**Original Article**

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# Assessment of Risk Factors in Patients who presented to the Outpatient Clinic for Breast Cancer-Related Lymphedema

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**ABSTRACT**

**Objective:** Lymphedema is one of the most debilitating outcomes of breast cancer treatment. We aimed to compare the demographic and clinical characteristics of breast cancer patients with and without lymphedema, to assess risk factors for lymphedema, and to evaluate treatment outcomes in lymphedema patients.

**Materials and Methods:** Demographic and clinical characteristics of 84 women with previous surgery for breast cancer who presented to the outpatient clinic between March 2014 and May 2015 were retrospectively extracted from patient records.

**Results:** Upper extremity lymphedema was detected in 34 of 84 patients (40.5%). The mean age, body mass index, the number of positive lymph nodes and the number of patients with postoperative radiotherapy were significantly higher among patients with lymphedema than those without ($p<0.05$). Educational level of patients with lymphedema was significantly lower than the other group ($p<0.05$). The correlation analysis revealed an association between age, educational level, body mass index, tumor stage, number of positive lymph nodes, postoperative radiotherapy and presence of lymphedema. Postoperative radiotherapy was detected as the only independent risk factor by logistic regression analysis. Fourteen out of 26 lymphedema patients were assigned to education, skin care, exercise and compression bandaging therapy. Upper extremity volumes and volume differences were significantly improved after treatment.

**Conclusion:** Advanced age, low educational level, obesity, tumor size, the number of positive lymph nodes and postoperative radiotherapy correlated with the development of lymphedema. Within these factors, postoperative radiotherapy was detected as an independent risk factor for the development of lymphedema. Patient education, skin care, exercise and compression bandage therapy are effective treatment options in breast cancer-related lymphedema.

**Keywords:** Breast cancer, lymphedema, risk factors

## Introduction

Breast cancer is the most common cancer type in women (1, 2). More than 1 million women are diagnosed with breast cancer annually worldwide (3). One in every eight women is expected to develop breast cancer during their lifetime (4).

Although breast cancer treatment is quite effective, post-treatment complications constitute major problems for patients (5). One of the complications occurring after breast cancer treatment is lymphedema and causes serious long-term disability (2, 6). Breast cancer associated upper extremity lymphedema develops because of surgical removal of axillary lymph nodes and/or axillary radiation therapy. The protein-rich lymph fluid accumulates in the interstitial space within the skin-subcutaneous area due to impairment of lymphatic flow and manifests with upper extremity swelling, limitations in mobility, and heaviness (7).

Breast cancer associated lymphedema frequently develops within the first 3 years of treatment, although there is a life-long risk of developing lymphedema (5, 8). Lymphedema incidence in breast cancer patients with axillary lymph node dissection and axillary radiotherapy is reported to be approximately 30% (6, 7). The intensity of lymphedema correlates with the number of axillary lymph nodes removed and the extent of radiation (5). The size of the tumor, advanced age, obesity, immobility, recurring cellulitis and erysipelas also increase the risk (1, 5, 6, 8, 9).

Lymphedema can cause serious physical problems such as limb swelling, pain, limitations in mobility, skin infections and subcutaneous fibrosis. It may impair the patient's quality of life and can develop psychological problems such as anxiety and depression. It can lead to

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social isolation and delays in time to return to work. That is why, the prevention, early diagnosis and treatment of lymphedema are significant issues (10).

The diagnosis of lymphedema is usually based on history and physical examination. It is often unilateral (5). Although it can affect the complete arm, it can be localized to the hand, forearm or the upper arm (8). Initially the edema is soft with pitting, while it progresses to a solid edema in time with subcutaneous fibrosis that develops due to inflammation (5). Girth and/or volume measurements are important in physical examination. The most commonly used diagnostic method is girth measurements. Ideally, circumference measurements should be made in the preoperative period and compared with measurements made at regular intervals in the postoperative period, and a difference above 2 cm should be considered as lymphedema. However, since this is not often possible, the postoperative difference between two arm circumferences above 2 cm is regarded as lymphedema. The most accurate measurement technique is the water displacement technique. This technique measures the volume of water that overflows when the arm is submerged in a container filled with water. If the difference between the two arms is greater than 10% or 200 ml then it is regarded as lymphedema (8).

Lymphedema is a disease that can be controlled, but cannot be cured (2). The most accepted lymphedema treatment method is complete decongestive therapy (CDT). CDT is designed to reduce limb volume and to maintain skin health (2, 5, 11). The treatment program consists of two phases of intensive phase (phase 1) and self-management phase (phase 2). The intensive phase is expected to decrease lymphedema volume with a 2-4 week treatment program. The intensive phase includes manual lymph drainage, multi-layer short stretch compression bandaging, patient education, skin care and exercise. The self-management phase is aimed to protect the volume reduction that was obtained in the intensive phase. This phase includes self-massage, compression garments, skin care, patient education and exercise, and lasts for a lifetime (2, 10).

Once lymphedema develops, it requires lifelong monitoring and treatment, without offering cure. Therefore, it is important to inform patients on the issue and prevent lymphedema. This study aimed to compare the demographic and clinical characteristics of breast cancer patients with and without lymphedema, to assess risk factors for lymphedema, and to evaluate treatment outcomes in lymphedema patients.

## Material and Methods

Demographic and clinical characteristics of 84 women with previous surgery for breast cancer who presented to the outpatient lymphedema clinic between March 2014 and May 2015 were retrospectively extracted from patient records. An approval was obtained from the hospital ethics committee.

The demographic characteristics, history on breast cancer and its treatment, co-morbidities, bilateral upper extremity circumference measurements and bilateral upper limb volume values based on girth measurements were evaluated in all patients with breast cancer who presented to our lymphedema outpatient clinics. The circumference measurements were made at the level of the metacarpophalengeal joint, wrist (proximal ulnar styloid), as well as 10 cm proximal and distal to the lateral epicondyle. The volumes were measured by using geometrical volume formulas based on circumference measurements (12). Patients with at least 2 cm difference between the two upper extremities in at least one level and/or at least a 10% difference between the two upper limb volumes were considered as lymphedema. The stage of lymphedema, severity and follow-up data during follow-up in patients with lymphedema were evaluated. For staging; Stage 1: soft edema with pitting, is reduced temporarily by limb elevation (reversible lymphedema), Stage 2: edema is harder and non-pitting, it does not regress with limb elevation (irreversible lymphedema), Stage 3: lymphedema is advanced, elephantiasis, massive hyperkeratosis and ulceration may occur (irreversible lymphedema). For severity, the lymphedema was considered as mild if the difference between the circumferences between two arms was <3 cm, moderate if between 3-5 cm, and as severe if >5 cm.

At our lymphedema outpatient clinic, patients with breast cancer surgery are evaluated and informed about lymphedema, the issues they should pay attention to in order to prevent lymphedema (eg avoiding trauma, compression, infection, barotrauma, heat and cold, and weight gain) are explained, early symptoms of lymphedema are taught (tightening of clothes, heaviness, redness, numbness and tingling), skin care is emphasized (using neutral pH soap and moisturizer, avoiding cuts, scratches and ingrown nails, keeping fingers and skin folds clean and dry), and the relevant exercises are taught. A multi-layer short-stretch compression bandaging is applied to patients identified to have upper extremity lymphedema as part of phase 1 treatment in addition to the issues mentioned above (education, exercise, skin care). The compression bandage is applied in our clinic on a daily basis and stays on for 23 hours in the extremities. Limb circumference measurements are made on a weekly basis, and the patient is switched to maintenance therapy with compression garment as soon as a plateau in reduction is reached. Patients are recommended to wear a tailor-made, one-piece, class 2-compression garment to the entire arm and hand during the day and asked to remove it during the night. After switching to compression garments, patients are followed-up at our clinic in every 3 months during the first year.

### Statistical analysis

The demographic and clinical characteristics of patients with and without lymphedema had a non-homogeneous distribution, and the intergroup differences were evaluated by the non-parametric Mann-Whitney U test and chi square test. The Spearman correlation coefficient (r) was used to determine factors associated with lymphedema. r 0-0.25 was regarded as no correlation, 0:25 to 0:50 as weak-to-moderate correlation, 0.50-0.75 as strong correlation, and 0.75-1 was regarded as a very strong correlation. Logistic regression analysis was made after correlation analysis to identify independent risk factors for lymphedema. The changes in pre- and post- treatment upper extremity volumes and volume differences between the two upper extremities in patients with lymphedema were evaluated with the non-parametric Wilcoxon test. The data were transferred to the electronic environment and were evaluated with the SPSS 13.0 for Windows (SPSS, Inc.; Chicago, IL, USA) software. Statistical significance was set at $p<0.05$.

## Results

The mean age of the 84 patients was 53.2±10.2 years, and their mean duration of education was 7.2±4.2 years. 70 percent of the patients were housewives, 20% were employed and 6% were retired. 73.3% of the patients were married while 26.7% were single. The mean body mass index was 29.4±6.5 kg/m². 86.7% of the patients were right-

handed. 31.7% of patients had hypertension, 15% thyroid disease, 13.3% diabetes mellitus, 6.7% chronic obstructive pulmonary disease, and 1.7% had coronary artery disease. 48.3% of patients underwent left-sided breast surgery, 46.7% had surgery on the right side, and 5% had bilateral disease. Eighty-five percent of patients underwent modified radical mastectomy, while the remaining 15% underwent breast conserving surgery and axillary lymph node dissection. 95% of patients had invasive ductal carcinoma, 3.3% papillary carcinoma and 1.7% tubular carcinoma. In the postoperative period, 71.7% of patients received chemotherapy, 55% received radiotherapy and 58.3% hormonal therapy. The mean period between the date of surgery and the study was 35.7±49.3 months.

Lymphedema was detected in at least one upper extremity in 34 out of 84 patients (40.5%). The average duration of swelling in patients with lymphedema was 27.8±39 months. 33 patients (97.1%) had lymphedema in one upper limb while 1 (2.9%) patient had involvement of both upper extremities. In 19 of the 34 patients with lymphedema (55.9%), lymphedema developed in the dominant upper extremity. Ten patients (29.4%) had stage 1, 22 patients (64.7%) stage 2, and 2 patients (5.9%) had stage 3 lymphedema. The severity of lymphedema was mild in 8 patients (23.5%), moderate in 13 patients (38.2%) and severe in 13 patients (38.2%). None of the patients had a family history of lymphedema. None of the patients had skin involvement (cellulitis, papillomatosis, hyperkeratosis).

The mean age, body mass index, the period between the date of surgery and the study, number of metastatic lymph nodes and number of patients with postoperative radiotherapy was significantly higher in the group with lymphedema than the group without ($p<0.05$). The mean education duration of patients with lymphedema was significantly lower than that of patients without ($p<0.05$). There was no difference between the groups in terms of occupation, marital status, dominant limb side, co-morbidity, breast cancer type and stage, breast cancer surgery, number of removed axillary lymph nodes, number of patients with postoperative chemotherapy and hormonal therapy ($p>0.05$). Demographic and clinical characteristics of patients with and without lymphedema have been presented in detail in Table 1.

Correlation analysis revealed weak-to-moderate association between lymphedema and age, education duration, body mass index, cancer stage, number of positive lymph nodes and postoperative radiotherapy ($r=0.25$-$0.40$; $p<0.05$). There was no correlation between lymphedema and number of removed lymph nodes and postoperative chemotherapy (r=0:14 to 0:18 $p>0.05$). The only independent risk factor was determined as postoperative radiotherapy by logistic regression analysis (OR: 7:09, $p=0.04$). Correlation analysis and logistic regression analysis results are shown in detail in Table 2 and Table 3, respectively.

Thirteen out of the 34 lymphedema patients (38.2%) did not attend treatment despite recommendations. Four patients (11.8%) did not accept the daily treatment due to transportation problems. Two patients (5.9%) were scheduled for treatment after completion of chemotherapy. Radial, median and ulnar neuropathy due to unilateral lymphedema compression was detected in one patient (2.9%) who was admitted for an inpatient treatment program. Fourteen patients (41.2%) were enrolled in the outpatient treatment program. The multi-layer short-stretch compression bandaging was applied daily for a mean of 4.5±1.2 weeks in patients who received outpatient treatment. The upper extremity volumes with lymphedema, and volume differences between the two upper limbs significantly decreased after

Table 1. Demographic and clinical features of patients with and without lymphedema

| | Patients with Lymphedema (n=34) | Patients Without Lymphedema (n=50) | p |
|---|---|---|---|
| Age (year) | 56.6±10.7 | 50.9±11.5 | 0.01* |
| Education duration (year) | 6.2±4 | 8.2±4.6 | 0.04* |
| Dominant hand (n, %) | | | |
| Right | 28 (%82.3) | 42 (%84) | 0.72 |
| Left | 6 (%17.7) | 8 (%16) | |
| Occupation (n, %) | | | |
| Housewife | 26 (%76.5) | 33 (%66) | |
| Employed | 6 (%17.6) | 11 (%22) | 0.25 |
| Retired | 2 (%5.9) | 6 (%12) | |
| Marital status (n, %) | | | |
| Married | 23 (%67.6) | 35 (%70) | 0.51 |
| Single | 11 (%32.4) | 15 (%30) | |
| Co-morbidity (n, %) | | | |
| Hypertension | 12 (%35.3) | 18 (%36) | 0.06 |
| Diabetes | 4 (%11.7) | 4 (%8) | 0.72 |
| COPD | 2 (%5.9) | 2 (%4) | 1.00 |
| Thyroid disease | 5 (%14.7) | 4 (%8) | 0.48 |
| CAD | 0 | 0 | |
| BMI (kg/m$^2$) | 31.4±6.6 | 27.5±5.1 | 0.003* |
| Period between the date of surgery and the study (months) | 62.1±59.6 | 18.5±26.1 | 0.000* |
| Breast cancer location (n, %) | | | |
| Right | 13 (%38.2) | 26 (%52) | |
| Left | 19 (%55.9) | 22 (%44) | 0.24 |
| Bilateral | 2 (%5.9) | 2 (%4) | |
| Breast cancer type (n, %) | | | |
| Invasive ductal carcinoma | 33 (%97.1) | 48 (%96) | |
| Tubular carcinoma | 1 (%2.9) | 0 | 0.66 |
| Papillary carcinoma | 0 | 2 (%4) | |
| Breast cancer stage (n, %) | | | |
| Stage 1 | 7 (%20.6) | 11 (%22) | |
| Stage 2 | 17 (%50) | 20 (%40) | |
| Stage 3 | 10 (%29.4) | 17 (%34) | 0.07 |
| Stage 4 | 0 | 2 (%4) | |
| Breast cancer surgery (n, %) | | | |
| MRM | 30 (%88.3) | 44 (%88) | 1.00 |
| BCS+ALND | 4 (%11.7) | 6 (%12) | |
| Postoperative CT (n, %) | 29 (%85.3) | 35 (%70) | 0.11 |
| Postoperative RT (n, %) | 27 (%79.4) | 20 (%40) | 0.000* |
| Postoperative HT (n, %) | 23 (%67.6) | 28 (%56) | 0.29 |

COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; BMI: body mass index; MRM: modified radical mastectomy; BCS+ALND: breast conserving surgery+ axillary lymph node dissection; CT: chemotherapy; RT: radiotherapy; HT: hormonotherapy

*statistically significant

Table 2. Correlation analysis between the presence of lymphedema and relevant factors

| | r (Spearman correlation coefficient) | p |
|---|---|---|
| Age | 0.27 | 0.015* |
| Education duration | 0.25 | 0.04* |
| Body mass index | 0.32 | 0.003* |
| Tumor size | 0.27 | 0.04* |
| Number of excised LNs | 0.14 | 0.37 |
| Number of positive LNs | 0.37 | 0.009* |
| Postoperative CT | 0.18 | 0.11 |
| Postoperative RT | 0.40 | 0.000* |

LN: lymph node; CT: chemotherapy; RT: radiotherapy

*statistically significant

Table 3. Logistic regression analysis results on factors related to the presence of lymphedema

| | OR (%95 CI) | p |
|---|---|---|
| Age | 1.05 (0.98-1.14) | 0.15 |
| Education duration | 0.92 (0.74-1.14) | 0.47 |
| Body mass index | 1.14 (0.97-1.33) | 0.09 |
| Tumor size | 1 | 0.68 |
| Number of positive LN | 1.21 (0.99-1.48) | 0.06 |
| Postoperative RT | 7.09 (1.03-48.94) | 0.04* |

LN: lymph node; RT: radiotherapy; OR: Odds ratio; CI: confidence interval

*statistically significant

treatment as compared to the pre-treatment values ($p<0.05$). Pre- and post-treatment evaluations of upper limb volumes are presented in Table 4.

## Discussion and Conclusions

The survival rate in breast cancer is increasing with advances in treatment. However, the morbidity rate is also increasing with the more aggressive treatment approaches (13). Upper extremity lymphedema is one of the most important morbidities developing after breast cancer treatment. In the long term, it poses serious physical and psychological consequences for the patients (11, 14, 15). Lymphedema is a chronic, progressive disease. As there is no cure; its prevention, early diagnosis and treatment are significant (10). We retrospectively evaluated the demographic and clinical characteristics as well as clinical differences between those with and without lymphedema, and response to treatment among breast cancer patients who were evaluated at our lymphedema outpatient clinic, which was established for this particular reason.

The vast majority of patients with and without lymphedema had undergone unilateral breast surgery (92.3% and 94.1%, respectively). In both groups, the most common tumor type was invasive ductal carcinoma (94.1% in those with lymphedema and 96.2% in those without). The rate of patients with modified radical mastectomy was 84.6% in the group of patients with lymphedema, while it was 85.3% in patients without lymphedema. The remaining patients in both groups had undergone breast conserving surgery and axillary lymph node dissection. Patients with and without lymphedema were similar in terms of demographic and clinical characteristics.

Table 4. The differences in pre- and post-treatment arm volumes and volume differences between the two arms in patients with lymphedema (mean value ± standard deviation)

| | Pre-treatment | Post-treatment | p |
|---|---|---|---|
| Arm volume with lymphedema (mL) | 184.9±44.3 | 163.9±41.8 | 0.001* |
| Volume difference between two arms (%) | 32.4±22.5 | 20.2±18.6 | 0.000* |

*statistically significant

In the literature, the development of breast cancer related lymphedema was associated with advanced age, lower educational level, tumor size (tumor stage), the number of removed lymph nodes, the number of positive lymph nodes, and recurrent episodes of cellulitis (1, 5, 6, 8, 9). The mean age of patients and the number of positive lymph nodes in patients with lymphedema was significantly higher in our study as compared to those without lymphedema. Educational level was significantly lower in patients with lymphedema. The most common tumor stage was stage 2 in both groups, and there was no significant difference between the two groups in terms of tumor stage or the number of lymph nodes removed. There were no history or physical findings of cellulitis in both groups. Compatible with the literature; older age, lower education level, advanced tumor stage and the number of positive lymph nodes were associated with the development of lymphedema. The logistic regression analysis revealed that none of these factors was independent risk factors. This result was attributed to the limited number of patients in our study.

Currently, the correlation between body mass index and lymphedema is well defined (16, 17). A high body mass index leads to chronic venous insufficiency and impair lymphatic return, thereby result in lymphedema (16). A body mass index above 30 kg/m² increases the risk of lymphedema (18). In our study, the mean body mass index of patients with lymphedema was above 30 kg/m² and was significantly higher than those without lymphedema. In accordance with the literature, a positive correlation was identified between the development of lymphedema and body mass index. However, it was not identified as an independent risk factor on logistic regression analysis. The limited number of patients, as mentioned earlier, may have led to such a result.

Breast cancer related upper extremity lymphedema is associated with breast cancer treatment (5, 8). In the literature, the prevalence of lymphedema following axillary lymphadenectomy and axillary radiotherapy is reported as approximately 30%, although varying between 24% and 49%. The difference in rates are related to the extent of axillary surgery and radiotherapy, different assessment methods, lack of standardization in diagnostic criteria, and differences in postoperative follow-up periods (6, 7, 19). In our study, 40.5% of patients who presented to our clinic with breast cancer were found to have upper extremity lymphedema. This rate in our study is consistent with the literature (6, 7).

Although there is a lifetime risk of developing breast cancer related lymphedema, approximately 80% of the cases occur within the first 3 years after treatment (5, 8, 19). In our study, lymphedema was detected at a mean of 5 years after breast surgery. This difference was thought to result from being overlooked by clinicians, lack of awareness among patients and limited number of lymphedema treatment centers in our country that lead to delays in both diagnosis and treatment of such patients.

Axillary radiotherapy may cause fibrosis in the lymph vessels and lymph nodes, disrupt lymphatic flow, and may trigger lymphedema (6). Similarly, postoperative chemotherapy may increase extracellular fluid volume with chronic inflammation, increase lymphatic load and result in lymphedema (20, 21). In our study, the rate of patients receiving postoperative radiotherapy was significantly higher in patients with lymphedema than those without. The rate of receiving chemotherapy was also higher in patients with lymphedema, but the difference was not statistically significant. Both postoperative radiotherapy and chemotherapy were associated with lymphedema, but only postoperative radiotherapy was determined as an independent risk factor in logistic regression analysis.

Complete decongestive therapy is the most accepted and widely used method in lymphedema treatment (22, 23). The most important component of CDT phase 1 treatment is short-stretch compression bandaging. Several studies showed that efficient and effective results could be obtained in mild and moderate lymphedema without MLD component (22, 24, 25). In our study, 14 patients were treated with phase 1 components including education, skin care, exercise, and daily multi-layer short-stretch compression bandaging. After an average of 4.5 weeks of treatment, the differences between the two upper-extremity circumferences and volumes significantly declined as compared to pre-treatment values. In their study on 35 patients with breast cancer related lymphedema, Johansson et al. (25) applied compression bandage and manual lymphatic drainage in 17, while applying compression bandaging alone in 18 patients for 3 weeks. At the end of treatment, a 26% volume reduction was achieved in patients with compression bandaging alone. They determined that there was a slightly increase in volume decrease with the addition of MLD to treatment, and stated that the maximum volume reduction in CBT treatment was achieved by the application of compression bandaging alone (25). In our study, the patient's upper limb volumes were decreased by 18.6% at the end of treatment. The low reduction rate in our study as compared to Johansson et al. (25) was attributed to the small number of patients and differences in patient assessment methods. Andersen et al. (22) used Class 2 compression garments, education, skin care and exercise without MLD and compression bandaging in 21 patients with breast cancer-related unilateral lymphedema, while they applied additional MLD to the other 21 patients. The limb volumes significantly decreased in both groups at the end of treatment; nevertheless, they emphasized that the addition of MLD did not have a significant contribution to volume reduction (22). We have also achieved a significant decline in our patients by compression therapy alone, without MLD component.

Patients treated for breast cancer have a life-long risk for lymphedema. Advanced age, lower education level, obesity, tumor size, number of positive lymph nodes and postoperative radiotherapy were detected as factors associated with lymphedema. Postoperative radiotherapy was identified as an independent risk factor for the development of lymphedema. Acceptable results are obtained in lymphedema treatment with patient education, skin care, exercise and compression therapy.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

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

**Peer-review:** Externally peer-reviewed.

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