Evaluation of Long-Term Lymphedema Rate in Patients With Subclinical Lymphedema Diagnosed in the Preoperative Period via Bioimpedance

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ABSTRACT

Objective: The aim of this study was to evaluate the relationship between subclinical lymphedema identified prior to surgical intervention and clinical lymphedema observed in the late period, the incidence of lymphedema in our cohort, and the associated risk factors.

Materials and Methods: This prospective study was conducted with early-stage breast cancer patients who had been enrolled in a previous study. For diagnosing lymphedema, physical examination, L-Dex® score, and circumferential measurement was used. The L-Dex® score was used as a screening test for preoperative, subclinical lymphedema since there were no clinical findings. Patients with subclinical lymphedema were provided with education and followed up more frequently with regular monitoring.

Results: The mean age of the 217 participants was 56.7±12.7 years (range 29–90), and the mean body mass index was 27.7±3.3 kg/m² (range 19.3–36.9). Among the 217 patients, lymphedema was detected in 31 (14.7%) at a median follow-up period of 89 months (range 73–108 months). Multivariable analysis of factors associated with late-stage lymphedema revealed positive lymph node count and capsular invasion as significant factors ($p = 0.001$ for both). Forty (18.4%) had preoperative subclinical lymphedema. At the end of the follow-up period, lymphedema persisted in 11 patients (27.5%) and resolved in 29 patients (72.5%). In multivariable analysis, the positive lymph node count was identified as an independent variable in these patients.

Conclusion: Identifying high-risk patients, regular monitoring, and early intervention can significantly reduce the risk of clinical lymphedema through timely treatment.

Keywords: Breast cancer; lymphedema; risk factors; early detection

Key Points

- This study identified lymphedema risk factors (positive lymph node count and capsular invasion) based on a median 89-month follow-up in 217 patients who were followed-up for lymphedema from the preoperative period.

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Introduction

Lymphedema, commonly observed following breast cancer therapy, is a significant complication affecting quality of life. Due to the increasing incidence of breast cancer globally-making it the most frequent type of cancer-and the success of modern treatments that have significantly improved survival rates, early detection and effective management of lymphedema have become increasingly important (1). Breast cancer-related lymphedema results from the accumulation of protein-rich lymphatic fluid in the extracellular compartment due to reduced lymphatic circulation capacity (2). This condition presents as a severe problem for breast cancer patients, causing swelling, pain, fatigue, susceptibility to infections, and impaired daily activities. It also induces psychological distress, including anxiety and depression, which can evoke memories of cancer (3). Currently, there is no definitive treatment for this condition. Early detection and treatment of lymphedema during the early stages, where subcutaneous fibrosis or fat tissue development has not occurred (stages 0 and 1), have been shown to improve patient outcomes (4). Close monitoring of high-risk patients is central to early detection. Thus, identifying risk factors and calculating the risk of developing lymphedema are of clinical importance.

Risk factors for lymphedema have ben reported to include axillary lymph node dissection (ALND), radiotherapy, a high number of dissected lymph nodes, and obesity. Chemotherapy, genetic predisposition, and hypertension are being investigated as potential risk factors (5). Early-stage risk calculation based on these factors allows the inclusion of high-risk patients in close monitoring programs (6).

In our breast center, subclinical lymphedema was detected preoperatively in 21.3% of patients using bioimpedance spectroscopy (L-Dex®) among 245 breast cancer surgery patients between 2012 and 2015 (7). Obesity and positive lymph node count post-surgery were identified as independent risk factors for lymphedema. The aim of the present study was to evaluate the relationship between preoperative, subclinical lymphedema and late-stage clinical lymphedema, the incidence of lymphedema in our patients, and the associated risk factors. A predictive model for high-risk patients is also proposed.

Materials and Methods

Patients from the previous study (7) on preoperative lymphedema were included in the current study. These patients underwent surgery for early-stage breast cancer (cT1-3, N0-3, M0) at a single center between 2012 and 2015 and were regularly monitored for lymphedema every three months during the first postoperative year and every six months thereafter. Patients monitored between 2012 and 2021 with a minimum follow-up of six years were enrolled.

Inclusion criteria were participation in the previous study; no contraindications for bioimpedance analysis; unilateral breast cancer; and consent to participate in the study. The exclusion criteria were conditions causing edema such as cardiac or renal failure; bilateral breast cancer; refusal to participate; and patient mortality.

Patient examinations were conducted by an experienced physiatrist. Clinical, histopathological and treatment findings, and preoperative bioimpedance measurements were recorded. In the pre-operative period, an L-Dex score of 7.1 was used as the threshold for bioimpedance analysis, as previously described (8).

Lymphedema diagnosis was based on circumferential measurements and bioimpedance analysis during physical examinations. A difference of more than 2 cm between arms was defined as lymphedema. L-Dex® scores ≥7.1 were used to diagnose lymphedema (8).

Patients with subclinical lymphedema received training on self-drainage methods, arm usage principles, and early lymphedema symptoms. Clinical lymphedema patients underwent manual lymph drainage and compression therapy.

The İstanbul Bilim University Clinical Research Ethics Committee approved the study (decision no: 30.04.2014/19-136, date: 30.04.2014). Informed consent was obtained from all participants.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 22 was used for statistical analyses (IBM Inc., Armonk, NY, USA). The Kolmogorov-Smirnov test assessed data distribution. Independent variables were analyzed using independent samples t-test, Mann-Whitney U, and chi-square tests, as appropriate. Logistic regression was used to develop a risk model. Receiver operator characteristics curve analysis determined cut-off values. Graphs were created using SPSS and Excel. Statistical significance was set at $p<0.05$.

Results

A total of 277 patients who had been included in our previous study on preoperative lymphedema were eligible. Among these, 28 (10.1%) were lost to follow-up for various reasons, and 32 (11.5%) could not be followed up. Thus, the study was completed with 217 patients. The mean age of the 217 participants was 56.7±12.7 years (range 29–90), and the mean body mass index (BMI) was 27.7±3.3 kg/m² (range 19.3–36.9). Lymphedema was observed in 31 (14.7%). The median duration of follow-up was 89 months (range 73–108). The demographic characteristics are presented in Table 1 and Figure 1.

In long-term follow-up, multivariable analysis revealed that positive lymph node count and capsular invasion were independent factors affecting lymphedema development (Table 2). The probability curve generated using these variables enabled the calculation of long-term lymphedema risk (model accuracy: 85.3%). This calculation is shown in Figure 2.

Among the 217 patients who underwent preoperative bioimpedance analysis, 40 (18.4%) were diagnosed with subclinical lymphedema (7). At the end of a mean follow-up period of 89 months, lymphedema persisted in 11 patients (27.5%) and resolved in 29 patients (72.5%). In multivariable analysis of these patients with preoperative subclinical lymphedema, the positive lymph node count was identified as the only independent variable for persistent lymphedema. The model's accuracy was calculated at 75% (Table 3, Figure 2).

In the descriptive evaluation of the 29 patients who had pre-operative subclinical lymphedema but later showed regression, the mean BMI was 28.4±3.2, 51.7% underwent axillary dissection, 17.2% received axillary radiotherapy, and 20.6% underwent neoadjuvant chemotherapy.

When considering risk factors for early-term lymphedema, the cut-off value was found to be 4 positive lymph nodes. The area under the curve for 4 positive lymph nodes (sensitivity: 72%, specificity: 86%) was higher compared to positive lymph node counts of 3, 5, and 6 (0.795 vs. 0.770-0.749-0.749) (Figure 3).

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Table 1. Demographic, pathological and treatment characteristics, and lymphedema rates of patients with long-term follow-up

Characteristics		Lymphedema		
		No LE (n=186)	LE present (n=31)	*p*-value
Age (mean ± SD)		56.24±12.9	60±10.9	0.081
BMI (mean ± SD)		27.5±3.1	28.7±3.9	0.085
Axillary intervention	SLNB alone	114 (61.3)	4 (12.9)	≤0.001
	SLNB+ALND	72 (38.7)	27 (87.1)	
Pathological lymph node status	N0	114 (61.3)	4 (12.9)	≤0.001
	N1	54 (29.0)	11 (35.5)	
	N2	10 (5.4)	4 (12.9)	
	N3	8 (4.3)	12 (38.7)	
Radiation Therapy	Breast	158 (84.9)	17 (54.8)	≤0.001
	Breast+AX	28 (15.1)	14 (45.2)	
Pre-operative LE	Absent	157 (84.4)	20 (64.5)	0.008
	Present	29 (15.6)	11 (35.5)	
Obesity	BMI ≥30	49 (26.3)	15 (48.4)	0.013
	BMI <30	137 (73.7)	16 (51.6)	
*Systemic chemotherapy	Absent	73 (39.2)	2 (6.4)	≤0.001
	Presence	113 (60.8)	29 (93.6)	

All data given as count and percentage [n (%)] unless otherwise stated
*Among the patients who received systemic chemotherapy, 14.3% underwent neoadjuvant chemotherapy
SD: Standard deviation; BMI: Body mass index; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection; AX: Axillary lymph nodes; LE: Lymphedema
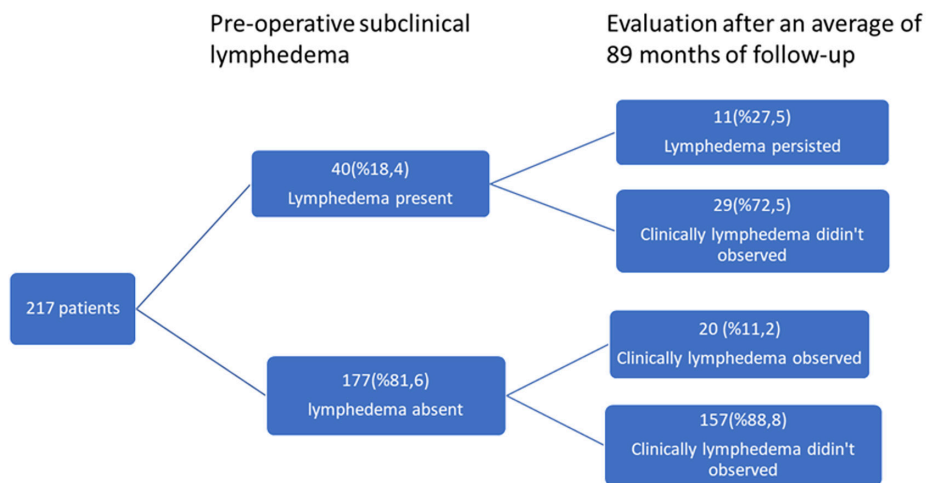

Figure 1. Changes in lymphedema over the follow-up period

Lymphedema was diagnosed at a median of 11 months (range 1–84 months) in patients with no preoperative lymphedema who later developed the condition (*n* = 20). The mean BMI in this group was 27.5±3.2, with daily arm usage reported as 4–6 hours. Infection in the operated arm was observed in only two (10%) patients. In multivariable analysis, capsular invasion, positive lymph node count, and a high L-Dex® score measured preoperatively were identified as independent variables.

At the time of the first study, the L-Dex® cut-off value was set at 10. However, using new data, the L-Dex® cutoff was adjusted to 7.1, increasing its sensitivity (8). The positive predictive values of L-Dex® 7.1 and L-Dex® 10 in detecting long-term clinical lymphedema were 23.5% and 26%, respectively. The negative predictive values were 89.9% and 88.8%, respectively.

Table 2. Logistic regression analysis of the factors affecting lymphedema in the long-term

	Single-variable analysis				Multi-variable analysis			
		95% CI EXP (B)				95% CI EXP (B)		
	OR	Lower	Upper	*p*-value	OR	Lower	Upper	*p*-value
**BMI	1.124	0.998	1.267	0.054				0.364
Positive lymph node count	**1.226**	**1.126**	**1.335**	**≤0.001**	1.162	1.064	1.269	**0.001**
Dissected lymph node count	1.118	1.069	1.169	≤0,001				0.142
Capsular invasion	**8.750**	**3.821**	**20.035**	**≤0.001**	4.882	1.967	12.115	**0.001**
Radiotherapy	4.651	2.060	10.04	≤0.001				0.329
Axillary intervention (SLNB/AD)	10.687	3.592	31.811	≤0.001				0.082
Pre-operative LE present/absent)	2.978	1.291	6.867	0.010				0.986
Obesity (present/absent)	2.621	1.206	5.697	0.015				0.161
Chemotherapy	2.702	1.405	5.923	0.01				0.225

**: BMI ≥30; CI: Confidence interval; OR: Odds ratio; BMI: Body mass index; SLNB: Sentinel lymph node biopsy; AD: Axillary dissection; LE: Lymphedema
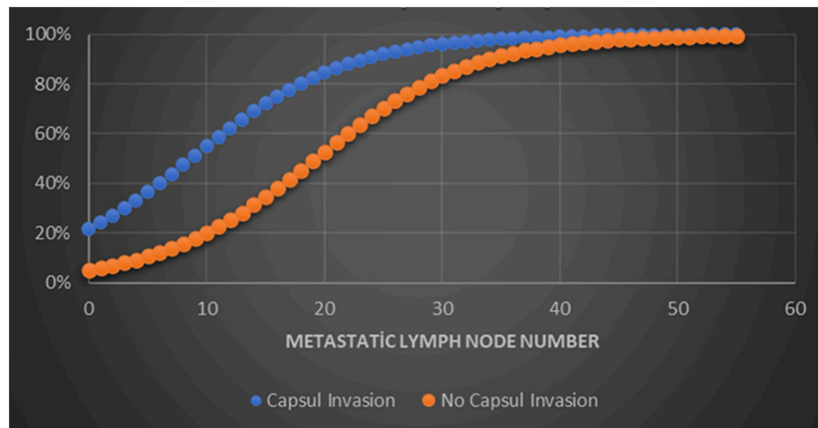

Figure 2. Estimated lymphedema risk based on the probability model

Discussion and Conclusion

The preliminary findings of this study revealed that preoperative, subclinical lymphedema was detected in 21.3% of early-stage breast cancer patients (cT1-3, N0-3) using bioimpedance spectroscopy (7). During a mean follow-up of 89 months, the clinical lymphedema rate was 14.7%. Of note, in patients who underwent ALND the lymphedema incidence was 27.3%, while it was only 3.4% in patients who underwent sentinel lymph node biopsy (SLNB).

Compared to other studies, the lymphedema rate in ALND patients in our study was similar, while the rate in SLNB patients was lower (3, 9, 10). The absence of clinical lymphedema in 29 of 40 patients (72.5%) diagnosed with preoperative, subclinical lymphedema may be attributed to early lymphedema education and timely intervention after surgical treatment. Kilgore et al. reported that lymphedema regressed to a subclinical stage in 82% of patients monitored with

bioimpedance, while clinical lymphedema was observed in patients with N2/N3 stages (10).

In the present study, positive lymph node count and capsular invasion were independent predictors of persistent lymphedema, consistent with findings from other studies (11, 12). While BMI, radiotherapy, and taxane-based chemotherapy were significant risk factors in univariate analysis, they were not identified as independent risk factors in multivariable analysis. N2/N3 patients likely received more aggressive chemotherapy and radiotherapy, making these variables dependent on lymph node count and capsular invasion.

The lower risk observed for BMI, chemotherapy, and radiotherapy in our study may be attributed to patient education, regular monitoring, and early interventions. These factors may mitigate the extracellular fluid buildup and reduced lymphatic flow caused by these variables.

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Table 3. Multi-variable analysis of the patients (n=40) who had preoperative sub-clinical lymphedema, patients whose lymphedema continued (n=11) and patients whose lymphedema resolved (n=29)

	Single-variable analysis				Multi-variable analysis			
	95% CI EXP (B)				95% CI EXP (B)			
	OR	Lower	Upper	*p*-value	OR	Lower	Upper	*p*-value
BMI	1.425	1.023	1.984	0.036				0.079
Positive lymph node count	**1.150**	**1.034**	**1.278**	**0.010**	1.150	1.034	1.278	**0.001**
Dissected lymph node count	1.108	1.018	1.206	0.018				0.225
Capsular invasion	4.364	0.950	20.036	0.058				0.276
RT (present/absent)	6.708	1.460	30.733	0.014				0.133
Axillary intervention SLNB/AD)	9.333	1.054	82.635	0.045				0.135
Obese*	4.821	0.884	26.300	0.069				0.201
Chemotherapy (present/absent)	2.638	1.105	6.735	0.006				0.117

*: Classified as BMI ≥30 *vs.* BMI<30; CI: Confidence interval; OR: Odds ratio; BMI: Body mass index; RT: Radiotherapy; SLNB: Sentinel lymph node biopsy; AD: Axillary dissection
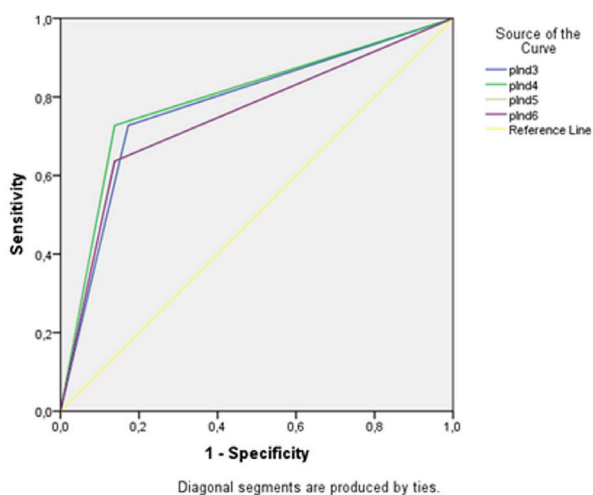

Figure 3. Effect of lymph node positivity on early-term lymphedema. Cut-off value calculations were performed sequentially according to 3, 4, 5, and 6 positive lymph nodes (PLND3, PLND4, PLND5, PLND6)

Byun et al. (13) identified BMI, lymph node dissection count, taxane-based chemotherapy, lymph node radiotherapy, and total mastectomy as independent risk variables for lymphedema. While these parameters were significant in our univariate analysis, they were not significant in multivariable analysis. Other studies conducted in our center found BMI to be an independent variable, along with lymph node dissection count (7, 14). The focus on weight management, dietitian support, and a mean BMI of <30 kg/m2 in our cohort probably contributed to these results.

According to previous research, early detection and treatment of lymphedema positively impacts treatment outcomes (15, 16). In our model, positive lymph node count and capsular invasion were the key predictors of lymphedema risk. Unlike symptom-based risk calculations (17), our model allows for risk assessment before chemotherapy and radiotherapy, enabling better follow-up and early treatment initiation. The long follow-up period and prospective design further strengthen our findings (18).

Positive lymph node count and capsular invasion were effective predictors of long-term lymphedema risk in early-stage breast cancer patients. Educating this high-risk patient group, initiating early treatment, and maintaining regular follow-up are crucial for reducing clinical lymphedema incidence.

Ethics

Ethics Committee Approval: The İstanbul Bilim University Clinical Research Ethics Committee approved the study (decision no: 30.04.2014/19-136, date: 30.04.2014).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Pracites: Z.E.İ., S.İ., E.Ö., F.Ç., A.Ö., Ç.O.; Concept: Z.E.İ., T.O., S.İ., E.Ö., A.Ö., G.S.; Design: Z.E.İ., T.O., S.İ., E.Ö., A.Ö., Ç.O., G.S.; Data Collection and/or Processing: Z.E.İ., S.İ., C.N., E.Ö., F.Ç., Ç.O.; Analysis and/or Interpretation: Z.E.İ., T.O., S.İ., C.N., E.Ö., F.Ç.; Literature Search: Z.E.İ., E.Ö., F.Ç., Ç.Ü., A.Ö., G.A., Ç.O., G.S.; Writing: Z.E.İ., T.O., S.İ., C.N., E.Ö., F.Ç., Ç.Ü., A.Ö., G.A., Ç.O., G.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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