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Original Article

Impact of axillary management approaches on postoperative complication rates in breast cancer and exploration of targeted prevention strategies

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Abstract: This study aimed to systematically identify axillary complication phenotypes after breast cancer surgery, characterize their evolutionary trajectories, and clarify how surgical approaches affect long-term complications. A total of 470 breast cancer patients (2020-2024) were retrospectively divided into SLNB (n = 192) and ALND (n = 278) groups. K-means clustering, multivariate logistic regression, mediation analysis, and multi-state models were used. Low-risk (SLNB-dominant, 42.13%), pain-dominant (ALND-related type, 26.17%), severe lymphedema (ALND-related type, 13.62%), and moderate-severe comorbidity (ALND-related type, 18.09%). ALND was the strongest predictor of the high-risk comorbidity phenotype (adjusted OR = 8.32, P < 0.001). Prolonged drainage mediated 35% of ALND's effect on lymphedema (P < 0.001). ALND increased chronic complication transition 5.2-fold and reduced recovery probability (P < 0.001). In conclusion, ALND is closely associated with high-risk axillary complication phenotypes, directly and indirectly (via prolonged drainage) elevating complication risk, altering their evolution and reducing recovery. Findings support phenotype-based individualized management and rational axillary lymph node management selection.

Keywords: Breast cancer surgery, axillary lymph node dissection, sentinel lymph node biopsy, postoperative complications, lymphedema

Introduction

Breast cancer is the most common malignant tumor among women worldwide. While pursuing radical cure, preserving patient function to the greatest extent possible and improving their long-term quality of life has become one of the core goals of surgical treatment [1]. The management of axillary lymph nodes is a crucial step in breast cancer surgery, mainly divided into sentinel lymph node biopsy (SLNB), which is less invasive, and axillary lymph node dissection (ALND), which involves a wider range of dissection [2, 3]. Although SLNB has become the standard procedure for patients with negative axillary lymph nodes and has significantly reduced the incidence of short-term complications, ALND remains an indispensable treatment for patients with lymph node metastasis [4].

However, both SLNB and ALND may cause a series of postoperative axillary complications, such as upper limb lymphedema, paresthesia, pain, and limited shoulder joint mobility [5]. These complications not only cause physical pain and functional impairment in patients but also seriously affect their psychological and social health and long-term quality of life [6]. At present, in clinical practice and research, various complications are often analyzed as independent events, neglecting their possible co-occurrence patterns and intrinsic connections [7]. In fact, the occurrence of complications may not be homogeneous, and different patients may present different clinical phenotypes. In addition, the specific pathways by which surgical approach (SLNB vs. ALND) affects long-term complications (such as whether it involves prolonging postoperative drainage time, increasing tissue trauma, etc.) have

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Table 1. Preoperative general information of the two groups

Variable	SLNB (n = 192)	ALND (n = 278)	Statistic	*p*-value
Age	55.0 ± 9.9	56.0 ± 9.7	t = -1.12	0.2652
BMI	25.1 ± 3.7	25.7 ± 3.9	t = -1.65	0.1007
Tumor Stage			χ^2 = 326.20	< 0.001
I	149 (77.60%)	0 (0.00%)		
II	43 (22.40%)	181 (65.11%)		
Histologic_Grade			χ^2 = 1.92	0.3826
G1	46 (23.96%)	81 (29.14%)		
G2	97 (50.52%)	137 (49.28%)		
G3	49 (25.52%)	60 (21.58%)		
Surgery_Type			χ^2 = 0.02	0.8981
Breast-Conserving	118 (61.46%)	168 (60.43%)		
Mastectomy	74 (38.54%)	110 (39.57%)		

Note: Data are presented as mean ± standard deviation for continuous variables (Age, BMI) and as number (percentage) for categorical variables. Group comparisons were performed using independent t-tests for continuous variables and chi-square (χ^2) tests for categorical variables. Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; BMI, body mass index.

not been fully elucidated [8]. The understanding of the dynamic evolution of complications is mostly limited to cross-sectional or short-term follow-up studies, lacking descriptions of their status transition patterns over several months or even years.

Therefore, identifying the potential phenotypes of postoperative axillary complications, revealing their risk pathways related to surgical methods, and depicting their long-term evolution trajectory are crucial for achieving accurate prediction, early identification, and personalized intervention of complications. This study retrospectively analyzed follow-up data of breast cancer patients 24 months after surgery, aiming to develop targeted prevention and management strategies for different risk phenotypes in clinical practice, especially to provide accurate intervention basis for high-risk patients receiving ALND, so as to ultimately improve the long-term prognosis and quality of life of breast cancer patients.

Materials and methods

General information

This retrospective study included 470 breast cancer patients who underwent surgery at the Ganzhou Cancer Hospital from January 2020 to December 2024 and completed follow-up. Patients were divided into a SLNB group (n = 192, 40.9%) and a ALND group (n = 278, 59.1%) based on the axillary surgical method. Except for tumor stage, there were no statistically significant differences in general characteristics between the two groups (**Table 1**). This study was approved by the Ethics Committee of Ganzhou Cancer Hospital (Approval No. 20250228).

Inclusion criteria: (1) Diagnosed with breast cancer according to the criteria and who underwent SLNB or ALND [9]; (2) Complete and accurate perioperative clinical pathology data and treatment records; (3) Regular follow-up after surgery for at least 24 months to meet the needs of analyzing the evolution trajectory of long-term complications.

Exclusion criteria: (1) Previous ipsilateral axillary surgery, breast cancer surgery, or emergency surgery due to tumor rupture, bleeding, etc.; (2) Severe preoperative comorbidities affecting upper limb function or lymphatic drainage, or other malignant tumors that may affect survival or complication assessment; (3) Mental illness or pregnancy.

Surgical procedure standards

A dual tracer method was used in the SLNB group [10]. 2-4 hours before surgery, 2 ml of methylene blue was injected subcutaneously around the areola. One day before surgery, 37-74 MBq technetium-99m sulfide colloid was injected into the tissue surrounding the tumor.

During surgery, a gamma probe was used to detect radioactive hotspots, and blue-stained lymph nodes were visually identified. All sentinel lymph nodes were removed and sent for frozen section pathological examination.

In the ALND group, ALND was performed on patients with positive sentinel lymph nodes or clinically confirmed axillary lymph node metastasis [11]. The dissection covered axillary lymph nodes at levels I and II. The number of lymph nodes dissected was strictly controlled to 10-20 to ensure therapeutic efficacy while avoiding excessive tissue damage. Level III lymph node dissection was not performed without clear evidence of metastasis.

Surgical physicians were randomly assigned to perform SLNB or ALND procedures based on the hospital's routine surgical schedule; no single physician performed only axillary procedures. Throughout the study, the proportion of SLNB and ALND performed by physicians within the team remained relatively balanced (difference < 10%). Simultaneously, the team developed standardized operating procedures for SLNB and ALND, referencing the Chinese Clinical Guidelines for Axillary Lymph Node Management in Breast Cancer [12]. The entire surgical process was supervised by senior attending physicians to ensure consistency in surgical procedures and avoid the impact of individual surgical technique differences on the study results.

Data extraction and quality control

All data were extracted from electronic medical records and follow-up databases. Two trained researchers independently performed the extraction using a pre-designed data extraction table. Extraction included baseline features, surgical information, postoperative indicators, and follow-up outcomes. If discrepancies arose in the extraction results, a third senior researcher reviewed the original medical records to arbitrate and ensure data accuracy. Logical checks were performed after data entry to remove obviously erroneous data. Due to strict inclusion criteria, no missing values were found for key variables. For continuous variables such as drainage volume, outliers were identified using box plots and the original medical records were reviewed; only clinically reasonable values were retained for analysis.

Follow-up methods

Outcome evaluation criteria: Bioelectrical impedance analysis and upper limb circumference measurement were used. A difference in limb volume between the affected and unaffected sides > 10% was defined as lymphedema. The Numerical Rating Scale (NRS) was used, with patients rating their pain intensity from 0 (no pain) to 10 (severe pain). Shoulder flexion, abduction, and external rotation angles were measured using a standard goniometer. Other complications were diagnosed through clinical examination and medical records.

Follow-up was conducted at 1, 3, 6, 12, and 24 months after surgery, using a combination of outpatient and telephone follow-ups. Patients who could not be reached by telephone were contacted again within one week to complete the outcome data collection. All follow-up personnel received training on standardized evaluation criteria to ensure consistency in outcome measurement. For patients lost to follow-up, information could be obtained by contacting their attending physician or family members; patients with incomplete key outcome data were excluded from the final analysis.

Model construction methods

All indicators were extracted from patients' electronic medical records.

To explore the independent effects of various clinical factors on postoperative continuous outcome variables and quantify their effect sizes, a multiple linear regression model was used. First, univariate analysis was performed to screen potential predictive variables. Continuous variables satisfying the assumptions of linearity, normality, and homogeneity of variance, as well as clinically significant categorical variables, were included in the initial model. Variables were screened using stepwise regression (inclusion threshold $P < 0.05$, exclusion threshold $P > 0.10$) to construct the final model. Model results are presented as partial regression coefficients (β), 95% confidence intervals (CIs), and standardized coefficients (Beta), used to illustrate the average impact of each unit change in the independent variables on the outcome variable.

Based on the statistically significant multiple linear regression or Cox regression model described above, a clinical prediction nomogram was constructed. This nomogram converts the regression coefficients of each independent variable in the model into a visual scoring scale (0-100 points). By summing the scores of each patient variable to obtain a total score, and then based on the functional correspondence between the total score and the predicted outcome, a graphical prediction of individualized risk was achieved. The model's discriminative power was assessed by calculating the coefficient of determination (R^2) or the concordance index (C-index). The calibration was evaluated by plotting a calibration curve between predicted and observed values; and internal validation was performed using the bootstrap method with 1000 repeated samplings. Finally, decision curve analysis (DCA) was used to quantify the net clinical benefit of the nomogram at different threshold probabilities to evaluate its clinical application value.

To identify independent risk factors for chronic complications and assess their HRs, a Cox proportional hazards regression model was used. Postoperative day 90 was set as the observation starting point, and the endpoint event was the first occurrence of any given chronic complication. Data from the last follow-up where no endpoint event occurred were censored. First, univariate Cox analysis was performed to screen for potential predictors, and then variables with statistical significance ($P < 0.10$) or clinical importance was included in the multivariate Cox model. The model rigorously tested the proportional hazards hypothesis, and the forward likelihood ratio method was used for variable selection. The final results are presented as adjusted hazard ratios (aHRs) and their 95% CIs.

To explore the specific pathway by which surgical procedures (SLNB vs. ALND) affect the occurrence of upper limb lymphedema, a mediation analysis was conducted. Postoperative drainage time was set as the mediating variable. Based on the theoretical assumption, ALND may indirectly increase the risk of lymphedema by prolonging drainage time. The analysis used Hayes' PROCESS macro program, with surgical procedure as the independent variable, lymphedema as the dependent variable, and drainage time (a continuous variable) as the mediating variable, adjusting for key confounding factors such as body mass index (BMI) and radiotherapy. The bootstrap method was used to calculate the CIs for the indirect effect. An interval not containing 0 indicated a significant mediation effect. The proportion of the indirect effect in the total effect was further calculated to quantify the contribution of this pathway.

Net benefit values were calculated for threshold probabilities ranging from 5% to 50%, at 5% intervals, to determine the optimal clinical decision interval.

Statistical methods

All statistical analyses were performed using R version 4.2.1 and SPSS version 26.0. The full analysis set included data from all 470 breast cancer patients who underwent SLNB or ALND and had complete follow-up records for axillary complications for 24 months.

For continuous variables, normally distributed data were presented as mean ± standard deviation (SD), and non-normally distributed data were expressed as median (interquartile range, IQR). Intergroup comparisons were performed using independent samples t-test or the Mann-Whitney U test; within-group comparisons were performed using paired t-tests or Wilcoxon signed-rank tests where applicable. Categorical variables were described statistically as number of cases and percentages (n, %), and intergroup comparisons were performed using χ^2 test or Fisher's exact test.

Baseline characteristics were compared between groups to verify comparability. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. Bonferroni correction was used for multiple comparisons. Three methods were used to validate the stability of the clustering results: ① Silhouette coefficient was calculated to assess intra-cluster cohesion and inter-cluster separation; a coefficient > 0.5 indicated good clustering performance; ② 1000 resampled samples (80% of the original data) were drawn from the original data, and K-means clustering was repeated each time. The consistency rate between the sample cluster assignments and the original results was calculated (a consistency rate > 85% indicated stable clustering results); ③ A curve was plotted showing the sum of squares within clusters as a function of the number of clusters, and the inflection point of the curve

Table 2. Analysis results of differences in postoperative indicators

Variable	SLNB (n = 192)	ALND (n = 278)	Statistic	*p*-value
Neoadjuvant Chemo	30 (15.63%)	133 (47.84%)	χ^2 = 50.62	< 0.001
Postop Radiotherapy	58 (30.21%)	194 (69.78%)	χ^2 = 69.94	< 0.001
Postop Chemo	77 (40.10%)	190 (68.35%)	χ^2 = 35.77	< 0.001
Endocrine Therapy	115 (59.89%)	185 (66.55%)	χ^2 = 1.90	0.228
Targeted Therapy	60 (31.25%)	110 (39.57%)	χ^2 = 3.05	0.081
Breast-Conserving	123 (64.06%)	123 (44.24%)	χ^2 = 8.68	< 0.001
Mastectomy	69 (35.94%)	155 (55.76%)	χ^2 = 9.37	< 0.001
Surgery Time	95.0 ± 19.1	144.8 ± 25.6	t = -24.16	< 0.001
Blood Loss	45.0 ± 14.0	85.1 ± 25.4	t = -21.96	< 0.001
Drain Days	5.8 ± 1.9	10.5 ± 3.1	t = -20.49	< 0.001
Drain Volume	177.7 ± 46.8	353.7 ± 81.5	t = -29.62	< 0.001
Follow-up Months	17.9 ± 3.6	17.8 ± 3.4	T = 0.52	0.815
Lymphedema	37 (19.27%)	130 (46.76%)	χ^2 = 36.28	< 0.001
Lymphedema Severity	5.3 ± 4.7	10.7 ± 8.2	t = -9.10	< 0.001
Pain	66 (34.38%)	167 (59.93%)	χ^2 = 28.98	< 0.001
Pain Severity	2.8 ± 2.2	4.7 ± 2.8	t = -8.44	< 0.001
Shoulder Limited	45 (23.44%)	128 (46.04%)	χ^2 = 23.99	< 0.001
Number of dissected lymph nodes	2.4 ± 1.1	16.8 ± 4.3	t = 29.54	< 0.001

was used to determine the optimal number of clusters (k = 4).

The variance inflation factor (VIF) was used to test for multicollinearity among the independent variables. A VIF < 10 was considered as the absence of significant multicollinearity.

To characterize the evolution of postoperative complications, this study constructed a three-state multistate model, including: state 0 (no complications), state 1 (early complications) (complications occurring within 3 months after surgery) and state 2 (long-term chronic complications) (complications persisting or newly occurring after 3 months postoperatively, such as chronic lymphedema). The main covariate of the model was the surgical procedure (SLNB vs. ALND). The mState package in R software was used to calculate the HR and cumulative metastasis probability between each state.

Results

Analysis of postoperative indicators

The incidences of neoadjuvant chemotherapy, postoperative radiotherapy, and postoperative chemotherapy were significantly lower in the SLNB group than those in the ALND group (all P < 0.001). In addition, the SLNB group had a higher rate of breast-conserving surgery and a lower rate of mastectomy (P < 0.001). There were no significant differences between the two groups in the use of endocrine therapy, targeted therapy, and follow-up time (all P > 0.05). In terms of surgical procedures, compared with the ALND group, the SLNB group had shorter operation time, less intraoperative bleeding, and significantly reduced postoperative drainage days and drainage volume. The average number of lymph nodes dissected in the SLNB group was 2.4 ± 1.1, while it was 16.8 ± 4.3 in the ALND group (P < 0.001). Multivariate analysis, adjusted for lymph node number, further showed that the number of lymph nodes dissected was not an independent risk factor for lymphedema, pain, or limited shoulder joint movement (all P > 0.05), while a significant association remained between surgical method and complication risk (both P < 0.001). Follow-up results indicated that the incidence and severity of lymphedema, pain, and limited shoulder joint movement in the SLNB group were significantly lower than those in the ALND group (all P < 0.001). All surgeries were performed by the same professional team with consistent surgical experience and skill levels, and there was no statistically significant difference in the distribution of surgeons between the two groups (P > 0.05), ensuring comparability of the two groups in terms of surgical implementation factors. See **Table 2**.

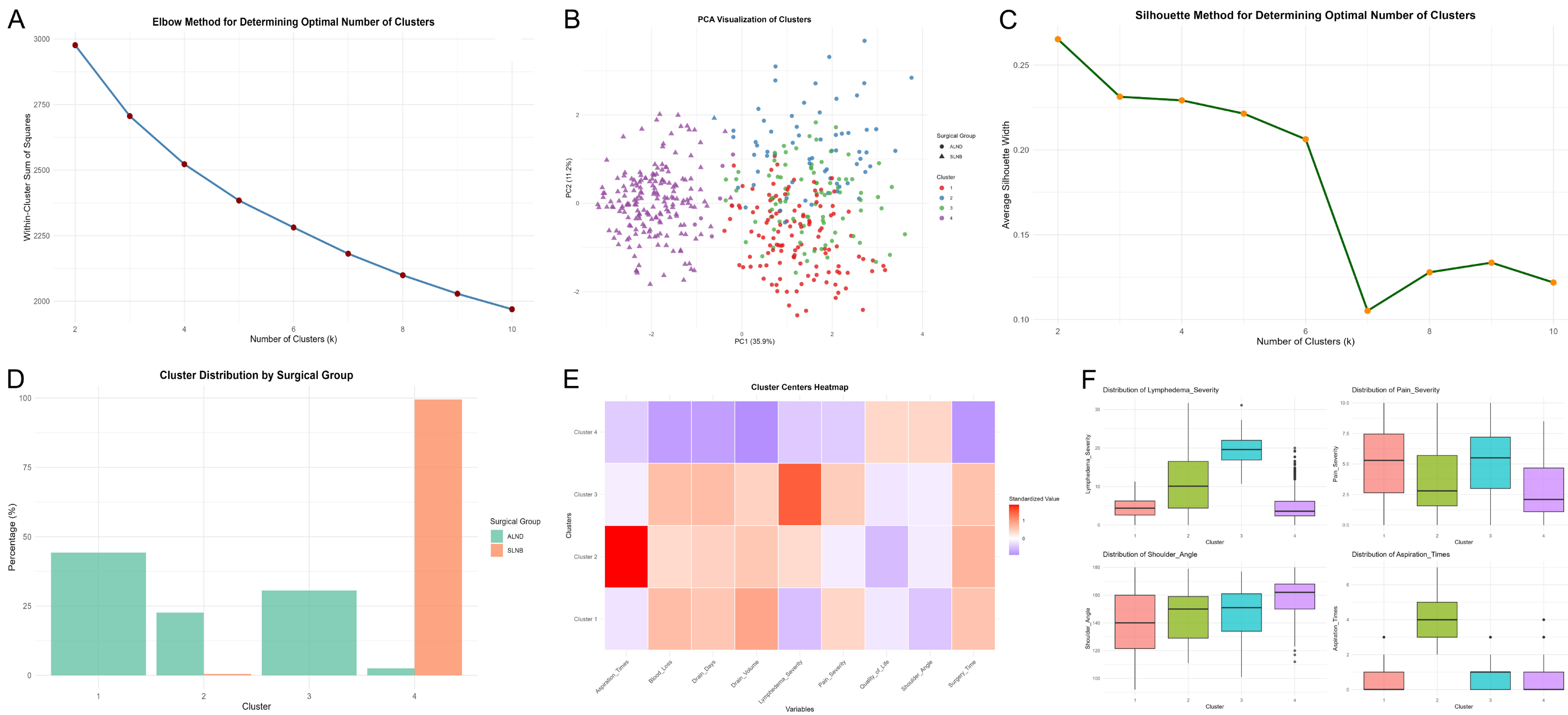

Figure 1. K-means cluster analysis verification and phenotype visualization of axillary complications after breast cancer surgery. Note: A: Elbow rule diagram. The horizontal axis represents the number of clusters (k), and the vertical axis represents the withincluster sum of squares. The curve shows a clear inflection point at k = 4, indicating that 4 is the optimal number of clusters. B: PCA visualization of clustering results. Principal component 1 (PC1, explaining 35.9% of the variance) and principal component 2 (PC2, explaining 11.2% of the variance) are used as coordinate axes. Four clusters are represented by different colors, and surgical groups are represented by different shapes (black dots = ALND, purple triangles = SLNB). Each cluster shows a clear separation trend in the dimensionalityreduced space. C: Silhouette coefficient plot. The horizontal axis represents the number of clusters (k), and the vertical axis represents the average silhouette coefficient. The average silhouette coefficient reaches a high level at k = 4, further confirming that 4 is the optimal number of clusters. D: Distribution bar chart of surgical groups within each cluster. The horizontal axis represents cluster numbers, and the vertical axis represents the proportion of each surgical group (green = ALND, orange = SLNB). Cluster 1 is dominated by SLNB, whereas clusters 2-4 are dominated by ALND. E: Cluster center heatmap. Rows represent the four clusters, and columns represent complicationrelated variables (e.g., lymphedema severity, pain severity). Color intensity corresponds to standardized variable values (red = high value, purple = low value), visually displaying the core feature differences of each cluster. F: Box plots of key indicators for each cluster, including lymphedema severity, pain severity, shoulder range of motion, and drainage duration (with cluster numbers on the horizontal axis). These plots clearly present the phenotypic differences of the clusters across each outcome indicator. ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy.

Table 3. Subgroup analysis results

Complication	Subgroup_Variable	Subgroup	OR	CI 95%	*P* value	Sample Size
Lymphedema	BMI	< 25	4.86	(1.77-13.75)	0.0024	227
Lymphedema	BMI	≥ 25	8.09	(2.98-23.2)	1e-04	243
Lymphedema	Radiotherapy	No	4.52	(1.51-14.06)	0.0077	218
Lymphedema	Radiotherapy	Yes	12.71	(4.45-39.75)	0	252
Lymphedema	Age	<50	7.89	(1.91-35.77)	0.0054	135
Lymphedema	Age	≥ 50	6.94	(3.05-16.32)	0	335

Note: Subgroup analysis was conducted to assess the odds ratio (OR) for lymphedema associated with the surgical approach (ALND vs. SLNB) within different patient strata. Multivariable logistic regression models were adjusted for age, tumor stage, and histologic grade. ORs with 95% confidence intervals (CI) and corresponding *P* values are shown. Sample size (n) indicates the number of patients in each subgroup.

Cluster analysis results

Cluster analysis successfully identified four clinical phenotypes of complications with significant differences. Among them, phenotype I (low-risk axillary functional type) accounted for the highest proportion (42.13%), characterized by extremely low complication risk. Almost all patients in this group underwent SLNB (96.46% of cases). The mean severity of lymphedema (5.26) and pain (2.81) was the lowest among all phenotypes, while the mean quality of life score (74.03) was the highest. Postoperative recovery was rapid, with the shortest drainage time (5.84 days) and the least drainage volume (180.77 ml), representing a typical patient group with good recovery after SLNB surgery; Phenotype II (pain-dominant ALND related-type) accounted for 26.17%, indicating significant pain problems after ALND. All patients in this group underwent ALND. The mean pain severity was the highest among all phenotypes (5.03), the lymphedema severity was moderate (4.67), and the mean quality of life score was relatively low (65.55). Postoperative drainage time and volume were both high, suggesting a correlation with surgical trauma. Phenotype III (severe lymphedema ALND-related type) accounted for 13.62%, characterized by severe lymphedema after ALND. Almost all patients in this group had undergone ALND (98.44%), with the most prominent feature being an extremely high mean score of lymphedema severity (11.10), significantly higher than other phenotypes, but relatively lower pain severity (3.50). They had the lowest mean quality of life score (60.33), representing the group with the most severe functional impairment. Phenotype IV (moderate to severe comorbidity type ALND-related type) accounted for 18.09%, characterized by multiple complications after ALND. All patients in this group underwent ALND and simultaneously experienced significant lymphedema (severity 19.54) and pain (severity 5.25), exhibiting comorbidity characteristics. Despite the relatively severe complications, the mean quality of life score (65.42) was relatively acceptable among patients undergoing ALND, and postoperative drainage-related indicators also increased. See **Figure 1**.

Subgroup analysis and interaction effect results

Subgroup analysis of lymphedema showed that in different strata of BMI, radiotherapy, and age, all relevant factors were significantly associated with the risk of lymphedema (all P < 0.01). Specifically, the OR for the BMI < 25 subgroup was 4.86 (95% CI 1.77-13.75, P = 0.0024, n = 227); for the BMI ≥ 25 subgroup, OR = 8.09 (95% CI 2.98-23.2, P = 1e-04, n = 243). For the no-radiotherapy subgroup, OR = 4.52 (95% CI 1.51-14.06, P = 0.0077, n = 218); for the radiotherapy subgroup, OR = 12.71 (95% CI 4.45-39.75, P = 0, n = 252). For the age < 50 subgroup, OR = 7.89 (95% CI 1.91-35.77, P = 0.0054, n = 135); for the age ≥ 50 subgroup, OR = 6.94 (95% CI 3.05-16.32, P = 0, n = 335). The ORs were higher in the radiotherapy subgroup and the subgroup with a BMI ≥ 25, suggesting a relatively higher risk of lymphedema in these individuals (**Table 3**). Interaction effect analysis showed no statistically significant interaction terms for BMI × Surgical Approach, Radiotherapy × Surgical Approach, or Age × Surgical Approach (*P*-values 0.3391, 0.2604, 0.8844, respectively; likelihood ratio *P*-values 0.3391, 0.2517, and 0.8842, respectively), with corresponding inter-

Table 4. Interaction analysis results

Interaction_Term	OR	*P* value	LRT *P* value
BMI × Surgical Approach	0.65	0.3391	0.3391
Radiotherapy × Surgical Approach	1.78	0.2604	0.2517
Age × Surgical Approach	0.93	0.8844	0.8842

Note: This table presents the results of interaction effect analysis. The interaction term was included in a multivariable logistic regression model with lymphedema as the outcome. An odds ratio (OR) for the interaction term not equal to 1, with a *P* value < 0.05, would indicate that the effect of the surgical approach on lymphedema risk differs significantly across levels of the modifier variable (BMI, Radiotherapy, or Age). LRT, likelihood ratio test.

action ORs of 0.65, 1.78, and 0.93. This indicates that the effect of surgical approach on the risk of lymphedema does not differ significantly with differences in patient BMI level, radiotherapy status, or age (**Table 4** and **Figure 2**).

Linear regression analysis

After adjusting for confounding factors such as age, tumor stage, histological grade, and neoadjuvant chemotherapy, this study used multivariate logistic regression and multivariate linear regression analysis to explore the impact of each factor on postoperative outcomes. Surgical procedures have a significant impact on postoperative outcomes: In terms of complication risk, compared with SLNB, ALND significantly increased the risk of lymphedema, pain, limited shoulder joint movement, seroma, axillary reticular syndrome, and readmission, while there was no statistically significant difference in infection risk (P = 0.155). Among continuous outcome measures, ALND significantly increased lymphedema (percentage of volume difference, β = 7.14, 95% CI 4.87-9.40, P < 0.001) and pain intensity (NRS score, β = 2.80, 95% CI 1.96-3.63, P < 0.001), while significantly reducing shoulder flexion angle (β = -14.36, 95% CI -20.46 - -8.26, P < 0.001) and quality of life score (Quality of Life Questionnaire Core 30 (QLQ-C30), β = -9.44, 95% CI -13.98 to -4.90, P < 0.001). Among other influencing factors, postoperative radiotherapy and BMI (per 1 kg/m^2 increase) showed no significant effect on the risk of various complications or continuous outcomes (both P > 0.05). The number of drainage days (each additional day) only slightly reduced the risk of readmission (P = 0.046) and had no significant effect on other outcomes. Drainage volume (each 100 ml increase) had a slight impact on complication risk and continuity outcomes, specifically a significant increase in the risk of lymphedema (logistic regression, P = 0.003), and a significant impact on the degree of lymphedema (β = -0.01, P = 0.003) and pain intensity (β = -0.00, P = 0.02), but no significant association with other outcomes (**Tables 5** and **6**).

Nomogram results

This study constructed a nomogram model for predicting postoperative lymphedema based on linear regression (**Figure 3A**), integrating relevant influencing factors to quantify the risk of lymphedema in patients. The calibration curve (**Figure 3B**) showed that both the apparent predictive probability and the bias-corrected predictive probability of the model are close to the ideal calibration line, indicating good calibration. The ROC curve (**Figure 3C**) suggested the model's good discriminative power, effectively identifying high- and low-risk individuals for lymphedema. Decision curve analysis (**Figure 3D**) indicated that, within a reasonable risk threshold, the model's net clinical benefit was superior to either the "all intervention" or "no intervention" strategies. The risk distribution plot (**Figure 3E**) showed a good match between predicted risk and actual lymphedema occurrence, validating the reliability and clinical value of the predictive model (**Figure 3**).

To enhance clinical interpretability, this study quantified the net benefit of the nomogram at key threshold probabilities. The model showed a positive net benefit across the 5%-45% threshold probability range, with the optimal net benefit occurring within the 20%-30% threshold range: net benefit = 0.18 (95% CI: 0.12-0.24) at 20% threshold; net benefit = 0.21 (95% CI: 0.15-0.27) at 25% threshold; and net benefit = 0.19 (95% CI: 0.13-0.25) at 30% threshold. From a clinical decision-making perspective, it is recommended that patients with a predicted risk of lymphedema exceeding 20% undergo preventative interventions (e.g., compression therapy and close monitoring), while patients with a risk below 10% can safely receive routine postoperative care. Detailed net

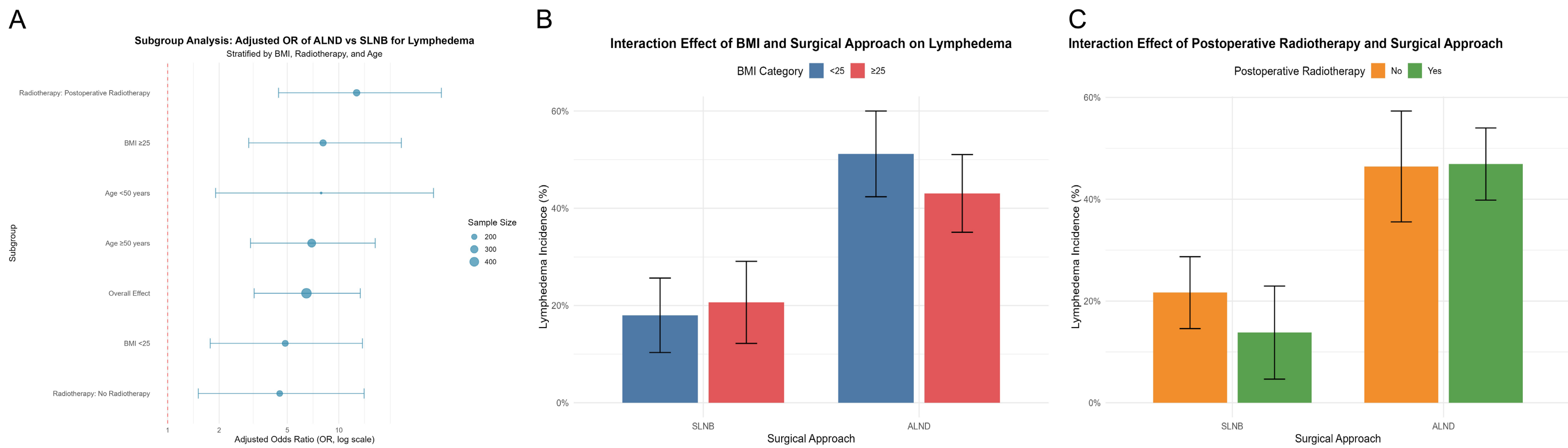

Figure 2. Visualization of Subgroup Analysis and Interaction Effects. Note: A: Subgroup analysis forest plot. This plot shows the odds ratio (OR) and 95% confidence interval (95% CI) for the risk of lymphedema associated with sentinel lymph node biopsy (SLNB) versus axillary lymph node dissection (ALND) across different BMI (< 25 vs. ≥ 25), postoperative radiotherapy (yes vs. no), and age (< 50 years vs. ≥ 50 years) subgroups. The horizontal line represents the 95% CI, the circular dots represent OR values, and the middle vertical line (OR = 1) represents the line of no effect. B: Bar chart of the interaction effect between BMI and surgical approach. This chart shows the risk of lymphedema in the SLNB and ALND groups under different BMI strata (error bars represent confidence intervals). C: Bar chart of the interaction effect between postoperative radiotherapy and surgical approach. This chart shows the risk of lymphedema in the SLNB and ALND groups stratified by the presence or absence of postoperative radiotherapy (error bars represent confidence intervals).

Table 5. Multivariate logistic regression analysis of major complications: adjusted odds ratios (OR) and 95% confidence intervals (CI)

Variable	Lymphedema	Pain	Shoulder Limited	Seroma	Infection	Axillary Web Syndrome	Readmission
ALND vs. SLNB							
OR (95% CI)	6.85 (3.32-14.44)	5.95 (2.97-12.25)	3.31 (1.66-6.69)	5.55 (2.76-11.37)	1.92 (0.78-4.73)	4.93 (1.93-13.22)	7.55 (2.59-23.10)
P-value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	0.155	**0.001**	**< 0.001**
Postoperative Radiotherapy							
OR (95% CI)	0.86 (0.55-1.33)	0.69 (0.45-1.05)	1.32 (0.87-2.02)	0.88 (0.57-1.35)	1.09 (0.64-1.87)	0.95 (0.56-1.62)	0.74 (0.39-1.41)
P-value	0.496	0.085	0.191	0.573	0.747	0.851	0.358
BMI (per 1 kg/m increase)							
OR (95% CI)	1.00 (0.95-1.05)	0.99 (0.94-1.04)	1.01 (0.96-1.06)	0.98 (0.93-1.04)	0.95 (0.88-1.01)	1.02 (0.95-1.08)	1.04 (0.96-1.12)
P-value	0.993	0.622	0.735	0.547	0.095	0.631	0.354
Drain Days (per day increase)							
OR (95% CI)	1.04 (0.97-1.12)	0.97 (0.90-1.04)	0.96 (0.89-1.03)	1.02 (0.95-1.10)	1.05 (0.96-1.14)	1.03 (0.94-1.11)	0.90 (0.81-1.00)
P-value	0.26	0.443	0.24	0.557	0.288	0.547	**0.046**
Drain Volume (per 100 ml increase)							
OR (95% CI)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.01)	1.00 (1.00-1.00)
P-value	**0.003**	0.081	0.73	0.341	0.505	0.26	0.699

Note: All models were adjusted for age, tumor stage, histologic grade, neoadjuvant chemotherapy, postoperative chemotherapy, endocrine therapy, targeted therapy, surgery type, surgery time, intraoperative blood loss, and follow-up duration. Significant *P*-values (< 0.05) are shown in bold. ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy.

Table 6. Multivariate linear results

Variable	Lymphedema Severity (Volume difference %)	Pain Severity (NRS score)	Shoulder Range of Motion (Flexion angle)	Quality of Life (QLQ-C30 score)
ALND vs. SLNB				
OR (95% CI)	7.14 (4.87-9.40)	2.80 (1.96-3.63)	-14.36 (-20.46 to -8.26)	-9.44 (-13.98 to -4.91)
P-value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Postoperative Radiotherapy				
OR (95% CI)	-0.70 (-2.06-0.67)	-0.49 (-1.00-0.01)	-0.91 (-4.59-2.77)	0.94 (-1.80-3.67)
P-value	0.317	0.055	0.627	0.501
BMI (per 1 kg/m increase)				
OR (95% CI)	-0.03 (-0.20-0.13)	-0.00 (-0.06-0.06)	-0.01 (-0.45-0.44)	-0.01 (-0.34-0.32)
P-value	0.709	0.918	0.977	0.949
Drain Days (per day increase)				
OR (95% CI)	0.20 (-0.04-0.44)	0.01 (-0.08-0.09)	-0.04 (-0.68-0.60)	-0.31 (-0.79-0.17)
P-value	0.094	0.876	0.909	0.203
Drain Volume (per 100 ml increase)				
OR (95% CI)	-0.01 (-0.02 to -0.01)	-0.00 (-0.01 to -0.00)	0.01 (-0.02-0.03)	0.00 (-0.02-0.02)
P-value	**0.003**	**0.02**	0.509	0.909

Note: All models were adjusted for age, tumor stage, histologic grade, neoadjuvant chemotherapy, postoperative chemotherapy, endocrine therapy, targeted therapy, surgery type, surgery time, intraoperative blood loss, and follow-up duration. β coefficients represent the change in outcome variable per unit increase in predictor variable. Significant *P*-values (< 0.05) are shown in bold. ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy; NRS: Numerical Rating Scale; QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

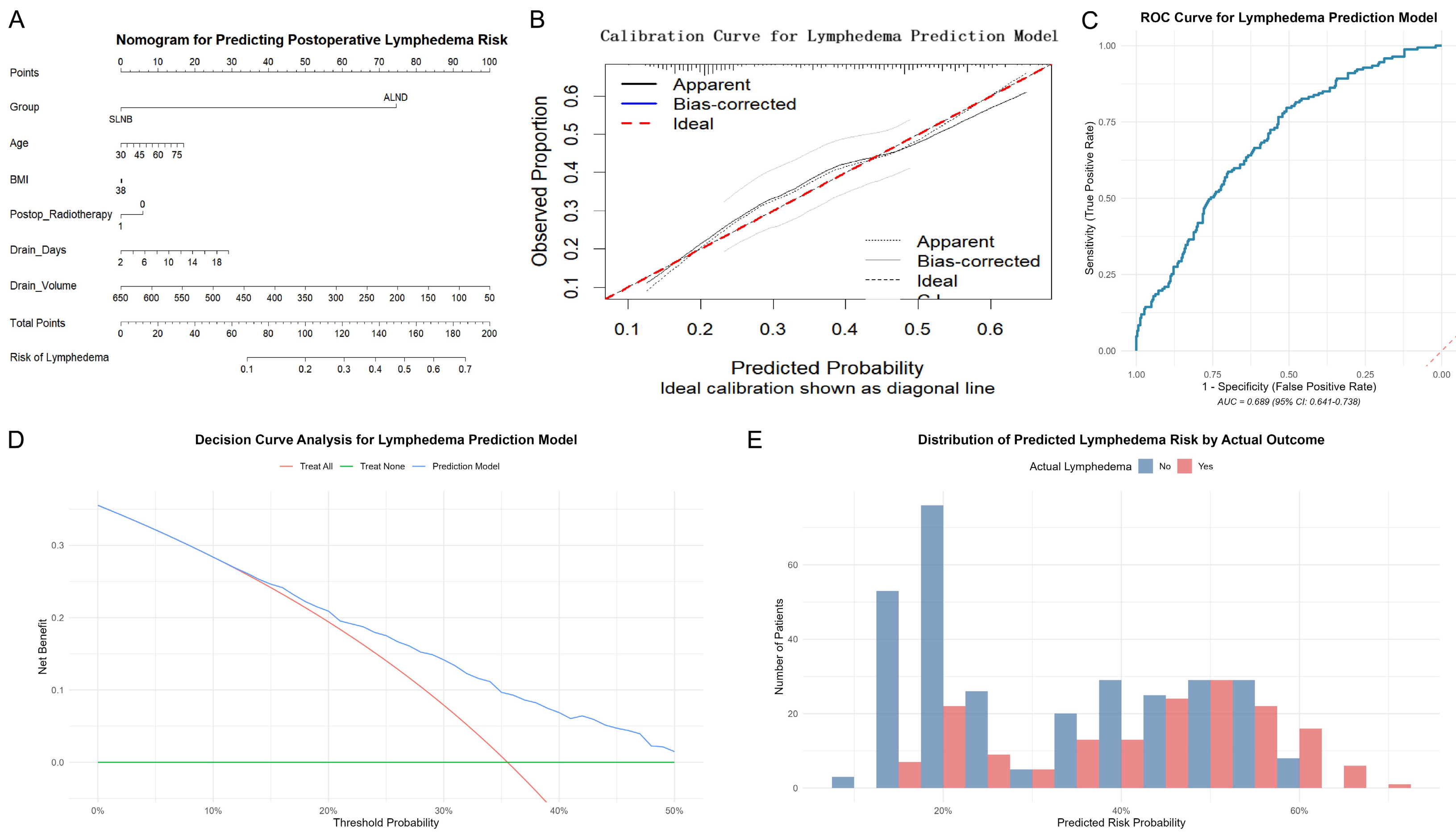

Figure 3. Nomogram model results. Note: A: Column chart for predicting the risk of postoperative lymphedema, integrating influencing factors including age, BMI, and surgical methods. When in use, scores are obtained from the corresponding scale of each variable, accumulated to match the "Total score" scale, and then mapped to the "Risk of lymphedema" scale to derive the predicted probability of lymphedema in patients. B: Calibration curve, showing the degree of fit among the model's apparent prediction probability (blue line), bias-corrected prediction probability (red line), and the ideal calibration line (dashed line, indicating complete consistency between the predicted probability and the actual probability), which suggests good calibration of the model. C: ROC curve, used to evaluate the discriminative ability of the model. The closer the curve is to the upper left corner, the stronger the model's ability to distinguish between the occurrence and non-occurrence of lymphedema. D: Decision curve analysis chart, showing the clinical net benefit of the model under different risk thresholds (red line), and comparing it with the "all intervention" (blue line) and "no intervention" (green line) strategies, indicating that the model has clinical practical value within a reasonable threshold range. E: Distribution chart of predicted risks and actual outcomes, presented as a histogram, showing the distribution of patients with actual lymphedema (red) and those without (blue) in different predicted risk intervals, reflecting the matching degree between predicted risks and actual outcomes.

Table 7. Net benefit values of the nomogram at different risk thresholds from decision curve analysis

Threshold Probability	Net Benefit (95% CI)
5%	0.06 (0.02-0.10)
10%	0.11 (0.06-0.16)
15%	0.15 (0.09-0.21)
20%	0.18 (0.12-0.24)
25%	0.21 (0.15-0.27)
30%	0.19 (0.13-0.25)
35%	0.16 (0.10-0.22)
40%	0.12 (0.06-0.18)
45%	0.07 (0.02-0.12)
50%	0.03 (-0.02-0.08)

Note: Data are presented as net benefit (95% confidence interval). Threshold probability represents the minimum predicted risk at which a clinician would recommend intervention. The optimal net benefit was observed at threshold probabilities between 20% and 30%.

benefit values in 5% increments within the 5%-50% range are shown in **Table 7**.

Cox results analysis

This study used a Cox proportional hazards model combined with the Kaplan-Meier method to analyze the event-free survival of postoperative lymphedema. The Log-rank test results showed a highly significant difference in the event-free survival rate of lymphedema between the SLNB and ALND group (P < 0.0001). The Kaplan-Meier curves indicated that during the follow-up period, the event-free survival rate of lymphedema in the SLNB group was consistently higher than that in the ALND group, suggesting that SLNB can significantly reduce the risk of postoperative lymphedema and prolong lymphedema-free survival (**Figure 4**).

Mediation effect analysis

The conceptual mediation model constructed in this study, "The Influence of Axillary Treatment Method on Lymphedema - Mediation by Postoperative Drainage", showed that axillary treatment method had a significant positive impact on both postoperative drainage days (path coefficient a1 = 4.1708, P < 0.001) and drainage volume (path coefficient a2 = 175.979, P < 0.001). Among the mediating variables, only drainage volume had a significant negative impact on lymphedema (path coefficient b2 = -0.004, P < 0.01), while the effect of drainage days on lymphedema was not statistically significant (path coefficient b1 = 0.023, P > 0.05). Simultaneously, axillary treatment method had a significant direct positive effect on lymphedema (path coefficient c2 = 1.197, P < 0.001). In this study, drainage volume played a partial mediating role in the association between axillary treatment method and lymphedema, while drainage days had no mediating effect (**Figure 5**). The multistate model showed that the risk of progression from a complication-free state to advanced chronic complications was 5.20 times higher in the ALND group than in the SLNB group (HR = 5.20, 95% CI: 3.28-8.24, P < 0.001). Simultaneously, the probability of recovery from early complications to a complication-free state was significantly lower in the ALND group than in the SLNB group (HR = 0.42, 95% CI: 0.28-0.63, P < 0.001). The model showed good goodness of fit (Akaike Information Criterion = 2845.6).

Discussion

Combining phenotypic analysis, subgroup interaction tests, predictive model construction, and mediating effect validation, this study provides multidimensional evidence for the precise clinical prevention and treatment of axillary complications.

The results of this study indicate that ALND is a key independent risk factor for multiple complications after breast cancer surgery, a conclusion consistent with existing clinical consensus and further deepening the research [13, 14]. Regarding the risk of complications, compared with SLNB, ALND significantly increased the risk of six adverse outcomes, including lymphedema, pain, and limited shoulder joint movement, while the risk of infection showed no statistical difference. In terms of the severity and functional impact, the ALND group had significantly higher differences in lymphedema volume and NRS scores for pain, and significantly lower scores for shoulder flexion angle and the QLQ-C30 scores. This suggests that ALND not only increases the incidence of complications but also directly impairs patients' physical function and quality of life, a result consistent with the study by Li [15] et al. Kaplan-Meier survival analysis further confirmed that the lymphedema-free survival rate of the SLNB group was

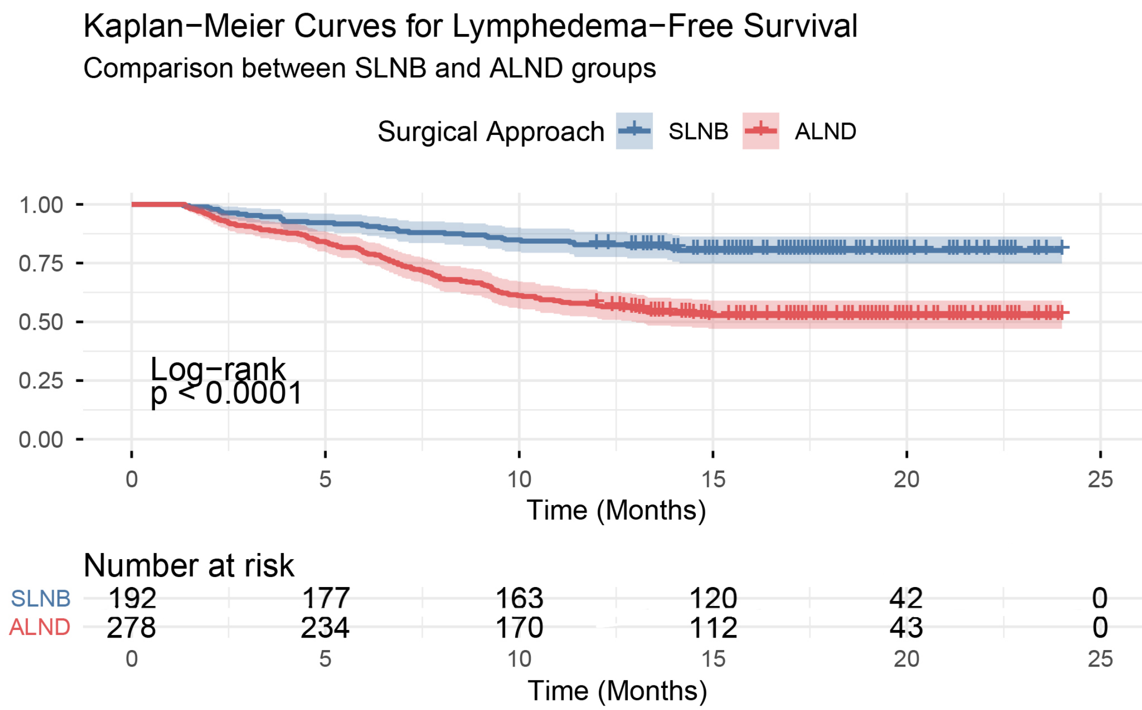

Figure 4. Kaplan-Meier curve for postoperative lymphedema event-free survival in SLNB and ALND groups. Note: This figure shows the trend of the postoperative lymphedema event-free survival rate over follow-up time (in months) in two groups of patients who underwent sentinel lymph node biopsy (SLNB, blue curve) and axillary lymph node dissection (ALND, red curve). The Log-rank test result labeled in the figure (P < 0.0001) indicates a highly significant difference in the event-free survival curves between the two groups. The "Number at risk" table below presents the number of at-risk individuals in the two groups at different follow-up time points, further confirming that the SLNB group has better lymphedema event-free survival than the ALND group.

consistently better than that of the ALND group (P < 0.0001), which is consistent with the results of Gherghe et al., verifying the advantages of SLNB in long-term prognosis and providing a core basis for the selection of clinical axillary treatment methods [4].

Subgroup analysis showed that ALND was more significantly associated with lymphedema in patients with a BMI ≥ 25 who received postoperative radiotherapy. Although the interaction test did not show a statistically significant difference, the results suggest that this population may be a high-risk group for complications related to ALND and should be given special attention in clinical practice [15]. Multivariate regression analysis, after excluding the direct and significant effects of postoperative radiotherapy and BMI on complications, further highlighted the importance of surgical method as a core risk factor; there was a weak correlation between drainage days and readmission risk, and between drainage volume and lymphedema risk, which provides a potential intervention target for postoperative management. The innovation of this study lies in breaking through the limitations of previous studies that only focused on a single complication. Through cluster analysis, four stable and clinically distinguishable phenotypes were identified: a low-risk axillary function preservation phenotype mainly based on SLNB (phenotype I, accounting for 42.13%), and three phenotypes associated with ALND, namely, pain-dominant phenotype (phenotype II, 26.17%), severe lymphedema phenotype (phenotype III, 13.62%), and moderate to severe comorbidity phenotype (phenotype IV, 18.09%). The above results are consistent with the conclusions of previous clinical studies [16]. This refined classification reveals that the risks associated with ALND are not uniform, but present a specific identifiable pattern. 96.46% of patients in phenotype I underwent SLNB, while 98.44% to 100% of patients in phenotypes II to IV underwent ALND. This significant grouping difference highlights the decisive role of the extent of axillary surgery in the phenotype of subsequent complications. This finding provides a new and refined perspective for precise risk stratification,

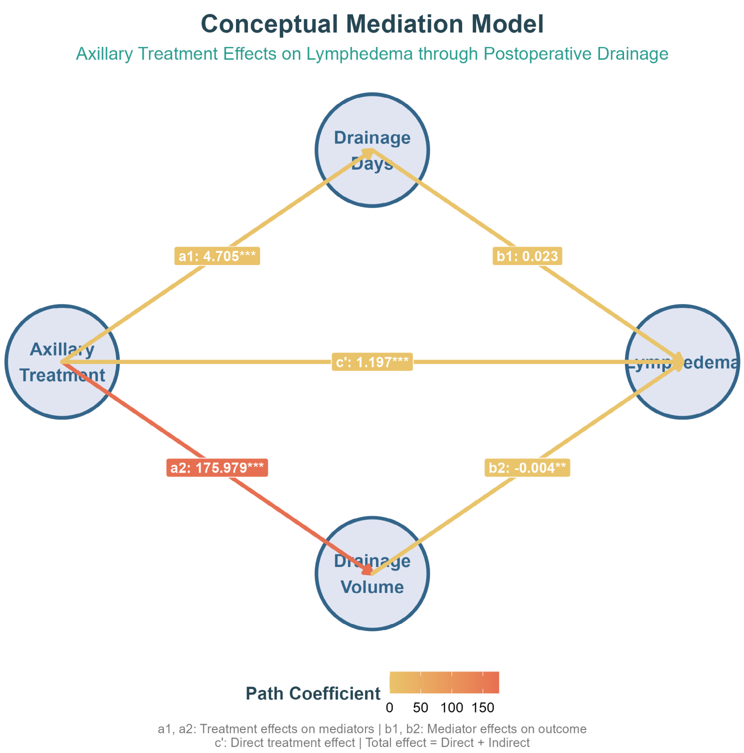

Figure 5. Conceptual mediation model of the impact of axillary treatment on lymphedema via postoperative drainage. Note: This figure illustrates the mediating effect pathway of axillary treatment (independent variable) → postoperative drainage (drainage days, drainage volume; mediator variable) → lymphedema (dependent variable). a1 and a2 represent the influence coefficients of axillary treatment on the mediator variable; b1 and b2 represent the influence coefficients of the mediator variable on lymphedema; and c2 represents the direct effect coefficient of axillary treatment on lymphedema. The values on the paths are the path coefficients, where "***" and "**" indicate that the corresponding coefficients are statistically significant ($P < 0.001$, $P < 0.01$). The color scale bar below the figure is used to visually display the numerical values of the path coefficients.

breaking the traditional understanding that complications related to ALND are treated as a single whole.

Mediation analysis further elucidated the pathway by which ALND affects lymphedema. ALND can significantly prolong drainage days and increase drainage volume, while drainage volume, as a partial mediator, indirectly mediates the effect of ALND on lymphedema [17]. The mediation analysis in this study further clarifies the potential pathway connecting ALND and lymphedema, confirming that postoperative drainage volume is a partial mediator. From a pathophysiological perspective, ALND causes a larger area of axillary trauma, which will destroy more lymphatic vessels and trigger a strong inflammatory response [18], leading to increased exudation of protein-rich fluid and inflammatory factors, clinically manifested as increased postoperative drainage [19]. Although increased drainage is a direct result of the surgical area, this study found that it has a negative mediating effect, which needs to be interpreted from a mechanistic perspective. Adequate drainage can reduce the risk of lymphedema by reducing interstitial fluid pressure and removing pro-inflammatory mediators (e.g., IL-6, TGF-β) from the surgical site [20]. Timely removal of such mediators can theoretically inhibit fibroblast activation and subsequent tissue fibrosis, protect residual lymphatic vessels from inflammatory damage, thereby maintaining lymphatic function to a certain extent and reducing the risk of overt lymphedema [21]. This interpretation is consistent with the hypothesis that excessive axillary effusion and persistent inflammation are key factors leading to lymphatic dysfunction [22, 23].

However, it must be emphasized that the mediating effect found in this study is only a statistical association derived from retrospective data, not a validated causal mechanism. The protective effect of increased drainage volume is more likely an external manifestation of the complex interaction between surgical trauma, inflammation resolution, and individual healing capacity. Unmeasured confounding factors, such as the precision of lymphatic vessel injury and differences in postoperative care, may simultaneously affect drainage volume and lymphedema outcomes. Therefore, although the results of this study provide clues for clinical practice, they cannot conclusively prove that increasing drainage volume has a direct protective effect. Future prospective studies are needed, ideally including biomarkers related to inflammation and lymphatic function, to verify this mechanism hypothesis.

The lymphedema prediction line graph constructed based on multivariate regression results underwent internal validation using the Bootstrap method, showing good calibration and reliable discriminative ability. Decision curve analysis confirmed that the model has a significant net clinical benefit within a reasonable risk threshold range. This model quantifies key factors such as age, BMI, and surgical procedure into intuitive scores, enabling rapid individualized risk assessment for patients. This addresses the lack of quantitative tools in traditional risk assessments in clinical practice, providing a theoretical basis for early identification of high-risk groups and the initiation of targeted interventions.

Based on the results of this study, especially the optimal risk threshold (20%) derived from the DCA of the lymphedema prediction nomogram, this study proposes a quantitative, risk-stratified individualized prevention system. The system combines nomograms to predict risk and clinical risk factors to guide intervention intensity: (1) Low-risk group (predicted risk of lymphedema < 10%): These patients are mostly those who have only undergone SLNB and have not received radiotherapy. They only need to carry out standard postoperative health education and early shoulder joint mobility training. The net benefit of additional intervention below this risk threshold is minimal [24]; (2) Intermediate-risk group (predicted risk 10%-20%): These are mostly patients who have undergone SLNB and radiotherapy, or patients who have undergone ALND without other risk factors. It is recommended to strengthen postoperative monitoring, including regular measurement of arm circumference and follow-up of patients' subjective symptoms. If subtle abnormalities are found, they should be referred for early rehabilitation treatment in a timely manner [25]; (3) High-risk group (predicted risk > 20%): This group mainly consists of patients who have undergone ALND, especially those with a body mass index ≥ 25 or who have received radiotherapy after surgery. DCA showed that intervention for this type of patient yielded significant net benefits, and intensive prevention strategies were recommended: preoperative education on lymphedema risk, wearing prophylactic pressure garments, developing standardized rehabilitation training programs, and regular bioelectrical impedance analysis to detect subclinical lymphatic dysfunction [26-28]. For patients undergoing ALND, mediation analysis in this study also suggested that optimizing drainage management and ensuring adequate drainage while avoiding unnecessary prolongation of drainage time may help reduce risk. This quantitative system applies the results of DCA, allowing clinicians to predict risks and develop intervention plans based on nomograms, maximizing clinical net benefits while avoiding overtreatment of low-risk patients [29, 30].

This study has certain limitations. First, this was a single-center retrospective study, and selection bias was unavoidable. For example, the proportion of patients with advanced tumors were higher in the ALND group (stage II patients accounted for 65%). Although multivariate regression was used to correct for known confounding factors such as age, tumor stage, and adjuvant therapy, residual confounding could not be completely eliminated. Second, the study did not systematically collect and include detailed data on preoperative comorbidities. Hypertension, diabetes, obesity (BMI partially reflects this factor), and preexisting vascular or lymphatic system diseases can all independently affect the risk and severity of postoperative complications, particularly lymphedema and abnormal wound healing. The lack of such detailed comorbidity data may introduce unmeasured confounding factors, affecting the accuracy and extrapolation of complication risk assessment. Future prospective studies should include comprehensive comorbidity assessments to more accurately separate the independent effects of different axillary surgical methods.

Third, the study did not include potential influencing factors such as gene polymorphisms and surgical details, which may have missed some key mechanisms. Further multicenter prospective cohort studies can be conducted to further validate the predictive model and intervention strategies of this study. The follow-up period can be extended to more than 5 years to explore the long-term natural course of complications. Biomarker detection and imaging technology can be combined to deeply analyze the molecular mechanisms of complication occurrence. At the same time, targeted randomized controlled trials can be carried out based on the phenotypic classification of this study to verify the effectiveness of individualized intervention programs, ultimately achieving accurate prediction, early intervention, and full-process management of axillary complications after breast cancer surgery, further improving patients' long-term quality of life.

Conclusion

This study shows that compared with SLNB, ALND significantly increases the risk of complications, and four distinct clinical phenotypes can be identified. Moderate to severe comorbidity phenotypes are closely associated with ALND, especially in patients receiving radiotherapy or with BMI $\geq$ 25. Prolonged postoperative drainage time plays a partial mediating role in the association between surgical method and lymphedema. The results support the development of individualized prevention strategies based on clinical phenotypes, providing clinical evidence for the rational selection of axillary management methods. Future research should include multicenter prospective studies to validate these conclusions and optimize the management of long-term postoperative complications in breast cancer patients.

Disclosure of conflict of interest

None.

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