

Evaluation of response to treatment in breast cancer-related lymphedema

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ABSTRACT

Objectives: The primary objective of this study was to assess and compare the response to the breast cancer-related lymphedema (BCRL) treatment with Breast Cancer-Related Lymphedema of the Upper Extremity (CLUE) scores, bioimpedance spectroscopy (BIS), and the volume-assessments /measurements. The secondary objective of the study was to investigate whether CLUE played a role in the treatment response and to examine its correlation with the other measures of lymphedema.

Patients and methods: Between January 2019 and June 2019, a total of 40 patients (2 males, 38 females; mean age: 57.8±12.5 years; range, 45 to 70 years) who were diagnosed with unilateral Stage 2-3 BCRL and underwent treatment were included. The patients' upper extremity volumes were assessed and the patients were evaluated with the CLUE score, the Disabilities of the Arm, Shoulder, and Hand Outcome Measure (QuickDASH) score, BIS, and hand grip strength before and after the complete decongestive therapy.

Results: Correlation analyses revealed that CLUE total score and BIS values were correlated with the reduction in the volumes ($p=0.04$ and $p<0.001$, respectively). The CLUE total score was also found to be positively correlated with the BIS values ($p<0.001$). Hand grip strength and QuickDASH scores were not found to be correlated with the changes in the volume and CLUE total scores.

Conclusion: The development of a structured clinical assessment such as CLUE provides clinicians for a standardized evaluation for BCRL. The diagnosis of subclinical lymphedema can be detected earlier by using the BIS and CLUE scale and lymphedema comorbidity and treatment costs can be reduced.

Keywords: Lymphedema, physical therapy, rehabilitation.

Breast cancer is the most common type of cancer in women worldwide.^[1] Increased survival rates due to screening and early treatment result in functional impairments and disabilities after survival rather than death, with long-term complications of the disease and the treatment becoming more and more common.^[2,3]

Breast cancer-related lymphedema (BCRL) is one of the most common problems in the course of the treatment. Having an incidence of 5 to 42%, BCRL has devastating effects on the quality of life and the healthcare costs in patients with breast cancer.^[4] After the treatment for malignancy, the lymphatic system may have dysfunctions resulting in excess protein-rich fluid in the interstitial compartment, which is manifested as lymphedema.

There are many methods for the diagnosis of lymphedema, including circumferential measurements, water displacement method volumetry, perometry, bioimpedance spectroscopy (BIS), tonometry, lymphography, lymphoscintigraphy, ultrasonography, and magnetic resonance imaging.^[5] Although there is no consensus regarding the preference for the methods, volume-related methods (circumferential measurements, water displacement method volumetry, perometry) are usually preferred over other methods, while BIS has become more common for the earlier diagnosis for the BCRL.^[6,7]

Breast Cancer-Related Lymphedema of the Upper Extremity (CLUE) is a tool which was originally

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developed by Spinelli et al.^[8] to assess the presence and severity of the lymphedema in these patients having both objective and subjective measures. The CLUE scores have been shown to be a valid and reliable scale to assess BCRL.^[8]

While there are many therapeutic approaches in the management of BCRL, the gold-standard method is considered the complete decongestive therapy (CDT).^[9] The lack of a consensus is also valid for the measures of follow-up in the course of the therapy, with volume-related methods preferred more often, like the diagnostic measures.^[10] The use of BIS and CLUE scores also requires more evidence for justification of their utilization in evaluating the effectiveness of the therapy.^[8]

In the present study, the primary objective was to assess and compare the response to the BCRL treatment with CLUE scores, BIS, and assessments/measurements. The secondary objective of the study was to investigate whether CLUE played a role in the treatment response and to identify its correlation with the other measures of lymphedema.

PATIENTS AND METHODS

Study design and study population

This single-center, retrospective, cross-sectional study was conducted at Ege University Faculty of Medicine, Department of Physical Medicine and Rehabilitation between January 2019 and June 2019. Initially, a total of 62 patients who were diagnosed with BCRL and underwent treatment were screened. Inclusion criteria were being older than 18 years and the presence of unilateral Stage 2-3 lymphedema in the affected upper extremity after mastectomy for breast cancer. Exclusion criteria were the presence of bilateral lymphedema, primary bone tumors or bone metastasis, circulatory problems of the upper extremities (peripheral vascular disease, thrombosis, etc.), elephantiasis, local infections involving upper extremities or systemic infections, lymphangitis carcinomatosa, congestive heart failure, ongoing radiotherapy, having a history of prosthetic for the upper extremities, and the use of medications which can affect fluids or electrodes, such as diuretics. Finally, a total of 40 patients (2 males, 38 females; mean age: 57.8±12.5 years; range, 45 to 70 years) who met the inclusion criteria were recruited. A written informed consent was obtained from each patient. The study protocol was approved by the Ege University Medical Research Ethics Committee (date:

31.07.2019, no: 19-7T/53). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Outcome measures

After the medical histories of the patients were taken, a detailed physical examination by a physician was performed. Details of the cancer therapy history and physical examination findings were recorded. Diagnosis of lymphedema was confirmed by a physician specialized in this area.

Assessment of the upper extremity volumes: Bilateral upper extremity volumes were assessed using circumferential measures according to the frustum model, with measurements being taken at 5 cm intervals, starting from first to fifth levels of the metacarpal joints and ascending upwards.^[11] Clinically significant lymphedema was defined as the 10% difference between extremity volumes, and patients were followed on a weekly basis with the measurements, with the final assessment being after the therapy.^[10]

CLUE score: The patients were evaluated with CLUE score before and after the therapy. Consisting of four domains defined as obscuration of anatomical architecture (0-18 points), deviation from normal anatomical architecture (0-18 points), tissue score (0-18 points), edema score (0-18 points), this tool was designed by Spinelli et al.^[8] in 2019 to assess the presence and the severity of the upper extremity lymphedema in patients with BCRL in three areas: hands and fingers, wrists and forearms, from elbows to shoulders. This tool was applied to the patients by an expert specialist in lymphedema.

Functional assessment of the upper extremities: Upper extremity functions were assessed using the Disabilities of the Arm, Shoulder, and Hand Outcome Measure (QuickDASH). The QuickDASH includes 19 questions regarding the functional use of the affected upper extremities. Each question has a score of 0 to 5, with higher scores indicating a worse functional state. This scale was shown to be valid and reliable in assessing the functional use of the upper extremity by Yakut E, Düger et al.^[12]

BIS: Before and after the therapy, a lymphedema index was measured using a BIS device, LDex U400 (Impedimed, Brisbane, Australia). The LDex U400 is a system which assists physicians in the clinical evaluation of unilateral lymphedema of the extremity. It ensures clinicians with a vehicle to assess the early phases of lymphedema, before visible swelling

appears in many cases. LDex surveying is obtained by a low frequency electrical signal transferred from the U400 to the patient via skin surface electrodes. The surveying is unnoticeable from patients and is not affected by weight or muscle changes which may consist in patients with lymphedema or at risk of lymphedema. The LDex U400 is practical to use and provides a rapid and cost-effective tool for occupied hospitals. This device, which uses electricity below the patients' sensory threshold, can detect changes in the interstitial fluid and produce a lymphedema index score. Indices higher than 10 are considered pathological and indicate the presence of lymphedema. The LDex U400 is used primarily in Australia, the United States, many European countries, and Türkiye. The reliability and validity of the BIS methods were shown by Avila et al.^[13]

Hand grip strength: Hand grip strength was measured using a Jamar hand dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA). Measurements were obtained with patients standing up, with their arms in a neutral position, and their elbows positioned in a 90-degree angle. This measurement was performed three times consecutively, and the average values were recorded as kgf. Hand grip strength measurements by Jamar dynamometers were shown to be valid and reliable in a study performed by Shechtman et al.^[14]

Complete decongestive therapy: All patients were included in the CDT program. In routine practice, this program includes patient education, skin care, exercises, manual lymphatic drainage (self), and compression bandage therapy. After this intensive phase of the therapy, the maintenance phase, which includes the preservation of the gains through the use of compression garments and maintaining the exercises and manual lymphatic drainage, is initiated. In this study, only the intensive phase of the CDT was applied.

All patients were informed about skincare and protective approaches for lymphedema. They were asked to hydrate adequately and control their weight.^[15] A booklet containing the information mentioned above, along with exercises and frequently asked questions, was also provided to all patients. The required tasks were explained to them during each visit.

All patients were prescribed lymphedema-specific exercises involving muscle contractions on the upper extremity joints while taking CDT, 30 min each day. They were specifically informed that exercise did not aggravate the severity of their

lymphedema. A daily self-applied manual lymphatic drainage technique which helps the drainage of the lymphatic fluid through anatomical pathways was also instructed.^[16]

Multi-layer short-stretch bandages were applied to the patients by qualified physicians and nurses in lymphedema at hospital after self-manual lymphatic drainage. The intensive phase was given five days a week and short stretch bandages were applied for 23 h a day at 1-h intervals.^[17] To increase the local pressure on the areas required, foams were added. The patients were screened with arm circumferential measurements once a week, and after gaining a plateau in the volumes, they were prescribed compression garments.^[17] All of the patients completed the therapy without any adverse events.

Statistical analysis

The power analysis and sample size calculation were performed using the G*Power version 3.1.9.4 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) to ensure the adequate sample size. The sample size was calculated based on the CLUE total score parameter in the study of Spinelli et al.^[8] Accordingly, it was calculated as 40 participants, with a level of significance of 95%, a power of 80% (effect size=0.71). One-tailed hypothesis test was applied to calculate the sample size. Simple random sampling was preferred as the sampling method in our study.

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean \pm standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. To assess whether the data were compatible with normal distribution, the Shapiro-Wilk test was used. For dependent non-normally distributed variables, the Wilcoxon signed-rank test was used. The Spearman correlation test was performed to assess the correlation between variables. A *p* value of <0.05 was considered statistically significant.

RESULTS

A total of 40 patients were included in the final analyses. The mean body mass index of the patients was 30.99 ± 4.69 kg/m². A total of 95% of the patients were right-handed, and the prevalence of the right arm lymphedema was 50%. Demographic and clinical characteristics of the patients are presented in Table 1.

TABLE 1
Demographic and clinical characteristics of the patients

Variables	n	%	Mean±SD
Age (year)			57.8±12.5
Body mass index (kg/m ²)			30.99±4.69
Sex			
Male	2	5	
Female	38	95	
Marital status			
Married	34	85	
Widowed	6	15	
Single	0	0	
Educational status			
Illiterate	3	7.5	
Elementary or middle school	25	62.5	
High school	7	17.5	
University or higher	5	12.5	
Occupation			
Housewife	29	72.5	
Retired	7	17.5	
Office worker	2	5	
Other	2	5	
Dominant hand			
Right	38	95	
Left	2	5	
Limb with lymphedema			
Right	20	50	
Left	20	50	
Cancer type			
Ductal carcinoma	35	87.5	
Lobular carcinoma	5	12.5	
Cancer type			
Ductal carcinoma	35	87.5	
Lobular carcinoma	5	12.5	
Type of surgery			
TM+AD	25	62.5	
PM+AD	11	27.5	
Lobectomy	4	10	
Lymphangitis attack-Yes	5	12.5	
Chemotherapy-Yes	38	95	
Radiotherapy-Yes	35	87.5	
The number of chemotherapy sessions			8.75±5.05
The number of radiotherapy sessions			22.72±10.31
Postoperative duration (mo)			82.25±60.5
Postoperative weight gain (kg)			5.35±4.87
Lymphedema duration (mo)			61.27±59.24
The number of excised lymph nodes			15.65±6.85
The number of pathological lymph nodes			5.75±6.35

SD: Standard deviation; AD: Axillary dissection; TM: Total mastectomy; PM: Partial mastectomy.

Comparisons of the outcomes before and after CDT showed improvements in volumes (14.43% reduction), BIS values (46.25% reduction), and CLUE scores (31.77% reduction in total score), including

CLUE total, anatomic, edema, and tissue subscale scores in the extremities with lymphedema ($p<0.05$). Changes in hand grip strength (3.59% reduction) and QuickDASH scores (1.35% reduction) were not found

TABLE 2
Changes before and after the treatment

	%	Pre-treatment			Post-treatment			p
		Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
Volume measurement (extremity with lymphedema)	14.43	3840.5±820.3	3562	2750-6536	3285.95±560.11	3231	2492-4703	<0.001
BIS value	46.25	54.85±31.88	56.80	6.30-126	29.48±15.51	29.40	2.60-80.50	<0.001
Hand grip strength	3.59	18.34±5.64	18.50	5.90-30.90	17.68±5.47	18.20	5.10-27.90	0.177
QuickDASH score	1.35	39.03±18.67	59.09	4.54-93.10	38.5±17.86	47.70	4.54-86.30	0.572
CLUE								
Total score	31.77	37.45±17.36	40	8-65	25.6±14.5	25	0-62	<0.001
Anatomic score	33.79	20.95±11.79	21	0-36	13.87±7.91	13.50	0-36	<0.001
Tissue score	36.55	7.25±4.06	6	0-16	4.6±3.92	4	0-16	<0.001
Edema score	23.72	8.85±4.23	9	0-18	6.75±4.38	7.50	0-18	<0.001

#: Difference before and after the treatment in percentage; SD: Standard deviation; BIS: Bioimpedance spectroscopy; QuickDASH: Disabilities of the Arm, Shoulder, and Hand Outcome Measure; CLUE: Breast Cancer-Related Lymphedema of the Upper Extremity.

TABLE 3
Correlation of change in clinical parameters after treatment^[18]

	Volume measurement	BIS value	Handgrip strength	QuickDASH score	Clue total score	Clue anatomic score	Clue tissue score
BIS value	0.749**						
Handgrip strength	0.116	0.151					
QuickDASH score	0.202	0.264	0.143				
Clue total score	0.324*	0.508**	0.092	0.201			
Clue anatomic score	0.457**	0.483**	0.162	0.130	0.835**		
Clue tissue score	0.263	0.401*	0.052	0.139	0.693**	0.409**	
Clue edema score	0.159	0.312*	0.124	0.200	0.593**	0.383*	0.173

BIS: Bioimpedance spectroscopy; QuickDASH: Disabilities of the Arm, Shoulder, and Hand Outcome Measure; Spearman's correlation analysis, R correlation coefficient. 0.10-0.30: low correlation, 0.30-0.50: medium correlation, 0.50-1: high correlation. * p < 0.05; ** p < 0.01.

to be statistically significant before and after the therapy ($p > 0.05$) (Table 2).

Correlation analyses revealed that CLUE total score and BIS values were correlated with the reduction in the volumes ($p = 0.04$ and $p < 0.001$, respectively) (Figure 1). Moreover, the CLUE total

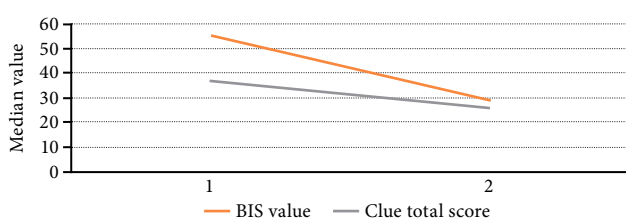


Figure 1. Change of bioimpedance spectroscopy value and clue total score.

score was also found to be positively correlated with the BIS values ($p < 0.001$). Hand grip strength and QuickDASH scores were not found to be correlated with the changes in the volume and CLUE total scores (Table 3).

DISCUSSION

In the present study, we assessed the response to the BCRL treatment with CLUE scores, BIS, and assessments/measurements. Our study results showed that CDT was an effective management method for patients with BCRL. Moreover, the improvements also accompanied changes in CLUE scores and BIS values, as evidenced by both comparative and correlation analyses. On the other hand, hand grip strengths and

QuickDASH scores did not show these changes.

Assessment of lymphedema with standardized measures is a critical issue for both clinical and academic purposes. Therefore, Spinelli et al.^[8] proposed a new method to assess BCRL of the upper extremity. Although this scoring system (CLUE) is based on a physical examination, the main difference is CLUE's being structured and having scores which require to be recorded for each area of the affected extremity, as well as the characteristic findings of lymphedema. Common clinical practice usually involves the recording of positive findings for BCRL, which is subjective for each observer in severity. In the current study, we compared this novel standardized tool for lymphedema with volumetric changes, BIS, hand grip strength, and disability related to the upper extremity (QuickDASH). Our other aim was to test CLUE's potential to be used in evaluating the treatment response. The only use of the CLUE in evaluating the treatment response was in a study conducted by Schmitz et al.^[19] which evaluated the effects of exercise or weight loss in patients with BCRL. All of the groups except for the controls were found to benefit from these interventions in their outcome measures without any differences in their interventions, including CLUE. Still, the study had a longer follow-up interval of 12 months, and the use of CLUE in a short-term, more intensive form of therapy along with BIS is a valuable contribution to the literature. In our study, there was a 31.77% reduction in CLUE scores using the CDT. Moreover, these changes were found to be correlated with the volume reductions and BIS values.

Volumetric measurements are used in follow-ups of BCRL extensively, both in clinical practice and scientific studies. Their utility for follow-ups was shown in a study evaluating the effects of CDT on quality of life, depression, neuropathic pain, and fatigue in patients with BCRL.^[20] Similarly, our study showed reductions in volumes (14.43%), which was found to be statistically significant.

The BIS values of the patients showed improvements after the therapy, which were found to be statistically significant. The value of BIS for treatment response has not been still clearly defined in the literature, making this study the first one to use BIS for this purpose. Stout Gergich et al.^[7] proposed BIS as a method to assess subclinical lymphedema. Shortly after its introduction to lymphedema assessment methods, BIS has been in use to assess subclinical lymphedema. Avila

et al.^[13] showed that BIS was a more sensitive indicator of lymphedema compared to volumetric methods. The major apprehension in detecting BCRL surveillance using BIS is the costs involved. However, while acknowledging the costs related to prospective BCRL surveillance, it is momentous to notice that costs related to chronic BCRL may include costs of managing chronic BCRL as well as higher rates of hospitalization compared to breast cancer patients who do not develop BCRL.^[21] Improvements in BIS scores and positive correlations between BIS and volumetric changes, as well as CLUE scores also indicate that BIS can help to assess treatment response and follow-up with BCRL patients. Therefore, studies have indicated the cost-effectiveness and significance of prospective BCRL surveillance.^[21] Stout et al.^[22] examined the expense of prospective surveillance compared to conventional care and found that the expense of early BCRL management was \$636 per patient annually, while late-stage BCRL was \$3,125, offering a significant cost-saving potential.

In the present study, although QuickDASH scores were found to be improved after the therapy, these changes were not found to be statistically significant. Gencay et al.^[23] used QuickDASH in their study evaluating the effects of kinesiophobia on BCRL patients, and they concluded that the presence of lymphedema and QuickDASH scores immediately after the therapy were significantly associated with the Tampa Scale for Kinesiophobia (TSK) scores. The CDT involves bandaging, immobilization, and problems related to these practices, such as pain and joint restrictions. Application of QuickDASH immediately after the therapy may have resulted in patients' being unable to realize the positive changes the volume reduction that may provide, and focus on the negative aspects of this therapy involving restriction of the affected extremity instead.

Hand grip strength is a commonly used measure of upper body skeletal muscle function in studies involving lymphedema. Johansson et al.^[24] used hand grip strength in a study for upper extremity lymphedema treatment. Similarly, O'Neill et al.^[20] showed that CDT improved hand grip strength in patients with upper extremity lymphedema. However, a recent study by Baklaci et al.^[17] showed that hand grip strengths might also decrease throughout the CDT, while not being statistically significant. Similarly, our study showed a 3.5% decrease in the hand grip strength, indicating statistically insignificance. As a result of the relative

immobilization as a part of the intervention, this finding underlines the importance of preserving strength in this group of patients through strengthening exercises. Although the patients were given remedial exercises, resistance exercises were not a part of the interventions in this intensive phase of the CDT. Since there is no data regarding this issue in the current literature, this may prove to be very important for clinical practice.

The most recent research has primarily focused on the use of ultrasonography in the determination of lymphedema.^[25] Ultrasonography is a relatively cost-effective process to notice soft tissue properties. Additionally, it is widely used in hospitals owing to its easy accessibility and radiation safety.^[26] Considering these advantages, studies on ultrasonography for lymphedema have focused solely on diagnosis and not on assessment of therapeutical intervention.

Strengths and limitations

There are some strengths of this study. This is the first study to use both the CLUE score and BIS for the follow-up of the CDT for BCRL. It also has volumetric measurements, hand grip strength, and functional status of the upper extremity outcome measures, which provide a multi-dimensional assessment of the therapy. Detection of a correlation between CLUE scores and volumetric changes, as well as the changes in BIS values strengthens the value of CLUE for the clinical practice.

Nevertheless, the main limitation to this study is its relatively small sample size. A higher number of patients may have provided a more precise result with the statistical analyses. In addition, this study has a single-center, retrospective design. Although inter-rater variability of CLUE was shown to be excellent,^[8] multi-center studies would yield more reliable conclusions for the use of the measures in this study in clinical practice. Furthermore, the fact that ultrasonography was not used in lymphedema follow-up in our study can also be deemed as a limitation. In future studies, ultrasonography can be used in BRCL follow-ups and compared with the CLUE scale.

In conclusion, the development of a structured clinical assessment such as CLUE provides clinicians for a standardized evaluation for BCRL. In future studies aiming to evaluate treatment responses of patients with BCRL, the use of CLUE and BIS, in addition to routinely used volumetric methods, should be encouraged. The diagnosis of subclinical lymphedema can be detected earlier by using the BIS

and CLUE scale and lymphedema comorbidity and treatment costs can be reduced.

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