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L-DEX RATIO IN DETECTING BREAST CANCER-RELATED LYMPHEDEMA: RELIABILITY, SENSITIVITY, AND SPECIFICITY

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ABSTRACT

Advances in bioelectrical impedance analysis (BIA) permit the assessment of lymphedema by directly measuring lymph fluid changes. The objective of the study was to examine the reliability, sensitivity, and specificity of cross-sectional assessment of BIA in detecting lymphedema in a large metropolitan clinical setting. BIA was used to measure lymph fluid changes. Limb volume by sequential circumferential tape measurement was used to validate the presence of lymphedema. Data were collected from 250 women, including healthy female adults, breast cancer survivors with lymphedema, and those at risk for lymphedema. Reliability, sensitivity, specificity and area under the ROC curve were estimated. BIA ratio, as indicated by L-Dex ratio, was highly reliable among healthy women (ICC=0.99; 95% CI = 0.99 - 0.99), survivors at-risk for lymphedema (ICC=0.99; 95% CI = 0.99 - 0.99), and all women (ICC=0.85; 95% CI = 0.81 - 0.87); reliability was acceptable for survivors with lymphedema (ICC=0.69; 95% CI = 0.54 to 0.80). The L-Dex ratio with a diagnostic cutoff of >+7.1 discriminated between at-risk breast cancer survivors and those with lymphedema with 80% sensitivity and 90% specificity (AUC=0.86). BIA ratio was significantly correlated with limb volume by sequential circumferential tape measurement. Cross-sectional assessment of BIA may have a role in clinical practice by adding confidence in detecting lymphedema. It is important to note that using a cutoff of L-Dex ratio >+7.1 still misses 20% of true lymphedema cases, it is important for clinicians to integrate other assessment methods (such as self-report, clinical observation, or perometry) to ensure the accurate detection of lymphedema.

Keywords: L-Dex, lymphedema, breast cancer, impedance, bioimpedance, impedance ratio

As a syndrome of chronic swelling and multiple symptoms, breast cancer-related lymphedema remains a major health problem presenting complex psychosocial distress and physical challenges to many thousands of breast cancer survivors (1-3). Breast cancer-related lymphedema is the result of obstruction or disruption of the lymphatic system associated with cancer treatment (e.g., removal of lymph nodes and/or radiotherapy), influenced by patient personal factors (e.g., obesity or higher body mass index), and triggered by factors such as infections or trauma (2,4-5). The American Cancer Society

estimates that in 2013 there will be approximately 232,340 new cases of breast cancer in the US and approximately 2.9 million breast cancer survivors living in the US are at life-time risk for lymphedema (6). Even with the most conservative estimate at 12-month after breast cancer surgery that 3% breast cancer survivors with sentinel lymph node biopsies and 20% of those who have axillary dissections have developed lymphedema (7), this is still a very large number of women who face the challenge of this progressive and debilitating condition.

It remains a major challenge to accurately detect and diagnose breast cancer-related lymphedema. The measurement of lymphedema presents particular difficulties for researchers and clinicians. Traditionally, lymphedema has been clinically diagnosed by healthcare providers' observations of swelling, and has often been defined in research as a 2-cm increase in limb girth or a 200-mL or more difference in limb volume comparing affected (or lymphedematous) and unaffected limbs (7-9). In clinical practice, the detection and diagnosis of lymphedema often relies on healthcare providers' observation of swelling. In research, indirect assessment methods are usually used focusing on measuring limb size or limb volume, such as water displacement (8), infrared perometry (9), and sequential circumference limb tape measurement (7,10). The criteria are inconsistent for determining the presence of lymphedema in research. The most commonly accepted definition of lymphedema is a 2-cm increase in limb girth or a 2-cm inter-limb difference, a 200 mL increase in limb volume or a 10% limb volume change (7-8,10). Such indirect assessment methods do not distinguish bones, muscle, fat, or other soft tissues from lymph or extracellular fluid (10). Changes in muscle, fat, and soft tissues may cause inaccurate limb size or limb volume and circumferential limb measurements, leading to misinterpretation and a false positive lymphedema diagnosis (10). In addition, circumferential limb measurement has limited inter- and intra-rater reliability (8), water displacement is cumbersome and messy, and infra-red perometry is costly (8).

Advances in bioelectrical impedance analysis (BIA) permit the assessment of breast cancer-related lymphedema by directly measuring lymph fluid changes (11). As a result of an accumulation of excess lymph fluid, breast cancer related lymphedema usually leads to an overall increase in the total amount of extracellular fluid in the affected limb (11). Using a single constant frequency of applied current, BIA assesses lymph fluid change by measuring the impedance or opposition to a low level electric current traveling through the body (12-13). Since the low frequency current travels predominately through the extracellular fluid due to its inability to pass through cell membranes, it is possible to measure directly the extracellular fluid (11-13). As extracellular fluid volume increases, impedance to current flow decreases (14). By measuring electrical impedance, BIA is able to provide an impedance ratio, i.e., the impedance of the low frequency current measured in the unaffected limb divided by that of the affected or at risk limb, to calculate a Lymphedema Index termed as L-Dex ratio (11,14). With development of lymphedema, impedance of the extremity decreases and the L-Dex ratios therefore increases. The L-Dex ratio ranges from -10 to +10, which is equivalent to the impedance ratio from 0.935 to 1.139 for at-risk dominant arms and 0.862 to 1.066 for at-risk non-dominant arms, respectively. Each one standard unit in L-Dex is equivalent to the impedance ratio of 0.03. Using an arbitrary scale relevant to normative standards, a patient is determined to have arm lymphedema or arm swelling if the patient's L-Dex ratio exceeds the normal value of +10, i.e., exceed impedance ratio means of 1.139 for at-risk dominant arms and 1.066 for at-risk non-dominant arms, respectively (14). *Table 1* shows the corresponding L-Dex ratio and impedance ratio indices.

TABLE 1
Examples of L-Dex Ratio Corresponding to Impedance Ratio Indexes

L-Dex	Ratio	L-Dex	Ratio
-10	0.935	1	1.047
-9	0.945	2	1.057
-8	0.955	3	1.068
-7	0.966	4	1.078
-6	0.976	5	1.088
-5	0.986	6	1.098
-4	0.996	7	1.108
-3	1.006	8	1.119
-2	1.017	9	1.129
-1	1.027	10	1.139
0	1.037		

Despite its value in assessing lymphedema, the use of BIA in clinical settings is still very limited. In part, this may be due to anecdotal complaints from clinicians about BIA's ability to identify true case of lymphedema in the clinical settings using L-Dex ratio >+10 as the cutoff point for lymphedema diagnosis. Perhaps, the main reason is that pre-surgical BIA baseline and sequential measures are not a common clinical practice in most clinical settings. This makes it difficult to use BIA as a detecting and diagnostic tool since pre-surgical BIA baseline measure is required as the reference because lymphedema is defined as 3 standard deviations from the pre-surgical BIA baseline measure recorded for each patient (11). In addition, there is a lack of clinical data to support the reliability, sensitivity, and specificity of cross-sectional assessment of BIA using L-Dex ratio. Research efforts are needed to establish the reliability, sensitivity and specificity of cross-sectional assessment BIA using L-Dex ratio in assessing lymphedema in clinical settings.

PURPOSE OF THE STUDY

The purposes of this study were to: (1) estimate the reliability, sensitivity, specificity, and area under the ROC curve for cross-sectional assessment of BIA to detect arm lymphedema; (2) explore the relationship between BIA and sequential circumferential tape measurement using the most commonly accepted definition of lymphedema as a 200-mL difference in limb volume when comparing the affected and unaffected limb; and (3) examine the relationships between BIA and lymphedema risk factor of body mass index (BMI).

METHODS

Ethical Consideration

This study was approved by the Institutional Review Board of NYU Langone Medical Center.

Research Design and Participants

This cross-sectional study used contrast-group and test-retest methods. A purposive sampling method was used to recruit participants with different representations of lymphedema. A sample of 250 adult female participants was recruited from a metropolitan cancer center and communities in the metropolitan area of New York City in 2010-2011. All participants met the following criteria: (i) 18 years of age or older and (ii) able to read and write in English language. Participants were divided into three groups: healthy female adults, breast cancer survivors with lymphedema and those at risk for lymphedema. Breast cancer survivors at risk for lymphedema must have completed surgical treatment as well as chemotherapy or radiation or both for breast cancer within prior five years of the study enrollment. Women were excluded from the study if they had bilateral breast disease, recurrent cancer, artificial limb or knee or hip, and kidney or heart failure, as the industry suggests BIA may not be accurate under these conditions.

Since the majority of breast cancer survivors are female adults, we selected

healthy female adults without a history of breast cancer and lymphedema to serve as a healthy comparison group. We hypothesized healthy female adults would not have L-Dex ratio >+10. We used breast cancer survivors who had no lymphedema diagnosis and were never treated for lymphedema as the at-risk group for lymphedema. We hypothesized at-risk breast cancer survivors would not have L-Dex ratio >+10.

Breast cancer survivors with lymphedema served as the known lymphedema group. To be included in the lymphedema group, the participants must have met all the following inclusion criteria: (a) had a lymphedema diagnosis and were treated for lymphedema at least 6 months prior to the enrollment of the study; (b) confirmed by self-report that they had lymphedema after breast cancer treatment; and (c) confirmed by the researchers to have at least a 200-mL difference in limb volume when comparing the affected and unaffected limb using sequential circumferential arm measurements (8,15). A sequential circumferential tape measurement protocol established by Armer and colleagues and used previously by the authors was used (8,15). A flexible, non-compliant woven Juzo tape measure was used on both the ipsilateral and contralateral limbs. The same two researchers were trained and completed the sequential circumferential tape measurement for all the participants. We hypothesized survivors with lymphedema would have L-Dex ratio >+10.

Measures and Instruments

Demographic and Medical Information: A structured interview tool (15,16) was used to gather demographic and medical and clinical information regarding breast cancer and lymphedema diagnosis, stage of diseases, cancer and lymphedema location, type of adjuvant therapy, weight and height, and treatment complications.

Body Mass Index (BMI): An electrical scale (Scale Tronix. Inc) was used to measure the participants' weight and height. The scale was able to calibrate each time before measuring a participant. BMI was calculated using the formula: weight (kg) / height (m^2).

Bioelectrical Impedance Analysis (BIA): The Imp XCA®, a FDA approved device, was used to measure the extracellular fluid. The Imp XCA® (Impedimed, Brisbane, Australia) uses a single frequency below 30 kHz to measure impedance and resistance of the extracellular fluid. The device uses an impedance ratio value relative to normative standards derived from healthy individuals (14) to calculate a Lymphedema Index termed as the L-Dex ratio. The L-Dex ratio ranges from -10 to +10, taking into consideration the ratio between dominant and non-dominant arms, which is equivalent to impedance ratios from 0.935 to 1.139 for at-risk dominant arms and 0.862 to 1.066 for at-risk non-dominant arms, respectively (14, 15). Using this arbitrary scale, a patient is determined to have arm lymphedema or arm swelling if the patient's L-Dex ratio exceeds +10 (14). Since there are no existing data to support the sensitivity and specificity of BIA using L-Dex ratio >+10 as the diagnostic cutoff point for lymphedema diagnosis in clinical settings, we determined the best cutoff point of L-Dex ratio for the sample, one that maximized the sum of sensitivity and specificity (17-18).

Procedures for Imp XCA® recommended by the industry were followed. Participants were placed in a fully supine position with arms extended 30 degrees from the body by their sides and legs not touching. Two dual-tab electrodes were placed respectively on the dorsum of the right and left wrists adjacent to the ulnar styloid process extending to just proximal to the third metacarpophalangeal joint of the dorsum of the hands; one dual-tab electrode was placed on anterior to the right ankle joints between the malleoli, extending to the dorsum of the right foot over the third metatarsal bone just proximal to the third metatarsophalangeal joint.

Data Collection

Researchers were oriented and trained to the procedure for obtaining informed consent and collecting data. After the institutional review board approved the study, the study invitation was distributed to patients by the physicians, nurses, and lymphedema therapists who cared for the patients and to the healthy female adults living in the communities in New York City. If a patient or a healthy female adult was interested in the study, the potential participant would notify the researchers. The researchers then met with all patients and healthy female adults who responded to the study invitation to confirm the study criteria and provide a detailed explanation of study. Participants were informed that their participation was voluntary, anonymous, and confidential. Participants were also told that they had the right to withdraw from the study at any time without any penalty and effect on their current treatment. Written consent to the study was obtained from each participant.

To measure the stability of BIA, a test-retest method was used with healthy group (n=60 healthy female adults), the lymphedema group (n=42 breast cancer survivors with lymphedema), and at-risk group (n=150 breast cancer survivors at risk for lymphedema). For test-retest procedures, the second administration generally is recommended about 2-14 days after the first administration (19). Because of the attributes of the phenomena being measured (extracellular fluid), we collected tests and retests of BIA consecutively at a five-minute interval between each measurement for three times of measurement to preclude any activities between each measurement (i.e. drinking coffee or physical exercises) that might influence the levels or stability of extracellular fluid. The same two researchers completed the repeated measures for all the participants.

Data Analysis

Data were analyzed using the freely-available, open-source *R* program (20) and SPSS version 20.0 (Chicago, IL, USA). All statistical tests were conducted at the 0.05 significance level and all estimates included a 95% confidence interval (CI). Descriptive statistics were calculated to describe the characteristics of the participants. Chi-Squared tests for contingency tables and one-way analysis of variance for continuous variables were used to compare study groups on demographic and clinical characteristics. The Pearson correlation coefficient was used to estimate associations between the BIA and BMI as well as the BIA and limb volume difference by sequential circumferential tape measurement.

Youden's method was used to examine the best cutoff point for the sample, one that maximizes the sum of sensitivity and specificity (17-18). Breast cancer survivors with arm lymphedema were used as the reference standard for calculation of sensitivity and specificity. **Sensitivity** represents the rate of true positive cases found by the index test, while **specificity** represents true negative cases. Diagnostic likelihood ratios (LR) were calculated (10):

LR+ = sensitivity / (1-specificity)
LR- = (1-sensitivity) / specificity

A LR+ greater than 5 and an LR- less than 0.2 provide meaningful information about the likelihood of having a given condition under assessment (10). Sensitivity and 1 minus specificity data over a range of lymphedema assessment outcomes were used to construct the ROC curves, and AUC was calculated with 95% Confidence Intervals (CIs) for continuous and dichotomous variables. Higher AUC values represent greater diagnostic accuracy (10). An AUC of 1.0 represents perfect sensitivity and specificity while an AUC of 0.5 represents a test with weak sensitivity and specificity (10). We also compared areas under the ROC curves using the L-Dex >+10 and the best cutoff point.

TABLE 2
Participants' Demographic Characteristics (n=250)

Variable	Lymphedema (n=42)		At Risk (n=148)		Healthy (n=60)		p value
	Mean	SD[a]	Mean	SD	Mean	SD	
Age	58.0	10.7	55.8	11.6	36.5	12.8	<0.001
Body Mass Index	28.8	7.11	25.5	4.99	26.9	7.12	0.02
Education	n	%	n	%	n	%	0.292
Less than High School	1	2.4	0	0	0	0	
High School	6	14.3	12	8.2	5	8.3	
Partial college	8	19.0	29	19.7	17	28.3	
College Graduate	15	35.7	43	29.3	21	35.0	
Graduate degree	12	28.6	62	42.2	17	28.3	
Marital Status	n	%	n	%	n	%	1.000
Single/ Divorced/Separated	20	47.6	69	46.6	-	-	
Married	22	52.4	79	53.4	-	-	
Employment	n	%	n	%	n	%	0.025
No	20*	48.8	43	29.3	0	0	
Yes	21	51.2	104	70.7	60	100	
Race	n	%	n	%	n	%	<0.001
White	23	54.8	119	82.1	24	40.0	
Non-White	19	45.2	26	17.9	36	60.0	

[a] SD: Standard Deviation
*One participant in lymphedema group missed employment data

Intraclass correlation coefficients (ICC) were used to assess stability (or agreement) among the three consecutive BIA measurements. To test the ability of BIA to differentiate the study groups, we compared the three study groups using one-way analysis of variance (ANOVA) and Tukey multiple comparisons of means for statistical significance of study group differences in terms of L-Dex ratio. We did not assume equal variances across the three study groups (21).

RESULTS

Description of Participants

A total sample of 250 participants completed the study. Data from 250 women included three study groups: 60 healthy female adults (24%), 42 breast cancer survivors who had been previously diagnosed with lymphedema (16.8%), and 148 breast cancer survivors who were at risk for lymphedema (59.2%). Participant demographic characteristics are presented in *Table 2*. Participants in the three groups were comparable in terms of education and marital status. The healthy adults were significantly younger than the breast cancer survivors with lymphedema and at-risk for lymphedema. Significantly more women in the lymphedema group were unemployed. Significantly more non-white women had lymphedema. Women in the lymphedema group had significantly higher BMI than women in the healthy and at-risk group. More women in the lymphedema

TABLE 3
Clinical Characteristics for Breast Cancer Survivors (n=190)

Variable	At-Risk (n=148)		Lymphedema (n=42)		P Value
	n	%	n	%	
Mastectomy	71	48.0	31	73.8	<0.01
Lumpectomy	97	65.5	16	38.1	<0.01
Radiotherapy	74	51.0	28	66.7	0.08
Chemotherapy	67	45.3	34	81.0	<0.01
Sentinel lymph node biopsy	134	90.5	23	54.8	<0.01
Axillary lymph node dissection	85	57.4	39	92.9	<0.01
	Mean	SD[a]	Mean	SD	
Number of nodes removed	8.0	8.7	19.4	11.9	<0.01
Years since cancer diagnosis	2.0	2.3	6.9	8.5	<0.01

[a] SD: Standard Deviation

TABLE 4
L-Dex Ratio by Study Group

L-Dex Ratio *†	Mean ± SD[a]	Median	Range Minimum	Range Maximum
Healthy	-1.0 + 3.6	-0.6	-9.7	7.7
At Risk	-0.1 + 6.0	-0.4	-9.6	36.9
Lymphedema	30.9 + 27.1	26.9	0.9	115.0

[a] SD: Standard Deviation; * Mean Scores differ significantly at p<0.001 between healthy and lymphedema group by the Tukey multiple comparisons of means; † Mean Scores differ significantly at p<0.001 between lymphedema and at-risk group by the Tukey multiple comparisons of means.

group had mastectomy, chemotherapy, and axillary lymph nodes dissection. *Table 3* shows breast cancer survivors' clinical characteristics in more detail.

Table 4 shows distributions of L-Dex ratio by study group, averaging the three measurements per participant. One-way analysis of variance without assuming equal variation across groups and followed by Tukey multiple comparisons showed large and significant L-Dex ratio differences among the three groups ($F[2,89.5] = 29.02$, $p < 0.001$). Specifically, the lymphedema group was significantly higher than both the healthy group ($p < 0.001$) and the at-risk group ($p < 0.001$). There was no significant L-Dex ratio difference between at-risk and healthy group ($p = 0.85$). As can be seen in *Table 4*, healthy adults and at-risk survivors had similar L-Dex ratio, which was rarely greater than +10, while women in the lymphedema group had L-Dex ratio that was greater than +10 for most women in that study group.

Reliability or Reproducibility of the BIA using L-Dex Ratio

TABLE 5
Reproducibility of BIA by Imp XCA® using L-Dex Ratio

	Test #1[a] Mean (SD)[b]	Test #2 Mean (SD)	Test #3 Mean (SD)	ICC (95% CI)[c]	*p Value*
Study Groups					
Total Sample	4.7 (16.0)	4.7 (16.0)	5.5 (20.7)	0.85 (0.81 to 0.87)	<0.0001
Healthy	-1.0 (3.6)	-1.0 (3.6)	-1.0 (3.6)	0.99 (0.99 to 0.99)	<0.0001
Lymphedema	29.3 (23.1)	29.4 (25.6)	34.0 (38.3)	0.69 (0.54 to 0.80)	<0.0001
At-Risk	0.0 (6.1)	0.0 (6.0)	0.0 (6.0)	0.99 (0.99 to 0.99)	<0.0001

[a] Raw L-Dex ratio scores; [b] SD: Standard Deviation; [c] CI: Confidence Interval; ICC: Intraclass Correlation Coefficient

A test-retest method was used to estimate reproducibility of BIA using L-Dex ratio by assessing consistency across three consecutive measurements among the healthy, lymphedema, and at-risk groups. As shown in *Table 5*, for BIA using L-Dex ratio, intraclass correlation coefficients (ICC) demonstrated strong stability (or agreement) among the three consecutive measurements for the healthy group with ICC = 0.99 (95% CI: 0.99 - 0.99) and at-risk group with ICC = 0.99 (95% CI: 0.99 - 0.99). Fair agreement of three consecutive measurements was achieved for lymphedema group with ICC =0.69 (95% CI: 0.58 - 0.82).

Sensitivity and Specificity

Analysis of the ROC curve for the BIA using L-Dex ratio as a continuous screening variable for discriminating between the lymphedema group and the healthy group yielded an AUC of 0.975 (95% CI: 0.951 - 0.999; p <0.001). Analysis of the ROC curve for BIA as a continuous screening variable for discriminating between the lymphedema group and the at-risk group yielded an AUC of 0.941 (95% CI: 0.907 - 0.976; p <0.001).

Using the recommended diagnostic cutoff of L-Dex ratio >+10, good discrimination of breast cancer survivors with lymphedema and healthy women was achieved [AUC=0.86 (95% CI: 0.76 - 0.91); sensitivity=0.66 (95% CI: 0.51 - 0.79); specificity=0.99 (95% CI: 0.93 - 0.99)]. Similarly, with the same diagnostic cutoff point of >+10, good discrimination of breast cancer survivors with lymphedema and at-risk women was achieved [AUC=0.81 (95% CI: 0.74 - 0.88); sensitivity=0.66 (95% CI: 0.51 - 0.79); specificity=0.95 (95% CI: 0.90 - 0.98)].

To discriminate breast cancer survivors with lymphedema from healthy women, the best diagnostic cutoff point was an L-Dex ratio of >+3.9 [AUC=0.93 (95% CI: 0.88 - 0.98); sensitivity=0.92 (95% CI: 0.80 - 0.97); specificity=0.93 (95% CI: 0.83 - 0.97)]. To discriminate breast cancer survivors with lymphedema from at-risk survivors, the best diagnostic cutoff point was an L-Dex ratio of >+7.1 [AUC=0.86 (95% CI: 0.79 - 0.92); sensitivity=0.80 (95% CI: 0.66 - 0.89); specificity=0.90 (95% CI: 0.84 - 0.94)].

Correlation of BIA and Sequential Circumferential Tape Measurements

Since greater than or equal to 200mL interlimb volume difference by sequential circumferential tape measurements between affected and unaffected limb has been used as the cutoff point for diagnosis of lymphedema in research (8,10), we dichotomized interlimb volume difference accordingly. We calculated

TABLE 6
Correlations between BMI and BIA using L-Dex Ratio

BMI	BIA as L-Dex Mean	Median	IQR[a]	BIA Correlation with BMI
Normal (< 25)	1.28	-0.57	5.500	-0.1017
Overweight (25 - 29)	4.30	0.70	7.750	0.0680
Obese (> 29)	9.31	1.53	8.200	0.1320

[a] IQR: the interquartile range

the limb volume ratio, comparing the affected with unaffected limbs so as to be able to compare the interlimb ratio to the L-Dex ratio. BIA and interlimb volume ratio were found significantly correlated (r=0.44; 95% CI: 0.16 to 0.66) (p<0.01).

Correlation of BMI and BIA

BMI levels were defined according to the World Health Organization classification system with normal being BMI values <25, overweight being BMI values 25-29, and obese being BMI values >29. The mean BMI of the healthy participants, known lymphedema and at-risk survivors was 26.9 (SD 7.12), 28.8 (SD 7.11) and 25.5 (SD 4.99), respectively. The BIA using L-Dex ratio measurements was observed to increase with increasing BMI values. The mean L-Dex ratio for normal BMI participants was 1.28, for overweight subjects 4.30, and for obese subjects 9.31. The BIA using L-Dex ratio was found to be weakly correlated with BMI within each defined level. The L-Dex ratio correlation with BMI was -0.101 in the normal range, 0.068 in the overweight range, and 0.132 in the obese (also see *Table 6*).

DISCUSSION

Lymphedema has been viewed by breast cancer survivors as the most feared and unfortunate outcome from breast cancer treatment given its negative impacts on survivors' overall quality of life (7,22). Over 50% of at-risk breast cancer survivors were found to be exceedingly worried about their risk of developing lymphedema (7). Multiple factors may be associated with the fear and worry of developing lymphedema among breast cancer survivors, including symptom experience, type of cancer surgery, education level, earlier experiences, or the way of how healthcare professionals provide education and counseling on risk reducing practices (23-24). It is possible that such fear and worry of developing lymphedema may also be associated with detecting and diagnostic inconsistency among multiple diagnostic methods, such as clinicians' diagnosis via observation, patients' symptom experience, and different cutoff point for lymphedema using different methods of tape measurement.

Accurate diagnosis of lymphedema following breast cancer requires reliable assessment. Our study provided evidence to support BIA using L-Dex ratio as a highly reliable method to assess lymphedema among healthy women and breast cancer survivors at-risk for lymphedema; reliability was acceptable for survivors with lymphedema. Since patients in the known lymphedema group have chronic lymphedema, the reduced reliability for BIA might be due to tissue changes (e.g., fibrosis), or adipose infiltration or more general adiposity. This is important because it underscores the need for observing

lymph fluid change using L-Dex ratio for each individual patient over time to guide lymphedema detection and diagnosis. Future study is needed to establish a baseline BIA measure prior to cancer surgery, and for consistent long-term, consecutive follow-up measures to confirm lymphedema diagnosis.

Our study demonstrated that survivors with lymphedema had significantly higher L-Dex ratios, indicating the potential use of cross-sectional assessment of BIA for detecting lymphedema without using pre-surgical BIA baseline as the reference. We hypothesized that both healthy female adults and breast cancer survivors who had no lymphedema diagnosis and were never treated for lymphedema would not have L-Dex ratio >+10, while breast cancer survivors with lymphedema were expected to have L-Dex ratios >+10. These expectations were confirmed in our data for most women.

Giving that all the women who were treated for breast cancer are at life-time risk for lymphedema, using assessment methods that can accurately identify true lymphedema cases among at-risk breast cancer survivors is of the ultimate importance for clinical practice. Perhaps, the most important contribution of our study was that it has provided evidence that, using a cutoff point of L-Dex ratio of >+7.1, cross-sectional assessment of BIA was able to discriminate at-risk breast cancer survivors and those with lymphedema. Using a cutoff point of L-Dex ratio of >+7.1 identified true lymphedema cases at 80% and discriminated true non-lymphedema case at 90%. In comparison, using the recommended cutoff point of L-Dex >+10 can only identity 66% of true lymphedema cases among at-risk breast cancer survivors, that is, miss 34% of true lymphedema cases (AUC=0.81 sensitivity=0.66 [95% CI: 0.51 - 0.79]), while achieve the identification of 95% of true non-lymphedema cases. Since early treatment usually leads to better clinical outcomes (25), it is important to have higher sensitivity to avoid missing a large number of true lymphedema cases. Using the diagnostic cutoff of L-Dex >+7.1, which is able to identify 80% of true lymphedema cases and 90% of non-lymphedema cases, may be an optimal choice for cross-sectional assessment of BIA.

Our study demonstrated a significant correlation between BIA by Imp XCA® and interlimb volume ratio by sequential circumferential tape measurements. This finding indicates that both objective measures of interlimb volume difference and lymph fluid change by BIA can be used to detect lymphedema objectively in clinical practice.

High BMI is a well-established risk factor for lymphedema, yet the causal relationship between lymphedema and high BMI remains unknown (26-28). Recent studies have postulated that a larger body mass may create a disparity in lymph transport and capacity, resulting in excess extracellular fluid (27). Despite the known link between BMI and lymphedema, our study only found an increasing trend of L-Dex ratio with increasing BMI, yet the correlations are weak and not significant. Further research is necessary to better elucidate the relationship between BMI and L-Dex ratio by BIA.

LIMITATIONS OF THE STUDY

Findings of our study should be considered with caution. Our study focused on the cross-sectional evaluation of reliability, sensitivity, and specificity of BIA in detecting lymphedema. Yet, it should be noted that the cross-sectional assessment of BIA limited the study's ability to prospectively examine the trajectory of lymphedema development among the breast cancer survivors. Additional studies are needed utilizing a longitudinal design to establish baseline (prior to treatment) using L-Dex ratio may be able to capture any change during and after treatment. It is possible some at-risk survivors might have developed lymphedema that was not clinically apparent, since some of the at-risk survivors did exceed L-Dex +10. Finally, it should be noted that at-risk breast cancer survivors had the lowest BMI, while healthy

adult women were younger and had lower BMI than breast cancer survivors with lymphedema. We recommend that in future research use healthy female women be more closely matched with breast cancer survivors on characteristics such as age and BMI.

CONCLUSIONS

Findings from our study showed that the BIA using L-Dex ratio was significantly related to interlimb volume difference by sequential circumferential tape measurement using the most commonly accepted definition of lymphedema as a 200-mL difference in limb volume when comparing the affected and unaffected limb. BIA was able to accurately discriminate healthy women, breast cancer survivors with lymphedema and at-risk survivors. Our study supports that cross-sectional assessment of BIA by Imp XCA® is a reliable measure for detecting arm lymphedema following breast cancer treatment with good sensitivity and specificity. The BIA by Imp XCA® is easy to operate and time-efficient, which makes it easy to adopt for clinical practice. In addition, the L-Dex ratio takes into consideration of the differences between dominant and non-dominant limbs, making it easy for clinicians to interpret the results, especially using the dichotomized L-Dex ratio of >+7.1 for lymphedema diagnosis. To lessen breast cancer survivors' worry about lymphedema development, the BIA may have a role in clinical practice by adding confidence in the detection of arm lymphedema among breast cancer survivors even when pre-surgical BIA baseline measures are not available. Finally, we recommend using the best cutoff point of L-Dex ratio >+7.1 instead of L-Dex >+10 to avoid missing a large number of false non-lymphedema cases when pre-surgical BIA baseline are not available. It should be noted that using the cutoff point of >+7.1 still misses 20% of true lymphedema cases. Given that lymphedema is a progressive and debilitating condition (7,22) and early treatment usually leads to better clinical outcomes (25), it is important for clinicians to integrate other assessment methods (such as self-report, clinical observation, or perometry) to ensure accurate detection and diagnosis of lymphedema.

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