Computed tomography scanning in the diagnosis of lower extremity phlebolymphedema

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ABSTRACT

Objectives: Phlebolymphedema, the most common cause of secondary lymphedema in Western societies, seldom gets the attention it deserves. Diagnosis is often missed and when evaluated is through lymphoscintigraphy (LSG) which is cumbersome. This study aims to assess the role of computed tomography (CT) scanning in the diagnosis of phlebolymphedema of the lower extremities by comparing CT characteristics with the International Society of Lymphology (ISL) grading system and LSG.

Methods: Patients presenting with chronic venous disease who underwent a CT scan and LSG of the lower extremities (diagnostic testing) formed the study cohort. Three assessors blinded to the patients' ISL stage and LSG results evaluated the CT for skin thickening (present/absent), subcutaneous interstitial edema (honeycombing; graded 0-2), and muscle compartment (MC) edema (graded 0-2), in the thigh (20 cm above apex of patella), leg (10 cm below apex of patella), and ankle (5 cm above lateral malleolus). Agreement from two of the three raters determined the value used for analysis. Additionally, the final score used for each variable for each limb was determined by taking the most severe value of the three levels. The three CT variables were then compared independently and together with ISL stage and LSG to determine their diagnostic potential for phlebolymphedema. Also assessed was the severity of each CT variable across each limb in addition to the evaluation of the extent of their inter-rater agreement.

Results: Of the 35 patients (50 limbs), 28 were female, with left laterality noted in 22 limbs. Clinical, Etiological, Anatomical, and Pathophysiological clinical class for the cohort included C0 to 2, 4 limbs (8%); C3, 13 limbs (26%); C4, 17 limbs (34%); C5, 9 limbs (18%); and C6, 7 limbs (14%). Thirty-one limbs underwent stenting for chronic iliofemoral venous obstruction after having failed conservative therapy. Of the 50 limbs, 8 (16%) were ISL stage 0, 10 (20%) ISL stage 1, 2 (4%) ISL stage 2, and 30 (60%) ISL stage 3. With LSG, 6 (12%) had a normal study, 21 (42%) mild disease, 0 (0%) moderate disease, and 23 (46%) severe disease. Correlation between LSG and ISL stage was poor ($r = 0.18$; $P = .20$). With ISL stage as a reference, the sensitivity, specificity, and accuracy of CT in diagnosing phlebolymphedema were as follows: skin thickening (95%/75%/92%), honeycombing (100%/0%/84%), MC edema (100%/0%/84%), any one CT variable (100%/0%/84%), any two CT variables (100%/0%/84%), and all three CT variables (93%/63%/88%). With LSG as a reference, the sensitivity, specificity, and accuracy of CT in diagnosing phlebolymphedema were as follows: skin thickening (82%/0%/72%), honeycombing (100%/0%/88%), MC edema (100%/0%/88%), any one CT variable (100%/0%/88%), any two CT variables (100%/0%/88%), and all three CT variables (82%/0%/72%). For CT variables, there was no significant difference between skin thickening in the thigh vs calf vs ankle ($P = .5$). MC edema, however, worsened from thigh to calf ($P < .0001$) without a difference between the calf and the ankle ($P = .3$). The severity of honeycombing was worst in the ankle and least in the thigh, with a significant difference between all 3 sites ($P = .008$). The inter-rater agreement (kappa statistic) varied from 0.2 for skin thickening to 0.7 for honeycombing.

Conclusions: CT scanning can be used as a screening tool for phlebolymphedema in the lower extremities. However, such a diagnosis depends on the reference standard used, ISL stage vs lymphoscintigram. Although skin thickness offered the greatest sensitivity, specificity, and accuracy when the ISL stage was used, honeycombing or MC edema had high sensitivity and accuracy but low specificity when LSG was used as the reference. Factoring in inter-rater agreement as well, honeycombing was noted to be the best CT variable to diagnose phlebolymphedema. (J Vasc Surg Venous Lymphat Disord 2025;13:102166.)

Keywords: Lymphedema; Chronic venous disease; Venous insufficiency; Phlebolymphedema; Chronic iliofemoral venous obstruction

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Chronic venous insufficiency has been noted to be the most common cause of lymphedema in the lower extremity in Western societies, accounting for 41.8% of limbs with lymphedema.[1] Phlebolymphedema, the term applied to such lymphedema has been noted to be present in about 20-30% of patients with chronic iliofemoral venous obstruction (CIVO).[2] The diagnosis of lymphedema has been a challenging issue. Clinical diagnosis is fraught with problems with Stemmer's sign being the only reliable criteria.[3] Lymphoscintigram (LSG), although being quite sensitive and specific,[4-6] is not easily obtainable regularly and comes with additional radiation and radioisotope exposure. Indocyanine green (ICG) lymphography faces similar problems relating to use of dye and technical expertise to perform the study. Although bioimpedance spectroscopy is useful for assessing early stages of lymphedema, it is expensive and labor intensive.[7] Limb volumetry enables the assessment of limb edema and changes with therapy, but does not help determine the cause of the edema. Cross-sectional imaging, either computed tomography (CT) scan or magnetic resonance imaging is easy to perform and readily available. This study evaluates the role of the CT scan in the diagnosis of phlebolymphedema.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective analysis
- **Key Findings:** Diagnosis of lower extremity phlebolymphedema on computed tomography (CT) scan depends on the reference standard used, the International Society of Lymphology (ISL) stage vs lymphoscintigraphy. With the ISL stage as reference, skin thickness offers the greatest sensitivity, specificity, and accuracy. With LSG, the use of subcutaneous interstitial edema (honeycombing) or muscle compartment edema, offers high sensitivity and accuracy, but low specificity. Factoring in inter-rater agreement as well, honeycombing was found to be the best CT scan variable to diagnose phlebolymphedema.
- **Take Home Message:** A CT scan can be used as a screening tool for phlebolymphedema in the lower extremity through the use of tissue characteristics, including skin thickening, subcutaneous interstitial edema, and/or muscle compartment edema. The diagnostic capacity of each variable either alone or in combination is a function of the reference standard, ISL stage vs lymphoscintigram, and inter-rater agreement.

METHODS

Study design. This study is a single-center retrospective analysis of prospectively collected data from 2015 to 2018. Informed consent was obtained from participants for all tests and procedures. Franciscan Missionaries of Our Lady University institutional review board approval was obtained for dissemination of deidentified patient information.

Setting. The study center is a tertiary center for the management of venous and lymphatic disorders.

Participants. Patients with chronic venous disease who underwent a CT scan and LSG of the lower extremities as part of diagnostic workup formed the study cohort. Patients with phlebolymphedema from acute deep venous thrombosis of the lower extremity and those with primary lymphedema or secondary lymphedema from non-venous causes were excluded. Also excluded were patients with other medical causes of leg edema (congestive heart failure, renal insufficiency, and hepatic insufficiency, among others).

CT scan. The 128-slice Siemens scanner (Siemens Healthineers, Erlangen, Germany) was used to perform CT scans. Because the CT scans were performed for the diagnosis of suspected femoroiliocaval obstruction, contrast enhancement was typically used to opacify the veins. When contrast was unable to be used owing to patient-related factors, a CT scan was done without contrast using a similar imaging protocol. With regard to the assessment of phlebolymphedema on CT scans, characteristics used included skin thickening, muscle compartment (MC) edema, and subcutaneous interstitial edema (honeycombing). The use of contrast did not make a difference; that is, there was no difference between contrast-enhanced and noncontrast-enhanced CT scans.

Lymphoscintigraphy. Lymphoscintigraphy (LSG) was performed via injection of approximtely 600 mCi of technetium-99m-labeled sulfur colloid radiotracer (filtered) into the intradermal space between the first and second toes using a 27G needle and tuberculin syringe. Patients were then asked to ambulate for 15 minutes. The feet were massaged for 15 minutes if the patient was unable to ambulate. LSG was then performed using a gamma camera with a large field of view, high resolution, and the collimator set on low energy. If a delay occurred in radiotracer uptake, reuptake images were obtained at 40 and 60 minutes. Images were saved on dual intensity whole-body display with masking and unmasking of injection sites. The LSG findings were scored using semiquantitative analysis and visual interpretation. This scoring represents an adaptation of the Mayo Clinic transport index derived from Kleinhans et al's scoring system.[4,8,9] Each limb was scored to have mild, moderate, or severe lymphedema.[9] Both the LSG technique and scoring system used have been described in prior publications.[3,9]

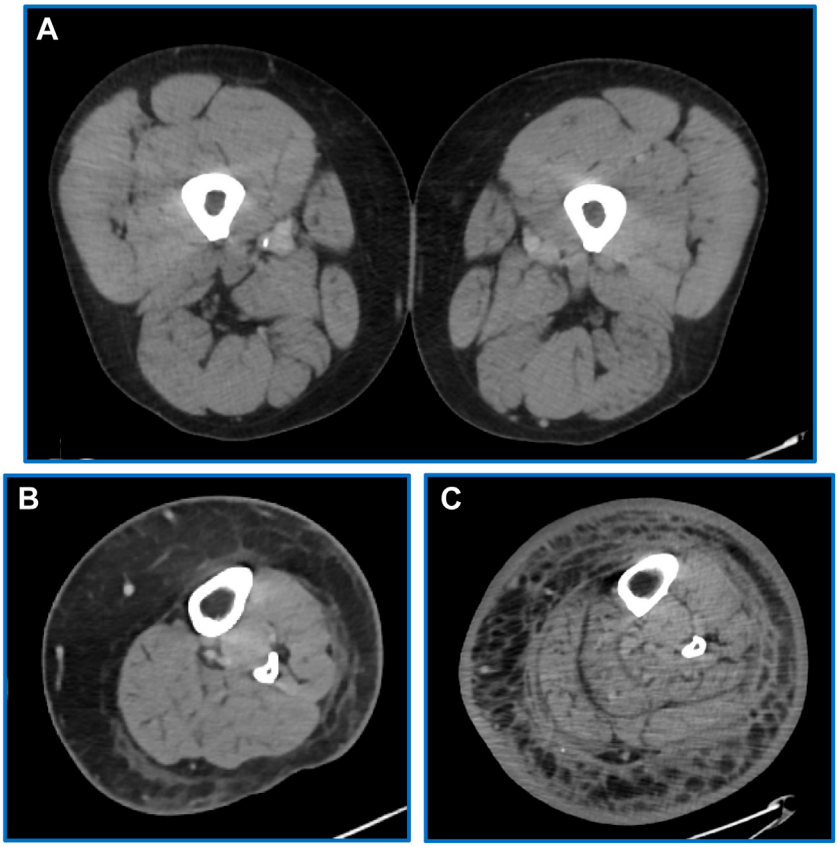

Fig 1. A) Normal skin without any thickening noted. **(B** and **C)** Skin thickening with **(C)** having greater skin thickening than **(B)**. **(C)** Also has extensive subcutaneous interstitial edema/honeycombing.

Stenting and follow-up. Patients presenting with quality-of-life-impairing symptoms owing to CIVO (Clinical, Etiological, Anatomical, and Pathophysiological [CEAP] class 4-6 or CEAP class 3 with no improvement from conservative therapy) underwent intravascular ultrasound (IVUS) interrogation for confirmation of the diagnosis and subsequent stenting. Clinical manifestations of CIVO include pain, tightness, swelling, heaviness, venous claudication, leg cramps, hyperpigmentation, lipodermatosclerosis, and/or venous stasis ulcers. Procedural access was obtained through the femoral or popliteal vein (dictated by best inflow). Flow characteristics were evaluated using venography, followed by IVUS investigation. Normal luminal areas in the common femoral, external iliac and common iliac veins of 125 mm^2, 150 mm^2, and 200 mm^2, respectively, were used as cutoffs for confirming the diagnosis of obstruction.[10] Luminal areas less than these values justified predilation, stenting, and postdilation.[11] Stent diameters were determined using the inflow channel luminal area.[12] The stent length extended from an area of good inflow to good outflow. Both IVUS interrogation and venography were performed after stenting to ensure the adequacy of angioplasty/stenting and determine final flow dynamics. Technique of stenting, perioperative and postoperative care, and follow-up have been outlined previously.[12,13]

Reintervention. In patients with recurrent quality-of-life-impairing symptoms, repeat IVUS interrogation was performed to correct the etiology of stent malfunction. Such malfunctions included in-stent restenosis, stent compression, a combination of both in-stent restenosis and stent compression, or stent occlusion. Diagnosis and technique of correction of stent malfunction have been previously described.[14,15]

Measurements. Three raters blinded to the patients' ISL stage and LSG results collected data from the CT images in the thigh (20 cm above the apex of the patella), leg (10 cm below the apex of the patella), and ankle (5 cm above the lateral malleolus). Values taken at each level included the skin thickening (present/absent), subcutaneous interstitial edema (also termed 'honeycombing': grades 0 to 2) and MC edema (grades 0 to 2). The severity of honeycombing and MC edema were subjectively assessed. Honeycombing was categorized as 0— no honeycomb pattern; 1— focal areas of honeycombing; and 2— circumferential/near circumferential areas of

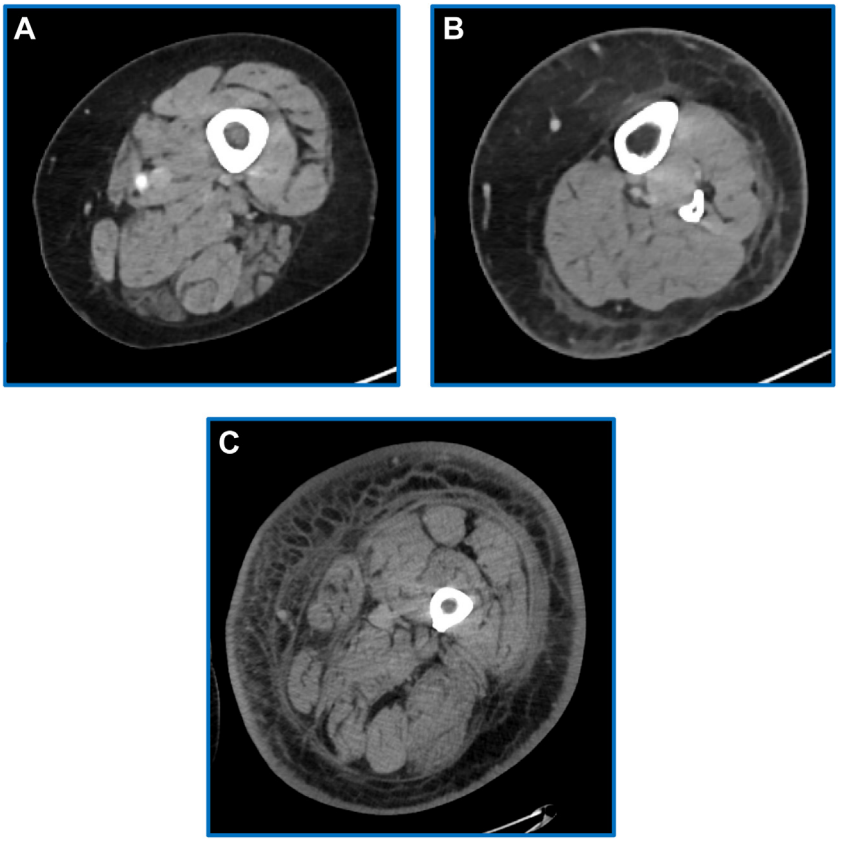

Fig 2. Grades of subcutaneous interstitial edema/honeycombing. **(A)** Grade 0 (normal: no honeycombing), **(B)** Grade 1 (focal areas of honeycombing). **(C)** Grade 2 (near circumferential or circumferential honeycombing).

honeycombing. MC edema was categorized as 0— absent; 1— partial blurring of muscular compartments; and 2— no differentiation between muscular compartments/complete blurring of muscle compartments. The grading of each variable is considered in Figs 1-3. These CT variables have been previously noted to be suggestive of a diagnosis of lymphedema.[16-19] Agreement from two of three raters determined values of skin thickening, honeycombing, and MC edema used for analysis. In the case of total disagreement, the three raters met, and regraded the limb to come to single value which was then used for the analysis. Skin thickening, honeycombing, and MC edema scores for each limb were determined by taking the most severe value of the three levels. Overall CT grade for analysis was determined by the median value between skin thickening, honeycombing, and MC edema. Clinical metrics evaluated included the CEAP clinical class in addition to the International Society of Lymphedema stage for each limb as well as grade of swelling (GOS). ISL grade was categorized as 0— latent or subclinical condition with no swelling evident; 1— early accumulation of fluid that subsides with elevation (pitting may occur); 2— involves changes in solid structures where limb elevation rarely reduces swelling and pitting is present; and 3— lymphostatic elephantiasis and skin changes have developed. LSG was graded into normal, mild, moderate, or severe disease for each limb based on five variables (Table I). GOS was evaluated as 0— no swelling; 1— pitting with nonobvious swelling; 2— visible ankle swelling; 3— gross swelling involving the leg up to the knee; and 4— gross swelling involving the entire leg including the thigh.

Statistical analysis. Statistical analysis was performed using prism version 10.2 (GraphPad)/SPSS statistics version 29 (IBM Corp) with each lower limb used as the unit of analysis. Spearman correlations were performed to investigate relationships between CT findings, ISL staging, GOS, and LSG severity. Analysis was also carried out to determine sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the CT variables in making a diagnosis of phlebolymphedema with ISL stage and LSG used independently as reference.

RESULTS

There was a total of 50 limbs (35 patients). The median age for the entire cohort was 63 years, with a preponderance of women (n = 28) and right laterality (28 limbs). The median body mass index was 38. Of the 35 patients (50 limbs), 28 were female, with left laterality noted in 22 limbs. CEAP clinical class for the cohort included class C0 to 2, 4 limbs (8%); C3, 13 limbs (26%); C4, 17 limbs (34%); C5, 9 limbs (18%); and C6, 7 limbs (14%). Thirty-one limbs

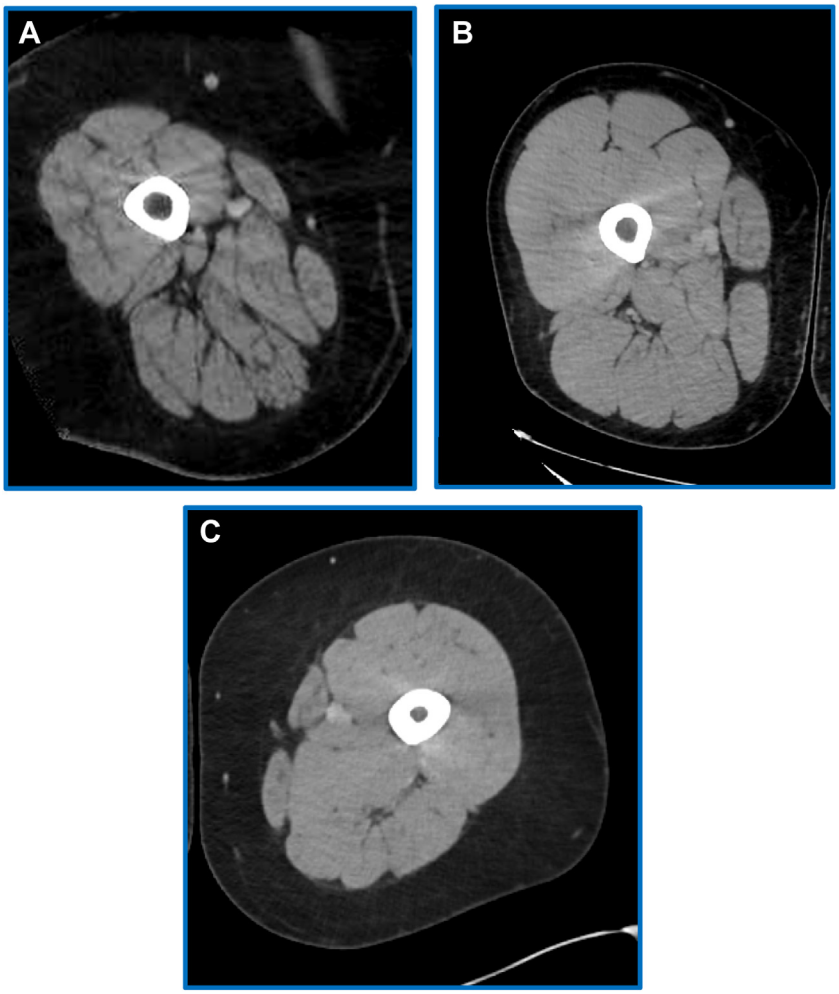

Fig 3. Grades of intramuscular edema. **(A)** Grade 0 (normal: no edema). **(B)** Grade 1 (partial blurring of muscle compartments [MCs]). **(C)** Grade 2 (complete blurring/no differentiation of MCs).

underwent stenting for CIVO after having failed conservative therapy. Of the 50 limbs, 8 (16%) were ISL stage 0, 10 (20%) ISL stage 1, 2 (4%) ISL stage 2, and 30 (60%) ISL stage 3. With LSG, 6 (12%) had a normal study, 21 (42%) mild disease, 0 (0%) moderate disease, and 23 (46%) severe disease. Thirty-six limbs (72%) had a diagnosis of phlebolymphedema on both ISL and LSG. Six limbs (12%) had phlebolymphedema as assessed by ISL stage but negative for phlebolymphedema as assessed by LSG, and 8 limbs (16%) had phlebolymphedema on LSG, but no phlebolymphedema as assessed by ISL stage. The correlation between ISL stage and LSG was poor ($r = -0.16$; $P = .26$). The correlation between ISL stage and GOS was good ($r = -0.63$; $P = .001$), whereas the correlation between GOS and ISL stage was weak ($r = 0.29$; $P = .04$).

CT diagnosis of phlebolymphedema using ISL stage as reference. When the ISL stage was used as a reference to diagnose phlebolymphedema, it was found that skin

Table I. Lymphoscintigraphic criteria for diagnosis of lymphedema

Variable	Normal	Mild	Moderate	Severe
Lymph nodes (n)	≥5	≤4 - abnormal		
Collateral channels	None	Present - abnormal		
Intensity of uptake	Normal	Reduced - abnormal		
Popliteal node(s)	Absent	Present - abnormal		
Transit time delay	<20 min	20-40 min	40-60 min	>60 min
Dermal backflow		Absent - normal		Present

Table II. Diagnostic performance characteristics of computed tomography (CT) with International Society of Lymphedema (ISL) stage as reference

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy
Skin thickening	95%	75%	95%	75%	92%
Honeycombing	100%	0%	84%	–	84%
Intramuscular edema	100%	0%	84%	–	84%
Any 1 variable	100%	0%	84%	–	84%
Any 2 variables	100%	0%	84%	–	84%
All 3 variables	93%	63%	93%	63%	88%

NPV, Negative predictive value; *PPV,* positive predictive value.
The NPV refers to inability to calculate on account of absence of true negatives.

thickening had a sensitivity of 95%, a specificity of 75%, and an accuracy of diagnosis of 92%. Honeycombing on CT had a sensitivity of 100%, a specificity of 0%, and an accuracy of diagnosis of 84%. When MC edema was used, the sensitivity was 100%, specificity was 0%, and accuracy of diagnosis was 84%. Use of any one or any two of these three variables to make a diagnosis of phlebolymphedema resulted in a sensitivity of 100%, specificity of 0%, and an accuracy of diagnosis of 84%. When the presence of all three variables was required to make a diagnosis of phlebolymphedema, the sensitivity was 93%, specificity was 63%, and accuracy of diagnosis was 88%. Details of performance characteristics are considered in Table II.

CT diagnosis of phlebolymphedema using lymphoscintigram as reference. When the lymphoscintigram results were used as a reference to diagnose phlebolymphedema, it was found that skin thickening had a sensitivity of 82%, a specificity of 0%, and an accuracy of diagnosis of 72%. Honeycombing on CT had a sensitivity of 100%, a specificity of 0%, and an accuracy of diagnosis of 88%. When MC edema was used, the sensitivity was 100%, specificity was 0%, and accuracy of diagnosis was 88%. The use of any one or any two of these three variables to make a diagnosis of lymphedema resulted in a sensitivity of 100%, specificity of 0%, and an accuracy of diagnosis of 88%. When the presence of all three variables was required to make a diagnosis of lymphedema, the sensitivity was 82%, specificity was 0%, and accuracy of diagnosis was 72%. Details of performance characteristics are considered in Table III.

Severity of CT characteristics based on limb location. When the severity of each of the three CT variables for each study limb was compared based on location (thigh vs calf vs ankle), it was found that there was no significant difference between skin thickening in the thigh vs calf vs ankle ($P = .5$). MC edema, however, worsened from thigh to calf ($P < .0001$) without a difference between calf and ankle ($P = .3$). The severity of honeycombing was worst in the ankle and least in the thigh with a significant difference between all three sites ($P = .008$).

Inter-rater comparisons. Inter-rater comparisons were made for each of the three CT variables. For skin thickening, Cohen's kappa was 0.2 ($P = .23$) between raters 1 and 2, 0.2 ($P = .74$) between raters 1 and 3, and 0.3 ($P = .004$) between raters 2 and 3. For MC edema, Cohen's kappa was 0.3 ($P = .03$) between raters 1 and 2, 0.5 ($P < .001$) between raters 1 and 3, and 0.3 ($P = .01$) between raters 2 and 3. For honeycombing, Cohen's kappa was 0.6 ($P < .001$) between raters 1 and 2, 0.6 ($P < .001$) between raters 1 and 3, and 0.7 ($P < .001$) between raters 2 and 3.

DISCUSSION

Lymphedema is a relatively common problem encountered in patients presenting to vascular clinics with leg edema. However, the diagnosis, especially clinical, remains a challenge, resulting in undiagnosed or misdiagnosed patients. A clinical diagnosis of lymphedema is problematic with a study noting that in patients with LSG-confirmed lymphedema, only 17% had positive clinical signs. Of the clinical signs, the study indicated that the Kaposi-Stemmer sign was the only significant predictor of lymphedema (odds ratio, 7.9; $P = .02$).[3] Although the International Society of Lymphology (ISL) staging of lymphedema is accepted widely, findings in the early stages (stage I and early stage II) could also be seen in edema from other conditions. This finding underscores the need for confirmation of lymphedema through diagnostic testing. LSG is usually the test used for such confirmation,[20] although in years past pedal lymphangiography and more recently ICG lymphography have been used. Each of these has its drawbacks including the need for isotope injection and radiation exposure for LSG; identification of lymphatic vessel(s), cutdown and exposure of the vessel, and ethiodized oil injection to opacify the lymphatic vessels in pedal

Table III. Diagnostic performance characteristics of computed tomgoraphy (CT) with lymphoscintigram as reference

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy
Skin thickening	82%	0%	86%	0%	72%
Honeycombing	100%	0%	88%	–	88%
Intramuscular edema	100%	0%	88%	–	88%
Any 1 variable	100%	0%	88%	–	88%
Any 2 variables	100%	0%	88%	–	88%
All 3 variables	82%	0%	86%	0%	72%

NPV, Negative predictive value; *PPV*, positive predictive value.
The NPV refers to inability to calculate on account of absence of true negatives.

lymphangiogram; and the difficulty in visualizing the deep lymphatic channels besides the challenge of capturing the entire limb during ICG lymphography. CT scans, in contrast, are widely available and represent a quick and easily performed study. These advantages persist when compared with magnetic resonance imaging as well. However, there is the issue of radiation exposure with CT scans. On balance, however, a CT scan represents an easier test to confirm the diagnosis of lymphedema when compared with other tests, particularly when trying to make the diagnosis without a referral to a higher acuity facility.

ISL and LSG in the diagnosis of lymphedema. Although the ISL staging of lymphedema is a commonly used tool and LSG is often considered the gold standard for diagnosing lymphedema,[21-23] the correlation between the two has not been studied thoroughly. In fact, a couple of studies[24,25] that evaluated LSG against ICG lymphography used the ISL stage as the reference. Using this factor, they noted that ICG is perhaps a better test; however, this result ignores the basic concept that characteristics of ISL staging stage I and II include pitting edema and amelioration of edema with leg elevation can be noted in other forms of edema as well. So, the use of ISL stage to help validate a confirmatory diagnostic test is problematic. Patients in our study had other causes of edema, including primary and secondary lymphedema (besides venous lymphedema) ruled out. When focused on lymphedema owing to venous etiology (phlebolymphedema) alone, the correlation between ISL stage and LSG was poor ($r = -0.16$; $P = .26$), even though 72% of limbs had a diagnosis of phlebolymphedema on both ISL and LSG. This finding underscores the need for a better clinical staging system for lymphedema.

The role of CT in the diagnosis of lymphedema. Over the years, multiple studies have evaluated the CT characteristics of lymphedema. Hadjis et al[16] in their evaluation of 12 patients with primary lymphedema of the lower limb noted that a characteristic honeycomb pattern of the subcutaneous compartment could be seen in 10 of these patients. CT scans in nine other patients with a swollen leg secondary to chronic venous disease or lipedema did not show this characteristic pattern.[16] Several years later, Marotel et al[17] in their review of 11 patients with unilateral lower limb lymphedema confirmed on LSG, observed the findings of soft tissue stranding, skin thickening, fat deposition in the epifascial compartment, and perimuscular fascial thickening/edema and related it to lymph stasis. Monnin-Delhom et al[18] in their study of 76 swollen limbs in 55 patients noted a sensitivity and specificity of CT scan for the diagnosis of lymphedema as being 93 and 100%, respectively; for lipedema, it was 95 and 100%, respectively; and for deep vein thrombosis (DVT) it was 91 and 99%, respectively. Skin thickening was found in 42 of 44 limbs with lymphedema (95%), in 9 of 12 limbs with DVT (75%), and in 2 of 20 limbs with lipedema (10%).[18] Subcutaneous edema accumulation was demonstrated in 42 legs (95%) with lymphedema and in 5 (42%) with DVT, but in none with lipedema. A honeycombed pattern was present only in lymphedema, whereas muscle enlargement was present in all patients with DVT, 9% of limbs with lymphedema, and no limbs with lipedema.[18] Weiss et al[26] noted the addition of single photon emission CT (SPECT) to LSG improved the anatomical correlation of lymphatic disorders and thereby enhanced the assessment of the extent of pathology owing to the particular advantages of tomographic separation of overlapping sources. Shin et al[19] in their comparison of characteristic CT findings of lymphedema, cellulitis, and generalized edema found that, although honeycombing is seen commonly in lymphedema, it was not a specific finding. The authors notes that inguinal lymph node enlargement is a specific sign of cellulitis, whereas truncal edema and bone marrow edema were specific findings of generalized edema.[19] More recently, Yamada et al[27] evaluated the use of interstitial CT-lymphography (intradermal injection of iopamidol into foot web space > CT > three-dimensional reconstruction) and found that it provided detailed three-dimensional imaging of the lymphatic system in lymphedema patients. However, such a CT scan in most cases provided adequate

visualization only up to the leg (knee).[27] Considering these studies, performed at various time points over the last 35 years, skin thickening, subcutaneous interstitial edema, and intramuscular edema seem to be noteworthy characteristics of lymphedema on CT and were evaluated in this study.

Impact of correlation coefficients of the CT variables. There was wide variation in the inter-rater agreement between the three raters depending on the variable assessed. For skin thickening, Cohen's kappa ranged from 0.2 to 0.3, indicating mostly fair agreement. For honeycombing, however, Cohen's kappa was 0.6 to 0.7, indicating substantial agreement. For MC edema, Cohen's kappa varied from 0.3 to 0.5, indicating again mostly fair agreement. So, if one were to choose a variable that could have the greatest agreement between assessors it would be honeycombing.

Using CT variables to make a diagnosis of phlebolymphedema. The diagnosis of lower extremity phlebolymphedema on CT depends on the reference standard used, ISL stage vs lymphoscintigram. With the ISL stage, the use of skin thickness offered the greatest sensitivity, specificity, and accuracy. With LSG, the use of subcutaneous interstitial edema (honeycombing) or MC edema, offers high sensitivity and accuracy but with low specificity. When the results of diagnostic testing of the three CT variables are combined with inter-rater agreement, the variable that stands out is subcutaneous interstitial edema or honeycombing. This variable had excellent sensitivity and accuracy with both ISL grade (100% and 84%) and LSG (100% and 88%), but very low specificity (0%). These findings are indicative of the fact that CT scan can be used as a screening tool for phlebolymphedema with honeycombing serving as a best diagnostic variable. Thus, using CT scanning, even lay practitioners can make a diagnosis of lymphedema and arrange for therapy or referral as appropriate.

The relatively small sample size of the study is a limitation. Additionally, the study had more patients with advanced ISL stage (stage III), which may have had an impact as well. The study cohort had 66% of limbs with CEAP C4 or higher clinical class (ie, limbs with end-organ damage, namely, hyperpigmentation, lipodermatosclerosis, and/or venous leg ulcers [active/healed]). This tilt toward more severe disease likely impacts the generalizability to the entire chronic venous disease population (C0-6). The quantum of limbs with no disease in this cohort either on ISL grade (grade 0 = 16%) and LSG (normal = 12%) is small and impacts the diagnostic assessment. The absence of true negatives for certain variables also represents a concern; however, this factor is more of a reflection of the impact of the reference used than the CT variable per se. Despite these shortcomings, this study represents one of the first of its kind to specifically evaluate the role of CT scanning in the diagnosis of phlebolymphedema.

CONCLUSIONS

A CT scan can be used as a screening tool for phlebolymphedema in the lower extremities using tissue characteristics, including skin thickening, subcutaneous interstitial edema/honeycombing, and/or MC edema. The diagnostic capacity of each variable either alone or in combination is a function of the reference standard used, ISL stage vs lymphoscintigram. When ISL grade is used, skin thickness offers the highest sensitivity, specificity, and accuracy. However, when LSG is used as the reference, honeycombing or MC edema offers high sensitivity and accuracy but low specificity. Factoring in inter-rater agreement, honeycombing was noted to be the best CT variable to diagnose phlebolymphedema. Further study is warranted.

AUTHOR CONTRIBUTIONS

Conception and design: AJ
Analysis and interpretation: DT, AJ
Data collection: DT, TP, AJ
Writing the article: DT, TP, AJ
Critical revision of the article: DT, TP, AJ
Final approval of the article: DT, TP, AJ
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DT TP contributed equally to this article and share co-first authorship.

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REFERENCES

1. Dean SM, Valenti E, Hock K, Leffler J, Compston A, Abraham WT. The clinical characteristics of lower extremity lymphedema in 440 patients. *J Vasc Surg Venous Lymphat Disord*. 2020;8:851–859.
2. Raju S, Furrh JBt, Neglen P. Diagnosis and treatment of venous lymphedema. *J Vasc Surg*. 2012;55:141–149.
3. Jayaraj A, Raju S, May C, Pace N. The diagnostic unreliability of classic physical signs of lymphedema. *J Vasc Surg Venous Lymphat Disord*. 2019;7:890–897.
4. Gloviczki P, Calcagno D, Schirger A, et al. Noninvasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphic examinations. *J Vasc Surg*. 1989;9:683–689. discussion: 90.
5. Ter SE, Alavi A, Kim CK, Merli G. Lymphoscintigraphy. A reliable test for the diagnosis of lymphedema. *Clin Nucl Med*. 1993;18:646–654.
6. Hassanein AH, Maclellan RA, Grant FD, Greene AK. Diagnostic accuracy of lymphoscintigraphy for lymphedema and analysis of False-negative tests. *Plast Reconstr Surg Glob Open*. 2017;5:e1396.
7. Hidding JT, Viehoff PB, Beurskens CH, van Laarhoven HW, Nijhuis-van der Sanden MW, van der Wees PJ. Measurement properties of instruments for measuring of lymphedema: systematic review. *Phys Ther*. 2016;96:1965–1981.
8. Kleinhans E, Baumeister RG, Hahn D, Siuda S, Bull U, Moser E. Evaluation of transport kinetics in lymphoscintigraphy: follow-up study in patients with transplanted lymphatic vessels. *Eur J Nucl Med*. 1985;10:349–352.

9. Jayaraj A, Thaggard D, Raju S. Inguinal intranodal lymphangiography reveals a high incidence of suprainguinal lymphatic disease in patients with leg edema undergoing stenting for symptomatic chronic iliofemoral venous obstruction. *J Vasc Surg Venous Lymphat Disord*. 2023;11:1192–11201.e2.
10. Raju S, Buck WJ, Crim W, Jayaraj A. Optimal sizing of iliac vein stents. *Phlebology*. 2018;33:451–457.
11. Jayaraj A, Powell T, Raju S. Utility of the 50% stenosis criterion for patients undergoing stenting for chronic iliofemoral venous obstruction. *J Vasc Surg Venous Lymphat Disord*. 2021;9:1408–1415.
12. Jayaraj A, Thaggard D, Lucas M. Technique of stent sizing in patients with symptomatic chronic iliofemoral venous obstruction-the case for intravascular ultrasound-determined inflow channel luminal area-based stenting and associated long-term outcomes. *J Vasc Surg Venous Lymphat Disord*. 2023;11:634–641.
13. Jayaraj A, Noel C, Kuykendall R, Raju S. Long-term outcomes following use of a composite Wallstent-Z stent approach to iliofemoral venous stenting. *J Vasc Surg Venous Lymphat Disord*. 2021;9:393–400.e2.
14. Jayaraj A, Fuller R, Raju S, Stafford J. In-stent restenosis and stent compression following stenting for chronic iliofemoral venous obstruction. *J Vasc Surg Venous Lymphat Disord*. 2022;10:42–51.
15. Jayaraj A, Crim W, Knight A, Raju S. Characteristics and outcomes of stent occlusion after iliocaval stenting. *J Vasc Surg Venous Lymphat Disord*. 2019;7:56–64.
16. Hadjis NS, Carr DH, Banks L, Pflug JJ. The role of CT in the diagnosis of primary lymphedema of the lower limb. *AJR Am J Roentgenol*. 1985;144:361–364.
17. Marotel M, Cluzan R, Ghabboun S, Pascot M, Alliot F, Lasry JL. Transaxial computer tomography of lower extremity lymphedema. *Lymphology*. 1998;31:180–185.
18. Monnin-Delhom ED, Gallix BP, Achard C, Bruel JM, Janbon C. High resolution unenhanced computed tomography in patients with swollen legs. *Lymphology*. 2002;35:121–128.
19. Shin SU, Lee W, Park EA, Shin CI, Chung JW, Park JH. Comparison of characteristic CT findings of lymphedema, cellulitis, and generalized edema in lower leg swelling. *Int J Cardiovasc Imaging*. 2013;29(Suppl 2):135–143.
20. Executive Committee of the International Society of L. The diagnosis and treatment of peripheral lymphedema: 2023 consensus document of the international society of lymphology. *Lymphology*. 2023;56:133–151.
21. Akita S, Mitsukawa N, Kazama T, et al. Comparison of lymphoscintigraphy and indocyanine green lymphography for the diagnosis of extremity lymphoedema. *J Plast Reconstr Aesthet Surg*. 2013;66:792–798.
22. Villa G, Campisi CC, Ryan M, et al. Procedural recommendations for lymphoscintigraphy in the diagnosis of peripheral lymphedema: the genoa protocol. *Nucl Med Mol Imaging*. 2019;53:47–56.
23. Barbieux R, Roman MM, Riviere F, et al. Scintigraphic investigations of the deep and superficial lymphatic systems in the evaluation of lower limb oedema. *Sci Rep*. 2019;9:13691.
24. Mihara M, Hara H, Narushima M, et al. Indocyanine green lymphography is superior to lymphoscintigraphy in imaging diagnosis of secondary lymphedema of the lower limbs. *J Vasc Surg Venous Lymphat Disord*. 2013;1:194–201.
25. Figueroa BA, Lammers JD, Al-Malak M, Pandey S, Chen WF. Lymphoscintigraphy versus indocyanine green lymphography—which should be the gold standard for lymphedema imaging? *Lymphatics*. 2023;1:25–33.
26. Weiss M, Baumeister RG, Frick A, Wallmichrath J, Bartenstein P, Rominger A. Primary lymphedema of the lower limb: the clinical utility of single photon emission computed tomography/CT. *Korean J Radiol*. 2015;16:188–195.
27. Yamada K, Shinaoka A, Kimata Y. Three-dimensional imaging of lymphatic system in lymphedema legs using interstitial computed tomography-lymphography. *Acta Med Okayama*. 2017;71:171–177.

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