Original Article

Quantitative evaluation of primary lower extremity lymphedema staging using MRI: a preliminary study

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Background: The staging of primary lower extremity lymphedema (LEL) is difficult yet vital in clinical work, and magnetic resonance imaging (MRI) can be used for quantitative assessment of primary LEL due to its high resolution for soft tissues. In this study, we evaluated the value of MRI-based soft tissue area measurements for staging primary LEL.

Methods: A total of 90 consecutive patients with clinically diagnosed primary lower limb lymphoedema from January 2017 to December 2019 in Beijing Shijitan Hospital were enrolled retrospectively. Short time inversion recovery (STIR) sequence was applied to measure the total, muscle, bone, and subcutaneous areas in the upper 1/3 level of the bilateral lower calf. The difference between the affected and unaffected calf regarding the subcutaneous area was obtained, and (subcutaneous area)/(bone area) and (subcutaneous area)/(muscle area) were calculated. According to the International Society of Lymphology (ISL) clinical staging standard established in 2020, all patients were divided into stages I, II, and III, accordingly. Statistical analysis was performed to determine the validity of MRI measurements in staging LEL.

Results: There were 33 patients classified as stage I clinically, 44 patients as stage II, and 13 patients as stage III. There were significant differences in total, subcutaneous, the difference in subcutaneous area of limbs, subcutaneous/bone (S/B), and subcutaneous/muscle (S/M) between stage I and II as well as between stage I and III (P<0.001), but not between stage II and III (P=0.706, 0.329, and 0.229, respectively). A positive correlation was detected between the clinical stage and difference in subcutaneous area of limbs (rho =0.752, P<0.001), S/B (rho =0.747, P<0.001), S/M (rho =0.709, P<0.001), and subcutaneous (rho =0.723, P<0.001). For staging primary LEL, receiver operating characteristic (ROC) curves indicated that the difference in subcutaneous area of limbs had the best discrimination ability among parameters [area under the ROC curve (AUC) =0.950; 95% confidence interval (CI): 0.875–0.987; sensitivity: 95.45%; specificity: 84.85%], followed by S/B (AUC =0.930; 95% CI: 0.848–0.975; sensitivity: 77.27%; specificity: 93.94%) and S/M (AUC =0.895; 95% CI: 0.804–0.953; sensitivity: 77.27%; specificity: 90.91%). The ROC curves indicated that subcutaneous area (AUC =0.927; 95% CI: 0.844–0.974; sensitivity: 84.09%, specificity: 90.91%) and total (AUC =0.852; 95% CI: 0.753–0.923; sensitivity: 70.45%; specificity: 90.91%) also had discrimination ability between stage I and II.

Conclusions: The measurement of the soft tissue area of the calf may be used as an auxiliary method for staging primary LEL. For patients with unilateral primary LEL, the difference in subcutaneous area of limbs

could be a specific indicator to distinguish clinical stage I from II.

Keywords: Lymphedema; magnetic resonance imaging (MRI); soft tissue area; lower extremity; clinical stage

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Introduction

Lower extremity lymphedema (LEL) is a pathological condition involving blockage of lymphatic reflux due to abnormal development or injury of the lymphatic system. Therefore, lymph-rich proteins accumulate in the interstitial fluid and stroma, resulting in connective tissue hyperplasia, fat sclerosis, and fascial thickening (1,2). LEL is a progressive condition characterized by gross swelling of the affected limb, which leads to chronic inflammation, fibrosis, and susceptibility to infection (3). It has been reported that lymphedema affects as many as 200 million people worldwide (4), and the incidence of LEL has increased recently (5). According to its etiology, clinical classification of lymphedematous swelling has been defined as primary (idiopathic) and secondary LEL by the International Society of Lymphology (ISL) (6). Primary LEL is a rare disease of congenital malformation in the lymphatic vessels. The prevalence of primary LEL is about 1/100,000, with a female/male ratio of approximately 2:1 for incidence (4). Secondary LEL follows obstruction to lymphatics caused by surgery, radiation therapy, and malignant involvement of lymph nodes (4). Secondary LEL is more common than primary LEL, frequently developing after gynecological malignant tumor surgery, especially in women (7).

The reference standard for clinical staging of primary LEL is the ISL's staging criteria for lymphedema (6): the ISL classifies LEL into stages 0, I, II, and III based on the signs and symptoms of the patient. Stage 0 refers to a subclinical condition where swelling is not yet evident despite impaired lymph transport, which may exist for months or years before overt edema occurs. Stage I represents an early accumulation of fluid relatively high in protein content in the interstitial interphase, which subsides with limb elevation. Stage II begins with fat deposition and fibrosis in the subcutaneous soft tissues; limb elevation rarely reduces tissue swelling and pitting is evident. Stage III represents elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, trophic skin changes, and warty overgrowths can occur. This clinical staging is the world's most recognized method for assessing the severity of lymphedema from a clinical perspective and is important for guiding clinical treatment and improving prognosis: stage I patients have a mild condition and can be treated with complete decongestive therapy (CDT; a combination of conservative treatments including lymphatic drainage manipulation, skin and nail care, multi-layer compression bandages, and therapeutic exercises). However, when patients enter stages II and III, with connective tissue hyperplasia and fatty deposits in the limbs, abnormal thickening of the lower limbs, loss of elasticity, segmental deformities, and even elephantiasis in advanced stages, poor results are achieved with CDT alone and combined surgical treatment is required (8).

Diagnosis of LEL is typically based on the clinical history and objective measurement. Objective measurement can provide a direct reference for patients with LEL, which has specific value for evaluating the severity of lymphedema, formulating an appropriate treatment plan, and predicting the effectiveness of therapy. Measurement of the volume of the lower extremity is widely adopted in clinical practice (9). The limitation of volumetric measurements is that because the volume of each subcutaneous tissue cannot be assessed, the cause of the limb swelling cannot be accurately determined. In addition, when the recommended value of 5% increase in the volume of the affected limb compared with that of the unaffected limb is used as the threshold value for mild lymphedema, some patients can be missed during the early stages (6). Therefore, there is a need for a new method to monitor and identify LEL in the early stage.

Accurate diagnosis and efficient therapy should be based on physical examination and imaging. Proper imaging can demonstrate the variety and characteristics of lymphoedema, enabling optimal clinical management and appropriate selection of protocols. Ultrasound, lymphoscintigraphy, and magnetic resonance imaging (MRI) have been considered the primary imaging modality in patients with LEL (10,11).

Ultrasonography is a feasible, non-invasive, and low-cost technique, available for patients with restricted activity. The disadvantages of ultrasonography include operator dependency, and subjective evaluation of images (10). Lymphoscintigraphy can observe not only the morphology of lymphatic vessels, but also the lymphatic reflux function. However, ionizing radiation and low spatial and temporal resolution limit its application in measuring lymphatic dysfunction (12). MRI is a non-invasive imaging technique with a high soft tissue resolution that can clearly illustrate the structures of the dermis, subcutaneous soft tissue, muscle and bone, and fluid infiltration and fat distribution in the diseased limbs. It is reliable and reproducible, especially in evaluating limb lymphedema (13).

The accumulation of edema in the subcutaneous soft tissues and the hypertrophic growth of fat have recently been reported to contribute to the increased volume of the lower limbs, whereas muscle and bone are rarely involved during the onset and progression of LEL (14). Lu *et al.*, Wang *et al.*, and Li *et al.* used MRI fat-suppressed T2-weighted imaging to measure the calf soft tissue thickness and edematous area of secondary LEL, revealing that the thickening of subcutaneous soft tissue and the area of edema significantly increased the volume of the affected limb, and the calf soft tissue thickness and edematous area were related to the stage of secondary LEL (15-17). However, the quantitative relationship between the measurement of lower extremity soft tissue area using MRI and the staging of primary LEL is unclear.

Primary lymphedema generally has two directions of progression, 1 is distal-proximal, and the other is proximal-distal (18,19). The anterior tibial lymphatic vessel has been identified as the weak point of the lymphatic pathway in the lower limb, where the earliest and most severe swelling occurs (20). Thus, assessing the calf area with MRI might enhance the sensitivity for early detection and staging of LEL. Therefore, we aimed to retrospectively analyze MRI images of the lower extremity derived from 90 patients with unilateral primary LEL and explore its value in clinical staging by measuring the soft tissue area of the calf. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-795/rc).

Methods

Ethical statement

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University. The requirement for informed consent was waived due to its retrospective nature.

Patients

Patients diagnosed with primary LEL from January 2017 to December 2019 in Beijing Shijitan Hospital, Capital Medical University, were enrolled consecutively from the hospital's electronic medical records (*Figure 1*). Lymphoscintigraphy was used to diagnose unilateral LEL, to include cases with the presence of dermal reflux or with no tracer. At the same time, all included patients had presented with lower limb lymphedema without secondary factors such as surgery, trauma, filariasis, and infection. Meanwhile, the lymphatic surgery clinician determined the direction of progression of lymphedema by taking the patient's medical history (proximal-distal or distal-proximal). The inclusion criteria were as follows: (I) patients were diagnosed with primary lymphedema; (II) underwent lower extremity MRI examination; (III) distal-proximal progression. The exclusion criteria were as follows: (I) bilateral limb swelling; (II) incomplete clinical or imaging data; (III) patients with reflux lymphedema (reflux of lymphatic fluid from the chylous cisterna down into the limb due to defective or non-functional lymphatic trunk valves (18) that progressed proximal-distal. The ISL relies on a 3-stage scale (I–III) for classification of a lymphedematous limb with recognition of stage 0, which refers to a latent or subclinical condition where swelling is not yet evident. stage I indicates early fluid accumulation with relatively high protein content which decreases with limb elevation, and pitting may be present. In stage II, limb elevation alone rarely decreases tissue enlargement, and pitting may also be present. Stage III encompasses lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed (6). In this study, no ISL stage 1 patients were enrolled; according to the ISL [2020] (6), all patients were divided into stages I, II, and III, respectively. The assessors of the reference standard were blinded to the clinical information and measurement results. All patients underwent lower extremity MRI. All patients were screened with lower extremity spectral Doppler ultrasonography to exclude lower extremity venous or arterial vascular diseases. This study was conducted from May 2022 to July 2022.

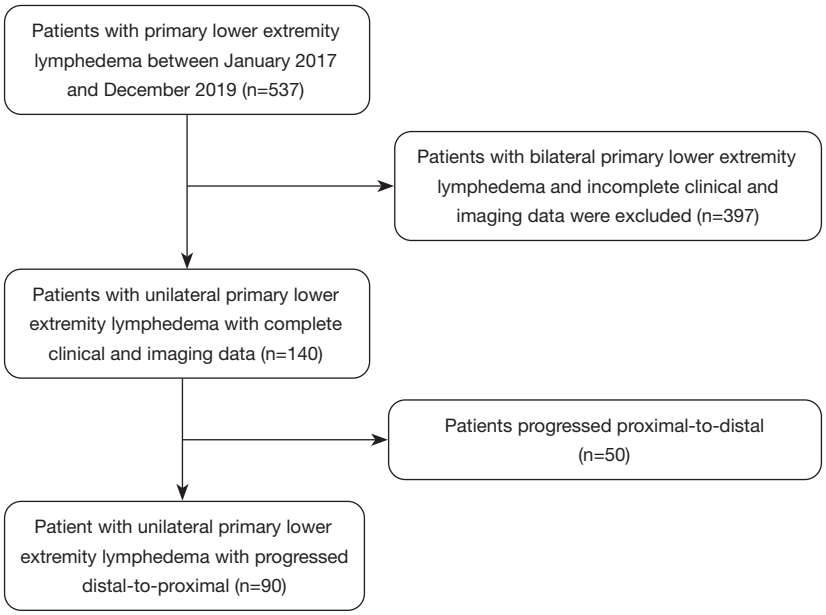

Figure 1 Flowchart of participants. Patients with primary LEL between January 2017 and December 2019 (n=537). A total of 447 patients were excluded from the analysis. The remaining 90 patients were included in this retrospective study. LEL, lower extremity lymphedema.

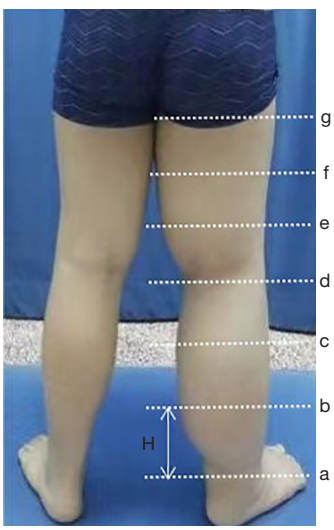

Figure 2 Lower extremity volume measurements by circumferential method. Primary LEL of stage II (13-year-old male, right calf). The patient's lower extremities were measured bilaterally and the circumference of the ankle was recorded (a), lower 1/3 of the calf (b), upper 1/3 of the calf (c), knee (d), lower 1/3 of the thigh (e), upper 1/3 of the thigh (f), and the root of the thigh (g) on the affected side and the normal side, respectively, as well as the height (H) between adjacent circumference levels, and used the calculation formula to derive the segmental volumes, and added the volumes of the corresponding segments to calculate the total volume. LEL, lower extremity lymphedema.

Volume measurements by circumferential method

A lymphatic surgery clinician with more than 5 years of experience in limb measurement measured the patient's lower extremities bilaterally and recorded the circumference (C) of the ankle, lower 1/3 of the calf, upper 1/3 of the calf, knee, lower 1/3 of the thigh, upper 1/3 of the thigh, and the root of the thigh on the affected side and the normal side, respectively, as well as the height (H) between adjacent circumference levels. Then, they used Eq. [1] to derive the segmental volumes, and added the volumes of the corresponding segments to calculate the total volume (V) (*Figure 2*).

$$V=\frac{(C1\times C1+C1\times C2+C2\times C2)H}{12\pi} \quad [1]$$

MRI protocols

MRI was performed with a 1.5-T MRI unit (Ingenia; Philips Medical Systems, Best, Netherlands) using a 16-channel body coil. The patients were in the supine position, with their feet entering the scanner first. All cases underwent MRI with the following sequences: short time inversion recovery (STIR)/axial and coronal planes [repetition time (TR) 5,200 ms, echo time (TE) 80 ms, inversion time (TI)

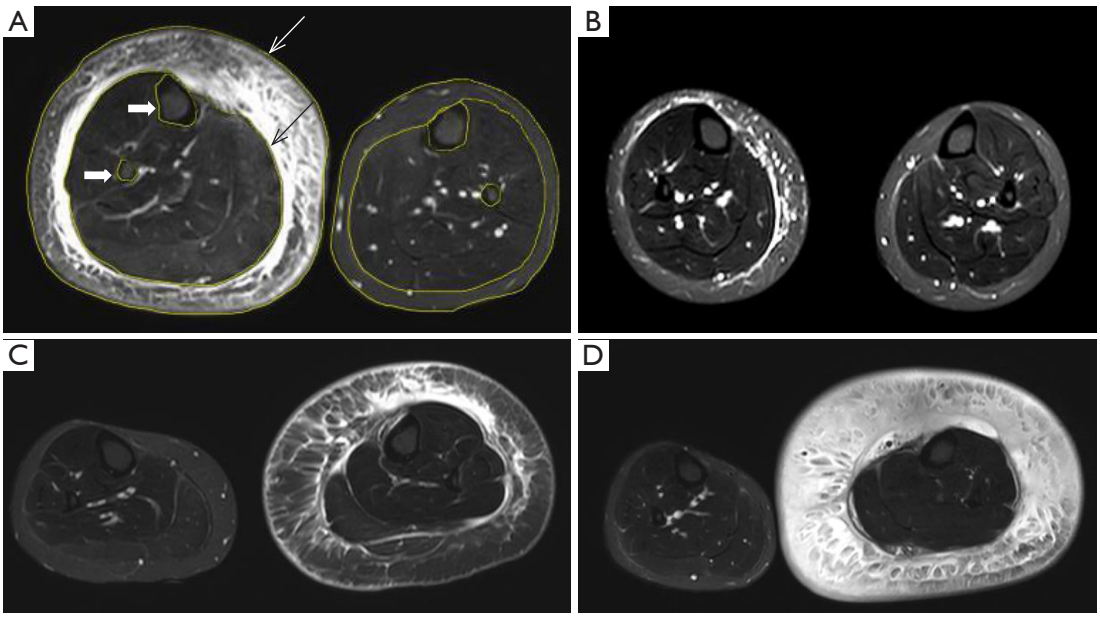

Figure 3 MRI measurements of patients with primary LEL and STIR images at different clinical stages. (A) MRI (axial STIR sequence) measurement of the lower extremity's total, muscle, bone, and subcutaneous area. The skin (white arrow) was defined as the outer boundary. The deep fascia (black arrow) was defined as the boundary between subcutaneous soft tissue and muscle. The boundaries of fibula and tibia were defined as the outer edge of the fibula and tibial bone cortex (thick arrow). The sum of the tibia and fibula areas was the bone area. The area within the calf skin was expressed as total area, the area between the muscle and bone boundary was expressed as muscle area, and the area between the deep fascia and the skin boundary was expressed as subcutaneous area. (B) Primary LEL of stage I (15-year-old female, right calf). (C) Primary LEL of stage II (30-year-old female, left calf). (D) Primary LEL of stage III (18-year-old female, left calf). MRI, magnetic resonance imaging; LEL, lower extremity lymphedema; STIR, short time inversion recovery.

160 ms, slice 5 mm, gap 0.5 mm, voxel 1.5 mm^2, field of view (FOV) 220 mm × 200 mm/320 mm × 240 mm, number of excitations (NEX) =2].

Data interpretation

The post-processed images were reviewed by two independent radiologists, each with 20 years of experience in MRI, and who were blinded to clinical stages. With a uniform window at a Philips MRI workstation (WorkSpace 2.6.3.4), STIR axial plane images of the calf were used to minimize the impact of fat on the edematous area when measuring soft tissue. The total area, muscle area, and bone area (cm^2), respectively, of the upper 1/3 layer of bilateral lower legs in the transverse axis position were measured. The upper 1/3 cross-section of the lower limb was defined as the image plane corresponding to 1/3 of the horizontal line from the tibial plateau to the lateral malleolus. The skin edge, the cortical edge of the tibia and fibula, and the boundary of deep fascia between muscle and subcutaneous soft tissue were drawn manually. Then, the workstation calculated the total area and musculoskeletal areas automatically. The total area of soft tissue, muscle area, and subcutaneous tissue area of the calf were obtained to depict potential changes in soft tissue areas in the affected lower extremity. Subcutaneous was calculated by total area minus muscle and bone (*Figure 3*). The differences between the subcutaneous of calves were calculated by subtracting the value of the affected calf from that of the contralateral unaffected calf. The subcutaneous-to-bone ratio and subcutaneous-to-muscle ratio in the affected and unaffected calves were also calculated.

Statistical analysis

Statistical analysis was carried out with SPSS 23.0 (IBM Corp., Armonk, NY, USA). A Kolmogorov-Smirnov (KS) test was adopted in order to determine whether the data conformed to a normal distribution. The (mean ± standard deviation) was used for normally distributed data, and the

Table 1 Patient clinical characteristics

Characteristics	Stage I	Stage II	Stage III
Age (years)	20.00±19.00†	36.48±18.69‡	30.85±18.77‡
Sex, n (%)			
Female	21 (63.64)	26 (59.09)	7 (53.84)
Male	12 (36.36)	18 (40.91)	6 (46.16)
Age at onset of disease (years)	17.00±16.00†	18.00±25.80†	17.00±20.34‡
Duration of edema (years)	2.00±9.40†	9.00±21.25†	13.61±9.84‡

†, median ± interquartile spacing; ‡, mean ± standard deviation.

(median ± interquartile spacing) was used for abnormally distributed data. If the data of the affected and healthy sides conformed to normal distribution, independent samples *t*-test was used for comparison between the affected and unaffected soft tissue areas, otherwise Mann-Whitney U test was used. Homogeneity of variance test was used to determine the homogeneity of variance; if the three groups (LEL stage I, II, and III) had equal variance and the data conformed to a normal distribution, all parameters were compared between LEL stages using one-way analysis of variance (ANOVA) followed by Bonferroni's post hoc multiple comparisons (the Bonferroni corrected P value level was 0.05 divided by 3); otherwise, the Kruskal-Wallis H test was used. Spearman correlation analysis was used to assess the correlation between lower extremity volume and soft tissue area and the relationship of the LEL stage with total, subcutaneous, difference in subcutaneous area of limbs, subcutaneous/bone (S/B), and subcutaneous/muscle (S/M) values. The Spearman's rho values (rho) were interpreted as follows: values 0.15–0.24, very low; 0.25–0.49, low; 0.50–0.69 moderate; 0.70–0.89 high; and 0.90–1.00 very high. If there were significant findings using the ANOVA or Kruskal-Wallis H test, the cut-off values of the parameters were then determined with receiver operating characteristic (ROC) analysis for classifying stages. The ROC was generated with MedCalc version 19.1 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2019). A P<0.05 (two-sided) was considered indicative of a significant difference. There were no missing data.

Results

Patients

A total of 90 patients (54 females; 36 males; age range, 2–74 years; median age, 29 years) were included. The duration of edema ranged from 0 to 50 years. There were 33 patients classified as stage I clinically, 44 patients as stage II, and 13 patients as stage III. There were 12 males and 21 females in stage I, 18 males and 26 females in stage II, and 6 males and 7 females in stage III. None of the patients had pelvic venous disease. None of the patients had received formal treatment prior to admission. There were no adverse events during the entire study. The patient clinical characteristics are summarized in *Table 1*.

Relationship between lower limb volume and soft tissue area

There were high and moderate positive correlations between volume and total area (rho =0.834) and subcutaneous (rho =0.677) and moderate and low positive correlations with muscle (rho =0.563) and bone (rho =0.399) on the affected side (P<0.001). At the same time, there were more than moderate positive correlations between unaffected volume and total area (rho =0.945), subcutaneous (rho =0.640), muscle (rho =0.707), and bone (rho =0.544) on the healthy side (P<0.001) (*Table 2*).

Comparison of the soft tissue area between the affected and the unaffected calves

The total area, subcutaneous area, S/B, and S/M of the affected calf was greater than that of the unaffected calf (P<0.001). However, there was no difference in muscle area (P=0.98) or bone area (P=0.92) between the affected and unaffected calves (*Table 3*).

Staging unilateral LEL with the soft tissue area of calves

With an increase in the stage of LEL, there was a trend

Table 2 The relationship between lower limb volume and soft tissue areas

Soft tissue area	Affected volume		Unaffected volume	
	Spearman's rho	P value	Spearman's rho	P value
Total area	0.834	<0.001	0.945	<0.001
Muscle area	0.563	<0.001	0.707	<0.001
Bone area	0.399	<0.001	0.544	<0.001
Subcutaneous area	0.677	<0.001	0.640	<0.001

Table 3 The comparison of the soft tissue area between the affected and the unaffected calves

Soft tissue area	Affected side	Unaffected side	P value
Total (cm^2)[§]	124.00±57.90[†]	91.12±19.34[‡]	<0.001
Muscle (cm^2)[§]	61.15±19.20[†]	63.45±14.20[‡]	0.98
Bone (cm^2)[¶]	5.15±1.15[‡]	5.13±1.12[‡]	0.92
Subcutaneous (cm^2)[§]	56.05±39.87[†]	21.60±13.15[†]	<0.001
S/B[§]	10.99±9.67[†]	4.54±1.84[‡]	<0.001
S/M[§]	0.87±0.74[†]	0.33±0.19[†]	<0.001

[†], median ± interquartile spacing; [‡], mean ± standard deviation; [§], Mann-Whitney U test; [¶], independent samples *t*-test. S/B, subcutaneous/bone; S/M, subcutaneous/muscle.

Table 4 Soft tissue areas of affected lower extremity corresponding to stages of LEL

Soft tissue area	Stage I	Stage II	Stage III	P value
Total (cm^2)[§]	104.36±17.06[ab‡]	144.15±35.48[a‡]	160.70±49.78[b‡]	<0.001
Muscle (cm^2)[§]	62.97±11.41[‡]	62.25±21.27[†]	60.10±16.42[‡]	0.53
Bone (cm^2)[¶]	5.35±0.96[‡]	5.15±1.26[‡]	4.63±1.12[‡]	0.16
Subcutaneous (cm^2)[§]	35.93±11.70[ab‡]	69.65±35.33[a†]	72.60±65.25[b†]	<0.001
Difference in subcutaneous area of limbs (cm^2)[§]	12.39±9.45[ab‡]	50.56±24.13[a‡]	52.60±59.15[b†]	<0.001
S/B[§]	6.83±2.25[ab‡]	14.71±5.42[a‡]	16.46±15.09[b†]	<0.001
S/M[§]	0.58±0.20[ab‡]	1.05±0.68[a†]	1.67±0.85[b‡]	<0.001

[a], the P value for statistical comparisons between stage I and stage II was less than 0.001; [b], the P value for statistical comparisons between stage I and stage III was less than 0.001; [†], median ± interquartile spacing; [‡], mean ± standard deviation; [§], Kruskal-Wallis H test; [¶], one-way ANOVA. LEL, lower extremity lymphedema; S/B, subcutaneous/bone; S/M, subcutaneous/muscle; ANOVA, analysis of variance.

toward an increase in total area, subcutaneous area, difference in subcutaneous area of limbs, S/B, and S/M of the affected calf, but not in muscle area or bone area (*Table 4*, *Figure 4*). Kruskal-Wallis H test identified significant differences in total area, subcutaneous area, S/B, and S/M of the affected calf and difference in subcutaneous area of the calves between LEL stage I and II as well as between LEL stage I and III (P<0.001) (*Table 4*). However, there was no difference in total area (P>0.99), subcutaneous area (P=0.65), difference in subcutaneous area of the calves (P=0.71), S/B (P=0.33), and S/M (P=0.23) between stage II and stage III comparisons (*Figure 4*).

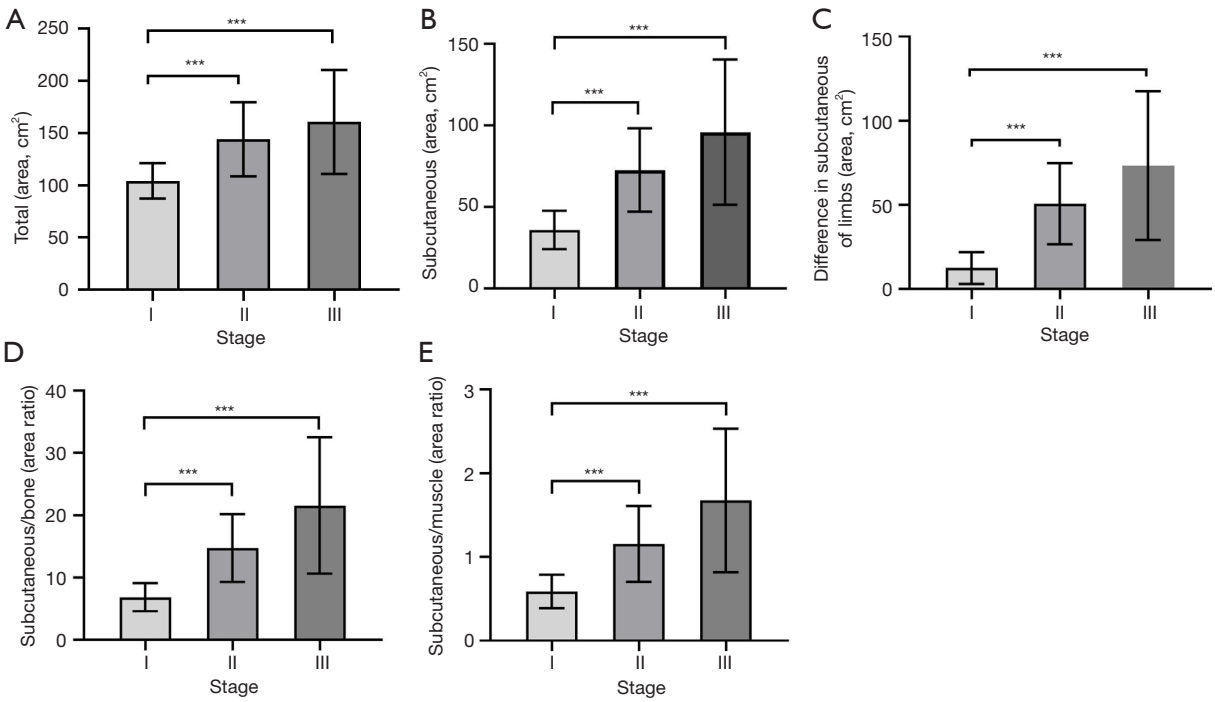

Figure 4 Associations between soft tissue areas of lower extremities and stages of LEL. (A-E) An association between the total, subcutaneous area, the difference in subcutaneous area of limbs, S/B, S/M with LEL stage, respectively. ***P<0.001. LEL, lower extremity lymphedema; S/B, subcutaneous/bone; S/M, subcutaneous/muscle.

Table 5 The relationship of LEL stage with soft tissue areas of affected lower extremity

Soft tissue area	LEL stage	
	Spearman's rho	P value
Total area	0.578	<0.001
Subcutaneous area	0.723	<0.001
Difference in subcutaneous area of limbs	0.752	<0.001
S/B	0.747	<0.001
S/M	0.709	<0.001

LEL, lower extremity lymphedema; S/B, subcutaneous/bone; S/M, subcutaneous/muscle.

Relationship of LEL stage with soft tissue area

The total area, subcutaneous area, difference in subcutaneous area of limbs, S/B, and S/M of the affected calf were positively correlated with clinical stage, with difference in subcutaneous area of limbs (rho =0.752) and S/B (rho =0.747) correlating more with clinical stage than total area (rho =0.578), subcutaneous area (rho =0.723), and S/M (rho =0.709) (P<0.001) (*Table 5*).

ROC of soft tissue area for LEL staging

Based on ROC analysis, the area under the ROC curve (AUC) for distinguishing stage I from II for total area, subcutaneous area, difference in subcutaneous area of limbs, S/B, and S/M was 0.852 [95% confidence interval (CI): 0.753–0.923], 0.927 (95% CI: 0.844–0.974), 0.950 (95% CI: 0.875–0.987), 0.930 (95% CI: 0.848–0.975), and 0.895 (95% CI: 0.804–0.953). The AUC for identifying stage II and III for total area, subcutaneous area, difference in subcutaneous area of limbs, S/B, and S/M was 0.591, 0.649, 0.649, 0.695, and 0.706, respectively. The corresponding 95% CI, Youden index, cut-off value, sensitivity, and specificity for distinguishing between LEL stages I and II are illustrated in *Table 6*. Thus, measured parameters might help distinguish stage I from stage II (*Figure 5*). Difference in subcutaneous area of limbs had the highest AUC value for distinguishing stage I from II.

Table 6 ROC curve analysis of soft tissue areas of affected extremity for identifying stage I and stage II of LEL

Parameters	Total	Subcutaneous	Difference in subcutaneous area of limbs	S/B	S/M
AUC	0.852	0.927	0.950	0.930	0.895
95% CI	0.753–0.923	0.844–0.974	0.875–0.987	0.848–0.975	0.804–0.953
Youden index	0.6136	0.7500	0.8030	0.7121	0.6818
Cut off value	125.90	49.60	19.90	10.20	0.79
Sensitivity (%)	70.45	84.09	95.45	77.27	77.27
Specificity (%)	90.91	90.91	84.85	93.94	90.91

ROC, receiver operating characteristic; LEL, lower extremity lymphedema; S/B, subcutaneous/bone; S/M, subcutaneous/muscle; AUC, area under the ROC curve; CI, confidence interval.

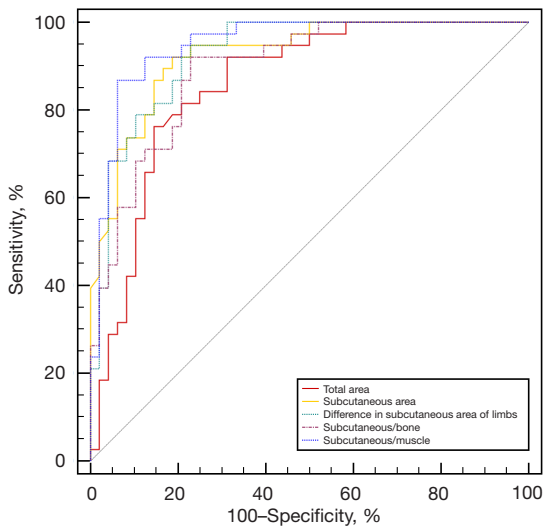

Figure 5 ROC-identified total, subcutaneous area, the difference in subcutaneous area of limbs, S/B, and S/M values for classifying LEL stage I *vs.* II. ROC, receiver operating characteristic; S/B, subcutaneous/bone; S/M, subcutaneous/muscle; LEL, lower extremity lymphedema.

Discussion

In this study, measuring the soft tissue area of the affected calf by MRI was shown to be sensitive to changes in the degree of limb swelling in early LEL, which could quantitatively assess the severity of unilateral primary LEL. This new method can be used to identify the early stage of primary LEL.

MRI has a high resolution for soft tissue, which can illustrate subcutaneous fat, muscle, and bone of the calf and clarify swelling sites in patients with lymphedema (15-17). In addition, STIR could suppress subcutaneous fat without compromising image resolution and clearly show the signal of lymphedematous areas located superficially in the muscle (21,22). Kim *et al.* used STIR sequences to observe the extent of LEL involvement in the upper extremity and to establish LEL imaging staging, which was found to have a high correlation with clinical staging (21). Cellina *et al.* used MRI to evaluate the relationship between imaging manifestations of LEL and clinical staging, and found that clinical staging was correlated with MRI manifestations (22).

In this study, except for muscle and bone of the affected calf measured by MRI, the soft tissue area of the bilateral calf and the lower limb volume obtained by the circumferential method were closely correlated, and more significantly, the total area and subcutaneous of the affected calf were strongly correlated with volume. Moreover, both the total area and the subcutaneous (but not muscle and bone) of the affected calf were significantly larger than the unaffected one, indicating that subcutaneous soft tissue swelling contributes to an increase in limb volume in patients with primary lower limb lymphedema. The extent of lymphedema is less in muscle and bone. This finding can be explained by pathophysiological changes of primary LEL as follows. Patients with primary lymphedema have dilated and tortuous lymphatic vessels due to dysplasia, gradual occlusion of lymphatic vessels in the distal limb, reduction in the number of normal lymphatic vessels, or an increase in the number of dysfunctional lymphatic vessels (4). This alteration would result in a poor lymphatic fluid return and continuous leakage of stagnant lymphatic fluid into the tissue interstices. Subsequently, a gradual increase in edema would develop in the subcutaneous soft tissue layer. As the disease progresses, hypertrophic adipose tissue and

fibrous tissue accumulate around subcutaneous soft tissue, exacerbating swelling in the affected limb (23). In this study, the correlation between subcutaneous and clinical stage was higher than that of total soft tissue area. That is, subcutaneous soft tissue area responded more accurately to the progression of lymphedema compared to total soft tissue area.

Bone, muscle, and subcutaneous fat contents within the limb can influence body mass index (BMI), whereas BMI may affect lymphedema clinical staging (24). To minimize the impacts of subcutaneous fat, bone, and muscle on individual measurement, difference in subcutaneous area of limbs, S/B, and S/M parameters were introduced to investigate specific value on the clinical staging of primary LEL. In the present study, the difference in subcutaneous area of the limbs, S/B, and S/M parameters correlated with the clinical stage (with difference in subcutaneous area of the limbs correlating more closely than that of S/B and S/M). The development of primary LEL is a dynamic process. Early detection and treatment can result in the preservation of a near-normal limb and a greater opportunity of minimizing or avoiding major complications (25). The accurate diagnosis of lymphedema relies on the patient's major complaints, such as swelling of the limbs; clinical symptoms are often not detected early, resulting in progression to stage II or even III by the time of diagnosis. Therefore, it is imperative to determine the latent or initial stage of lymphedema by quantitative methods. With an increase in clinical stage, difference in subcutaneous area of limbs, S/B, and S/M gradually increases, with significant differences between stage I and II and stage I and III. There is no significant difference between stage II and III. Thus, MRI can provide additional diagnostic value for identifying early lymphedema. When lymphedema progresses to stage II, fat and fibrous tissues overgrow, whereas skin gradually develops fibrotic changes with increased thickness and hardness, decreased elasticity, and more pronounced swelling (26). When lymphedema progresses to stage III, pathologic changes in the limb are mainly in the skin, such as fatty deposits, hyperpigmentation, echinodermata, verrucous hyperplasia, and elephantiasis. Contrastingly, swelling of the limb becomes inapparent.

In our previous study, we found that MRI-based measurements of calf soft tissue thickness could be used to quantitatively assess the clinical staging of primary LEL (27). However, the swollen lower extremity is not a regular circle and the thickness of the calf does not accurately reflect the actual condition of the limb. Therefore, this study further measured the area of different structures at the cross-sectional level of the calf, aiming to more directly and accurately assess the site of primary LEL onset and to explore its value for identifying clinical staging. Meanwhile, in the previous study, we concluded that the difference in subcutaneous soft tissue thickness between the affected and healthy calf could be used as the best thickness index to discriminate stage I from stage II primary LEL (AUC =0.945; sensitivity: 90.91%). In this study, we found that the difference in subcutaneous area of limbs had the highest AUC value (AUC =0.950) and the sensitivity (95.45%) was greater than that of the difference in subcutaneous thickness of limbs, indicating that the difference in subcutaneous area of limbs can more accurately and sensitively identify patients with stage I and stage II compared to thickness. The difference in subcutaneous area of limbs can minimize the effect of subcutaneous fat on the degree of limb swelling and reflect the increased edematous area of subcutaneous soft tissue in the lymphedema limb, which is a good indicator of the clinical stage of patients with unilateral primary LEL. However, either the subcutaneous thickness or area difference needs to be referenced to the healthy side of the limb and is not fully applicable to patients with bilateral limb edema.

This study proposes two parameters, S/B and S/M, which do not require comparison with the contralateral limb. These parameters have the potential to be used to assess the staging of bilateral primary LEL. In this study, the AUC of S/B was similar to that of the difference in subcutaneous area of limbs for differentiating stage I from II, with lower sensitivity (77.27%) but higher specificity (93.94%) than the difference in subcutaneous area of limbs. The S/B has a high positive correlation with clinical staging, indicating that S/B has a diagnostic value for unilateral primary LEL, which may be applicable for predicting the severity of bilateral lymphedema. The sensitivity and specificity are the highest when the S/B value equals 10.2, which might serve as the cut-off value to distinguish stage I from II. In this study, the diagnostic efficacy of S/M for clinical staging was lower than that of S/B, which may be explained by the following: (I) the venous and lymphatic systems are interdependent. Due to venous alignment within muscularis, when the lymphatic system becomes diseased and challenging to compensate for, the venous system, as an "inseparable" entity, produces mixed veno-lymphoedema (28); (II) in later stages of primary LEL, edema can infiltrate the muscle surface and even muscle septum (29), so that muscle area can be affected; (III) muscle

area is affected by limb mobility, whereas the bone area is not affected by limb mobility, so S/B has better diagnostic efficacy compared to S/M.

A previous study proposed the concept of volume index (total lower extremity volume/BMI) based on MRI volume measurements (30), however, the patients were secondary LEL and only 1 measurement parameter was presented and not compared with the common clinical approach. The present study focused on primary LEL and multiple measurement parameters were presented and compared with the volume measured by the clinical circumferential measurements method.

This study has several limitations. First, selection bias was present because all patients were identified as having lymphatic insufficiency on clinically standard imaging by lymphoscintigraphy, and the validity of this quantitative method for patients with bilateral LEL was not explored. Further studies will investigate its value in relation to bilateral LEL. Second, the validity of this quantitative approach to assessing LEL therapy has not been demonstrated. Future studies are necessary to determine the validity of MRI measurements in LEL treatment. Third, this study did not include patients with reflux lymphedema that progressed from proximal to distal, but only those that progressed from distal to proximal. We will continue to collect patients with lymphedema progressing in both of these directions for comparative analysis in future studies. Fourthly, our finding needs to be validated in a prospective, independent cohort before it can be recommended for further translation to practice. Finally, patients in this study were selected for primary LEL and secondary patients were not included. In future studies, we will continue to include patients with secondary LEL for comparative studies.

Conclusions

In conclusion, the STIR sequence of MRI enables quantitative diagnosis of primary LEL and assists in clinical staging in order to plan the best treatment and improve prognosis. The difference in subcutaneous area of limbs measured by MRI has potential for distinguishing between stage I and II primary LEL.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-795/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-795/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University. The requirement for informed consent was waived due to its retrospective nature.

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