



# Comparison of Volume Measurements and Bioimpedance Spectroscopy Using A Stand-on Device for Assessment of Unilateral Breast Cancer-Related Lymphedema

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## ABSTRACT

**Objective:** Breast cancer related lymphedema (BCRL) may be assessed through objective measurement of limb swelling with common techniques including volumetric measurement using a tape measure or perometry, and measurement of extracellular water using bioimpedance spectroscopy (BIS). This study aimed to evaluate the performance of a stand-on BIS device for detection of BCRL, introduce a novel graphical method to compare volumetric and BIS methods alongside traditional specificity and sensitivity analysis, and determine and compare BIS thresholds with those published previously.

**Materials and Methods:** Female participants with indocyanine green lymphography confirmed unilateral arm lymphedema (n=197) and healthy controls (n = 267) were assessed using a cross-sectional study design. BIS and volumetric measures were obtained in a single session.

**Results:** The BIS lymphedema index (L-Dex) method had a significantly higher sensitivity than the excess volume approach (area under the curve = 0.832 vs. 0.649,  $p = 0.0001$ ). A threshold of L-Dex 6.5 had a higher true positive rate (70.6%) than L-Dex 10 (68.5%) although false positive rate increased from 0.4% to 2.6%. A threshold of 5% excess volume improved the true positive rate (68.5%) compared with 10% excess volume (49.7%) however the false positive rate increased to an unacceptable 47%. The L-Dex ranges in this study were not significantly different from previously published ranges.

**Conclusion:** BIS was superior for identifying BCRL compared with volume measurements, reaffirming the value of this technique. However, it is recommended that BIS be used in conjunction with comprehensive evaluation of symptoms and clinical presentation. The proposed graphical method provides a simple and easily interpretable approach to compare and define concordance between the two commonly used methods for BCRL assessment namely limb volume and BIS L-Dex indices. The existing BIS (L-Dex) thresholds for presence of BCRL were also validated.

**Keywords:** Lymphedema; bioimpedance spectroscopy; impedance; L-Dex

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## Key Points

- BIS was superior for detecting BCRL compared with volume measurements.
- The current BIS (L-Dex) thresholds for lymphoedema presence were validated by this study.
- It is recommended that BIS be used as part of a comprehensive assessment of symptoms and clinical presentation.

## Introduction

Breast cancer related lymphedema (BCRL) is a dysfunction of the lymphatic system resulting from treatment for breast cancer (1). The precise etiology of the condition may vary due to direct surgical damage to the lymphatics through to damage due to radiation treatment rather than damage due to the presence of a tumour *per se* (2). BCRL is

characterised by swelling of the arm on the side of treatment due to accumulation of excess lymph through compromised lymph transport. The precise incidence of BCRL is uncertain, with estimates varying from 3 to 65% following surgery (3). Presentation may occur at any time but first occurrence is more prevalent within the first 2 years following treatment.

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It is generally recognised that the treatment of BCRL is most effective when commenced at the earliest opportunity (4). Early detection of BCRL is frequently by the patient first noting symptoms of early limb of heaviness and swelling, e.g. clothing or jewellery no longer fitting. However, limb swelling is not definitively diagnostic for BCRL. Confirmation of BCRL is best measured by assessing lymphatic function, e.g., by indocyanine green (ICG) lymphography coupled with full clinical appraisal (5). ICG lymphography is not, however, widely available and in addition to clinical assessment, the presence of BCRL is routinely assessed by objective but not consistent measurement of limb swelling. A wide variety of techniques are available for this purpose (6) but most commonly are firstly, simple volumetric measurement, either from geometric calculation from manual arm dimensional measures using a tape measure or by opto-electronic devices such as the Perometer™ and secondly, measurement of extracellular water (ECW) volume of which lymph is a principal component, by bioimpedance spectroscopy (BIS) (7). Neither arm volume nor BIS assessments measure lymph accumulation directly. The former measures overall limb volume and typically, the excess volume of the affected or at-risk arm is compared to that of the contralateral unaffected limb. Excess volume thresholds vary but typically an increase in limb size of 5% or larger is considered abnormal swelling and, in conjunction with clinical picture, is considered indicative of the presence of BCRL in an at-risk limb of affected individual (8). Bioimpedance spectroscopy measures the electrical impedance (resistance at zero frequency, R0) of the limbs and, as with volumetric measurements, compares the resistance of the affected limb to that of the unaffected limb, typically as a ratio or as a linearized ratio, the L-Dex score (9). Thresholds indicative of BCRL for BIS have been established based on the normal distribution of values seen in a healthy control population (10). These thresholds were determined using first generation BIS devices with measurements performed while the individual was in supine. Current model BIS instruments are stand-on devices with measurements made while the individual is standing (11). In addition, owing to the different postures, electrode locations are slightly different. Comparative studies have demonstrated that, while measurements with the two devices are highly correlated, they are not entirely interchangeable (11). Both volumetric and BIS methods exhibit high sensitivity and specificity although no consensus exists as to which method is optimal for BCRL assessment (12).

The current study aimed to assess the performance of the current stand-on BIS device for detection of BRCL. Secondly, a novel graphical method for comparison of volumetric and BIS methods was developed as an adjunct to conventional specificity and sensitivity analysis [receiver operating characteristic (ROC) curves]. Additionally, BIS thresholds were determined and compared to existing published thresholds.

## Materials and Methods

### Participants

Female participants (n = 197) with unilateral BCRL were recruited from those attending the Australian Lymphoedema Education, Research and Treatment Centre (ALERT) at Macquarie University. All participants underwent clinical evaluation by experienced lymphedema therapists and the existence of lymphedema was confirmed by ICG lymphography. All measurements were obtained in a single session by trained research assistants.

Healthy control women (n = 267) with no history of BCRL were drawn from a number of sources. Firstly, participants were recruited from the Macquarie University staff and students. Measurements were obtained in a single attendance session at the ALERT clinic. Secondly, healthy controls were drawn from a database of comparable measurement data maintained by the authors and were drawn from participants in two previously published studies (13, 14).

All participants were female aged between 18 and 83 years of age. Exclusion criteria were minimal reflecting the general population; participants fitted with an implantable device, e.g., a pacemaker or were pregnant (determined by self-attribution) were excluded as these are contraindicated for BIS measurements. Additionally, participants were excluded if they reported a health condition or medication that might affect body water status as this would confound BIS measurements.

Originating research studies providing data for the current analysis were all approved by their respective institutions; Macquarie University (11) and University of Queensland (13) and abided by the Helsinki Declaration governing human experimentation. All participants provided informed written consent.

### Measurements

#### Demographic Characteristics

Information was obtained at interview for each participant and included self-described medical history (for participants with BCRL this included type of cancer, adjuvant treatments, and lymphedema history) and self-ascribed limb dominance. Height was measured standing without shoes using a stadiometer (to the nearest 0.1 cm) and weight in light clothing using electronic scales to the nearest 0.1 kg. For participants with BCRL confirmed by ICG lymphography (5), the arm on the side of cancer treatment was deemed as “affected”.

#### Volumetric

Arm volumes were determined using a number of different methods reflecting current clinical practice. In 30 (11.2%) of control participants, circumferential measurements at 4 cm or 10 cm intervals proximally from the wrist were obtained and arm volume for each segment calculated according to frustum cone geometry and total volume calculated as the sum of the segments (15). In the remaining 237 (88.8%) of control participants, whole arm volume was assessed from dual energy X-ray absorptiometry (DXA) measurements of limb composition (bone mineral, fat and lean masses) as described previously (13). DXA-derived masses were converted to their equivalent volumes using the coefficients of Wilson et al. (16) and whole arm volume calculated as the sum of the individual tissue volumes. For participants with BCRL, limb volume was calculated from circumferentially-derived geometric calculations as described above (n = 71, 36.1%) with the remaining 126 (63.9%) assessed using perometry (17).

#### Bioimpedance Spectroscopy (BIS)

Whole arm BIS measurements were obtained with either an ImpediMed SFB7/U400 impedance spectroscopy device or an ImpediMed SOZO® impedance spectroscopy device (ImpediMed Ltd., Brisbane). The SFB7 device is a lead-type device primarily designed for supine measurements. Measurements in standing were obtained using a bespoke footplate fitted with stainless steel electrodes and hand-grips with stainless steel electrodes mimicking the SOZO® electrode arrangement. Comparative studies showed no significant

difference in measurements between the two systems. In one-fifth (n = 55) control participants, measurements were available for the SFB7 in supine only (13). These measurements were converted to standing equivalent values using regression equations determined previously (11). All measurements were obtained following manufacturer's recommendations for participant preparation and measurement protocol as described previously (11).

For all BIS measurements, whole-arm impedance data were analysed according to Cole theory (18) using Bioimp software (Bioimp v4.12, ImpediMed Ltd. Brisbane) to provide estimates of resistance at zero frequency (R0) for each arm as described previously (9, 11) L-Dex scores were those provided by the device manufacturer and are calculated according to limb dominance (9).

**Statistical Analysis**

The absolute differences in volumes between the affected (BCRL) or dominant (control) arms and the respective contralateral arms were calculated and these volume differences expressed as % of the unaffected or non-dominant arm for the BCRL and control participants respectively. The ratio of R0 resistances between the two arms was calculated as unaffected R0: affected R0 for participants with BCRL and as the non-dominant R0 : dominant R0 as originally described (19). L-Dex scores, provided by the device manufacturer, represent the R0 ratios linearized with reference to the normal distribution of ratios observed in a healthy control population where an L-Dex value of 0 represents the mean R0 ratio; L-Dex 6.5, the mean + 2 standard deviation (SD) and L-Dex 10, the mean + 3 SD. The control reference values are proprietary information of the manufacturer.

Descriptive statistics are presented as mean ± SD and the range of values. Statistical significance of difference between BCRL and control data was assessed using independent t-tests and between arms using paired t-tests with Medcalc v22.007 (MedCalc Software Ltd, Ostend, Belgium). The normal distribution of R0 ratios was calculated using Medcalc and distributions compared using the Z statistic. Sensitivity and specificity of the volumetric and BIS methods was assessed using receiver operating characteristic curves (20) constructed using Medcalc and the Youden index (21) with significance of difference being assessed by the Z statistic for correlated variables (22).

Volumetric and BIS approaches for BCRL assessment were compared graphically using an adaptation of error grid analysis (23). The proportions of false negatives and positives were calculated for each method and compared using a Z test for proportions.

**Results**

**Characteristics of Participants**

Participant characteristics are presented in Table 1. The BCRL group was significantly older and heavier although there was no difference in height. The control cohort were generally classed in the healthy BMI range (70% <25 kg/m<sup>2</sup>); in contrast, only 25% of participants with BCRL were in the healthy range and 39.6% having a BMI >30 kg/m<sup>2</sup>. The R0 of the dominant arm in the control group was on average 3.1% and significantly (p<0.0001) smaller than the contralateral non-dominant arm concomitant with a mean 4.6% larger volume (p<0.0001). The resistance of the affected arm for the participants with BCRL was, on average, 15%

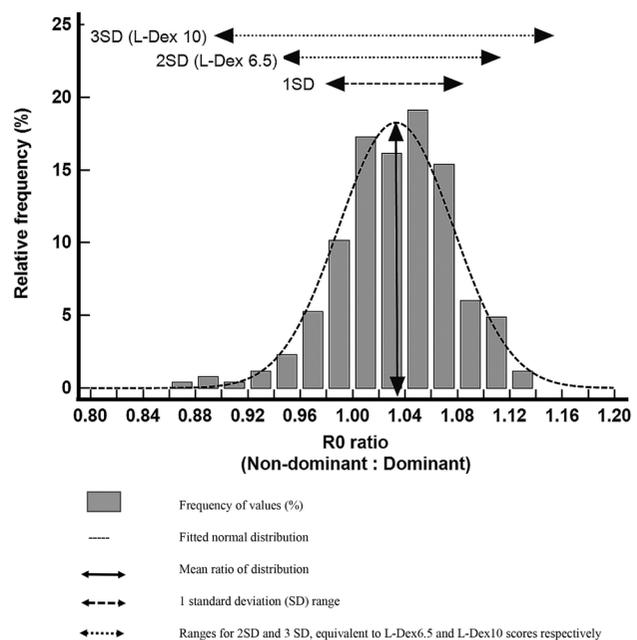
smaller than the unaffected arm again reflecting the same % volume excess of the affected limb; this difference being highly significant (p<0.0001). The computed mean L-Dex scores were -5.5 and 22.8 for control and participants with BCRL respectively. The mean value for the controls is within the -10 to +10 L-Dex range for a healthy population without excess ECW. However, the mean value for the BCRL group was 22.8 which is in excess of the L-Dex 10 (3SD) threshold indicative of excess ECW. Notably, the range in values was markedly larger for the participants with BCRL than for the controls reflecting the different lymphedema stages. Both groups include negative values indicating that either the non-dominant or unaffected arm was larger than the contralateral limb; an observation confirmed by negative absolute volumes.

**Distribution of R0 Ratios and L-Dex Scores**

The frequency distribution of R0 ratios for the control participants is presented in Figure 1. Values were normally distributed around a mean value of 1.033 (Non-dominant: Dominant ratio). The ranges of ±1, 2 and 3 SD are also shown with the 2 and 3 SD ranges being equivalent to L-Dex thresholds of 6.5 and 10 units respectively. Table 2 presents a comparison of the present control distribution, as L-Dex ranges, with previously published ranges. The ranges were not significantly different and were combined to provide overall average values.

**Sensitivity and Specificity Analysis**

There was highly significant difference (p<0.0001) between the volume-based ROC curve and the L-Dex ROC curve (Figure 2). The respective area under the curve (AUC) values, a measure of overall sensitivity, were 0.649 and 0.832; an AUC value greater than 0.8 is considered to exhibit excellent diagnostic accuracy with values below this having marginal acceptability (24). Youden J values were 0.375 and 0.800 for the excess volume and L-Dex methods respectively.



**Figure 1.** Distribution of ratios of arm R0 (Non-dominant: Dominant) in control population

*L-Dex: Lymphedema index*

Table 1. Participant characteristics

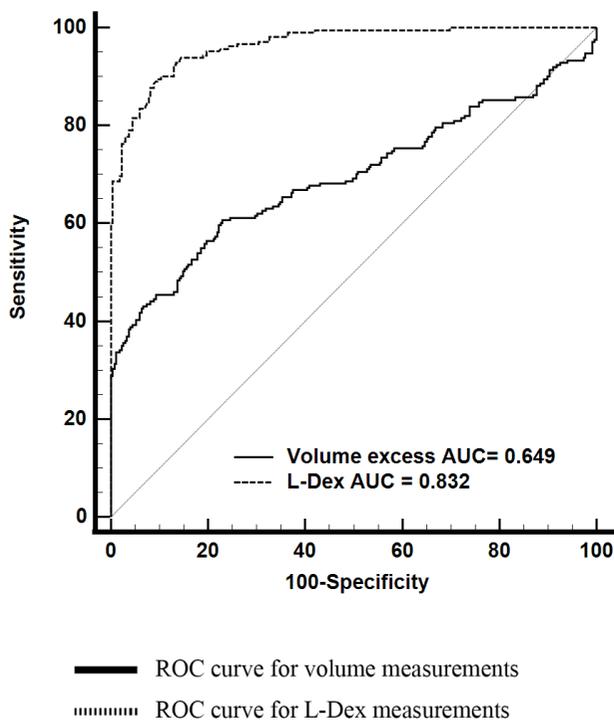
Characteristic	Group		P
	Control	BCRL	
Number	267	197	
Dominance (R:L)	249:18	200:12	ns
At risk (R:L)		103:109	
Age (y)	50.8±14.1 (18.3 to 83.0)	58.1±11.7 (32.0 to 82.0)	0.001
Height (cm)	162.4±7.5 (142.0 to 183.5)	163.1±6.4 (144.0 to 178.0)	ns
Weight (kg)	62.5±10.8 (39.0 to 104.7)	76.9±15.0 (46.2 to 149.8)	0.0001
Body mass index (kg/m <sup>2</sup> )	23.7±3.7 (17.1 to 36.4)	28.9±5.4 (18.7 to 50.3)	0.0001
R0 dominant arm (ohm)	410±45 <sup>a</sup> (298 to 538)		
R0 non-dominant arm (ohm)	423±46 <sup>b</sup> (311 to 561)		
R0 ratio (non-dominant: dominant)	1.033±0.041 (0.870 to 1.133)		
R0 unaffected arm (ohm)		361±43 <sup>a</sup> (269 to 488)	
R0 affected arm (ohm)		302±63 <sup>b</sup> (147 to 462)	
R0 ratio (unaffected: affected)		1.234±0.248 (0.915 to 2.226)	
L-Dex score	-5.5±4.8 (-15.2 to 11.0)	23.1±24.1 (-8.1 to 116.5)	0.001
Dominant arm volume (mL)	2867±718 <sup>a</sup> (1222 to 5275)		
Non-dominant arm volume (mL)	2746±708 <sup>b</sup> (1163 to 4858)		
Excess volume (mL)	125±160 (-599 to 782)		
Excess volume (%)	4.7±5.7 (-19.8 to 20.8)		
Unaffected arm volume (mL)		2679±727 <sup>a</sup> (1346 to 5769)	
Affected arm volume (mL)		3068±913 <sup>b</sup> (1528 to 5826)	
Excess volume (mL)		389±511 (-1902 to 2292)	
Excess volume (%)		14.9±17.5 (-32.9 to 81.6)	0.0001

Data presented as mean ± SD (range); difference statistically significant: <sup>a</sup>: versus; <sup>b</sup>: p<0.0001; SD: Standard deviation, BCRL: Breast cancer related lymphedema; L-Dex: Lymphedema index

Table 2. L-Dex thresholds indicative of excess extracellular water

	Number	Dominant at risk					Non-dominant at risk				
		Threshold					Threshold				
		Mean	SD	1SD	2SD (L-Dex 6.5)	3SD (L-Dex 10)	Mean	SD	1SD	2SD L-Dex 6.5)	3SD (L-Dex 10)
Cornish et al. (19)	60	1.037	0.034	1.071	1.102	1.102	0.964	0.034	0.998	1.032	1.066
Ridner et al. (34)	32	1.024	0.027	1.051	1.078	1.105	0.986	0.027	1.013	1.040	1.067
Ward et al. (10)	172	1.014	0.040	1.054	1.094	1.134	0.986	0.040	1.026	1.066	1.106
Wang et al. (35)	391	1.018	0.045	1.063	1.108	1.153	0.984	0.045	1.029	1.074	1.119
This study	267	1.033	0.041	1.072	1.114	1.156	0.972	0.041	1.013	1.055	1.097
Weighted average	922	1.022	0.042	1.064	1.106	1.145	0.980	0.042	1.021	1.063	1.105

Statistical analysis: There was no significant difference in ranges between studies; owing to the larger difference in sample sizes mean values were calculated weighted according to sample size; SD: Standard deviation; L-Dex: Lymphedema index



**Figure 2.** Receiver operator characteristic (ROC) curves for lymphedema assessment by either L-Dex or excess volume measurements

L-Dex: Lymphedema index

### Graphical Comparison of Methods

A method comparison plot is presented in Figure 3. The plot presents L-Dex scores for all participants plotted against their excess limb volume. The vertical line represents either a 10% volume difference

(Panel A) or 5% volume difference (Panel B) between arms, commonly used indices of presence of lymphedema, with values that fall to the right of this line being deemed positive for lymphedema. The horizontal line is either the L-Dex 10 threshold (Panel A) or L-Dex 6.5 threshold (Panel B) with data points that fall above this line being indicative of BCRL. Consequently, data points that fall in the upper right quadrant representing participants that are deemed positive for BCRL by both methods. Notably, only one control participant exceeded the L-Dex 10 threshold while 39 (14.6%) of participants exceeded the 10% volume difference threshold (false positives). Ninety-nine participants with BCRL (50.3%) were below this threshold (false negatives); the comparable figure for L-Dex 10 was 62 participants (31.5%); the corresponding true positive rates were 49.7% and 68.5% for volume and L-Dex respectively. These differences were significant (Table 3). Eighty-eight participants with BCRL (44.7%) were positive by both criteria, L-Dex >10 and excess volume >10%. If the more liberal thresholds of >5% excess volume and L-Dex 6.5 are used, then agreement between methods increase only slightly to 91 (46.2%) despite the number of BCRL positive subjects increasing to 135 (68.5%) and 139 (70.6%) for volume and L-Dex measurements respectively.

### Discussion and Conclusion

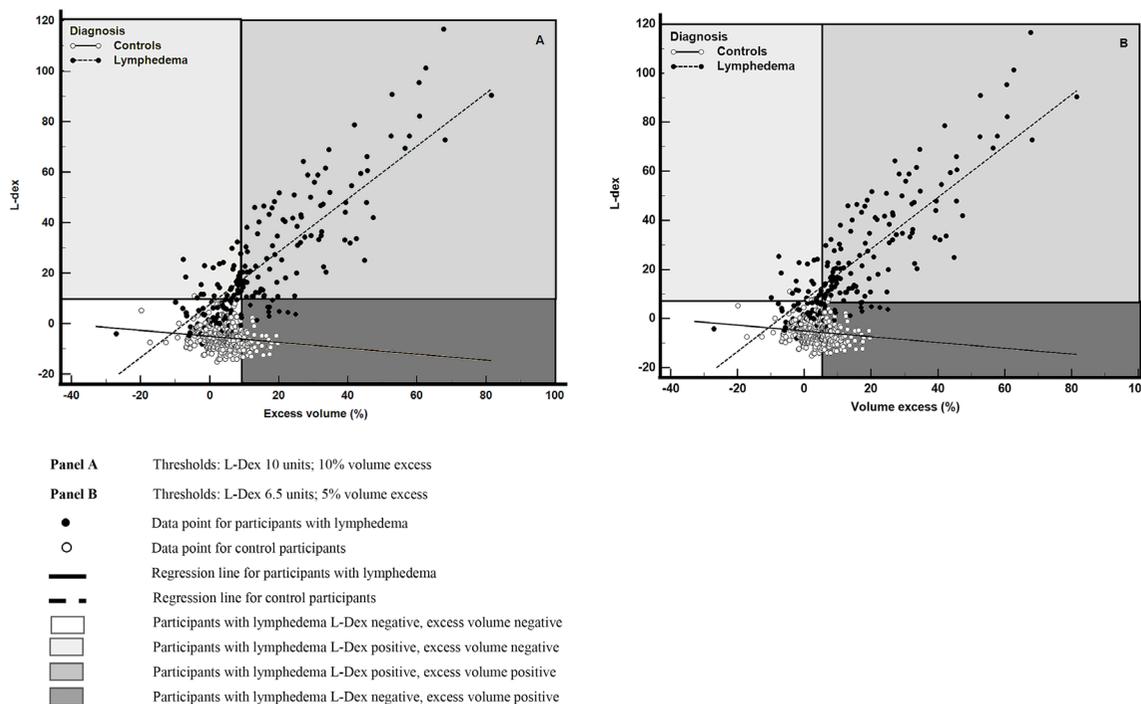
The present study confirmed that both excess volume and BIS can discriminate women with BCRL from healthy controls although with different degrees of sensitivity and specificity. In addition, the different methods do not always identify the same individuals. The present study found that the BIS (L-Dex) method had a higher true positive rate with a smaller false negative rate than the excess volume approach with sensitivity similar to that observed in other studies (9). The more liberal threshold of L-Dex 6.5 had the higher sensitivity than L-Dex 10 in accord with the findings of others (25) although false positive rate increased 6-fold albeit still only 2.6% of participants. By contrast,

using a threshold of 5% excess volume improved sensitivity to almost the same as L-Dex but with an unacceptable false positive rate of 47%.

The relative merits of volumetric and impedance assessments for BCRL have been studied previously with different findings and conclusions being drawn. Barrio et al. (26) in a prospective study found volumetric assessment (10% volume excess threshold) and BIS (L-Dex 10) demonstrated poor correlation with, as observed here, inconsistent overlap of measurements between methods in individuals. Similarly, Spitz et al. (27) found poor sensitivity of BIS for detection of BCRL. In contrast, a number of studies have found that the BIS method is a reliable and valid assessment tool that correlates well with clinical assessment and physiologic measurements of lymphatic function (28) while Borman et al. (29) found that BIS detected more and earlier patients with BCRL than circumferentially-derived volume measurements. Some studies have concluded that neither volume nor BIS approaches should be considered as definitive for BCRL detection and, appropriately, have suggested that both tools should be used in conjunction with patient symptomology and comprehensive clinical evaluation (30).

In the majority of studies comparing volume and BIS, the volume method has been set a priori as the reference method (26). In the present study, the presence of lymphedema was determined by the independent method of ICG lymphography. Consequently, the volume and BIS were analysed as independent methods against this reference assignment of BCRL rather than directly against each other with one method pre-designated as the reference method. If the presence of BCRL is defined a priori by volume change, inevitably volume change will be deemed to perform better than BIS, for example, as stated in Keeley (31). Indeed, Keeley (31) acknowledged that volume change was a “reasonable” although “imperfect” gold standard for BCRL in the absence of an international consensus of an agreed method. Notably, Varagur et al. (32) also found BIS to have high sensitivity and specificity when BCRL was assessed by the lymphatic function measure of magnetic resonance lymphangiography.

Most of the aforementioned studies have considered comparison of volume and BIS techniques in terms of sensitivity and specificity and have frequently not commented on whether true positive detections for BCRL by both methods are the same individuals. This study



**Figure 3.** Relationship of excess volume measurements to L-Dex 10 scores

L-Dex: Lymphedema index

**Table 3.** Numbers and percentages of participants with BCRL exceeding thresholds for excess arm volume or L-Dex score

Participants	Threshold	Volume measurement		Impedance measurements	
		10% excess volume	5% excess volume	L-Dex 10	L-Dex 6.5
BCRL	> threshold	98 (49.7) <sup>c</sup>	135(68.5)	126 (64.0) <sup>d</sup>	139 (70.6)
	< threshold	99 (50.3) <sup>c</sup>	62 (31.5)	71 (36.0) <sup>d</sup>	58 (29.4)
Control	> threshold	39 (14.6) <sup>a</sup>	126 (47.2) <sup>a</sup>	1 (0.4) <sup>b</sup>	7 (2.6) <sup>b</sup>
	< threshold	228 (85.4) <sup>a</sup>	141 (52.8) <sup>a</sup>	266 (99.6) <sup>b</sup>	267 (98.0) <sup>b</sup>

Data present as n (%). Difference (volume versus L-Dex) significant: <sup>a</sup>: Versus <sup>b</sup>: p<0.0001; <sup>c</sup>: Versus; <sup>d</sup>: p<0.004; BCRL: Breast cancer related lymphedema; L-Dex: Lymphedema index

has demonstrated that concordance between methods is relatively poor. The proposed graphical presentation provides a simple way to not only assess individuals against both criteria, volume and BIS, but also to show which individuals are being identified by each method. The graphical approach also has potential for assessing the relative performance of volumetric and BIS methods when used for longitudinal BCRL assessment by tracking loci at each time-point on the grid plot.

In the present study, L-Dex thresholds were those provided by the manufacturer of the BIS device. These are proprietary information and of unknown provenance. A number of studies to date have determined the distribution of R0 ratios used to generate L-Dex thresholds but have used the older device that obtains measurements in supine, not the current stand-on model. While the two devices perform very similarly, they are not totally interchangeable (11). The present study provided the opportunity to determine R0 ratios and calculated L-Dex ranges for measurements when standing. No significant differences were observed which is perhaps not surprising since these are either directly inter-limb ratios or inter-limb L-Dex scores where presumably any physiological effects on fluid volumes due to positional change will impact similarly on each arm. This suggests that existing L-Dex thresholds are robust and may be used with confidence.

The present study has a number of strengths and weaknesses. Volumetric measurements were obtained using a number of different techniques (perometry, DXA, geometric calculation). This may be perceived as a weakness since these methods do not measure exactly the same limb volume. However, since data are expressed as inter-limb differences or ratios then any methodological differences will be mitigated. Furthermore, the use of different methods reflects lack of standardisation where different methods are used in current clinical practice. Similarly, BIS measurements were obtained using different BIS devices and for some control participants while supine and converted to their standing equivalents. It has been shown previously that there are no statistical differences in device-specific measurement of R0 when used under identical measurement conditions (33). There are differences, however, due to posture (11). The regression procedures used to interconvert supine to standing measurements exhibit high correlation (>0.93) with standard error of the estimate of <3%. The study only considered participants with ICG-confirmed BCRL and was cross-sectional with measurements at a single time-point only. Also, participants were included irrespective of lymphedema stage although BIS was originally conceived for detection of early-stage lymphedema. The study design precluded assessment of predictive performance in longitudinal prospective studies. As such it also precluded, using the preferred method of comparing either volume or BIS change relative to a baseline, ideally pre-treatment, measure.

In conclusion, BIS performed better than volume measurements for identification of women with BCRL. The study has reaffirmed the value of this technique, although its use in conjunction with patient symptomology and comprehensive clinical evaluation using other assessment tools is recommended. The proposed graphical method for presentation of both volume assessment and BIS indices of BCRL facilitates comparison of these different approaches in an easily interpretable manner. It has also conformed the validity of existing BIS (L-Dex) thresholds indicative of the presence of BCRL.

**Ethics Committee Approval:** The study was conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007), the

CPMP/ICH Note for Guidance on Good Clinical Practice and consistent with the principles that have their origin in the Declaration of Helsinki (Macquarie University Ethics Committee - no: 5201700439; date: 30.05.2017).

**Informed Consent:** Retrospective study.

#### Authorship Contributions

Concept: L.C.W.; Design: L.C.W., L.A.K.; Data Collection and/or Processing: L.C.W., B.T., K.G., L.A.K.; Analysis and/or Interpretation: L.C.W., B.T., K.G., L.A.K.; Literature Search: L.C.W.; Writing: L.C.W., B.T., K.G., L.A.K.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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