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CLASSIFICATION OF BREAST LYMPHEDEMA IN A RACIALLY DIVERSE COHORT

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ABSTRACT

Breast lymphedema is a common sequela of breast conservation that delays healing and reduces quality of life. No rigorous classification system exists for this condition. We explored approaches for classifying breast lymphedema based on breast ultrasound, physical exam, and patient-reported outcomes. We enrolled 80 patients from two institutions. Each site enrolled 30 invasive breast cancer patients treated with breast conservation and radiotherapy, and 10 control patients evaluated for benign breast complaints. All patients underwent bilateral breast ultrasound to measure dermal thickness and were assessed for physical signs of breast lymphedema. Patients reported quality of life impacts on standard questionnaires. We derived breast lymphedema classifiers using (1) a simple ultrasound-based metric of dermal thickness difference, and (2) a multiparameter machine learning classifier based on dermal thickness difference, physical exam, and patient-reported impacts. Ultrasound-defined breast lymphedema was present in 72% (95% CI: 59 to 82%) of invasive breast cancer patients. The multiparameter classifier identified three distinct patient groups: one with little evidence of breast lymphedema, and two with increasingly severe breast lymphedema. A simple ultrasound-based measure and a novel multiparameter classifier both show promise for rigorous classification of breast lymphedema and warrant further development in larger patient cohorts.

Keywords: Breast cancer, breast surgery, lymphedema, ultrasound, racial disparities

Breast conservation surgery (BCS) with radiation therapy (RT) is the treatment of choice for over half of women diagnosed with invasive breast cancer (1). Sentinel lymph node biopsy (SLNB) allows local control with more conservative treatment for node-negative patients and is associated with fewer side effects and improved quality of life (QOL) compared with axillary lymph node dissection

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(ALND) (2,3). With SLNB replacing ALND in the treatment of early, clinically node-negative breast cancer patients, breast lymphedema (BLE) has overtaken arm lymphedema as a prominent sequela of BCS (4,5). BLE results from disrupted lymphatic drainage and accumulation of excess interstitial fluid, leading to pain, swelling, erythema, and a heavy sensation in the affected breast. These symptoms impact physical function, psychosocial well-being, and activities of daily living (5-7). Published estimates of BLE incidence vary widely, ranging from 20–50% of patients treated with BCS and RT (7,8). This variability is likely a function of the disparate and often subjective criteria used to define BLE. BLE incidence may be associated with the extent of lymph node sampling (5,8), breast density, tumor size, and characteristics of adjuvant breast radiotherapy (9). However, as with the estimates of BLE incidence, interpretation of etiologic studies is hampered by lack of a rigorous, reproducible, and uniform BLE classification system (10).

Objective measurement methods for arm lymphedema (e.g., tissue dielectric constant, bioimpedance scanning, perometry, tonometry and lymphoscintigraphy) require specialized instruments that are not typically available in breast clinics, and most are not practical for use on the breast (11). Ultrasound measurement of dermal thickness–representing the extent of dermal edema–offers an objective measurement technique for BLE that is low-cost, easily applied to the breast, requires minimal training to perform, and relies on instruments that are increasingly standard in breast clinics (9). A recent systematic review by Fearn et al has concluded that ultrasound is the most promising of the currently studied methods for measuring BLE (9,12-19). A limitation of ultrasound-only classification of BLE is that it fails to account for severity of signs and symptoms as assessed by providers and reported by patients. We have therefore expanded on our previous work (9) by enumerating a larger and more diverse patient population, in which we explore the feasibility of developing a BLE classifier using in-clinic ultrasound in combination with physical exam findings and patient-reported outcomes.

METHODS

Study Population

This study was approved by the Committee on Human Research in the Medical Sciences at University of Vermont Medical Center (UVMMC; Burlington, Vermont) and by the Institutional Review Board at Rush University Medical Center (RUMC; Chicago, Illinois). Study participants were recruited during scheduled follow-up visits at breast surgical oncology clinics between 2020–2022. At both UVMMC and RUMC we enrolled 40 patients; 30 of whom were diagnosed with invasive breast cancer and treated with BCS, SLNB, and radiotherapy (and were therefore at risk of BLE), and 10 control patients evaluated for benign complaints and were not treated with surgery or radiotherapy. Thus, our entire study comprised 80 patients. Patient recruitment from Rush University focused on enrolling women from traditionally underserved communities of color. Patients eligible for the invasive group included adult (age ≥18) women with a history of unilateral breast cancer treated with BCS, SLNB, and radiation therapy, and who had completed surgery 6–24 months prior. Exclusion criteria for the invasive group were presence of bilateral breast disease, history of arm lymphedema, prior treatment for BLE, history of upper extremity thrombosis, and history of lymphoma or another malignancy involving axillary lymph nodes. Patients eligible for the control group included adult women presenting to the breast clinic with a benign complaint (e.g., breast pain, nipple discharge, or a benign mass). Control group exclusion criteria were the same as those for the invasive group, with the addition of invasive breast cancer history and any prior breast surgery or radiation treatment. All participants provided written informed consent. Participants with signs and symptoms of BLE were referred to physical therapy per usual protocol. However, all study

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data were collected before patients started treatment for BLE.

Data Collection

Study data were collected by attending physicians or by research coordinators during a single office visit and were entered directly into a secure REDCap database. Participants underwent a routine clinical breast exam. Visual exams were performed to evaluate asymmetry, with the patient in both seated and supine positions. Bimanual examination of both breasts and regional lymph nodes was also performed, evaluating for soft tissue changes associated with chest wall lymphedema. The physical exam also evaluated for the presence of facial swelling, neck swelling, supraclavicular fullness, breast size and texture, chest wall swelling, and pitting edema. The nipple exam evaluated fullness, presence of discharge, and change in texture. Bilateral upper extremity exam was performed to note the presence or absence of edema in the upper extremities and cording of the axilla. Bilateral breast ultrasound was performed by the attending surgical oncologist using a GE Logiq S8 with ML6-15 linear transducer (UVMMC) or a Fujifilm SonoSite SII with HFL50x linear transducer (RUMC) ultrasound system (*N.B.*: both linear transducers operate in the 6-15MHz range). Dermal thickness measurements were made at the 6 o'clock position, as the most dependent portion of the breast is usually the most lymphedematous. Patient-reported outcomes were captured with a modified Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire, which assessed physical and social discomfort associated with BLE symptoms (*i.e.*, impact on sexual activities, impact on social activities, ability to work, presence of tingling sensation, sleep disturbance, and overall confidence) on a 5-point Likert scale. Patient characteristics and details on surgical treatment were collected from electronic medical records, including tumor size, tumor location, number of lymph nodes removed, body mass index, history of breast infection, race/ethnicity, and mammographic breast density according to the breast imaging-reporting and data system (BIRADS). Radiotherapy parameters were collected from electronic medical records and from radiotherapy instruments and included the number of fractions, the dose per fraction, whether radiation boost was delivered to the tumor bed, the extent of radiation (whole breast only, whole breast plus axillary lymph nodes, or whole breast plus comprehensive nodal irradiation), volume of breast tissue targeted, and the volume of breast tissue receiving >105% of the prescribed radiation dose.

Definitions of Analytic Variables

We calculated the difference in dermal thickness (in millimeters) between the affected and unaffected breasts based on ultrasound measurements. We classified ultrasound-defined BLE status by applying a dermal thickness difference threshold of 0.5mm. This was the maximum dermal thickness difference observed in the control group (and was also approximately 3 standard deviations above the mean difference in controls). We therefore consider this threshold a suitable estimate of the upper limit of normal breast dermal thickness difference. We defined relative size of the affected breast as smaller, larger, or about the same size as the unaffected breast based on clinician impression. We categorized tumor location as upper outer quadrant versus all other quadrants. We categorized the number of lymph nodes removed as 0, 1, 2, 3, or ≥4. We categorized tumor size as <10mm, 10–20mm, and >20mm. We summarized physical exam findings with indicator variables for the presence of facial swelling, neck swelling, supraclavicular fullness, chest wall swelling, breast size, breast pitting edema, fullness of the nipple, nipple discharge, change in nipple texture, edema of the upper extremity, and cording of the axilla. Responses to the modified DASH questionnaire were dichotomized into "any impact" (slight, moderate, or extreme impact) versus "no impact at all." Age was estimated from birthdate using the approximate date of enrollment (January 1, 2020, for UVMMC patients and January 1, 2022, for RUMC patients) and was categorized

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by decade for descriptive purposes. Race and ethnicity were tabulated in individual self-reported categories for descriptive purposes, and ultimately summarized into "White women" or "women from communities of color" because frequencies were sparse in more specific race/ethnicity groups. We placed body mass index into standard categories of underweight (BMI<18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), or obese (BMI≥30).

Statistical Analysis

We tabulated patient demographics and clinical characteristics within joint strata of invasive/benign status and institution. We further tabulated characteristics of invasive patients according to summarized race/ethnicity (White women vs. women from communities of color) and presence or absence of ultrasound-defined BLE. We generated a stratified dot plot to visualize the distribution of dermal thickness values in affected and unaffected breasts by institution and according to patient-reported race/ethnicity. We characterized the prevalence of ultrasound-based BLE according to summarized race/ethnicity by fitting both crude and adjusted log-binomial regression models and calculating exact binomial 95% confidence limits. To further explore the distribution of BLE by summarized race/ethnicity, we generated kernel density plots of the difference in dermal thickness (a continuous measure representing the severity of BLE) within summarized race/ethnicity categories.

Finally, we explored the feasibility of classifying BLE using combined data from ultrasound, physical exam, and patient reported outcomes. To do this, we built a Kohonen self-organizing map (SOM)–a type of unsupervised machine learning algorithm–to classify or cluster observations based on the similarity of the associated input data between individuals (20). A key strength of SOMs is that they do not require pre-specification of the underlying number of unique classes or categories. Rather, relationships among the attribute values drive the clustering. Using this approach, we characterized clusters of breast cancer patients according to continuous differences in ultrasound-measured dermal thickness difference, ultrasound-defined BLE status, modified DASH patient-reported outcomes (6 variables), and findings from physical exam (8 variables). This preliminary study was focused on development of a multi-parameter classifier for breast lymphedema and was not designed with sufficient precision for estimating risk factor associations. No hypothesis testing was performed (21-23).

RESULTS

Characteristics of the Study Population

Table 1 reports characteristics of invasive and benign patients by enrollment institution. Patients enrolled at the University of Vermont and at Rush University differed mainly by race/ethnicity. The Vermont patient population was overwhelmingly White (100% of benign control patients and 97% of invasive patients), whereas the patient population from Rush University–which serves a predominantly urban population–was more diverse. Of the 40 total patients enrolled at Rush, 43% were African American (n=17), 28% were non-Hispanic White (n=11), 23% were Hispanic (n=9), 5% were Asian (n=2), and 1 patient identified as other/multiracial. Patients recruited from Rush were more likely to be obese or overweight compared with patients from UVMMC (e.g., among invasive patients, 80% of Rush patients were overweight or obese vs. 60% of UVMMC patients). At both institutions, benign patients were more likely to have heterogeneously, or extremely dense breasts compared with invasive patients.

Table 2 summarizes characteristics of invasive breast cancer patients within strata of summary-level race/ethnicity and ultrasound-defined BLE. Compared with White patients, patients from communities of color had a higher mean BMI (mean=32.1 vs. 28.1), were less likely to exhibit higher breast density (39% vs 46% heterogeneously or extremely dense), had more lymph nodes removed (mean=3.0 nodes vs. 2.2 nodes), and were less likely to report any impact on QOL (39% vs

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TABLE 1
Characteristics of the Invasive and Benign (Control) Patient Groups According to Institution

Characteristics	Invasive breast cancer patients				Benign breast patients (controls)			
	University of Vermont n=30		Rush University n=30		University of Vermont n=10		Rush University n=10	
Age group, n (%)								
<40	4	(13)	2	(6.7)	3	(30)	5	(50)
40-49	2	(6.7)	3	(10)	2	(20)	0	(0)
50-59	8	(27)	7	(23)	3	(30)	4	(40)
60-69	9	(30)	15	(50)	2	(20)	0	(0)
≥70	7	(23)	3	(10)	0	(0)	1	(10)
Mean ±sd	58.7	(13.7)	59.3	(10.6)	46.9	(15.6)	42.8	(16.6)
Body mass index, n (%)								
normal weight	12	(40)	6	(20)	5	(50)	1	(10)
overweight	9	(30)	7	(23)	2	(20)	3	(30)
obese	9	(30)	17	(57)	3	(30)	6	(60)
Mean ±sd	27.5	(5.6)	31.7	(7.7)	28.2	(8.9)	30.3	(6.6)
Race/ethnicity, n (%)								
Non-Hispanic White	29	(97)	8	(27)	10	(100)	3	(30)
Hispanic/Latina	1	(3.3)	6	(20)	0		3	(30)
African American	0	(0)	13	(43)	0		4	(40)
Asian	0	(0)	2	(6.7)	0		0	(0)
Other or multiracial	0	(0)	1	(3.3)	0		0	(0)
BIRADS breast density, n (%)								
almost entirely fatty	5	(17)	2	(6.7)	0	(0)	0	(0)
scattered density	11	(37)	16	(53)	3	(43)	2	(25)
heterogeneously dense	14	(47)	10	(33)	3	(43)	2	(25)
extremely dense	0	(0)	2	(6.7)	1	(14)	4	(50)
(missing)	0		0		3		2	
Tumor size, n (%)								
<10mm	7	(26)	10	(37)				
10-19mm	9	(33)	11	(41)				
≥20mm	11	(41)	6	(22)				
(missing)	3		3					
Mean ±sd	17.8	(12.2)	14.7	(9.3)				
Nodes removed, n (%)					Not applicable			
0	3	(10)	0	(0)				
1	8	(27)	8	(27)				
2	8	(27)	13	(43)				
3	5	(17)	2	(6.7)				
≥4	6	(20)	7	(23)				
Mean ±sd	2.4	(2.0)	2.6	(2.0)				
Positive nodes, n (%)								
0	26	(90)	26	(87)				
1	2	(6.9)	3	(10)				
2	1	(3.5)	1	(3.3)				
(missing)	1		0					
Radiation therapy characteristics:								
Dose (Gy), median (range)	5240	4240–6276	5005	2600–				
Fractions (n), median (range)	21	16–33	20	6000				
Breast volume (cc), median	860	334–1636	1167	5–30				
(range)	29	(100)	17	339–				
Boost received, n (%)	8.9	2.3–141	55	4203				
Boost volume (cc), median				(57)				
(range)				24–135				
Extent of radiotherapy, n (%)								
whole breast	25	(89)	21	(78)				
whole breast + axilla	1	(3.6)	3	(11)				
whole breast + CNI	2	(7.1)	3	(11)				
(missing)	2		3					

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TABLE 2
Characteristics of Invasive Patients by Race/Ethnicity and by BLE Status Defined by Ultrasound

	Race/ethnicity		Ultrasound-defined breast lymphedema	
	White N=37	Communities of color N=23	Present N=43	Absent N=17
Age group, n (%)				
<40	5 (14)	1 (4.4)	5 (12)	1 (5.9)
40-49	2 (5.4)	3 (13)	4 (9)	1 (5.9)
50-59	10 (27)	5 (22)	10 (23)	5 (29)
60-69	12 (32)	12 (52)	19 (44)	5 (29)
≥70	8 (22)	2 (8.7)	5 (12)	5 (29)
Mean ±sd	58.7 ±13.5	59.3 ±9.7	58 ±12	61 ±12
Body mass index, n (%)				
normal weight	14 (38)	4 (17)	14 (33)	4 (24)
overweight	11 (30)	5 (22)	12 (28)	4 (24)
obese	12 (32)	14 (61)	17 (40)	9 (53)
Mean ±sd	28.1 ±6.1	32.1 ±7.8	29 ±7	30 ±7
BIRADS breast density, n (%)				
almost entirely fatty	5 (14)	2 (8.7)	6 (14)	1 (5.9)
scattered density	15 (41)	12 (52)	16 (37)	11 (65)
heterogeneously dense	17 (46)	7 (30)	19 (44)	5 (29)
extremely dense	0 (0)	2 (8.7)	2 (4.7)	0 (0)
Tumor size, n (%)				
<10mm	10 (30)	7 (33)	10 (26)	7 (47)
10-19mm	12 (36)	8 (38)	16 (41)	4 (27)
≥20mm	11 (33)	6 (29)	13 (33)	4 (27)
(missing)	4	2	4	2
Mean ±sd	16.3mm ±11.4	16.0mm ±10.2	17.4mm ±10.8	12.9mm ±10.7
Tumor location, n (%)				
upper outer	22 (65)	9 (45)	8 (50)	23 (61)
upper inner	2 (5.9)	6 (30)	3 (19)	5 (13)
lower inner	4 (12)	1 (5.0)	2 (13)	3 (7.9)
lower outer	3 (8.8)	2 (10)	1 (6.3)	4 (11)
central	3 (8.8)	2 (10)	2 (13)	3 (7.9)
(missing)	3	3	1	5
Nodes removed, n (%)				
0	3 (8.1)	0 (0)	1 (2.3)	2 (12)
1	11 (30)	5 (22)	11 (26)	5 (29)
2	11 (30)	10 (43)	15 (35)	6 (35)
3	5 (14)	2 (8.7)	6 (24)	1 (5.9)
≥4	7 (19)	6 (26)	10 (23)	3 (17.7)
Mean ±sd	2.2 ±1.7	3.0 ±2.3	2.7 ±2.0	2.1 ±1.8
Positive nodes, n (%)				
0	32 (89)	20 (87)	38 (88)	14 (88)
1	3 (8.3)	2 (8.7)	3 (7)	2 (12.5)
2	1 (2.8)	1 (4.4)	2 (4.7)	0 (0)
(missing)	1	0	0	1
Any quality-of-life domain affected, n (%)*				
yes	24 (65)	9 (39)	27 (63)	6 (35)
no	13 (35)	14 (61)	16 (37)	11 (65)
Facial swelling, n (%)				
yes	1 (2.8)	0 (0)	1 (2)	0 (0)
no	35 (97)	23 (100)	41 (98)	17 (100)
(missing)	1	0	1	0

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Neck swelling, n (%)				
yes	1 (2.8)	0 (0)	1 (2)	0 (0)
no	35 (97)	23 (100)	41 (98)	17 (100)
(missing)	1	0	1	0
Supraclavicular fullness, n (%)				
yes	1 (2.8)	0 (0)	1 (2)	0 (0)
no	35 (97)	23 (100)	41 (98)	17 (100)
(missing)	1	0	1	0
Chest wall swelling, n (%)				
yes	2 (5.6)	1 (4.4)	3 (7)	0 (0)
no	34 (94)	22 (96)	39 (93)	17 (100)
(missing)	1	0	1	0
Affected breast relative size, n (%)				
same	16 (44)	9 (39)	18 (43)	7 (41)
smaller	9 (25)	9 (39)	9 (19)	10 (59)
larger	11 (31)	5 (22)	16 (38)	0 (0)
(missing)	1	0	1	0
Breast pitting edema, n (%)				
yes	21 (58)	11 (48)	30 (71)	2 (12)
no	15 (42)	12 (52)	12 (29)	15 (88)
(missing)	1	0	1	0
Fullness of nipple, n (%)				
yes	17 (47)	8 (35)	22 (52)	3 (18)
no	19 (53)	15 (65)	20 (48)	14 (82)
(missing)	1	0	1	0
Nipple discharge, n (%)				
yes	0 (0)	0 (0)	0 (0)	0 (0)
no	36 (100)	23 (100)	42 (100)	17 (100)
(missing)	1	0	1	0
Changes in nipple texture, n (%)				
yes	15 (42)	4 (17)	18 (43)	1 (5.9)
no	21 (58)	19 (83)	24 (57)	16 (94)
(missing)	1	0	0	0
Edema in upper extremity, n (%)				
yes	1 (2.8)	0 (0)	1 (2)	0 (0)
no	35 (97)	23 (100)	41 (98)	17 (100)
(missing)	1	0	1	0
Cording of axilla, n (%)				
yes	1 (2.8)	0 (0)	1 (2)	0 (0)
no	35 (97)	23 (100)	41 (98)	17 (100)
(missing)	1	0	1	0

* Impact on ≥1 of the following domains: sexual activities, social activities, ability to work, tingling sensation, sleep quality, and confidence. ** Comparing the size of the affected breast with the size of the unaffected breast.

65%). Most invasive patients did not have lymphedema-related symptoms on physical exam (*i.e.*, facial swelling, neck swelling, supraclavicular fullness, chest wall swelling, edema of upper extremity, cording of the axilla, or nipple discharge). Cording of the axilla was relatively uncommon in our cohort, with a highest observed prevalence of 2.8% among White women. While this low figure is within the wide prevalence range reported in a recent systematic review (24), it may also be a consequence of the relatively early follow-up in our study. Compared with White patients, patients from communities of color were less likely to exhibit breast pitting edema (48% vs. 58%), fullness of the nipple (35% vs. 47%), and changes in nipple texture (17% vs. 42%).

Ultrasound-Defined Breast Lymphedema

Figure 1 shows the distribution of ultrasound-derived breast dermal thickness values according to breast status (affected/unaffected) and institution, color coded by self-reported race/ethnicity. Measurements of unaffected breasts represent normal variability in

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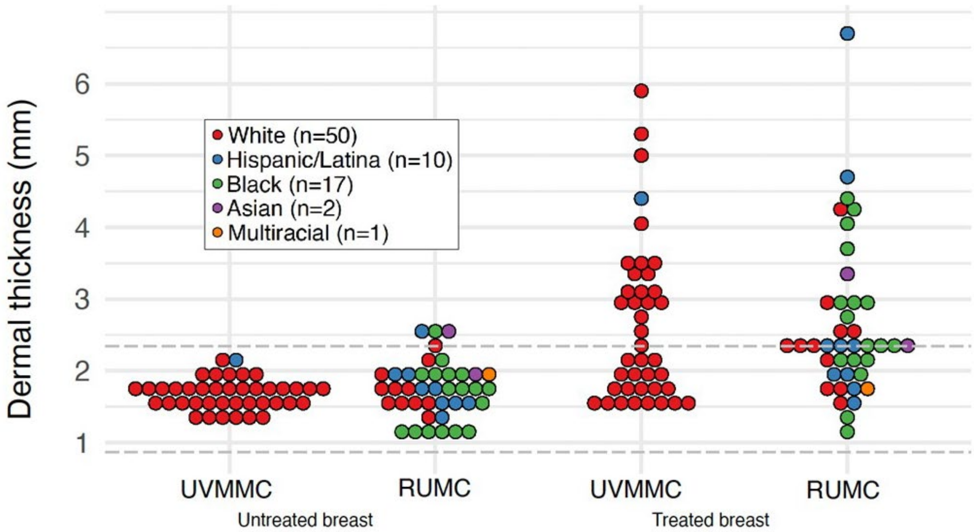

Fig. 1. *Distribution of breast dermal thickness measurements by point-of-care ultrasound among all patients (invasive and benign control), according to breast status (unaffected or affected), institution (UVMMC: University of Vermont Medical Center; RUMC: Rush University Medical Center), and patient-reported race/ethnicity. Dashed horizontal lines depict the normal range of healthy breast dermal thickness reported by Shi et al (22) in a sample of 137 women with unknown race/ethnicity distribution.*

breast dermal thickness; the distribution of these values was similar between UVMCC and Rush patients, and most fell within the published benchmark range (i.e., the dashed horizontal lines in *Fig. 1*) (25). We note that 3 patients from Rush—all of whom were from communities of color—showed dermal thickness values in unaffected breasts that were higher than the published benchmark range. As expected, affected breast dermal thickness values occupied a wider range, with a substantial number of observations falling above the normal benchmark, indicative of BLE among invasive cases.

The overall prevalence of ultrasound-defined BLE (defined as difference in dermal thickness ≥0.5mm) in invasive breast cancer patients was 72% (95% CI: 59 to 82%). Compared with patients without ultrasound-defined BLE, patients with ultrasound-defined BLE tended to have more dense breasts (49% heterogeneously or extremely dense vs. 29%), more lymph nodes removed (mean 2.7 vs. 2.1 nodes), and larger relative size of the affected breast (38% vs 0%). Most patients, regardless of BLE status, did not have notable clinical symptoms. The exceptions were that BLE patients were more likely to have breast pitting edema (71% vs 12%), fullness of the nipple (52% vs 18%), and changes in nipple texture (43% vs 5.9%).

Table 3 reports estimates of ultrasound-defined BLE prevalence among invasive patients by summarized race/ethnicity. BLE prevalence was lower in patients from communities of color (prevalence=61%, 95% CI: 40%, 79%) than in White patients (prevalence=78%, 95% CI: 62%, 89%), yielding a prevalence ratio of 0.77 (95% CI: 0.53, 1.1). This prevalence ratio did not change substantially after adjustment for BMI, tumor size, or tumor location (simplified as upper-outer vs. otherwise due to sparse data; results not shown). Despite their lower prevalence for BLE, patients from communities of color had a higher range for difference in dermal thickness than White patients, as seen from the density distributions in *Fig. 2*, potentially indicating that higher-severity BLE is more common in women of color.

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TABLE 3
Estimates of Ultrasound-Defined Breast Lymphedema Prevalence by Race/Ethnicity

Group	Ultrasound-defined breast lymphedema prevalence (95% CI)		Prevalence ratio (95% CI)	
White patients	78%	(62–89%)	1.	(reference)
Patients from communities of color	61%	(40–79%)	0.77	(0.53, 1.1)

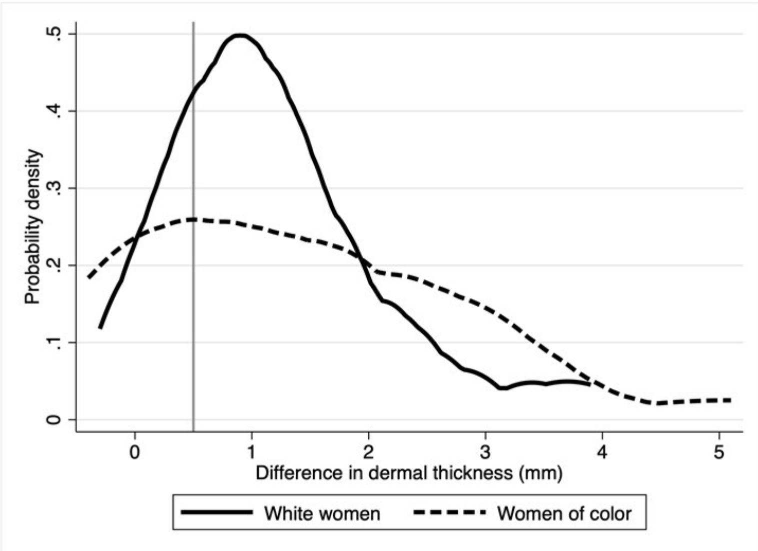

Fig. 2. *Distributions of dermal thickness difference values among invasive breast cancer patients treated with breast conservation surgery and radiotherapy, according to summarized race/ethnicity. The gray vertical reference line depicts the 0.5mm threshold that demarcates presence or absence of ultrasound-defined BLE.*

Novel Multi-Parameter Clustering of Breast Lymphedema

The data from the SOM self-clustered into 3 groups, which we deemed to strike an appropriate balance between demonstration of patient subgroups and adequate size of each group to support *post-hoc* descriptive analyses. A larger study of BLE classification by the SOM would likely reveal additional, distinct patient clusters. Each SOM cluster represents a different patient profile with respect to the input parameters—all of which describe different manifestations of BLE. In *Fig. 3*, Clusters 1 and 2 have similarly high proportions of patients with ultrasound-defined BLE (89% and 85%, respectively), but differ in severity and presentation, which is delineated by mean difference in dermal thickness, relative breast size, and the 6 patient-report DASH quality-of-life domains. These observations indicate more severe or impactful BLE among patients in Cluster 1 compared with patients in Cluster 2. Cluster 3 comprises patients with little or no evidence of BLE; these patients have the smallest mean dermal thickness difference, and virtually no patient-reported impact in any DASH quality-of-life domain.

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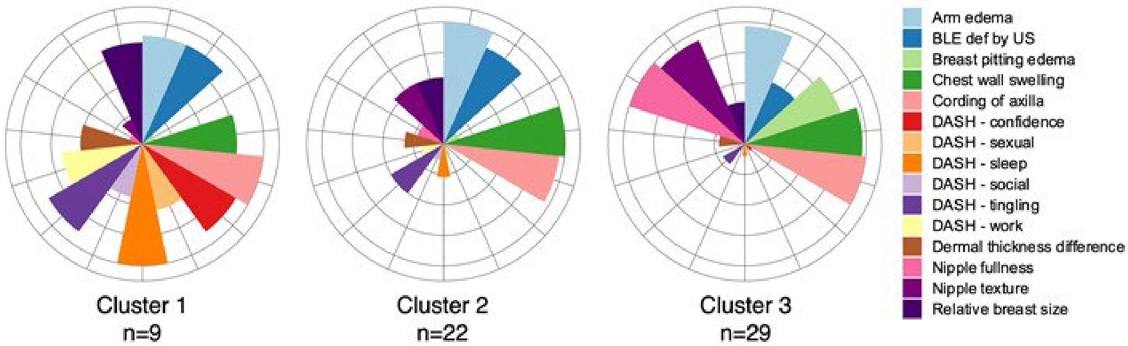

Fig. 3. *Composition of the 3 breast lymphedema patient clusters identified by the Kohonen self-organizing map fit to our pilot study data. Clustering is based on features from ultrasound measurements, physical examination, and patient-reported outcomes (DASH). Radial lengths correspond to cluster proportions for dichotomous variables and to cluster averages for continuous dermal thickness difference, scaled to a [0, 1] interval.*

DISCUSSION

Dermal thickness measurements on unaffected breasts were consistent with published normal ranges (25,26), suggesting good fidelity and transportability of the ultrasound method. We noted that 3 women from communities of color had dermal thickness measurements on the unaffected breast that were higher than the upper limit of the published normal range, which may indicate that the normal range was not evaluated in a diverse patient sample. Overall, 43 (72%) of the 60 invasive patients in our study developed BLE as measured by ultrasound. BLE was somewhat less prevalent among underserved/under-represented women than among White women. Despite lower BLE prevalence, women of color had a positively skewed distribution of difference in dermal thickness values, which may indicate more severe BLE in this patient subgroup. Higher severity of BLE may be partially explained by adverse factors such as age at diagnosis, BMI, number of lymph nodes removed, tumor location, and less radiation/differential treatment. Patients from communities of color presented at an older age and had more lymph nodes removed despite having smaller tumors, which may lead to impaired lymphatic drainage and thus increased BLE severity. These patients also had higher breast density, which is positively associated with developing breast cancer and with diagnosis at later stages, which necessitates more extensive surgery (27). Concordant with the increased prevalence of BLE in White women is the higher reported impact on QOL and more positive physical exam findings. Despite patients from communities of color having a potentially higher burden of disease due to risk factors such as later age at diagnosis, higher BMI, higher breast density, and more lymph nodes removed, they had fewer lymphedema-related physical exam findings and reported less impact on QOL compared with their White counterparts. Black women are twice as likely to develop arm lymphedema, less likely to receive guideline treatment, and experience higher mortality (28-30). Black women also tend to experience higher symptom burden and are under-treated for such symptoms (31,32). Other systemic factors such as differences in socioeconomic status, higher rates of exposure to environmental risk factors, lower access to health care, and explicit and implicit clinician bias are considerations that need further exploration (31). Our findings of lower impact on QOL for patients from communities of color may also suggest a difference in resilience and/or tolerance of symptoms or could be due to the subjective nature of the self-reported DASH questionnaire. It is

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possible that impact on QOL was under-reported in patients of under-represented communities of color compared with White women. If so, this would be consistent with the results of Fayanju et al, who showed that Black breast cancer patients were more likely to report "no distress" than White patients, despite having the same number of stressors, in a phenomenon termed "Superhero syndrome" (33).

Novel Classification Using Self-Organizing Maps

Results from the SOM suggest that the prevalence of BLE in treated patients is about 52%, when only Cluster 1 and 2 are included in the definition of BLE (*Fig. 3*). Clusters 1 and 2 have high proportions of patients with ultrasound-defined lymphedema (89% and 85%, respectively) and differ only in severity of impact, whereas Cluster 3 comprises patients with little or no evidence of BLE on any component measure. Among patients with invasive breast cancer, the prevalence of severe BLE (Cluster 1) is about 15%. The radial plots in *Fig. 3* also show that some variables appear to be independent of BLE presence and severity (i.e., arm lymphedema, chest wall swelling, and cording of the axilla), as they have radials with similar magnitudes across all three clusters. Self-organizing maps are a robust tool for further characterizing groups of patients with similar BLE characteristics based on objective ultrasound measures, physical exam findings, and patient-reported outcomes. It is important to note that given the relatively small size of this study, the current SOM is limited to 3 clusters or patient profiles. In future studies in larger cohorts, the SOM may fit the resulting data into more clusters than the 3 we identified. Currently, our SOM clusters combine all invasive breast cancer patients; however, with more data we could refine clusters within clinically important strata such as race/ethnicity and other sociodemographics or clinical variables.

Limitations

The chief limitation of our study is its small size and focused data collection. Future studies in larger cohorts will more accurately reflect the distribution and determinants of BLE and should collect richer data on candidate etiologic and mitigating factors such as comorbidity (*e.g.*, congestive heart failure), breast size, breast ptosis, and bra usage. Another limitation is that most White patients were recruited at UVMMC, and most of the patients from communities of color were recruited at RUMC; some differences observed by race may therefore be related to geography. The use of different ultrasound instruments may have also introduced systematic differences in dermal thickness measurements by institution, but this is unlikely given the similar measurement distributions and concordance with published benchmarks (*Fig. 1*). Future work on this topic should include carefully designed reliability studies to assess variability across ultrasound platforms and their operators. The modified DASH questionnaire may not be an ideal instrument to measure the subjective impact of BLE on QOL, as it was not specifically developed for that purpose. Future studies should consider using an instrument more specific to BLE, such as the EORTC-BR23 (34). We also did not have data on breast cancer subtype, which may impact treatment aggressiveness and thus clinical exam findings and impact on QOL in patient subgroups (35). However, our conclusions were not materially affected when estimates were adjusted for other breast tumor parameters (e.g., stage and grade). Nonetheless, future studies should address potential modifiers and confounders such as breast cancer sub-type, comorbidities, socioeconomic status, and time since surgery and radiotherapy.

CONCLUSIONS

Our racially and geographically diverse pilot study suggests that ultrasound-based comparison of dermal thickness is an objective, robust, and transportable method for quantifying BLE in women with unilateral breast cancer. Our results also demonstrate that unsupervised machine learning tools can effectively combine information from ultra-

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sound, physical exam, and patient-reported outcomes into a cohesive, multi-parameter BLE classifier. We found that while BLE was more prevalent among White patients, there was slight evidence that BLE can be more severe among women of color, as measured by the magnitude of the dermal thickness difference. However, White patients were also more likely to report impacts of BLE on their QOL. Definitive prospective studies are required to validate ultrasound- and multiparameter-based classifiers of BLE and to determine how incidence and severity of BLE vary in racially and geographically diverse patient populations.

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CONFLICT OF INTEREST

All authors declare no financial conflict of interest exists.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Data collection was performed by Michelle Sowden, Claudia Perez, Thomas Kim, Carl Nelson, Karen Ohara, Elizabeth Watson, and Alison Coogan. Data analysis was performed by Jennifer Chen, Thomas Ahern, Donna Rizzo, and Jeremy Matt. The first draft of the manuscript was written by Jennifer Chen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are not publicly available due ongoing data collection but are available from the corresponding author on reasonable request.

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