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Use of a Novel Portable Three-Dimensional Imaging System to Measure Limb Volume and Circumference in Patients with Filarial Lymphedema

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Abstract. The World Health Organization's Global Program to Eliminate Lymphatic Filariasis (LF) has reduced LF transmission worldwide, but millions remain affected by filarial lymphedema. Tools for clinically monitoring lymphedema in developing nations are limited. We tested a novel, portable, infrared three-dimensional imaging system (3DIS) against water displacement (WD) and tape measurement of limb circumference (TMLC) among patients with filarial leg lymphedema in Galle, Sri Lanka. Outcomes were accuracy and reproducibility of imaging system measurements. In parallel, we also tested the reproducibility of skin thickness ultrasound (STU) measurements. We examined 52 patients (104 limbs) with lymphedema of stages 0–6 ($N = 28, 19, 20, 21, 2, 4$, and 10 , respectively). 3DIS measurements correlated nearly perfectly with WD ($r^2 = 0.9945$) and TMLC values ($r^2 > 0.9801$). The median time required to acquire imaging system measurements for both legs was 2.1 minutes, compared with 17, 7, and 29 minutes, respectively, for WD, TMLC, and STU. Median interexaminer coefficients of variation (CVs) for volume measurements were 1.1% (interquartile range [IQR] 0.5–2.1%) for WD and 1.7% (IQR 1.2–2.4%) for the 3DIS. CVs for circumference measurements were 1.4% (IQR 0.8–2.4%) by TMLC and 1.3% (0.8–1.9%) by 3DIS. Median interexaminer CV for STU was 13.7% (IQR 8.5–21.3%). The portable imaging system noninvasively provided accurate and reproducible limb volume and circumference measurements in approximately 2 minutes per patient. This portable technology has the potential to greatly improve assessment and monitoring of lymphedema in the clinic and in the field.

INTRODUCTION

Lymphatic filariasis (LF) is a debilitating, mosquito-borne, parasitic infection that causes hydroceles and disfiguring lymphedema in millions of patients worldwide. Since its initiation in 2000, the World Health Organization's Global Program to Eliminate LF (GPELF) has achieved remarkable success in reducing LF transmission through mass drug administration (MDA),¹ which has cured millions and prevented over 80 million new infections.² Unfortunately, MDA does not usually reverse lymphedema in those already affected, and there is a great need for expanded and improved strategies for reducing LF-related morbidity.

Efforts to study lymphedema are hampered by the difficulty of measuring its severity and monitoring changes over time. The seven-stage system of lymphedema severity developed by Dreyer et al.³ is clinically useful, but as a noncontinuous scale it is difficult to use as an outcome in clinical trials. The gold standard for measuring limb volume is water displacement (WD),^{4,5} but this method is cumbersome and impractical for use in field studies. Tape measures of limb circumference (TMLC) are frequently used, but can be difficult to standardize and do not predict volume adequately for lower extremity lymphedema.^{6,7} Ultrasound can be used to measure the thickness of skin and soft tissues over the malleolus (skin thickness ultrasound [STU]),⁸ but this method requires expensive equipment and adequate training, and it is difficult to standardize.

Three-dimensional (3D) optical imaging is a promising new technology for lymphedema measurement and monitoring. An opto-electronic device called Perometer[®] (Pero-System Messgeraete, Wuppertal, Germany) was the first infrared-based

system developed for limb geometry measurement and has been used to monitor lymphedema.⁹ Other techniques using stereophotogrammetry and infrared structured light depth sensors from XBOX Kinect[™] (Microsoft Corporation, Redmond, WA) have also been reported.^{10–13} However, these techniques are limited by large hardware requirements and/or limited accuracy, and this has prevented their widespread use. Recently, LymphaTech, Inc. (Atlanta, GA) developed a novel lymphedema measuring and monitoring tool that uses a 3D infrared depth sensor integrated into a computer tablet with custom software. Given the need for improved methods of measuring lymphedema in filariasis patients, we tested this technology in patients with filarial lower extremity lymphedema to determine whether it could produce accurate and reproducible limb geometry measurements suitable for monitoring disease progression or improvement over time.

MATERIALS AND METHODS

Ethics statement. The study protocol was reviewed and approved by the institutional review board at the Washington University School of Medicine and the Ethical Review Committee, Faculty of Medicine, University of Ruhuna in Sri Lanka. Printed participant information sheets and written consent forms were provided to participants in Sinhalese. Written consent was obtained from all participants who were eligible for this study (age ≥ 18 years).

Patient population and setting. Volunteers with varying stages of limb lymphedema were recruited from among those receiving care at the Filariasis Research Training and Service Unit (FRTSU), Faculty of Medicine, in Galle, Sri Lanka. Patients were contacted by mail or phone and offered the opportunity to participate. Interested patients presented to the FRTSU clinic between March 20 and 31, 2017, for enrollment and

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measurements. Adults with any stage of lymphedema were eligible to participate.

Study procedures. Six examiners were trained to perform WD, TMLC, STU, and 3D imaging system (3DIS) lymphedema measurements during the first 2 days of the study period (March 20–31, 2017) with nine patient volunteers. Training day measurements were not included in the data analysis. Study measures and examination methods are shown in Table 1. TMLC, STU, and 3DIS measures were performed by three separate examiners per patient. WD was performed twice per patient, as we found it impractical to perform thrice per patient during the training period. Examiners recorded a start time and stop time for each examination so that the cumulative time needed for each could be reported. In this article, we define an “examination” as the measurement of *both* legs from one patient by one examiner. However, most patients with unilateral lymphedema had only the affected limb (stages 1–6) examined by STU. In such cases, the examination time for STU of one limb was doubled to provide a time estimate for a complete (bilateral) examination.

WD was measured using a rectangular water tank fitted with a drainage spout at a height of 32 cm above the inner base of the tank. The tank was filled until water drained from the spout and was allowed to drip to cessation. The patient placed his/her leg inside a disposable, transparent, watertight cellophane bag and immersed the leg in the tank (Figure 1C). The patient stood with the knee of the measured limb straight until water stopped dripping from the spout. Patients with trouble balancing could hold a nearby countertop for support. The displaced water volume was measured using standard graduated cylinders (2 L, 500 mL, or 250 mL). This procedure was performed on both legs of each patient by two independent examiners. Start time for WD began after the water tank had equilibrated, and examination duration included the time it took to measure the first leg, re-equilibrate the tank, and then measure the second leg. Some examiners also included the time it took to reset the tank after measurement of the second leg (completing the cycle), but this was not uniformly done, so the mean examination times reported represent at least the time taken to measure both

legs and reset the tank once, but less than the complete cycle time.

TMLC was measured around the foot at 10 cm proximal to the great toe and around the leg at heights of 12, 24, and 36 cm above the floor while the patient sat with the knee directly above the ankle.¹⁴ For the foot measurement, a line on the surface on which the foot rested marked 10 cm from the tip of the great toe. The examiner marked the medial and lateral sides of the foot where they crossed this line and then aligned a tape measure to those markings to measure the circumference. For the leg measurements, a height pole positioned parallel to the leg from the knee to the ankle malleolus was used to mark the correct height on the medial and lateral sides of each leg (Figure 1B), and circumference was measured by positioning a tape measure around the marks. Three examiners independently measured each leg; the marks were wiped off the skin between each examination.

Ankle STU measurements were performed essentially as described by Mand et al.,⁸ using a linear transducer (L12-4, Phillips Healthcare, Bothel, WA) connected to an 8-inch S2 tablet (Samsung Electronics America, Inc., Ridgefield Park, NJ) equipped with the downloadable Phillips Lumify app (Phillips Healthcare). The patient sat or reclined on an examination table with the knee extended and the toes pointing upward. Holding the transducer parallel to the table and perpendicular to the leg, the examiner located the malleolus by scanning along the leg to the narrowest distance between the skin surface and the tibia (medial) or fibula (lateral) (Figure 1A). The examiner then brought the tendon sheath posterior to the malleolus into view (tibialis posterior on the medial side, peroneal tendon sheath on the lateral side); with this marker in view, the examiner captured the image and measured the distance between the skin surface and the malleolus using the software calipers. Each examiner took four measurements over each malleolus (repositioning the probe and capturing a new image each time to give independent measurements), and each patient was examined by three separate examiners. For each site, the four measures of each individual examiner were compared to determine intraobserver variability. The individual measures were then averaged and the averages

TABLE 1
Study measurements and examination methods

Parameter	Water displacement	Tape measure limb circumference	Skin thickness ultrasound (STU)	Three-dimensional imaging system
Examiners per participant	2	3	3	3
Examinations per participant per examiner	1	1	1	2
Total examinations per patient	2	3	3	6
Number of measurements per examination				
Leg volume (floor to 32 cm height)	1	—	—	1
Circumference measurements				
Foot (10 cm from the tip of the great toe)	—	1	—	—
Leg, 12 cm height	—	1	—	1
Leg, 24 cm height	—	1	—	1
Leg, 36 cm height	—	1	—	1
Skin thickness over the malleolus				
Left lateral	—	—	4	—
Left medial	—	—	4	—
Right medial	—	—	4	—
Right lateral	—	—	4	—
Intraexaminer comparison*	No	No	Yes	Yes
Interexaminer comparison†	Yes	Yes	Yes	Yes

* For STU, variability among the four replicate measurements at each site was assessed; for the 3D imaging system variability between the first and second examinations of each examiner.

† The four replicate measurements for each STU examination were averaged and the mean was compared between examinations. All 3D imaging system measurements for each patient, regardless of examiner, were included.

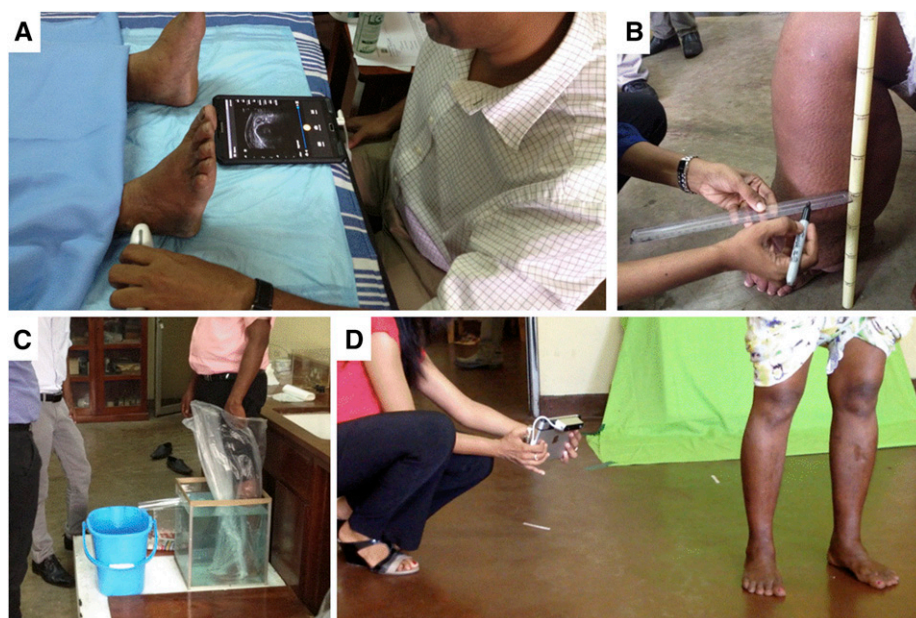


FIGURE 1. Study measurements: (A) skin thickness ultrasound, (B) limb circumference, (C) water displacement volume, and (D) three-dimensional imaging system. This figure appears in color at www.ajtmh.org.

from each of the separate examiners compared to determine interobserver variability. Because of the time burden of performing STU, we did not perform STU on most stage 0 (unaffected) limbs.

The 3DIS (LymphaTech) combines an infrared depth sensor with a tablet computer using proprietary software. The system integrates 3D depth data acquired from the sensor with accelerometer data from the tablet to perform real-time point cloud fusion, producing complete point cloud reconstructions with submillimeter resolution. Custom software extracts specific limb volume and circumference measurements. The 3DIS procedure starts with the patient standing in the center of an open space with his/her feet approximately shoulder-width apart. The examiner stands 2–3 feet away from the patient and points the tablet camera at the patient's legs. A sizing box superimposed on the tablet screen's live camera view is adjusted to set the data capture window for the depth sensor. As the examiner walks in a circle around the standing patient to capture visual data (Figure 1D, Supplemental Video 1), the tablet screen shows a 3D model acquisition overlaid on the image of the leg so that the examiner can verify adequate data capture. The examiner ensures that the entire surface of both legs is captured, then stops data capture and views the 3D reconstruction of the patient's limbs, rotating the image to ensure it contains no gaps or artifactual distortions (Figure 2). For this study examiners captured data from just above a patient's knees to the floor, and the imaging system software calculated limb volume from the floor to a height of 32 cm and leg circumference measurements at heights of 12, 24, and 36 cm, from the 3D model. Each patient was imaged twice by each of three separate examiners. An example of the 3D point-cloud model generated by the imaging system can be viewed online (Supplemental Video 2).

Data capture and analysis. WD, STU, and TMLC measurements were recorded on paper forms and transcribed into an MS Excel database. Transcribed data were independently

checked against the primary data forms by a second reviewer. 3DIS data were electronically transferred to MS Excel. All analyses were performed in Stata, version 12.1 (College Station, TX). Means and standard deviations are reported for data that were normally distributed (skew between -1.0 and 1.0). Medians and interquartile range (IQR) are reported for skewed data. Because most data were not normally distributed, we used the Kruskal–Wallis test and the Wilcoxon rank-sum test to determine statistical significance for group or pairwise comparisons, respectively. Replicate measurements from each examiner were averaged and compared across examiners to generate interexaminer coefficients of variation (CVs).

RESULTS

Fifty-two patients with varying stages of lymphedema were examined. The median time required to acquire 3DIS measurements of both legs was 2.1 minutes, compared with 17, 7, and 29 minutes, respectively, for WD, TMLC, and STU (Table 2).

Accuracy of 3DIS. Limb volume and circumference measurements obtained by 3DIS were highly accurate and tightly correlated with WD and TMLC measurements ($r^2 > 0.98$, Figure 3). Linear regression correlation coefficients (and 95% confidence intervals) obtained by comparing 3DIS estimates with mean WD and TMLC measurements at 12, 24, and 36 cm heights were 1.02 (1.01–1.02), 0.99 (0.98–0.99), 0.97 (0.96–0.98), and 0.95 (0.94–0.97), respectively. A coefficient of 1.00 would indicate exact agreement between 3DIS and comparator measurements.

Intraexaminer variability. Intraexaminer CVs for 3DIS measurements ranged from 0% to 4.9% and varied by examiner and lymphedema stage. Median CVs for 3DIS volume measurements (1.1%, IQR 0.5–2.1%) were somewhat higher than those for 3DIS circumference measurements (0.8%, IQR 0.4–1.3%; $P < 0.001$). Intraexaminer CVs for STU ranged

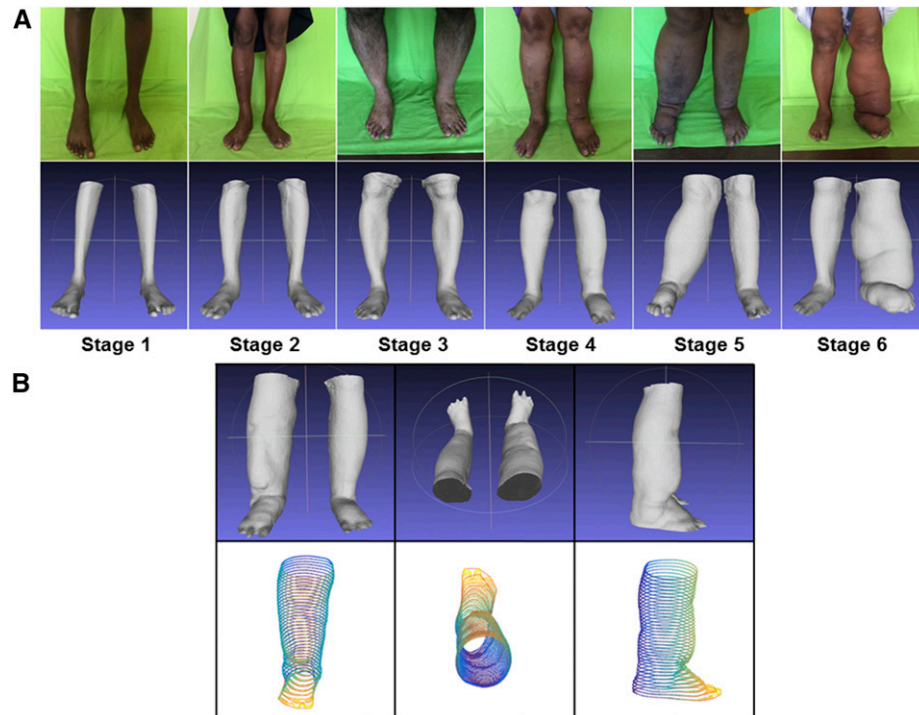


FIGURE 2. Reconstructions created by the three-dimensional (3D) imaging system. (A) Photos and imaging system reconstructions from patients with different stages of lymphedema. (B) One patient's point-cloud reconstruction, demonstrating how the model can be rotated and analyzed for circumference measures. A video of a rotating 3D model showing the level of detail captured can be viewed online (Supplemental Video 2). This figure appears in color at www.ajtmh.org.

from 0.2% to 39.9%, with a median of 4.8% (IQR 2.9–8.0%), and also varied by examiner and lymphedema stage (Supplemental Table 1). Because WD and TMLC were measured only once per examiner per patient, no intra-examiner comparisons for these measurements were possible.

Interexaminer variability. Interexaminer variability for all methods is shown in Figure 4. Median interexaminer CVs were not significantly different between the 3DIS and TMLC measurements at 12 cm and 36 cm, but they were lower at 24 cm for the 3DIS (1.3%, IQR 0.8–1.9%) than for TMLC measurements (2.0%, IQR 1.0–3.1%; $P = 0.0001$). CVs for TMLC at

24 cm were also slightly but significantly higher than each of the other TMLC measurements (Supplemental Table 2). Median interexaminer CVs for TMLC of the foot was 1.2% (IQR 0.7–2.0%), but this could not be compared with 3DIS because the imaging system software could not provide foot circumference measurements. For limb volume measurements, median interexaminer CVs for the 3DIS (1.7%, IQR 1.2–2.4%) were slightly higher than for WD (1.2%, IQR 0.5–2.1%; $P = 0.0001$). In no interexaminer comparison did the 3DIS CV exceed 6%, whereas some CV values exceeded 10% for all other measures. STU was the only modality for which inter-examiner variability differed by stage (Supplemental

TABLE 2
The number of patients and limbs examined, and time required per examination

	Water displacement (WD)	Tape measures of limb circumference (TMLC)	Skin thickness ultrasound (STU)	Three-dimensional imaging system (3DIS)
Patients examined	49	49	52	49
Total limbs examined	98	98	74	98
Stage of examined limbs				
Stage 0	26	26	1	26
Stage 1	18	18	19	18
Stage 2	20	20	20	20
Stage 3	19	19	21	19
Stage 4	2	2	2	2
Stage 5	3	3	4	3
Stage 6	10	10	7	10
Total examinations performed*	94	147	154	287
Number of examinations timed	92	145	152	268
Minutes required per examination, median (IQR)†	17 (14.5–20)	7 (6–8)	29 (25–34)	2.1 (1.7–2.4)

IQR = interquartile range.

* Not all patients completed all intended examinations; four patients declined a second WD examination, four patients received only two (rather than three) STU examinations because of time constraints, and four patients had one or more 3DIS examinations unintentionally skipped by the study team (one patient received 3 of 6, one 4 of 6, and two 5 of 6). For STU, 70 examinations included both legs and 84 included only one because most unaffected (stage 0) limbs were not measured by STU.

† For STU examinations that included only one leg, the examination time was doubled so that all values approximate the time required to measure both legs.

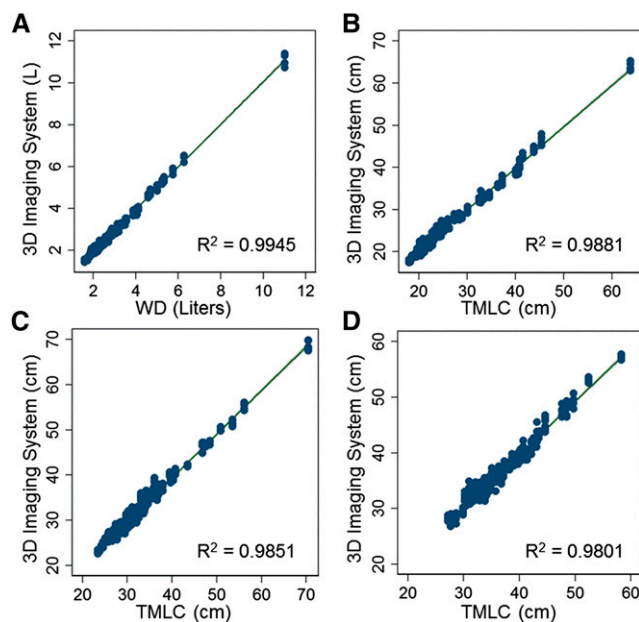


FIGURE 3. Correlation of three-dimensional imaging system measurements with water displacement (A) or with tape measurements of limb circumference (TMLC) at heights of 12 cm (B), 24 cm (C), and 36 cm (D). Gray shading around the regression line indicates 95% confidence intervals for the regression. This figure appears in color at www.ajtmh.org.

Table 2), with stages 5 and 6 having significantly lower CVs than stages 0–4 (median 9.2% versus 15.2%, $P = 0.0004$). A linear regression of interexaminer CV versus mean skin thickness confirmed that STU was significantly less variable at greater skin thicknesses (regression coefficient -4.0 , 95% confidence interval -6.1 to -1.9).

DISCUSSION

While much of the attention of GPELF has focused on reducing LF transmission through MDA, the program also aims to improve morbidity management for persons with clinically evident filariasis. The latter activity will last long after transmission of the infection has been interrupted. Improved methods for assessing and monitoring changes in filarial lymphedema are needed to improve clinical management of patients and for clinical trials that assess the impact of new treatments or management strategies. In addition, methods capable of reliably detecting small volume changes might help identify patients needing therapy earlier, preventing progression to advanced disease. A major study documented an impressive regression of lymphedema in some filariasis patients after doxycycline treatment,⁸ and additional studies are planned to confirm this important finding (ClinicalTrials.gov Identifiers: NCT02929134, NCT02927496, NCT02929121). Part of the motivation for the current study came from a desire to use the best possible outcome measures in these trials.

Each examination method used in our study had different strengths and weaknesses. WD was the most reliable but also the slowest method assessed; it was also difficult to use in patients with advanced lymphedema. Some patients with very large limbs required assistance to lift their leg into the tank, and occasionally water spilled from the tank that could not be

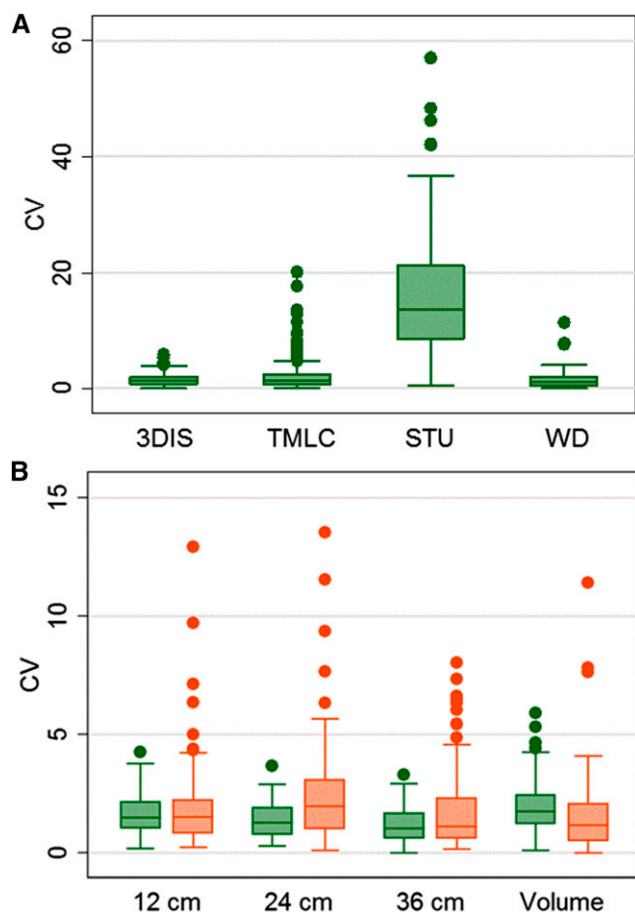


FIGURE 4. Interexaminer variability for each examination method is shown in Panel A. Panel B compares variability obtained with the three-dimensional imaging system (3DIS) (in green) with variability observed with tape measures of limb circumference (TMLC) at different levels and water displacement (WD) (orange). The two highest CV outliers for TMLC shown in panel A were foot measurements. There was no 3DIS comparison for this TMLC measurement and that is why this comparison is not shown in panel B. STU = skin thickness ultrasound. This figure appears in color at www.ajtmh.org.

measured. Patients also had difficulty standing still for the several minutes it took for water to completely drain from the tank during limb measurement. As a result, three patients with stage 5 or 6 lymphedema in our study could only tolerate a single WD examination. The time required to reset the tank after each examination also contributed to the long examination times.

TMLC was easier for the patients but less reliable than WD, and it was relatively labor and time intensive. The use of a pole to mark height measurements on both the medial and lateral sides of each leg increased reproducibility and decreased the risk of measuring oblique circumferences. As expected, irregular contours seem to increase the difficulty of obtaining reproducible measurements. TMLC was statistically less reliable at the 24 cm height, a height at which the curvature of the calf muscle is prominent. In addition, the highest outliers were seen among foot circumference measurements, presumably because the irregular anatomy of the foot makes it difficult to ensure that the measurement is performed at the same angle and at exactly 10 cm from the tip of the great toe each time.

STU was the most difficult method to standardize. None of the examiners were trained radiologists or ultrasound technicians. Although a standard operating procedure (SOP) was taught, it did not address every contingency, especially for patients with atypical anatomy. The higher interexaminer versus intraexaminer variability suggests that examiners developed their own habits for dealing with these uncertainties. In addition, examiners were not blinded to their own replicate measurements and may have been biased to obtain replicate values that matched their initial measurement. By contrast, examiners were blinded to measurements of other examiners, making interobserver variability a more meaningful outcome in our study. Probe positioning habits likely contributed to high interexaminer variability. For example, examiners were taught to deliberately decompress the skin after finding the STU markers, but it is difficult to know how effectively this was done. Improved training, a more comprehensive SOP, and the use of formally trained ultrasonographers would likely reduce STU variability, but this would also make it less practical for use in resource-limited settings.

The infrared 3DIS had several advantages and few limitations compared with the other methods studied. It was essentially equivalent to TMLC and WD in terms of accuracy and reproducibility, but much faster, providing volume and circumference measurements for both legs in less than one-tenth of the combined time required for WD and TMLC. The 3DIS does not require physical contact with the patient, which is important for patients with skin ulcers or infected wounds that are common in patients with advanced lymphedema. To reduce the risk of infection and contamination of equipment, we did not obtain TMLC or STU measurements over open wounds, and we used disposable plastic bags to cover limbs during WD. None of these precautions were necessary for 3D imaging. The primary limitation of the 3DIS in our study was that image-derived circumference measurements at the 36 cm height had to be discarded for four patients whose clothing obscured the leg surface (the examiner failed to ensure that the patient's legs were bare up to the knee). Similar to WD, the 3DIS requires that patients stand still to obtain accurate measurements, but this limitation is offset by the speed of the process and by software that prompts the examiner to abort and restart the examination if patient movements are detected. Although each patient was imaged twice by each of the three examiners, no patients in our study declined imaging because of difficulty in tolerating the procedure.

One potential limitation of the 3DIS for widespread use in filariasis is cost. It is not clear what the cost of the system will be once the manufacturer brings the device to market, but the total cost of the hardware (computer tablet, infrared sensor) used in this study was approximately \$1,300, which does not include software development and licensing costs or support. Assuming that the market price will be higher than the hardware costs, it may be difficult for clinics in extremely resource-limited settings to acquire a system without external support. On the other hand, the current cost is relatively low compared with that of other clinical laboratory technologies. It may also be possible to further reduce costs if the system software can be modified for use on personal tablets or smartphones and distributed through an app store. Another limitation of the 3DIS in this study was the inability to take foot circumference measurements. This is because the manufacturer had not yet created software algorithms for extrapolating foot

circumference measurements, although such software is in development. Given the accuracy of the imaging system's volume measurements, which include the volume of the foot, it seems highly likely that accurate foot circumference and/or dedicated foot volume measurements should also be possible with updated image processing code. Although the lack of dedicated foot measurements was a limitation of 3DIS measurements for this study, it also illustrates the flexibility of the technique. Once the point-cloud model is acquired, it requires only the appropriate software code to extrapolate any number of potential additional measurements. In this study, we chose to extrapolate leg volume with a cutoff of 32 cm height and circumference measurements at 12, 24, and 36 cm height to match the WD and TMLC measurements. In future studies, however, any number of circumference or volume measurements might be extracted, including foot circumference, breadth, and height of the foot dorsum, etc., with appropriate modification of the scanner software currently under development.

To our knowledge, this is the first time that infrared 3D imaging technology has been used in patients with filarial lymphedema, and the results are highly encouraging. The 3DIS provided estimates of limb volume and circumference that were highly correlated with global standard methods (WD and TMLC) for patients with a wide range of limb sizes and varying stages of lymphedema. The intra- and interexaminer variability for 3DIS measurements were very low and comparable with those observed with WD. However, 3D imaging is much faster and more feasible for use in clinical or field settings than WD, particularly when one considers that a single 2- to 3-minute scan can generate both volume and any desired circumference measurements. Ninety-five percent of interexaminer comparisons for the 3DIS had CV values less than 3.3%, and all were less than 6%, suggesting that this technology should be able to reliably detect true changes in limb volume or circumference of 6% or more with a high degree of confidence. Although these results require confirmation, it appears that this novel 3D imaging technology will greatly improve our ability to accurately assess and monitor changes in leg lymphedema over time in the clinic and in the field.

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