

Risk Factors for Lymphedema After Breast Cancer Surgery: A Prospective Cohort Study Evaluating Axillary Surgical Approaches

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AIM: Breast cancer-related lymphedema remains a major complication that follows axillary surgery. This prospective study evaluated the effects of axillary surgical techniques and treatment-related factors on the development of lymphedema in patients undergoing breast cancer surgery.

METHODS: This prospective observational cohort study included 119 patients who underwent breast and axillary surgery for invasive breast cancer between June 2020 and April 2022. Arm volume measurements were recorded preoperatively and during follow-up at 10–15 days, 1–3 months, 6 months, and 1 year postoperatively using a standardized circumferential method. Lymphedema was defined as a $\geq 10\%$ increase in the volume difference between the operated and contralateral arm relative to the individual baseline inter-arm difference. Demographic, clinical, and treatment-related variables, including the axillary surgical procedure, radiotherapy, chemotherapy, body mass index, and number of removed lymph nodes, were analyzed. Univariate and multivariable logistic regression analyses were performed to identify potential risk factors associated with lymphedema development.

RESULTS: Lymphedema developed in 18 (15.1%) of 119 patients. The incidence of lymphedema was significantly higher in patients who underwent axillary lymph node dissection (ALND; 24.4%) than in those who underwent sentinel lymph node biopsy (SLNB; 10.3%, $p = 0.040$). No significant association was observed between axillary radiotherapy and lymphedema development ($p = 0.809$). No variables remained statistically significant after multivariable adjustment. However, ALND showed a trend toward an increased risk of lymphedema (odds ratio [OR] 6.14, 95% confidence interval [CI] 0.91–41.49, $p = 0.063$), whereas neoadjuvant chemotherapy (NACT) showed a trend toward a reduced risk (OR 0.34, 95% CI 0.10–1.19, $p = 0.091$).

CONCLUSIONS: In univariable analyses, ALND was associated with a higher occurrence of lymphedema following breast cancer surgery. However, no variable remained statistically significant after multivariable adjustment, likely reflecting the limited number of lymphedema events and the resulting limited statistical power. In this cohort, NACT was not associated with an increased risk of lymphedema. Although exploratory subgroup analyses suggested a lower incidence of lymphedema among patients undergoing SLNB following NACT, these findings should be interpreted cautiously given the limited subgroup size and require confirmation in larger prospective studies. These findings support ongoing efforts to minimize unnecessary axillary dissection whenever oncologically appropriate.

Keywords: breast cancer; lymphedema; axillary surgery; sentinel lymph node biopsy; neoadjuvant chemotherapy; prospective study

Introduction

Breast cancer is the most common malignancy among women and remains a major global health burden. When both sexes are taken into account, breast cancer is the second most common cancer worldwide after lung cancer, according to the most recent GLOBOCAN data [1].

Due to the prevalence of this illness, therapeutic strategies are crucial and constantly evolving. From radical mastec-

tomy to oncoplastic surgery, breast cancer treatments have developed over time. The number of surgical procedures performed has increased in parallel with the rising incidence of breast cancer. As the frequency of these procedures has grown, procedure-related complications have become more apparent, prompting efforts to improve preventive and therapeutic strategies.

Arm lymphedema is a major complication associated with breast cancer surgery. Lymphedema is commonly defined as a clinically meaningful increase in arm volume relative to the contralateral extremity or baseline measurements [2], although definitions vary across studies. Disruption of lymphatic circulation and increased protein transfer to the interstitial space following the excision of lymph nodes in the axillary region are the causes of lymphedema [3]. Patients with lymphedema can have arm swelling, redness, re-

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stricted movement, and eventual Stewart-Treves syndrome, an angiosarcoma linked to lymphedema [4].

Understanding the causes of lymphedema is crucial to avoid its progression. Radiotherapy (RT) and axillary surgery (e.g., axillary dissection or sentinel lymph node biopsy [SLNB]) are known risk factors for the development of lymphedema. Distinct risk factors other than axillary surgical operations are yet to be identified because most lymphedema investigations are retrospective. The objectives of this study were to prospectively assess patients who had breast cancer surgery and investigate the variables that contributed to the development of lymphedema in these individuals.

Methods

This prospective observational cohort study comprised patients between ages 20 and 90 years who had axillary and breast surgery for invasive breast cancer at the Department of General Surgery of Ege University Hospital between June 2020 and April 2022. 119 participants who gave their consent to participate and had complete data were included in the study. These patients were prospectively followed up for routine examinations at our clinic: preoperatively and 10–15 days, 1–3 months, 6 months, and 1 year postoperatively.

The same nurse at the breast clinic recorded the arm circumference measurements. Measurements were performed with patients in a standardized position, with the upper limbs relaxed and positioned consistently. A flexible measuring tape was used with consistent tension to minimize measurement variability. Patients were prospectively followed up for a minimum of 1 year according to the predefined lymphedema assessment schedule (i.e., 10–15 days, 1–3 months, 6 months, and 1 year postoperatively). In patients who continued routine clinical follow-up, for patients who continued routine clinical surveillance, observation was extended beyond 1 year, with a median follow-up duration of 3.72 years; lymphedema events identified during this extended follow-up were included in the cumulative incidence analysis. Lymphedema events occurring during the available follow-up period were recorded and included in the cumulative analyses. Patients who had bilateral surgery, did not show up for follow-up, or already had surgery on the other breast or axilla were excluded. Patients who had lymphedema during follow-up were treated with compression sleeves and referred for a physical therapy consultation. This study was approved by the Medical Research Ethics Committee of Ege University School of Medicine (approval no: 20-5T/34).

Data Collection and Measurement Methods

Before surgery, arm circumference measurements were recorded bilaterally at four standardized anatomical landmarks: the metacarpal level, the wrist, 2 cm below the elbow epicondyle, and 2 cm above the elbow epicondyle.

Based on these measurements, each arm was divided into three segments, and the distance between adjacent measurement points was recorded. Circumferential arm measurements were selected because they represent a standardized, inexpensive, and widely accepted method for prospective lymphedema surveillance. This approach was also the most feasible option within routine clinical practice during the coronavirus disease 2019 (COVID-19) pandemic. Circumference measurements (c) for each segment were recorded, and arm volume was calculated using the truncated cone formula according to the measured distance intervals. The truncated cone formula:

$$V = (\pi h/3) \times (r_1^2 + r_1 r_2 + r_2^2)$$

where r_1 and r_2 represent the radii of adjacent circumference measurements and h represents the distance between measurement points. Then, the volumes of the three regions were added to obtain the volume of the arm.

At baseline, the volumes of both the operated-side arm and the contralateral healthy arm were measured, and the natural inter-arm volume difference was recorded for each patient. The relative inter-arm volume difference was calculated as:

$$\text{Relative inter-arm difference (\%)} = ((\text{Operated arm volume} - \text{Contralateral arm volume}) / \text{Contralateral arm volume}) \times 100.$$

Lymphedema was defined as a $\geq 10\%$ increase in this relative inter-arm volume difference compared with each patient's own preoperative baseline measurement. This individualized approach accounts for natural baseline asymmetry between upper extremities and minimizes misclassification related to arm dominance or pre-existing differences, compared with a simple postoperative comparison of raw arm volumes between the operated and contralateral arms. The $\geq 10\%$ threshold was adopted according to previously published definitions of breast cancer-related lymphedema. For descriptive analyses, patients were further categorized according to the magnitude of baseline-adjusted relative inter-arm volume difference ($<10\%$, $10\text{--}39.9\%$, and $\geq 40\%$) [5,6]. These categories were used solely to describe the extent of relative volume change and do not represent established clinical lymphedema severity grades.

All patients were discussed in a multidisciplinary tumor board meeting involving breast surgery, medical oncology, radiation oncology, radiology, pathology, and nuclear medicine specialists. Decisions regarding adjuvant treatment and axillary radiotherapy were made according to tumor characteristics, pathological findings, and institutional multidisciplinary consensus.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY,

USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were presented as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]) according to data distribution, whereas categorical variables were expressed as frequencies and percentages.

For intergroup comparisons, the independent samples *t*-test was used for normally distributed continuous variables, while the Mann–Whitney U test was applied for non-normally distributed variables where appropriate. Categorical variables were compared using the Chi-squared test or Fisher’s exact test, as appropriate. Fisher’s exact test was used when expected cell counts were small, including analyses involving postoperative surgical-site infection because of the limited number of events.

Univariable logistic regression analyses were performed to identify potential risk factors associated with lymphedema development. Variables that were considered clinically relevant or showed an association at $p < 0.20$ in univariable analysis were included in the multivariable logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. A two-sided p -value < 0.05 was considered statistically significant.

Results

The study comprised a total of 119 patients. The patients’ median age was 57 years (26–86), and their mean age was 56.19 ± 13.98 years. 58 (48.74%) patients had a total mastectomy, while 61 (51.26%) had a partial mastectomy. BMI categories were distributed as follows: 35.29% of patients had a BMI of 20–25 kg/m², 31.93% had a BMI of 26–30 kg/m², and 32.77% had a BMI ≥ 31 kg/m². SLNB was performed on 78 (65.55%) patients, while axillary lymph node dissection (ALND) was done on 41 (34.45%) patients. Radiotherapy was administered to 63 (52.94%) patients during the postoperative phase (Table 1). All patients completed at least 1 year of follow-up. Table 2 presents lymphedema status at each predefined assessment time point within the first postoperative year, whereas the 18 lymphedema events reported in this study represent cumulative cases identified over the entire available follow-up period (median follow-up, 3.72 years).

The patients’ preoperative arm volumes were compared to the arm volumes measured during their follow-up. For descriptive analyses of postoperative volume changes, patients were categorized according to the magnitude of baseline-adjusted relative inter-arm volume difference as $<10\%$, 10–39.9%, and $\geq 40\%$ (Table 2).

Table 2 presents baseline-adjusted relative inter-arm volume difference categories at predefined follow-up time points during the first postoperative year. These assessments were limited to the scheduled 1-year follow-up visits, whereas lymphedema events were recorded throughout the entire available follow-up period. Therefore, the 18 cases represent cumulative lymphedema incidence identi-

Table 1. Data on patients’ disease characteristics and treatments.

Variable	Category	n	%
Dominant hand	Right	116	97.48
	Left	3	2.52
Infection	Present	3	2.52
	Absent	116	97.48
Operated side	Right	54	45.38
	Left	65	54.62
Type of surgery	PM	61	51.26
	TM	58	48.74
Axillary procedure	SLNB	78	65.55
	ALND	41	34.45
Axillary radiotherapy	Received	63	52.94
	Not received	56	47.06
NACT	Yes	51	42.86
	No	68	57.14
Adjuvant chemotherapy	Yes	45	37.82
	No	74	62.18
Tumor location	UOQ	56	47.06
	Non-UOQ	63	52.94
Tumor size	≤ 2 cm	53	44.54
	> 2 cm	66	55.46
	20–25 kg/m ²	42	35.29
BMI	26–30 kg/m ²	38	31.93
	≥ 31 kg/m ²	39	32.77

Notes: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; RT, radiotherapy; NACT, neoadjuvant chemotherapy; UOQ, upper outer quadrant; BMI, body mass index; PM, partial mastectomy; TM, total mastectomy.

fied during follow-up beyond the first postoperative year when applicable. All patients were prospectively followed up for a minimum of 1 year; however, follow-up was extended in patients who continued routine clinical surveillance (median follow-up: 3.72 years). Accordingly, the 18 cases reported in this study represent lymphedema events identified during the available follow-up period, including events detected beyond the first postoperative year among patients with extended follow-up, whereas the frequencies presented in Table 2 reflect lymphedema status at specific postoperative follow-up visits during the first year. Therefore, the frequencies shown in Table 2 should not be interpreted as cumulative incidence.

Subsequently, treatment-related and surgical factors potentially associated with lymphedema development were evaluated.

During the postoperative follow-up period, lymphedema developed in 10 (15.9%) of 63 patients who received axillary radiotherapy and in 8 (14.3%) of 56 patients who did not receive radiotherapy. Although the incidence was slightly higher among patients receiving radiotherapy, the difference was not significant ($p = 0.809$; Table 3).

Table 2. Assessment of postoperative baseline-adjusted relative inter-arm volume difference at predefined follow-up time points during the first postoperative year.

Follow up time interval (vs preoperative)	Relative inter-arm volume change category	n (%)
Postoperative day 10–15 vs Preoperative	<10% baseline-adjusted relative inter-arm volume increase	117 (98.32)
	10–39.9% baseline-adjusted relative inter-arm volume increase	2 (1.68)
	≥40% baseline-adjusted relative inter-arm volume increase	0 (0.00)
1–3 months vs preoperative	<10% baseline-adjusted relative inter-arm volume increase	112 (94.12)
	10–39.9% baseline-adjusted relative inter-arm volume increase	7 (5.88)
	≥40% baseline-adjusted relative inter-arm volume increase	0 (0.00)
6 months vs preoperative	<10% baseline-adjusted relative inter-arm volume increase	116 (97.48)
	10–39.9% baseline-adjusted relative inter-arm volume increase	3 (2.52)
	≥40% baseline-adjusted relative inter-arm volume increase	0 (0.00)
1 year vs preoperative	<10% baseline-adjusted relative inter-arm volume increase	110 (92.44)
	10–39.9% baseline-adjusted relative inter-arm volume increase	8 (6.72)
	≥40% baseline-adjusted relative inter-arm volume increase	1 (0.84)

Table 3. Association between axillary radiotherapy and lymphedema.

Axillary radiotherapy	Lymphedema, n (%)	No lymphedema, n (%)	<i>p</i> -value
Yes	10 (15.9)	53 (84.1)	0.809
No	8 (14.3)	48 (85.7)	

Percentages were calculated using the total number of patients in each axillary radiotherapy group as the denominator. The *p*-value represents the comparison of lymphedema incidence between the axillary radiotherapy groups using the Chi-squared test. A *p*-value < 0.05 was considered statistically significant.

Postoperative surgical-site infection was documented in 3 patients, one of whom subsequently developed lymphedema. The association was evaluated using Fisher's exact test because of the small number of infection events.

Univariable logistic regression analyses were first performed, followed by multivariable logistic regression as the primary adjusted analysis to identify factors independently associated with lymphedema development (Table 4). Variables entered into the multivariable model included axillary surgery type, axillary radiotherapy, number of removed lymph nodes, number of metastatic lymph nodes, postoperative infection, neoadjuvant chemotherapy (NACT), and BMI. None of the evaluated variables remained statistically significant after multivariable adjustment. However, ALND showed a trend toward an increased risk of lymphedema (OR 6.14, 95% CI 0.91–41.49, *p* = 0.063), whereas NACT showed a trend toward a reduced risk (OR 0.34, 95% CI 0.10–1.19, *p* = 0.091).

Following the primary adjusted analysis, the relationship between axillary surgical approach, neoadjuvant chemotherapy (NACT) status, and lymphedema development was further explored using unadjusted group comparisons (Tables 5,6,7). Overall, lymphedema occurred more frequently in patients who underwent ALND than in those who underwent SLNB (24.39% vs. 10.25%, *p* = 0.040).

The subsequent subgroup comparisons according to NACT status were considered exploratory analyses. No statistically significant differences were observed according to NACT status within either surgical group or between the corresponding primary surgery and post-NACT subgroups, although numerically lower lymphedema rates were observed in the post-NACT SLNB subgroup.

Discussion

Breast cancer is the most common malignancy among women and the second most common cancer worldwide when both sexes are considered [1]. Consequently, surgical treatment for breast cancer is frequently performed, and surgeons involved in its management are required to be familiar with potential postoperative complications [7]. Among these complications, lymphedema is of particular importance, as it can lead to chronic symptoms, such as arm swelling, redness, discomfort, recurrent cellulitis, and functional impairment, and in rare cases can progress to Stewart–Treves syndrome, an angiosarcoma associated with long-standing lymphedema [8]. Therefore, identifying risk factors associated with lymphedema development is essential for prevention and early intervention.

There are few prospective studies that evaluate lymphedema development and associated risk factors following breast cancer surgery. Although many clinicopathological variables related to lymphedema risk can be retrospectively obtained, retrospective studies frequently rely on symptom-based documentation or non-standardized clinical records, which can underestimate early or subclinical cases. In contrast, prospective follow-up with predefined assessment timepoints and standardized arm volume measurements could provide a more objective and longitudinal evaluation of lymphedema development and improve the identification of clinically relevant risk factors.

Various methods have been used to assess lymphedema, including bioimpedance spectroscopy, arm circumference measurement, patient self-report, and volume change anal-

Table 4. Univariate and multivariable logistic regression analysis for lymphedema.

Variable	Univariate OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Axillary surgery (ALND vs SLNB)	2.82 (1.02–7.84)	0.046	6.14 (0.91–41.49)	0.063
Axillary radiotherapy (yes vs no)	1.13 (0.41–3.10)	0.809	1.14 (0.30–4.25)	0.850
Number of removed lymph nodes (≥ 10 vs < 10)	1.41 (0.53–3.73)	0.491	0.47 (0.08–2.72)	0.399
Number of metastatic lymph nodes (≥ 5 vs < 5)	2.47 (0.67–9.10)	0.173	1.04 (0.19–5.78)	0.967
Infection (yes vs no)	2.26 (0.20–26.12)	0.513	2.48 (0.19–31.80)	0.485
NACT (yes vs no)	0.56 (0.21–1.50)	0.250	0.34 (0.10–1.19)	0.091
BMI 26–30 kg/m ² (vs ≤ 25)	0.34 (0.09–1.22)	0.098	0.52 (0.13–2.10)	0.355
BMI ≥ 31 kg/m ² (vs ≤ 25)	2.73 (1.06–7.05)	0.038*	1.66 (0.49–5.63)	0.417

Notes: ALND, axillary lymph node dissection; BMI, body mass index; OR, odds ratio; CI, confidence interval; SLNB, sentinel lymph node biopsy; NACT, Neoadjuvant chemotherapy. * $p < 0.05$ was considered statistically significant.

Table 5. Association between the primary axillary surgical approach and lymphedema development.

Variable	Category	Lymphedema negative (n = 101)		Lymphedema positive (n = 18)		p-value
		n	%	n	%	
Type of axillary surgery	SLNB	70	89.74	8	10.25	0.040*
	ALND	31	75.61	10	24.39	

The comparison presented in this table is an unadjusted group comparison evaluating differences in lymphedema incidence between surgical groups. In contrast, the multivariable logistic regression analysis presented in Table 4 assesses independent associations with lymphedema after adjustment for potential confounding factors.

* $p < 0.05$ was considered statistically significant.

Table 6. Subgroup comparisons according to neoadjuvant chemotherapy within each axillary surgical approach.

Comparison	Category (n)	Lymphedema negative (n = 101)		Lymphedema positive (n = 18)		p-value
		n	%	n	%	
Primary SLNB vs	Primary SLNB (57)	50	87.72	7	12.28	0.307
NACT-SLNB	NACT-SLNB (21)	20	95.24	1	4.76	
Primary ALND vs	Primary ALND (11)	7	63.64	4	36.36	0.246
NACT-ALND	NACT-ALND (30)	24	80.00	6	20.00	

Table 7. Comparison of axillary surgical approaches according to neoadjuvant chemotherapy status.

Comparison	Category (n)	Lymphedema negative (n = 101)		Lymphedema positive (n = 18)		p-value
		n	%	n	%	
Primary SLNB vs Primary	Primary SLNB (57)	50	87.72	7	12.28	0.124
ALND	Primary ALND (11)	7	63.64	4	36.36	
NACT-SLNB vs NACT-ALND	NACT-SLNB (21)	20	95.24	1	4.76	0.125
	NACT-ALND (30)	24	80.00	6	20.00	

$p < 0.05$ was considered statistically significant. Subgroup comparisons were performed as exploratory unadjusted analyses. Percentages were calculated within each comparison group.

ysis. Although arm circumference measurement is a simple and cost-effective method, it might not always accurately reflect the presence of lymphedema since it can be influenced by changes in body weight. Among these techniques, volume change analysis is widely accepted as the most reliable and objective diagnostic method [9]. Recent reviews have similarly emphasized the importance of objective and standardized measurement approaches for the diagnosis, prevention, and longitudinal monitoring of breast cancer-related lymphedema [10]. Although the four-point circumferential measurement method offers advantages in terms of simplicity, cost-effectiveness, and clinical feasibility,

it may be less sensitive for detecting localized or subtle early-stage lymphedema changes compared with more advanced techniques such as perometry, bioimpedance spectroscopy, or three-dimensional imaging.

Although our study was initially designed to use more advanced volume change analysis methods, we were unable to perform these assessments due to practical difficulties and incompatibility with hygiene requirements during the COVID-19 pandemic [11,12]. Therefore, lymphedema assessment was based on changes in inter-arm volume difference relative to each patient's preoperative baseline rather than a single postoperative comparison be-

tween arms. Because natural asymmetry between dominant and non-dominant upper extremities can exist at baseline, this approach enabled individualized assessment and reduced the risk of misclassification. Lymphedema was therefore defined as a $\geq 10\%$ increase in the operated-to-contralateral arm volume difference compared with baseline measurements [13]. Furthermore, measuring both arms and expressing the difference as a percentage minimized the potential effect of bodyweight fluctuation on the results [14].

ALND is known to be associated with a higher risk of lymphedema compared with SLNB. Furthermore, previous studies have shown that a higher number of excised axillary lymph nodes is associated with a greater risk of lymphedema [15,16]. Consistent with these findings, our univariable analyses demonstrated a higher occurrence of lymphedema among patients who underwent ALND or had more than ten lymph nodes removed [17,18]. However, these associations were not retained after multivariable adjustment. This may partly reflect the limited number of lymphedema events and the resulting limited statistical power. In addition, ALND is inherently associated with a greater number of harvested lymph nodes; therefore, the simultaneous inclusion of axillary surgical approach and the number of removed lymph nodes in the multivariable model may have introduced collinearity between these related variables and reduced the precision of their individual effect estimates. This may also partly explain the wide confidence interval observed for the adjusted ALND estimate. Accordingly, the adjusted findings should be interpreted cautiously and should not be considered evidence of the absence of an association between ALND and lymphedema. Recent contemporary evidence has also shown a substantially higher burden of lymphedema and upper-extremity functional impairment following ALND compared with SLNB, further supporting ongoing efforts toward axillary de-escalation strategies [19]. Furthermore, the 2024 Multinational Association of Supportive Care in Cancer (MASCC) clinical practice guidance identifies axillary lymph node dissection, a greater number of dissected lymph nodes, postoperative radiotherapy, and elevated BMI as important risk factors for lymphedema development, supporting individualized surveillance and risk-reduction strategies in high-risk patients [19,20].

To our knowledge, there is scarce evidence directly comparing lymphedema development between patients undergoing primary SLNB and those undergoing SLNB following NACT. In this context, our study is noteworthy in that it compares these patient groups and shows no significant difference in lymphedema incidence. Although previous studies have suggested that NACT can increase the risk of lymphedema by inducing axillary fibrosis, our findings did not support this association. Although a numerically lower incidence of lymphedema was observed among patients undergoing SLNB following NACT, this subgroup consisted

of only 21 patients with a single lymphedema event. Therefore, these findings should be interpreted with considerable caution, regarded as exploratory and hypothesis-generating, and validated in larger prospective cohorts before any clinical implications can be inferred.

In our study, surgical-site infection was identified in three (2.52%) patients, all of whom were hospitalized for non-operative management. Among these patients, lymphedema developed in one case during follow-up. Although postoperative surgical-site infection appeared to be associated with lymphedema development in our cohort, this finding should be interpreted cautiously given the limited number of infection events and the resulting statistical uncertainty. Therefore, these observations should be considered exploratory rather than conclusive.

The use of adjuvant radiotherapy to the axilla has reduced the need for ALND, even in patients with axillary metastasis who did not receive NACT. However, Warren et al. [21] reported that radiotherapy alone might also contribute to lymphedema development [22]. In contrast to these findings, our study showed no statistically significant association between axillary radiotherapy and the development of lymphedema ($p = 0.809$). This discrepancy might be attributed to our limited sample size. No significant association was observed between the type of surgery (mastectomy vs partial mastectomy), tumor location, changes in BMI, or the administration of adjuvant or NACT and the development of lymphedema.

First, only 18 patients developed lymphedema, whereas seven variables were entered into the multivariable logistic regression model. This corresponds to fewer than the commonly recommended 10 outcome events per predictor variable, which may have increased the risk of model overfitting, reduced the stability of the adjusted estimates, and resulted in wide confidence intervals. Therefore, the multivariable analysis should be considered exploratory, and the observed associations should be interpreted cautiously as hypothesis-generating rather than definitive. Since this was a single-center cohort conducted within a specific clinical setting, the generalizability of the findings to broader breast cancer populations might be limited, and external validation in larger prospective cohorts is warranted. Because lymphedema occurrence was analyzed as a binary outcome using logistic regression, differences in follow-up duration and potential censoring were not explicitly accounted for, which may have influenced the estimation of risk factors. Furthermore, several potentially relevant factors associated with lymphedema development, including postoperative rehabilitation practices, bodyweight changes during follow-up, use of prophylactic compression sleeves, and lymphatic drainage-related interventions, were not systematically recorded and could not be incorporated into the analyses. Detailed treatment parameters, including radiotherapy dose/fractionation and specific chemotherapy regimens, were not systematically analyzed, which may have

limited assessment of treatment-related effects on lymphedema risk. Accordingly, residual confounding cannot be excluded. Additionally, arm volume calculations were performed based on total arm volume rather than analyzing regional segments separately. The circumference-based volume estimation approach may have limited sensitivity for detecting localized proximal upper-arm volume changes. Furthermore, advanced measurement techniques, such as surface area calculations or imaging-based assessment methods (e.g., perometry or bioimpedance spectroscopy), were not used in addition to volume measurements, which might have restricted the evaluation of different dimensions of lymphedema. Lastly, although patients were followed up prospectively for at least 1 year, the relatively limited follow-up duration might have prevented the identification of late-onset lymphedema cases.

Despite these limitations, the prospective design of the study and the use of a standardized measurement approach allowed our findings to be evaluated within a clinically meaningful framework. The prospective nature of the study enabled reliable assessment of the temporal course of lymphedema development. Serial arm measurements performed during both the preoperative and postoperative periods allowed individual baseline arm volume differences to be considered, thereby reducing the risk of misclassification in lymphedema diagnosis. This approach is also aligned with contemporary expert recommendations emphasizing prospective surveillance, individualized risk assessment, and structured follow-up strategies for patients at risk of breast cancer-related lymphedema [23]. The use of a standardized and objective volume-based assessment method further enhanced the reliability of the findings. Moreover, performing all measurements according to the same protocol and by the same investigator minimized inter-observer variability.

Another important strength of this study is the inclusion of patients who underwent SLNB following NACT, a group for which published data are still limited. This inclusion has enabled the evaluation of the relationship between contemporary axillary surgical approaches and lymphedema development within the context of current treatment paradigms, thereby enhancing the originality of the study. Lastly, the findings of this study provide clinically relevant information for axillary surgical planning and can help inform individualized treatment strategies for patients at risk of lymphedema following breast cancer surgery.

Conclusions

This prospective cohort study investigated treatment-related factors associated with postoperative lymphedema. Bilateral arm volume measurements before surgery may improve the accuracy of lymphedema assessment by accounting for potential preoperative asymmetry between the operated and contralateral extremities. Reliance on unilat-

eral postoperative assessments alone could therefore lead to misclassification in lymphedema diagnosis.

No independent predictors of lymphedema were identified after multivariable adjustment. The limited number of outcome events may have reduced statistical power and contributed to model instability. Unadjusted analyses suggested a higher occurrence of lymphedema after ALND, while exploratory subgroup analyses showed numerically lower rates among patients undergoing SLNB after NACT; however, these observations should be considered hypothesis-generating and require confirmation in larger prospective cohorts.

Future adequately powered prospective multicenter studies are warranted to identify independent predictors of breast cancer-related lymphedema and to validate these exploratory findings.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

BC: Conceptualization, Investigation and Writing – Original Draft. BG: Methodology, Data Curation and Writing – Original Draft. SV: Supervision, Validation and Writing – Review & Editing. LY: Supervision, Validation and Writing – Review & Editing. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Medical Research Ethics Committee of Ege University School of Medicine (Approval No: 20-5T/34). Written informed consent to participate was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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