Original Article

Eur J Breast Health 2022; 18(2): 148-154
DOI: 10.4274/ejbh.galenos.2022.2021-9-2

The Comparative Frequency of Breast Cancer-Related Lymphedema Determined by Bioimpedance Spectroscopy and Circumferential Measurements

Pınar Borman[1], Ayşegül Yaman[2], Lütfi Doğan[3], Ayşe Arıkan Dönmez[4], Esra Gizem Koyuncu[5], Ayşegül Balcan[5], Sercan Aksoy[6], Cihangir Özaslan[3], Rabiye Akın[4], Kaniye Üneş[5]

[1]Department of Physical Medicine and Rehabilitation, Ankara City Hospital, University of Health Sciences Turkey, Ankara, Turkey
[2]Department of Physical Medicine and Rehabilitation, Gülhane Training and Research Hospital, University of Health Sciences Turkey, Ankara Turkey
[3]Department of Surgical Oncology, Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, University of Health Sciences Turkey, Ankara, Turkey
[4]Hacettepe University Faculty of Nursing, Ankara, Turkey
[5]Department of Physical Medicine and Rehabilitation, Hacettepe University Faculty of Medicine, Ankara, Turkey
[6]Department of Medical Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: The survival of patients with breast cancer has prolonged due to early diagnosis and modern methods of treatment and lymphedema has become the most important morbidity secondary to the treatment of the disease. Early detection and timely intervention have potential to reduce advanced breast cancer-related lymphedema. The aims of this study were to comparatively determine the frequency of subclinical/clinical lymphedema by using prospective monitoring with bioimpedance spectroscopy (BIS) and circumferential measurements in a group of patients who underwent breast cancer surgery.

Materials and Methods: Patients having breast cancer surgery were recruited between October 2018 and December 2019. Demographical and surgical properties were recorded. Extremity volumes by circumferential and BIS measurements were performed after surgery (baseline) and monitorizations were carried out at third and sixth months, in order to determine the frequency of subclinical/clinical lymphedema. L-Dex value of >6.5 was recently taken attention as subclinical lymphedema and values >7 were considered as clinical lymphedema. The presence of subclinical and clinic lymphedema was assessed by inter-limb volume difference (>5% and >10 respectively) based on the serial circumferential measurements in both affected and non-affected extremities. The functional status and quality of Life (QoL) were determined by quick-DASH and LYMQOL-Arm questionnaires respectively. The relationship between volume measurements, functional status and QoL scores were determined.

Results: Eighty-two female patients with a mean age of 49.6 years were included to the study. 30 (36.5%) and 21 (25.6%) of patients were determined as having subclinical/clinical lymphedema by BIS, while 18 (21.9%) and 19 (23.1%) of patients had subclinical/clinical lymphedema by circumferential-measurements at third-and-sixth months respectively. The functional and QoL scores were not correlated with circumferential volume measurements and BIS scores. There was a moderate-high correlation with BIS and circumferential measurements.

Conclusion: In conclusion 36.5% and 25.6% of our study group had subclinical and clinical lymphedema by BIS respectively during the 6 months surveillance period. Periodic monitoring of women with BIS allows early detection for lymphedema in more patients than in circumferential volume measurements, which may have implications for timely and necessary management.

Keywords: Bioempedance spectroscopy; breast cancer; circumferential volume measurement; lymphedema; quality-of-life; Turkish

Cite this article as: Borman P, Yaman A, Doğan L, Arıkan Dönmez A, Koyuncu EG, Balcan A, Aksoy S, Özaslan C, Akın R, Üneş K. The Comparative Frequency of Breast Cancer-Related Lymphedema Determined by Bioimpedance Spectroscopy and Circumferential Measurements. Eur J Breast Health 2022; 18(2): 148-154

Key Points

- Early detection of breast cancer-related lymphedema (BCRL) can prevent progression to its chronic stage eliminating morbidity and the need for more intensive costly treatments, and helps to reach the most successful outcomes in reducing the burden of disease.
- Herein we reported that periodic monitoring with the use of bioimpedance spectroscopy (BIS) allowed us to identify more patients with subclinical and/or clinical BCRL, compared to evaluation with circumferential volume measurements during the 6-month period.
- We suggest the implementation of BIS assessments into routine breast cancer follow-up programs in order to prevent and manage the potentially devastating effects of chronic BCRL, in patients with breast cancer surgery.

Corresponding Author:
Pınar Borman; pinarborman@gmail.com

Received: 09.09.2021
Accepted: 05.02.2022
Available Online Date: 01.04.2022

Introduction

Breast cancer is the most common cancer amongst women worldwide, with approximately two million cases each year. The incidence of breast cancer has been increased in recent decades, both in developed and developing countries (1). A report from Turkey reported that the incidence of breast cancer increased more than twice from 24/100,000 in 1993 to 50/100,000 in 2017 (2). In the same study the 5-year survival rate was found to be 86%. With improved surgical procedures and enhanced effectiveness of breast cancer treatment, the number of breast cancer survivors has increased dramatically and a significant number of women are dealing with the potential complications of treatment, including breast cancer-related lymphedema (BCRL) (1-3).

BCRL is a chronic, progressive condition characterized by accumulation of protein-rich fluid in the interstitial spaces due to disruption of the local lymphatic system after treatment with breast cancer surgery and/or radiation (3, 4). As lymphedema is under-recognized and under-documented, it is likely that the currently accepted rates of incidence and prevalence underestimate its magnitude (5, 6). Estimates of the risk of lymphedema after breast cancer treatment vary widely from 15%–94%, depending on differences in the extent and modality of therapies, discrepancies in diagnostic methods and duration of follow-up (4, 6, 7). Approximately 90% of the expected BCRL cases occur during the first 24 months after treatment (4, 8). Early or subclinical lymphedema can be objectively detected and serially assessed with appropriate surveillance methods but currently there is no consensus on the optimal screening regimen (8-11). Although a widely accepted methodological approach to the early diagnosis and/or surveillance of BCRL is lacking, bio-impedance spectroscopy (BIS) is perhaps the most commonly used approach for widespread clinical surveillance (8-14). Screening all patients for the development of BCRL has proven difficult, secondary to logistical and cost-related issues. Therefore, it may be useful to identify which patients are at highest risk of developing BCRL so that they can be targeted and enrolled in prospective surveillance programs. This would facilitate simple preemptive intervention, thereby reducing the development of irreversible, chronic BCRL (15-18).

Several studies and current guidelines have reported early detection and treatment of BCRL can prevent progression to its chronic stage, eliminating morbidity and the need for more intensive costly treatments (10, 17-19). Although there are numerous studies supporting the value of prospective surveillance with BIS compared to other methods, prospective studies with Turkish breast cancer patients are lacking (5, 20). Additional data about the frequency of lymphedema in this specific population may be useful to further validate the use of appropriate methods in BCRL screening programs.

The purpose of this study was to report the results of a 6-month surveillance program in order to determine the comparative frequency of subclinical and clinical BCRL, identified by BIS and circumferential volume measurements in a group of breast cancer patients.

Materials and Methods

Study Sample

Female patients who underwent breast cancer surgery in two different oncology centers (Hacettepe University Oncology Hospital and Abdurrahman Oncology Hospital), were enrolled to the study between October 2018 to December 2019. This prospective and descriptive study was approved by the local ethics committee and written informed consent was obtained from all participants. The study met the requirements of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Hacettepe University (G0: 17/645).

Eligibility

The inclusion criteria were as follows: 1) aged between 18–65 years; and 2) having unilateral breast cancer surgery (breast conservation or mastectomy) with axillary lymph node dissection (ALND). Patients were excluded if they met the following criteria: 1) patients with history of contralateral breast cancer surgery; 2) previously documented diagnosis of BCRL; 3) having metal implants and/or pacemakers; 4) Patients having locoregional or distant metastases; 5) patients having musculoskeletal or venous disorders on the affected arm which may simulate or mask symptoms of lymphedema; 6) patients having renal and/or heart failure; 7) pregnancy; 8) immobile patients; and 9) patients with cognitive or neurological disorders. Chemotherapy and radiation therapy were allowed during the study.

Demographic and Clinical Data

Demographic and clinical properties including age, gender, Body Mass Index (BMI), marital status, and occupation were recorded. BMI was classified as normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) (21). Surgical characteristics, including type of breast surgery, either breast conserving therapy (BCT) or mastectomy, axillary surgery type including sentinel lymph node biopsy (SLNB) or ALND and stage of cancer [tumor, node, metastasis (TNM) staging 0–4] (22), and number of removed lymph nodes was collected from medical records. In addition therapeutic information was also collected including adjuvant chemotherapy, radiation therapy (axillary, breast/chest wall) and hormonal therapy.

Volume Measurements

Limb volume was measured using circumferential and BIS measurements (23-26). The baseline circumferential and BIS measurements were taken 3–6 weeks after the final breast cancer surgery in order to avoid misclassifying transient, post-operative swelling as BCRL. Then all patients underwent postoperative follow-up measurements at regular intervals of three months, during a 6-month period.

Circumferential Volume Measurements

For circumferential measurements, subjects sat straight on a chair with their arms relaxed by their sides and elbows straight. Both arms were measured at each test date. Circumferential measurements were performed using a standard 1-inch retractable tape, starting at the level of ulnar styloid, at 4 cm intervals along the arms and converted to an approximate arm volume to enable estimation of volume. Calculation of the limb segment volumes (millilitres-cm^3) was undertaken using a simplified truncated cone formula. Excess limb volume comparing affected and unaffected limbs and difference in excess volume (excess limb volume was expressed as a percentage of the unaffected limb volume, indicating how much larger the affected limb was compared to the unaffected limb) were calculated (23-25). The presence of subclinical and clinic lymphedema was assessed by inter-limb volume difference (>5% and >10% respectively) based on the serial circumferential measurements in both affected and non-affected extremities (25). Every patient was assessed by the same researcher.

BIS Measurements

BIS measurement was performed using an L-Dex U 400 device (Impedimed, Australia) and analyzed as previously described (26-28). Measurements were taken with patients in the supine position on a non-metallic surface, with their arms relaxed with palms facing down on a cushion. Electrodes were placed on each hand at the dorsal surface of the wrist between the process of the radial and the ulnar bones and on the dorsal surface of the hand, 1 cm proximal from the peak of the knuckle of the middle finger. A foot electrode was placed midway between the lateral and medial malleol processes on the ankle in the front of the foot (28). Two trained researchers performed all measurements.

The L-Dex ratio is the recommended metric when using BIS (13, 28, 29). The ratio of impedance at RO in the affected versus intact limb, adjusted for gender, upper limb and right left dominance, is expressed as the L-Dex ratio. An L-Dex ratio of -10 to +10 was considered normal. But L-Dex value of ≥6.5 was recently reported to indicate subclinical lymphedema and values ≥7 were considered to indicate clinical lymphedema (19).

Diagnosis of Lymphedema

Diagnosis of subclinical or clinical lymphedema is dependent on history, physical examination (3, 29, 30) and objective arm volume changes, which were assessed by arm circumferential measurements (23) and BIS given as an L-Dex value (19, 26).

Functional Status

Functional disability of the affected extremity was evaluated by the Turkish version of quick Disability of Arm, Shoulder and Hand questionnaire (Q-DASH). Q-DASH is a self-reported questionnaire evaluating symptoms and functional tasks associated with limitations of the arm, shoulder and hand. The validated Turkish version of Q-DASH contains 11 items and results in a score ranging from 0–100 with higher scores indicating more functional disability (31).

Quality of Life Assessment

Quality of Life (QoL) was assessed by the Turkish version of the Lymphedema Quality of Life Questionnaire-Arm (LYMQOL-Arm) (32). The LYMQOL-Arm was developed by Keeley et al. (33) to assess the impact of lymphedema of the arms on the QoL of the patients. It consists of four domains with 28 items. These domains are function, appearance, symptoms, and mood. The answers were evaluated on a four-point Likert scale (1 = not at all 2 = a little, 3 = quite a bit, 4 = a lot). Each item received a score between 1 and 4, with higher scores indicating a worse QoL. There is also an overall QoL rating. The 'overall QoL' item was scored 0–10. QoL and functional status assessments were performed by the same researcher.

At the first presentation of subclinical lymphedema, patients were provided with preventive methods. Preventive strategies included meticulous skin care, exercises and self-decongestive massage. In addition, they were prescribed over-the-counter compression garments. Patients with clinical lymphedema were referred to the lymphedema unit for complex decongestive therapy (CDT).

Statistical Analysis

Descriptive statistics were used to examine the frequency distributions and calculate the scores of scales and subscales, and defined using either mean ± standard deviation (SD), median and range or percentage values. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Student's t-test or Mann-Whitney U test were used as appropriate to compare differences in quantitative variables at different time points. The relationship between volume changes and QoL scores, functional status, as well as with clinical variables, was assessed using Pearson's correlation for parametric data and with Spearman's rho (correlation) for nonparametric data. All tests of statistical significance were two sided and considered statistically significant at $p<0.05$. Analyses were conducted using SPSS, version 21.0 (IBM Inc., Armonk, NY, USA).

Results

Between October 2018 and December 2019, a total of 134 females were screened among the patients who had breast cancer surgery. Of these 27 patients were excluded because of study eligibility criteria and seven patients did not agree to take part in the study. Therefore, the final study cohort size was 100 patients. Due to the unexpected coronavirus disease-2019 (COVID-19) pandemic, the sixth month follow-up measurements of 18 patients could not be performed and thus the data of 82 patients were reported.

The demographic and clinical characteristics of the patients are shown in Table 1. The mean age of the cohort was 49.6±10.42 years old (range: 27–65), and mean of BMI was 27.11 kg/m². A majority of participants were married, overweight/obese, and mostly housewives.

Concerning breast cancer treatment, the most common type of surgery was mastectomy followed by BCT. The majority of the patients had infiltrative ductal carcinoma. The median number of lymph nodes excised was 10 (min: 2–max: 28). The mean (median) time to measurement from surgery was 38 (29) days for all patients. Most of patients received chemotherapy and/or radiation therapy.

The difference in volumes and excess volumes, and L-Dex ratio, which were evaluated at baseline, three and six month follow-up are shown in Table 2. There were significant volume changes determined by circumferential measurements at all time points. Using circumferential measurements, 12 (14.6%) and 10 (12.2%) patients were diagnosed as subclinical lymphedema at the third and sixth month follow-ups, respectively. In regard to clinical lymphedema, 6 (7.3%) and 9 (10.9%) patients were identified at the third and sixth month follow-up respectively. The mean baseline L-Dex score was 2.15±7.69 (range: -14 to 17). Overall, 51 patients (62%) had an abnormal L-Dex score at some point during surveillance. Statistically significant changes during monitoring were observed in L-Dex ratios ($p<0.05$). Using L-Dex measurement, 19 (23.1%) and 7 (8.53%) subclinical lymphadema was diagnosed in the third and sixth-month follow-up respectively. In contrast, lymphedema based on an L-DEX ratio >10 was found in 11 (13.4%) and 14 (17.1%) patients at the third and sixth month follow-ups respectively. There was a moderate to high correlation between BIS and excess volume by circumferential measurements at both the third and sixth months ($r = 0.342^*$, $p = 0.011$, $r = 0.464^{**}$, $p<0.001$, respectively).

Functional status indicated by Q-DASH scores and the QoL scores are shown in Table 3. The mean values of Q-DASH scores tended to increase during follow-up but did not reach significance at any time point. No significant change in the mean scores of LYMQoL-subgroups was observed at the third and sixth month follow up. There was no correlation between volume measures by either by L-DEX or circumferential measurement and functional and QoL scores at the sixth month follow-up.

Table 1. The demographic and clinical variables of the patients

	(n = 82)
Age (years) mean (±SD)	49.60 (±10.42)
BMI (kg/m²) mean (±SD)	27.11 (±4.78)
Normal, n (%)	30 (36.6%)
Over-weight, n (%)	31 (37.8%)
Obese, n (%)	21 (25.6%)
Education	
Illiterate	1 (1.2%)
Primary school	31 (37.8%)
High school	23 (28%)
University	27 (32.9%)
Marital status	
Married	66 (80.5%)
Single	12 (14.6%)
Widow	4 (4.9%)
Occupation	
Housewife	38 (46.3%)
Officer	27 (32.9%)
Worker	4 (4.9%)
Retired	7 (8.5%)
Other	6 (7.3%)
Type of surgery	
BCT	30 (36.6%)
Mastectomy	52 (63.4%)
Axillary surgery	82 (100%)
SLNB	29
ALND	82
Breast cancer stage	
1	9 (11%)
2	49 (59.7%)
3	22 (26.8%)
4	2 (2.4%)
Histopathologic diagnosis	
Infiltrative ductal	58 (70.7%)
Infiltrative lobular	11 (13.4%)
Infiltrative mix type	3 (3.7%)
Others	10 (12.2%)
Adjunctive therapies	
Chemotherapy	60 (73.2%)
Radiation therapy	43 (52.4%)
Axillary	38 (46.3%)
Breast/chest wall	19 (23.2%)
Hormonal therapy	5 (6.1%)
None	10 (12.2%)
#excised lymph nodes	9.74 (± 6.87)

BMI: Body mass index; BCT: breast conserving therapy; SLNB: Sentinal lypmh node biopsy; ALND: Axillary lymph node dissection; SD: standard deviation; n: number

There was a positive correlation between the mean L-DEX ratio and excised lymph node number (r = 0.424, p = 0.001) and BMI (r = 0.324, p = 0.017).

The differences in clinical variables, excess volume and L-DEX ratio changes between patients with and without lymphedema are shown in Table 4. In regard to surgical factors, only the mean number of excised lymph nodes was significantly different in patients with and without lymphedema, indicating the impact of axillary node dissection on development of subclinical lymphedema. L-DEX ratio change and excess volume change during the six-month were different between the groups according to the presence of lymphedema, but did not reach significance.

The patients with a diagnosis of subclinical lymphedema were prescribed pressure garments and educated about self-management techniques, while the patients who were diagnosed with clinical lymphedema required CDT.

Discussion and Conclusion

The findings of this study demonstrated that prospective surveillance using BIS can detect subclinical and/or clinical BCRL more sensitively than circumferential volume measurements at the sixth month follow up. BIS identified 36.5% and 25.6% of patients with subclinical/clinical lymphedema at the third and sixth month of follow up, respectively, while 21.9% and 23.1% of patients had subclinical/clinical lymphedema by circumferential measurements at third and sixth months, respectively. However, there was a moderate to high correlation between BIS and circumferential measurements at 3 and 6-month follow-up. Furthermore, this study showed that the number of dissected lymph nodes was significantly associated with the development of lymphedema.

The number of breast cancer survivors is increasing globally and the likelihood of BCRL development as a consequence of breast cancer treatments is of worldwide significance (34). BCRL is a chronic, potentially devastating condition that may require long-term management and is associated with a risk of functional disability and psychosocial impact which may compromise the overall QoL. The optimal management of BCRL is based on early detection and timely intervention in order to prevent chronic and possibly irreversible complications and to reach most successful outcomes in reducing the burden of disease (3, 4, 10). During the earlier subclinical phase, the edema can easily be treated by education, self-massage and compression garments. However, when fibrosis is established more costly treatments, like manual lymphatic drainage multilayer bandaging, and pumps are needed and the lymphedema may not be reversible at advanced stages (10, 17). Current data support a surveillance approach and close monitoring of patients for the early diagnosis and treatment of BCRL in patients with breast cancer (4, 18, 35).

There is no gold standard for measuring sub-clinical lymphedema and it is difficult to know which measure is best for early detection. Current objective measures of BCRL include circumferential tape measurements, water displacement, BIS and perometry, which incorporate differences between limbs or from baseline (3, 7, 30). BIS is considered a reliable and sensitive measurement method which can predict the onset of lymphedema up to 10 months prior to clinically evident lymphedema and has been recommended to define subclinical lymphedema in previous studies (17-19, 26-28, 34). Early studies documented a conservative normal range between L-Dex scores >10

Table 2. The mean volume, excess volume and L-Dex ratio parameters of the patients at baseline and follow-ups

	Baseline	3 months	6 months	*p*-value
Volumes (cm^3) mean (± SD)	1960 (±426.5)	2075 (±463.9)	2086 (±462)	**<0.001**
Excess volume (%) mean (± SD)	4.05±2.47	7.73±5.54	8.62±6.19	**<0.001**
L-Dex ratio	2.15±7.69	7.11±13.99	10.71±14.02	**<0.001**

SD: standard deviation

Table 3. The functional and QoL scores in regard to follow-up periods

LYMQoL Scores	Baseline	3 months	6 months	*p*-value
Function	1.77±0.75	1.54±0.27	1.62±0.17	0.880
Appearance	1.54±0.74	1.20±0.33	1.26±0.28	0.881
Symptom	1.93±0.66	1.94±0.60	1.79±0.31	0.886
Mood	1.95±0.74	1.94±0.58	1.89±0.37	0.853
Overall	6.42±1.35	7.11±3.26	7.28±1.25	0.900
Q-DASH Score (mean ± SD)	38.54±20.88	37.29±19.06	39.81±13.42	0.104

p<0.001; Q-DASH: Quick Disability of Arm, Shoulder and Hand questionnaire; LYMQoL: Lymphedema Quality of life; SD: standard deviation

Table 4. The distribution of risk factors in regard to the presence of lymphedema

	Lymphedema (+)	Lymphedema (-)	*p*-value
Age (years)	48.56±10.55	47.39±9.2	0.686
BMI (kg/m^2)	26.82±4.57	24.50±5.22	0.092
Excised lymph node number (median)	14	8	**0.034***
Radiation therapy	50.1%	56.7%	0.875
L-Dex change (0^{th}–6^{th} month) (%)	13.82±15.44	5.07± 9.6	0.059
Excess volume change (0^{th}–6^{th} month) (%)	7.78 ±5.74	4.03± 3.28	0.062

Significant values are shown in bold.
*p<0.05; BMI: Body Mass Index

but more recently L-Dex score of >7 was considered as an indicator of subclinical lymphedema. (6, 8, 17, 19). Growing data support changing the cut-off point from >10 to >7 and thus improving the sensitivity for detecting subclinical BCRL (11, 18, 34), but few studies have used this cut-off point (19). Our study indicated a difference between comparative frequencies of subclinical/clinical lymphedema by BIS and circumferential volume measurements, supporting the use of this relatively new cut-off point.

Several studies have compared the estimated prevalence of lymphedema using different tools and diagnostic criteria. Previous studies highlighted L-DEX measurements as being more sensitive than circumferential measurements and other, subjective tools (11, 12, 19). One study with 176 women reported the prevalence with circumferential measurements as 0.6% but 11.9% with BIS (36). Kaufman et al. (11) reported 9.8% of patients with subclinical BCRL by BIS, whereas Keeley (18) reported lymphedema rate as 45.6% at 24 months. On the other hand, Soran et al. (34) reported the incidence of subclinical lymphedema to be as 33.8% with monitoring by BIS and only 4.4% were progressed to clinical lymphedema. Ridner et al. (19) compared BIS and circumference tape measurements to detect the magnitude of reduction in the rate of chronic BCRL with structured surveillance and found 17% of patients with clinical lymphedema. From Istanbul, Erdogan Iyigun et al. (20) found 21% of BCRL cases detected by BIS in their cross-sectional study, while Ozaslan and Kuru (5) reported the frequency of lymphedema to be 28% in 245 breast cancer patients. According to our data, overall subclinical and clinical lymphedema rates were 36.5% and 25.6% respectively by BIS measurements, which was higher than in previous studies, probably due to the use of the recently described lower cut-off points. In contrast to early studies from Turkey, we monitored the patients during the sixth months after treatment as a surveillance program and included assessment of functional status and QoL within the follow-up measurements.

Lymphedema impairs QoL, decreases physical functioning and affects psychosocial well-being (3, 24). Few studies have examined the relationship between clinical, functional and QoL variables and objective lymphedema measurements (36, 37). Lee et al. (36) explored the potential impact of the severity of lymphedema, determined by

L-Dex, on function and overall QoL in their patient group who had moderate to severe lymphedema. Higher L-Dex was related to poorer function but was not related to overall QOL of their limb lymphedema participants (36). In our study we could not find a relationship between volume changes, by either method assessed, and QoL or functional scores, which may be due to the subclinical and/or newly diagnosed and short-term lymphedema.

Prophylactic intervention could help to prevent and reduce BCRL but it may not be feasible to offer this approach to all patients who undergo breast cancer surgery. Implementing early interventions to only those who need it seems to be more logical and cost-effective. The risk factors for BCRL have previously been identified by several studies and highlighted in recent guidelines (3, 7, 15, 18, 24). Axillary radiation therapy, and BMI were found to increase the incidence of lymphedema (5, 24). The recent study by Erdogan Iyigun et al. (20) evaluated preoperative risk factors and found patient BMI, number of nodes involved and capsular invasion to be associated with preoperative BCRL. According to our results, the number of dissected lymph nodes was the most important factor for the development of subclinical lymphedema. The association of L-DEX scores with risk factors for BCRL was also consistent with previous data (18, 20, 27). Understanding the related factors can be an important strategy to improve postoperative status for high-risk patients, in order to avoid the need to screen all patients, which would be more costly and less efficient. Neither the baseline to six month change in L-Dex nor in excess volume was statistically different between the patients with and without lymphedema, a finding which could be due to the small group size with heterogeneous distribution of the significant variables.

Our study was limited by small sample size and relatively short follow-up, which may limit the power to detect differences and excludes any ability to comment concerning long-term outcomes. Due to the pandemic conditions, we could not complete the follow-up to the end of one year, but the study is ongoing. We plan to follow the patients for at least two years for better long-term data. Another limitation of our study was the lack of preoperative L-Dex data, which may limit definitive conclusions. However, the prospective design and implementation of L-DEX in the first month at initial consultation, as well as regular follow-up during a substantial period, add value to our data. Besides, our findings may add information about the national prevalence of subclinical BCRL in terms of surveillance method, as the first prospective study with a six month follow-up in this country.

In conclusion, regular periodic monitoring using BIS technology allowed the identification of more patients with subclinical and/or clinical BCRL compared to evaluation with circumferential volume measurements during the six month follow up period. This is further evidence to support prospective monitoring for lymphedema in patients with breast cancer. We suggest the implementation of BIS assessment into routine breast cancer follow-up programs in order to prevent and manage the potentially devastating effects of chronic BCRL, in patients after breast cancer surgery.

Acknowledgements: We thank Hacettepe University Scientific Research Project Coordination Unit for the funding of the Bioimpedance device (BAP-Project #16391).

Ethics Committee Approval: The study met the requirements of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Hacettepe University (G0:17/645, date: 27.09.2017).

Informed Consent: This prospective and descriptive study was approved by the local ethics committee and written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: L.D., A.B., S.A., C.Ö.; Concept: P.B., E.G.K., C.Ö.; Design: P.B., S.A.; Data Collection and/or Processing: A.Y., A.A.D., E.G.K., S.A., R.A., K.Ü.; Analysis and/or Interpretation: A.Y., R.A.; Literature Search: A.Y., R.A.; Writing: P.B., A.A.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This research received a grant from Hacettepe University Scientific Research Project Coordination Unit (2017/16391).

References

1. Torgbenu E, Luckett T, Buhagiar MA, Chang S, Phillips JL. Prevalence and incidence of cancer related lymphedema in low and middle-income countries: a systematic review and meta-analysis. BMC Cancer 2020; 209: 604. (PMID: 32600278) [Crossref]
2. Özmen V, Özmen T, Doğru V. Breast Cancer in Turkey; An Analysis of 20.000 Patients with Breast Cancer. Eur J Breast Health 2019; 15: 141-146. (PMID: 31312788) [Crossref]
3. McLaughlin SA, Staley AC, Vicini F, Thiruchelvam P, Hutchison NA, Mendez J, et al. Considerations for Clinicians in the Diagnosis, Prevention, and Treatment of Breast Cancer-Related Lymphedema: Recommendations from a Multidisciplinary Expert ASBrS Panel : Part 1: Definitions, Assessments, Education, and Future Directions. Ann Surg Oncol 2017; 24: 2818-2826. (PMID: 28766232) [Crossref]
4. Rockson SG. Lymphedema after breast cancer treatment. N Engl J Med 2018; 379: 1937-1944. (PMID: 30428297) [Crossref]
5. Ozaslan C, Kuru B. Lymphedema after treatment of breast cancer. Am J Surg 2004; 187: 69-72. (PMID: 14706589) [Crossref]
6. Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. Diagnosis of upper quadrant lymphedema secondary to cancer: Clinical practice guideline from the oncology section of the American Therapy Association. Phys Ther 2017; 97: 729-745. (PMID: 28838217) [Crossref]
7. Dylke ES, Schembri GP, Bailey DL, Bailey E, Ward LC, Refshauge K, et al. Diagnosis of upper limb lymphedema development of an evidence-based approach. Acta Oncol 2016; 55: 1477-1483. (PMID: 27333213) [Crossref]
8. Bulley C, Gaal S, Coutts F, Blyth C, Jack W, Chetty U, et al. Comparison of breast-cancer-related lymphedema (upper limb swelling) prevalence estimated using objective and subjective criteria and relationship with quality of life. Biomed Res Int 2013; 2013: 807569. (PMID: 23853774) [Crossref]
9. Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, et al. Compasiron of multi-frequency bioimpedance with perometry for the early detection and intervention of lympheoedema after axillary node clearance for breast cancer. Breast Cancer Res Treat 2015; 151: 121-129. (PMID: 25850535) [Crossref]
10. Heller DR, Killelea BK, Sanft T. Prevention is key: Importance of early recognition and referral in combating breast cancer-related lymphedema. J Oncol Pract 2019; 15: 263-265. (PMID: 31075214) [Crossref]
11. Kaufman DI, Shah C, Vicini FA, Rizzi M. Utiliation of bioimpedance spectroscopy in the prevention of chronic breast cancer-related lymphedema. Breast Cancer Res Treat 2017; 166: 809-815. (PMID: 28831632) [Crossref]
12. Coroneos CJ, Wong FC, DeSynder SM, Shaitelman SF, Schaverian MV. Correlation of L-Dex Bioimpedance spectroscopy with limb volume and

lymphatic function in lymphedema. Lymphat Res Biol 2019; 17: 301-307. (PMID: 30388062) [Crossref]

13. Seward C, Skolny M, Brunelle C, Asdourian M, Salama L, Taghian AG. A comprehensive review of bioimpedance spectroscopy as a diagnostic tool for the detection and measurement of breast cancer-related lymphedema. J Surg Oncol 2016; 114: 537-542. (PMID: 27393376) [Crossref]
14. Soran A, Menekşe E, Girgis M, DeGore L, Johnson R. Breast cancer-related lymphedema after axillary lymph node dissection: does early posteoperative prediction model work? Support Care Cancer 2016; 24: 1413-1419. (PMID: 26349574) [Crossref]
15. Vicini F, Shah C, Whitworth P, Walker M, Shi J. Correlation of bioimpedance spectroscopy with risk factors for the development of breast cancer-related lymphedema. Lymphat Res Biol 2018; 16: 533-537. (PMID: 30133336) [Crossref]
16. Whitworth PW, Cooper A. Reducing chronic breast cancer-related lymphedema utilizing a program of prospective surveillance with bioimpednace spectroscopy. Breast J 2018; 24: 62-65. (PMID: 29063664) [Crossref]
17. Gebruers N, Verbelen H, De Vrieze T, Vos L, Devoogdt N, Fias L, et al. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphoedema: A best practice guideline. Eur J Obstet Gynecol Reprod Biol 2017; 216: 245-253. (PMID: 28811052) [Crossref]
18. Keeley V. The Early Detection of Breast Cancer Treatment-Related Lymphedema of the Arm. Lymphat Res Biol 2021; 19: 51-55. (PMID: 33270493) [Crossref]
19. Ridner SH, Dietrich MS, Spotanski K, Doersam JK, Cowher MS, Taback B, et al. A prospective study of L-Dex values in breast cancer patients pretreatment and through 12 months postoperatively. Lymphat Res Biol 2018; 16: 435-441. (PMID: 30130147) [Crossref]
20. Erdogan Iyigun Z, Selamoglu D, Alco G, Pilancı KN, Ordu C, Agacayak F, et al. Bioelectrical impedance for detecting and monitoring lymphedema in patients with breast cancer. Preliminary results of the flörence nightingale breast study group. Lymphat Res Biol 2015; 13: 40-45. (PMID: 25526543) [Crossref]
21. Purnell JQ. Definitions, Classification, and Epidemiology of Obesity. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al. editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. (PMID: 25905390) [Crossref]
22. Cserni G, Chmielik E, Cserni B, Tot T. The new TNM-based staging of breast cancer. Virchows Arch 2018; 472: 697-703. (PMID: 29380126) [Crossref]
23. De Vrieze T, Gebruers N, Tjalma WA, Nevelsteen I, Thomis S, De Groef A, et al. What is the best method to determine excessive arm volume in patients with breast cancer-related lyphoedema in clinical practice? Reliability, time efficiency and clinical feasibility of five different methods. Clin Rehabil 2019; 33: 1221-1232. (PMID: 30880473) [Crossref]
24. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology 2020; 53: 3-19. (PMID: 32521126) [Crossref]
25. Karges JR, Mark BE, Stikeleather SJ, Worrell TW. Concurrent validity of upper extremity volume estimation: Comparison of calculated volume derived from girth measurements and water displacement volume. Phys Ther 2003; 83: 134-145. (PMID: 12564949) [Crossref]
26. Laidley A, Anglin B. The Impact of L-Dex(®) Measurements in Assessing Breast Cancer-Related Lymphedema as Part of Routine Clinical Practice. Front Oncol 2016; 6: 192. (PMID: 27656420) [Crossref]
27. Vicini F, Shah C, Lyden M, Whitworth P. Bioelectrical impedance for detecting and monitoring patients for the development of upper limb lymphedema in the clinic. Clin Breast Cancer 2012; 12: 133-137. (PMID: 22444720) [Crossref]
28. Shah C, Vicini FA, Arthur D. Bioimpedance spectroscopy for breast cancer related lymphedema assessment: clinical practice guidelines. Breast J 2016; 22: 645-650. (PMID: 27487985) [Crossref]
29. Ward LC, Dylke E, Czerniec S, İsenring E, Kilbreath SL. Confirmation of the reference impedance ratios used for assessment of breast cancer-related lymphedema by bioelectrical impedance spectroscopy. Lymphat Res Biol 2011; 9: 47-51. (PMID: 21417767) [Crossref]
30. Greene AR, Goss JA. Diagnosis and staging of lymphedema. Semin Plast Surg 2018; 32: 12-16. (PMID: 29636648) [Crossref]
31. Koldas Dogan S, Ay S, Evcik D, Baser O. Adaptation of Turkish version of the questionnaire of the Quick disability of the arm, shoulder and hand (Quick DASH) in patients with carpal tunnel syndrome. Clin Rheumatol 2011; 30: 185-191. (PMID: 20411289) [Crossref]
32. Borman P, Yaman A, Denizli M, Karahan S, Özdemir O. The reliability and validity of Lymphedema Quality Of Life Questionnaire-Arm in Turkish patients with upper limb lymphedema related with breast cancer. Turk J Phys Med Rehabil 2018; 64: 205-212. (PMCID: PMC6657787) [Crossref]
33. Keeley V, Crooks S, Locke J, Veigas D, Riches K, Hilliam R. A quality of life measure for limb lymphoedema (LYMQOL). Journal of Lymphoedema 2010; 5: 26-37. [Crossref]
34. Soran A, Ozmen T, McGuire KP, Diego EJ, McAuliffe PF, Bonaventura M, et al. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection; a prospective observational study. Lymphat Res Biol 2014; 12: 289-294. (PMID: 25495384) [Crossref]
35. O'Toole J, Jammallo LS, Skolny MN, Miller CL, Elliott K, Specht MC, et al. Lymphedema following treatment for breast cancer: A new approach to an old problem. Crit Rev Oncol Hematol 2013; 88: 437-446. (PMID:23777977) [Crossref]
36. Lee TS, Morris CM, Czerniec SA, Mangion AJ. Does Lymphedema Severity Affect Quality of Life? Simple Question. Challenging Answers. Lymphat Res Biol 2018; 16: 85-91. (PMID: 28453410) [Crossref]
37. Lanza M, Bergmann A, Ferreira MG, de Aguiar SS, Dias Rde A, Abrahão Kde S, et al. Quality of Life and Volume Reduction in Women with Secondary Lymphoedema Related to Breast Cancer. Int J Breast Cancer 2015; 2015: 586827. (PMID: 26843988) [Crossref]