Original Article

Risk Profiling of Breast Cancer-Related Lymphedema (BCRL) in Patients With Breast Cancer Via Using Body Composition and Tissue Dielectric Constant (TDC) Method: A Cross-Sectional Study

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Abstract

Breast cancer-related lymphedema (BCRL) is one of the most fearsome side effects of breast cancer treatment. Higher body mass index (BMI) is a well-known risk factor for BCRL. A total of 72 patients were included. The fat mass was significantly and linearly correlated with dielectric ratios which might be indicative of preclinical BCRL.

Background: Breast Cancer-Related Lymphedema (BCRL) is one of the most prominent long-term side effects of breast cancer (BC) treatment. Although an increased BMI is a well-recognized risk factor for BCRL, there is a lack of knowledge regarding the potential associations between body composition and the risk of BCRL. Therefore, this study aimed to analyze the BCRL risk profiles of surgically operated BC patients via body composition and the Tissue Dielectric Constant (TDC) method, respectively. **Methods:** A total of 72 patients were included. Patients' risk for BCRL was assessed with Moisture MeterD (Delfin, Finland) in 4 different probes each has unique penetration depths from 0.5 (10 mm) to 5.0 (55 mm) at both upper extremities. The body composition was analyzed with Tanita-BC-420 (TANITA, Japan). Comparing the dielectric values of extremities and proportioning to one another as TDC ratio (at-risk side/unaffected side) was used to profile BCRL risk. **Results:** TDC values of the thorax reference point were significantly higher in all four probes on the at-risk side ($P < .05$). TDC ratios in the forearm and Thorax points were significantly correlated with fat mass ($r = 0.256$, $P = .030$; $r = 0.269$, $P = .022$) as well as with visceral fat rating (VFR) ($r = 0.340$, $P = .003$; $r = 0.466$, $P < .001$). **Conclusion:** This study highlights the need for further care and investigation in the assessment and prediction of BCRL by considering body composition. Since the risk reduction of BCRL can be maximized by considering the individual features, we can conclude that patients with higher body fat irrespective of the BMI should be followed up regularly.

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Keywords: Fat mass, Body fat, Arm lymphedema, Obesity, Local tissue water

Introduction

Breast cancer (BC) is the most frequent type of cancer seen in women worldwide. The incidence of BC was reported as 12%.[1] Although the incidence of BC has tremendously increased over the past few decades, the survival rate of BC has also improved due to early screening, diagnosis, and advancements in the treatment. According to the SEER report, the median survival doubled within the 40-year timeframe from 1978 to 2018.[2]

Patients with BC can experience a wide variety of symptoms due to the multimodal nature of the associated treatment. Breast cancer-related lymphedema (BCRL) is one of the most fearsome and cumbersome complications of BC treatment associated with axillary lymph node clearance and disrupted lymph flow in the operated side extremity and torso.[3] Due to disrupted lymph flow, the accumulation of protein-rich fluid in the interstitial spaces not only causes swelling but also advanced changes in the skin such as fibrosis.[4] Patients with BCRL can experience a broader aspect of additional

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burden such as disrupted shoulder mobility, decreased quality of life, and financial toxicities associated with BCRL.[5-7] Since there is no total cure for BCRL, management of this condition as soon as possible is of utmost importance.[8] Studies revealed that detecting preclinical BCRL carries a great opportunity to manage potential debilitating side effects. Thus, using an objective, sensitive, and specific measurement to track subtle changes in the ipsilateral extremity is a prerequisite to improve future clinical outcomes. In this manner, the Tissue Dielectric Constant (TDC) method presents itself as a promising option for detecting early changes in patients with breast cancer at risk for BCRL due to its noninvasive, safely repeatable, and objective results wherever it is needed.[9,10]

To date, many risk factors of BCRL development have been identified, such as axillary lymph node dissection (ALND), systemic taxane chemotherapy, obesity, locoregional radiotherapy, and so forth. However, increased body mass index (BMI) has been maintained as a major risk factor for the development of BCRL.[8,11,12] However, the potential role of body fat has raised questions with the term "sarcopenic obesity" which refers to increased body fat and decreased muscle mass while having a stable BMI. Body fat not only plays a crucial role in the potential development of BCRL but also acts on poorer survival which is well-recognized among cancer patients.[13] To the best of our knowledge, there is a lack of potential associations between body composition and potential risk profiling of BCRL by the TDC method in patients at risk for BCRL. Since timely fashion of measurement especially for BCRL has great importance, especially in acute settings,[8] this study aimed to analyze the potential associations between body composition parameters specifically in the context of body fat and interpretable dielectric values and ratios of ipsilateral and contralateral upper extremities, respectively.

Material and Methods

Study Design

This observational study was held in the medical oncology unit of Izmir Bakircay University Faculty of Medicine between February 2022 and 2024 according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was granted from Izmir Bakircay University Ethical Board of Clinical Studies with the following number (1463/1483) The nonprobability sampling method was used.

Patients

Patients diagnosed with breast cancer and referred to the medical oncology unit after surgical operation were screened according to the predefined inclusion and exclusion criteria. Being a volunteer to participate, age between 18 and 75 years old, female gender, having had unilateral surgical operation for breast cancer with or without axillary procedure were set as inclusion criteria. Having had bilateral breast cancer surgery, confirmed distant metastasis, mental/cognitive deficits, widespread allergic reactions, and ongoing surgical complications such as seroma, systemic edema, confirmed diagnosis of BCRL prior to the participation, and breast surgery for aesthetic reasons were set as exclusion criteria. A signed informed consent was gathered for each patient after information was given prior to participation. The following assessments were completed in 1-month after breast cancer surgery.

Assessments

Tissue Dielectric Constant Measurement. Tissue Dielectric Constant (TDC) was measured via Moisture MeterD (Delfin Technologies, Kuopio, Finland) in 4 different probes each has a unique penetration depth from 0.5 mm to 5.00 mm. In simple terms, the 300 MHz electromagnetic wave is produced in the control unit of the device and then transmitted by the probe that comes into touch with the skin. The central unit of the device processes the reflected signal to determine the measuring site's dielectric value. At room temperature, air has a dielectric value of 1, whereas pure water has a value of 78. Greater fluid content is indicated by a greater dielectric value, or vice versa. The reflected portion is mostly determined by the tissue's fluid content and is ascribed to extracellular fluid and/or edema.[9,14,15] In this case, comparing the dielectric values of extremities and proportioning to one another (at risk side/unaffected side) can give valuable insight into the potential preclinical BCRL.

Patients' risk for BCRL was assessed with Moisture MeterD (Delfin Technologies, Kuopio, Finland) in 4 different probes each has unique penetration depths and contact diameters from 0.5 (10 mm) to 5.0 (55 mm) at the following reference points: 10 cm proximal and 6 cm distal volar side reference points for the upper arm and forearm, the dorsum of the web-space, and 8 cm distal reference point from the axillary space for the thorax, respectively. Reference points were marked with a soft pen before and after cleaning the measurement sites with a wet wipe with alcohol prior to the measurement on both upper extremities. Each patient was rested for at least 5 minutes in the supine position. A gentle pressure was applied for nearly 5-7 seconds and maintained perpendicularly at the reference point until an audible signal was received and transferred to the application interface via a Bluetooth sensor. A triplicate measurement was performed for each reference point and the mean of them was automatically recorded. This procedure was followed for each probe for each reference point except for the reference point of hand in the largest probe (55 mm) due to incompatible diameter and surface area. TDC measurement was performed before the afternoon to provide standardization for potential diurnal fluctuations. The total completion of the TDC measurement nearly took 30 minutes for each patient. TDC measurement was performed by was performed by A.T.

Body Composition. The body composition was analyzed with Tanita-BC-420 MA (TANITA Corporation, Sportlife Tokyo, Japan). Patients were requested to stand upright with bare feet on the device's footpads. Prior to the measurement, patients were informed about the measurement process according to the manufacturer's guideline that they avoid vigorous physical exertion, alcohol and/or caffeine consumption, and being with an empty stomach in order to standardize measurement results for each. Objects which might intervene in the measurement process such as jewelry and metals were requested to be taken off before measurement. After selecting gender by the device's interface, each patient was informed that they needed to preserve their upright posture till the completion

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of the measurement. Briefly, an alternating current passes through the body, and a single-frequency analyzer roughly estimates the percent body fat and total body water, fat and muscle mass, fat-free mass, visceral fat rating, and bone mineral mass.[16] In addition, the Skeletal Muscle Mass Index (SMM) was also calculated by multiplying fat-free mass and 0.566 according to the previous reports. Thereafter, SMM index (SMMI) was calculated as follows: SMM/height squared (m^2).[17,18] To avoid potential diurnal fluctuations, all patients were analyzed before the afternoon after the completion of the TDC measurement. A thirty-minute interval was set between TDC and body composition measurements. Body composition measurement was performed by Ö.Ç.

Statistical Analysis

The data was shown as means and standard deviation or numbers and percentages according to the type of data. The normality of the data was checked via the KS-SW tests, skewness, and kurtosis as well as graphical representation. The continuous data between groups was analyzed with independent samples t-test or Mann Whitney U test in case of the violation of normality assumptions (ie, patients with Sentinel lymph node biopsy [SLNB] or ALND). Dichotomous variables were handled via the Chi^2 test. Pearson's r or Spearman's rho correlation analyses were performed between parameters according to the normality assumptions. Correlation coefficients are interpreted as follows: $r < 0.20$ poor, $0.21 < r < 0.40$ fair, $0.41 < r < 0.60$ moderate, $0.61 < r < 0.80$ good and $0.81 < r < 0.1$ excellent.[19] TDC ratios of each reference point between probes were analyzed by repeated measures ANOVA within factor design. All analyses were 2-tailed, and the p-value was accepted as significant below 0.05. A posthoc power analysis which was performed via the GPower 3.1 program showed that we achieved 82% of power within 95% CI when taking into account partial eta squared .02. In addition, we also performed the posthoc power analysis by taking into account the deepest probe (5.0 mm) between the affected and unaffected sides of patients in which we achieved over 95% power by getting a large effect size (.90) for paired t-tests with a total of 72 patients.[20] Statistical analysis was performed with IBM SPSS v.20 (IBM Corp, NY).

Results

A total of 99 patients with confirmed diagnosis of BC after surgically operated and referred to the medical oncology were screened. According to the predefined inclusion and exclusion criteria, 27 of them were excluded from participation due to several reasons. A detailed participation process flow chart is shown in Figure 1. Therefore, this study was completed with a total of 72 BC patients (Mean age and BMI: 50.94 ± 11.56 years and 28.93 ± 4.84 kg/m^2). Thirty-four out of seventy-two patients underwent a breast-conserving surgery while the rest of them underwent a modified radical mastectomy. Fifty-four out of Seventy-two patients underwent an axillary lymph node dissection (ALND), while 18 of them underwent sentinel lymph node biopsy (SLNB) without any further axillary clearance. The majority of patients (63.8%) had stage II BC. The detailed clinical characteristics of patients are shown in Table 1.

There was no significant difference in the mean of the TDC values between affected and nonaffected (at risk/no risk) extremities in each reference point in all 4 different probes ($P > .05$) except for the thorax reference point which was significantly higher in all 4 probes on the at-risk side compared to the unaffected side ($P < .05$). In addition, the affected side's TDC value of web space was significantly lower in 0.5 probe ($t = 4.468$, $P \leq .001$). When it comes to the TDC ratio, there was no significant difference between probes in the arm ($F [3,69] = 0.492$, $P = .68$, $\eta p^2 = 0.021$), web

Figure 1 Flow chart of the study participation process.

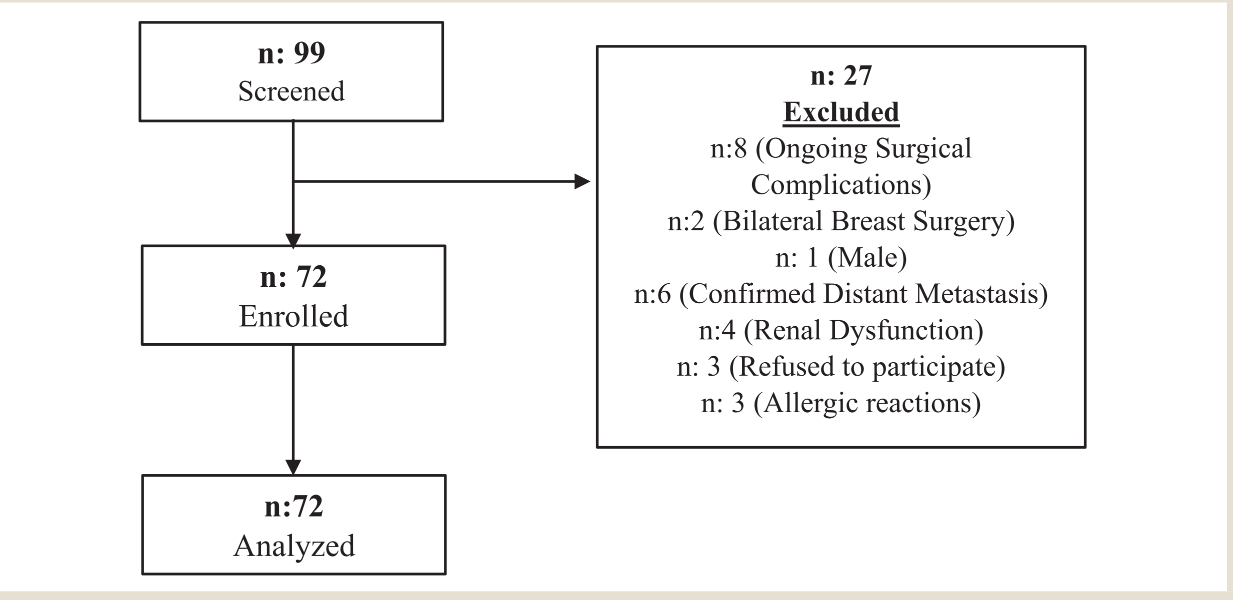

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Table 1 Clinical Characteristics of Patients

n = 72	*n* (%)
Type of breast surgery	
BCS	34 (47.2)
MRM	38 (52.8)
Type of axillary procedure	
ALND	54 (75)
SLNB	18 (25)
Grade	
pT1	16 (22.4)
pT2	46 (63.8)
pT3	10 (13.8)

Abbreviations: BCS = breast-conserving surgery; MRM = modified radical mastectomy; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy.

space (F [2,70] = 2.256, P = .112, ηp^2 = 0.061) and thorax F (3,69) = 0.362, P = .78, ηp^2 = 0.016) reference points, respectively. However, there was a significant difference in TDC values between probes in the forearm reference point (F [3,69] = 3.164, P = .03, ηp^2 = 0.121). Yet, adjustments after the Bonferroni correction showed no significant difference between all of those. The comparisons of mean TDC values and ratios are shown in Table 2. There were also significantly higher mean TDC ratios in patients who underwent ALND compared to the ones with SLNB in arm reference point at 0.5 (1.03 vs. 0.97, t = 2.131, P = .037) and 2.5 (1.03 vs. 0.97, t = 2.170, P = .033) probes. Besides, there was no significant difference in age (t = -0.586, P = .56) and BMI (t = 0.655, P = .51) between patients who had ALND or SLNB. No significant difference was observed in TDC values and ratios in each probe and reference points between patients with MRM or BCS. When taking into consideration of TDC ratios of patients in the 2.5 mm depth probe, there were 3 or 4 out of 72 patients whose TDC ratios exceeded to mean ± 2SD value in all reference points (4.1%-5.6%). Patients who had an exceeded TDC ratio showed higher values of BMI (Min: 27.51, Max: 36.40).

The mean percent of fat mass and total body water were found as 36.96 ± 6.64 and 44.15 ± 4.02, respectively. The visceral fat rating and SMMI were found as 9.65 ± 0.85 and 24.44 ± 2.27, respectively. According to the European Working Group on Sarcopenia in Older People (EWGSOP) definition (< 7.4 for women for SMMI[21]), no patient was categorized as having low skeletal muscle mass index (Mean: 9.65 ± 0.85). The details of body composition parameters are shown in Table 3.

There were also significant correlations between TDC ratios and body composition parameters that should be acknowledged. Though the arm and web space reference points' TDC ratios did not correlate significantly with any body composition parameters as well as with age and BMI, there were fair but significant correlations between TDC ratios and body composition parameters in forearm and thorax reference points. However, no significant difference was obtained between body composition parameters, type of surgery, and type of axillary procedure. Table 4 shows the significant correlations between these parameters.

Discussion

The present study showed a significant increase in sub-tissue fluid proportion at the thorax region on the operated side compared to the unaffected side irrespective of the depth of the TDC measurement as expected. Yet, it might be more plausible to use the TDC ratios instead of TDC values since it might be more sensitive to catch potential changes associated with BCRL with an individual-

Table 2 Comparison of the Mean TDC Values and Ratios in the Arm, Forearm, Web Space, and Thorax Reference Points

n = 72	PROBES	At risk Side	Unaffected Side	t	*P*	Ratio	Ratio (Mean ± 2SD)
ARM	**0.5 mm**	34.36 ± 5.02	33.75 ± 3.75	1.552	.12	1.01 ± 0.10	1.21
	1.5 mm	30.10 ± 4.90	29.91 ± 3.88	.449	.65	1.00 ± 0.12	1.24
	2.5 mm	26.44 ± 3.70	26.03 ± 2.88	1.326	.18	1.01 ± 0.10	1.21
	5.0 mm	20.36 ± 3.26	19.93 ± 2.46	1.447	.15	1.02 ± 0.13	1.28
FOREARM	**0.5 mm**	36.30 ± 4.88	36.18 ± 3.99	.412	.61	1.00 ± 0.07	1.14
	1.5 mm	31.98 ± 4.06	31.71 ± 3.58	.851	.39	1.01 ± 0.08	1.17
	2.5 mm	27.77 ± 3.59	27.81 ± 2.97	-0.196	.84	.99 ± 0.06	1.11
	5.0 mm	21.81 ± 3.71	21.38 ± 2.77	1.625	.10	1.02 ± 0.09	1.20
THORAX	**0.5 mm**	37.23 ± 5.11	35.74 ± 3.83	3.053	.003*	1.04 ± 0.11	1.26
	1.5 mm	33.41 ± 4.24	31.92 ± 3.90	3.291	.002*	1.05 ± 0.13	1.31
	2.5 mm	29.85 ± 3.65	28.66 ± 3.13	3.386	.001*	1.04 ± 0.10	1.24
	5.0 mm	23.00 ± 3.32	21.96 ± 2.87	3.366	.001*	1.05 ± 0.12	1.29
WEB SPACE	**0.5 mm**	34.25 ± 3.92	35.94 ± 3.70	4.468	<.001*	1.02 ± 0.08	1.18
	1.5 mm	34.25 ± 3.92	33.71 ± 4.04	1.207	.23	1.02 ± 0.11	1.24
	2.5 mm	33.60 ± 3.97	33.55 ± 3.51	.119	.90	1.00 ± 0.09	1.18
	5.0 mm	-	-	-	-	-	-

Abbreviations: Mm = millimeter; SD = standard deviation; P < .05 = paired t test. *: Significant at the 0.01 level.

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Table 3 The Mean Values of Percent Fat and Total Body Water, Muscle Mass, Bone Mineral Mass, and Visceral Fat Rating of Patients

n = 72	Fat (%)	TBW (%)	MM (kg)	BMM) (kg)	VFR	SMMI
Body composition	36.96 ± 6.54	44.15 ± 4.02	43.18 ± 4.00	2.31 ± 0.20	8.51 ± 3.22	9.65 ± 0.85

Abbreviations: TBW = total body water; MM = muscle mass; BMM = bone mineral mass; VFR = visceral fat rating; SMMI = skeletal muscle mass index.

Table 4 Correlations Between Age, BMI, TDC Ratios, and Body Composition Parameters of Patients

n = 72	Age	BMI	FM (%)	TBW	BMM	VFR	SMM	SMMI
Age (years)	-	NS	r = 0.250 *P* = .034	r = - 0.346 *P* = .003	NS	r = 0.644 *P* < .001	NS	NS
BMI (kg/m²)		-	r = 0.876 *P* < .001	r = -0.850 *P* < .001	r = 0.695 *P* < .001	r = 0.843 *P* < .001	r = 0.699 *P* < .001	r = 0.834 *P* < .001
ratio-forearm_0.5 mm	NS	NS	NS	NS	r = 0.253 *P* = .032	r = 0.258 *P* = .029	r = 0.239 *P* = .043	NS
ratio-forearm_1.5 mm	NS	NS	NS	NS	r = 0.280 *P* = .017	NS	r = 0.280 *P* = .017	NS
ratio-forearm_2.5 mm	r = 0.282 *P* = .016	R = 0.251 *P* = .033	r = 0.256 *P* = .030	r = -0.261 *P* = .027	NS	r = 0.340 *P* = .003	NS	NS
ratio-forearm_5.0 mm	r = 0.250 *P* = .034	r = 0.244 *P* = .039	NS	NS	NS	r = 0.301 *P* = .010	NS	NS
ratio-Thorax_0.5 mm	r = 0.241 *P* = .041	r = 0.330 *P* = .005	NS	r = -0.257 *P* = .029	NS	r = 0.332 *P* = .004	NS	r = 0.282 *p* = .016
ratio- Thorax _1.5 mm	r = 0.241 *P* = .041	r = 0.320 *P* = .006	r = 0.269 *P* = .022	r = -0.286 *P* = .015	NS	r = 0.353 *P* = .002	NS	NS
ratio-thorax _2.5 mm	r = 0.321 *P* = .006	r = 0.398 *P* = .001	r = 0.371 *P* = .001	r = -0.390 *P* = .001	NS	r = 0.466 *P* < .001	NS	r = 0.276 *P* = .019
ratio- Thorax _5.0 mm	r = 0.354 *P* = .002	r = 0.318 *P* = .006	r = 0.323 *P* = .006	r = -0.361 *P* = .002	NS	r = 0.453 *P* < .001	NS	NS

Abbreviations: BMI = body mass index; FM = fat mass; TBW = total body water; BMM = bone mineral mass; VFR = visceral fat rating; SMM = skeletal muscle mass; SMMI = skeletal muscle mass index; NS = not significant; r = Pearson's correlation coefficient; $P < .05$.

ized frame in the context of early diagnosis. On the other hand, we suggest that patients who underwent ALND and higher BMI should be thoroughly monitored due to the potential higher risk of BCRL manifestation in line with the literature findings. Significant associations between the parameters of body composition related to fat and TDC ratios in the forearm and thorax reference points also support our suggestion.

Breast cancer-related lymphedema (BCRL) is 1 of the most fearsome complications in breast cancer survivorship due to its chronic nature and BCRL cannot be fully curable. Since patients with BCRL can experience a wide range of symptoms, especially in the aspect of physical function, the early diagnosis of BCRL is of utmost importance.[3] However, using a sensitive and objective method in order to track changes that might be clinically meaningful is crucial so that an action can be taken as soon as earlier. The wide range of reported BCRL incidence was also attributed to the different measurement techniques.[22] Thus, the TDC method has been accepted as a promising and objective option to detect changes associated with early BCRL due to it is directly linked to sub-tissue fluid proportion and is advantageous to use this method, especially in patients at risk of unilateral BCRL.[10,23] In the literature, its usability was reported in varied conditions such as diabetes,[24] lower extremity lymphedema,[25] healthy individuals,[26] trunk[27] and breast lymphedema,[28] and even differentiation in benign and breast tumors[29] and so forth. In our study, there was no significant difference in TDC values in all probes and reference points except for the thorax reference point on the affected side. This was an expectable result since the timing of the measurements was nearly close or in parallel with the healing process of the surgery. Although using the TDC ratio taken by a 2.5 mm depth probe which is quite focused on dermo-epidermal junction and accepted as the main area of potential accumulation of interstitial fluid was reported to be useful, we did not find any significant differences in TDC ratios between four probes. However, using the ratios taken by a 2.5 mm probe might give more interpretable results in terms of clinical implications.[27,30] For instance, setting the threshold for TDC ratio as 1.20 yielded 65% and 94% sensitivity and specificity in patients with breast cancer with or without BCRL.[31] These rates seem parallel with the previous literature findings.[23] In our study, only in arm and thorax reference points mean TDC ratios exceeded the 1.20 threshold according to the mean ± 2SD calculation in 2.5 mm depth. There were 3 or 4 patients out of 72 who had over 1.20 in all reference points and probes. Not surprisingly, their mean BMI could be categorized as overweight to obese (27.41 through 36.40

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kg/m^2). Nonetheless, it should be noted that no patient showed any signs or symptoms of BCRL, therefore regular follow-ups should be necessary to classify whether preclinical BCRL is present or not. Since BCRL can manifest within days after surgery,[32] and studies reported that over 80% of BCRL cases manifested within 2 years of breast cancer surgery, regular follow-ups are necessary within a 2-year framework. Leray et al.[11] also reported nearly 70% of their sample reported BCRL within a 2-year after breast cancer surgery. On the other hand, ALND, which is reported to be a major risk factor for BCRL,[33,34] was also on the stage in our study when considering significantly higher TDC ratios in arm reference points between patients who underwent ALND or SLNB. This was an expectable result due to ALND shows itself to a greater extent in surgery compared to the SLNB not only in the context of long-term consequences but also surgical edema in acute settings. Though there were significantly higher TDC values on the affected side, these findings should be carefully interpreted taking into account the TDC ratios since differences seemed not clinically meaningful. Yet, Keeley et al.[8] reported that a relative arm volume increase of 5%-10% in the first month after breast cancer surgery was a significant risk factor by having a 5.27-fold increase in the risk of developing BCRL at 36 months (OR: 5.27 [95% CI: 3.30-8.41]). Although relative volume changes and TDC ratios cannot be used interchangeably, it might be plausible to conclude that having a 1.05-1.10 actual TDC ratio in the early settings can give an insight into the potential BCRL in the future. When our fictive TDC ratios in arm reference point taken by 2.5 mm depth probe fictionalized, 16 out of 72 of our patients (22.2%) showed actual TDC ratios above 1.05 and as expected, their mean BMI and body fat percentage were found to be 31.04 kg/m^2 and 38.63%, respectively. Only 3 out of 16 patients with a higher actual TDC ratio over 1.05 were categorized as having normal range body fat. Therefore, it might be reasonable to conclude that the TDC method can be used further with an acceptable superiority over the other measurement techniques such as circumference measurement which takes into account both muscles and bones.[10] The authors also stated that this method is quite useful in trunk lymphedema which is a not suitable area for circumference measurement to detect potential changes associated with BCRL.[27]

To date, numerous risk factors have been studied in the context of BCRL development. Increased BMI, which is reported to be a major factor along with ALND still carries its importance.[11] It is a well-recognized fact that overweight and obese breast cancer have a higher risk of experiencing BCRL.[12] Studies stated that women with breast cancer tend to gain weight through the trajectory of systemic treatment and patients who have normal weight at the time of diagnosis are prone to gain more weight. On the other hand, not only weight gain, but also increased fat mass and percentage is also another concern that is known as having both associated with increased risk of BCRL and poorer survival due to potential interactions, especially for hormone-positive breast cancer.[35] A significant linear upward trend in increased body fat even though patients attended an exercise program during the first year.[36] Although increased BMI is accepted as a significant risk factor for the development of BCRL, studies highlighted the need for further data due to raising concerns about the term sarcopenic obesity which refers to the increased body fat relative to lean body mass while having a decrease in muscle mass.[13] Cheeney et al.[37] reported an increase in body fat irrespective of the change whether up or down in body weight in breast cancer survivors after completion of adjuvant systemic treatment. In our study, body composition parameters were found relatively good and acceptable according to the body composition manufacturer's manual and previous studies. For instance, the range between 1 and 12 of VFR indicates a healthy level of fat rate while above 13 shows excess adipose tissue.[38] Only four patients were above this rate (mean VFR: 16) and not surprisingly, their mean BMI was nearly 40 kg/m^2 in our study. Our results were expectable because our sample consisted of relatively younger breast cancer patients and they were measured before systemic treatments which have well-known significant impacts on muscle and fat mass. For instance, the use of tamoxifen was reported to be associated with increased visceral fat.[39] Although sarcopenia refers to not only having SMMI below the threshold but also lower muscle strength, no patient in our study had below the threshold of 7.4[21] according to the Turkish population (Min: 8.2). When age-adjusted healthy body fat percentages were analyzed according to the Gallagher et al.'s[40] study, 76.4% of our sample (55 out of 72) showed higher body fat. Not surprisingly, for patients with higher body fat according to the age-adjusted body fat percentages, their BMI was significantly higher than those with healthy levels. In addition, the former showed higher TDC ratios in each reference point compared to the TDC ratios of the latter; however, these results did not reach statistical significance (data not shown). When it comes to the risk of BCRL development by having higher BMI, significant correlations among the ratios of the forearm, and thorax as well as BMI, VFR, and percentage of fat mass can be attributed to the confirming reflections of the previous results.[11,12,22] Yet, the only significant but weak correlations between the TDC ratios and SMMI were reached in the thorax reference point. This result can be attributed to the anatomical features of the region. However, further studies should elaborate on the potential associations between muscle mass and TDC ratios.

This study has some strengths and limitations. A cross-sectional design of this study can account for the limitation because we were not able to compare any potential effects either on body composition or TDC values and ratios. The nonprobability sampling method of this study can also be accounted for as a limitation. In addition, we did present only the passive measurements in which a patient cannot take an active role or report any symptom(s) due to we did not desire any potential impact that can be misinterpreted regarding preclinical BCRL such as on ongoing surgical symptoms such as pain by not using any patient-reported outcomes. Since this study was held in a single center and consisted of white Caucasian women, the generalizability of our results can be a bit arguable. However, to the best of our knowledge, this is the first study to assess potential associations between the TDC method and body composition parameters in patients with breast cancer after surgical operation. Further studies might integrate a symptom-based assessment in different trajectories and timings.

Conclusion

The presented results in this study highlight the need for further care and investigation in the assessment and prediction of BCRL

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in patients after breast cancer surgery by taking into account body composition. Since risk reduction can be maximized by considering the individual features, we can conclude that patients with higher age and body fat irrespective of the BMI as well as undergone ALND should be followed up regularly. It might also be plausible to state that education of patients associated with BMI should also strengthen with further information associated with the role of fat, diet, and exercise throughout the whole trajectory of breast cancer treatment. Finally, using the actual TDC ratio as 1.05 in patients with higher body fat percentage might be a useful indicator of potential BCRL in the future. We suggest that further studies are needed to verify this.

Clinical Practice Points

- **What is already known about this subject?**

Breast cancer-related lymphedema (BCRL) is one of the most fearsome side effects of breast cancer treatment due to its noncurable chronic nature. To date, many risk factors have been reported in which higher body mass index (BMI) or obesity is pronounced mostly. Yet, many studies generally rely on patient-reported BMIs or waist-to-hip ratio when assessing the potential association on BCRL among breast cancer patients. Although rarely reported, sarcopenic obesity which is characterized by increased fat mass while having a stable BMI should be elucidated in terms of the risk of BCRL by using objective methods.

- **What are the new findings?**

There were significant results in patients who underwent axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) in the context of dielectric ratios which were higher in patients with ALND. In addition, the fat mass was significantly and linearly correlated with dielectric ratios which might be indicative of preclinical BCRL in patients without any signs or symptoms of BCRL.

- **How might it impact clinical practice in the foreseeable future?**

Using solely of BMI of the patients with breast cancer who are at risk for BCRL might not be elucidative in the trajectory of potential BCRL assessment. Patients who underwent ALND and with higher fat mass irrespective of BMI should be thoroughly evaluated due to significantly increased dielectric ratios.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

CRediT authorship contribution statement

Alper Tuğral: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Murat Akyol:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation. **Öykü Çolakoğlu:** Validation, Supervision, Data curation. **Yeşim Bakar:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424. doi:10.3322/caac.21492.
2. Abraham HG, Xia Y, Mukherjee B, Merajver SD. Incidence and survival of inflammatory breast cancer between 1973 and 2015 in the SEER database. *Breast Cancer Res Treat*. 2021;185:229–238. doi:10.1007/s10549-020-05938-2.
3. McLaughlin SA, Brunelle CL, Taghian A. Breast cancer–related lymphedema: risk factors, screening, management, and the impact of locoregional treatment. *J Clin Oncol*. 2020;38:2341–2350. doi:10.1200/JCO.19.02896.
4. Yusof KM, Avery-Kiejda KA, Suhaimi SA, et al. Assessment of potential risk factors and skin ultrasound presentation associated with breast cancer-related lymphedema in long-term breast cancer survivors. *Diagnostics*. 2021;11:1303. doi:10.3390/diagnostics11081303.
5. Jørgensen MG, Toyserkani NM, Hansen FG, Bygum A, Sorensen JA. The impact of lymphedema on health-related quality of life up to 10 years after breast cancer treatment. *NPJ Breast Cancer*. 2021;7:70. doi:10.1038/s41523-021-00276-y.
6. Rashid N, Koh HA, Baca HC, Lin KJ, Malecha SE, Masaquel A. Economic burden related to chemotherapy-related adverse events in patients with metastatic breast cancer in an integrated health care system. *Breast Cancer (Dove Med Press)*. 2016:173–181. doi:10.2147/BCTT.S105618.
7. Bian J, Shen A, Yang W, Zhang L, Qiang W. Financial toxicity experienced by patients with breast cancer-related lymphedema: a systematic review. *Support Care Cancer*. 2023;31:354. doi:10.1007/s00520-023-07800-9.
8. Keeley V. The early detection of breast cancer treatment-related lymphedema of the arm. *Lymphat Res Biol*. 2021;19:51–55. doi:10.1089/lrb.2020.0097.
9. Nuutinen J, Ikäheimo R, Lahtinen T. Validation of a new dielectric device to assess changes of tissue water in skin and subcutaneous fat. *Physiol Meas*. 2004;25:447–454. doi:10.1088/0967-3334/25/2/004.
10. Lahtinen T, Seppälä J, Viren T, Johansson K. Experimental and analytical comparisons of tissue dielectric constant (TDC) and bioimpedance spectroscopy (BIS) in assessment of early arm lymphedema in breast cancer patients after axillary surgery and radiotherapy. *Lymphat Res Biol*. 2015;13:176–185. doi:10.1089/lrb.2015.0019.
11. Leray H, Malloizel-Delaunay J, Lusque A, et al. Body mass index as a major risk factor for severe breast cancer-related lymphedema. *Lymphat Res Biol*. 2020;18:510–516. doi:10.1089/lrb.2019.0009.
12. Jammallo LS, Miller CL, Singer M, et al. Impact of body mass index and weight fluctuation on lymphedema risk in patients treated for breast cancer. *Breast Cancer Res Treat*. 2013;142:59–67. doi:10.1007/s10549-013-2715-7.
13. Sheean PM, Hoskins K, Stolley M. Body composition changes in females treated for breast cancer: a review of the evidence. *Breast Cancer Res Treat*. 2012;135:663–680. doi:10.1007/s10549-012-2200-8.
14. Alanen E, Lahtinen T, Nuutinen J. Variational formulation of open-ended coaxial line in contact with layered biological medium. *IEEE Trans Biomed Eng*. 1998;45:1241–1248. doi:10.1109/10.720202.
15. Lahtinen T, Nuutinen J, Alanen E. Dielectric properties of the skin. *Phys Med Biol*. 1997;42:1471–1472. doi:10.1088/0031-9155/42/7/020.
16. Jebb SA, Cole TJ, Doman D, Murgatroyd PR, Prentice AM. Evaluation of the novel Tanita body-fat analyser to measure body composition by comparison with a four-compartment model. *Br J Nutr*. 2000;83:115–122. doi:10.1017/s0007114500000155.
17. Kotler DP, Burastero S, Wang J, Pierson RNJ. Prediction of body cell mass, fat-free mass, and total body water with bioelectrical impedance analysis: effects of race, sex, and disease. *Am J Clin Nutr*. 1996;64:489S–497S. doi:10.1093/ajcn/64.3.489S.
18. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *T J Gerontol A Biol Sci Med Sci*. 2002;57(2002):M772–M777. doi:10.1093/gerona/57.12.m772.
19. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg*. 2018;126(5):1763–1768. doi:10.1213/ANE.0000000000002864.
20. Faul F, Erdfelder E, Lang AG, G* Buchner A. Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39:175–191. doi:10.3758/bf03193146.
21. Bahat G, Tufan A, Tufan F, et al. Cut-off points to identify sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) definition. *Clin Nutr*. 2016;35:1557–1563. doi:10.1016/j.clnu.2016.02.002.
22. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14(6):500–515. doi:10.1016/S1470-2045(13)70076-7.
23. Mayrovitz HN, Weingrad DN, Lopez L. Assessing localized skin-to-fat water in arms of women with breast cancer via tissue dielectric constant measurements in pre-and post-surgery patients. *Ann Surg Oncol*. 2015:1483–1489. doi:10.1245/s10434-014-4185-5.

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24. Mayrovitz HN, McClymont A, Pandya N. Skin tissue water assessed via tissue dielectric constant measurements in persons with and without diabetes mellitus. *Diabetes Technol Ther*. 2013;15:60–65. doi:10.1089/dia.2012.0197.
25. Tugral A, Viren T, Bakar Y. Tissue dielectric constant and circumference measurement in the follow-up of treatment-related changes in lower-limb lymphedema. *Int Angiol.*. 2018;37:26–31. doi:10.23736/S0392-9590.17.03843-3.
26. Mayrovitz HN, Corbitt K, Grammenos A, Abello A, Mammino J. Skin indentation firmness and tissue dielectric constant assessed in face, neck, and arm skin of young healthy women. *Skin Res Technol*. 2017;23:112–120. doi:10.1111/srt.12310.
27. Koehler LA, Mayrovitz HN. Tissue dielectric constant measures in women with and without clinical trunk lymphedema following breast cancer surgery: a 78-week longitudinal study. *Phys Ther*. 2020;100:1384–1392. doi:10.1093/ptj/pzaa080.
28. Tuğral A, Akyol M, Bakar Y. The effect of adjuvant radiotherapy on skin biophysical properties in patients with breast cancer at risk for breast lymphedema: a prospective study. *Clin Physiol Funct Imaging*. 2023;43:263–270. doi:10.1111/cpf.12815.
29. Mayrovitz HN, Weingrad DN. Tissue dielectric constant differentials between malignant and benign breast tumors. *Clin Breast Cancer*. 2022;22:473–477. doi:10.1016/j.clbc.2022.02.007.
30. Mayrovitz HN, Davey S, Shapiro E. Local tissue water assessed by tissue dielectric constant: anatomical site and depth dependence in women prior to breast cancer treatment-related surgery. *Clin Physiol Funct Imaging*. 2008;28:337–342. doi:10.1111/j.1475-097X.2008.00814.x.
31. Bakar Y, Tuğral A, Üyetürk Ü. Measurement of local tissue water in patients with breast cancer-related lymphedema. *Lymphat Res Biol*. 2018;16:160–164. doi:10.1089/lrb.2016.0054.
32. Armer J, Stewart B. Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. *Lymphology*. 2010;43(3):118–127.
33. Wernicke AG, Shamis M, Sidhu KK, et al. Complication rates in patients with negatve axillary nodes 10-years after local breast radiotherapy following either sentinel lymph node dissection or axillary clearance. *Am J Clin Oncol*. 2013;36:12–19. doi:10.1097/COC.0b013e3182354bda.
34. McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. *J Clin Oncol*. 2008;26:5213–5219. doi:10.1200/JCO.2008.16.3725.
35. Nissen MJ, Shapiro A, Swenson KK. Changes in weight and body composition in women receiving chemotherapy for breast cancer. *Clin Breast Cancer*. 2011;11:52–60. doi:10.3816/CBC.2011.n.009.
36. DeNysschen CA, Brown JK, Cho MH, Dodd MJ. Nutritional symptom and body composition outcomes of aerobic exercise in women with breast cancer. *Clin Nurs Res*. 2011;20:29–46. doi:10.1177/1054773810379402.
37. Cheney CL, Mahloch J, Freeny P. Computerized tomography assessment of women with weight changes associated with adjuvant treatment for breast cancer. *Am J Clin Nutr*. 1997;66:141–146. doi:10.1093/ajcn/66.1.141.
38. Vasold KL, Parks AC, Phelan DML, Pontifex MB, Pivarnik JM. Reliability and validity of commercially available low-cost bioelectrical impedance analysis. *Int J Sport Nutr Exerc Metab*. 2019;29:406–410. doi:10.1123/ijsnem.2018-0283.
39. Nguyen M, Stewart RB, Banerji MA, Gordon DH, Kral JG. Relationships between tamoxifen use, liver fat and body fat distribution in women with breast cancer. *Int J Obes Relat Metab Disord*. 2001;25:296–298. doi:10.1038/sj.ijo.0801488.
40. Gallagher D, Hemsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr.2000 72: 694-701. doi: 10.1093/ajcn/72.3.694.

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