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Optimizing Diagnostic Accuracy in Peripheral Oedema Using Quantitative Assessment of Lymphoscintigraphy.

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ABSTRACT:

Objectives: To assess the prevalence of equivocal cases in interpretation of routine lymphoscintigraphy at an Egyptian nuclear medicine medical center and to investigate the enhanced diagnostic precision provided by quantitative analysis of lymphoscintigraphy in the diagnosis of peripheral lymphedema. **Patients and methods**: Fifty patients (100 limbs), presenting with lymphedema in either upper or lower limbs underwent lymphoscintigraphy following a standardized protocol. Both qualitative and quantitative analyses were conducted. For quantitative analysis, a region of interest (ROI) was delineated around the injection site and regional lymph nodes for each limb on the 1.5-hour static images. The count of each ROI was recorded, and the regional lymph node uptake percentage for each limb was calculated. **Results**: The occurrence of equivocal cases was determined to be 8.0%. Employing the non-parametric Mann-Whitney test, a significant discrepancy was observed in the percentage of lymph node uptake between normal limbs (mean=36.54%) and abnormal limbs (mean=14.56%). The Receiver Operator Characteristic (ROC) curve analysis revealed a cut-off value of 6.87, which provided the optimal balance between sensitivity (60.3%) and specificity (81%) ($P < 0.001$).

Conclusion: Combining qualitative and quantitative lymphoscintigraphy methods has potential value for optimizing diagnostic accuracy of lymphedema, particularly in cases where equivocal results are obtained through qualitative indices which will eventually result in better patient management.

Keywords: Peripheral lymphedema – lymphoscintigraphy – qualitative analysis – quantitative analysis.

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INTRODUCTION:

The lymphatic system is a one-way circulatory network that supplements the blood vascular system [1]. Lymphatic vessels are present in nearly all tissues with the exception of specific areas such as the eyeball, cornea, central nervous system, bone marrow, cartilage, epidermis, internal ear, teeth, and placenta [2]. Despite its crucial role in human health and pathology, the understanding of the dynamics of this system is still limited [3]. Its primary role involves the extraction of proteins and fluids from the interstitial tissues, subsequently returning them to the systemic circulation [4, 5]. Additionally, lymphatic vessels contribute to the transportation of lipids absorbed within the digestive tract. In addition to these functions, the widespread distribution of lymphatic vessels throughout the whole body allows rapid identification of antigens and immunological responses[6]. If this active removal of the proteins from the interstitial tissue does not occur by the lymphatic system, accumulation of the proteins in the interstitial tissue leads to progressive interstitial oedema [5]. Lymphedema arises from the gradual build-up of protein-rich fluid within the interstitial spaces of the skin[7]. This condition stems from aberrant development of the lymphatic system, manifesting as either aplasia or hypoplasia (primary lymphedema), or as damage to lymphatic vessels and nodes due to injury (secondary lymphedema).[8]. Secondary lymphedema is the commonest form of lymphedema[1]. Primary lymphedema involves three types described in the literature: congenital primary lymphedema, known as Milroy disease; lymphedema praecox, which occurs during puberty; and lymphedema trade, which develops in patients over 35 years old [9]. Precise diagnosis and effective management play pivotal roles in the successful treatment of patients with lymphedema [10]. Lymphoscintigraphy is considered the gold standard imaging modality for diagnosing lymphedema [10]. It serves as a diagnostic imaging tool for assessing lymphatic flow disorders. It can be performed on patients of any age, including those in critical conditions [11]. Its interpretation generally relies on qualitative criteria [12]. Quantitative analysis was proposed in previous studies to complement qualitative analysis of lymphoscintigraphy providing a standardized approach, to evaluate lymphatic function and identify minor alterations. [12, 13] Despite this, its application in clinical practice settings remains limited. The aim of this study is to reaffirm the utility of quantitative analysis of lymphoscintigraphy in a group of Egyptian patients to enhance diagnostic precision of this technique in assessing peripheral oedema.

PATIENTS AND METHODS:

Patients: This retrospective analysis included 50 consecutive patients of both genders and various ages (34 females and 16 males, with a mean age of 36.76 ± 18.7 years) who underwent lymphoscintigraphy in the Nuclear Medicine and Radiation Oncology department (NEMROCK), Faculty of Medicine, Cairo University

between January 1st, 2022, and December 31st, 2022. All patients were presenting with peripheral edema and they met the inclusion and exclusion criteria. The details of the clinical data of the included group of patients **are listed in Table 1**. The exclusion criteria comprised patients with other systemic problems (such as cardiac, hepatic, or renal conditions), as well as pregnant and breast-feeding women. **Ethical approval:** Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Cairo University, in accordance with the ethical standards set forth by the Declaration of Helsinki. The protocol for this study was reviewed and approved under approval number **(Approval Code: MS-17-2023).**

Lymphoscintigraphy: the studies were performed according to the Procedural Recommendations for Lymphoscintigraphy in the Diagnosis of Peripheral Lymphedema (Genoa Protocol) [14]. An average dose of 30–50 MBq 99mTc nano colloid, colloidal particles of human albumin (at least 95% of the total size between 20 and 80 nm) in a volume of 0.1–0.2 ml was used for each limb for all patients. Intra-dermal injection was done in the first interdigital web space of the extremities either upper or lower limbs using insulin syringes and a 25-gauge needle. The same volume and activity of the radiotracer were used for both sides of every patient. Injection of the tracer was preceded by disinfection with an iodine solution or alcohol. The injection was done without the use of local anaesthetics. Bilateral upper or lower limbs were studied simultaneously, regardless of whether the complaint is unilateral or bilateral oedema. All lymphoscintigraphies were obtained as planar images using a GE dual head Discovery NM 630 Gamma camera equipped with a parallel hole low energy high-resolution (LEHR) collimator for low energy and high resolution (± 15% window centred on the 140-keV energy peak of 99mTc). Patients were positioned supine on the gamma camera table. Anterior and posterior static images of the injection site, as well as the bilateral draining lymph nodes of concern, were acquired at 5 minutes post-injection using a 256 × 256 matrix. Additionally, hemi-planar images of both limbs of concern, with the entire injection site within the field of view, were obtained. Subsequently, the patients performed recommended exercises, such as walking or massaging the lower limbs and squeezing a rubber ball repeatedly for the upper limbs. At 1.5 hours post-injection, anterior and posterior static images of the bilateral draining lymph nodes of concern, along with hemi-body planar images, were acquired using the same 256 × 256 matrix. No processing is required for planar images for qualitative analysis.

Qualitative image interpretation included evaluation of clinical data and study images findings including the state of lymphatic trunk, regional draining lymph nodes, presence or absence of collaterals, presence or absence of popliteal/epitrochlear lymph nodes and presence or absence of dermal backflow in both early and late (after stress) images. In qualitative analysis, the cases were we classified according to the pattern of the lymphatic drainage of limbs into normal, abnormal and equivocal cases**.** Eequivocal cases were identified when the pattern of lymphatic drainage cannot be categorized as either normal or abnormal, particularly in patients with early or mild stages of lymphedema.

For quantitative analysis a region of interest (ROI) was drawn around the injection site (B) and draining lymph nodes of concern (axillary or inguinal) (A) at late post 1.5-h static images in both limbs for all cases. The gamma count was acquired from Xeleris software workstation (GE Medical Systems) where the gamma count represented the total radiopharmaceutical uptake in the ROI. Then the lymph node (L.N.) uptake calculated as follows:

Lymph node uptake %= A/ (A+ B) ×100

Statistical analysis: Microsoft excel 2013 was used for data entry. Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test (Chan, 2003a). For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 (Chan, 2003b). ROC curve was constructed with area under curve analysis performed to detect best cut-off value of L.N. uptake value % for detection of lymphedema. P-values less than 0.05 were considered as statistically significant.

RESULTS:

The clinical data of the studied group of patients **(Table 1)**

Qualitative analysis of lymphoscintigraphy is summarized in **(Table 2)**. **Quantitative analysis of lymphoscintigraphy** is summarized in **(Table 3)**. The examined 100 limbs had different: Lymph node uptake value (%) with a mean of 24.82 ± 27.69 %. Using non-parametric Mann-Whitney test, the percentage of lymph node uptake value in normal limbs **showed significant difference** in comparison to abnormal limbs as described in **(Table 4)**.

Table 1: The clinical data of the studied group of patients

		Number	Percentage
Limb	**Upper**	10	20.0%
	Lower	40	80.0%
Unilateral or bilateral	**Unilateral**	31	62.0%
	Bilateral	19	38.0%
Type of lymphedema	**1ry lymphedema**	30	60.0%
	2ry lymphedema	20	40.0%
Secondary lymphedema	**Complete obstruction**	7	35.0%
	Partial obstruction	13	65.0%
Primary lymphedema	**Hypoplasia**	19	63.3%
	Aplasia	11	36.7%
Primary lymphedema according to age of onset of oedema	**Lymphedema Tarda**	10	33.3%
	Lymphedema precox	14	46.7%
	Lymphedema congenita	6	20.0%

Table 2: Qualitative Analysis of Lymphoscintigraphy.

		Number	Percentage
Qualitative Analysis	**Normal**	42	42.0%
	Equivocal	8	8.0%
	Abnormal	50	50.0%

Table 3: Quantitative Analysis of lymphoscintigraphy.

Count	Mean	±SD	Min.	Max.
Site of tracer injection	28753.99	32040.41	856.00	164125.00
Draining LN	8630.71	17794.96	0.00	110990.00
L.N. uptake value%	24.82	27.69	0.00	91.25

Table 4: Comparison between the results of the qualitative analysis and the quantitative analysis of lymphoscintigraphy.

	qualitative analysis							
	Normal				Abnormal			
	Mean	±SD	Min.	Max.	Mean	±SD	Min.	Max.
L.N. uptake value %	36.54	30.77	0.90	91.25	14.56	21.95	0.00	78.6
p value	<0.001*							

Receiver Operator Characteristics

For calculation of lymph node uptake value for detection of lymphedema, **we considered the equivocal cases to be abnormal cases** in Roc curve. Using different cutoff values of the draining lymph nodes uptake percentage, specificity and sensitivity were calculated, and the values obtained were used to plot a receiver operator characteristic (ROC) curve **(Figure 1)**. Area under the curve (AUC) was also estimated. AUC was 0.757. The cutoff value giving the best trade-off between sensitivity and specificity is **6.87 (sensitivity = 60.3%, specificity = 81%) (Table 5).**

The 8 equivocal limbs (7 patients) (diagnosed according to qualitative analysis) show lymph node uptake value's mean of 21.44 and median of 20.7 in analysis.

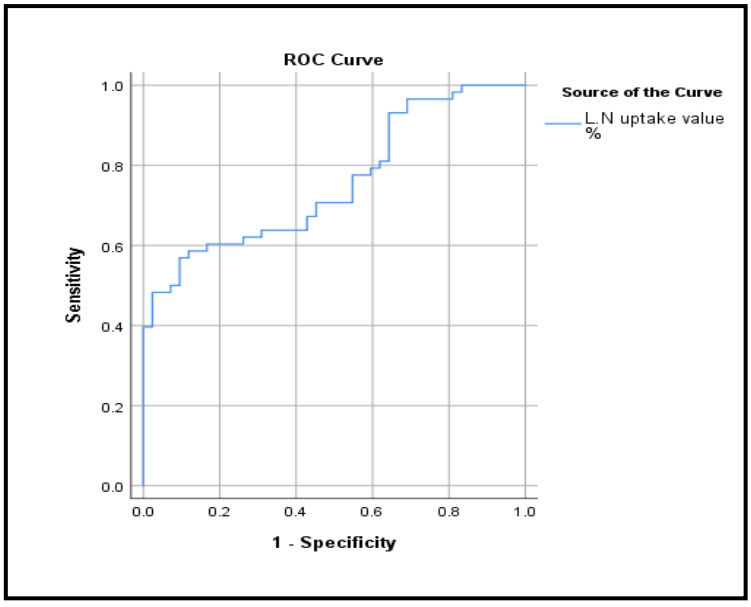

Figure 1: ROC curve for detection of lymphedema using L.N. uptake value%

Table 5: Cut off value, sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

	AUC	95% CI		Cut-off	Sens. %	Spec. %	PPV %	NPV %	Acc.
		Lower	Upper						
L.N. uptake value %	0.757	0.664	0.849	<6.8692	60.3	81	81.40	59.65	69.00
***p* value**	**< 0.001***								

By quantitative analysis, we diagnosed 3 of them as abnormal limbs and 5 as normal ones, so quantitative analysis helps in the differentiation between normal and abnormal limbs.
(Figure 2) represent patient diagnosed as normal and (**Figure 3)** represent patient with left lower limb primary lymphedema**.**

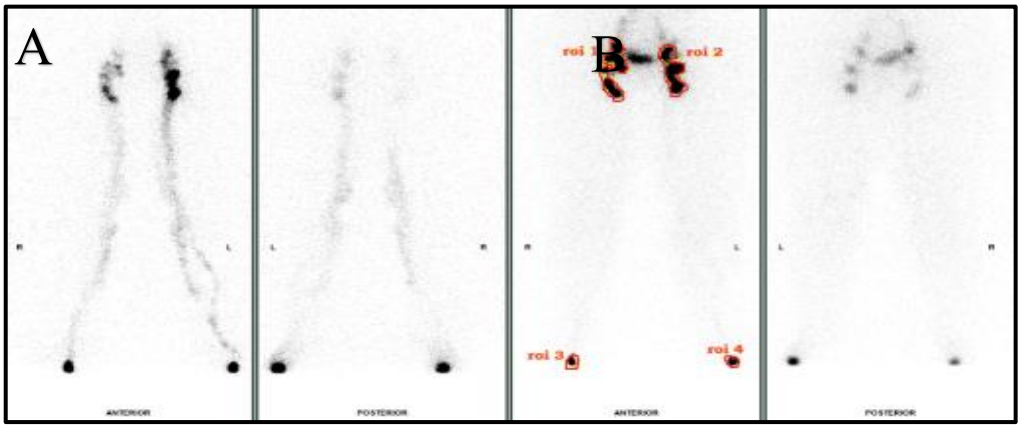

Figure 2: A case of normal lymph flow kinetics. **A** shows the early image **& B** shows the late image with ROI around the regional draining lymph nodes and site of tracer injection**.**
Inguinal lymph node uptake value on the right side= 88.33%. Inguinal lymph node uptake value on the left side= 85.09%

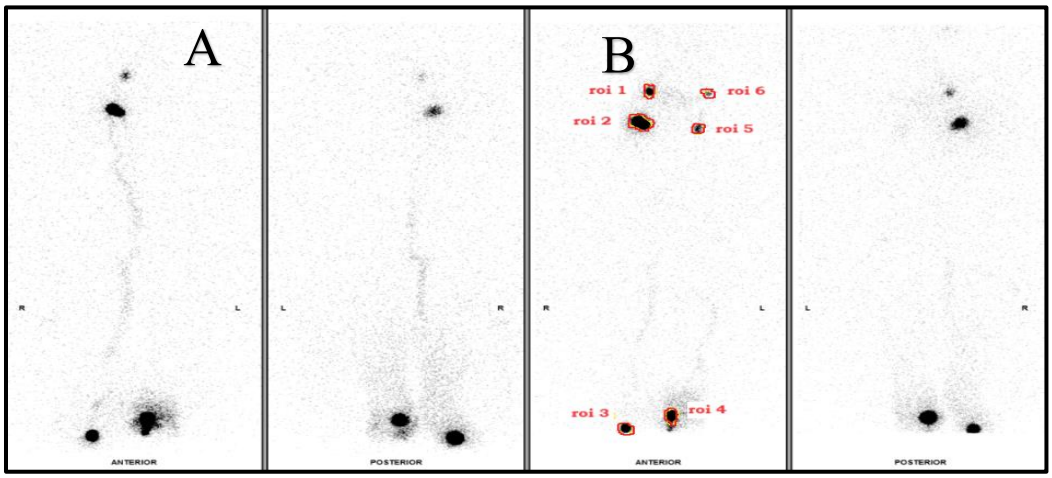

Figure 3: A case of hypoplasia of the left lower limb lymphatic system. **A** shows the early image **& B** shows the late image with ROI around the regional draining lymph nodes and site of injection**.** Inguinal lymph node uptake value on the right side= 71.14%. Inguinal lymph node uptake value on the left side= 2.13%

DISCUSSION:

Peripheral lymphedema is a chronic progressive and debilitating disease [14]. Early diagnosis helps for effective treatment and prevention of its complications, including disuse atrophy, extremity deformity and increased susceptibility to recurrent infections [15]. Despite the recent emphasis on the advantages of lymphoscintigraphy for detection of lymphedema, a standardized and reliable method of evaluating and reporting imaging results is still needed [16]. Although lymphoscintigraphy is an objective and sensitive approach for the diagnosis and evaluation of lymphatic dysfunction and associated severity, a qualitative interpretation based on a visual assessment might overlook a case of mild disease that lacks typical positive findings and could potentially disregard the small differences between the ipsilateral and contralateral sides [17]. It is easier for nuclear medicine physicians to diagnose abnormalities seen during the late phase of lymphedema [16]. Several grading systems have been established to evaluate the severity of lymphedema [17]. There is a need for a simple tool to use in everyday practice. With the development of quantitative analysis of the lymphoscintigraphy, it may have potential to make more precise diagnosis of lymphedema, especially in patients who have early stages of lymphedema. In this study, we included 50 patients, with a mean age of

36.76 ± 18.7 years, ranging from 0.75 to 66 years. The majority of participants were female (68%), with a female-to-male ratio of approximately 2:1. The duration and age of onset of oedema varied among patients, with a mean duration of 6.06 ± 8.52 years and a mean age of onset of 30.57 ± 18.06 years. The youngest patient presented with congenital lymphedema, while the oldest was diagnosed with secondary lymphedema at 66 years. These findings are comparable to those reported by **Nganga** et al. [13] who observed a mean patient age of 37.9 years, with a range of 3 to 90 years, and a similar gender distribution. Unilateral limb oedema was more common in our study (62%) than bilateral limb oedema (38%), which aligns with the findings of **Yuan** et al. [16] who reported that two-thirds of lymphedema cases are unilateral. However, our results differ from those of **Dalia** et al. [17], who reported that 27.3% of patients had unilateral extremity involvement, while 72.7% had bilateral involvement. In terms of laterality, there was no statistically significant difference between right and left limb involvement (30% right unilateral limb oedema, 32% left unilateral limb oedema). This contrasts with the findings of **Nganga** et al. [13], who observed a trend toward more frequent involvement of the left limb in unilateral cases. Regarding to the final diagnosis of lymphedema according to qualitative analysis alone, we found out of the examined 100 limb, 42 limbs (42 %) were diagnosed as normal, 8 limbs (8 %) were equivocal and 50 limbs (50%) were diagnosed as abnormal. Many similar studies since 1988 studied the value of qualitative lymphoscintigraphy. The studies include **Weissleder**, et al 1988 [21] report that with qualitative interpretation alone, the diagnosis of lymphedema was established in 216 of 308 extremities (70.1%). **Dalia**, et al 2005 reported that 21.44% of limbs were classified as normal, 61.68% of limbs were classified as mildly altered and 16.88% of limbs classified as much altered[19]. **Keramida**, et al 2018 reported 122 scintigraphically normal limbs of total 204 limbs and 82 abnormal limbs[22]. **Ebrahim**, et al, 2017 reported that out of 81 patient 54 of these patients had no scintigraphic findings indicating lymphedema or a blockage in the lymphatic system in either leg while 27 patients had some scintigraphic findings corresponding to lymphedema[16]. The abnormal limbs are divided into 30 limbs (60 % of the abnormal limbs) were diagnosed as 1ry lymphedema and 20 limbs (40 % of the abnormal limbs) were diagnosed as 2ry lymphedema with a 1ry to 2ry lymphedema ratio 3:2. The primary lymphedema is more common. **Yuan**, **et al,** 2006 reported that out of 82 cases diagnosed as lymphedema, only 6 cases were caused by primary lymphedema (7.3%) which is discordant with the current study. This may be explained by the larger

sample size (110 patients) with different mean age and range (mean age 42.6 years and range 5-68 years) in their study[20]. **Ter**, et al 1993, stated that final diagnoses of 20 extremities examined were 3 extremities with primary lymphedema, 8 with secondary lymphedema, and 9 with oedema due to other causes. Our study includes 16 males (32 limb) and 34 female (68 limbs). 19 limbs of 32 are with positive scan finding in males and 31 limbs of 68 are with positive scan finding in females. The proportion of males with positive scans show no significant difference (59 % vs. 48% P = 0.330) [23]. **Nganga**, **et al** 2019 reported the proportion of males with positive scans was significantly higher than females (78% vs. 36% P = 0.000). It may be explained by presence of number of females who had lymphedema after mastectomy in the current study increasing the percentage of female patients with positive scans[18]. Following the quantitative analysis of lymphoscintigraphy the diagnosed normal limbs we found the regional lymph nodes uptake value mean 36.54 ± 30.77 while in the scintigraphy of diagnosed abnormal limbs we found the regional lymph nodes uptake value mean 14.56 ± 21.95. Using non-parametric Mann-Whitney test, the percentage of lymph node uptake value in qualitatively diagnosed normal limbs showed significant difference in comparison to qualitatively diagnosed abnormal limbs with p value <0.001. The obtained results in this study, were in agreement with reported results in literature, showing reduced regional lymph node accumulation of radiotracer in lymphedema. Dalia et al. (2005 [19] reported that there was a regionally decreased lymph node accumulation of radiotracers, mainly in the strongly altered members (p=0.0081). **Nganga** et al 2019 reported that on quantitative analysis of ilio-inguinal lymph node uptake, the limbs with lymphedema also had reduced uptake (mean 5.5, SD ±4.8) as compared to normal limbs that had significantly higher ilio-inguinal uptake values (SD ± 10.1) with statistically significant difference between the means of the two groups (p value < 0.001). In the receiver operator characteristic (ROC) curve, the area under the curve (AUC) was 0.757. The cutoff value giving the best trade-off between sensitivity and specificity is 6.87 (sensitivity = 60.3%, specificity = 81%)[18]. **He also** reported that in the receiver operator characteristic (ROC) curve, the area under the curve (AUC) was 0.924. An ilio-inguinal node uptake of 9.7%, lymphedema could be diagnosed with 86.8% sensitivity and 82.4% specificity [18]**.** This difference between this study and our study may be attributed to the involvement of upper and lower limbs lymphoscintigraphy in the current study. Other studies used a different method for quantitative analysis of lymphoscintigraphy. **Partsch, et al,** 2003 had done quantitative analysis by comparing the injected dose with

the corrected lymph node activity. They gave the mean percent uptake of radioactivity in the inguinal lymph nodes (D%) after 15 min of exercise of 14.3±4.2% and a lower limit of normal of 6% [24].

CONCLUSION:

Combining qualitative and quantitative lymphoscintigraphy methods has potential value for optimizing diagnostic accuracy of lymphedema, particularly in cases where equivocal results are obtained through qualitative indices, which will eventually result in better patient management.

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