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A Cross-sectional Study Examining the Risk Factors Associated with Lymphedema and its Prevalence in Breast Cancer Patients after Level 3 Axillary Lymph Node Dissection

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Abstract

Objective: To determine the prevalance of lymphedema after breast cancer treatment with level 3 axillary lymph node dissection (ALND) and to evaluate the risk factors which underlie this condition.
Material and Methods: A total of 190 women >18-years-old who underwent breast cancer treatment with level 3 ALND >6 months ago were included in this cross-sectional study. The sociodemographic and clinical characteristics of all of the patients were recorded, and all patients were evaluated for lymphedema of the upper extremity by a circumferential measurement method.
Results: On examination, 79 (41.5%) women had lymphedema with a mean development time of 12.7±26.62 months. After univariate analysis, the patients' age, body mass index (BMI), and number of metastatic lymph nodes (LNs) were found to increase the development of lymphedema. In addition, chemotherapy, breast or chest wall radiotherapy, and axillary radiotherapy also played a role. In the multivariate model, BMI (OR=5.491; 95% CI: 1.382-21.82), metastatic LNs (OR=0.314; 95% CI: 0.118-0.839), axillary radiotherapy (OR=15.34; 95% CI: 5.526-42.581), chemotherapy (OR=5.325; 95% CI: 1.48-19.153), and age (OR=1.044; 95% CI: 1.007-1.083) were significantly associated with an increased risk of lymphedema.
Conclusion: This study demonstrated that there was a higher lymphedema prevalence ratio of 41.5% in breast cancer patients who underwent level 3 ALND and found that the risk factors for lymphedema development were axillary radiotherapy, chemotherapy, number of metastatic LNs, age, and BMI.
Keywords: Breast cancer, lymphedema, prevalence, risk factors

Introduction

Lymphedema is a chronic and progressive complication which develops secondary to breast cancer treatment (1,2). It is still a common problem despite recent advances in the treatment of breast cancer (3). Lymphedema may develop during breast cancer treatment or it may occur years later. Pain, tightness, heaviness, and skin infections such as recurrent cellulitis may be observed in the arm of affected patients and lymphangiosarcoma can occur in rare cases (4). This treatment complication may affect the social, vocational, and sexual life as well as the physical and emotional status of patients, resulting in a decrease in the quality of life (QOL) (5).

Lymphedema lasting >3 months is known as persistent or chronic lymphedema (3,6). In some patients, mild to moderate lymphedema turns into severe lymphedema over a period of

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time (7). Finding a cure becomes almost impossible once the chronic advanced stage is reached. However, strategies for risk management, early diagnosis, and treatment can stop the progression of early lymphedema (3).

The exact mechanism of lymphedema and its risk factors have not yet been defined. It has been reported that the incidence and severity of this condition are well correlated with the extent of surgical dissection (8,9); however, other factors may also play a role because many patients who undergo axillary lymph node dissection (ALND) do not develop lymphedema (8). On the other hand, in recent years, sentinel lymph node dissection (SLND) has decreased the incidence of lymphedema because it allows for the detection of the first metastatic node, thereby limiting the number of ALNs extracted. On the other hand, the addition of adjuvant radiotherapy, particularly axillary radiotherapy, has been shown to increase the incidence of lymphedema (10). Despite the efforts to ensure breast cancer patients undergo conservative surgery and SLND, one-third of patients with breast cancer suffer from an invasive type of cancer; therefore, ALND and complications due to ALND is inevitable for these patients (11).

A few studies have investigated ALND levels as a possible risk factor; however, these have not been sufficiently evaluated in studies that have focused on breast cancer-induced lymphedema. Bevilacqua et al. (12) reported the 5-year cumulative incidence rate of lymphedema in breast cancer patients who underwent ALND was 30.3%; however, it was 79.5% for those for underwent level 3 ALND. They also emphasized the importance of the ALND levels as a risk factor for lymphedema. In addition, a new meta-analysis also reported that mastectomies were a risk factor (13). Most of our study population underwent mastectomies and all underwent level 3 ALND; therefore, we investigated an almost homogenous study population in terms of surgical methods.

This study aimed to determine the prevalence of lymphedema in breast cancer patients who underwent level 3 ALND, which is known as the most destructive axillary surgery, and to evaluate the risk factors related to this condition. Predefined risk factors could be helpful in identifying the proper type of postoperative follow-up and for developing the necessary treatment plans. They could also prove to be beneficial for the patients themselves to help them change their daily living activities, which could result in a decrease in the development of lymphedema or perhaps prevent it altogether.

Material and Methods

Participants

Between 2008 and 2010, 262 Caucasian women with breast cancer who underwent level III ALND subsequent to a modified radical mastectomy or lumpectomy together with chemotherapy or radiotherapy were evaluated for the development of lymphedema at the General Surgery Outpatient Clinic of Ankara Oncology Training and Research Hospital Patients >18 years of age and those with a minimum post-surgical period of 6 months were included in this cross-sectional study. Eighteen patients decided not to participate in the study, and 54 patients with bilateral breast cancer, regional recurrence, or distant metastasis were excluded. In addition, patients with any systemic disease, which caused edema of the extremities, as well as those with a history of upper extremity fracture or surgery that may affect the evaluation process were also excluded. Hence, a total of 190 patients with unilateral breast cancer met the inclusion criteria and participated in the study.

Data Collection and Measurements

The sociodemographic characteristics of all of the patients were recorded, and the body mass index (BMI) (W-kg)/H^2-m^2) was calculated after measuring the weight and height. All of the operations were performed by the same team using the same surgical method. All patients underwent level I, II, and III ALND; pectoralis minor muscle was conserved. In addition, modified radical mastectomy technique was often preferred by the surgical team that we collaborated with in this study. Other treatment methods, including breast-chest wall radiotherapy, axillary radiotherapy (25-28 sessions over a period of 5-7 weeks, 40-60 Gy), adjuvant and neoadjuvant chemotherapy (4-8 courses), and hormone therapy, were also documented via the medical charts of the patients. We also identified other surgical complications, including seroma, surgical wound infections, hematoma, and flap necrosis. In addition, we investigated recurrent upper extremity skin infections as another possible complication. Patients who tested positive for one or more of these infections were regarded as having a postoperative complication. Furthermore, we also recorded the elapsed time until the diagnosis of lymphedema after the operation, number of extracted LNs, and number of existing metastatic LNs.

All patients were evaluated for lymphedema of the upper extremities using a circumferential measurement method (14,15). Measurements were performed at the level of the metacarpophalangeal joint, wrist, 10 cm distal to the lateral epincondyle, and 15 cm proximal to the lateral epicondyle with a flexible non-stretch tape. A circumferential difference of ≥2 cm at any of these four points between the affected and non-affected arms was defined as lymphedema (14,15). The patients were also questioned about the time it took for the lymphedema to develop and when they first recognized the differences in size between their right and left hands as well as their upper and lower arms (14). All of the lymphedema patients were evaluated with respect to lymphedema stage (4). Stage 1 presents with pitting edema and is reversible. Stage 2 occurs as the edema progresses and becomes more intense, non-pitting, and irreversible. Stage 3 is characterized by advanced lymphedema. In addition, cartilaginous hardening is observed in conjunction with papillomatous outgrowths and hyperkeratosis of the skin in this stage (4).

All of the patients were also questioned regarding any potential risk factors that may have predisposed them to lymphedema, such as bad hygiene, poor nutrition, and special hobbies. Bad hygiene was evaluated using three questions related to personal hygiene and cleaning. The patients were asked about their daily handwashing habits (hand care), weekly body washing routine, and the cleanliness of their clothes. Those who answered that they washed their hands, bodies, or clothes at the most once a week were then considered to have poor hygiene.

We also evaluated the patients with respect to poor nutrition during the lymphedema development period. The patients answered questions about their body weight and weight loss in the 6 months before this condition began and about their current body weight at the same time and then we calculated their BMI. The patients were classified as having poor nutrition if they had an unintentional weight loss of >10% of their body weight during the previous 6 months or a BMI of <20. Furthermore, we asked the patients if they had any hobbies that involved the possible overuse of the hands and arms, such as painting, sewing, playing a musical instrument, or garden work, and recorded their answers. We also questioned them regarding whether they had been informed about the lymphedema before or after the operation.

The study was approved by the Ethics Committee of the Ankara Physical Medicine and Rehabilitation Training and Research Hospital. In addition, all patients signed the study consent form and were instructed about lymphedema, preventive measures, positioning, and skin care via an informational brochure and exercise form. Furthermore, those diagnosed with lymphedema were included in a physical therapy and rehabilitation program.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 11.5 for Windows software package (SPSS, Inc., Chicago, Illinois, USA) was used for statistical analysis. Descriptive statistics were expressed as mean, standard deviation, minimum, maximum, and median for continuous variables, while categorical variables were expressed as a percentage. Single variable logistic regression analysis was used to evaluate the effects of the demographic and clinical characteristics on the development of lymphedema. After univariate analysis, variables with a value of $p<0.25$ were entered into the multivariate model (16), and multivariable backward stepwise logistic regression was used to identify the effects of the clinical factors determined to affect lymphedema together with some of the risk factors. For every variable, the odds ratio (OR) and 95% confidence intervals (CIs) were calculated, and a p value <0.05 was considered to be statistically significant.

Results

Demographic Variables

The mean age of the 190 patients was 52.31±10.40 years (range: 27-86). A BMI ≤25 was observed in 12.62% of patients, and 87.3% had a BMI >25. The demographic characteristics of the patients according to the presence of lymphedema are shown in Table 1.

Table 1. Demographic variables according to lymphedema development

Variables		Total (n=190)	Non-LE (n=111)	LE (n=79)
Age		52.31±10.40	50.9±10.2	54.3±10.4
<40		17 (8.9%)	12 (10.8%)	5 (6.3%)
40–60		135 (71.1%)	84 (75.7%)	51 (64.6%)
>60		38 (20.0%)	15 (13.5%)	23 (29.1%)
Educational level				
University		13 (6.8%)	10 (9.0%)	3 (3.8%)
High school		27 (14.2%)	17 (15.3%)	10 (12.7%)
Middle school		11 (5.8%)	8 (7.2%)	3 (3.8%)
Primary school		63 (33.2%)	34 (30.6%)	29 (36.7%)
Illiterate		76 (40.0%)	42 (37.8%)	34 (43.0%)
Marital status				
Single/widow		22 (11.5%)	13 (11.7%)	9 (11.4%)
Married		168 (88.4%)	98 (88.3%)	70 (88.6%)
Work status				
Employed		17 (8.9%)	12 (10.8%)	5 (6.3%)
Unemployed		173 (91.1%)	99 (89.2%)	74 (93.7%)
BMI				
≤25		24 (12.6%)	21 (18.9%)	3 (3.8%)
>25		166 (87.3%)	90 (81.1%)	76 (93.7%)
Family history	(-)	153 (80.5%)	85 (76.6%)	68 (86.1%)
	(+)	37 (19.5%)	26 (23.4%)	11 (13.9%)
Comorbidity				
DM	(-)	152 (80.0%)	91 (82.0%)	61 (77.2%)
	(+)	38 (20.0%)	20 (18.0%)	18 (22.8%)
HT	(-)	25 (65.8%)	73 (65.8%)	52 (65.8%)
	(+)	65 (34.2%)	38 (34.2%)	27 (34.2%)
Other	(-)	183 (96.3%)	106 (95.5%)	77 (97.5%)
	(+)	7 (3.7%)	5 (4.5%)	2 (2.5%)

LE: lymphedema; BMI: body mass index; DM: diabetes mellitus; HT: hypertension

Prevalence of Lymphedema

On examination, 79 (41.5%) out of the 190 patients had lymphedema. The mean time period of our evaluation after breast cancer surgery was 51.88±54.90 months (range: 6-244), and the mean time for the development of lymphedema after surgery was 12.7±26.62 months (range: 1-177).

We determined that 44 of the patients had Stage 1 (55.7%), 25 had stage 2 (31.6%), and 10 had stage 3 lymphedema (12.7%). The distribution is shown in Figure 1. We also investi-

Table 2. Assessment of demographic variables as risk factors for lymphedema

Variables		Non-LE (n=111)	LE (n=79)	p value	OR (95% CI)
Age		50.9±10.2	54.3±10.4	0.028*	1.033 (1.004-1.063)
<40		12 (10.8%)	5 (6.3%)	-	1.000[a]
40-60		84 (75.7%)	51 (64.6%)	0.502	1.457 (0.485-4.376)
>60		15 (13.5%)	23 (29.1%)	0.038*	3.680 (1.076-12.583)
Education					
University		10 (9.0%)	3 (3.8%)	-	1.000[a]
High school		17 (15.3%)	10 (12.7%)	0.382	1.961 (0.434-8.860)
Middle school		8 (7.2%)	3 (3.8%)	0.813	1.250 (0.196-7.956)
Primary school		34 (30.6%)	29 (36.7%)	0.138	2.843 (0.714-11.324)
Illiterate		42 (37.8%)	34 (43.0%)	0.155	2.698 (0.688-10.589)
Marital status					
Single/Widow		13 (11.7%)	9 (11.4%)	-	1.000[a]
Married		98 (88.3%)	70 (88.6%)	0.946	1.032 (0.418-2.547)
Work status					
Employed		12 (10.8%)	5 (6.3%)	-	1.000[a]
Unemployed		99 (89.2%)	74 (93.7%)	0.286	1.794 (0.606-5.314)
BMI		29.1±4.7	31.9±4.9	<0.001*	1.131 (1.058-1.208)
≤25		21 (18.9%)	3 (3.8%)	-	1.000[a]
>25		90 (81.1%)	76 (96.2%)	0.002*	5.911 (1.698-20.583)
Family history	(-)	85 (76.6%)	68 (86.1%)	-	1.000[a]
	(+)	26 (23.4%)	11 (13.9%)	0.103	0.529 (0.244-1.146)
Comorbidity					
DM	(-)	91 (82.0%)	61 (77.2%)	-	1.000[a]
	(+)	20 (18.0%)	18 (22.8%)	0.418	1.343 (0.657-2.744)
HT	(-)	73 (65.8%)	52 (65.8%)	-	1.000[a]
	(+)	38 (34.2%)	27 (34.2%)	0.993	0.997 (0.543-1.832)
Other	(-)	106 (95.5%)	77 (97.5%)	-	1.000[a]
	(+)	5 (4.5%)	2 (2.5%)	0.701	0.551 (0.104-2.913)

LE: lymphedema; OR: odds ratio; CI: confidence interval; BMI: body mass index; DM: diabetes mellitus; HT: hypertension; [a]: reference category * p<0.05

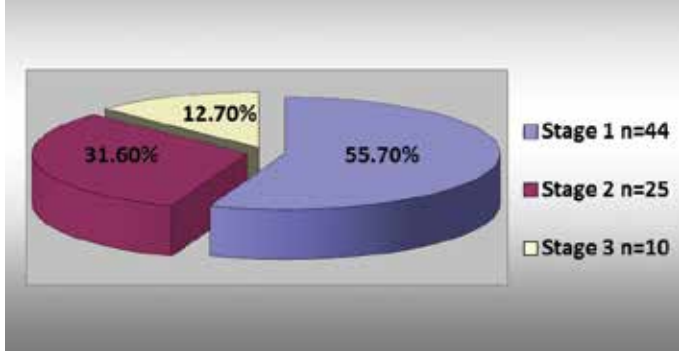

Figure 1. The distribution of the stages of lymphedema

gated the distribution of the lymphedema in the upper extremities and determined that it was located 15 cm proximal to the elbow in 94.9% of the patients and 10 cm distal to the elbow in 73.4% of the patients. Furthermore, 25.3% of the patients had lymphedema on the wrist and 5.6% at the metacarpophalangial joint level.

Univariate Analysis of Demographic Variables

After univariate analysis, the patients' ages (p= 0.028, OR= 1.033, 95% CIs= 1.004-1.063) and BMIs (p<0.001, OR=1.131, 95% CIs= 1.058-1.208) were found to increase the development of lymphedema, whereas the other sociodemographic variables had no effect. The effects of demographic variables on the development of lymphedema are shown in Table 2.

Univariate Analysis of Clinical Variables

While 179 patients (97.21%) underwent a modified radical mastectomy, only 11 underwent a lumpectomy (5.78%). We found that neither the surgical method (modified radical mastectomy or lumpectomy) (p=0.126) nor the number of extract-

Table 3. Assessment of clinical variables as risk factors for lymphedema

Variables	Category	Non-LE (n=111)	LE (n=79)	p value	OR (95% CI)
Postoperative Time		51.9±54.9	44.3±41.6	0.3	0.997 (0.991-1.003)
Operated side	Dominant	45 (40.5%)	29 (36.7%)	-	1.000[a]
	Non-dominant	66 (59.5%)	50 (63.3%)	0.593	1.176 (0.649-2.129)
Surgery	MRM	102 (91.9%)	77 (97.5%)	-	1.000[a]
	Lumpectomy	9 (8.1%)	2 (2.5%)	0.126	0.294 (0.062-1.402)
Number of LNs extracted		21.2±7.7	21.8±8.0	0.622	1.009 (0.973-1.047)
	<15	29 (26.1%)	17 (21.5%)	-	1.000[a]
	15-25	55 (49.5%)	39 (49.4%)	0.607	1.210 (0.585-2.500)
	>25	27 (24.3%)	23 (29.1%)	0.37	1.453 (0.642-3.290)
Number of metastatic LNs		1.8±4.4	5.2±7.9	<0.001*	1.115 (1.043-1.192)
Metastatic LNs	-	60 (54.1%)	28 (35.4%)	-	1.000[a]
	+	51 (45.9%)	51 (64.6%)	0.011*	2.143 (1.184-3.878)
RT					
(Breast-Chest)	-	60 (54.1%)	21 (26.6%)	-	1.000[a]
	+	51 (45.9%)	58 (73.4%)	<0.001*	3.249 (1.742-6.060)
Axillary RT	-	94 (84.7%)	34 (43.0%)	-	1.000[a]
	+	17 (15.3%)	45 (57.0%)	<0.001*	7.318 (3.700-14.475)
Chemotherapy					
	-	21 (18.9%)	4 (5.1%)	-	1.000[a]
	+	90 (81.1%)	75 (94.9%)	0.005*	4.375 (1.439-13.306)
Hormone Therapy	-	39 (35.1%)	38 (48.1%)	-	1.000[a]
	+	72 (64.9%)	41 (51.9%)	0.073	0.584 (0.324-1.53)
Postoperative complications	-	88 (79.3%)	58 (73.4%)	-	1.000[a]
	+	23 (20.7%)	21 (26.6%)	0.345	1.385 (0.703-2.729)
Presence of risk factors	-	85 (76.6%)	51 (64.6%)	-	1.000[a]
	+	26 (23.4%)	28 (35.4%)	0.07	1.795 (0.949-3.393)
LE information	-	63 (56.8%)	49 (62.0%)	-	1.000[a]
	+	48 (43.2%)	30 (38.0%)	0.467	1.244 (0.690-2.444)

LE: lymphedema; OR: odds ratio; CI: confidence interval; MRM: modified radical mastectomy; LNs: lymph nodes; RT: radiotherapy; a: reference category; * p<0.05

ed axillary LNs (p=0.622) were clinical factors that increased the risk for lymphedema. However, the relationship between the number of metastatic LNs and the development of lymphedema was statistically significant (p<0.001, OR= 1.115, 95% CIs=1.043-1.192). Moreover, adjuvant therapies such as breast-chest radiotherapy (p<0.001, OR= 3.249, 95% CIs=1.742-6.060) and axillary radiotherapy (p<0.001, OR= 7.318, 95% CIs= 3.700-14.475) were observed to increase the development of lymphedema significantly. Of the patients who developed lymphedema, 73.4% were treated via radiotherapy of the breast or chest wall, and 57% were treated by additional axillary radiotherapy. Furthermore, 94.9% of the patients who developed lymphedema underwent chemotherapy, which increased the risk of obtaining this condition (p= 0.005, OR= 4.375, 95% CIs= 1.439-13.306). We also determined that only 38% of the patients with lymphedema were informed about it before or after the operation. Table 3 shows the assessment of clinical variables as risk factors for lymphedema.

Multivariate Analysis of Clinical Variables

Among the variables (p<0.25) in the multivariate model, BMI >25 (p=0.016, OR: 5.491, 95% CIs= 1.382-21.82), metastatic LNs (p=0.021, OR: 0.314, 95% CIs=0.118-0.839), axillary radiotherapy (p<0.001, OR: 15.340, 95% CIs=5.526-42.581), chemotherapy (p=0.010, OR: 5.325, 95% CIs=1.48-19.153), and age (p=0.020, OR: 1.044, 95% CIs=1.007-1.083) were significantly associated with an increased risk of lymphedema. However, we found that having a family history of lymphedema played no part in being afflicted with this condition and neither did any of the associated risk factors. In addition, lumpectomy had no association with lymphedema. Table 4 shows the results of the multivariable backward stepwise logistic regression analysis.

Table 4. Results of multivariable logistic regression analysis

Models	Variables	Odds Ratio	p	95% CI Lower Limit	95% CI Upper Limit
1st	BMI >25	5.695	0.015	1.394	23.26
	Family history	0.722	0.497	0.283	1.845
	Lumpectomy	0.546	0.225	0.206	1.45
	Metastatic LNs	0.322	0.024	0.12	0.863
	Axillary RT	15.319	<0.001	4.797	48.922
	RT (Breast-CW)	0.992	0.987	0.397	2.482
	CT	4.926	0.019	1.293	18.764
	Risk Factor	0.997	0.994	0.461	2.154
	Age	1.043	0.025	1.005	1.083
2nd	BMI >25	5.697	0.015	1.398	23.218
	Family History	0.723	0.493	0.286	1.827
	Lumpectomy	0.546	0.225	0.206	1.449
	Metastatic LNs	0.322	0.024	0.121	0.862
	Axillary RT	15.314	<0.001	4.809	48.761
	RT (Breast-CW)	0.992	0.986	0.398	2.475
	CT	4.925	0.019	1.296	18.713
	Age	1.043	0.023	1.006	1.082
3rd	BMI >25	5.693	0.015	1.399	23.16
	Family History	0.723	0.493	0.286	1.827
	Lumpectomy	0.546	0.221	0.207	1.438
	Metastatic LNs	0.322	0.024	0.121	0.862
	Axillary RT	15.244	<0.001	5.43	42.8
	CT	4.913	0.017	1.334	18.093
	Age	1.043	0.023	1.006	1.082
4th	BMI >25	5.542	0.016	1.369	22.433
	Lumpectomy	0.538	0.203	0.207	1.398
	Metastatic LNs	0.319	0.022	0.119	0.851
	Axillary RT	15.855	<0.001	5.668	44.352
	CT	5.01	0.015	1.366	18.379
	Age	1.044	0.021	1.007	1.082
5th	BMI >25	5.491	0.016	1.382	21.82
	Metastatic LNs	0.314	0.021	0.118	0.839
	Axillary RT	15.34	<0.001	5.526	42.581
	CT	5.325	0.01	1.48	19.153
	Age	1.044	0.02	1.007	1.083

CI: confidence interval; BMI: body mass index; LNs: lymph nodes; RT: radiotherapy; CT: chemotherapy; CW: chest wall

Discussion

The incidence and prevalence of lymphedema has been reported as 0%-94% within various populations (17,18). The main reasons for this broad range are a lack of a standardized definition of this condition, the use of different measurement methods, and varying follow-up periods (2,19). In addition, the average incidence rate was reported as 21.4% in a recent meta-analysis by DiSipio et al. (13). The high prevalence ratio in our study (41.5%) was inconsistent with other studies, particularly those in which SLND was performed and those that had low prevalence ratios (3%-5%) (20,21). Various authors have also reported a decrease in the postoperative development of lymphedema in conjunction with more conservative surgical techniques as well as limited ALND (13,18,20). Modified radical mastectomy has also been identified as an important risk factor (13). The reason for our higher ratio may be due to the level 3 ALND that was performed over a wide area along with the mastectomies. Therefore, because our study population consisted solely of breast cancer patients who underwent level 3 ALND, the higher ratio indicated the prevalence of the lymphedema induced by level 3 ALND. In recent years, the number of patients with breast cancer who have undergone SLND has continued to increase. However, ALND is still necessary for some patients who suffer from an invasive type of cancer (11). In our opinion, our data is remarkable for these patients who undergo level 3 ALND.

Previous studies have demonstrated that as the extent of ALND increases, the rate of lymphedema development also increases as a result of more surgical damage to the lymphatic canals (13, 22). In our study, we found a significant relationship between the development of lymphedema and the number of metastatic LNs; however, this was not true for the number of extracted LNs. Similarly, other authors found no association between the number of extracted LNs and lymphedema (23).

Postoperative radiotherapy decreases the regional recurrence by three or four times. Therefore, it has an important role in the treatment of breast cancer (24). However, it can also cause lymphedema by obstructing the lymphatic vessels with radiation-induced fibrosis (25). In some studies, radiotherapy of the breast region and axillary radiotherapy were found to be significant risk factors for lymphedema on univariate analysis; however, with multivariate analysis, only axillary radiotherapy was identified as a risk factor (7,10). We found similar results in our study with an increase in lymphedema development after axillary radiotherapy alone.

Chemotherapy has also been determined to be a significant risk factor for the development of lymphedema (12,23,26,27). In a study investigating the cosmetic results of breast cancer treatment, the patient group who underwent adjuvant chemotherapy was determined to have far more complications (26). Similarly, our findings revealed that chemotherapy was a significant risk factor. The exact mechanism is not known; however, one may speculate that those patients receiving chemotherapy may have received more aggressive treatment (27). There are also studies that have reported a lack of association between chemotherapy and lymphedema (1,23,28). These authors argue that although the use of chemotherapy is more frequent in young patients, they experience less lymphedema compared with that in older patients (29). In our study, older patients form the majority of the population that underwent chemotherapy, which may explain why it was a significant risk factor.

Axillary dissection at an advanced age is a significant risk factor for the development of lymphedema (7,23,29,30), and

advanced age was also found to be a significant risk factor for the development of lymphedema on both univariate and multivariate analyses in our study. This may be explained by the fact that the lymphovenous anastomoses formation occurs more easily at a younger age rather than later in life (31). In contrast, some studies have indicated that advanced age is not a risk factor for the development of lymphedema (13,28,32). A study by Werner et al. (33) explained that these opposing views were because of the more aggressive nature of breast cancer in young women, characterized by the higher incidence of lymphedema associated with intensive cancer treatment, and the vulnerability of young patients to infection and trauma-induced lymphedema because of a more active lifestyle.

Many studies (2,10,13,15,28,32,34) have also reported that BMI is a significant risk factor for the development of lymphedema, and this study agrees with this conclusion. In a recent study, a significant reduction was observed in arm edema in patients whose body weight and BMI had decreased after a 12-week diet program, and the authors emphasized the importance of weight loss in the treatment of lymphedema (35). In addition, Johansson et al. (36) determined that patients who developed lymphedema were determined to be more inactive, and lymphedema was reported to induce weight gain by limiting daily activities (36). Therefore, patients should be encouraged to return to optimum daily physical activity as quickly as possible after their breast cancer treatment (37). In addition, it should be remembered that obesity may also play a role in causing lymphedema via poor and delayed wound healing due to fat necrosis, secondary infection, regional lymphangitis, and lymphatic obstruction (31). However, some recent reports have surfaced that counteract these conclusions (6,7).

We did not find any relationship between potential risk factors such as bad hygiene, poor nutrition, extremity overuse, and lymphedema. It has been suggested that these factors do not have a direct effect on the development of this condition but that they affect it indirectly by increasing infection and disturbing the healing of the wound (38). Controversy also exists regarding whether recurrent infection is a cause of lymphedema. Lymphedematous tissues are extremely sensitive to infection and even a small open wound can cause lymphatic damage or obstruction by means of a severe infection (23). However, we found that postoperative complications and postoperative recurrent skin infections had no effect on lymphedema.

Systemic diseases, on the other hand, are not thought to play a role in the development of lymphedema (23), and we found nothing to contradict this notion in our study. However, there are some studies that have reported a connection between hypertension and the development of lymphedema (39). Kocak et al. (30) suggested that hypertension should be considered as a factor which increases lymphedema but that it should not be declared as an actual risk factor. It has also been reported that in patients taking antihypertensive drugs, capillary leakage decreases as the arterial pressure decreases, consequently decreasing the rate of lymphedema (40).

It has been reported that lymphedema most commonly develops up to 2 years after surgery for breast cancer (13); however, some authors have suggested that it can take as long as 3-4 years (32,34). Late-onset lymphedema is considered to be mainly due to trauma and infection (34). Brennan et al. (41) determined that one patient developed lymphedema 30 years after a mastectomy and ALND and that this patient's blood glucose had been measured on the affected side a few days prior to the diagnosis. In our study, 81.01% of the patients developed lymphedema within the first year, and 92.4% had it within 3 years. In the end, lymphedema may develop within the first month after the operation or even as much as 30 years later. Moreover, the determination of a true incidence rate is also associated with the follow-up period (2,3,19,30). As previously mentioned, the mean time for patient evaluation after breast cancer surgery in our study was 44.3 months. It was also reported that 90% of the late effects of radiotherapy arise after 3.9 years (42). Therefore, assessments that take place approximately 4 years similar to the evaluation duration of this study would be reasonable. Nonetheless, the effect of the follow-up period on lymphedema development could not be accurately evaluated in this study because of the cross-sectional study design.

In our study, 49 (62.0%) patients with lymphedema were not informed about lymphedema. Although we did not find a significant relationship between patient education and the development of lymphedema, we believe that in the future, patient education needs more attention because lymphedema mostly develops as a result of infection or trauma. Park et al. (2) reported a higher incidence of lymphedema in patients who were not informed before breast cancer surgery, and preventive self-care activities could prevent the progression of lymphedema. Because lymphedema is not a curable disease, prevention becomes much more important in clinical practice. However, this requires educating patients at the right time.

This study has some limitations. Firstly, we could not use more reliable methods such as perometry to evaluate lymphedema in our study because of technical insufficiencies. We preferred the circumferential measurement technique, which is considered to be the easiest method for application and evaluation (43). The main disadvantage of this method lies in the fact that there may generally be a circumferential difference between dominant and non-dominant extremities. However, this difference generally does not exceed our measurement limit of 2 cm (20). Although we demonstrated that some risk factors have a negative effect on the development of lymphedema, our cross-sectional design meant that these factors could not be regarded as a precise cause of this condition. In addition, the effect of the follow-up period on lymphedema development also could not be accurately evaluated in this study because of the cross-sectional study design.

Conclusion

Lymphedema is a disturbing complication which develops secondary to the treatment of breast cancer and affects the patients' QOL. Broad incidence rates have also been reported

in previous studies, and this has been attributed to different evaluation methods and surgery types. Herein, we evaluated a homogenous patient population in terms of surgical methods and determined that the lymphedema prevalence ratio of the patients who underwent modified radical mastectomy with level 3 ALND was 41.5%. The independent risk factors for lymphedema development in breast cancer patients who underwent level 3 ALND were found to be axillary radiotherapy, chemotherapy, number of metastatic LNs, age, and BMI. It is known that the lymphedema prevalence ratio in breast cancer patients after ALND is higher than those after SLND. In our opinion, physicians treating breast cancer should meticulously diagnose high-risk breast cancer patients who underwent ALND with respect to lymphedema before and after surgery to prevent the development of this condition. Furthermore, these patients should be followed up more rigorously in the post-operative period, and they should be educated, particularly with respect to modifiable risk factors such as obesity.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Physical Medicine and Rehabilitation Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author contributions: Concept - M.D.A.; Design M.D.A, S.U.D.; Supervision - M.D.A, S.U.D., B.F.K.; Resource - S.K.; Materials - S.K.; Data Collection and/or Processing - S.K., S.U.D.; Analysis and/or Interpretation - S.K.; Literature Search - S.K.; Writing - S.K., S.U.D., M.D.A.; Critical Reviews - M.D.A, B.F.K.

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