ULTRASONOGRAPHY

Ultrasonographic features of the skin and subcutis: correlations with the severity of breast cancer–related lymphedema

Ji Youn Park, Jae Yong Jeon, Seungwoo Cha

Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Correspondence to:
Seungwoo Cha, MD, Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

Tel. +82-2-3010-3779
Fax. +82-2-3010-1174
E-mail: miracleofs@naver.com

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Purpose: Assessing the severity of breast cancer-related lymphedema (BCRL) requires various clinical tools, yet no standardized methodology is available. Ultrasonography shows promise for diagnosing lymphedema and evaluating its severity. This study explored the clinical utility of ultrasonography in patients with BCRL.

Methods: In this retrospective cross-sectional study, patients with unilateral BCRL were examined. The analyzed data included demographics, lymphedema location, International Society of Lymphology (ISL) stage, surgical history, treatment regimens, and arm circumference. Skin, subcutis, and muscle thicknesses were assessed ultrasonographically at predetermined sites, and the percentage of excess thickness was calculated. Multivariate logistic regression analysis was employed to identify associations between ultrasonographic measurements and advanced lymphedema (ISL 2 or 3). The Lymphedema Quality of Life arm questionnaire was used to evaluate patient-reported outcomes regarding lymphedema and their correlations with ultrasonographic findings.

Results: Among 118 patients, 71 were classified as ISL 0−1 and 47 as ISL 2−3. Patients with advanced lymphedema were older, had higher nodal stages, underwent more axillary lymph node dissections, and had higher rates of dominant-arm lymphedema. Multivariate logistic regression revealed significant associations of greater skin thickness (adjusted odds ratio [OR], 4.634; 95% confidence interval [CI], 1.233 to 17.419), subcutis thickness (adjusted OR, 7.741; 95% CI, 1.649 to 36.347), and subcutis echogenicity (adjusted OR, 4.860; 95% CI, 1.517 to 15.566) with advanced lymphedema. Furthermore, greater skin thickness (P=0.016) and subcutis echogenicity (P=0.023) were correlated with appearance-related discomfort.

Conclusion: Ultrasonographic measurements were significantly associated with advanced lymphedema in BCRL. Ultrasonography represents a valuable diagnostic and severity assessment tool for lymphedema.

Keywords: Lymphedema; Ultrasonography; Breast neoplasm; Lymphatic system

Key points: Ultrasonography of the skin and subcutis is useful in assessing the clinical severity of breast cancer-related lymphedema and associated patient-reported outcomes.

Introduction

Breast cancer remains a serious and challenging health concern worldwide, impacting millions annually [1]. One debilitating consequence of breast cancer treatment is lymphedema, which is characterized by the accumulation of protein-rich extracellular fluid. This accumulation results in chronic inflammation, excessive formation of fibrous connective tissue, and muscle fibrosis [2,3]. Lymphedema substantially reduces the quality of life for patients, imposing physical, emotional, and social burdens that interfere with daily activities and general well-being [4,5].

In light of the elevated risk of lymphedema following breast cancer treatment, it is essential to prioritize early and accurate diagnosis, along with prompt therapeutic intervention, as part of comprehensive patient care. However, the efficacy and precision of existing diagnostic tools for lymphedema assessment are limited, posing challenges for timely intervention [6].

Recent research has underscored the usefulness of ultrasonography in the diagnosis and monitoring of lymphedema progression [6–8]. Ultrasonography has emerged as a particularly promising tool for assessing lymphedema because it enables the visual examination of individual compartments—skin, subcutis, and muscle—for localized fluid accumulation and changes in fibroadipose tissue within the affected limb [9]. Nevertheless, a considerable knowledge gap remains regarding the impact of ultrasonography on lymphedema prognosis and patient-reported outcomes.

Addressing this research gap, the present study comprehensively explored the role of ultrasonography in the context of post-breast cancer lymphedema. Specifically, it aimed to clarify the relationships between ultrasonographic findings and the severity of lymphedema, as well as patient-reported outcomes. Through this thorough examination, the authors hope to contribute to a deeper understanding of the diagnostic capabilities of ultrasonography, ultimately fostering more effective management strategies for lymphedema and associated challenges.

Materials and Methods

Compliance with Ethical Standards

The ethics committee of Asan Medical Center approved this research (IRB No. 2023-1120). The requirement for informed consent in this study was waived by the committee due to its retrospective design.

Study Design and Population

To examine potential relationships between ultrasonographic measurements and the clinical severity of lymphedema, a retrospective, cross-sectional study was performed (Fig. 1). Researchers screened the electronic medical records of 190 patients over the age of 18 years with unilateral breast cancer-related lymphedema (BCRL). These patients visited the outpatient department of rehabilitation medicine at Asan Medical Center between March 2023 and August 2023, where they underwent ultrasonography for lymphedema. The diagnosis of BCRL was established by two experienced physiatrists at the lymphedema clinic. Due to the absence of a universally accepted objective definition of BCRL, the diagnosis was made clinically, considering the patients' subjective reports of swelling, their breast cancer history and treatment, and a detailed physical examination that assessed skin texture and color, the presence of pitting, and arm circumference measurements. Ultrasonographic examination was independently conducted by five physiatrists. The quality of the examination and the accuracy of the ultrasonographic parameters were reviewed and discussed at monthly meetings. Medical records, including the ultrasonographic findings of the patients, were evaluated by two authors to determine eligibility. The exclusion criteria included bilateral breast cancer, recurrence or metastasis after primary tumor resection, history of lymphovenous anastomosis or vascularized lymph node transfer, and recent infection, thrombosis, or trauma in the affected limb. Patients who received low-quality ultrasonography (characterized by compression during scanning of the skin and subcutis or incorrect measurements) and those with incomplete documentation of clinical data (cancer stage, surgical details, arm circumference, and ultrasonographic measurements) were also excluded. Ultimately, 118 patients were included in the study.

The analysis included the International Society of Lymphology (ISL) stage of the affected limb and the circumference measurements of both arms, which were routinely recorded during medical

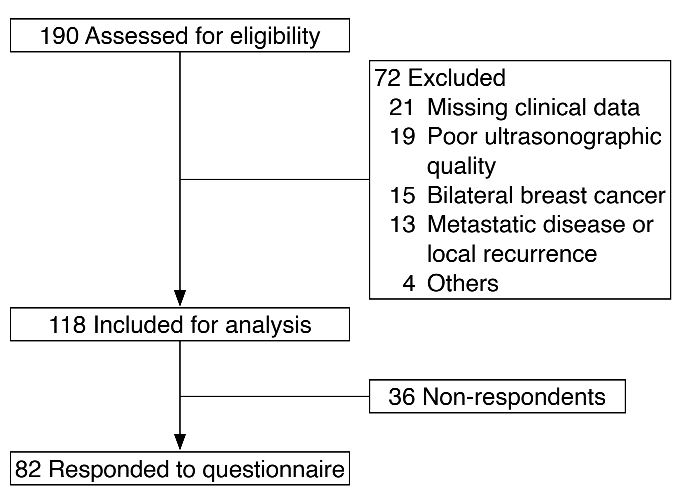

Fig. 1. Study flowchart.

examinations at the lymphedema clinic. The ISL staging system defines stage 1 as swelling that subsides with limb elevation, stage 2 as swelling that is typically not reduced by limb elevation due to increased subcutaneous tissue fibrosis (regardless of the presence of pitting), and stage 3 as severe tissue fibrosis without pitting, potentially with elephantiasis and trophic skin changes [10]. The use of tape measurement for arm circumference is a common and reliable technique, particularly when conducted by experienced medical professionals [11]. In this study, arm circumference was measured at five different points by two authors who were responsible for the clinical diagnosis of BCRL at the lymphedema facility. The measurement points were 10 cm above the elbow, 5 cm above the elbow, 5 cm below the elbow, 10 cm below the elbow, and on the dorsum of the hand. These measurements were used to calculate the percentage of excess circumference (PEC), defined as $[(C_{aff}-C_{unaff})/C_{unaff}\times100(\%)]$, where C represents circumference, "aff" denotes the affected limb, and "unaff" indicates the unaffected limb [12]. The maximum PEC (PEC_{max}) was then determined and categorized into three groups for analysis: less than 5%, between 5% and 10%, and greater than 10%. This categorization facilitated comparisons between patients with early-stage lymphedema (ISL 0 or 1) and those with advanced-stage lymphedema (ISL 2 or 3).

Ultrasonography Protocol and Measures

Lymphedema ultrasonography was performed using an HS70A ultrasound machine (Samsung Medison, Seoul, Korea) with the patient in the supine position. A 12-MHz linear probe was placed directly over the center of the arm to obtain a transverse view. The thicknesses of the skin, subcutis, and biceps brachii muscle were measured (Fig. 2). For the skin and subcutis, thickness was measured at five sites: 10 cm above the elbow, 5 cm above the elbow, 5 cm below the elbow, 10 cm below the elbow, and on the dorsum of the hand. Additionally, the subcutaneous echogenicity grade (SEG), which ranges from 0 to 2, was assessed at these sites using the grading criteria proposed by Suehiro et al. [13]. Previous research has confirmed the inter-rater and intra-rater reliability of SEG in patients with BCRL [8]. For the purposes of this study, increased echogenicity was defined as an SEG of 1 or 2.

The thickness of the biceps brachii was measured cross-sectionally at a point 10 cm above the elbow. During the measurement of muscle thickness, minimal pressure was applied, which differed from the no-pressure technique utilized when scanning the skin and subcutis. With the exception of SEG, values were converted into a percentage of excess thickness (PET), defined as $[(T_{aff}-T_{unaff})/T_{unaff}\times100\ (\%)]$, where T represents thickness. The maximum PET (PET_{max}) values for the skin and subcutis were determined and divided into three categories for comparative analysis: less than 25%, between 25% and 50%, and greater than 50%. Similarly, the PET for muscle was classified into three groups: less than −10%, between −10% and 0%, and greater than 0%.

Patient-Reported Outcomes

The Korean version of the Lymphedema Quality of Life (LYM-QOL) arm questionnaire was used to evaluate patient-reported outcomes associated with upper limb lymphedema. This questionnaire covers five domains: function, appearance, symptoms, mood, and overall quality of life (QOL). It consists of 28 items, including 10 for function, five for appearance, six for symptoms, six for mood, and one for overall QOL. A previous study that assessed the reliability and validity of the Korean version of the LYM-QOL demonstrated high internal consistency across all domains (Cronbach α: function, 0.862; appearance, 0.915; symptoms, 0.876; mood, 0.877) and significant correlations with most scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Breast Cancer Module 23 [14]. All patients who visited the lymphedema clinic were given a printed copy of the LYM-QOL questionnaire to complete while waiting for their appointment. Of the 118 patients included in the study, 82 completed the LYM-QOL questionnaire.

Statistical Analysis

Descriptive analysis was conducted to summarize patient demographics and to compare clinical parameters between those with early and advanced lymphedema. Regarding baseline characteristics, age and the number of postoperative physiotherapy sessions were compared using t-tests, while the chi-square test was applied to the remaining factors. A P-value of less than 0.05 was considered to indicate statistical significance. The Kruskal-Wallis test was employed to compare patient-reported outcomes with the values of ultrasonographic parameters. All statistical analyses were conducted using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline Characteristics

The study included 118 patients with unilateral BCRL. On average, enrollment occurred 943.7 days after surgery. Among these patients, 71 were diagnosed with early lymphedema, including five at stage 0 and 66 at stage 1 according to the ISL classification. The remaining 47 patients were diagnosed with advanced lymphedema, with 45 at ISL stage 2 and two at ISL stage 3.

The baseline characteristics of the study population are detailed in Table 1. In summary, patients with advanced lymphedema tended to be older, with an average age of 54.3±8.3 years compared to

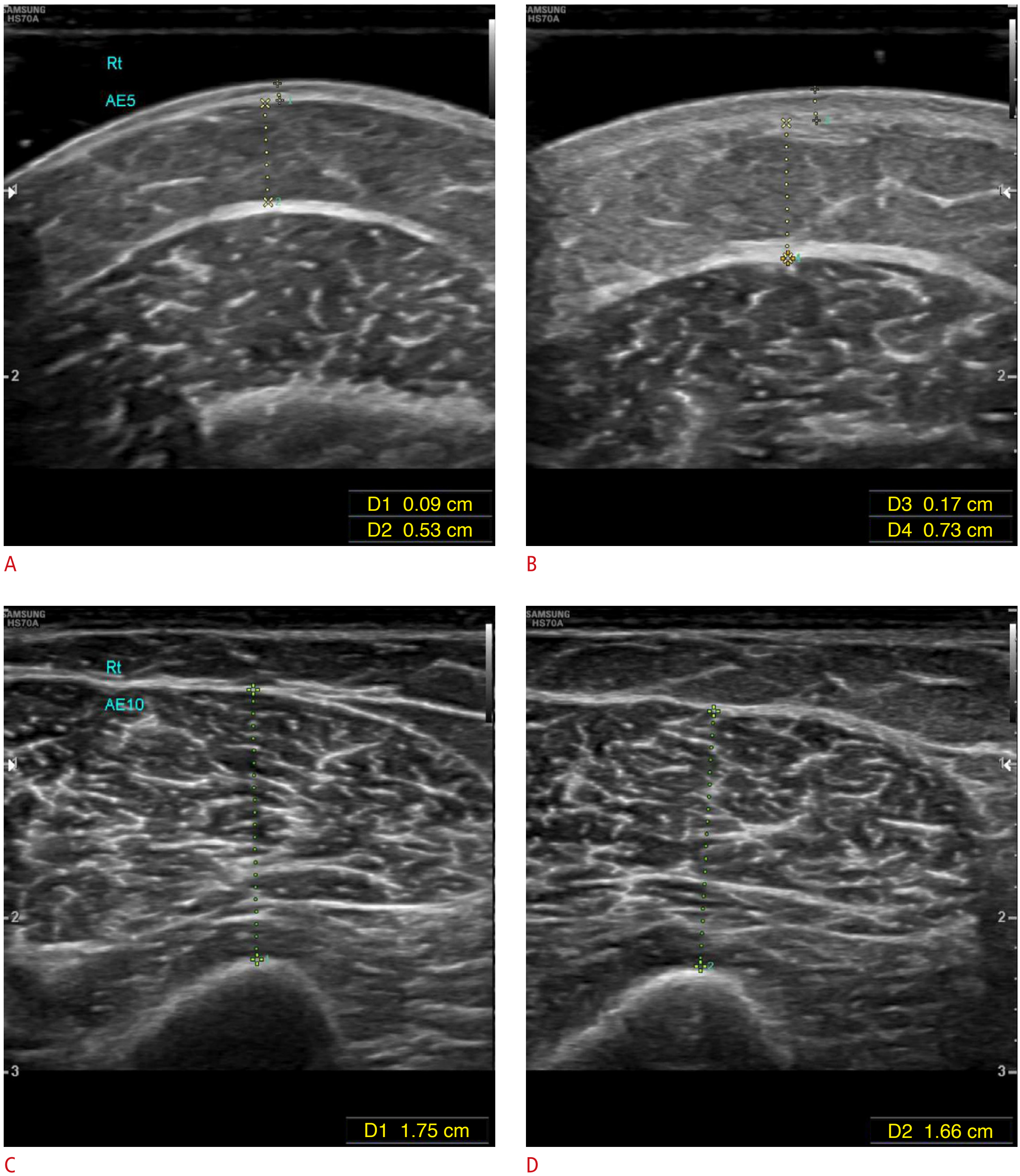

Fig. 2. Case of a 64-year-old woman with left lymphedema.
A, B. Images display measurements of skin and subcutaneous thickness, obtained without pressure, resulting in a convex appearance of the skin. C, D. Images present measurements of muscle thickness, taken with minimal pressure. Compared to the opposite side, the affected side exhibited increased skin and subcutaneous tissue thickness, with no significant difference in muscle thickness observed.

47.1±9.4 years for patients with early lymphedema ($P<0.001$). The advanced lymphedema group also had a higher prevalence of lymphedema in the dominant arm (55.3% vs. 31.0%, $P=0.008$), a more advanced overall breast cancer stage ($P=0.003$), a higher nodal stage ($P<0.001$), more frequent axillary lymph node dissections ($P<0.001$), and a greater number of dissections involving ≥10 lymph

Table 1. Baseline characteristics (n=118)

Variable	ISL 0–1 (0, n=5; 1, n=66)	ISL 2–3 (2, n=45; 3, n=2)	P-value
Age (year)	47.1±9.4	54.3±8.3	<0.001*
BMI (kg/m^2)			0.208
≥25	18 (25.4)	17 (36.2)	
<25	53 (74.6)	30 (63.8)	
Medical history			
Hypertension	6 (8.5)	8 (17.0)	0.159
Heart failure	0	0	
Reduced kidney function (GFR <90 mL/min/1.73 m^2)	5 (7.1)	6 (13.0)	0.289
No. of postoperative physiotherapy sessions	1.6±3.1	6.4±6.7	<0.001*
Location of lymphedema			0.008*
Dominant limb	22 (31.0)	26 (55.3)	
Non-dominant limb	49 (69.0)	21 (44.7)	
Breast cancer stage			
Stage			0.003*
0	9 (12.7)	1 (2.1)	
1	16 (22.5)	6 (12.8)	
2	32 (45.1)	16 (34.0)	
3	14 (19.7)	22 (46.8)	
4	0	2 (4.3)	
T category			0.188
0	11 (15.5)	2 (4.3)	
1	28 (39.4)	17 (36.2)	
2	27 (38.0)	20 (42.6)	
3	4 (5.6)	7 (14.9)	
4	1 (1.4)	1 (2.1)	
N category			<0.001*
0	37 (52.1)	7 (14.9)	
1	24 (33.8)	19 (40.4)	
2	8 (11.3)	14 (29.8)	
3	2 (2.8)	7 (14.9)	
Type of surgery			0.213
BCO	37 (52.1)	19 (40.4)	
NASSM/SSM/TM	34 (47.9)	28 (59.6)	
Type of LND			<0.001*
SNB	45 (63.4)	9 (19.1)	
ALND	26 (36.6)	38 (80.9)	
No. of LNDs			0.001*
<10	40 (56.3)	12 (25.5)	
≥10	31 (43.7)	35 (74.5)	
Radiation therapy	60 (84.5)	41 (87.2)	0.680
Chemotherapy	60 (84.5)	40 (85.1)	0.929

Continued

Table 1. Continued

Variable	ISL 0–1 (0, n=5; 1, n=66)	ISL 2–3 (2, n=45; 3, n=2)	P-value
Hormonal therapy	51 (71.8)	32 (68.1)	0.663
PEC_{max} (tape circumference)			<0.001*
<5%	62 (87.3)	14 (29.8)	
5% to 10%	8 (11.3)	17 (36.2)	
>10%	1 (1.4)	16 (34.0)	
Ultrasonographic parameters			
Skin PET_{max}			0.006*
<25%	44 (62.0)	16 (34.0)	
25% to 50%	17 (23.9)	15 (31.9)	
>50%	10 (14.1)	16 (34.0)	
Subcutis PET_{max}			0.006*
<25%	30 (42.3)	8 (17.0)	
25% to 50%	29 (40.8)	22 (46.8)	
>50%	12 (16.9)	17 (36.2)	
Muscle PET			0.884
>0%	36 (50.7)	26 (55.3)	
−10% to 0%	22 (31.0)	13 (27.7)	
<−10%	13 (18.3)	8 (17.0)	
Subcutis echogenicity			<0.001*
Not increased	53 (74.6)	19 (40.4)	
Increased	18 (25.4)	28 (59.6)	

Values are presented as mean±SD or number (%).
ISL, International Society of Lymphology; BMI, body mass index; GFR, glomerular filtration rate; BCO, breast-conserving operation; NASSM, nipple areolar skin-sparing mastectomy; SSM, skin-sparing mastectomy; TM, total mastectomy; LND, lymph node dissection; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; PEC or PET, percentage of excess circumference or thickness, calculated as [(affected arm–unaffected arm)/unaffected arm×100 (%)]; max, maximum.
*P<0.05 (t-test, Pearson chi-square test, or Fisher exact test).

nodes (P=0.001). Additionally, they underwent a greater number of postoperative physiotherapy sessions (P<0.001). No significant differences were observed in body mass index (BMI), hypertension, heart failure, reduced kidney function (glomerular filtration rate <90 mL/min/1.73 m^2), the location of lymphedema, T category, the type of primary tumor resection, or the proportions of patients who received radiation therapy, chemotherapy, and hormone therapy. Tape measurements indicated a significantly higher PEC_{max} in the patients with advanced lymphedema (P<0.001). Ultrasonographic parameters also displayed significant differences, including a higher PET_{max} for the skin (P=0.006) and subcutis (P=0.006) as well as a higher prevalence of increased subcutis echogenicity (SEG 1 or 2) (P<0.001). However, muscle thickness did not vary significantly with

Table 2. Multivariate logistic regression analysis for the prediction of advanced lymphedema (ISL stage ≥2)

Variable	Univariate analysis		Multivariate analysis			
			Model 1[a)]		Model 2[b)]	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Skin PET_{max}						
<25%	Reference		Reference		Reference	
25% to 50%	2.426 (0.987–5.966)	0.053	2.222 (0.856–5.772)	0.101	3.024 (0.853–10.726)	0.087
>50%	4.400 (1.659–11.671)	0.003*	3.474 (1.243–9.712)	0.018*	4.634 (1.233–17.419)	0.023*
Subcutis PET_{max}						
<25%	Reference		Reference		Reference	
25% to 50%	2.845 (1.093–7.405)	0.032*	3.412 (1.206–9.656)	0.021*	3.298 (0.905–12.014)	0.070
>50%	5.312 (1.814–15.556)	0.002*	5.618 (1.742–18.120)	0.004*	7.741 (1.649–36.347)	0.010*
Subcutis echogenicity						
Not increased	Reference		Reference		Reference	
Increased	4.339 (1.968–9.568)	<0.001*	3.162 (1.372–7.290)	0.007*	4.860 (1.517–15.566)	0.008*
Muscle PET						
>0%	Reference		Reference		Reference	
−10% to 0%	0.818 (0.349–1.917)	0.644	0.615 (0.241–1.568)	0.309	0.409 (0.113–1.483)	0.174
<−10%	0.852 (0.309–2.351)	0.757	0.677 (0.223–2.052)	0.490	0.241 (0.057–1.026)	0.054

ISL, International Society of Lymphology; OR, odds ratio; CI, confidence interval; PET, percentage of excess thickness, calculated as [(affected arm−unaffected arm)/unaffected arm×100 (%)]; max, maximum.
*P<0.05 in logistic regression analysis.
a)Adjusted for age. b)Adjusted for age, body mass index ≥25 kg/m², location of lymphedema, type of surgery, type of lymph node dissection, stage ≥2, T category ≥2, N category ≥2, chemotherapy, radiation therapy, hormone therapy, and number of postoperative physiotherapy sessions ≥5.

the severity of lymphedema.

Factors Associated with Advanced Lymphedema

The results of the logistic regression analysis are summarized in Table 2. Univariate regression analysis identified greater measurements for skin PET_{max} (for a >50% increase: odds ratio [OR], 4.400; 95% confidence interval [CI], 1.659 to 11.671; P=0.003), subcutis PET_{max} (for a 25%–50% increase: OR, 2.845; 95% CI, 1.093 to 7.405; P=0.032; for a >50% increase: OR, 5.312; 95% CI, 1.814 to 15.556; P=0.002), and subcutis echogenicity (OR, 4.339; 95% CI, 1.968 to 9.568; P<0.001) as significant factors individually associated with advanced lymphedema. These variables remained significant even after adjusting for age (model 1). To reduce bias, multivariate analysis was performed (model 2), adjusting for a broader range of clinical variables that could contribute to the occurrence of lymphedema. These variables included age, BMI ≥25 kg/m², lymphedema location, type of primary tumor resection, type of lymph node dissection, overall stage ≥2, T category ≥2, N category ≥2, and history of chemotherapy, radiation therapy, and hormone therapy. Multivariate analysis revealed that a skin PET_{max} of more than 50% (OR, 3.341; 95% CI, 1.018 to 11.565; P=0.047), a subcutis PET_{max} exceeding 50% (OR, 6.502; 95% CI, 1.566 to 27.003; P=0.010), and an increase in subcutis echogenicity (OR, 5.021; 95% CI, 1.663 to 15.163, P=0.004) were all significantly associated with the presence of advanced lymphedema.

Associations between Patient-Reported Outcomes and Ultrasonographic Parameters

The results of a comparative analysis of patient-reported outcomes, as measured using the LYM-QOL arm questionnaire, in relation to ultrasonographic findings are summarized in Table 3. Higher skin PET_{max} (P=0.016) and higher SEG_{max} (P=0.023) were significantly associated with greater discomfort regarding appearance, as reflected by higher scores in the appearance domain of the LYM-QOL. Furthermore, a trend was noted suggesting that higher values in these parameters were linked with greater discomfort in terms of function, symptoms, and mood, as well as poorer overall QOL. However, the LYM-QOL results did not display significant correlations with subcutis PET_{max} or muscle PET.

Discussion

The primary finding of this study is that ultrasonographic measurements of skin thickness, subcutis thickness, and subcutis

Table 3. Associations between patient-reported outcomes and ultrasonographic parameters

		Function		Appearance		Symptoms		Mood		Overall QoL	
		Mean±SD	P-value	Mean±SD	P-value	Mean±SD	P-value	Mean±SD	P-value	Mean±SD	P-value
Skin PET_{max}	<25%	13.28±3.74	0.187	6.81±2.57	0.016*	10.71±3.66	0.751	9.52±3.19	0.821	6.62±2.26	0.622
	25% to 50%	13.76±3.25		6.90±2.19		11.00±3.05		9.76±4.24		6.57±2.62	
	>50%	16.06±6.34		9.25±3.75		12.19±4.75		10.75±4.73		6.13±1.71	
Subcutis PET_{max}	<25%	13.28±3.10	0.639	7.14±2.46	0.206	10.93±4.30	0.615	9.83±3.67	0.396	6.10±2.28	0.136
	25% to 50%	13.71±4.41		6.84±2.75		10.61±2.65		9.29±3.58		7.13±2.35	
	>50%	15.47±5.61		8.42±3.53		12.11±4.37		10.79±4.35		6.11±1.91	
SEG_{max}	Not increased	13.31±3.31	0.126	6.78±2.37	0.023*	10.59±3.01	0.343	9.75±3.50	0.826	6.63±2.47	0.379
	Increased	15.18±5.67		8.32±3.49		12.00±4.75		10.00±4.36		6.29±1.80	
Muscle PET	>0%	14.48±4.62	0.647	7.50±3.21	0.590	12.21±4.32	0.083	10.97±4.40	0.060	6.32±2.44	0.673
	−10% to 0%	13.52±4.34		7.04±2.76		10.24±2.85		8.88±3.06		6.80±1.94	
	<−10%	13.56±3.83		7.38±2.36		9.75±2.84		8.63±2.47		6.50±2.31	

QoL, quality of life; SD, standard deviation; PET, percentage of excess thickness, calculated as [(affected arm−unaffected arm)/unaffected arm×100 (%)]; max, maximum; SEG, subcutaneous echogenicity grade.
*P<0.05 on Kruskal-Wallis test.

echogenicity are strongly associated with the clinical severity of BCRL. Furthermore, skin thickness and subcutis echogenicity are linked to a significant decrease in QOL, especially concerning the appearance of the affected arm.

To date, BCRL is diagnosed through clinical assessment, as no single gold standard diagnostic tool is available. Clinicians must thoroughly review the patient's symptoms and medical or surgical history, particularly factors commonly associated with lymphedema, while ruling out other potential causes of edema. However, this approach is often inadequate, necessitating the use of additional imaging or diagnostic techniques to confirm the accumulation of fluid within specific tissue compartments [15]. One limitation of volumetric evaluation tools is their lack of differentiation between soft tissue and accumulated lymphatic fluid. Bioelectrical impedance analysis is frequently employed to address this issue, although its utility is more pronounced in the early stages of lymphedema, which are marked by a predominance of excess water rather than the formation of fibroadipose tissue [16,17]. In this context, ultrasonography is gaining importance in the diagnosis of lymphedema. This tool provides noninvasive, real-time evaluation of structural changes in tissue compartments, particularly the development of fibroadipose tissue, which is critical for determining the prognosis of lymphedema. Furthermore, quantitative ultrasound analysis has exhibited strong correlations with measurements of limb circumference and volume [18].

While previous research has established the importance of skin and subcutis thickness, as well as SEG, in relation to ISL stage in secondary lower limb lymphedema, studies focusing on upper limb lymphedema are scarce [7]. A 2016 study by Suehiro et al. [19] highlighted significant increases in skin and subcutis thickness, along with echogenicity, in the affected arms of 30 patients with BCRL at ISL stage 2. The present study corroborated these findings and included a broader spectrum of patients with BCRL across various stages. The analysis included 71 patients (60.17%) at ISL stage 0 or 1 and 47 patients (39.83%) at ISL stage 2 or 3. Significant associations were revealed between the clinical severity of lymphedema and skin thickness, subcutis thickness, and echogenicity, as observed on ultrasonography.

Anatomical studies of the human lymphatic system have revealed that superficial lymphatics, which are uniformly distributed around the wrist, converge toward the anteromedial aspect of the elbow before ultimately draining into the axillary region [20]. Previous research on upper limb BCRL has shown that the affected arm exhibits significant increases in skin and subcutis thickness, as well as SEG, compared to the unaffected arm. Among measurements taken at the medial and lateral aspects of both the upper arm and forearm, the most pronounced differences were observed in the medial forearm [19]. However, in cases of early lymphedema, only a few superficial lymph collecting vessels are obstructed, leading to localized dermal backflow in the corresponding areas [20]. To date, insufficient research has examined the specific patterns of these early obstructions. Consequently, the present study included measurements taken 5 and 10 cm below and above the elbow to encompass a variety of regions within the lymphosome. The probe was positioned perpendicular to the longitudinal axis of the arm, with its center aligned with the arm's midline, to ensure consistent measurements and minimize inter-rater variability.

The results of this study indicate that among patients with BCRL, increased SEG is significantly associated with not only advanced lymphedema stage but also greater patient-reported discomfort. Pathology research has shown that prolonged lymphatic overload leads to the formation of fibroadipose tissue, marking an irreversible stage of progression [21]. Increased subcutaneous echogenicity is indicative of heightened collagen deposition and cell density within the tissue, a phenomenon that is not exclusive to lymphedema and can be observed in various nonspecific chronic inflammatory conditions [19]. In the present study, increased SEG was associated with worse patient-reported functional outcomes, negative mood, and more severe symptoms, along with more pronounced discomfort associated with appearance. These findings suggest that irreversible fibrosis of tissue and delayed volume reduction after arm elevation lead to lumpiness, heaviness, and shoulder pain in the affected arm, resulting in decreased functional use of the arm. Prior research indicates that an increased load on the arm makes it vulnerable to chronic ischemia and disruption of rotator cuff tendons, and the stiffness of the skin, subcutis, and even the biceps muscle are increased in lymphedema [22,23]. A positive correlation between upper limb dysfunction or shoulder pain and overall QOL has been demonstrated in previous studies [23,24]. The present findings suggest that increased echogenicity may reflect both the clinical and the pathological progression of lymphedema, raising questions about therapeutic approaches for patients with increased echogenicity in the affected limb. The current understanding suggests that the status of extracellular fluid is a significant predictor of response to physiotherapy. Retrospective analysis has shown that patients with subcutaneous echo-free space, indicative of fluid collection, exhibited more favorable outcomes after 1 year of physiotherapy [25]. Conversely, a greater accumulation of subcutaneous adipose tissue, a history of cellulitis, and moderate to severe BCRL at the time of diagnosis were associated with poor treatment response [12,21]. Therefore, early mechanical treatment initiated before the deposition of fibroadipose tissue is recommended in cases of advanced-stage lymphedema [16]. Ultrasonographic evaluation of subcutaneous echogenicity could aid in clinical decision-making by identifying patients at a later stage of lymphedema, who may show a suboptimal response to physiotherapy, necessitating the consideration of alternative therapeutic approaches.

The primary treatment for BCRL currently involves a multimodal approach, which includes physiotherapy. In contrast to the present findings, the literature suggests that chronic lymphedema is associated with muscle stiffness and a decrease in muscle mass, which contribute to a lower functional capacity and exacerbation of lymphedema [6,22]. Therefore, the current emphasis is on the importance of progressive resistance exercise (PRE) for the affected arm, as well as aerobic exercise, with a growing body of evidence supporting their safety and effectiveness [26]. The beneficial effects of exercise on physical fitness, fatigue, and overall QOL in patients with breast cancer are well-documented in the literature [4]. Studies of these patients have indicated that PRE is associated with a lower risk of developing lymphedema, greater muscle thickness, lower subcutis thickness, and greater physical endurance when combined with aerobic exercise [6,27,28]. In cases of BCRL, muscle contractions during exercise help facilitate lymphatic flow, thereby relieving symptoms of lymphedema and mitigating functional decline [4,5]. A study using a rat hindlimb lymphedema model, in which animals underwent treadmill exercise for 5 weeks following lymph node dissection, showed histopathological improvements in lymphatic drainage and the formation of collateral lymphatic vessels [29]. To substantiate the clinical effects of PRE on BCRL, it appears necessary to explore the relationships between the severity of lymphedema and multiple factors. These include not only muscle mass measured at a single time point but also muscle quality, changes in muscle mass, and the dose and intensity of exercise during the follow-up period.

This retrospective observational study, conducted at a single institution, faced limitations due to the small number of patients involved. Consequently, future research should include long-term follow-up with a larger population.

The present research findings have limited applicability because the study compared only early and advanced BCRL, without including healthy individuals or those with other conditions that cause swelling, such as deep vein thrombosis, infection, post-thrombotic syndrome, drug side effects, or generalized edema. Furthermore, the investigation was restricted to patients with unilateral BCRL who exhibited swelling in the arm on the same side as the previous breast cancer and who underwent ultrasonographic examination of both arms. To compensate for the absence of a healthy control group, ultrasonographic measurements from the asymptomatic arms of the patients were employed as a proxy for normal controls and were then compared to the affected arm. Previous studies of healthy individuals indicate that the thicknesses of the skin and subcutis are strongly associated with multiple factors, including age, sex, and BMI [30,31]. By using the contralateral arm as a control, the present study matched for age, BMI, and lifestyle factors. Currently, the literature includes a scarcity of research on the normal variation in skin and subcutis thickness, as well as the echogenicity of the subcutis, between arms. Clarifying this could pave the way for future studies that compare PEC_{max}, PET_{max}, and SEG values obtained from both arms of healthy matched controls with those from patients with unilateral BCRL.

Several aspects of the study design and measurement methods may have impacted the results. First, the retrospective cross-sectional nature of the study introduced variability in the timing of lymphedema and the postoperative day. Additionally, the study lacked data on baseline muscle thickness before the onset of BCRL, baseline activity levels, and participation in strengthening exercises. Due to the absence of longitudinal follow-up, the analysis was also limited to cross-sectional measurements of muscle thickness. Second, the method used to measure muscle thickness was not standardized and lacked adequate validation. Muscle thickness of the biceps brachii was measured at a single point, 10 cm above the elbow, and current evidence is insufficient to support that this measurement accurately reflects decreases in muscle quantity and quality. Recent studies using ultrasound elastography to measure muscle quality have revealed positive correlations between shear wave speed and increases in the diameter and volume of the affected arm compared to the unaffected side ($0.51 \le r \le 0.70$). This suggests a relationship between the clinical severity of lymphedema and muscle stiffness [22]. Further research, including the use of shear-wave elastography, is warranted to explore the impact of lymphedema on muscle function.

In the present research, the ultrasonographic examinations were conducted by five different physiatrists. The protocol stipulated that the examiners should consistently apply minimal pressure with the probe when measuring the thickness of the skin and subcutis and slightly greater pressure when assessing muscle thickness. Despite these guidelines, the amount of pressure applied may have varied between patients. To improve consistency, monthly discussions and protocol review sessions were held. Additionally, a previous study revealed that measurements of skin and subcutis thickness in lymphedema cases demonstrated high consistency [32].

The present study demonstrates that ultrasonography can be effectively utilized in clinical settings for diagnosing and evaluating the severity of BCRL. Furthermore, ultrasonographic findings are correlated with the levels of discomfort reported by patients with BCRL.

ORCID: Ji Youn Park: https://orcid.org/0009-0001-9630-2438; Jae Yong Jeon: https://orcid.org/0000-0003-1534-7931; Seungwoo Cha: https://orcid.org/0000-0003-0236-9330

Author Contributions

Conceptualization: Jeon JY, Cha S. Data acquisition: Park JY, Cha S. Data analysis or interpretation: Park JY, Jeon JY, Cha S. Drafting of the manuscript: Park JY, Cha S. Critical revision of the manuscript: Park JY, Jeon JY, Cha S. Approval of the final version of the manuscript: all authors.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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