Original Article

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Reliability of L-Dex Scores for Assessment of Unilateral Breast Cancer-Related Lymphedema

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ABSTRACT

Objective: Breast cancer-related lymphedema (BCRL) is a common complication of breast cancer treatment that may result in swelling of the affected arm due to compromised lymphatic function. Implementing a screening program and early intervention for BCRL are important for effective management. Bioimpedance spectroscopy (BIS) is a commonly used tool for assessing BCRL. This study aimed to compare different normative ranges for BIS L-Dex scores in the detection of BCRL.

Materials and Methods: Data from 158 women with clinically ascribed and indocyanine green confirmed BCRL were analysed. BIS measurements were obtained using an ImpediMed standing device, and L-Dex scores were calculated using published normative ranges for healthy individuals. Statistical analysis was performed to compare the concordance between different reference ranges in classifying individuals with lymphedema.

Results: The study found that L-Dex scores calculated using different normative ranges were highly correlated and essentially interchangeable in detecting BCRL. Approximately 90% of participants exceeded the L-Dex threshold for lymphedema, with minimal discrepancies between reference ranges. False negative rates were observed in some participants, likely due to early-stage BCRL with minimal lymph accumulation.

Conclusion: The findings suggest that BIS L-Dex scores are a valid indicator of BCRL, regardless of specific normative ranges used. Detection rates of clinically confirmed BCRL were consistent across different reference ranges, with minimal discrepancies. BIS remains a valuable tool for early detection and monitoring of BCRL. Future research should focus on longitudinal assessments and use of change in L-Dex scores for lymphedema monitoring and progression.

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

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Key Points

- Breast cancer-related lymphedema (BCRL) is a common complication of breast cancer treatment that can result in swelling of the affected arm.
- Implementing a screening program and early intervention for BCRL are crucial for effective management.
- L-Dex scores calculated using different normative ranges were highly correlated and essentially interchangeable in detecting BCRL.
- Future research should focus on longitudinal assessments and use of change in L-Dex scores for lymphedema monitoring and progression.

Introduction

Secondary lymphedema is a chronic condition of lymphatic dysfunction characterised by swelling of a body region due to accumulation of excess lymph fluid through compromised lymph transport (1). The aetiology of lymphedema is varied but is well recognised as an adverse sequala of breast cancer and its treatment; this is breast cancer-related lymphedema (BCRL) (2). Estimates of BCRL incidence vary but range from 3 to 65% with presentation occurring most commonly within two years of surgery (3, 4). The precise mechanisms for development of BCRL are uncertain but is likely due to direct damage to the lymphatics through either surgery or radiation treatment rather than damage due to the presence of a tumour *per se* (2-5).

Increasingly, it is recognised that the recommended standard of care for those undergoing breast cancer treatment is a prospective surveillance and early intervention model (6-9) with lymphedema treatment being most effective when commenced at the earliest opportunity (10). Definitive diagnosis of BCRL is by comprehensive clinical evaluation with objective assessment of lymphatic function by an imaging technique, such as indocyanine green (ICG) lymphography (11) or lymphoscintigraphy (12). In practice, however, initial recognition of

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BCRL is frequently self-assessment of symptoms by the individual or simple visual observation of arm swelling (13). Furthermore, since imaging techniques such as ICG lymphography are frequently only available in tertiary referral settings, objective assessment of BCRL is routinely undertaken by measurement of limb swelling. Although various techniques are available, the most commonly used are simple volumetric measurement of the at-risk limb or assessment of extracellular water (ECW) volume, of which lymph is a principal component, by bioimpedance spectroscopy (BIS) (14). Both of these methods are recommended in best practice guidelines and position statements, e.g., National Comprehensive Cancer Network, USA (15) and the Australasian Lymphology Association (https://www.lymphoedema.org.au/public/7/files/Position%20Statements/ALA%20Position%20Statement_Early%20Detection%20of%20BCRL.pdf).

Although widely used and recommended, neither volumetric assessment nor BIS measure lymphatic dysfunction or lymph accumulation directly. In volumetric assessment, the excess size of the at-risk limb in unilateral BCRL is determined relative to the contralateral limb in either absolute (mL) or relative (%) terms, ideally as volume increase relative to a pre-surgery or pre-treatment baseline measurement where available (16, 17). Volume excess or change in volume of 5 or 10% are commonly used as indicative of BCRL (18, 19). In contrast, BIS provides an indirect index of lymph accumulation. BIS measures the electrical impedance of the arm, which is inversely but quantitatively related to the volume of ECW, including lymph (20). Like volumetric measurements, the low frequency impedance (typically resistance at zero current frequency, R0) of the at-risk limb is compared to that of the contralateral unaffected limb but as a ratio ($R0_{unaffected}$: $R0_{at-risk}$) rather than as an absolute or percentage difference. Unlike volumetric measurements, impedance ratios typically compared normative values for the impedance ratio observed in a healthy non-BCRL population with the mean control value plus either two (2SD) or three (3SD) standard deviations being used as thresholds indicative of presumptive lymphedema (20). Since impedance ratios are not immediately intuitively understandable, it has become common practice to convert ratios to a linear scale, an L-Dex score, where 2SD and 3SD thresholds correspond to L-Dex scores of 6.5 and 10 respectively (20, 21). Consequently, the utility of L-Dex scores for the early detection and monitoring of BCRL is dependent upon the L-Dex thresholds that are reliant upon using appropriate normative standards. An additional concern is that protocols for BIS assessment have changed since its initial introduction in 2001 (22) with the advent of new BIS devices and a move from measurements made in the supine position to those made when standing (23).

The current study compared BIS L-Dex normative ranges determined with different impedance devices and measurement protocols using published data. The concordance between ranges in classifying individuals with lymphedema was assessed in a cohort of women with ICG lymphography-confirmed BCRL.

Materials and Methods

Participants - BCRL

Data for 158 women with clinically ascribed BCRL and confirmed by ICG lymphography were drawn from a database maintained by the Australian Lymphoedema Education, Research and Treatment Program at Macquarie University. All women had consented to data, collected as part of routine clinical practice, being used for research purposes approved by Macquarie University Ethics Committee (approval number: 52020613914268, date: 27.02.2020) abiding by the Helsinki Declaration governing human experimentation. Clinical evaluations were conducted by experienced lymphedema therapists with BIS measurements obtained by trained research assistants within a single session described previously (24). Presence of BCRL was confirmed by ICG lymphography (11), the arm on the side of cancer treatment was deemed as "affected".

Exclusion criteria were minimal: Participants were required to be female, aged over 18 years, not fitted with an implantable device, e.g., a pacemaker or were pregnant (self-ascribed) as these are contraindications for BIS measurements or had a health condition or were receiving medication that affected body water status which would confound BIS measurements.

Participants With BCRL-Measurements

Measurement procedures have been described in detail elsewhere (24). Briefly, height and weight were measured to 0.1 cm and 0.1 kg resolution using a calibrated wall mounted stadiometer and electronic scale, respectively. Whole arm impedance was measured with an ImpediMed SOZO BIS device (ImpediMed Ltd., Brisbane, Australia) with the participant in standing posture in accordance with manufacturer's recommendations as described previously (23). BIS data was stored in a cloud-based database maintained by the SOZO manufacturer.

Participants-Healthy Non-BCRL Normative Data Ranges

A literature search (using Medline-PubMed) was undertaken to find publications in which either impedance ratios or L-Dex scores had been determined for healthy control populations. Six publications were identified, and details are presented in Table 1 (22, 24-28). Details of participants and measurement procedures in these studies can be found in the relevant publications.

Data Analysis

BIS For Participants With BCRL

BIS data for each arm of all participants were retrieved from the SOZO cloud-based database to provide estimates of resistance at zero frequency (R0) for each arm as described previously (20, 29). R0 ratios were calculated for each participant in the conventional manner as R0_unaffected arm: R0_affected arm. The L-Dex scores were calculated using each of the published normative ranges according to whether the affected limb was dominant or non-dominant.

Statistical Analysis

Impedance data are presented as means ± SD and range. Normal distributions for the published normative range mean and SD were calculated using the normal distribution spreadsheet template provided by Vertex 42 (https://www.vertex42.com/ExcelArticles/mc/NormalDistribution-Excel.html) and distributions compared using the Z statistic. Statistical significance of differences between 2SD L-Dex 6.5 scores calculated using the different normative ranges was determined using a two-factor (range and dominance) repeated measures analysis of variance (ANOVA) (Sigmastat v3.5, Systat software, Chicago, USA). Spearman-rank correlations between L-Dex scores for BCRL participants were calculated using the correlation matrix module of NCCS version 2022 (NCSS LLC, Kaysville, USA). Descriptive statistics and distribution plots of L-Dex scores by reference range were prepared using MedCalc Statistical Software v 22.023 (MedCalc Software Ltd, Ostend, Belgium).

Results

Characteristics of Participants

Characteristics of the BCRL participants are presented in Table 2. The majority of participants with BCRL were overweight (75.3%) according to WHO criteria of body mass index (BMI) >25 kg/m^2 with 39.8% having a BMI >30 kg/m^2. Mean R0 of the affected arm was, on average, 18.4% smaller than that of the unaffected arm reflecting the larger volume of the affected limb. Mean R0 ratio (1.27) was notably larger than the mean values seen in healthy control individuals irrespective of reference population (1.011 to 1.037, Table 1).

Impedance Ratio Normative Ranges

Published reference ranges for impedance ratios and the 2SD and 3SD thresholds, equivalent to L-Dex 6.5 and 10 units respectively, are presented in Table 1. The normal distribution curves are presented in Figure 1. Distributions were overlapping and not significantly different, although not identical, reflecting not only different populations but also devices and measurement protocols. Most studies measured impedance at zero frequency (R0), although Ridner et al. (27) obtained measurements at an unspecified but <30 kHz frequency, while Jung et al. (28) obtained measurements at both 1 and 5 kHz and provided reference values for each.

L-Dex Scores of Participants With BCRL

The relative distributions of L-Dex scores calculated using each of the reference ranges are presented in Figure 2. Values between ranges were highly correlated (Table 3) but were not in absolute agreement. Two-factor ANOVA found no significant overall difference in mean L-Dex score between the different reference ranges although pair-wise comparison showed significant differences (p<0.0001) between all paired comparisons except for the two ranges provided from the same study by Jung et al. (28). Although absolute magnitude of L-Dex values varied with dominance of the affected arm according to dominance-defined normative ranges (Table 1), this was irrespective of the reference range used.

Table 1. Published impedance ratio thresholds for detection of BCRL

Publication	Population	Device	Protocol	Number	Dominant at-risk				Non-dominant at-risk			
					Mean	SD	Mean + 2SD	Mean + 3SD	Mean	SD	Mean + 2SD	Mean + 3SD
Cornish et al. (22)	Caucasian Australia	BIS ImpediMed SFB3	Supine lead electrodes 40-cm segment proximal to wrist	60	1.037	0.034	1.102	1.139	0.964	0.034	1.032	1.066
Ridner et al. (27)	Predominantly Caucasian USA	SFBIA (<30 kHz) ImpediMed XCA	Seated lead electrodes Whole arm (wrist to axilla)	32	1.024	0.040	1.104	1.144	0.986	0.027	1.040	1.060
Ward et al. (25)	Caucasian/ Chinese Australia & New Zealand	BIS ImpediMed SFB3 & SFB7	Supine lead electrodes Whole arm (wrist to axilla)	172	1.014	0.040	1.094	1.134	0.986	0.040	1.066	1.106
Wang et al. (26)	Chinese China	BIS ImpediMed SFB7	Supine lead electrodes Whole arm (wrist to axilla)	391	1.018	0.045	1.108	1.153	0.984	0.044	1.072	1.116
Jung et al. (28)	Korean Korea	MFBIA (1 & 5 kHz) InBody 3.0	Standing plate whole arm (wrist to axilla)	643	[a]1.013	0.030	1.073	1.103	0.998	0.029	1.056	1.085
					[b]1.011	0.029	1.069	1.098	0.990	0.028	1.046	1.074
Ward et al. (24)	Predominantly Caucasian Australia	ImpediMed SOZO & SFB3/7	Standing plate electrodes whole arm (wrist to axilla)	267	1.033	0.041	1.114	1.156	0.972	0.041	1.055	1.097
Weighted average				1565	1.017	0.034	1.085	1.119	0.988	0.034	1.056	1.091

Owing to the larger difference in sample sizes, mean values were calculated weighted according to sample size

BCRL: Breast cancer related lymphedema; BIS: Bioimpedance spectroscopy; MFBIA: Multi-frequence bioimpedance analysis; SD: Standard deviation; [a]: R at 1 kHz; [b]: R at 5 kHz

Table 2. Participant characteristics

Characteristic	BCRL
Number	158
Dominance (right: left)	151:7
At risk (dominant: non-dominant)	76:82
Years since lymphedema diagnosis	4.5±6.1
MDACC ICG stage (number)	
0	1 (0.6%)
1	20 (12.7%)
2	79 (50%)
3	45 (28.5%)
4	13 (8.2%)
Age (years)	57.5±11.8 (32.0 to 82.0)
Height (cm)	163.1±6.6 (144.0 to 178.0)
Weight (kg)	77.4±15.3 (46.2 to 149.8)
Body mass index (kg/m^2)	29.1±5.6 (18.7 to 50.3)
R0 unaffected arm (ohm)	359±43[a] (269 to 488)
R0 affected arm (ohm)	292±63.3[b] (147 to 462)
R0 ratio (unaffected: affected)	1.270±0.254 (0.922 to 2.226)

Data presented as mean ± SD (range)
BCRL: Breast cancer related lymphedema; ICG: Indocyanine green; MDACC: MD Anderson Cancer Center; cm: centimetre; kg: kilogram; m: meter

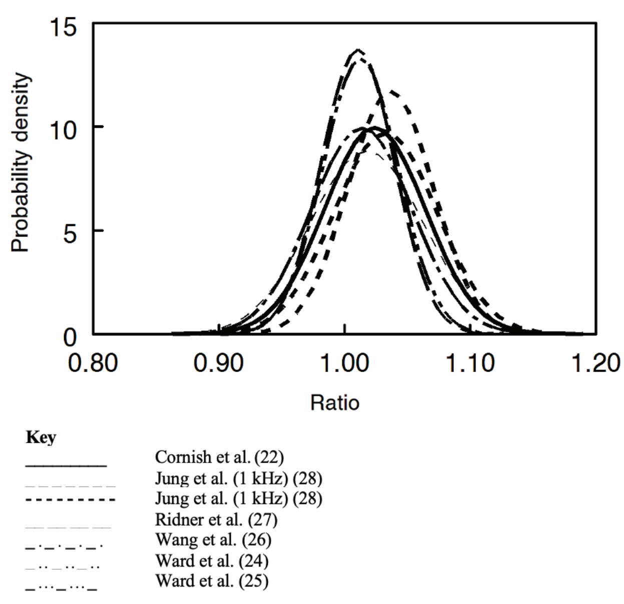

Figure 1. Normal distribution of published R0 ratios

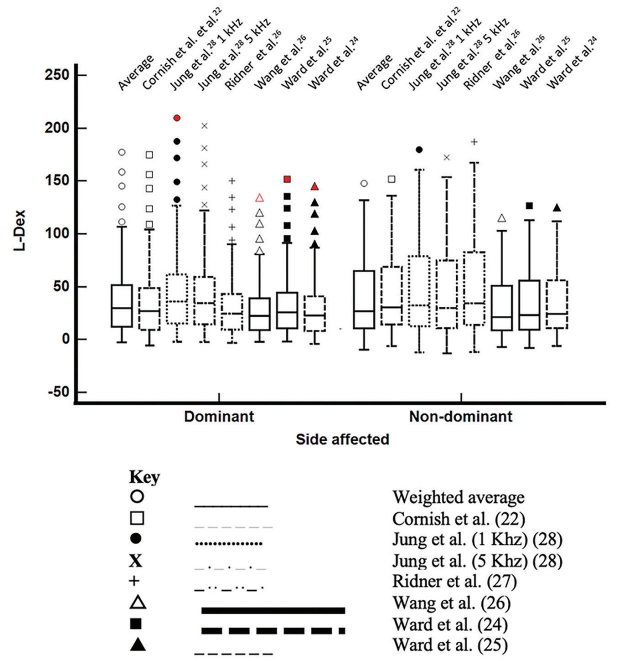

Figure 2. Distributions of L-Dex scores by published reference range

Detection of BCRL by L-Dex Score

An L-Dex score of 6.5 is widely used as a threshold presumptive of the presence of BCRL (30). Although all participants with BCRL on the present study had clinically and ICG lymphography-confirmed lymphedema, 14 (8.9%) provided L-Dex scores <6.5, a consistent finding across all reference ranges (Table 4). A further 3 participants (1.9%) had L-Dex scores ≥6.5 but were negative indicating that the unaffected arm was larger than the affected arm. One hundred and forty-one (89.2%) participants were found to exceed the L-Dex 6.5 threshold by at least one reference range, with 123 (77.8%) of these exceeding this threshold according to all reference range criteria. For the 18 participants in which there were non-concordant L-Dex scores (Table 5), no one reference range was consistently discrepant. The Wang et al. (26) reference range was the only one to be consistent in scoring these participants under the threshold.

Discussion and Conclusion

The present study has demonstrated that the different published reference ranges to establish L-Dex thresholds are highly comparable and essentially interchangeable. This is important since there is no universal consensus on precise measurement procedures or devices to be adopted when BIS is used to assess lymphedema. The detection rate of clinically confirmed lymphedema was approximately 90% irrespective of measurement procedure, with this dropping to 78% where there was 100% agreement between ranges. This lower value is typical of detection rates observed within studies that adopt a single specified reference range (20). Where discrepant results were observed between ranges, the magnitude of L-Dex scores were only just in excess of the 6.5 threshold value. This suggests that in these particular participants, lymphedema may have been at an early or sub-clinical stage where marked lymph accumulation had yet to occur. It is also noteworthy that L-Dex scores fluctuate daily and that a value above a threshold cut-off should not be considered absolutely definitive of the presence of lymphedema, and trends over time are important considerations (27).

Table 3. Correlation matrix for L-Dex scores according to published normative range

Range	Cornish	Ridner	Ward a	Wang	Jung a	Jung b	Ward b	Weighted average
Cornish et al. (22)	1	0.9928	1.0000	0.9996	0.996	0.9781	0.9993	0.9998
Ridner et al. (27)		1	0.9925	0.9951	0.9993	0.9903	0.9888	0.9915
Ward et al. (25)			1	0.9995	0.9957	0.9779	0.9994	0.9998
Wang et al. (26)				1	0.9976	0.982	0.9983	0.9993
Jung et al. (28) (1 kHz)					1	0.9886	0.9928	0.9949
Jung et al. (28) (5 kHz)						1	0.9745	0.9777
Ward et al. (24)							1	0.9997
Weighted average								1

Owing to the larger difference in sample sizes mean values were calculated weighted according to sample size

Table 4. Concordance between reference ranges for detection of lymphedema by L-Dex score ≥6.5

Threshold	Ranges concordant	Participant number (%)
L-Dex <6.5		14 (8.9%)
L-Dex ≥-6.5		3 (1.9%)
	All	141
	6	1
	5	0
L-Dex ≥6.5	4	3
	3	4
	2	7
	1	3

Although not a primary aim of the study, it was found that 17 participants (10.8%) had L-Dex scores negative for lymphedema. This false negative rate is consistent with that observed in other studies (31), but lower than that observed in others (32). A small false negative rate is expected since the thresholds indicative of the presence of lymphedema are defined statistically according to the normal distribution; a 2SD threshold (L-Dex 6.5) means that approximately 5% of a population fall outside a mean + 2SD range. The false negative rate observed here is approximately two-fold greater. It is likely that participants in the early stages of lymphedema have minimal lymph accumulation although ICG lymphography indicates a degree of lymphatic dysfunction. The participants in the present study who provided negative L-Dex (<6.5) were MD Anderson Cancer Center (MDACC) ICG stage 0 (at-risk) (1 participant), 1 (9 participants) or 2 (7 participants) and relatively recently diagnosed, most within two years and a maximum of six years post-lymphedema diagnosis. Three participants presented with L-Dex scores indicating that the unaffected limb was larger, albeit slightly, than the affected limb. The reasons for this are unclear. One was MDACC ICG stage 1 and two were stage 2. All participants had well-managed BCRL, and none were within the obese range where excess adiposity increases ECW. A review of medical records showed two had no obvious confounding characteristics, however one participant had metal in the affected arm from a previous injury which would potentially impact the calculated L-Dex score.

The study has a number of limitations. BIS is used to assess all presentations of lymphedema, unilateral and bilateral, in both arms and legs. The present findings are only appropriate to BIS when used for assessment of unilateral BCRL. Bilateral lymphedema poses difficulty in assessment since there is no contralateral limb for normalization of impedance. L-Dex scores are alternatively calculated, for example, as the ratio of leg to arm impedance values for bilateral lymphedema of the legs (33-36). Few normative ranges for such assessments have been published for comparative analysis. A further limitation is that this analysis is restricted to single L-Dex assessments. It has not considered the preferred use of change in L-Dex scores as an index of lymphedema or when used to monitor progression or response to treatment. This is, however, not considered a major problem since L-Dex scores are calculated in an identical manner using the same reference ranges for determination of threshold values. Three reference ranges considered [Ridner et al. (27) and Jung et al. (28)] were determined using resistance measured at a low frequency but not zero, the optimal frequency for measurement of ECW. The rate change in resistance with frequency however has a low-rate constant (21). York et al. (37) showed that correlation between R0 and resistance measured at frequencies up to 30 kHz ranged from 0.998 to 0.992 while limits of agreement analysis showed that bias was limited to 1.3% at 30 kHz. The generally high agreement found between these studies and those using conventional R0 are consistent with these observations. Finally, L-Dex scores using a 6.5 threshold only were considered. The original BIS protocol used a 3SD threshold. Subsequent research has found that this was too conservative and that a more liberal cut-off of 2SD provided better sensitivity and specificity. Since a change from 2SD to 3SD is a constant scaling effect, this will not affect comparison between reference ranges as considered here; the magnitude of the L-Dex score will be different and the detection rate will be decreased but relativity between ranges will be unaffected.

In conclusion, the current study has confirmed that L-Dex scores are a robust indicator associated with the presence of BCRL. Impedance measurements are reliable for this purpose irrespective of measurement protocol and across different devices. The results also indicate that, assuming electronic accuracy, transferring or upgrading from one device to another will have minimal effect on the value of impedance technology for BCRL detection or monitoring. While this study has affirmed the use of BIS for assessment of BCRL, it should be

Table 5. Lack of agreement between reference ranges for detection of lymphedema by L-Dex score >6.5

	Reference range						
Participant	**Cornish et al. (22)**	**Ward et al. (25)**	**Wang et al. (26)**	**Ward et al. (24)**	**Ridner et al. (27)**	**Jung et al. (28) (1 kHz)**	**Jung et al. (28) (5 kHz)**
A	1.8	4.4	3.4	2.0	3.1	6.0	**6.6**
B	2.0	4.6	3.6	2.1	3.3	6.3	**6.8**
C	**6.7**	3.0	2.9	4.6	4.4	2.0	3.5
D	2.3	4.8	3.9	2.4	3.6	**6.6**	**7.2**
E	3.5	5.9	4.8	3.4	4.6	**8.0**	**8.6**
F	2.4	4.9	3.9	2.5	3.6	**6.7**	**7.3**
G	3.4	5.8	4.7	3.3	4.5	**7.9**	**8.5**
H	2.8	5.3	4.2	2.8	4.0	**7.2**	**7.8**
I	**9.0**	4.9	4.7	**6.5**	**7.3**	4.7	6.3
J	**8.9**	4.8	4.6	6.4	**7.2**	4.6	6.2
K	4.3	**6.5**	5.3	4.0	5.3	**8.9**	**9.5**
L	5.6	**7.6**	6.3	5.1	6.4	**10.3**	**11.0**
M	5.2	**7.3**	6.1	4.8	6.1	**9.9**	**10.6**
N	**9.1**	5.0	4.7	**6.5**	**7.3**	4.8	6.4
O	**9.4**	5.2	5.0	**6.8**	**7.7**	5.1	**6.7**
P	**10.1**	5.9	5.6	**7.4**	**8.7**	6.0	**7.7**
Q	**9.7**	5.5	5.2	**7.0**	**8.1**	5.5	**7.1**
R	**10.9**	**6.5**	6.1	**8.1**	**9.6**	**6.9**	**8.6**

Data presented as L-Dex scores, scores ≥6.5 highlighted in bold

emphasised that BIS is but one technique in the armoury of tools available to a lymphoedema therapist. It is incumbent upon the clinician to be familiar with the relative advantages and disadvantages of each, practicality of use and to use these as an adjunct to their clinical expertise (38).

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Ethics Committee Approval: The study approved by Macquarie University Ethics Committee (reference number: 52020613914268, date: 27.02.2020).

Informed Consent: All women had consented to data routinely collected data analysed for research purposes.

Authorship Contributions

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

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

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