Research Report

Development and Validation of a Self-Report Lower-Extremity Lymphedema Screening Questionnaire in Women

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Background. Patient-reported signs and symptoms are often the first indication of clinically relevant lymphedema.

Objective. The purpose of this study was to develop and assess the diagnostic accuracy of a screening questionnaire to detect lower-extremity lymphedema (LEL) among normal-weight women and women with obesity.

Design. This was a cross-sectional survey study.

Methods. The authors reviewed existing questionnaires assessing upper-extremity lymphedema (UEL) for potential questions and worked with content experts to generate new items. A draft questionnaire with 59 items was reviewed by 5 physicians and 5 physical therapists who specialized in lymphedema management and 5 female patients with clinically confirmed secondary LEL. A revised questionnaire with 45 items was administered by mail to 186 women with clinically confirmed LEL (n=116) or UEL (n=70). A total of 99 women (53.2% of 186) completed the mailed survey, and 28 women with lymphedema who were recruited directly in a lymphedema clinic waiting area also completed the survey. A parsimonious subset of items that best discriminated patients with and without LEL was identified using chi-square tests and logistic regression. Sensitivity and specificity for detecting LEL and positive and negative likelihood ratios (LR+, LR−) were estimated for the entire sample and for subsamples defined by obesity (body mass index ≥30 versus <30 kg/m^2), which may confound the accurate diagnosis of LEL.

Results. Questionnaires were completed by 127 women (LEL group, n=88; UEL group, n=39). A sum of 13 items (score range=0–52) was the most discriminating. Using a cutoff score of ≥5 points, the sensitivity and specificity for detecting LEL among all participants were 95.5% and 86.5%, respectively (LR+=7.1, LR−=0.05), and 94.8% and 76.5%, respectively (LR+=4.0, LR−=0.07), for participants who were obese.

Limitations. By enumerating a sample with a high prevalence of LEL, a spectrum bias may have been introduced, which may have affected the accuracy of the screening questionnaire.

Conclusions. The brief, 13-item self-report questionnaire is a sensitive and specific tool for detecting clinically relevant LEL among women, including those with a body mass index of ≥30 kg/m^2.

Lymphedema is a serious and potentially debilitating condition that occurs when the transport capacity of the lymphatic system falls below the lymphatic load, resulting in the accumulation of protein-rich lymph fluids in the subcutaneous tissues.[1,2] Onset may be gradual or sudden, and it often develops after surgery or radiation therapy for certain types of cancer. If untreated, lymphedema generally progresses to more advanced stages, increasing patients' risk for cellulitic infections, functional decline, and unhealing wounds.[1,3] Once established, lymphedema becomes a chronic condition that cannot be cured, but rather can only be managed[4–6]; therefore, it is imperative to intervene early to halt or slow its progression. Early intervention, however, requires early detection.

Secondary lymphedema can be easily missed without specific screening, and it can develop within months to several years after the completion of cancer treatment.[5–7] As a result, the incidence of secondary lymphedema is greatly underestimated,[8] and, consequently, many patients fail to receive timely treatment. Patient-reported signs and symptoms are often the first indication of clinically relevant lymphedema.[7–9] Self-report questionnaires have been successfully used to diagnose upper-extremity lymphedema (UEL),[8,10] but less attention has been dedicated to lower-extremity lymphedema (LEL).[5] The availability of a validated LEL screening questionnaire would allow patients to be monitored over great distances and long periods at relatively low cost, facilitating the early detection and treatment of lymphedema.

Our objectives were to develop and assess the diagnostic accuracy of a screening questionnaire to detect LEL among women with normal weight and those with obesity. For the purpose of this study, we define the lower extremity as anything below the navel. Therefore, in addition to legs and feet, the lower abdomen, hips, buttocks, and genitals are included.

Method

Content Development

In the summer of 2009, we conducted a nonsystematic literature review of existing self-report measures of lymphedema. We identified several tools for measuring UEL, but none for LEL. We reviewed the following sources for potential questions that could be used or modified for our instrument: the Memorial Symptom Assessment Scale, as adapted by Norman et al[10]; the 27-item Upper-Limb Lymphedema (ULL-27) questionnaire[11]; and the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system.[12] We also reviewed the lymphedema questionnaire used in the Gynecology Oncology Group protocol #236, a trial in which our institute participated; this questionnaire is not currently in the public domain. Candidate items were selected or modified from these sources, and gaps in content were filled with new questions developed by experts in lymphedema (A.L.C.) and patient-reported outcome measure development (K.J.Y.).

Questions were organized into 4 sets. The first set of questions measured the absolute extent of signs or symptoms in different locations of the lower extremity. Instructions directed the respondents to consider the more affected side of the body if both sides were affected. Example questions in set 1 were "I have swelling around my ankle" and "When I press my calf with my finger for 15 seconds, I leave a dent (pit or depression) in the skin." All set 1 questions were answered on a 5-point rating scale (0="not at all," 1="a little bit," 2="somewhat," 3="quite a bit," and 4="very much"). General categories of signs and symptoms included swelling, pitting, pain or discomfort, limb heaviness, skin texture, skin tightness, numbness and tingling, range of movement, leaking fluid, and visibility of anatomic landmarks.

The second set of questions measured the relative extent of signs and symptoms by asking respondents to compare their left and right sides. Example questions in set 2 were: "My pants feel tighter on one side than the other at the calves" and "One ankle looks bigger than the other." The same response scale from set 1 was used. General categories of questions included swelling, pitting, pain or discomfort, limb heaviness, skin texture, limb weakness, tightness of clothing, and visibility of anatomic landmarks.

The third set of questions measured only swelling and was based on the instrument for detecting UEL used in the study by Norman et al.[10] Figures showing a side view of the lower torso, leg, and foot and a partial front view of the lower abdomen and upper leg were presented with 3 sections of the lower extremity delineated: (1) upper leg, buttocks, hips, and lower abdomen, (2) lower leg and knee, and (3) foot and ankle. For each section, the respondents were asked to endorse one of the following narratives describing how obvious their swelling would be to others: 0="no swelling," 1="slight: you are the only one who would notice," 2="moderate: the swelling would be noticeable to people who know you well, but not to strangers," and 3="severe: even strangers would notice the swelling."

The fourth set of items also referred to the 3 sections of the lower body illustrated in the figures and asked the respondents to rate the appearance of different anatomical

structures on their lower bodies. For example, respondents were instructed to mark only 1 of the following regarding their upper leg, buttocks, hips, and lower abdomen: 0="you can easily see both of your hip bones," 1="it is slightly difficult to see one or both of your hip bones," 2="it is moderately difficult to see one or both of your hip bones," and 3="it is very difficult to see one or both of your hip bones."

Expert Panel Review

We reviewed draft questions and figures, and revisions were made. Set 1 had 34 questions, set 2 had 19 questions, and sets 3 and 4 asked about 3 sections of the lower extremity (upper leg, buttocks, hip, and lower abdomen; lower leg, including knee; and foot and ankle). Content validity was established through review of the questions by an expert panel comprising 5 physicians and 5 physical therapists who specialized in lymphedema management and 5 female patients with clinically confirmed secondary LEL. One method for assessing content validity is to have a panel of independent reviewers judge whether the questions are relevant to the domain being measured and whether they provide good coverage of the various aspects of the domain.[13,14] Members of the expert panel were e-mailed a copy of the draft questionnaire and were asked to rate the questions separately with respect to relevance for measuring LEL and clarity of wording on a 3-point scale (1="not at all," 2="somewhat," and 3="very"). A space was provided for comments after each question. Within each of the 4 sets, the questions were ordered by the average rating across the 15 experts. We reviewed the questions with the lowest mean ratings, along with the expert panel's comments, and either deleted or modified those questions.

Participants

Based on results from the expert panel review, the questionnaire was revised and validated in a sample of patients identified from the Mayo Clinic Lymphedema Clinic. Female patients were eligible for this study if they were: (1) 21 years of age or older, (2) had a recent (ie within the previous 2–3 months) encounter at the Mayo Clinic Lymphedema Clinic, (3) had sufficient information in the medical record for a clinician or physical therapist to determine the presence or absence of LEL, and (4) could be classified as having LEL only or UEL only.

Currently, there is no definitive and internationally accepted standard for lymphedema diagnosis. The Common Toxicity Criteria (CTC) version 3.0[15] has been utilized in a number of large clinical trials. Cheville et al[15] described the specific CTC version 3.0 criteria and their development from preexisting scales by a multidisciplinary group of experts. The CTC version 3.0 criteria are distinct from exclusively volume-based or limb circumference-based criteria in that they incorporate other pathognomonic stigmata of lymphedema, such as subdermal fibrosis. Both LEL and UEL diagnoses for participants in this study were based on the CTC version 3.0,[15] and the International Society of Lymphology staging system[16] was utilized to assess severity. One of 3 physician lymphologists staffing the Mayo Clinic Lymphedema Service, each with over 12 years of lymphedema management experience, made the diagnoses and assessments of severity.

Patients with LEL could have primary or secondary lymphedema at stages I to III. Patients without LEL could have upper-extremity/upper-torso lymphedema, also from any cause. Patients in the UEL group could not have evidence of lymphedema below the waist, as determined by a clinician or physical therapist.

Two methods were used to identify and recruit participants. The first involved a clinician (M.A.H.) reviewing medical records of all patients with a visit to the Lymphedema Clinic within the previous 2 to 3 months. Records were reviewed in 2 waves to obtain the desired sample size. Thus, records reviewed represent patients seen in the Lymphedema Clinic over a period of approximately 4.5 consecutive months. Data abstracted from the medical record included limb affected, limb volume, height, and recent weight for body mass index (BMI) calculation. Weight is measured at each appointment in the Lymphedema Clinic; therefore, we used the weight recorded during the visit for which the patient was sampled for this study to calculate current BMI. Patients were purposefully sampled based on BMI to obtain roughly comparable numbers of women who were underweight or of normal weight (BMI <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), obese (BMI 30 to <40 kg/m^2), and morbidly obese (BMI 40+ kg/m^2).

The second method involved recruiting patients directly in the Lymphedema Clinic. The Lymphedema Clinic desk staff dispensed the study questionnaire and consent form, along with standard Lymphedema Clinic intake forms to all patients seen at the clinic prior to physician visits or lymphedema therapy sessions. One author (A.L.C.) reviewed the characteristics (eg, BMI, UEL, LEL) of patients who completed questionnaires, but was naive to the responses of the questionnaires themselves, and consecutively submitted these questionnaires to the research team for data entry and analysis until a more

desired distribution of participants with BMI <30 and ≥30 with and without LEL was achieved. Data in the medical record were insufficient for classifying all women with LEL into categories of severity (ie, mild, moderate, and severe).

Our sample size calculations were based on the analysis that compared the gold standard clinician or physical therapist classification of LEL (none versus any) with classification based on set 3 question scores, which were modeled after the Norman et al[10] approach to detecting UEL. A sample size of 35 participants with LEL and 60 participants without LEL provides sufficient precision to estimate sensitivity and specificity with at least the same precision as Norman et al. For the assessment instrument used by Norman et al, sensitivity for detecting any UEL ranged from 0.93 to 0.96 and specificity ranged from 0.69 to 0.75.[10] We assumed a response rate of roughly 50%; thus, we aimed to send the survey to approximately 190 women.

Data Collection

A total of 188 patients meeting the eligibility criteria were identified following a review of 224 medical records of patients in the Lymphedema Clinic. Survey mailing occurred in 2 waves, matching the 2 waves of record review described above. At the time the survey packets were mailed, 2 patients were deceased, leaving 186 eligible patients, of whom 116 had clinically confirmed LEL and 70 had clinically confirmed UEL. Survey packets containing a cover letter, LEL screening questions, and a $4.00 coffee card incentive were sent to eligible patients. The cover letter clearly stated that a woman's responses were important even if she did not have lymphedema in her lower body. If a completed questionnaire was not received within 3 weeks of the initial mailing, a second mailing was sent with a reminder letter and questionnaire; a second incentive was not sent. Response bias was assessed by comparing age, lymphedema status (no LEL versus LEL), and BMI between respondents and nonrespondents.

An interim analysis of the returned mail questionnaires indicated an insufficient number of respondents in certain categories defined by BMI and lymphedema location (UEL, LEL). To address this problem, we added a second method for identifying and recruiting patients that involved purposeful sampling of women with a prior diagnosis of lymphedema who were being followed in the Lymphedema Clinic. Patients being seen in the Lymphedema Clinic for follow-up visits were identified by clinical assistants based on the scheduling database and were asked to complete the questionnaire in the waiting area prior to their physician or therapist appointments. Data for all questionnaires were double entered, and conflicts were resolved.

Statistical Analyses

The overall objective of the analyses was to assess the criterion validity[13,17] of self-reported questions of LEL signs and symptoms, where the gold standard criterion was a clinical diagnosis of LEL. We established 3 *a priori* characteristics the final screening instrument should possess, which guided our analyses: (1) brief, (2) easy to complete and score, and (3) content coverage consistent with clinical understanding of signs and symptoms commonly reported in patients with LEL. To address the first characteristic, we used strict criteria for statistical significance in the univariate analyses to identify the most discriminating items. To address the second characteristic, we decided the final screening instrument would comprise items from only 1 of the 4 sets (ie, absolute signs and symptoms [set 1], relative signs and symptoms [set 2], swelling severity [set 3], or anatomical landmarks [set 4]) rather than a mixture of items from different sets. Our rationale was that the 3 sets differ in their instructions and response scales, and switching among these different item types could introduce response errors and respondent burden.[18] Furthermore, combining questions with different response scales would complicate scoring. Finally, an expert in lymphedema (A.L.C.) reviewed the final subset of items to confirm that it had good content coverage.

We first evaluated the ability of each question to discriminate no LEL versus LEL using univariate methods (ie, chi-square test, 2-sample *t* test, and Wilcoxon rank sum test). Because of our concern regarding the ability of women to distinguish between lymphedema and adipose tissue when answering the questions, these tests were done once for the total sample and again for women with BMI ≥30 kg/m^2. Within each of the sets of questions, the statistical significance level for univariate analyses was adjusted to account for multiple comparisons using a Bonferroni correction. Questions that were statistically significant predictors of LEL in the overall sample and the subsample of women with obesity were retained for further evaluation in the multivariable analysis. Questions that were not significant were retained if deemed critical for content validity by an expert in lymphedema.

Because question sets 1 and 2 were fairly large, additional item reduction was planned using logistic regression with stepwise selection to further identify the subset of questions within those 2 sets that was most predictive of lymphedema status (no LEL versus LEL). Statistical signifi-

cance for the multivariable analyses was set at $P<.05$.

To facilitate ease of use in a clinical setting, a single score for each patient was computed for the final subset of questions within each set as a simple prorated sum of question responses, if the patient answered more than 50% of the questions comprising the subset.[19] Receiver operating characteristic (ROC) analysis was utilized to evaluate the usefulness (ie, predictive ability) of the prorated scores as a marker for LEL (versus no LEL). Sensitivity and specificity were calculated for each level of a score by varying the score level that signified a positive test (threshold level). *Sensitivity* was defined as the proportion of patients with clinically confirmed LEL who had a score greater than or equal to the given threshold level. *Specificity* was defined as the proportion of patients without LEL who had a score less than the given threshold level. We also calculated the positive likelihood ratio (LR+) and negative likelihood ratio (LR−) for the screening test and used the following guidelines for interpretation: LRs >10 or <0.1 generate large and often conclusive changes from pretest to posttest probability, 5 to 10 and 0.1 to 0.2 generate moderate changes, and 2 to 5 and 0.5 to 0.2 generate small but sometimes important changes; LRs between 1 to 2 and 0.5 to 1 generate small and rarely important changes.[20] An estimate of the area under the ROC curve (AUC) (and its standard error) was made using nonparametric methods, which require no distributional assumptions.[21] All analyses were performed with SAS statistical software version 9.2 (SAS Institute Inc, Cary, North Carolina).

Sensitivity Analysis

One of the first intended uses of this tool is to estimate prevalence of secondary LEL in women with gynecologic cancer. There was an insufficient volume of patients with a history of gynecologic cancer in the Lymphedema Clinic within the study time frame to conduct an analysis to confirm the accuracy of the tool in this subset of women. We were, however, able to conduct a sensitivity analysis to confirm that the final item set had good sensitivity and specificity in a subset of participants with secondary lymphedema, which is the type of lymphedema expected following surgery for cancer. No sensitivity analyses were conducted based on comorbid condition status (eg, congestive heart failure, kidney disease).

Results

Expert Review

Three valuable comments were made regarding the set 3 questions, which asked about swelling observable by others. The first was to add a full image of the front view of the lower extremity rather than just a portion. The second comment was to add the words "if you were wearing a bathing suit" to the instructions. The final comment made by several experts was that more than 3 sections should be delineated on the figures, and genitals should be included as a location about which patients may comment regarding swelling and discomfort. These 3 suggestions were incorporated in the revised survey. Set 4 questions, which asked about appearance of anatomical landmarks, were consistently rated poorly by experts, and comments suggested that patients would have problems distinguishing "slight" versus "moderate" difficulty seeing the landmarks. Another concern was that the high prevalence of obesity in the target population might lead to these questions detecting obesity rather than lymphedema.

Based on expert ratings of the clarity and relevance of questions, set 1 (absolute symptoms) was reduced from 34 to 25 questions, set 2 (relative symptoms) was reduced from 19 to 15 items, and set 3 (swelling severity) was changed as described above and reformatted to fit on 1 page. Because of the concerns noted above regarding set 4, we dropped that entire set from the revised questionnaire.

Participants

A total of 99 (53.2% of 186) women completed the mailed survey (67 with LEL, 32 without LEL); 28 women with lymphedema who were recruited directly in the Lymphedema Clinic also completed the survey. Characteristics of the 127 participants are summarized in Table 1. We evaluated response bias for the mailed data collection (Tab. 2) and observed that respondents and nonrespondents did not differ with respect to age, lymphedema status, or BMI. All patients approached in the Lymphedema Clinic completed the survey, obviating the need to assess response bias within that group.

Statistical Analysis

Twenty (80%) of the 25 set 1 questions (absolute signs and symptoms) were significantly associated with lymphedema status in women with obesity at the $P<.05$ level, and 14 questions (56%) were significant at the $P<.002$ level (after Bonferroni correction). Eight (53%) of the 15 questions in set 2 (relative signs and symptoms) asking respondents to compare 1 side of the lower extremity to another were able to discriminate no LEL versus LEL in women with obesity at the $P<.05$ level, but only 3 (20%) were significant at the $P<.003$ level (after Bonferroni correction). Set 3 questions asked about swelling observable by others in the lower extremity separated into 5 segments. For 4 segments in the total sample and 3 segments in women with obesity, these questions discriminated women with and without

LEL at the $P<.01$ level (after Bonferroni correction). Based on these results, we concluded that set 2 questions were less discriminating overall than set 1 or set 3 questions, and they were not evaluated further.

The 14 questions from set 1 with $P<.002$ in the univariate analysis were evaluated in the stepwise logistic regression along with 4 other questions that were retained for purposes of content coverage and included questions on swelling in the buttocks, hips, lower abdomen, and genital area. With the exception of genital swelling, these questions were significant at $P<.001$ in the full sample and at $P<.05$ in the women with obesity. Because swelling is the most common presenting symptom in LEL,[22] the 8 questions in set 1 dealing with swelling in discrete locations of the lower extremity were entered into a logistic model as a set. We then used forward stepwise selection to identify additional questions that were significant in the multivariable analysis at the $P<.05$ level. Five additional questions were selected that assess symptoms of pain and discomfort in different locations of the lower extremity, skin texture and tightness, and sensation of heaviness. The 13 final questions from set 1 (Appendix) were scored as a prorated sum, with a possible range of 0 to 52 points. An optimal cutoff score of 4 points was identified based on sensitivity, specificity, LR+, and LR− (Tab. 3). As expected, the ability of self-report questions to correctly predict LEL was worse among the women with obesity. In particular, specificity (the ability of the self-report questions to correctly identify women who do not have LEL) was low, and the LR+ (the likelihood of a woman with LEL having a positive screen relative to the likelihood of a woman without LEL having a positive screen) was small.

Table 1.
Characteristics of 127 Female Participants

Characteristic	Lymphedema	
	Upper Extremity Only (n=39)	Lower Extremity Only (n=88)
Age (y)		
$\bar{X}$	64.2	60.9
SD	11.0	13.5
Range	46–90	26–88
Limb affected, n (%)		
Left arm only	21 (53.8)	
Right arm only	12 (30.8)	
Both left and right arms	6 (15.4)	
Left lower extremity only		16 (18.2)
Right lower extremity only		13 (14.8)
Both left and right lower extremities		59 (67.0)
Body mass index category (kg/m^2), n (%)		
Underweight/normal (<25)	10 (25.6)	12 (13.6)
Overweight (25 to <30)	11 (28.2)	18 (20.5)
Obese (30 to <40)	16 (41.0)	31 (35.2)
Morbidly obese (≥40)	2 (5.1)	27 (30.7)
Etiology, n (%)		
Primary lymphedema	3 (7.7)	16 (18.2)
Secondary lymphedema	36 (92.3)	27 (30.7)
Lipedema	0	7 (8.0)
Phlebolymphedema	0	3 (3.4)
Mixed etiology	0	28 (31.8)
Other	0	7 (8.0)

Although swelling in the lower abdomen, hips, and buttocks and swelling in the genital area questions in set 3 were not significantly associated with lymphedema status in the women who were obese ($P>.05$), this set was kept intact based on expert input in order to reflect swelling for the entire lower extremity. All 5 questions in set 3 were scored as a prorated sum and had a possible range of 0 to 20 points. The optimal cutoff score was 2 points. Similar to set 1, statistics were worse for women with obesity than for normal-weight women. We compared the results in Tables 3 and 4 and concluded that the 13 set 1 questions were better for detecting LEL.

Sensitivity Analysis

Only 23 participants had a history of gynecologic cancer, and 22 of them had LEL. Thus, we were unable to confirm the sensitivity and specificity of our screening tool in this small subset. We were, however, able to confirm the tool had good sensitivity and specificity (92.6 and 86.1, respectively), moderate LR+ (6.7), and large LR− (0.09) in a subset of 63 participants with secondary lymphedema (Tab. 5). For the 26 women with obesity, sensitivity and specificity were fair (90.0 and 75.0, respectively), and LR− was moderate (0.13); however, LR+ was small (3.6). Twenty-seven of these 63 women had LEL, and 36 did not.

Table 2.
Evaluation of Response Bias for the Mailed Questionnaire[a]

Variable	Respondents (n=99)	Nonrespondents (n=87)	p[b]
Age (y)			.15
$\bar{X}$	62.6	59.6	
SD	13.4	14.4	
Range	28–90	26–93	
Lymphedema, n (%)			.11
UEL	32 (32.3)	38 (43.7)	
LEL	67 (67.7)	49 (56.3)	
BMI (kg/m^2), n (%)			.11
$\bar{X}$ (SD)	33.6 (10.5)	36.1 (12.2)	
Median (IQR)	32 (26–39)	33 (28–41)	
BMI category (kg/m^2), n (%)			.39
Underweight/normal	20 (20.2)	10 (11.5)	
Overweight	21 (21.2)	19 (21.8)	
Obese	34 (34.3)	31 (35.6)	
Morbidly obese	24 (24.2)	27 (31.0)	

[a] UEL=upper-extremity lymphedema, LEL=lower-extremity lymphedema, BMI=body mass index, IQR=interquartile range.
[b] The mean age was compared between the 2 groups using the 2-sample *t* test; median BMI was compared using the Wilcoxon rank sum test; lymphedema location and BMI categories were compared using the chi-square test.

Discussion

We developed and validated a brief screening tool for identifying women with LEL based on self-reported signs and symptoms. Our tool has good predictive properties in both women with normal weight and women with obesity. Sensitivity was consistently higher than specificity, a finding that also was reported for a UEL screening questionnaire.[10] The final set of 13 questions (Appendix) ask about absolute signs or symptoms (eg, "I have swelling around my ankle") and include instructions for respondents to answer with respect to the worst side if the sign or symptom is experienced on both left and right sides of their lower extremity. In contrast, questions asking about relative signs or symptoms comparing one side to the other (eg, "One ankle looks bigger than the other") were less predictive of LEL. We anticipated that self-report of relative signs and symptoms would be informative based on the literature for UEL screening tools. Secondary UEL generally occurs in patients with breast cancer following unilateral axillary lymphadenectomy with or without radiation.[23,24] Upper-extremity lymphedema in the overwhelming majority of these patients is confined to 1 extremity, with the contralateral upper extremity remaining unaffected. Thus, comparing signs and symptoms in the affected arm with the unaffected arm is an efficient way of detecting UEL. Secondary LEL also is often the result of lymphadenectomy or radiation treatment for cancer, including gynecologic cancers. However, treatment for gynecologic cancers often involves bilateral removal or radiation of pelvic and para-aortic lymph nodes, leading to compromised lymphatic drainage from both legs and lower truncal quadrants. Of the 88 participants with clinically confirmed LEL, 59 (67%) experienced it on both their right and left sides. Given the bilateral involvement in LEL in this sample, it is clear how reporting on relative symptoms would be less valuable for detecting LEL. For example, a patient with moderate lymphedema in both legs could likely endorse lower categories of the response scale (ie, "not at all," "a little bit") for a relative sign or symptom question, but could endorse higher response categories (ie, "quite a bit," "very much") for an absolute sign or symptom question, which would better discriminate her from someone without the sign or symptom.

Set 3 questions also asked about absolute signs and symptoms and included figures of the lower extremity separated into 5 segments. As with set 1 questions, participants with swelling on both sides of their lower extremity were instructed to report on the side that was affected the most. There are several possible reasons why this set of questions was less predictive overall compared with set 1. First, set 3 questions only ask about swelling, whereas the final set of 13 set 1 questions includes 5 questions about pain and discomfort, skin texture and tightness, and sensation of heaviness, in addition to the 8 questions about swelling. Thus, it appears that some women with LEL may experience these symptoms in the absence of bothersome swelling. This finding is consistent with previous reports for UEL in which women treated for breast cancer reported symptoms such as pain and discomfort prior to showing discernible swelling.[9] Furthermore, people with LEL present a wider variety of symptoms than people with UEL.[22] Although swelling is the predominant presenting symptom for people with UEL, swelling, heaviness, and tightness are all very common for people with LEL, with heaviness

Table 3.
Predictive Properties of a Prorated Score Based on 13 Questions From Set 1

Sample Used in Analysis	AUC[a]	Based on a Cutoff of ≤4 vs ≥5			
		Sensitivity (%)	Specificity (%)	LR+[b]	LR−[b]
Full sample (n=125[c])	0.935	95.5	86.5	7.06	0.05
Obese (BMI[d] ≥30 kg/m^2; n=75)	0.882	94.8	76.5	4.03	0.07
Normal weight (BMI <30 kg/m^2; n=50)	0.983	96.7	95.0	19.33	0.04

[a] AUC=area under the curve for the total prorated score, estimated using logistic regression.
[b] LR+=likelihood ratio for a positive test, LR−=likelihood ratio for a negative test.
[c] Although 127 women completed the questionnaire, 125 had complete data for this analysis.
[d] BMI=body mass index.

Table 4.
Predictive Properties of a Prorated Score Based on All 5 Set 3 Questions, Cutoff Score ≤2 vs ≥3

Sample Used in Analysis	AUC[a]	Sensitivity (%)	Specificity (%)	LR+[b]	LR−[b]
Full sample (n=124[c])	0.924	94.3	83.3	5.66	0.07
Obese (BMI[d] ≥30 kg/m^2; n=74)	0.884	96.6	68.8	3.09	0.05
Normal weight (BMI <30 kg/m^2; n=50)	0.950	90.0	95.0	18.00	0.11

[a] AUC=area under the curve for the total prorated score, estimated using logistic regression.
[b] LR+=likelihood ratio for a positive test, LR−=likelihood ratio for a negative test.
[c] Although 127 women completed the questionnaire, 124 had complete data for this analysis.
[d] BMI=body mass index.

Table 5.
Predictive Properties of a Prorated Score Based on 13 Questions From Set 1 in a Subset of 63 Women With Secondary Lymphedema, Cutoff Score of ≤4 vs ≥5

Sample Used in Analysis	AUC[a]	Sensitivity (%)	Specificity (%)	LR+[b]	LR−[b]
Full sample (n=63)	.927	92.6	86.1	6.67	0.09
Obese (BMI[c] ≥30 kg/m^2; n=26)	.878	90.0	75.0	3.60	0.13
Normal weight (BMI <30 kg/m^2; n=37)	.975	94.1	95.0	18.82	0.06

[a] AUC=area under the curve for the total prorated score, estimated using logistic regression.
[b] LR+=likelihood ratio for a positive test, LR−=likelihood ratio for a negative test.
[c] BMI=body mass index.

and tightness being present at nearly twice the rate in those with LEL compared with those with UEL.[22] A second possible reason why set 3 questions were less predictive than set 1 questions is that set 3 questions ask women to speculate on their appearance as observed by others. Roughly 60% of our sample was obese or morbidly obese by design. These women may be more inclined to wear loose or baggy clothing to conceal their body size and shape, making it difficult for them to speculate on how swelling might appear to others.

Not only is obesity a risk factor for secondary LEL,[2,4] but it also may mask the perception by women of signs and symptoms of lymphedema such as swelling and sensations of heaviness or discomfort. We carefully considered the effect of obesity throughout the development and validation of our instrument. In the content development phase, questions about ease of seeing anatomic landmarks such as hip bones, kneecaps, and ankle bones were eliminated based on expert comments that women with obesity would have difficulty distinguishing these landmarks due to adipose tissue rather than lymphedema. When selecting the final parsimonious subset of questions and identifying the optimal cutoff score, we observed that the predictive properties (ie, sensitivity, specificity, AUC, LR+, and LR−) were consistently worse among the women with obesity compared with normal-weight women. We are not aware of other lymphedema screening questionnaires for either UEL or LEL that con-

sidered obesity in their development and validation.

Limitations

Our study is not without limitations. The UEL group was not an ideal control group because they already experienced lymphedema in the upper extremity. Therefore, they may be more adept at reporting on symptoms such as skin changes or at distinguishing swelling from adipose tissue, which could inflate specificity. We demonstrated the ability of our questionnaire to detect any LEL, but we were unable to demonstrate whether it could distinguish severity of LEL or changes in severity over time. These properties of the questionnaire should be assessed in a future study. We evaluated sensitivity, specificity, LR+, and LR− within broad categories of BMI. A future study should evaluate these properties within more narrowly defined categories (eg, <25, 25 to <30, 30 to <40, and 40+ kg/m^2). By enumerating a sample with a high prevalence of LEL, we may have introduced spectrum bias, which may have affected the accuracy of our screening questionnaire. Diagnostic accuracy should be confirmed in a study in which participants are consecutively enrolled and where completion of the screening questionnaire and clinically determination of LEL status are determined concurrently. Finally, because we enrolled women with LEL who had recent visits to the Lymphedema Clinic, their lymphedema may have been optimally managed when they completed the questionnaire. We did not capture this information and can only speculate on the effect of recent or active treatment on the test's accuracy—women in treatment may have milder signs and symptoms (if the treatment is effective) and may score lower on the screening tool, possibly decreasing the sensitivity and LR+ of the test.

Despite these limitations, our self-report questionnaire is a sensitive and specific tool for detecting clinically relevant LEL among women, including those of obese and normal body weights. Our brief, 13-item instrument is a useful tool to improve our understanding of the burden of lymphedema in patients following cancer treatment.

Dr Yost, Dr Cheville, and Dr Dowdy provided concept/idea/research design. Dr Yost, Dr Cheville, Ms Weaver, and Dr Dowdy provided writing and data analysis. Dr Yost, Dr Cheville, Dr Al Hilli, and Dr Dowdy provided data collection. Dr Dowdy provided project management, fund procurement, institutional liaisons, and clerical support. Dr Cheville provided facilities/equipment. Ms Weaver and Dr Dowdy provided consultation (including review of manuscript before submission).

This study was approved by the Mayo Clinic Institutional Review Board.

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Appendix.

Final 13 Items Selected to Measure Lymphedema[a]

INSTRUCTIONS: PLEASE CHECK THE APPROPRIATE BOX OR FILL IN THE BLANK AS INDICATED.

The following statements are about sensations you may have on one or both sides of your lower body.

Please mark one box for each statement that best describes how your lower body felt on average in the past 4 weeks. If you have one of these sensations on both sides of your lower body, describe the side that seems to be affected the most.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
The skin on my leg feels tight	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
The skin above my ankle feels tight	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
My leg feels heavy	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have pain or discomfort in my leg	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
My leg is noticeably smaller when I get out of bed in the morning	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling in my foot	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling around my ankle	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling in my lower leg (including knee)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling in my upper leg	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling in my buttocks	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling in my hip (on the side below the waist)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling below my stomach (below the belly button)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐
I have swelling in my genital area	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

[a] Scores are summed, with a possible range of 0–52 points. Scores of 5 or more points indicate a positive screen.