Original Article

Using four-point subcutaneous injection of lymphatic contrast-enhanced ultrasound to diagnose lymphedema of lower extremity

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Background: The diagnosis of lymphedema primarily relies on the clinical symptoms, signs, medical history and imaging. Objective lymphatic imaging helps improving the diagnosis of lymphedema. This study aimed to develop an effective imaging tool to diagnose lymphedema.

Methods: This is a single-center retrospective study. From September 2022 to November 2023, we enrolled thirty-two patients, involving 40 lower extremities who underwent lymphatic contrast-enhanced ultrasound (CEUS) following a subcutaneous injection of contrast agent at four points in the First Affiliated Hospital of Sun Yat-sen University. Cohen's kappa value, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated. Lymphoscintigraphy was the reference standard.

Results: Successful lymphatic-CEUS detection was defined as the situation that lymphatic drainage of medial or lateral lower limbs were observed. The successful detection rate was 100% (40 of 40). The diagnosis of lymphedema was based on the presence of either medial or lateral lymphatic obstructions, or subcutaneous lymphatic enhancement. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for diagnosing lymphedema by lymphatic-CEUS were as follows: 91.2% (31 of 34), 100% (6 of 6), 100% (31 of 31), 66.7% (6 of 9) and 92.5% (37 of 40), respectively. The Cohen's Kappa value was 0.756. The area under the receiver operating characteristic curve (AUC) for the subcutaneous injection of four-point lymphatic-CEUS was 0.956.

Conclusions: This study put forward a novel four-point lymphatic-CEUS method to detect the functions of the lymphatics of lower extremities and established a lymphatic-CEUS standard for diagnosing lymphedema of lower extremities. Four-point lymphatic-CEUS is a considerable option for diagnosing lymphedema of lower extremities.

Keywords: Contrast-enhanced ultrasound (CEUS); lower extremity; lymphedema; lymphoscintigraphy

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Introduction

Dysfunction of the lymphatic system, a part of the circulatory system and immune system, leads to multiple diseases (1-3). The diagnosis of lymphedema primarily relies on the clinical symptoms, signs, medical history and imaging. To date, lymphoscintigraphy (4), computed tomography (CT), magnetic resonance lymphography (MRL) (5), ultrasound (US) (6,7) and near-infrared fluorescence lymphangiography (NIRF-L) (8) provide objective evidences for diagnosing lymphedema. So far, lymphoscintigraphy is the gold standard for lymphedema diagnosis and staging (9-11). It takes overview of the lymphatic uptake of the 99m-Technetium-labeled agent and diagnoses lymphedema by evaluating the visualization of lymph nodes, lymphatic vessels and dermal backflow (11,12). However, the patients and therapists have to expose to the radiation and it takes a long time to perform the lymphoscintigraphy imaging. There is a lack of a cost-effective, with no radiation and high-resolution novel imaging to detect the functions of the lymphatics.

US is used widespread for diseases screening and diagnosis because it is low-cost, real-time and with no radiation. Contrast-enhanced ultrasound (CEUS), a novel technique combined convention US and microbubbles, improves the diagnoses of diseases by distinguishing the details among the differential pathologies of masses (13,14), showing the microcirculations of tissues (15,16) and so on. The recent studies showed that lymphatic-CEUS has a good performance to locate the sentinel lymph nodes of breast cancer after injecting the contrast agents in the peri-areolar area (17-19). Interestingly, the lymphatic-CEUS was used to map the lymphatic vessels of upper extremities before performing lymphaticovenous anastomosis (LVA) surgery (20). However, whether the lymphatic-CEUS can be used to detect the functions of the lymphatics of lower extremities still remain uncertain. In addition, a proper method to perform the lymphatic-CEUS of lower extremities and the suitable diagnosis standard are needed.

In this study, we present a novel method with subcutaneous injection of four-point lymphatic-CEUS novel method to detect the functions of the lymphatics of lower extremities. We put forward a diagnosis method of the four-point lymphatic-CEUS to diagnose patients with lymphedema of lower extremities, suggesting that the four-point lymphatic-CEUS would be a considerable option for lower extremities lymphedema diagnosis. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-300/rc).

Methods

Study design

This is a single-center retrospective study. We enrolled the patients who underwent four-point lymphatic-CEUS for the diagnosis lymphedema of lower extremities in The First Affiliated Hospital of Sun Yat-sen University from September 2, 2022 to November 30, 2023. In total, forty extremities were involved. Among them, thirty-four extremities were diagnosed as lymphedema and six extremities were diagnosed as non-lymphedema. Lymphoscintigraphy was the reference standard. Time interval of the lymphatic-CEUS and lymphoscintigraphy was within one month. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of The First Affiliated Hospital of Sun Yat-sen University (No. [2023]641) and informed consent was taken from all the patients.

Lymphatic-CEUS imaging protocol

US doctors with more than 10-year experience in US performed all the lymphatic-CEUS scans in this study. We used the US imaging system (Sequoia, Siemens Healthineers, Erlangen, Germany) and the Sequoia 10L4 linear array transducer for scanning the multimode ultrasonic technologies, including B-mode US, color Doppler flow imaging (CDFI) and CEUS. The contrast agent SonoVue (Bracco, Milan, Italy) was mixed with 5 mL of saline and injected 0.8–1.0 mL to each injection point successively. We performed lymphatic-CEUS to detect the lymphatics of lower extremities by subcutaneously injecting four points in the foot (referred as four-point lymphatic-CEUS): below the medial malleoli (Point 1), the arch of foot (Point 2), below the lateral malleoli (Point 3) and the calcaneal tuberosity (Point 4, *Figure 1*). The injection points were selected based on the previous anatomical studies of lymphatic vessels of lower extremities (anteromedial, anterolateral, posteromedial and posterolateral around the ankle) (21).

Firstly, we detected the functions of the medial lymphatic vessels of the lower limbs. We subcutaneously injected the contrast agents in point 1 to 3 successively

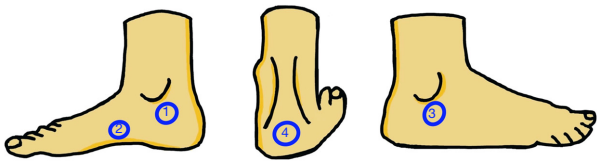


Figure 1 Schematic diagram of the injection points. Point 1, below the medial malleoli; Point 2, the arch of foot; Point 3, below the lateral malleoli; Point 4, the calcaneal tuberosity.

Table 1 The characteristics of lower extremities

Characteristics	Values (n=40)
Age (years)	60 (24–85)
Sex	
Male	5
Female	35
Surgery	
Yes	35
No	5
Radiotherapy	
Yes	12
No	28
Diagnosed by lymphoscintigraphy	
Primary lymphedema	4
Secondary lymphedema	30
Non-lymphedema	6
Diagnosed by CEUS	
Lymphedema	31
Non-lymphedema	9

Data are presented as median (range) or number. CEUS, contrast-enhanced ultrasound.

(*Figure 1*), pressed around the injection points. We scanned around the injection point immediately after the injection respectively, observed the movement of the contrast agents and noted whether the contrast agents ran to the lymph nodes. In general, we can immediately observe and trace the enhanced lymphatics after the injection. If we failed to trace the track in approximately six minutes, we needed to reinject. Then, we subcutaneously injected the contrast agents in point 4 (*Figure 1*), which were mainly draining to the lateral lymphatic vessels of the lower limbs. In the meantime, we needed to observe the subcutaneous lymphatics enhancement. We defined the lymphatic drainage obstructions as the contrast agents being failed to run from the injection points to the lymph nodes along the linear lymphatic vessels. Finally, we recorded the medial lymphatics obstructions, the lateral lymphatics obstructions and the subcutaneous lymphatics enhancement.

Statistical analysis

We used the SPSS software (version 26.0) to calculate the Cohen's kappa value, sensitivity, specificity, positive predictive value, negative predictive value and accuracy for evaluating the diagnosis efficacy of lymphatic-CEUS.

Results

Totally, thirty-two participants were enrolled in this study (five men and twenty-seven women; age range from 24 to 85 years). We examined forty lower extremities by four-point lymphatic-CEUS and the characteristics are shown in *Table 1*. We defined successful lymphatic-CEUS as the situation that lymphatic drainage of medial or lateral lower limbs were observed. The successful detection rate was 100%, including 26 extremities with the medial lymphatics obstructions, 18 extremities with the lateral lymphatics obstructions and 30 extremities with subcutaneous lymphatic enhancement.

Considering lymphatic obstructions lead to lymphedema, we diagnosed lymphedema when either the medial lymphatics obstructions (drainage after injecting point 1 to 3) or the lateral lymphatics obstructions (drainage after injecting point 4), or the subcutaneous lymphatics enhancement were observed (*Figure 2*, *Videos 1*,*2*). In this study, all the extremities underwent lymphoscintigraphy. In terms of the diagnosis result, 34 of 40 extremities were diagnosed as lymphedema and 6 of 40 extremities were diagnosed as non-lymphedema. In terms of the four-point lymphatic-CEUS result, 31 of 40 extremities were diagnosed as lymphedema and 9 of 40 extremities showed no lymphatic obstructions. The Cohen's Kappa value was 0.756, indicating excellent consistence. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for diagnosing lymphedema by four-point lymphatic-CEUS were as follows: 91.2% (31 of 34), 100% (6 of 6), 100% (31 of 31), 66.7% (6 of 9) and 92.5% (37 of 40), respectively. The area under the receiver operating characteristic curve (AUC) for diagnosing

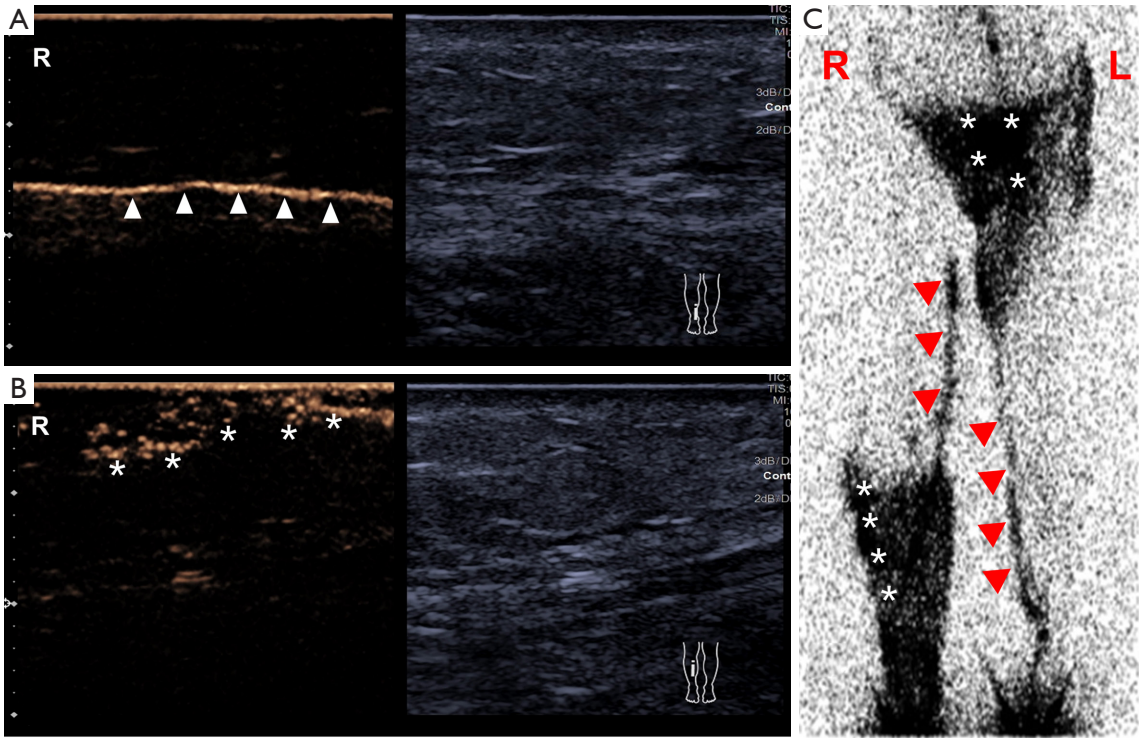
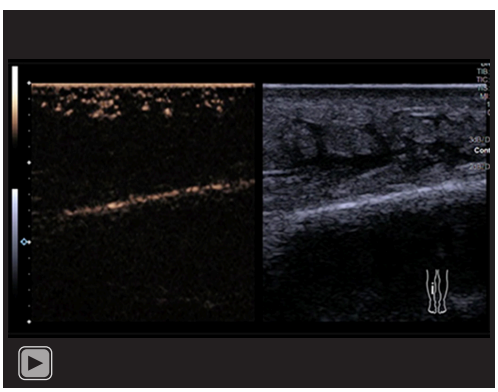
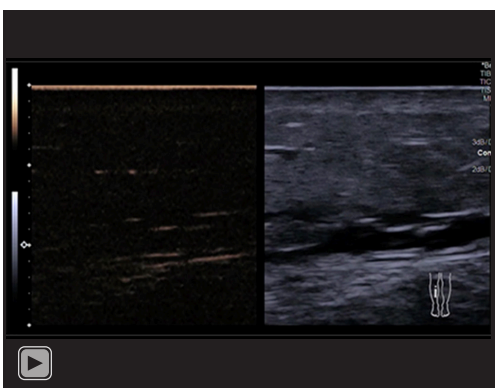


Figure 2 A 65-year-old woman diagnosed with lymphedema in both lower extremities after gynecological malignant tumor surgery and radiation therapy. (A) Lymphatic-CEUS showed that there was a linear lymphatic vessel of the right calf (white triangle), but it was obstructed in the right thigh. (B) Subcutaneous enhancement was observed in the right calf (white star), leading to diagnose of lymphedema by lymphatic-CEUS. (C) Lymphoscintigraphic images taken two hours after injection showed the reduced uptake of inguinal lymph nodes, obstructed linear lymphatic vessels (red triangle) and the dermal backflow (white star) which was most obvious in the right calf and the inguinal region, leading to diagnose of lymphedema. R, right; L, left; CEUS, contrast-enhanced ultrasound.



Video 1 The representative imaging of the subcutaneous enhancement.



Video 2 The representative imaging of the linear lymphatic vessels.

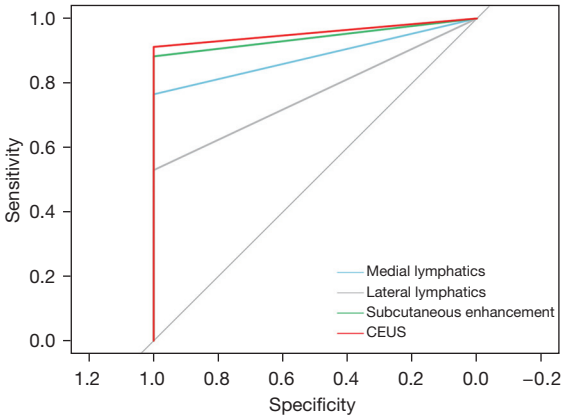


Figure 3 The receiver operating characteristic curve for diagnosing lymphedema. CEUS, contrast-enhanced ultrasound.

lymphedema by the medial and the lateral lymphatics obstructions, the subcutaneous lymphatics enhancement respectively was 0.882 (95% confidence interval: 0.778, 0.987), 0.765 (95% confidence interval: 0.608, 0.921), 0.941 (95% confidence interval: 0.870, 1.000), respectively. Moreover, the AUC for diagnosing lymphedema by the novel standard of four-point lymphatic-CEUS was 0.956 (95% confidence interval: 0.894, 1.000).

Discussion

Lymphedema causes swelling, pain and weakness of the affected extremities. Nowadays, diagnosing lymphedema depends on the clinical symptoms, signs and imaging so that the precise lymphatic imaging evidence helps improving the diagnosis of lymphedema. In this study, we put forward the four-point lymphatic-CEUS novel imaging method to detect the lymphatics of lower extremities. The sensitivity, specificity, positive predictive value, negative predictive value, accuracy and the AUC of four-point lymphatic-CEUS for diagnosing lymphedema were excellent, suggesting that four-point lymphatic-CEUS is a considerable option for lower extremities lymphatic detection.

Compared with lymphography (9) and indocyanine green (ICG) fluorescence imaging (4,7), lymphatic-CEUS is low-cost, with no radiation and high resolution. Several studies showed that lymphatic-CEUS is a promising tool to identify the lymphatics of upper extremities (20,22). Doctors can observe the real-time drainage situation of the lymphatic vessels and mark the lymphatic running map. Moreover, lymphatic-CEUS could show the anatomical positions and the functions of the enhanced drainage lymphatic vessels, providing the detailed information for surgical treatment (20,22). In our study, we put forward a novel four-point lymphatic CEUS method to perform the lymphatic detection of lower extremities. Consistent with previous anatomical studies (8,21), we observed that the contrast agents were mainly draining to the medial lymphatics after injecting in point 1, 2, 3 and mainly draining to the lateral lymphatics after injecting in point 4 (*Figure 1*). Considering the contrast agent of lymphatic-CEUS of having shorter half-value period, which is different from the 99m-Technetium-labeled agent of lymphoscintigraphy, we chose four injection points to detect the functions of the lymphatics more comprehensively. The injection points were chosen based on the lymphatic drainage regions (anteromedial, anterolateral, posteromedial and posterolateral around the ankle) and the severity of pain feeling. The high successful detection rate in our study showed the four-point lymphatic-CEUS has an excellent performance in presenting the lymphatics of lower extremities.

Nowadays, lymphedema is diagnosed mainly according to the symptoms, signs and medical history. The lymphatic imaging provides the direct evidence for diagnoses and the details of locations of the lymphatic obstructions. So far, lymphoscintigraphy is the gold standard lymphatic imaging of diagnosing lymphedema by evaluating the visualization of lymph nodes, lymphatic vessels and dermal backflow (11,12). Consistently, lymphatic-CEUS also shows the functions of lymph nodes, lymphatic vessels, suggesting that lymphatic-CEUS may be a promising tool to diagnose lymphedema. In this study, we established a diagnosis standard of four-point lymphatic-CEUS for diagnosing lymphedema which showed good diagnosis efficacy (*Figure 3*). We found that the AUC of diagnosing lymphedema only based on the medial lymphatic obstructions was higher than that of the lateral lymphatic obstructions of the lower limbs, indicating that the medial lymphatic drainage had more important lymphatic drainage function for lower extremities.

We noticed that three lower extremities were diagnosed as lymphedema based on the lymphoscintigraphy, while they were diagnosed non-lymphedema based on the performance of lymphatic-CEUS. According to the diagnosis standard of lymphoscintigraphy, the reduced uptake of proximal lymph nodes or the presented the intermediate lymph nodes are ascribed to abnormal lymphatic drainage. These three cases were diagnosed as lymphedema because of the reduced uptake of inguinal lymph nodes and the presentation of dermal backflow by performing lymphoscintigraphy,

which was inconsistent with that in lymphatic-CEUS. In our center, lymphoscintigraphy is performed by injecting into the first interdigital space of foot, which is drained to the medial lymphatic of the lower limbs. In contrast to lymphoscintigraphy (12), we injected more points to identify the lymphatic drainage to inguinal lymph nodes so that it was believed that the detection of inguinal lymph nodes by performing lymphatic-CEUS was better than lymphoscintigraphy. It was likely that the contrast agent was hard to sufficiently present the inguinal lymph nodes after injecting in the distal of lower extremities because of the durability. Changing contrast agents may help presenting more inguinal lymph nodes and better diagnosis of lymphedema, but it needs more explorations.

Several limitations of this study were noted. Firstly, this was a small sample size retrospective study so that there was unavoidable bias though this study set up the inclusion and exclusion criteria. Secondly, this was a single-center investigation and the lymphatic-CEUS was performed by using only one system (Sequoia, Siemens Healthineers), whether these findings were appropriate for other systems remain uncertain. Thus, a larger sample size further research is needed.

In general, this study put forward a novel four-point lymphatic-CEUS method to detect the functions of the lymphatics of lower extremities. Moreover, we also established a lymphatic-CEUS standard to diagnose lymphedema of lower extremities and the diagnosis standard showed excellent performance. Based on the encouraging findings of this study, four-point lymphatic-CEUS is a considerable option for diagnosing lymphedema of lower extremities.

Conclusions

This study put forward a novel four-point lymphatic-CEUS method to detect the functions of the lymphatics of lower extremities and established a lymphatic-CEUS standard to diagnose lymphedema of lower extremities. Four-point lymphatic-CEUS is a considerable option for diagnosing lymphedema of lower extremities.

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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-24-300/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-300/coif). X.X. reports that this work was supported by the Major Research Plan of the National Natural Science Foundation of China (No. 92059201). J.L. reports that this work was supported by China Postdoctoral Science Foundation (No. 2022M723619). The other 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of The First Affiliated Hospital of Sun Yat-sen University (No. [2023]641) and informed consent was taken from all the patients.

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