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Accuracy, sensitivity, and specificity of the LLIS and ULL27 in detecting breast cancer-related lymphedema

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Abstract

Introduction: Breast cancer-related lymphedema occurs in up to 30% of women following axillary lymph node dissection (ALND) and less commonly following sentinel lymph node biopsy. To quantify disability in these patients, patient-reported outcome measures (PROMs) have proven useful; however, given the overlap of symptoms between ALND and lymphedema, examination of their accuracy, sensitivity, and specificity in detecting lymphedema in breast cancer patients undergoing ALND is needed.

Methods: The Lymphedema Life Impact Scale (LLIS) and the Upper Limb Lymphedema-27 scale (ULL27) were administered to patients who had undergone ALND at least 2 years prior and either did or did not develop lymphedema. Survey responses and the degree of disability were compared to generate receiver operator characteristic (ROC) curves and the sensitivity and specificity of PROMs to diagnose lymphedema were analyzed.

Results: Both PROMs were highly accurate, sensitive, and specific for detecting lymphedema. The LLIS had an accuracy of 97%, sensitivity of 100%, and specificity of 84.8% at a cutoff of ≥ 5.88 overall percent impairment score (higher scores indicate worse disability). The ULL27 had an accuracy of 93%, sensitivity of 88.6%, and specificity of 90.9% at a cutoff of ≤ 83.3 global score (lower scores indicate worse disability).

Conclusions: The LLIS and the ULL27 appear to be highly specific for lymphedema and capable of differentiating it from symptoms resulting from ALND alone. Our findings suggest that use of these questionnaires with a threshold may be effective for diagnosing lymphedema, potentially reducing the need for frequent clinic visits and time-consuming measurements.

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Keywords

lymphedema; patient-reported outcome measures; LLIS; ULL-27; prediction; sensitivity; specificity; accuracy

Introduction

Lymphedema is a devastating disease characterized by fluid accumulation and progressive fibroadipose deposition resulting from primary or secondary deficits of the lymphatic system. Afflicted patients develop chronic symptoms including limb swelling, pain, heaviness, and decreased range of motion[1,2]. Nearly a third of patients develop recurrent, severe skin infections requiring hospitalization and antibiotic therapy. In developed countries, lymphedema most commonly occurs as a consequence of lymphatic injury resulting from cancer surgery. Axillary lymph node dissection (ALND) for breast cancer is a notable cause of secondary lymphedema due to the high prevalence of breast cancer; lymphedema can also result from treatment for other solid tumors such as melanoma, sarcoma, and genitourinary cancers[3–5].

Lymphedema is typically diagnosed by comparing the circumference or volume measurements of the affected limb with preoperative values or with measurements of the unaffected contralateral limb. Although a variety of diagnostic criteria have been described, a commonly accepted criterion is an increase of ≥ 10% in limb volume[6]. However, diagnosis based solely on physical measurements or static cutoffs in limb volumes has been criticized because many of the symptoms associated with lymphedema, such as numbness, tingling, and heaviness, are subjective in nature. These subjective changes may be modulated or amplified by differences in body habitus between patients. For example, a 10% volume differential in a patient with a body mass index (BMI) of 19 may be much more disabling than a similar difference in a patient with a BMI of 35. As a result, patient-reported outcome measures (PROMs) have become important adjuncts for evaluating quality of life and symptom progression in patients with lymphedema[7,8]. Several validated PROMs have been developed for quantifying the degree of disability with lymphedema, ranging from disease-specific to general quality of life tools[9]. Our group has had experience using the Upper Limb Lymphedema-27 scale (ULL27) and the Lymphedema Life Impact Scale (LLIS)[10–14], which were designed to assess the physical, social and psychological issues associated with lymphedema over the past week (LLIS) or the past month (ULL27).

However, most PROMS, including the LLIS and ULL27, were developed and validated using a heterogenous group of patients with lymphedema or without controls. The LLIS was validated using patients with either unilateral or bilateral lymphedema, upper or lower extremity lymphedema, and with multiple etiologies (primary lymphedema, trauma, obesity, cancer)[12,13]. The ULL27 used a group of patients with unilateral breast cancer-related lymphedema, but without a control group[11]. The primary symptoms of lymphedema, namely localized swelling, pain, limited range of motion, and skin numbness, overlap with symptoms following ALND without lymphedema[15–17]. Given this overlap, whether the ULL27 and LLIS can detect lymphedema-specific symptoms in a population of patients who

have undergone ALND requires direct evaluation. Another question of interest is whether PROMs can be used as a screening tool for diagnosing lymphedema, which would decrease the need for frequent office visits and time-consuming limb volume measurements.

The goal of this study was to determine whether the LLIS and ULL27 can discriminate between symptoms resulting from ALND alone as compared with ALND and subsequent development of lymphedema, defined as a ≥ 10% increase in limb volume compared to the contralateral arm. In addition, we aimed to determine the accuracy, sensitivity, and specificity of the LLIS and the ULL27 for diagnosing lymphedema by analyzing threshold disability values to discriminate between patients who did or did not develop lymphedema.

Methods

This study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board and patients were recruited to the study between January 2017 and August 2020. Patients presenting to plastic surgery clinic, ages 18 to 70 years old who underwent a unilateral ALND for breast cancer treatment ≥ 2 years prior to study entry were enrolled and divided into two groups: patients who developed lymphedema (volume change ≥ 10% compared with the contralateral limb) following surgery and patients who had not developed lymphedema. Many patients in the former group were those being evaluated for lymphedema treatment. Many patients in the latter group were those who had undergone breast reconstruction at our institution and were returning for routine follow up. Additional exclusion criteria included active cancer, current treatment with chemotherapy, recent infection of the extremity within the last 3 months, and pregnancy.

Patients who elected to participate in the study completed the LLIS and ULL27 questionnaires at their most recent follow-up visit[11,12]. The LLIS is a lymphedema-specific tool consisting of 18 questions for which patients report symptoms over the previous week, addressing 3 subscales: physical, psychosocial, and functional. The total percent impairment score, where a higher score indicates a worse outcome, is calculated by adding the subscale scores, dividing by the maximum possible score (68), and multiplying by 100. The ULL27 is another lymphedema-specific tool consisting of 27 questions for which patients report symptoms over the previous 4 weeks, also addressing 3 subscales: physical, psychological, and social. The global score, ranging from 0 to 100 where a lower score indicates a worse outcome, is calculated by subtracting the minimum score (27) from the total raw score (range 27 to 108), then dividing by the maximum score and multiplying by 100.

Arm volume measurements were performed as described by Brorson et al.[18]. Briefly, circumference measurements were taken at 4-cm intervals beginning at the wrist and extending to the axillary crease with a no-stretch tape measure. Total arm volume and differences between limbs were then calculated using the truncated cone formula.

Descriptive analysis was carried out using SPSS software (IBM Corp, Armonk, New York). Average age, BMI, follow-up duration, percent volume difference between arms, and LLIS and ULL27 scores were calculated for the lymphedema and control groups. Differences between groups were examined using Student’s t-test for continuous variables and chi

square or Fisher's exact test for categorical variables. Associations between questionnaire scores and arm volume difference were assessed using Spearman's correlation. Statistical significance was set at 0.05.

To assess the diagnostic accuracy of the LLIS and ULL27 in detecting patients with lymphedema, receiver operating characteristic (ROC) curves were created, which plot the true positive rate (sensitivity) vs. the false negative rate (1-specificity). The accuracy of the LLIS and ULL27 in detecting lymphedema was determined by calculating the area under the curve (AUC) with 95% confidence intervals by DeLong's method[19]. Youden's index was calculated for all points of the ROC curve using the formula: Youden's index = (sensitivity + specificity) − 1. The maximum calculated Youden's index value was used to determine the optimal cutoff score for each ROC curve[20]. Sensitivity and specificity were reported for the optimal cutoff points. The LLIS and ULL27 were further examined by creating ROCs for each subscale, and the accuracy of each subscale to detect lymphedema was determined by calculating the AUC with 95% confidence intervals.

Results

One hundred and three patients who underwent unilateral ALND were recruited to the study, of which 70 had lymphedema and 33 did not. The lymphedema patients were older at the time of ALND (average age 58.5 vs. 52 years, $p = 0.005$), had shorter follow-up (8.0 vs .11.1 years, $p = 0.006$), and were more likely to have had radiation to regional lymph nodes (78.6% vs. 30.3%, $p < 0.001$) (Table 1). The lymphedema group scored significantly worse overall and in all dimensions of the LLIS and the ULL27 compared to the non-lymphedema group ($p < 0.001$) (Table 1, Figure 1). However, LLIS percent impairment score and ULL27 overall score did not correlate with percent volume difference ($r = 0.248$, $p = 0.04$; $r = -0.255$, $p = 0.03$, respectively) (Figure 2).

Comparison of ROCs for the LLIS and ULL27 scores revealed that both were highly accurate in distinguishing patients with lymphedema from those without (LLIS AUC 0.970, 95% CI 0.935–1.0, $p < 0.001$; ULL27 AUC 0.930, 95% CI 0.869–0.991, $p < 0.001$) (Figure 3). For the LLIS, a cutoff score of ≥ 5.88 (Table 2) identified 100% of patients who underwent ALND and had lymphedema (true positives or sensitivity) and 84.8% of patients who underwent ALND and did not have lymphedema (true negatives or specificity). For the ULL27, the optimal cutoff point was ≤ 83.33, for which the sensitivity was 85.8% and the specificity was 90.9% for lymphedema diagnosis (Table 2).

To further examine the subscales of each PROM tool to determine whether one dimension was the driver for their excellent accuracy, 3 additional ROC curves were drawn for each dimension (Figure 4). The physical, psychosocial, and functional dimensions of the LLIS all had a high degree of accuracy (AUC 0.963, 95% CI 0.927–0.998, $p < 0.001$; AUC 0.947, 95% CI 0.903–0.991, $p < 0.001$; AUC 0.950, 95% CI 0.899–1.000, $p < 0.001$, respectively), suggesting that the overall accuracy of the LLIS was multidimensional. In contrast, the physical, psychological, and social dimensions of the ULL27 all had high but decreasing degrees of accuracy (AUC 0.922, 95% CI 0.856–0.988, $p < 0.001$; AUC 0.876,

95% CI 0.799–0.952, p < 0.001; AUC 0.787, 95% CI 0.689–0.885, p < 0.001, respectively), suggesting that the physical dimension may be a driver for the ULL27's overall accuracy.

Discussion

Our study indicates that both the LLIS and ULL27 are highly accurate, sensitive, and specific for detecting lymphedema when a threshold is used. Thus, while there is some overlap between the symptoms caused by ALND alone and lymphedema, use of a cutoff point allows both the LLIS and ULL27 to correctly identify lymphedema-specific symptoms. Further, these cutoff points indicate that patients who undergo ALND and do not develop clinical lymphedema do not experience moderate or significant disability from lymphedema-associated symptoms.

Our examination of these PROMs' usefulness in differentiating lymphedema from post-surgical symptoms independent of lymphedema is especially important given their overlap. The LLIS was validated in 71 lymphedema patients, including upper extremity and lower extremity[12,13], and the ULL27 was validated in 304 patients with upper extremity lymphedema[11,14]. A recent analysis of lymphedema PROMs showed that the LLIS and ULL27 had very good or adequate internal consistency, criterion validity, and convergent validity, and the ULL27 also had very good structural validity and general design[21]. However, other measurement parameters such as reliability and measurement error were not rated as highly. As this detailed examination of the LLIS and ULL27 did not evaluate the accuracy, sensitivity, or specificity of these tests to diagnose lymphedema in the breast cancer population, our study addresses an outstanding question regarding their utility.

We found that both the LLIS and the ULL27, when applied using Youden index-determined thresholds, are highly accurate, sensitive, and specific in identifying patients with lymphedema. The Youden index sets a diagnostic cutoff by determining the optimal sensitivity and specificity for each test, i.e. the greatest degree to which they can correctly identify patients with and without lymphedema, respectively, from the ROC curve. Our results therefore show that the LLIS and ULL27 may be useful in diagnosing lymphedema in addition to documenting the disability resulting from this disease.

The LLIS and ULL27's high sensitivity is especially valuable for diagnosing lymphedema[22] because of this condition's progressive nature, as early intervention leads to better outcomes. Interventions to treat lymphedema, including compression garments, physical therapy, and surgery (lymphovenous bypass), lead to greater volume reductions and improved quality of life when initiated early, before progression to lifelong lymphedema[23–27]. Therefore, capturing all patients who may have lymphedema is more important than identifying those who do not.

Examination of all subscales for both measures shows that while no single subscale drives LLIS scores, with excellent AUCs (> 0.9) for physical, psychological and functional dimensions, the accuracy of ULL27 subscales varies slightly. The most accurate was the physical dimension (AUC 0.9), followed by the psychological and the social. The accuracy of the physical dimension is expected given the direct relationship of its questions to

common symptoms of lymphedema such as swelling, pain, heaviness, and range of motion limitations. However, the psychological and social scores may reflect the lymphedema diagnosis itself, as Fu et al. found that patients with a diagnosis of lymphedema have worse perceptions related to body image, appearance, sexuality, and social barriers compared with those without lymphedema[28]. Further, patients with lymphedema report decreased self-confidence, anxiety, frustration, sadness, anger, fear, and increased self-consciousness[29]. Determining the reasons for the difference in accuracy among the ULL27 subscales would require further examination.

This study suggests that either the LLIS or ULL27 could be used to accurately diagnose lymphedema. Further, PROMs can be completed online and therefore do not require an in-office visit as is required for objective measurements such as limb volume or bioelectric impedance. Electronic administration of PROMs at close intervals can be used to monitor patients and those with scores above the LLIS threshold or below the ULL27 threshold can be referred for an in-office visit for limb volume measurements and to initiate treatment, thus decreasing the time and cost burden of monitoring patients for lymphedema. Further simplifying screening, because the physical dimension drives the ULL27's accuracy, sensitivity, and specificity, use of this subscale alone would be just as reliable for diagnosing lymphedema as using the entire PROM. High-risk patients could therefore be easily screened using just the physical dimension questions, completed online every few months.

The straightforward questionnaires evaluated herein represent an alternative to the more sophisticated use of machine learning procedures applied to real-time symptom reports[22]. In a recent study, using an artificial neural network algorithm to analyze scores on the Breast Cancer and Lymphedema Symptom Experience Index (BCLE-SEI) in 355 women led to the best accuracy (94%), sensitivity (96%) and specificity (91%) for lymphedema diagnosis. Our results with the more widely used ULL27 and LLIS have similar accuracy, sensitivity, and specificity.

This study has multiple limitations. First, this is a retrospective review where follow-up periods varied widely and PROMs were not completed at specific time intervals. A larger study to validate the efficacy of PROMs to diagnose and eventually predict lymphedema, as well as comparison with other standard PROMs such as the LYMQOL, is needed[30]. Additionally, these measures should be evaluated in an unselected group of patients to ensure the accuracy, sensitivity and specificity remain high. Also, application of machine learning algorithms in addition to conventional statistical procedures would be useful.

An additional limitation of this study is that baseline arm measurements were not obtained. As the average follow up time in this study was 8.0 years for patients with lymphedema and 11.1 for patients without lymphedema, pre-operative arm measurements were not routinely performed on patients undergoing ALND at the time of their surgery. Indeed, many contemporary papers still use postoperative measurements as used in our study to diagnose lymphedema[31–45]. And while some consider water displacement method as gold standard for measurement of lymphedema, circumferential measurements are reliable, easy to perform and therefore commonly used in practice[6,8,46]. Further, the recent 2020

Consensus Document of the International Society of Lymphology does not state a gold standard method for lymphedema diagnosis[47]. Nevertheless, future examination of the LLIS and ULL27 would benefit from preoperative baseline measurements to obtain a relative volume change.

Conclusions

The LLIS and the ULL27 appear to be highly specific for lymphedema and capable of differentiating it from symptoms resulting from ALND alone. Our findings suggest that use of these questionnaires with a threshold may be effective for diagnosing lymphedema. Thus, patients who score above the threshold should be followed with objective measures to confirm the diagnosis. In patients with low scores, it may be possible to decrease the frequency of clinic visits and measurements thus decreasing resource utilization and perhaps patient anxiety.

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Disclosures:

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Synopsis:

In 103 breast cancer patients who underwent axillary lymph node dissection, the Upper Limb Lymphedema-27 scale (ULL27) and the Lymphedema Life Impact Scale (LLIS) were found to be highly accurate, sensitive, and specific for detecting lymphedema symptoms.

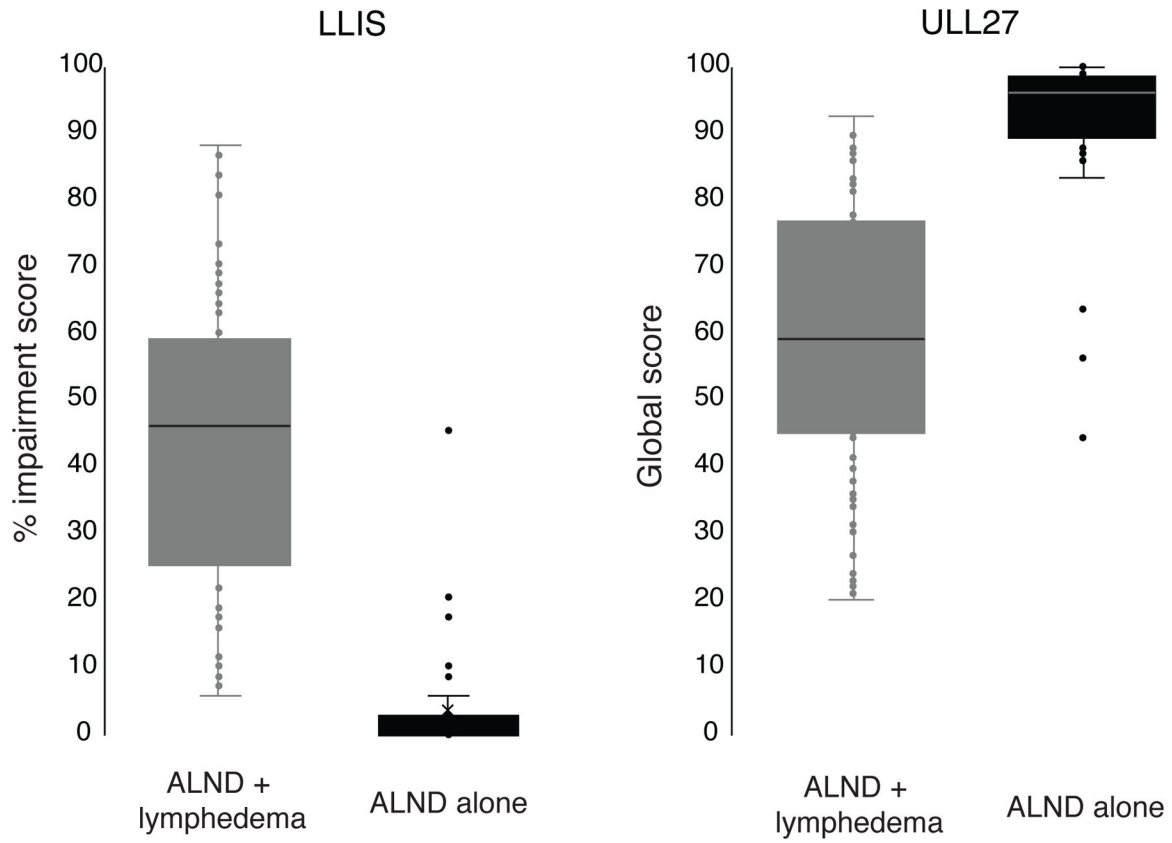

Figure 1. Lymphedema severity survey scores in lymphedema patients and controls.
Left, LLIS (higher scores indicate greater disability); right, ULL27 (lower scores indicate greater disability).

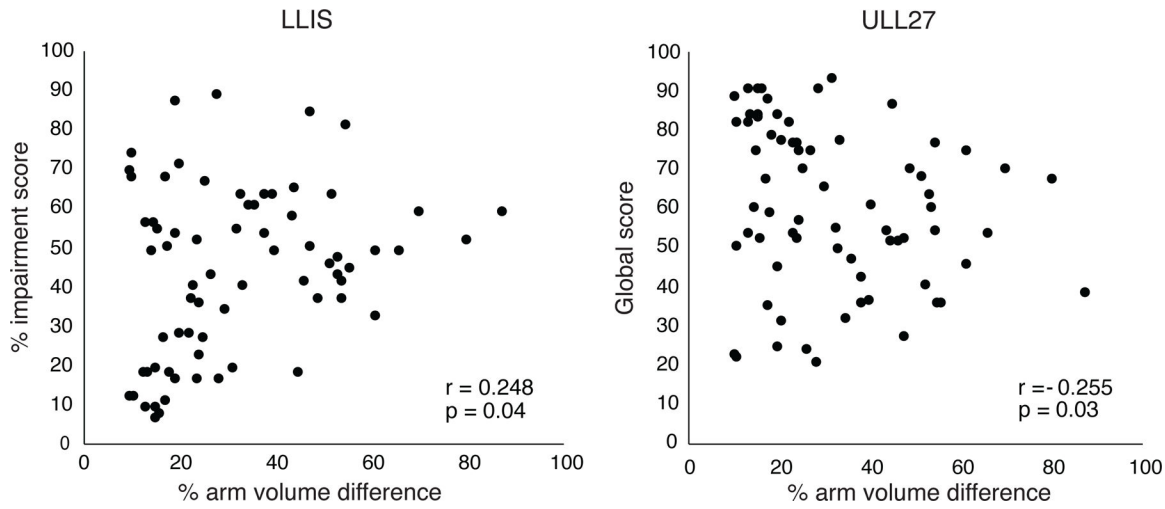

Figure 2. Lymphedema severity survey score correlation with arm volume difference.
Left, LLIS; right, ULL27.

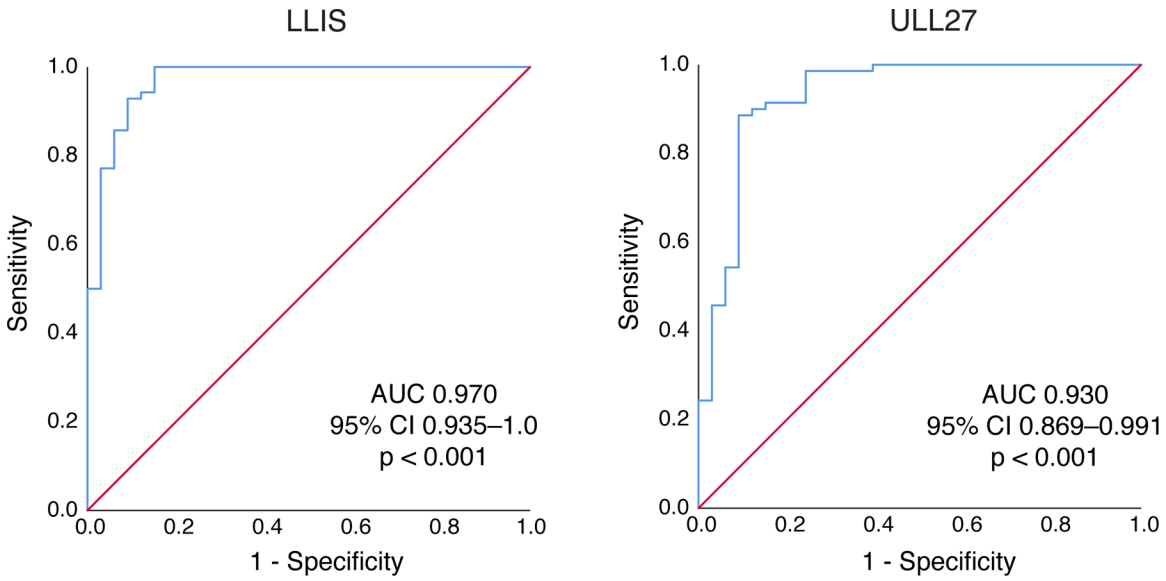

Figure 3. Sensitivity and specificity of each lymphedema severity survey.
Left, LLIS; right, ULL27.

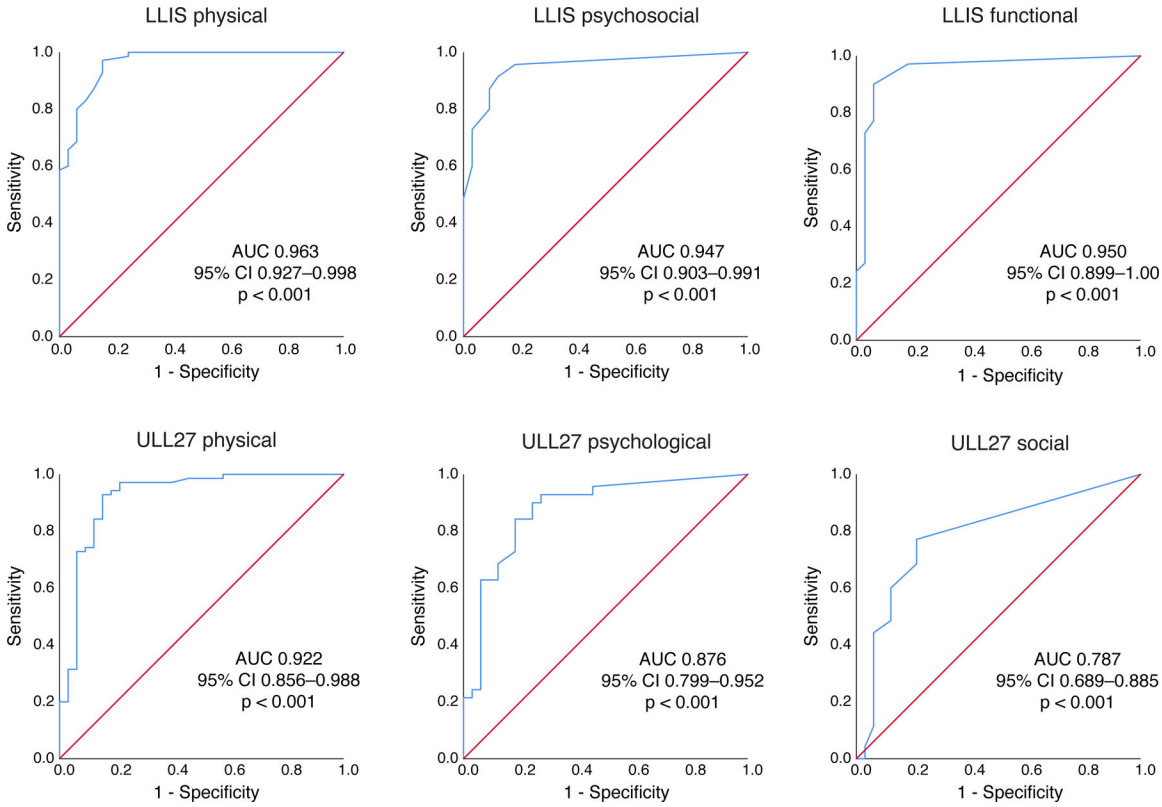

Figure 4. Subscale scores.
Top, LLIS; below, ULL27.

Table 1.

Patient demographics.

Categorical data reported as n (%) and continuous as mean ± standard deviation.

	Lymphedema patients (n = 70)	Control patients (n = 33)	p
Age	58.5 ± 10.6	52 ± 10.5	**0.005**
BMI	26.5 ± 5.2	26.3 ± 4.9	0.86
Chemotherapy	66 (94.3%)	32 (97.0%)	0.67
Radiation to regional nodes	55 (78.6%)	10 (30.3%)	**< 0.001**
Follow-up from ALND (years)	8.0 ± 5.5	11.1 ± 4.8	**0.006**
Average percent volume difference from contralateral arm	32.4% ± 18.2%	−0.03% ± 3.8%	**< 0.001**
LLIS scores			
Physical dimension	12.6 ± 5.9	1.3 ± 2.8	**< 0.001**
Psychosocial dimension	8.8 ± 5.3	0.6 ± 1.7	**< 0.001**
Functional dimension	8.1 ± 4.6	0.6 ± 2.0	**< 0.001**
Overall percent impairment	43.4 ± 21.2	3.6 ± 8.9	**< 0.001**
ULL27 scores			
Physical dimension	54.5 ± 23.3	90.8 ± 15.7	**< 0.001**
Psychological dimension	61.4 ± 21.2	91.2 ± 15.2	**< 0.001**
Social dimension	73.4 ± 22.8	93.0 ± 17.8	**< 0.001**
Overall	59.8 ± 20.3	91.3 ± 12.6	**< 0.001**

BMI, body mass index; LLIS, lymphedema life impact scale; ULL27, upper limb lymphedema 27 questionnaire

Table 2.

Optimal parameters for the LLIS and ULL27 determined by Youdens method.

	LLIS	ULL27
Cutoff	≥ 5.88	≤ 83.33
Sensitivity	100.00%	85.80%
Specificity	84.80%	90.90%