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Predictors of early arm lymphoedema in breast cancer patients treated with modified radical mastectomy -a prospective observational study

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Abstract

Background Breast cancer is the most common malignancy among women globally, with 2.3 million new cases in 2022. Advances in early detection and treatment have improved survival, but long-term complications like breast cancer-related lymphoedema (BCRL) remain underrecognized. Affecting 6–40% of patients following axillary lymph node dissection, BCRL leads to chronic swelling, pain, and reduced quality of life. The risk is heightened in low- and middle-income countries (LMICs), where delayed diagnosis and limited awareness necessitate more aggressive interventions. Despite its profound physical, psychosocial, and economic impact, BCRL remains understudied in LMICs, highlighting the need for region-specific data and preventive strategies.

Methods This prospective observational study, which was conducted in a tertiary care centre over 18 months (July 2022–December 2023), aimed to identify clinicopathological predictors of the development of early ipsilateral arm lymphoedema in patients undergoing Modified radical mastectomy (MRM). We diagnosed lymphoedema via circumferential measurements (≥ 10% increase in ipsilateral arm) at 1 day pre-surgery and followed up the patients at 1-, 3-, and 6-months post-surgery. Variables included patient demographics, tumour characteristics, and treatment factors.

Results We recruited 80 patients, and 21 of them (26.25%) developed lymphoedema in 6 month period, with significant predictors identified as BMI (mean 28.42 vs. 26.04 kg/m^2, $p = 0.008$), Left-sided tumours (40% vs. 18% for right-sided, $p = 0.03$), number of lymph nodes removed (mean 21.14 vs. 13.49, $p = 0.003$), and positive lymph nodes (mean 3.81 vs. 1.15, $p = 0.009$), Axillary radiation (55% vs. 16.7%, $p < 0.001$). Multivariate analysis confirmed BMI (aOR = 1.19, 95%CI:1.00–1.42; p = 0.045), total lymph nodes removed (aOR = 1.08, 95%CI:1.01–1.15; $p = 0.027$), and axillary radiation (aOR = 4.57, 95%CI:1.37–15.26; p = 0.013) as independent predictors, while positive lymph nodes lost significance when adjusted for confounders (aOR = 1.04, $p = 0.718$). Age, hormone receptor status, and chemotherapy type showed no significant associations.

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Conclusion The study highlights the critical role of pre-operative risk stratification. These findings underscore the need for personalized surgical and adjuvant strategies to mitigate Lymphoedema risk, enhancing long-term survivorship care in breast cancer patients.

Trial registration Clinical Trials Registry India—CTRI/2023/08/056411 (Registered prospectively on 11/08/2023).

Keywords Breast cancer, Lymphoedema, Survivorship, Prospective studies, Axillary dissection

Background

Breast cancer remains the most prevalent malignancy among women globally, with an estimated 2.3 million new cases diagnosed in 2022, as per GLOBOCAN 2022 data, accounting for nearly 12% of all cancer diagnoses worldwide [1]. While advancements in early detection and multimodal therapies—including surgery, radiation, and systemic treatments—have significantly improved 5-year survival rates to over 90% for localized disease, these interventions often carry long-term sequelae that may compromise survivorship outcomes [2]. Among these, lymphoedema stands out as a debilitating and underrecognized complication. Characterized by progressive swelling of the ipsilateral arm due to impaired lymphatic drainage, it affects 6–40% of patients undergoing axillary lymph node dissection (ALND), with variability attributed to surgical techniques, adjuvant therapies, and patient-specific risk factors [3, 4]. In low- and middle-income countries (LMICs), delayed diagnoses leading to advanced disease, often necessitates more aggressive interventions, further amplifying the lymphedema burden. However, region-specific data remain scarce, hindering tailored preventive strategies [5].

The pathophysiology of lymphoedema is multifactorial, rooted in the disruption of lymphatic architecture during surgery and exacerbated by post-treatment inflammation and fibrosis. Axillary clearance, a cornerstone of breast cancer staging, disrupts axillary lymph nodes and collateral pathways, impairing fluid transport and increasing hydraulic resistance within the lymphatic system [6]. Subsequent radiation therapy compounds this damage by inducing perivascular fibrosis and sclerosis, reducing lymphatic contractility by up to 60% [7]. Molecular mechanisms further drive chronicity: transforming growth factor-beta (TGF-β) activation promotes fibroblast proliferation and extracellular matrix (ECM) deposition. In contrast, vascular endothelial growth factor-C (VEGF-C)-mediated lymphangiogenesis often yields dysfunctional vessels incapable of restoring drainage [8, 9]. Concurrent oxidative stress, mediated by reactive oxygen species (ROS), exacerbates endothelial damage, perpetuating a cycle of inflammation and tissue remodelling [10]. These processes culminate in the hallmark features of lymphoedema—non-pitting oedema, hyperkeratosis, and recurrent cellulitis, which diminish quality of life and impose substantial economic burdens.

The ramifications of lymphoedema extend far beyond physical morbidity. Psychosocially, patients report profound anxiety, depression, and body image disturbances, often exacerbated by cultural stigmatization of visible disfigurement [11]. Functionally, reduced range of motion and chronic pain limit activities of daily living, with 30% of patients unable to return to work within two years of diagnosis [12]. Economically, the lifelong costs of compression garments, physiotherapy, and hospitalizations exceed US$1,800 annually per patient in high-income countries. At the same time, out-of-pocket expenses frequently lead to catastrophic health expenditures in resource-limited settings like India, with a recent study reporting a mean total cost of breast cancer treatment alone to be INR/₹ 258,095/US$ 3531, with adequate data for lymphoedema treatment in Indian setting not available [13]. Despite these challenges, lymphoedema remains underprioritized in oncology care pathways, particularly in regions where survival outcomes dominate clinical focus.

Globally, obesity, extensive nodal dissection, and post-operative radiation to the axilla are well-established risk factors for BCRL. However, emerging evidence suggests regional disparities in risk profiles. In South Asia, for instance, higher rates of advanced-stage diagnoses—40% of Indian patients present with stage III/IV disease—necessitate more aggressive surgical interventions, potentially elevating lymphoedema incidence [14]. Cultural factors, including delayed healthcare-seeking behaviour and limited lymphoedema awareness, further complicate early detection and intervention. Such gaps underscore the urgent need for context-specific research to inform risk stratification and guide resource allocation in LMICs.

The primary aim of this study was to identify clinicopathological predictors associated with the development of ipsilateral arm lymphoedema in breast cancer patients undergoing Modified Radical Mastectomy (MRM). The study sought to stratify risk and inform targeted strategies for lymphoedema prevention and early intervention in a resource-limited setting by analysing patient demographics, tumour characteristics, and surgical and adjuvant treatment factors.

Methods

This prospective observational study was conducted at a tertiary care centre over 18 months (July 2022–December 2023) following approval by the Institutional Ethics Committee (AIIMS/IEC/23/212). Consecutive sampling of eligible patients was done, with adherence to inclusion and exclusion criteria rigorously maintained throughout the study. All patients were treated in a specialised breast unit, with standardised pre-operative protocols, workup, standard surgical technique, post operative care and rehabilitation protocols, with no major changes over the period of 18 months.

Eligible participants included in the study were female patients aged ≥ 18 years with histologically confirmed breast carcinoma scheduled for Modified Radical Mastectomy (MRM), while exclusion factors were preexisting ipsilateral arm lymphoedema, pre-operative axillary vein thrombosis confirmed via imaging, metastatic disease at presentation, or a history of recurrent breast malignancy. Consecutive sampling was performed within the specified time frame.

The diagnostic criteria for lymphoedema were a ≥ 10% increase in ipsilateral arm circumference relative to the contralateral arm using circumferential measurements at four anatomical landmarks, a method validated in resource-constrained settings for its cost-effectiveness and reproducibility. All measurements were done by single trained observer. Arm measurements were made at 8AM ± 1 h, all patient were asked not to wear compression garment on day of measurement and were not given instructions with regard to activity before measurement (Fig. 1,) [15].

Pre-operative assessment documented clinical and tumour characteristics, including baseline arm circumference measurements. Postoperatively, patients were evaluated at 1, 3, and 6 months to monitor arm circumference changes, with lymphoedema defined as a ≥ 10% increase in circumference compared to pre-operative measurements or the contralateral limb.

The data collected was tabulated in Microsoft Excel (Microsoft Corporation). Qualitative (categorical) variables were expressed in frequency, percentage, and proportions, and quantitative (continuous) variables were expressed by means and standard deviation or median with inter-quartile range. The chi-square test was used to determine the association between the patient, tumour, and treatment factors and the development of lymphoedema. Unpaired t-tests were used to check the hypothesis in normally distributed variables (tested by the Shapiro–Wilk test). The Wilcoxon-Mann–Whitney U test was used to compare variables that were not normally distributed in the two subgroups of the variable lymphoedema.

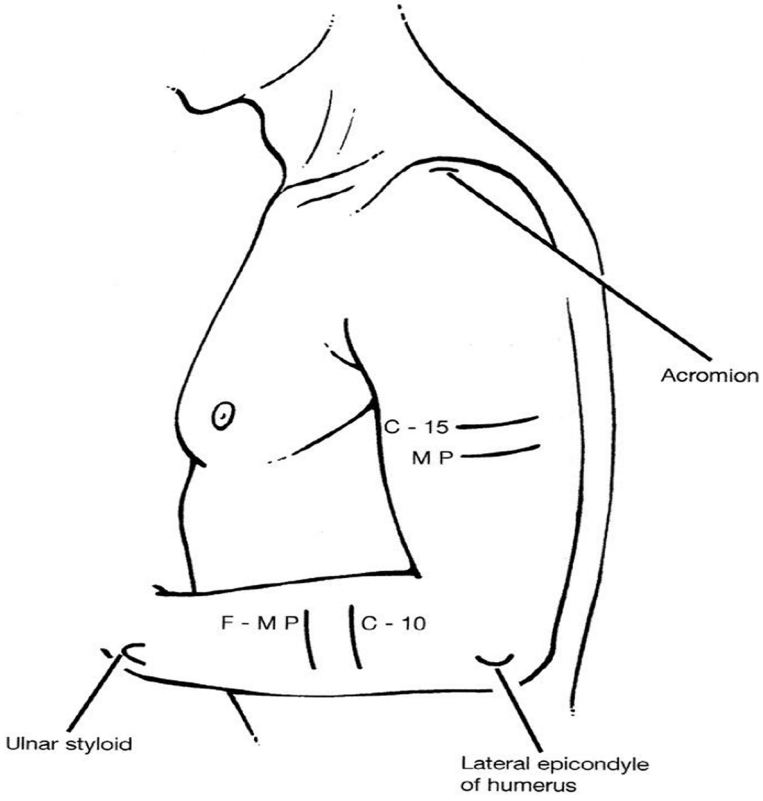

Fig. 1 4 points of arm measurement. F-MP: Midpoint of forearm; C-10: 10 cm below lateral epicondyle of humerus; MP: Midpoint of arm; C-15: 15 cm above lateral epicondyle of humerus

Fisher's exact test was used to explore the association between lymphoedema and variables where more than 20% of the total number of cells had an expected count of less than 5. Regression analysis was done using backward selection and bidirectional selection method. All Analyses were done using SPSS v25 (IBM Corporation). A p-value of < 0.05 was considered statistically significant.

Results

The following table summarizes the regression analysis for the dependent variable using all the predictor variables together in one go. The 'OR (univariable)' column lists the odds ratios for each of the variables with respect to the dependent variable, when these variables are used as single predictors of the dependent variable, without entering the rest of the variables in the model. The 'OR (multivariable)' column lists the odds ratios for all the variables when they are entered in the model together (and are now thus controlling for each other). The first category in each of the categorical variables is the reference category, against which the odds ratios of the rest of the variables is calculated.

The following table is the same as the previous table, except in this table bidirectional stepwise selection is used to select only the most useful variables to include in the final multivariable predictive model for the dependent variable.

This study recruited 86 eligible patients, of whom four were lost to follow-up after surgery, and two patients died before completion of the study duration. The attrition rate in our study was 7% ($n = 6$). So, data from 80 patients was taken up for the final Analysis (Fig. 2).

The clinicodemographic characteristics of the patients are detailed in Table 1. Table 2 presents the final histopathological profile obtained postoperatively, providing insight into the spectrum of pathological entities encountered in the cohort. Table 3 outlines the results of univariate Analysis, identifying factors significantly

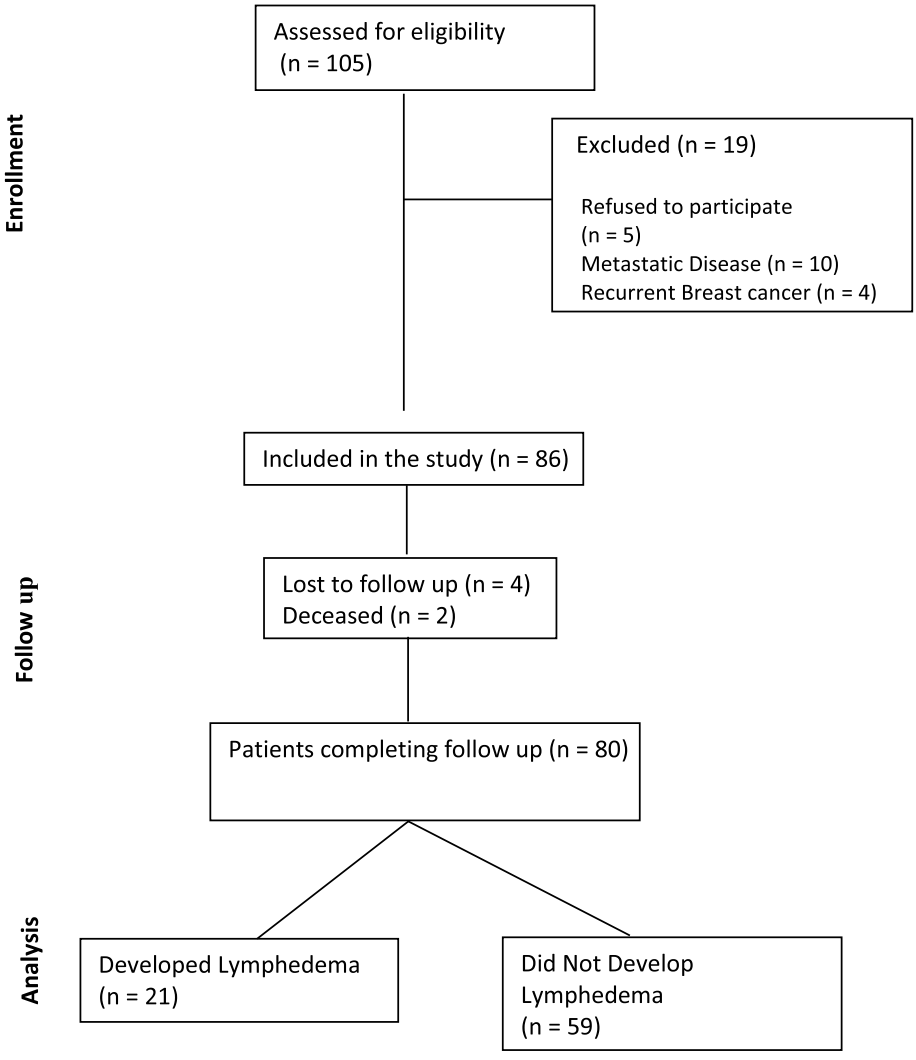

Fig. 2 Flowchart for patient assessment for eligibility, inclusion, follow up, attrition and final analysis

Table 1 Clinicodemographic profile of patients and treatment received

Factors	Mean ± SD || Median (IQR) || Min–Max OR N (%)
Age (Years)	47.11 ± 11.74 || 45.00 (38.00–55.00) || 28.00—77.00
Age	
< 40 Years	24 (30.0%)
41- 60 Years	43 (53.8%)
61–70 Years	13 (16.2%)
Gender	
Female	79 (98.8%)
BMI (kg/m^2)	26.67 ± 3.86 || 27.15 (24.00–29.13) || 18.97—35.30
Dominant Limb	
Left	0 (0.0%)
Right	80 (100.0%)
Side of Carcinoma	
Left	30 (37.5%)
Right	50 (62.5%)
Stage As Per 8th AJCC	
IA	
IB	
IIA	23 (28.7%)
IIB	16 (20.0%)
IIIA	10 (12.5%)
IIIB	30 (37.5%)
IIIC	1 (1.2%)
Chemotherapy Regimen	N (%)
Neoadjuvant Therapy	
Not Given	19 (23.8%)
Taxane Based	48 (60.0%)
Trastuzumab Based	13 (16.2%)
Chemotherapy Drug Given	
Taxane-Based Given	67 (83.8%)
Trastuzumab Based Given	13 (16.2%)

Table 2 Histopathology features

Tumour factors	Mean ± SD || Median (IQR) || Min–Max OR N (%)
Hormone Receptor Status (Positive)	51 (63.7%)
HER-2-Neu Receptor (Positive)	20 (25.0%)
Nottingham Grade	
1	4 (5.0%)
2	18 (22.5%)
3	58 (72.5%)
DCIS Component	
Present	16 (20.0%)
Not Present	64 (80.0%)
Lymphovascular Invasion	
Present	9 (11.2%)
Not Present	71 (88.8%)
Capsular Invasion	
Present	10 (12.5%)
Extra Nodal Extension	
Present	11 (13.8%)
Not Present	69 (86.2%)
Number of Lymph Nodes Removed	15.50 ± 9.60 || 14.00 (9.75–20.00) || 0.00—48.00
Positive Lymph Nodes Removed	1.85 ± 3.48 || 0.00 (0.00–2.00) || 0.00—18.00

associated with the outcome of interest, while Tables 4 and 5 displays the multivariate analysis, demonstrating the independent predictors after adjusting for potential confounders Tables 6 and 7.

In this prospective study of 80 breast cancer patients undergoing Modified Radical Mastectomy (MRM), *26.25% (n = 21)* developed ipsilateral arm lymphoedema within 6 months post-surgery. Key predictors included:

- *Body Mass Index (BMI)*: Patients with lymphoedema had significantly higher BMI (mean 28.42 vs. 26.04 kg/m^2, $p = 0.008$). With T test identifying a significant difference between the two groups in terms of BMI (kg/m^2) (t = 2.783, $p = 0.008$). Strength of Association measured by Point-Biserial Correlation = 0.27 (Medium Effect Size). Univariable OR: 1.20 (95% CI: 1.04–1.43, $p = 0.02$). On multivariate Analysis (Stepwise Model), aOR: 1.19 (95% CI: 1.00–1.42, $p = 0.045$). Thus, BMI remains an independent predictor after controlling for nodal dissection and radiation. Each 1-unit increase confers 19% higher lymphedema risk.
- *Side of tumour*: Left-sided tumours were associated with a higher lymphoedema incidence (40% for left side vs. 18% for right side. On the chi-square test, there was a significant difference between the various groups in terms of the distribution of lymphoedema ($\chi 2 = 4.688$, $p = 0.030$). The odds ratio and relative risk are 3.04 (CI = 1.09–8.48) and 2.22 (CI = 1.08–4.59), respectively, for the development of lymphoedema on the left side. Laterality was not included in multivariate analysis as it is less likely affected by other confounders.
- *Lymph node dissection*: A greater number of lymph nodes were removed in patients who developed lymphoedema (mean 21.14 vs. 13.49, $p = 0.003$). Univariable analysis confirmed this association (OR = 1.09, 95% CI: 1.03–1.16, $p = 0.004$). Crucially, the total number of nodes removed remained a significant independent predictor in both

Table 3 Univariate analysis

Parameters	Lymphoedema		*p*-value
	Present (*n* = 21)	Absent (*n* = 59)	
Age (Years)	46.14 ± 10.24	47.46 ± 12.29	0.635
BMI (kg/m^2)	28.42 ± 3.13	26.04 ± 3.93	0.008
Side of Carcinoma			0.030
Left	12 (57.1%)	18 (30.5%)	
Right	9 (42.9%)	41 (69.5%)	
Dominant Limb			1.000
Left	0 (0.0%)	0 (0.0%)	
Right	21 (100.0%)	59 (100.0%)	
Chemotherapy Drug Given			0.496
Taxane-Based Given	19 (90.5%)	48 (81.4%)	
Trastuzumab Based Given	2 (9.5%)	11 (18.6%)	
Stage As Per 8th AJCC			0.614
IIA	6 (28.6%)	17 (28.8%)	
IIB	5 (23.8%)	11 (18.6%)	
IIIA	1 (4.8%)	9 (15.3%)	
IIIB	6 (28.6%)	18 (30.5%)	
IIIC	0 (0.0%)	1 (1.7%)	
Nottingham Grade			0.536
1	0 (0.0%)	4 (6.8%)	
2	6 (28.6%)	12 (20.3%)	
3	15 (71.4%)	43 (72.9%)	
DCIS Component			0.751
Present	5 (23.8%)	11 (18.6%)	
Not Present	16 (76.2%)	48 (81.4%)	
Lymphovascular Invasion			0.433
Present	1 (4.8%)	8 (13.6%)	
Not Present	20 (95.2%)	51 (86.4%)	
Hormone Receptor Status (Positive)	14 (66.7%)	37 (62.7%)	0.746
HER-2-Neu Receptor (Positive)	4 (19.0%)	16 (27.1%)	0.463
Capsular Invasion			0.118
Present	5 (23.8%)	5 (8.5%)	
Not Present	16 (76.2%)	54 (91.5%)	
Number of Lymph Nodes Removed	21.14 ± 10.33	13.49 ± 8.55	0.003
Extra Nodal Extension			0.146
Present	5 (23.8%)	6 (10.2%)	
Not Present	16 (76.2%)	53 (89.8%)	
Radiation to Axilla (Post-Operative)	11 (52.4%)	9 (15.3%)	< 0.001
Positive Lymph Nodes Removed	3.81 ± 4.92	1.15 ± 2.50	0.009
Level of Lymph Node Dissection			0.262
ALND	20 (95.2%)	59 (100.0%)	
ALND + Level 3	1 (4.8%)	0 (0.0%)	
Seroma (Post-Operative) (Yes)	6 (28.6%)	11 (18.6%)	0.363
Wound Infection (Post-Operative) (Yes)	3 (14.3%)	8 (13.6%)	1.000
Restriction in Arm Movement (Post-Operative) (Yes)	12 (57.1%)	21 (35.6%)	0.085

Table 4 Multivariate analysis

Dependent: Lymphoedema		Absent	Present	OR (univariable)	OR (multivariable)
BMI (kg/m^2)	**Mean (SD)**	**26.0 (3.9)**	**28.4 (3.1)**	**1.20 (1.04–1.43, *p* = 0.020)**	**1.19 (1.01–1.44, *p* = 0.048)**
Number of Lymph Nodes Removed	Mean (SD)	13.5 (8.5)	21.1 (10.3)	1.09 (1.03–1.16, *p* = 0.004)	1.07 (1.01–1.16, *p* = 0.037)
Positive Lymph Nodes Removed	Mean (SD)	1.2 (2.5)	3.8 (4.9)	1.23 (1.06–1.47, *p* = 0.010)	1.04 (0.85–1.29, *p* = 0.718)
Radiation to Axilla (Post-Operative)	No	50 (83.3)	10 (16.7)	-	-
	Yes	9 (45.0)	11 (55.0)	6.11 (2.05–19.28, *p* = 0.001)	3.87 (0.85–18.38, *p* = 0.077)

MODEL FIT: $\chi^2(4) = 21.67$, $p = < 0.001$ Pseudo-$R^2 = 0.24$

Number in data frame = 80, Number in model = 80, Missing = 0

AIC = 80.4, C-statistic = 0.82, H&L = Chi-square (8) 10.33 ($p = 0.243$)

Table 5 Multivariate analysis (bidirectional stepwise selection)

Dependent: Lymphoedema		Absent	Present	OR (univariable)	OR (multivariable)
BMI (kg/m^2)	**Mean (SD)**	**26.0 (3.9)**	**28.4 (3.1)**	**1.20 (1.03–1.41, *p* = 0.020)**	**1.19 (1.00–1.42, *p* = 0.045)**
Number of Lymph Nodes Removed	Mean (SD)	13.5 (8.5)	21.1 (10.3)	1.09 (1.03–1.16, *p* = 0.004)	1.08 (1.01–1.15, *p* = 0.027)
Positive Lymph Nodes Removed	Mean (SD)	1.2 (2.5)	3.8 (4.9)	1.23 (1.05–1.44, *p* = 0.010)	-
Radiation to Axilla (Post-Operative)	No	50 (83.3)	10 (16.7)	-	-
	Yes	9 (45.0)	11 (55.0)	6.11 (2.01–18.58, *p* = 0.001)	4.57 (1.37–15.26, *p* = 0.013)

MODEL FIT: $\chi^2(3) = 21.54$, $p = < 0.001$ Pseudo-$R^2 = 0.23$

Number in data frame = 80, Number in model = 80, Missing = 0

AIC = 78.6, C-statistic = 0.816, H&L = Chi-square (8) 11.86 ($p = 0.158$)

multivariable models. After adjusting for BMI, positive nodes, and radiation, each additional node removed increased risk by 7% (aOR = 1.07, 95% CI: 1.01–1.16, $p = 0.037$). In the optimized stepwise model (adjusting for BMI and radiation), each

Table 6 Performance of study parameters for predicting lymphedema

Variable			Total Positives	True Positives	True Negatives	False Positives	False Negatives
Lymphoedema	Present	Absent	21 (26.2%)	-	-	-	-
BMI (kg/m^2) (Cutoff: 27.2 by ROC)	>= 27.2	< 27.2	40 (50.0%)	16 (20.0%)	35 (43.8%)	24 (30.0%)	5 (6.2%)
Number of Lymph Nodes Removed (Cutoff: 16 by ROC)	>= 16	< 16	37 (46.2%)	16 (20.0%)	38 (47.5%)	21 (26.2%)	5 (6.2%)
Positive Lymph Nodes Removed (Cutoff: 3 by ROC)	>= 3	< 3	18 (22.5%)	10 (12.5%)	51 (63.7%)	8 (10.0%)	11 (13.8%)

Table 7 Performance of study parameters for predicting lymphedema

Variable	AUROC	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
BMI (kg/m^2) (Cutoff: 27.2 by ROC)	0.696 (0.57–0.82)	76.2% (53–92)	59.3% (46–72)	40.0% (25–57)	87.5% (73–96)	63.7% (52–74)
Number of Lymph Nodes Removed (Cutoff: 16 by ROC)	0.719 (0.60–0.84)	76.2% (53–92)	64.4% (51–76)	43.2% (27–61)	88.4% (75–96)	67.5% (56–78)
Positive Lymph Nodes Removed (Cutoff: 3 by ROC)	0.674 (0.54–0.81)	47.6% (26–70)	86.4% (75–94)	55.6% (31–78)	82.3% (70–91)	76.2% (65–85)

additional node removed increased risk by 8% (Adj. OR = 1.08, 95% CI: 1.01–1.15, $p = 0.027$).

- *Number of positive lymph nodes*: The Number of positive lymph nodes was higher in patients who developed lymphoedema (mean 3.81 vs 1.15). On using the Wilcoxon-Mann–Whitney U Test, there was a significant difference in terms of Positive Lymph Nodes Removed ($p = 0.009$), strength of Association (Point-Biserial Correlation) = 0.34 (Medium Effect Size). univariable analysis indicated a significant association (OR = 1.23, 95% CI: 1.05–1.44, p = 0.010), *this variable was not an independent predictor of lymphoedema risk in the multivariate models*. When included in the full multivariable model simultaneously adjusting for BMI, total lymph nodes removed, and post-operative axillary radiation, the association became non-significant (aOR = 1.04, 95% CI: 0.85–1.29, $p = 0.718$). Furthermore, the number of positive lymph nodes *was excluded* from the final optimized model derived through bidirectional stepwise selection.
- *Post-operative radiation*: Axillary radiation significantly increased risk (55% vs. 16.7%). Chi-square test showed a significant difference between the various groups in terms of distribution of lymphoedema ($\chi 2 = 11.386$, p = < 0.001). Strength of association by Cramer's V test = 0.38 (Moderate Association) and strength of association by Bias Corrected Cramer's V = 0.36 (Moderate Association). Univariable OR: 6.11 (95% CI: 2.01–18.58, p = 0.001). On Multivariate Analysis (Stepwise Model): aOR: 4.57 (95% CI: 1.37–15.26, $p = 0.013$). which implies radiation remains the strongest independent predictor, with 357% higher risk after adjusting for BMI/nodal dissection.

BMI (kg/m^2) demonstrated poor diagnostic performance for predicting lymphoedema with an AUROC of 0.696 (95% CI: 0.57—0.82), which was statistically significant ($p = 0.008$); at a cutoff ≥ 27.2, sensitivity was 76% and specificity was 59%. The Number of Lymph Nodes Removed showed fair diagnostic performance with an AUROC of 0.719 (95% CI: 0.60—0.83), statistically significant ($p = 0.003$); at a cutoff ≥ 16, sensitivity was 76% and specificity was 64%. Positive Lymph Nodes Removed demonstrated poor diagnostic performance with an AUROC of 0.674 (95% CI: 0.53—0.81), statistically significant ($p = 0.009$); at a cutoff ≥ 3, sensitivity was 48% and specificity was 86%. All three parameters demonstrated high negative predictive values (82.3–88.4) (Fig. 3).

Non-significant factors included age ($p = 0.635$), chemotherapy type (taxane vs. trastuzumab, $p = 0.496$), hormone receptor status ($p = 0.746$), pre-operative T- stage and N- stage, presence of in situ component ($p = 0.751$), Lymphovascular invasion ($p = 0.433$), capsular invasion ($p = 0.116$), extra nodal extension ($p = 0.146$) and post-operative complications like seroma ($p = 0.363$) or wound infection ($p = 1.000$).

Discussion

This prospective observational study sought to address gaps by identifying clinicopathological predictors of early lymphoedema in Indian breast cancer patients undergoing modified radical mastectomy (MRM).

Lymphoedema developed in 21 out of 80 patients (26%). This finding is concordant with data projected by similar studies in the literature, reporting incidence ranging from 10 to 45%. In a recent meta-analysis, in which 57 studies were analysed, the overall estimated incidence of chronic arm oedema following axillary lymph node dissection was documented to be 21.4% [16].

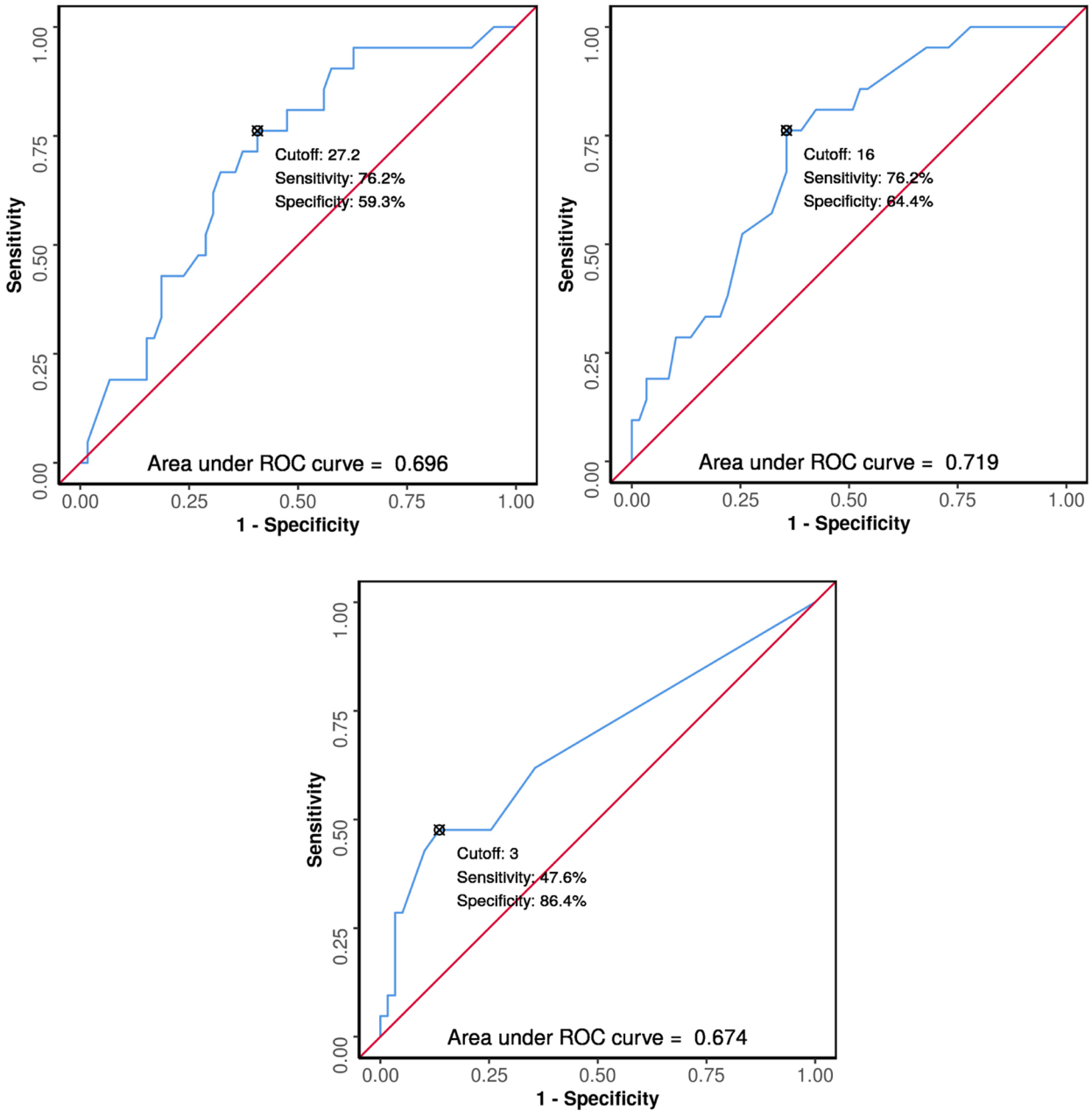

Fig. 3 Area under ROC curve analysis for predictors of Lymphedema (BMI, Total number of Lymph nodes Removed, Number of Positive lymph nodes)

Higher BMI (mean 28.42 vs 26.04 kg/m^2; t = 2.783, $p = 0.008$) and left-sided tumours (40% vs 18% incidence; $\chi^2 = 4.688$, $p = 0.030$; OR = 3.04, CI = 1.09–8.48) emerged as significant clinical predictors of lymphoedema. Crucially, BMI maintained independent predictive status after multivariate adjustment (Adj. OR = 1.19, 95% CI:1.00–1.42, $p = 0.045$), with each unit increase conferring 19% higher risk. The total number of lymph nodes removed demonstrated robust independent association (mean 21.14 vs 13.49; W = 891.000, $p = 0.003$), remaining significant in both full (Adj. OR = 1.07, 95% CI:1.01–1.16, $p = 0.037$) and stepwise models (Adj. OR = 1.08, 95% CI:1.01–1.15, $p = 0.027$), indicating 7–8% increased risk per additional node excised after controlling for confounders. Post-operative axillary radiation constituted the strongest independent predictor (55% vs 16.7% incidence; $\chi^2 = 11.386$, $p < 0.001$; stepwise Adj. OR = 4.57, 95% CI:1.37–15.26, $p = 0.013$), translating to 357% elevated risk when adjusted for BMI and nodal dissection. While positive lymph node count was elevated in lymphoedema cases (mean 3.81 vs 1.15; W = 835.500, $p = 0.009$) and significant univariably (OR = 1.23, 95% CI:1.05–1.44, $p = 0.010$), it lost independence in multivariate analysis (full model Adj. OR = 1.04, 95% CI:0.85–1.29, $p = 0.718$)

and was excluded from the stepwise model, suggesting its effects are mediated through total nodal excision. Non-significant factors included age ($p = 0.635$), chemotherapy type ($p = 0.496$), hormone receptor status ($p = 0.746$), pre-operative T/N stage, histopathological features (in situ component $p = 0.751$; LVI $p = 0.433$; capsular/extra nodal invasion $p = 0.116$–0.146), and post-operative complications (seroma $p = 0.363$; infection $p = 1.000$).

The association of a higher BMI with increased incidence of lymphoedema concurs with similar studies documented in the literature, including meta-analysis of 57 studies by Manirakiza et. al. and prospective studies by Degnim et al., Clark et al., Dominick et al., and Kwan et al., among others [17–21]. In our study, we observed that patients with lymphoedema had a higher BMI (28.42) than those without (26.04) ($p = 0.0081$), indicating that a higher BMI could increase the risk for lymphoedema. The cause of this effect is complex and multifactorial. A functional link has emerged between lymphatic malfunction and the pathogenesis of obesity. Patients with higher BMI may require more lymphatic channels for higher lymph flow to facilitate drainage. It is likely to result from the capacity of the lymph and circulatory imbalance [22]. So, either it could be that a heavier arm needs more lymph flow to maintain optimum lymph content, or it is because the surgery is more extensive/destructive due to the presence of more adipose tissue in the axilla [16, 23]. Studies have also claimed that obese patients are susceptible to fat necrosis, poor wound healing, and infection, and the separation of deep lymphatic channels by additional subcutaneous fat, thus leading to lymphoedema [24].

In our study, patients with left-sided breast carcinoma demonstrated a significantly higher incidence of ipsilateral arm lymphoedema (40%) compared to those with right-sided carcinoma (18%), with this difference being statistically significant ($\chi^2 = 4.688$, $p = 0.030$). While this association is clearly observed, the underlying mechanisms remain speculative and require further investigation. Potential explanations *might* include anatomical asymmetries in venous or lymphatic drainage between sides, or the fact that all patients had right-hand dominance—possibly leading to differential limb use patterns that *could theoretically* influence fluid dynamics. However, these remain hypotheses needing rigorous validation; causation cannot be inferred from the present data. Similar associative findings were reported by Singh et al. [25], though the biological or behavioural basis for this lateralization effect warrants dedicated mechanistic studies.

A significant difference emerged in lymph node removal between groups (mean 21.14 vs. 13.49; $W = 891.000$, $p = 0.003$), with univariable analysis showing each additional node increased lymphedema risk by 9% (OR 1.09, 95% CI 1.03–1.16, $p = 0.004$). Crucially, this association persisted after multivariate adjustment for BMI and radiation (Adj. OR 1.08, 95% CI 1.01–1.15, $p = 0.027$), suggesting an independent 8% risk increase per node. While this effect *may* reflect mechanical disruption of lymphatics, alternative explanations like more aggressive disease biology in extensively dissected cases *could theoretically* contribute – particularly given these patients' higher positive node burden (mean 3.81 vs 1.15). The findings align with Clark et al. and Dominick et al. [18, 19] but contradict Yen et al. and Beaulac et al. [26, 27], highlighting the need for larger studies dissecting causal pathways between surgical extent, tumour biology, and lymphedema development.

A significant difference was observed in positive lymph node counts between groups (mean 3.81 vs. 1.15; $W = 835.500$, $p = 0.009$), with univariable analysis indicating a 23% increased lymphedema risk per positive node (OR 1.23, 95% CI 1.05–1.44, $p = 0.010$). *However, this association did not persist in multivariate analysis* when adjusted for BMI, total nodes removed, and radiation (Adj. OR 1.04, 95% CI 0.85–1.29, $p = 0.718$). While this univariable relationship *might* theoretically reflect greater lymphatic disruption or more aggressive disease biology, *causation cannot be established* from these data. The effect appears largely explained by its correlation with the extent of nodal dissection (total nodes removed), which remained independently significant. Similar associative patterns were reported by Ahmed et al. and Zou L et al. [28, 29], though the non-independent nature of this variable in our models suggests these findings require careful reinterpretation in light of surgical extent confounders.

Notably, the study found no association between hormone receptor status or chemotherapy type (taxane vs. trastuzumab) and lymphoedema, contrasting with Western cohorts where HER2-targeted therapies correlate with higher incidence [30].

The ROC-derived cutoffs (BMI ≥ 27.2 kg/m^2; nodal dissection ≥ 16 nodes; positive nodes ≥ 3) offer clinically actionable thresholds for risk stratification despite suboptimal individual diagnostic performance (AUCs ≤ 0.72). These parameters should be integrated into a combinatorial risk assessment model rather than used in isolation, prioritizing patients with multiple risk factors—particularly those receiving axillary radiation (highest independent risk) or with left-sided tumours. We propose intensified surveillance (e.g. Clinical examination and assessment patient-reported outcomes, quarterly bioimpedance measurements, early physiotherapy referral) for high-risk cohorts defined by:

1. Major criterion: Axillary radiation
2. Minor criteria:
    - o BMI ≥ 27.2 kg/m.^{2}

- o ≥16 lymph nodes removed
- o Left-sided primary tumour

The high negative predictive values (NPV 82–88%) support using these cutoffs to identify low-risk patients who may require less intensive monitoring. Future studies should validate these algorithms and incorporate radiation status and laterality to optimize resource allocation in lymphedema prevention programs.

By bridging critical gaps in region-specific evidence, this study provides hope for prioritizing high-risk patients and adopt preventive measures such as pre-operative BMI optimization, tailored radiation planning, early identification and referrals for high-risk cohorts. Future research should explore genetic and biomarker profiles (e.g., miR-21, TGF-β levels) to refine predictive models and enable precision medicine approaches. In resource-constrained settings, integrating BCRL surveillance into national cancer control programs and training community health workers in early symptom recognition could mitigate long-term disability, underscoring the imperative of holistic, patient-centred survivorship care.

Limitations

The study's sample size limits its statistical power for detecting small-effect associations and subgroup analyses, increasing Type II errors for small-effect predictors. While BMI, nodal dissection, and radiation emerged as robust predictors in our cohort, their effect sizes and clinical utility require validation in larger, multi-centre studies before implementation in guidelines. While our findings identified risk factors for early-onset lymphedema, long-term studies are needed to assess predictors of late onset lymphedema. Several confounders exist, like comorbidity granularity (diabetic status recorded but not glycaemic control/neuropathy severity), treatment specifics (chemotherapy timing/agents and radiation dosimetry/fields), and post-operative factors (drain duration, compression compliance, rehabilitation intensity),) may influence risk estimates. Future studies should incorporate detailed treatment and comorbidity data. This study lacks patient-reported outcomes, potentially limiting sensitivity for stage 0–1 lymphedema. Circumferential measurement with 10% cut- off was chosen due to resource-limited settings, balancing specificity (reducing false positives) with feasibility. The association of left-sided tumours remains speculative. Though inter observer reliability was not done which may contribute to systemic error, but similar studies on circumferential methods demonstrate high intra observer reliability [31]. Generalizability is limited by single-centre model and may not reflect community-level LMIC resource limitations affecting treatment decisions.

Conclusion

This study confirms a substantial early onset lymphoedema burden (26%) in Indian patients after Modified Radical Mastectomy. Key findings support a practical risk-stratification approach using readily available clinical factors: elevated BMI, left-sided tumour laterality, extent of nodal dissection, and post-operative axillary radiation. Notably, the novel finding of increased lymphoedema risk with left-sided tumours suggests potential anatomical or biomechanical influences, but needs further exploration before causation can be determined. Future studies should combine circumferential measurements with validated PRO tools to correlate objective findings with symptom burden. We propose prioritizing intensified surveillance for patients possessing multiple risk factors (Axillary radiation, higher BMI, extensive lymph node dissection). This targeted strategy can be crucial for optimizing resource allocation in constrained settings, enabling pre-operative weight management and early intervention in high-risk groups. Validation of these predictors through larger multi-centre studies is essential to establish standardized, evidence-based lymphoedema prevention protocols.

Abbreviations

AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ALND	Axillary Lymph Node Dissection
aOR	Adjusted Odds Ratio
AUC	Area Under the Curve
AUROC	Area Under the Receiver Operating Characteristic Curve
BCRL	Breast Cancer-Related Lymphoedema
BMI	Body Mass Index
CI	Confidence Interval
CTRI	Clinical Trials Registry—India
DCIS	Ductal Carcinoma In Situ
ECM	Extracellular Matrix
FOXC2	Forkhead Box Protein C2
HER2	Human Epidermal Growth Factor Receptor 2
H&L	Hosmer-Lemeshow test
IEC	Institutional Ethics Committee
IQR	Interquartile Range
LMICs	Low- and Middle-Income Countries
LVI	Lymphovascular Invasion
miR-21	MicroRNA-21
MRM	Modified Radical Mastectomy
NPV	Negative Predictive Value
OR	Odds Ratio
PPV	Positive Predictive Value
ROC	Receiver Operating Characteristic
ROS	Reactive Oxygen Species
SD	Standard Deviation
TGF-β	Transforming Growth Factor Beta
VEGF-C	Vascular Endothelial Growth Factor-C

Authors' contributions

Conceptualization: FH, SB. Data Collection: MO, FH, SR, VSK, KA, NR, AJ, AA. Manuscript Preparation (Drafting): MO. Manuscript Review & Editing: FH, SB. Final Approval of Manuscript: All authors. Accountability for All Aspects of the Work: All authors. Guarantor of the Article: FH. All authors meet the ICMJE criteria for authorship and have read and approved the final manuscript.

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Data availability
Data supporting research can be accessed/obtained by contacting the first author, Mohd Ozair Khan: [mailto:ozairkhan321@gmail.com] (mailto:ozairkhan321@gmail.com).

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Ethics Committee (All India Institute of Medical Sciences, Rishikesh) (AIIMS/IEC/23/212) (In accordance with the Declaration of Helsinki).
All Patients provided informed consent to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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