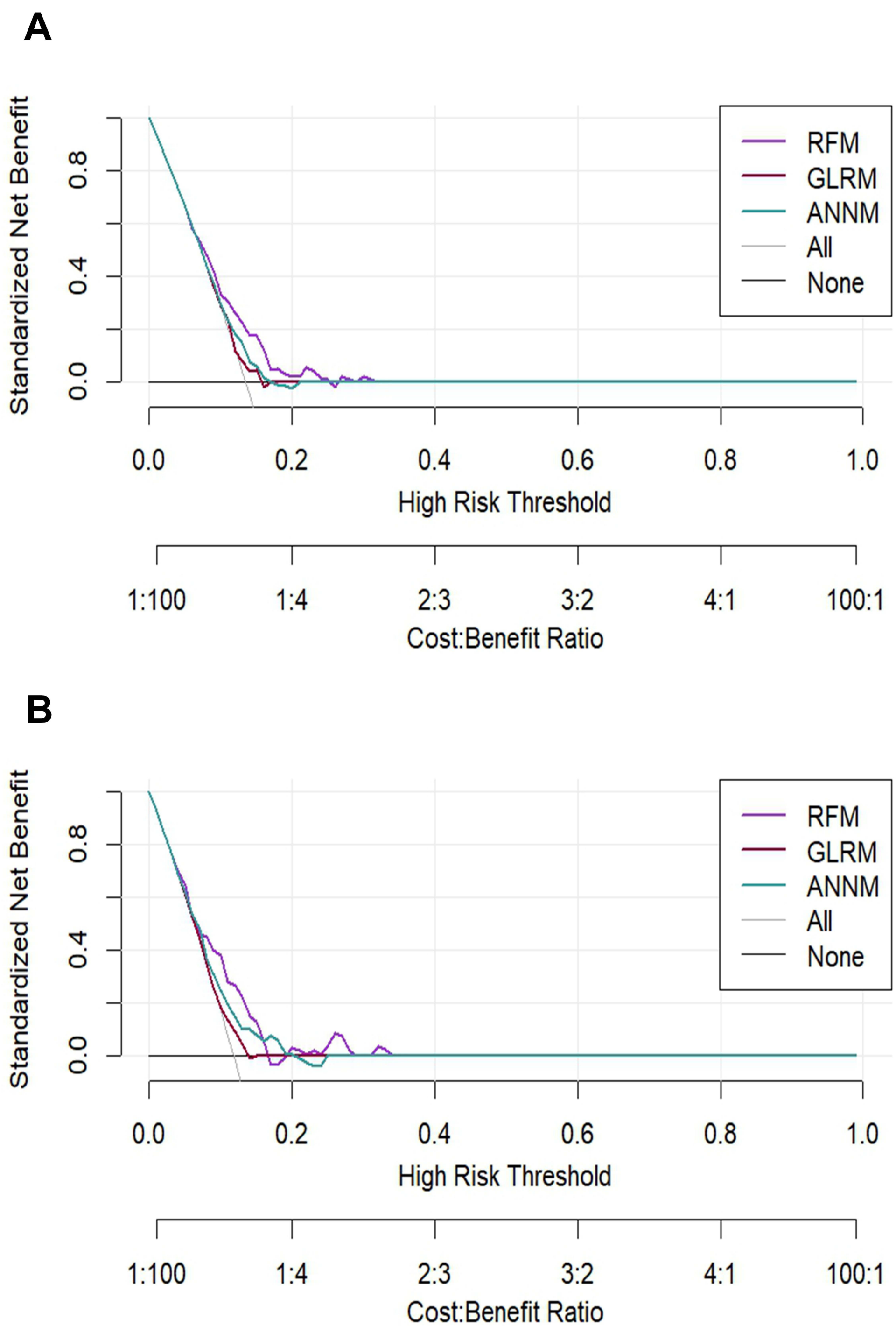

Figure 5 Performance evaluation of predictive models based on DCA (**A**). Training cohort; (**B**) Testing cohort.

Consistent with the results reported in previous studies, the risk of limb lymphedema in breast cancer patients with hypertension after surgery is significantly higher than that in patients with normal blood pressure, and a history of hypertension is a risk factor for upper limb lymphedema in breast cancer patients after surgery.[21,22]

In this study, patients with TNM stage IIIa had a higher risk of upper limb lymphedema due to the progression of the disease to the middle and late stages (ie, high risk of lymph node metastasis), and the expansion of the surgical scope, which exacerbated the damage to lymphatic tissue. Moreover, Yuan et al found that both breasts of patients with bilateral lesions of breast cancer have canceration, whose clinical symptoms are more complex than those of patients with unilateral lesions, and the patients' physical resistance is lower, which makes them more prone to postoperative infection, causing lymphatic vessel damage and blockage, thus increasing the risk of upper limb lymphedema.[23,24] This study also found that axillary lymph node dissection level III is an independent risk factor for postoperative upper limb lymphedema, consistent with previous research results. Due to the large scope of level III axillary lymph node dissection, the lymph vessel tissue is severely damaged, which can seriously damage the lymphatic pathway, resulting in lymph retention at the end of the affected limb, thus increasing the incidence rate of upper limb lymphedema. In addition, postoperative radiotherapy and chemotherapy not only kill tumor cells, but also cause damage to normal tissue cells, leading to venous occlusion, lymphangitis, and local muscle fibrosis, which is not conducive to upper limb lymphatic reflux and promotes the occurrence of upper limb lymphedema.[13,25,26]

Previous studies have shown that infection after breast cancer surgery, skin flap necrosis, and high-dose radiotherapy are all high risk factors leading to upper limb lymphedema.[27,28] If not observed and treated in time, it may lead to complete or partial loss of function or disability of patients' upper limbs. Therefore, nursing plays a crucial role in prevention and treatment, and in order to further improve the effectiveness of prevention and treatment, comprehensive postoperative care should be strengthened. This study also found that nursing measures are an independent risk factor affecting postoperative upper limb lymphedema in patients. Indeed, patients receiving a comprehensive postoperative nursing rehabilitation plan can effectively reduce the incidence and degree of postoperative lymphedema, improve nursing effectiveness, and thus improve patient prognosis.[29,30]

There have been no fully validated tools for the rapid identification of surgical patients at risk of limb lymphedema. In this study, we found that the machine learning-based prediction model had possibly helpful discrimination, adequate calibration, and acceptable overall performance for predicting limb lymphedema. For example, the optimal prediction model random forest, which divides patients into two groups, effectively identifies patients with low or high risk of limb lymphedema after surgery. Given that the predictive model has been modified to be an easy-to-use, convenient, and freely accessible mobile application, to some extent, it seems to be ready for further clinical applications. Consistent with previous research reports, we also found that random forest emphasizes risk stratification rather than estimating the digital risk of individual patients, so our main interest is discrimination rather than calibration.[31] Compared with the logistic regression model, the advantage is that although the average calibration is reasonable, through our verification, the risk of limb lymphedema in some patients is also overestimated or underestimated.[32] Therefore, before further refinement and satisfactory calibration at different levels, we recommend using the random forest model to predict the exact probability of patients at risk of limb lymphedema. Collectively, we developed and validated four machine learning algorithms to predict the risk of limb lymphedema. Among them, the random forest model has the best performance, and the SHAP method ensures the performance and clinical interpretability of the model. This will help doctors better understand the decision-making process of the model and promote the use of prediction results.

Our study inevitably has three limitations. First, this is a retrospective study, some variables are missing. For example, we intend to include more predictor variables that may affect limb lymphedema; however, the missing values are over 70%. Therefore, risk bias regarding data is inevitable Second, all data are derived from a single center, so the applicability of our model remained unclear in other populations. Third, due to the lack of an external validation cohort, the applicability of the developed RFM may not be very efficient in clinical practice. Of course, this still requires large sample data to test and optimize more robust model parameters. In the future, we will gradually conduct multi center population cohort validation and external promotion to ensure the universality and reproducibility of the prediction model.

In conclusion, we have developed an interpretable RFM prediction model that has better performance in estimating the risk in patients with limb lymphedema. In addition, the interpretable machine learning can be applied to accurately explore the risk factors of patients with limb lymphedema and enhance physicians' trust in prediction models. This practical prediction model allows for early identification of patients at high risk of limb lymphedema and individual adjustment of treatment interventions, which may improve the surgical prognosis of patients and reduce postoperative complications.

Disclosure

The authors report no conflicts of interest in this work.

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