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Comparison of quantitative analysis to qualitative analysis for interpretation of lower-limb lymphoscintigraphy

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Original article

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ABSTRACT

Qualitative analysis of lymphoscintigrams is subject to wide variability and may miss subtle differences in ilioinguinal uptake between normal and abnormal limbs. This study compared quantitative analysis to qualitative analysis of lower-limb lymphoscintigraphy in diagnosing lymphedema. Fifty-two lymphoscintigrams performed using standardized protocol, 99-metastable technetium nanocolloid intradermal injection at the first interdigital space, were analyzed quantitatively. Fifty-three normal and 51 abnormal limbs were analyzed. For each limb, a region of interest (ROI) was drawn around the injection site, and ilioinguinal nodes on the 1.5 h static images and the counts in these ROIs were recorded. Percentage ilioinguinal nodes uptake was then computed. Analysis of variance (ANOVA) was performed to determine the difference in ilioinguinal uptake between normal and abnormal limbs. Specificity and sensitivity were calculated and the figures were used to plot a receiver operator characteristic (ROC) curve. Thirty-six females and 16 males (104 limbs) were analyzed. ANOVA revealed a significant difference between the mean uptake in normal (19.7%) and abnormal limbs (5.5%) ($F = 81$, $P < 0.001$). ROC had a maximal area under the curve of 0.924 ($P < 0.001$). The significant difference in the means of ilioinguinal uptake between normal and lymphedema limbs infers reduced lymphatic function. Ilioinguinal lymph node uptake is thus a reliable parameter in quantitative analysis of lymphoscintigrams.

Keywords: Lymphedema, lymphoscintigraphy, nuclear medicine, qualitative analysis, quantitative analysis

INTRODUCTION

Lymphedema is a painless, progressive accumulation of protein-rich fluid in the interstitial spaces of the skin, resulting from an anatomic or functional obstruction of the lymphatic system.[1,2] It is most common in the lower limbs, about 80% of cases, but can also occur in the arms, trunk, and external genitalia.

The primary pathology leading to lymphedema is dysfunction of the lymphatic transportation system.[3] Disruption of the lymphatic systems by pathological processes such as trauma, surgery and radiotherapy, infection, and congenital abnormalities can lead to lymphedema.[4] Primary lymphedema is usually as a result of congenital abnormalities in the lymphatic system which can be either aplasia or hypoplasia.[5,6] Lymphedema praecox is early-onset lymphedema, typically before 35 years. It is characterized by hypoplastic lymphatic system and is usually unilateral. Lymphedema tarda usually presents after 35 years of age, and there is much debate regarding its etiology. Milroy disease is the autosomal dominant form of typically bilateral primary lymphedema with the very early age of onset and is due to agenesis of the lymphatic system.[7]

Secondary lymphedema results from obstruction or interruption of the normal lymphatic channels. This can be iatrogenic (surgery and/or radiotherapy) or due to trauma or infections such as filariasis.[8]

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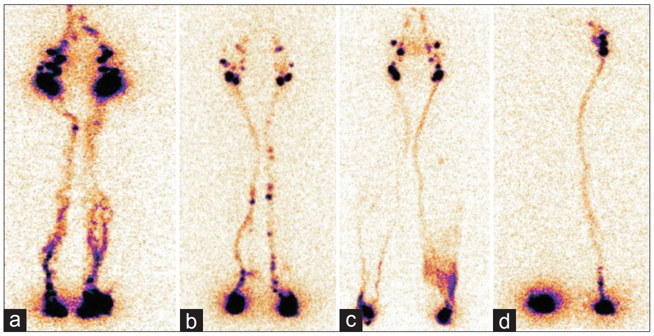

Figure 1: 1.5-h images of normal (a and b) and abnormal (c and d) lymphoscintigrams. 1.5-h images of normal (a and b) and abnormal (c and d) lymphoscintigrams. (a and b), There is fairly uniform migration of tracer to the ilioinguinal lymph nodes. (c) There is dermal backflow in the left lower limb, due to interruption of the lymphatic channels, and although not readily apparent, slightly less tracer reaches the left ilioinguinal nodes compared to the right; hence quantitative analysis would be of value in this case. (d) There is congenital aplasia of the lymphatic channels on the right and no tracer reaches the ilioinguinal nodes

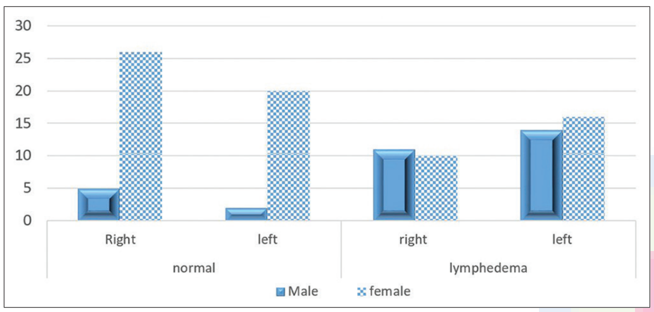

Figure 3: Bar graph showing distribution of lymphedema by sex and side

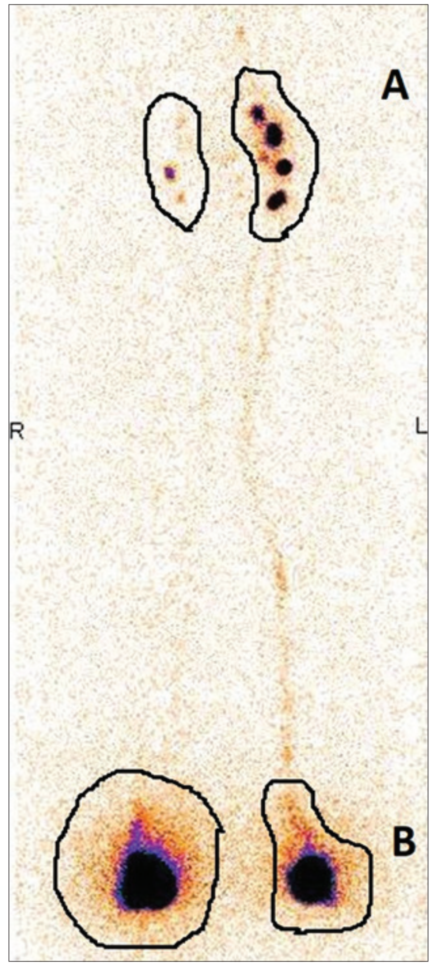

Figure 2: Lymphoscintigraphy image showing the regions of interest drawn around the injection site (A) and ilioinguinal nodes (B) for computation of ilioinguinal uptake

Lymphoscintigraphy is the primary imaging modality used in determining a diagnosis in patients with suspected extremity lymphedema.[5,6,9] The current protocol in our institution utilizes 20–40 mega-Becquerels (MBq) of 99-metastable technetium (Tc-99m) nanocolloid, injected intradermally, with static image acquisition at 5-min, 15-min, and 1.5-h intervals. Field of view is at the injection site on 5-min images and from the feet to the pelvis for the 15 minutes and 1.5 hour images. The patients walk for at least 5 min before the 15-min image.

Quantitative and semiquantitative analysis parameters can be used to complement visual analysis, to better characterize discrete changes, or to monitor therapeutic assessment in sequential studies.[10]

Quantitative parameters that can be assessed include the clearance of activity from the injection site, the fraction of the injected dose that accumulates in the draining lymph node groups, and the appearance of the radioactivity in the liver or blood.[3,11]

Quantitative analysis provides a means to unify the interpretation of scintigraphic findings, allowing for

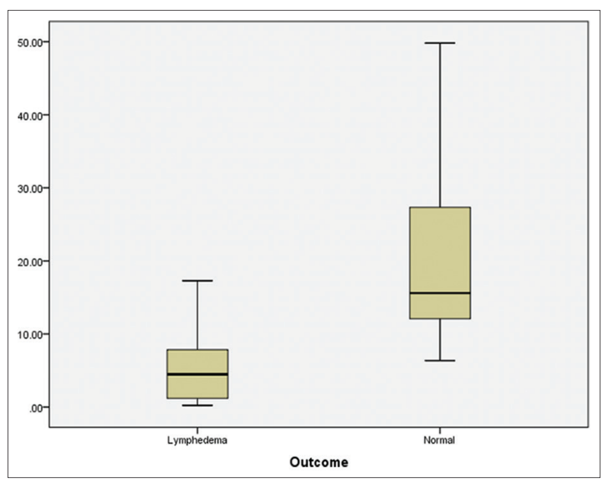

Figure 4: Bar and whisker plot of uptake in lymphedema limbs and normal limbs

the detection of small changes in lymphatic function. Furthermore, the quantitative analysis can facilitate the comparison between studies during follow-up or after

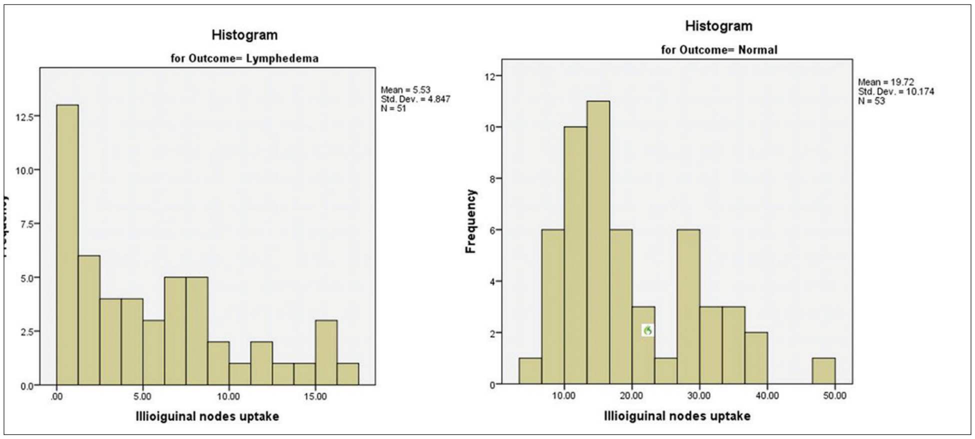

Figure 5: Histograms showing distribution of percentage lymph node uptake

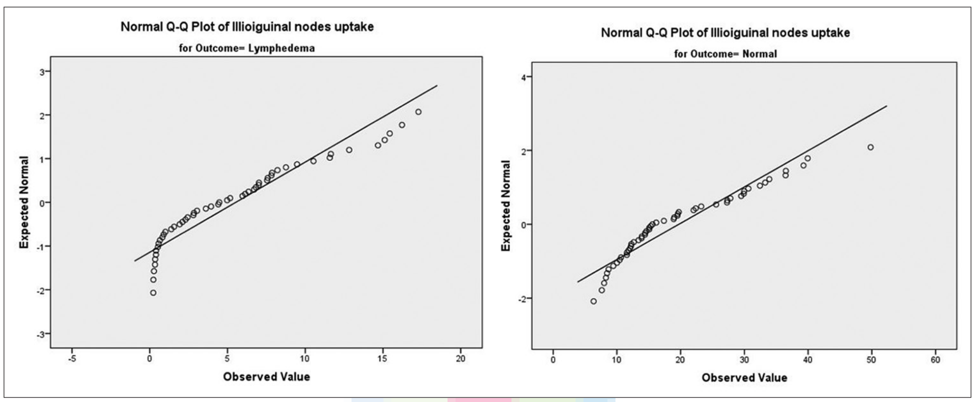

Figure 6: Q–Q plots showing distribution of ilioinguinal uptake in normal limbs and lymphedema limbs

therapeutic interventions in a patient. Analysis by less experienced radiologists and nuclear physicians can be enhanced by quantitative analysis.

The data obtained would provide a more sensitive and reproducible approach to differentiate normal patients from those with mild lymphedema, more so for the less experienced radiologist.

MATERIALS AND METHODS

This was a prospective cross-sectional study, in which consecutive patients undergoing lymphoscintigraphy at the Nuclear Medicine Department for suspected lymphedema, on the basis of unexplained lower-limb swelling, were recruited.

Patients without images at 1.5 h were excluded from the study.

The sample size was calculated using the formula for studies comparing two means; the equation used for the sample size calculation is as follows:

$$N = \frac{4\sigma^2 (Z_{crit} + Z_{pwr})}{D^2}$$

The study had a power of 80% and with 0.05 margin of error.

The estimated sample size was 102, 51 for the group with lymphedema and 51 for the group with normal limbs.

Patients were positioned supine and the Tc-99m nanocolloid was injected intradermally to the first interdigital web of both limbs – if the dose was uneven, the larger dose was administered to the affected or more edematous limb. A static planar image of the feet with the entire injection site in the field of view was obtained 5-min postinjection, on a 256 × 256 matrix. The patients were then asked to walk up and down the hallway 4–5 times (at least 2 min) and return back for 15-min delay images. A hemi-body planar image (starting from hip to feet) was obtained at 15-min and 1.5-h postinjection, using a 256 × 1024 matrix.

Normal or abnormal limbs were selected on the basis of qualitative analysis by a consultant nuclear medicine physician with a 15-year experience. Normal limbs showed

Table 1: Demographic characteristics of the subjects

	n	Minimum	Maximum	Mean	Median	SD
Age of subject (years)	52	3	90	37.9	37.5	19.7
Age at onset of edema (years)	52	0	70.0	32.3	30	17.1
Duration of edema (years)	52	0	30	5.5	3	7.0

SD: Standard deviation

Table 2: Distribution of lymphedema by sex

Sex	Outcome (/limb)		Total
	Lymphedema	Normal	
Male	25	7	32
Female	26	46	72
Total	51	53	104

Table 3: Ilioinguinal lymph node uptake among normal and lymphedema limbs

Outcome	*n*	Mean (%)	SD	SEM
Ilioinguinal node uptake				
Lymphedema	51	5.5	4.8	0.7
Normal	53	19.7	10.2	1.4

SD: Standard deviation; SEM: Standard error of mean

prompt and uniform migration of the radionuclide through discrete lymph vessels. Abnormal limbs had a combination of any of the following findings: interruption of lymphatic flow, collateral lymph vessels, progressive dermal backflow, delayed flow, delayed visualization or nonvisualization of lymph nodes, reduced number of lymph nodes, dilated lymphatics, and in severe cases no visualization of the lymphatic system at all [Figure 1].

For all the normal limbs, a region of interest was drawn around the injection site (B) and inguinal nodes (A) at 1.5-h static images [Figure 2]. Inguinal node uptake was computed as follows:

$$\frac{A}{(A+B)}\times 100$$

A similar analysis was done for the abnormal limbs.

Approval for the study was obtained from the institutional ethics review committee. All the study participants gave written informed consent. Consent was obtained from all the adult study participants and from the guardians of participants aged below 18 years.

This study portends no harm to the participants, and the standard imaging protocol was not altered. The study investigators have no conflict of interest to declare.

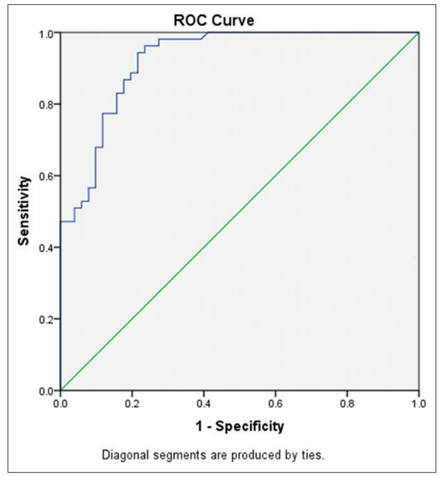

Figure 7: Receiver operator characteristic curve

All statistical analysis was performed using SPSS version 17 (SPSS Statistics for Windows, SPSS Inc: Chicago, USA).

RESULTS

Fifty-five bilateral lymphoscintigraphic examinations were performed between August 2014 and January 2015. Fifty-two patients (25 males and 26 females) were included in the final study. Excluded patients included one where 1.5-h images were not acquired and two patients in whom both injection sites and ilioinguinal nodes were not in the field of view on the 1.5-h images. The median age was 37.5 years, with a standard deviation (SD) of 19.7; their mean duration of lymphedema was at least 5.5 years [Table 1].

The proportion of males with positive scans (diagnosis of lymphedema) was significantly higher (78% vs. 36% $P < 0.001$). Both limbs were equally affected with lymphedema, with no preference for either side [Figure 3 and Table 2].

Quantitative analysis

The mean for each of the groups is illustrated in [Table 3 and Figure 4].

The data were skewed to the right in both the normal group and the group with lymphedema [Figure 5]. The Kolmogorov–Smirnov test for normality, however, showed a lognormal distribution which is a common finding in many biologic samples [Figure 6].

Analysis of variance

Following analysis of variance (ANOVA), the difference of the means between the two groups was statistically significant ($P \leq 0.0001$). An F value (a measure of intergroup vs. intragroup variance) of 81.37 indicates a large difference.

Receiver operator characteristics

Using different cutoffs of percentage ilioinguinal uptake, specificity and sensitivity were calculated, and the values obtained were used to plot a receiver operator characteristic (ROC) curve [Figure 7]. Area under the curve (AUC) was also estimated. AUC was 0.924.

The cutoff value giving the best trade-off between sensitivity and specificity (highest and most to the left) is 9.74 (sensitivity = 86.8%, specificity = 82.4%).

DISCUSSION

The study sample consisted of 36 females and 16 males. The mean age of the population was 37.9 years, with a range from 3 to 90 years. It was noted that most patients presented in their 30s to 40s, which perhaps represents patients with lymphedema tarda.

Secondary lower-limb lymphedema is not common in our setting. This is in sharp contrast to studies in Europe and Asia where secondary causes predominate.

The average onset of lymphedema was 32 years. This could be partly explained by lymphedema tarda which prior authors have given as onset of lymphedema after 35 years.[12] The patients whose onset of edema was between puberty and 30 years represent patients with lymphedema praecox. A small number of patients with congenital lymphedema presented before puberty.

The average duration of edema at the time of presentation was 5.4 years (0–30 years). The fact that most patients sought intervention after a mean duration of 5 years may reflect onset of other clinical symptoms besides edema or worsening edema.

Following qualitative lymphoscintigraphy, only one male patient had a normal examination while the rest had either unilateral (5 subjects) or bilateral lymphedema (10 subjects). In contrast, 16 females had normal limbs, while 14 had unilateral lymphedema and six had bilateral lymphedema. The proportion of males with positive scans was significantly higher (78% vs. 36% $P = 0.000$). This suggests that edema of whatever etiology may be more common in females, while edema in males is more likely to be lymphedema. Most other studies have indicated a higher incidence of lymphedema among females. Indeed, some causes of lower-limb swelling such as lipedema are exclusive to women.[13] Obesity which is a recognized risk factor for lymphedema[14] is more common in females. In a study by Dalia *et al*., a total of 77 patients (66 women, 11 men) were studied.[15] Of these, 21 patients had unilateral extremity involvement and 56 had bilateral lymphedema. It seems that unilateral lymphedema is more common in our population.

Among the patients with unilateral edema, there was a trend toward more involvement of the left limb. The level of physical activity aids in lymphatic clearance, and most people in the general population are right-handed, which may partially explain the higher number of abnormal left limbs, but this may be further investigated with more robust research. On quantitative analysis of ilioinguinal lymph node uptake, the limbs with lymphedema had reduced uptake: mean 5.5, SD 4.8. Normal limbs had significantly higher ilioinguinal uptake values and a large SD of 10.1. A statistically significant difference between the means of the two groups was observed after ANOVA. F statistic of 81 indicates a large difference between the two means. The data described in this study are compatible with that in the literature, showing reduced ilioinguinal lymph node accumulation of radiotracer in lymphedema.[15,16]

Using qualitative lymphoscintigraphy as the reference standard, sensitivity and specificity for each ilioinguinal uptake value were computed and an ROC curve was plotted. The AUC was 0.924 ($P < 0.001$). This indicates that quantitative analysis is an accurate tool in the diagnosis of lymphedema.

By selecting an ilioinguinal node uptake of 9.7%, lymphedema could be diagnosed with 86.8% sensitivity and 82.4% specificity. When lymphatic dysfunction is bilateral, quantification of lymph node accumulation and clearance of activity from the injection site both become important parameters. Again, it should be emphasized that these parameters are strongly influenced by the amount of exercise a patient can perform.[17] In addition, the uptake index can be used to monitor progression of disease as well as response to therapeutic measures.

CONCLUSION

Ilioinguinal lymph node uptake can be used for the differentiation of normal limbs from limbs with lymphedema. Quantitative analysis if developed and standardized can be an accurate tool in the diagnosis of lymphedema. Quantitative indices would be useful for monitoring of disease progression and efficacy of therapeutic measures.

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Conflicts of interest

There are no conflicts of interest.

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