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Research Article

Predictive Values of Upper Extremity Function and Body Composition Parameters for Upper Extremity Lymphedema Occurring within 12 Months after Breast Cancer Surgery

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Abstract

Purpose: This study aimed to evaluate the values of early postoperative body composition and upper limb function as predictive indicators for the development of breast cancer-related lymphedema (BCRL).

Methods: The study included women who underwent axillary lymph node dissection between 2022 and 2024. Extracellular water ratio, low-frequency impedance, and phase angle measurements using segmental multifrequency bioelectrical impedance analysis and shoulder range of motion and grip strength assessments were performed preoperatively and at 1, 3, 6, and 12 months postoperatively. Lymphedema was defined as an increase in limb volume by 10% or more, and the data of the affected and unaffected groups were compared at each time point.

Results: The group that developed lymphedema within 6 months had increased extracellular water ratio and decreased low-frequency impedance and phase angle by 3 months relative to the unaffected group. The group that developed lymphedema within 12 months had decreased low-frequency impedance and phase angle by 6 months relative to the unaffected group. The range of external shoulder rotation was only significantly reduced for the lymphedema group at 12 months. The grip strengths of the affected and unaffected groups did not differ at any time point.

Conclusion: Body composition changes were observed before an increase in limb volume in patients who developed lymphedema within 12 months after breast cancer surgery. Restriction of shoulder range of motion was likely secondary to lymphedema progression. Body composition measures are useful for predicting lymphedema progression and may facilitate early preventive interventions as screening indicators.

Keywords: Breast cancer-related upper limb lymphedema; Body composition; Upper limb function; Limb volume

Abbreviations: 5kHz impedance: Low-frequency impedance; ALND: Axillary lymph node dissection; AUC: Area under the curve; BCRL: Breast cancer-related lymphedema; DSM-BIA: Direct segmental multi-frequency impedance analysis; ECW/TBW: Extracellular water ratio; PhA: Phase angle; ROC: Receiver operating characteristic curve

Introduction

Lymphedema is characterized by excessive accumulation of protein-rich fluid in the interstitial space due to impaired lymphatic drainage. In Japan, secondary lymphedema after cancer treatment accounts for approximately

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90% of all lymphedema cases [1]. More than 90,000 Japanese women are diagnosed with breast cancer annually and this number continues to increase [2]. The incidence of breast cancer-related lymphedema (BCRL) after breast cancer surgery ranges from 9.1% to 39% [3], and the number of lymphedema patients with BCRL is expected to increase in the future. BCRL is not only a cosmetic issue. It also causes discomfort and functional impairment in the affected limb, significantly reducing the quality of life of survivors of breast cancer [4]. For severe cases, irreversible changes, such as fat deposition, elephantiasis, and fibrosis of the subcutaneous tissues, can occur in the affected limb, necessitating lifelong specialized and costly treatment. Therefore, prevention and early detection of BCRL are critical from both patient and societal perspectives. The 2024 Japanese Lymphedema Management Guidelines identified several risk factors for BCRL, including axillary lymph node dissection (ALND), radiation therapy, chemotherapy, obesity, and infections such as cellulitis [1]. However, preventive measures based solely on these risk factors are insufficient to prevent the onset of BCRL completely. For example, risk stratification based on treatment methods can help enhance the observation of certain patients, but limiting treatment options is not realistic because the treatment is vital for patient survival. Additionally, infection is a significant risk factor for BCRL, but it is incidental, and proactive prevention has its limitations. The impact of obesity on patients with BCRL in Japan may be less significant than that in Western countries [5,6], making it difficult to target for primary prevention.

Moreover, delayed diagnosis and initiation of BCRL treatment can lead to symptom progression [7]. The clinical diagnostic criteria for BCRL used in Western countries include an increase in circumference of 2 cm or more relative to that of the unaffected limb, an increase in volume of 200 mL or more, or a volume increase of 10% or more [8]. However, lymphedema-related volume increments may be relatively small and underdiagnosed, given that Japanese have smaller bodies than Westerners [9]. In addition, volume-dependent assessments make it difficult to distinguish between bone, fat, muscle, other soft tissues, extracellular fluids, and lymphatic fluids. For example, if muscle or fat atrophy and lymphedema occur simultaneously after breast cancer surgery, the increase and decrease in volume may offset each other, potentially leading to the missed detection of lymphedema. Therefore, it is necessary to identify the potential indicators of lymphedema progression before an apparent increase in volume is observed. Recently, direct segmental multi-frequency impedance analysis (DSM-BIA) has gained attention as a supplementary tool for lymphedema diagnosis. DSM-BIA allows noninvasive measurements of composition for each segment of the body, including the upper and lower limbs and trunk, by passing a weak electric current through the body. These measurements include the extracellular water ratio (ECW/TBW), low-frequency impedance (5kHz impedance), and phase angle (PhA). Previous studies using the DSM-BIA have shown that groups that have already developed lymphedema after breast cancer surgery have higher ECW/TBW and lower PhA than those that have not, suggesting that these body composition indicators are associated with lymphedema severity [10]. However, these studies were limited to cross-sectional validation, and longitudinal changes in body composition have not been clarified. A previous study reported that 77% of BCRL cases occur within three years postoperatively [11], with the highest incidence within 12 months. It has also been reported that the peak onset of lymphedema occurs between 12 and 30 months postoperatively [12, 13]), indicating the need to examine the relationship between early postoperative changes in body composition and the onset of lymphedema. Exercise has been suggested to play a crucial role in the prevention and progression of BCRL, but the specific mechanisms remain unclear. Some previous studies have reported that stretching and resistance training of the upper limbs in patients are effective in reducing upper limb volume and improving upper limb function [14]. Other studies have reported that exercise reduces the incidence of BCRL in patients who have undergone ALND [15]; however, how these effects contribute to the onset or progression of BCRL remains unclear. To understand the impact of exercise on BCRL, the relationship between upper limb function and lymphedema onset should be further examined. This study aimed to evaluate upper limb function, including shoulder joint range of motion and upper limb muscle strength, before surgery and at 1, 3, 6, and 12 months postoperatively in patients who underwent ALND and investigate its relationship with the onset of BCRL. Additionally, it aimed to assess the PhA, 5kHz impedance, and ECW/TBW ratio as indicators of upper limb body composition to determine their usefulness for the early prediction of BCRL. The study focused on BCRL that develops within 12 months after breast cancer surgery to determine whether early postoperative changes in body composition can serve as indicators of the progression of BCRL and provide new insights into its risk assessment and prevention strategies.

Materials and Methods

Ethical Considerations

This study was conducted following ethical standards per the Declaration of Helsinki and its subsequent amendments after receiving approval from the Ethics Committee of the International University of Health and Welfare (Approval Number: 22-Ig-280). Informed consent was obtained from all participants using the opt-out method.

Study Design and Patients

This retrospective, observational study included women diagnosed with breast cancer who underwent surgery, including ALND, at the International University of Health

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and Welfare Narita Hospital between April 1, 2022, and June 31, 2024. The exclusion criteria were as follows: (a) bilateral breast cancer; (b) history of diseases other than lymphedema that could cause edema; (c) acute or chronic infectious or inflammatory diseases during the observation period; (d) preoperative lymphedema; (e) musculoskeletal disorders in the upper limb or shoulder girdle; and (f) missing data.

Measurement Periods and Evaluation Items

Measurements were conducted preoperatively and 1, 3, 6, and 12 months postoperatively. The primary evaluation items were limb volume, body composition, shoulder range of motion, and muscle strength of both upper limbs. Upper limb volume was calculated using the frustum mode [16,17] l based on circumferential measurements taken with a tape measure. Circumferences were measured 5 and 10 cm proximal to and 5, 10, and 15 cm distal to the cubital fossa. Distal measurements from the wrist joint were excluded from the volume calculations. Body composition was assessed using a body composition analyzer (Inbody770®, InBody Japan Inc.), and ECW/TBW, 5kHz impedance, and PhA were measured for both upper limbs. Shoulder joint range of motion was measured using a goniometer, with a focus on shoulder flexion, abduction, and external rotation at 90° abduction. The upper limb muscle strength was measured using a digital grip strength dynamometer. As secondary evaluation items, surgical procedures (total or partial mastectomy), level of axillary lymph node dissection (levels I-III), and adjuvant therapies were extracted from the medical records.

Criteria for Lymphedema Onset and Grouping

Based on previous studies [9,10], the onset of lymphedema was defined as an increase of 10% or more in the interlimb volume ratio. At each measurement point, the patients were classified into lymphedema and non-lymphedema groups based on the defined criteria, and their body composition, shoulder range of motion, and muscle strength at earlier measurement points were compared. To account for individual differences in body size and reduce data variability, the ratio of the affected to unaffected limb counts was used for comparison. This was targeted at improving the accuracy of the statistical analysis. The ratio was calculated as follows:

$$Ratio_{unaff/aff} = \frac{number\ of\ unaffected\ limbs}{number\ of\ affected\ limbs} \times 100\%$$

Statistical Analysis

Lymphedema was graded based on the limb volume ratio (Grade I: 10–19%, Grade II: 20–29%, Grade III: 30–39%) [18], and the proportions of cases for the grades at each measurement point were compared. Two-way repeated-measures ANOVA was performed with measurement time points (preoperative and 1, 3, 6, and 12 months postoperatively) and the presence or absence of lymphedema as independent variables and limb volume, body composition, shoulder range of motion, and muscle strength as dependent variables. This assessed the effect of changes in these variables on the onset of lymphedema at each time point. Those who developed lymphedema were excluded from subsequent analyses, and the number of participants varied at each time point. Multiple comparisons using the Bonferroni method were used to evaluate the differences between the mean limb volume, body composition, shoulder range of motion, and muscle strength values of the lymphedema and non-lymphedema groups at each measurement point if two-way ANOVA provided significant results.

Additionally, receiver operating characteristic curve analysis was used to evaluate the predictive values of the body composition indicators ECW/TBW, 5kHz impedance, and PhA for the onset of lymphedema. A receiver operating characteristic curve was generated, and the area under the curve (AUC) was calculated to assess the predictive value of each indicator. The cut-off value of each indicator for predicting the onset of lymphedema was determined by selecting the point at which the Youden index was maximized and used to calculate the sensitivity, specificity, and positive and negative predictive values. Secondary evaluation parameters were compared for the lymphedema and non-lymphedema groups at each time point using unpaired t-test, chi-square test, or Fisher's exact test. Statistical significance was set at $p<0.05$, and all statistical analyses were performed using SPSS (Version 23.0, IBM).

Results

Changes in Body Composition

The background characteristics of the participants at each time point are listed in Table 1. The incidence of lymphedema (incidence rate) was 0/114 (0%) at 1 month postoperatively, 5/104 (4.8%) at 3 months, 17/86 (19.7%) at 6 months, and 15/78 (19.2%) at 12 months. There were no significant differences in age or BMI between the lymphedema and non-lymphedema groups at any time point. Regarding severity, the 3-month and 6-month lymphedema cases were all Grade I; however, by 12 months, 20% of the cases in the lymphedema group had progressed to Grade II.

Regarding surgical procedures, the lymphedema group had more cases of total mastectomies and ALND levels II-III than the non-lymphedema group at each time point. Regarding adjuvant therapy, a higher proportion of patients received postoperative chemotherapy in the lymphedema than in the non-lymphedema group. However, no significant differences related to preoperative chemotherapy or hormone therapy were found between the groups. Radiation therapy was significantly more common for the 12-month lymphedema group than for the non-lymphedema group.

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Table 1: Backgrounds of the patient with and without of BCRL at 1,3,6 and 12 months postoperatively.

Characteristic	1 Month Post-op (n= 114)		3 Months Post-op (n= 104)		6 Months Post-op (n= 86)		12 Months Post-op (n= 78)	
	Onset (n= 0)	Non-onset (n= 114)	Onset (n= 5)	Non-onset (n= 99)	Onset (n= 17)	Non-onset (n= 79)	Onset (n= 15)	Non-onset (n= 63)
Age, y	—	60.5 ± 7.6	62.1 ± 9	64.8 ± 6.6	58 ± 8.9	60.8 ± 8.1	64 ± 6	59.2 ± 9.2
Body Mass Index, kg/m²	—	23.2 ± 4.8	24 ± 3.2	24.8 ± 3.6	23.5 ± 2.9	23.1 ± 3	23.5 ± 3.2	23.2 ± 4.1
severity, %								
stage	—	—	5 (100.0)	—	17 (100.0)	—	12 (80.0)	—
stage	—	—	0 (0.0)	—		—	3 (20.0)	—
Surgical Side, % - Right	—	61 (53.5)	3 (60.0)	45 (45.0)	9 (52.9)	39 (49.4)	48 (20.0)	33 (52.0)
Mastectomy, %								
Partial	—	79 (69.0)	0 *	58 (58.6)	4 (23.5) *	65 (82.7)	4 (26.7) *	42 (66.7)
Total	—	35 (31.0)	5 (100.0) *	41 (41.4)	13 (76.4) *	14 (17.7)	11 (73.3) *	21 (33.3)
Axillary Lymph Node Dissection, %								
Level 1	—	12 (10.9)	0	34 (34.3)	1 (5.9)	18 (22.8)	3 (20.0)	17 (27.0)
Level 2	—	76 (66.7)	1 (20.0)	46 (46.5)	7 (41.1)	40 (50.6)	6 (40.0) *	25 (39.7)
Level 3	—	30 (26.3)	4 (80.0) *	19 (19.2)	6 (35.3) *	21 (26.6)	6 (40.0) *	21 (33.3)
Adjuvant Therapy, %								
Preoperative Chemotherapy	—	38 (33.5)	2 (40.7)	35 (35.4)	6 (35.3)	15 (19.0)	6 (40.0)	22 (34.9)
Postoperative Chemotherapy	—	80 (69.8)	3 (55.8)	60 (60.6)	11 (64.7) *	16 (20.3)	8 (53.3) *	38 (60.4)
Postoperative Hormone Therapy	—	0	0	18 (18.2)	7 (41.2)	29 (36.7)	5 (33.3)	23 (36.5)
Postoperative Radiotherapy	—	0	0	13 (13.1)	6 (35.3) *	18 (22.5)	10 (66.7)	21 (33.3)

Mean ± standard deviation or n (%)

For comparisons of continuous variables (e.g., age, BMI, etc.) of the incident and non-incident groups.

Independent T-tests were used. For comparisons of categorical data (e.g., percentage of total mastectomies, etc.).

Fisher's exact probability test was used for small sample sizes (e.g., 3-month incident vs. non-incident group) and chi-square test for other categorical data.

*: p<0.05 vs non-onset

Table 2 shows the changes in body composition of the 3-month lymphedema group. At 3 months, the lymphedema group showed increased ECW/TBW and decreased 5kHz impedance and PhA relative to their values at 1 month. The non-lymphedema group also showed increased ECW/TBW and decreased 5kHz impedance and PhA at 1 month relative to the preoperative and 3-month values. There were no significant differences in body composition between the lymphedema and non-lymphedema groups at 1 month.

Table 3 shows the changes in the body composition of the lymphedema group at 6 months. At 3 months, the lymphedema group had significantly higher ECW/TBW and lower 5kHz impedance and PhA than the non-lymphedema group. The cutoff values were 1.10 for ECW/TBW (AUC: 0.72, sensitivity: 0.70, specificity: 0.65), 0.90 for 5 kHz impedance (AUC: 0.75, sensitivity: 0.68, specificity: 0.66), and 0.85 for PhA (AUC: 0.71, sensitivity: 0.65, specificity: 0.60).

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Table 2: Comparison of the body composition indicators of the of the 3-month-onset group (n = 5) and no-onset group (n = 99).

Evaluation item	Group	Pre-operative			1 month			3 months		
ECW/TBW	Onset	1	±	0.04	1.09	±	0.07	1.12	±	0.19
	No-Onset	0.98	±	0.04	1.07	±	0.08	1.01	±	0.04
5kHz- impedance	Onset	1.02	±	0.03	0.87	±	0.05	0.85	±	0.04
	No-Onset	0.98	±	0.03	0.91	±	0.04	0.95	±	0.07
Phan	Onset	1.02	±	0.05	0.81	±	0.07	0.77	±	0.15
	No-Onset	0.98	±	0.05	0.87	±	0.05	0.96	±	0.06

Data are presented as ratios of the values for the affected side to those of the healthy side expressed as a percentage.

Mean ± SD

This table presents the descriptive statistics of the study's variables. No inferential statistical analyses were conducted, and the data are summarized using means, standard deviations, and proportions. The results are intended to provide an overview of the characteristics of the sample, without drawing conclusions about statistical significance.

Table 3: Comparison of the body composition indicators of the 6-month-onset (n=17) and no-onset (n=79) groups.

Evaluation item	Group	Pre-operative				1 month				3 months				6 months			
ECW/TBW	Onset	1	±	0.04	‡§‖	1.09	±	0.07	†‖	1.12	±	0.06	*†	1.18	±	0.07	*†‡§
	No-Onset	0.98	±	0.04	‡	1.07	±	0.08	†§‖	1.01	±	0.04	‡	1	±	0.03	‡
5kHz-impedance	Onset	1.02	±	0.03	‡§‖	0.87	±	0.05	*†	0.85	±	0.04	*†	0.81	±	0.03	*†‡§
	No-Onset	0.98	±	0.03	‡	0.91	±	0.04	†§‖	0.95	±	0.07	‡	0.98	±	0.02	‡
PhA	Onset	1.02	±	0.05	‡§‖	0.81	±	0.07	*†‖	0.77	±	0.15	*†	0.75	±	0.14	*†‡
	No-Onset	0.98	±	0.05	‡	0.87	±	0.05	†§‖	0.96	±	0.06	‡	0.98	±	0.03	†

Data are presented as ratios of the values for the affected side to those of the healthy side expressed as a percentage

Mean ± SD

* $p < 0.05$ vs no-onset, † $p < 0.05$ vs pre, ‡ $p < 0.05$ vs 1 month

§ $p < 0.05$ vs 3 months, < 0.05 vs 6 months

Table 4 shows the changes in body composition for the 12-month lymphedema group. At 6 months, the lymphedema group had significantly lower 1 kHz and 5 kHz impedance s and PhA than the non-lymphedema group. The cutoff values were 0.88 for 5kHz impedance (AUC, 0.68; sensitivity, 0.65; specificity, 0.64) and 0.84 for PhA (AUC, 0.70; sensitivity, 0.66; specificity, 0.64) (Table 5).

Changes in Shoulder Range of Motion and Grip Strength

Tables 6 and 7 show the changes in the shoulder range of motion and grip strength of the lymphedema group based on comparison with those of the non-lymphedema group at 6 and 12 months. For both the lymphedema and non-lymphedema groups, the ratio of the number of affected to unaffected limbs for all shoulder movements and grip strength decreased at 1 month postoperatively but gradually recovered after 3 months. The range of external rotation of the shoulder of the lymphedema group was not significantly different from that of the non-lymphedema group at 6 months but was significantly reduced at 12 months. However, no significant differences were observed in grip strength between the lymphedema and non-lymphedema groups at any time point.

Table 4: Comparison of the body composition indicators of the 12-month-onset (n=15) and no-onset (n=63) groups.

Evaluation item	Group	Pre-operative				1 month				3 months				6 months				12 months			
ECW/TBW	Onset	1.02	±	0.04	‡‖¶	1.9	±	0.07	†§‖¶	1.04	±	0.06	‡¶	1.04	±	0.09	‡¶	1.1	±	0.14	†‡§
	No-Onset	0.98	±	0.09	‡§	1.08	±	0.05	†§‖¶	1.01	±	0.04	‡	1.01	±	0.06	‡	0.99	±	0.06	‡
5kHz- impedance	Onset	1.04	±	0.04	‡§‖¶	0.85	±	0.07	†§	0.89	±	0.04	†‡‖	0.86	±	0.03	†§¶	0.83	±	0.05	†‡§
	No-Onset	0.98	±	0.13	‡	0.89	±	0.04	†§‖¶	0.95	±	0.07	‡‖	0.97	±	0.02	‡	0.99	±	0.03	‡§
PhA	Onset	1.02	±	0.08	‡§‖¶	0.88	±	0.05	†§‖¶	0.84	±	0.07	†‡‖¶	0.81	±	0.06	†‡§¶	0.77	±	0.06	†‡§
	No-Onset	0.99	±	0.05	‡§	0.87	±	0.05	†§‖¶	0.94	±	0.07	†‡‖¶	0.98	±	0.05	‡§	0.99	±	0.04	‡§

Data are presented as ratios of the values for the affected side to those of the healthy side expressed as a percentage

Mean ± SD

Two-way ANOVA

* $p < 0.05$ vs no-onset, † $p < 0.05$ vs pre, ‡ $p < 0.05$ vs 1 month

§ $p < 0.05$ vs 3 months, ‖ $p < 0.05$ vs 6 months, ¶ $p < 0.05$ vs 12 months

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Table 5: Receiver operating characteristic curve analysis of body composition indicators of the 6- and 12-month lymphedema onset groups.

Evaluation item		6-month onset group	12-month onset group
ECW/TBW	AUC	0.72 (0.64 - 0.80)	-
	Sensitivity (%)	70	-
	Specificity (%)	65	-
	Cut-off Value	1.1	-
5kHz-impedance	AUC	0.75 (0.67 - 0.83)	0.68 (0.59 - 0.77)
	Sensitivity (%)	68	65
	Specificity (%)	66	64
	Cut-off Value	0.9	0.88
PhA	AUC	0.71 (0.63 - 0.79)	0.70 (0.62 - 0.78)
	Sensitivity (%)	65	66
	Specificity (%)	60	64
	Cut-off Value	0.85	0.84

( ) Figures in parentheses indicate 95% confidence intervals

Table 6: Comparison of the upper extremity functions of the 6-month onset (n=17) and no-onset (n=69) groups.

			Pre-operative				1 month				3 months				6 months			
Shoulder joint range of motion	**flexion**	**Onset**	**1.05**	±	**0.42**	‡§‖	**0.73**	±	**0.27**	†§‖	**0.88**	±	**0.3**	†‖	**0.96**	±	**0.57**	†§
		No-Onset	0.98	±	0.41	‡§‖	0.7	±	0.35	†§‖	0.92	±	0.58	†‖	0.97	±	0.67	†§
	abduction	Onset	1.03	±	0.44	‡§‖	0.7	±	0.27	†§‖	0.85	±	0.57	†‖	0.93	±	0.82	†§
		No-Onset	1.02	±	0.37	‡§‖	0.73	±	0.29	†§‖	0.85	±	0.72	†‖	0.93	±	0.4	†§
	external rotation (Second position)	Onset	0.97	±	0.36	‡§‖	0.62	±	0.64	†§‖	0.81	±	0.44	†‖	0.78	±	0.74	†§
		No-Onset	1.04	±	0.4	‡§‖	0.6	±	0.72	†§‖	0.78	±	0.6	†‖	0.81	±	0.72	†§
Grip		Onset	1.03	±	0.76	‡§‖	0.7	±	0.65	†§‖	0.84	±	0.4	†‖	0.9	±	0.5	†§
		No-Onset	0.99	±	0.36	‡§‖	0.73	±	0.4	†§‖	0.8	±	0.65	†‖	0.92	±	0.71	†§

Data are presented as ratios of the values for the affected side to those of the healthy side expressed as a percentage

Mean ± SD

Two-way ANOVA

† p < 0.05 vs pre, < 0.05 vs 1 month

§ p < 0.05 vs 3 months, < 0.05 vs 6 months

Table7: Comparison of the physical functions of the 12-month onset (n= 15) and no-onset (n= 63) groups.

			Pre Operation				1 Month				3 Month				6 Month				12 Month			
Shoulder joint range of motion	**Flexion**	**Onset**	**1.05**	±	**0.43**	‡§	**0.73**	±	**0.63**	†‡	**0.92**	±	**0.31**	†	**0.97**	±	**0.26**	†‡§	**0.95**	±	**0.56**	†‡
		No-Onset	0.98	±	0.45	‡§	0.71	±	0.55	†‡	0.92	±	0.6	†	0.96	±	0.66	†‡§	98	±	0.39	†‡
	Abduction	Onset	1.03	±	0.52	‡§	0.77	±	0.78	†‡	0.88	±	0.74	†	0.93	±	0.85	†‡§	0.98	±	0.5	†‡‖
		No-Onset	1.02	±	0.54	‡§	0.75	±	0.45	†‡	0.85	±	0.82	†	0.93	±	0.38	†‡§	0.96	±	0.29	†‡‖
	External rotation (Second position)	Onset	0.97	±	0.68	‡§	0.67	±	0.62	†‡	0.79	±	0.43	†	0.86	±	0.8	†‡§	0.77	±	0.4	‖†‖
		No-Onset	1.04	±	0.39	‡§	0.66	±	0.7	†‡	0.78	±	0.65	†	0.84	±	0.53	†‡§	0.86	±	0.64	†‡
Grip		Onset	1.03	±	0.73	‡§	0.7	±	0.82	†‡	0.83	±	0.58	†	8.7	±	0.3	†‡§	0.94	±	0.42	†‡‖
		No-Onset	0.99	±	0.25	‡§	0.74	±	0.31	†‡	0.84	±	0.33	†	8.9	±	0.31	†‡§	0.92	±	0.73	†‡‖

Data are presented as ratios of the values for the affected side to those of the healthy side expressed as a percentage

Mean ± SD

Two-way ANOVA

*p < 0.05 vs no-onset, † p < 0.05 vs pre, ‡ p < 0.05 vs 1 month

§ p < 0.05 vs 3 months, ‖ p < 0.05 vs 6 months

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Discussion

Changes in Body Composition

Kim et al [10]. reported that the PhA, limb volume, and ECW/TBW were correlated in patients with BCRL when they were divided into mild and moderate-to-severe groups, and body composition was measured using the BIA method. Additionally, Solji [19] used PhA to evaluate the effectiveness of lymphaticovenular anastomosis for secondary lymphedema following breast cancer surgery and demonstrated that PhA decreased with increasing lymphedema severity but increased 6 months after the procedure. These reports indicate that ECW/TBW increases and PhA decreases proportionally with severity in cases where lymphedema has already developed. In contrast, this study confirmed increased ECW/TBW and decreased PhA before a noticeable increase in limb volume, suggesting that these are important indicators of volume increase. Changes in body composition at 3, 6, and 12 months were consistently observed in the lymphedema group. Notably, changes in body composition were observed in the 6-month lymphedema group at 3 months and in the 12-month lymphedema group at 6 months. These indicators may facilitate the early detection of lymphedema and help prevent its progression through early intervention. Lymphedema is characterized by excessive accumulation of interstitial fluid in the subcutaneous tissue due to impaired lymphatic drainage. With the BIA method, interstitial fluid is calculated as ECW. ECW/TBW is the ratio of ECW to TBW. Typically, ECW tends to increase relative to TBW when there is edema, resulting in a higher ECW/TBW ratio [20]. Therefore, a slight increase in ECW was observed even when there was no apparent increase in the limb volume, leading increased ECW/TBW ratio. For DSM-BIA, high-frequency currents can pass through cell membranes, but low-frequency currents near zero frequency cannot, because the cell membrane acts as an insulator [21]. Therefore, the resistance values obtained from the low-frequency currents were less affected by the ICW and reflected the state of the ECW more sensitively. Similarly, the 5kHz impedance of the 6-month lymphedema group was significantly higher at 3 months than that of the non-lymphedema group, suggesting changes in the characteristics of extracellular fluid such as its viscosity and protein concentration.

The PhA is the angle calculated from the resistance and reactance, which represents the opposition to the current flow through the tissues of the body. Resistance represents the direct resistance to current flow due to body fluids and electrolytes, and reactance represents the phase delay caused by the cell membrane. The PhA is useful for predicting cellular health and nutritional status, particularly as an indicator of muscle quality [22]. In limbs affected by lymphedema, ECW increases and low-frequency impedance decreases with PhA reduction as a potential mechanism. The pathophysiology of lymphedema involves not only the accumulation of lymphatic fluid but also multiple factors acting in combination. For example, in lymphedema-affected limbs, there is a breakdown in the acquired immune response breaks down; dendritic cells fail to present antigens to the lymph nodes via the lymphatic vessels, leading to local immunodeficiency [23]. Moreover, tissues with lymphedema are dominated by helper T cells and type 2 macrophages, which are associated with a chronic inflammatory state [24]. As these reports suggest, prolonged inflammation may lead to electrolyte imbalance between the vascular and extravascular compartments. This increases ECW and 5kHz impedance, which adds strain to the lymphatic system. Tassenoy [25] demonstrated changes in the subcutaneous tissue with lymphedema in patients with breast cancer using ultrasound imaging and suggested that these changes preceded the volume increase. Furthermore, Mihara et al [26]. reported that histological changes in the collecting lymphatic vessels due to increased pressure within the lymphatic vessels caused by lymph node dissection preceded the onset of lymphedema. Therefore, PhA may reflect inflammation and increased cell membrane permeability in the affected limb due to immune dysfunction resulting from lymphatic dysfunction, as well as subtle structural changes in the subcutaneous tissue and lymphatic vessels.

Regarding the progression of body composition, the 6-month lymphedema group showed changes in all parameters (ECW/TBW, 5kHz impedance, and PhA) at 3 months relative to the non-lymphedema group, while the 12-month lymphedema group only showed changes in 5kHz impedance and PhA at 6 months. This suggests that 5kHz impedance and PhA are sensitive indicators of changes in extracellular fluid status and subtle changes in cell membranes, which may reflect the gradual progression of lymphedema in the 12-month lymphedema group. The range of motion for shoulder external rotation for the 12-month lymphedema group was significantly reduced relative to that of the non-lymphedema group, although no significant difference was observed between the groups at 6 months. Initially, it was hypothesized that a decrease in the shoulder range of motion would contribute to the onset of lymphedema. However, the results differed from our hypothesis, suggesting that the reduced range of motion is a secondary phenomenon accompanying the progression of lymphedema rather than a contributing factor to its onset. A possible reason for the restriction of the shoulder range of motion is the increased weight of the affected limb due to a noticeable increase in volume. The upper limb is supported by the scapula. Therefore, the scapula tends to abduct, rotate internally, tilt anteriorly, and rotate downward as the weight of the affected limb increases. In the 90° abduction position of the shoulder, changes in the position of the scapula may reduce the mobility of the glenohumeral joint, resulting in restricted external rotation. Additionally, tissue damage around the shoulder joint caused by ALND and radiation therapy can significantly

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affect the range of motion. Kissin et al [27]. reported that radiation therapy affects shoulder flexibility in patients with lymphedema after breast cancer treatment. External rotation motion can be restricted to the shoulder abduction position, where the pectoralis minor and major muscles, impacted by ALND, are stretched. Moreover, after the onset of BCRL, patients may unconsciously avoid external shoulder rotation to prevent pain and discomfort, leading to functional decline in the upper limb. Mak et al [28]. suggested that movement of the shoulder joint is restricted in patients with lymphedema to avoid pain, which could result in reduced external rotation range of motion. If such avoidance behaviors persist over time, the muscle strength in the external rotators may deteriorate, further limiting the range of motion. Thus, the decrease in shoulder external rotation range of motion following BCRL onset appears to result from multiple factors that act in combination with its gradual progression. The reduction in the external rotation range of motion of the 12-month lymphedema group likely progressed gradually between 6 and 12 months postoperatively. Rietman et al. reported long-term upper limb functional impairment after breast cancer treatment, suggesting that range of motion limitations may become more apparent over time [29]. During this period, the progression of lymphedema and associated tissue changes may have gradually accumulated, eventually manifesting as a significant restriction in range of motion at 12 months. In conclusion, the onset of lymphedema may affect shoulder range of motion. In the 12-month lymphedema group, changes in upper limb body composition were observed at 6 months, indicating an increased risk of restricted shoulder external rotation range of motion with increased volume. Therefore, it is important to consider direct treatments for edema, such as preventive compression therapy, when changes in body composition are detected to minimize lymph fluid stasis and prevent an increase in upper limb volume. In addition, it is necessary to incorporate rehabilitation approaches aimed at maintaining and improving the shoulder range of motion at an early stage. Maintaining and improving the external rotation range of motion at 90° of shoulder abduction is crucial, as this may help mitigate the impact of BCRL. The grip strengths of the 12-month lymphedema and non-lymphedema groups were not significantly different. This suggests that grip strength was not significantly affected by the onset or progression of lymphedema.

Several factors may explain the lack of significant differences in grip strength between the groups. First, shoulder use in a dependent position may not have been significantly restricted. Grip strength is often exerted with the shoulder in a dependent position, where it is less influenced by shoulder or upper limb movements, and lymphedema-related joint range of motion restrictions may have had a less direct impact on grip strength. In daily life, many tasks involving the hands are performed with the shoulders in a dependent position, which may help maintain grip strength. A study by Mistry et al [30]. suggested that lymphedema has a limited impact on grip strength during movements performed with the shoulder in a dependent position. Furthermore, as the BCRL progresses and the volume of the upper limb increases, a sustained load is applied to the upper limb and shoulder girdle muscles. This load may act as a natural resistance to maintain grip strength and prevent muscle weakness. Gomes et al [31]. suggested that an increase in upper limb weight due to lymphedema contributes to maintaining muscle strength, which may paradoxically help preserve grip strength. Additionally, lymphedema primarily develops from the proximal lymph nodes and gradually progresses distally, meaning that the muscles of the forearm and fingers may be less directly affected. This preserves grip strength even when the volume increase becomes apparent [30].

Association Between Adjuvant Therapy and Onset

The 6-month and 12-month lymphedema groups had higher rates of chemotherapy relative to the non-lymphedema groups at the same time points, and the 12-month lymphedema group had a higher rate of radiation therapy. Chemotherapy can increase capillary permeability [32], and radiation therapy may directly damage lymphatic vessels and lymph nodes, leading to soft tissue fibrosis, which can obstruct lymphatic flow and cause lymphedema [33]. The results of this study support previous reports that adjuvant therapies such as chemotherapy and radiation therapy are associated with the onset of lymphedema. However, the body composition of the 6-month lymphedema group was compared with that of the non-lymphedema group at 3 months and with that of the 12-month lymphedema group at 6 months. Therefore, the timing of the body composition measurements may have included cases in which adjuvant therapy had not yet started or was ongoing. As a result, it was not possible to determine the extent to which adjuvant therapy influenced the changes in body composition. Changes in body composition before lymphedema onset may be affected by adjuvant therapy, but detailed data on adjuvant therapy are necessary to accurately assess the degree of this influence. Jinbo et al [34]. identified a significant association of the extent of axillary lymph node dissection with the risk of lymphedema onset using decision tree analysis. In this study, all patients in the 3-month lymphedema group underwent total mastectomy and Level III lymph node dissection. The 6- and 12-month lymphedema group had more advanced lymph node dissection. This suggests that these highly invasive surgeries, involving extensive lymph node removal and damage to lymphatic vessels, significantly disrupted lymphatic circulation and increased the risk of lymphedema. Therefore, subtle changes in body composition may have occurred early after surgery due to the direct impact of the surgery, and they may have triggered the onset of lymphedema when combined with adjuvant therapy.

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Limitations of the Study

This study has several limitations. First, it was a retrospective observational study, and it was limited in determining causality. The participants were also limited to those with breast cancer from a single institution, which necessitates caution when generalizing the results. In addition, technical errors and subjective differences in body composition, joint range of motion, and muscle strength assessments must be considered. This study lacked detailed data on adjuvant therapy. Specifically, information on the type, dose, and duration of chemotherapy and radiation therapy were not included, making it difficult to accurately assess the impact of these treatments on the onset and progression of lymphedema. Therefore, future studies should consider the impact of adjuvant therapy on body composition and upper limb function. Future studies should collect more detailed data on adjuvant therapy to accurately assess the effect of treatment on the onset and progression of lymphedema. Additionally, conducting multicenter collaborative studies is important for generalizing the results across different patient populations. Furthermore, prospective studies are needed to evaluate the effectiveness of preventive interventions to strengthen the evidence for lymphedema prevention and treatment and facilitate their adoption in clinical practice.

Conclusion

This study revealed that changes in ECW/TBW, 5kHz impedance, and PhA during the early period after breast cancer surgery are useful indicators for predicting the onset of lymphedema. Additionally, the reduction in shoulder external rotation range of motion may be a secondary phenomenon accompanying the progression of lymphedema. These findings provide foundational insights for early detection and prevention of lymphedema. Future clinical applications are anticipated.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest.

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