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CORRELATION OF INGUINAL LYMPH NODE NUMBER AND VOLUME WITH LOWER EXTREMITY LYMPHEDEMA SEVERITY

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ABSTRACT

There are very limited studies on the relationship of inguinal lymph node number and volume correlated with lower extremity lymphedema severity. In this IRB-approved retrospective study, patients who obtained an MRI for lower extremity lymphedema and who did not have lymph node resection or biopsy were identified. The MRI images were used to determine the number and volume of inguinal lymph nodes for each limb in addition to fat and fluid-based scoring using a validated grading system. Wilcoxon signed-rank tests were used to compare the greater-affected limbs with the lesser-affected limbs. The spearman-rank correlation was performed on a 'per limb' basis for MRI-based scoring and clinical parameters with ipsilateral lymph node number and volume and for differences between the limbs. A total of 32 patients were included. The greater-affected limb had higher MRI fluid scores (median (interquartile range) = 3 (3 - 3) vs. 0 (0 - 1), ($p < 0.01$) relative to the contralateral limb and had a median fat asymmetry score of 2 (1 - 3). On the per-limb analysis, lymph node number and volume inversely correlated with total MRI scores ($\rho = -0.47$, $p < 0.01$ for node number and volume). The difference of lymph node number and volume correlated with MRI score difference (node number: $\rho = -0.66$, $p < 0.01$; node volume: $\rho = -0.64$, $p < 0.01$) and perometer difference (node number: $\rho = -0.58$, $p < 0.01$; node volume: $\rho = -0.59$, $p < 0.01$). Inguinal lymph node number and volume inversely correlate with lower extremity edema presence and severity.

Keywords: Lymphedema, Lymph node, Magnetic Resonance Imaging

Lymphedema is a chronic condition that reduces the quality of life of affected patients and causes high systemic healthcare costs (1). It has been reported to affect up to 3 million people in the United States, with a female predominance, a predilection for the lower extremity, and a tendency for asymmetric distribution between limbs (2–4). The pathophysiology is related to dysfunctional or absent lymphatic drainage, which normally removes protein-rich fluid from the interstitium following filtration at the level of the capillaries (5). The etiology of lymphedema can be further classified as either primary (congenital) or secondary (acquired) (6).

Lower extremity lymphedema often results from surgery or radiotherapy for genitourinary malignancies (7). Previous studies have shown that the number of lymph nodes removed during surgery for malignancies is associated with the development and severity of secondary lymphedema (8–10). Primary lower extremity lymphedema has also been associated with hypoplasia or the absence of lymphatic channels histologically (11). Inguinal lymph nodes collect lymph from superficial channels throughout the lower extremities. If these channels are compromised, afferent flow to the nodes will be reduced or eliminated, which could lead to atrophy. Conversely, a loss in nodal surface area may predispose to ipsilateral lymphedema (12). This may have implications on radiological reporting of lymphedema and predicting response to certain treatments, such as lymph node transplant, or lymphovenous bypass.

An inverse relationship of lymph node asymmetry with clinical severity of lower extremity lymphedema has been suggested for secondary lymphedema (8,13,14). A recently validated MRI based score not only allows quantification of lymphedema severity but also allows differentiation between fat and fluid levels based on imaging (15). Use of this scoring method could delineate the relationship of fluid and fat accumulation with ipsilateral superficial lymph node number and volume with greater granularity. Additionally, it is not known whether this relationship exists for primary lymphedema patients as well. In this study, we look to see if the presence, severity (radiological and clinical), and chronicity of primary and secondary lower extremity lymphedema correlates with the number and volume of ipsilateral superficial inguinal lymph nodes.

MATERIALS AND METHODS

This IRB-approved HIPAA-compliant retrospective study was performed at a multidisciplinary lymphedema clinic at a single tertiary referral center. Records from January 1, 2018, to December 31, 2020, were reviewed. The subjects selected for the study were patients presenting to the clinic that were (1) diagnosed with lower extremity lymphedema, (2) received an MRI for this indication, and (3) did not have a history of lymph node resection or biopsy. Data from the online medical record was collected for demographics, disease duration, limb volumes by perometer, bioimpedance (L-DEX™) scores, International Society of Lymphology (ISL) staging score (16), and Quality of Life (QOL) scores.

Determination of Lymph Node Number and Volume

All patients were scanned on a 3.0 T (750W, General Electric) magnet with a dedicated lower extremity runoff coil. The protocol includes an axial single tau inversion recovery (STIR, TR 7080 ms, TE 52 ms, echo-train 16, field of view 40 x 20 cm, matrix size 384 x 192, slice thickness 6 mm) and pre-and post-contrast axial 3D gradient echo recall (GRE) with a 2-point Dixon technique (LAVA-FLEX, General Electric, TR 3.0 ms, TE 1.4 ms, field of view 40 x 20 cm, matrix size 512 x 384, slice thickness 2.2 mm). These sequences were obtained at three stations: the pelvis from the aortic bifurcation, the thighs, and the calves (including the ankles and upper feet). Gadobenate dimeglumine (0.1 mM/kg) was administered intravenously via an antecubital vein, and, following a 2-minute delay, venous-phase imaging was acquired with LAVA-FLEX at all three stations. The total number of inguinal lymph nodes was measured in three dimensions (long axis followed by two orthogonal planes; *Fig. 1*) using the 3D post-contrast GRE sequences by two independent observers, and the volume of each node was calculated by ellipsoid approximation by multiplying the three dimensions by $\pi/6$ (= 0.52).

MRI-Based Fat and Fluid Scoring

The degree of lymphedema and associated subcutaneous fat accumulation was scored using an adaptation of a 3-point scale using axial STIR and Dixon fat images (15). The first component of the scoring involved assigning a score for fluid accumulation (0 = no fluid, 1 = honeycombing / reticular fluid pattern within the subcutaneous fat, and 2 = continuous visible fluid stripe between the

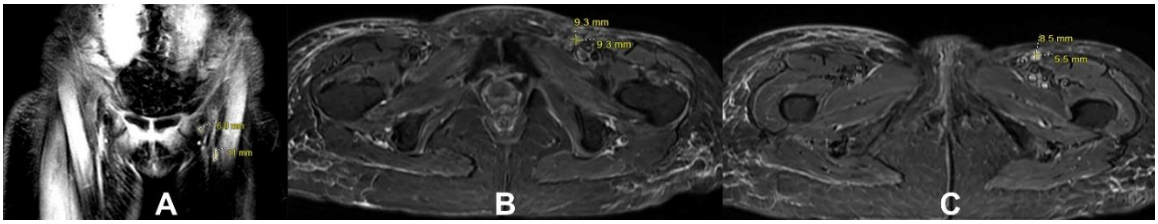

Fig. 1: *MR images from a 67-year-old female with secondary lymphedema demonstrating measurement of lymph nodes using MRI. Nodes were measured in the coronal plane (A) and in two orthogonal planes in axial view (B, C).*

fat and investing muscle fascia). The second component of the score graded the degree of asymmetric fat accumulation by scoring the amount of fat in the greater-affected limb relative to the lesser affected limb (0 = no excess fat, 1 = fat accumulation less than twice the width of the widest fat stripe on the less affected side, and 2 = fat accumulation greater than twice the width of the widest fat stripe on the less affected side). The calf and the thigh were scored separately. Greater and lesser affected limbs (referring to both lesser and unaffected limbs) were determined based on the larger versus lesser total score for each limb, respectively. Fluid scores for each limb were calculated by adding the fluid scores for the thigh and the calf. Total scores were determined by adding fluid scores with fat asymmetry scores as follows:

Total score for lesser affected extremity = Fluid score,

Total score for greater affected extremity = Fluid score + Fat asymmetry score

Statistical Analysis

Data analysis was performed using R version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). As MRI scores, limb volumes, lymph node number, and volumes were determined to be not normally distributed by the Shapiro-Wilk tests, non-parametric tests were used for analysis. Differences between the affected limb and the other limb were determined by Wilcoxon signed rank tests, and correlation analysis was performed by Spearman's Rank-Order correlation. As appropriate, data are reported as mean ± SD or median (interquartile range). Statistical significance was defined as $p < 0.05$. The false discovery rate was controlled by the Benjamini-Hochberg method.

Correlation analysis was performed for the overall cohort, and then a sub-analysis was performed for patients with primary and secondary lymphedema. The first was a per-limb analysis, comparing node number, volume, and MRI scores across each limb individually. The second was an ‘analysis of differences’ where lymph node number and volume, MRI fluid and total scores, and perometer measurements were analyzed by taking the difference between the right and left limbs for each patient. Indicators for disease severity, such as L-DEX™ scores, QOL scores, and chronicity (in years), were also included in the analysis.

RESULTS

Patient Characteristics

Baseline patient characteristics are summarized in *Table 1.* A total of 32 patients (mean age ± SD = 53 ± 16 years, 28/32 = 88% females) were included in the analysis. A majority were diagnosed with secondary lymphedema (20/32 = 63%). A greater number demonstrated worse or unilateral disease on the left side (19/32 = 59%). Bilateral lower extremity edema was present in 11 patients (12/32 = 38%) while 20 (20/32 = 63%) had one lower extremity without any fluid or fat asymmetry on MRI.

TABLE 1
Characteristics of Patients Included in the Study

Characteristic	Mean ± SD or n (%)
Age	53 ± 16 years
Sex	
Female	28 (87.5%)
Male	4 (12.5%)
Lymphedema type	
Primary	12 (37.5%)
Secondary	20 (62.5%)
Lymphedema asymmetry	
Left	19 (59.4%)
Right	13 (40.6%)
Laterality	
Bilateral	12 (37.5%)
Unilateral	20 (62.5%)
***ISL score**	
Stage II	30 (93.8%)
Stage III	2 (6.2%)
L-DEX	63.2 ± 38.5
Quality of life scores	6.4 ± 1.9
Duration of Lymphedema, years	11.9 ± 13

*ISL = International Society of Lymphology

Comparison Between Greater-Affected Versus Lesser-Affected Lower Extremities

Differences between the two lower extremities are summarized in *Table 2*. The greater-affected limb had greater MRI fluid scores (3 (3 - 3) vs. 0 (0 - 1), p < 0.001) relative to the contralateral limb and had a median fat asymmetry score of 2 (1 - 3). Limb volumes of the greater-affected limb were similarly greater than the lesser-affected limb (10573.0 (9405.2 - 12713.8) ml vs. 8057.5 (7382.5 –8986.2) ml, p < 0.001). The greater-affected limb also had fewer lymph nodes (4 (3–6) vs 7 (6–9), p = 0.005), and smaller lymph node volumes (392.3 (106.3–1032.7) vs 1051.7 (192.4 –1887.9), p = 0.001).

Per-Limb Analysis

Lymph node number showed moderate inverse correlation with MRI fluid scores (ρ= –0.44, p < 0.01), MRI fat scores (ρ= –0.43, p < 0.01) and total scores (ρ= –0.47, p <0.01). Similarly, lymph node volume also had an

TABLE 2
Comparison of the Greater-Affected Limb vs. the Less-Affected Limb

	Greater-affected limb Median (Interquartile range)	Less-affected limb Median (Interquartile range)	P value
MRI Scoring			
Fluid score*	3 (3 - 3)	0 (0 - 1)	<0.001
Calf fluid score	2 (2 - 2)	0 (0 - 1)	<0.001
Thigh fluid score	1 (1 - 1.5)	0 (0 - 0)	<0.001
Fat asymmetry**	2 (1 - 3)	-	-
Calf fat asymmetry	1 (1 - 1)	-	-
Thigh fat asymmetry	1 (0 - 2)	-	-
Total score	5 (4 - 6)	0 (0 - 1)	<0.001
Perometer			
Limb Volume (ml)	10573.0 (9405.2 - 12713.8)	8057.5 (7382.5 - 8986.2)	<0.001
Lymph Nodes			
Number	4 (3 - 6)	7 (6 - 9)	0.005
Volume	392.3 (106.3 - 1032.7)	1051.7 (192.4 - 1887.9)	0.001

* Fluid scores: 0 = no fluid, 1 = honeycombing / reticular fluid pattern within the subcutaneous fat, and 2 continuous visible fluid stripe between the fat and investing muscle fascia.
**Fat asymmetry: 0 = no excess fat, 1 = fat accumulation less than twice the width of the widest fat stripe on the unaffected side, and 2 = fat accumulation greater than twice the width of the widest fat stripe on the unaffected side

TABLE 3
Per Limb and Right-Left Difference Analysis

		Overall (n = 32)		Primary (n = 12)		Secondary (n =20)	
		ρ	P value	ρ	P value	ρ	P value
Per limb analysis							
Lymph Node Number	MRI Fluid Score	-0.44	< 0.01*	-0.22	0.32	-0.55	<0.01*
	MRI Fat Score	-0.43	< 0.01*	-0.45	0.046*	-0.42	<0.01*
	MRI score total	-0.47	< 0.01*	-0.36	0.12	-0.53	<0.01*
Lymph Node Volume	MRI Fluid Score	-0.43	< 0.01*	-0.29	0.21	-0.53	<0.01*
	MRI Fat Score	-0.40	< 0.01*	-0.31	0.18	-0.49	<0.01*
	MRI score total	-0.47	< 0.01*	-0.36	0.12	-0.57	<0.01*
Right - Left limb analysis							
Lymph Node Number Difference	Total score difference	- 0.66	< 0.01*	-0.74	0.03*	-0.68	< 0.01*
	Fluid score difference	- 0.60	< 0.01*	- 0.56	0.21	-0.70	< 0.01*
	Perometer difference	- 0.58	< 0.01*	- 0.55	0.21	-0.57	0.02*
Lymph Node Volume Difference	Total score difference	- 0.64	< 0.01*	-0.49	0.25	-0.77	< 0.01*
	Fluid score difference	-0.71	< 0.01*	-0.51	0.25	- 0.81	< 0.01*
	Perometer difference	- 0.59	<0.01*	-0.32	0.46	-0.73	<0.01*
Correlation of clinical parameters							
Quality of Life	Chronicity	0.55	0.03*	0.27	0.82	0.26	0.45

* Statistically significant result

inverse correlation with MRI fluid scores ($\rho = -0.43$, $p < 0.01$), MRI fat scores ($\rho = -0.40$, $p < 0.01$) and total scores ($\rho = -0.47$, $p < 0.01$). These relationships held for patients with secondary lymphedema; however, for primary lymphedema, the only significant correlation was between lymph node number and fat scores ($\rho = -0.45$, $p = 0.045$) (***Table 3***). There was no correlation between the absolute number and volume of lymph nodes with ipsilateral limb volumes as determined by the perometer.

Analysis of Differences (Right-Left)

The results of the analysis based on right-left difference are summarized in ***Table 3***. For the overall cohort, there was a moderate to strong inverse correlation of the total score difference (node number: $\rho = -0.66$, $p < 0.01$; node volume: $\rho = -0.64$, $p < 0.01$), fluid score difference (node number: $\rho = -0.60$, $p < 0.01$; node volume: $\rho = -0.71$, $p<0.01$) and perometer difference (node number: $\rho = -0.58$, $p < 0.01$; node volume. $\rho = -0.59$, $p<0.01$) with the difference of lymph node number and volume (***Fig. 2***). These significant relationships held for the secondary lymphedema cohort. For the primary lymphedema cohort, node number was significantly correlated with total score difference and perometer difference. No significant correlation was found for QOL scores, L-DEX∑ , and disease chronicity with MRI-based score differences, lymph node number, or volume difference (***Fig. 3***).

DISCUSSION

There was a clear negative correlation between inguinal lymph node number and volume with increased severity of disease on lower extremity MRI across all subjects, for both per-limb as well as difference analyses. This negative correlation was maintained for

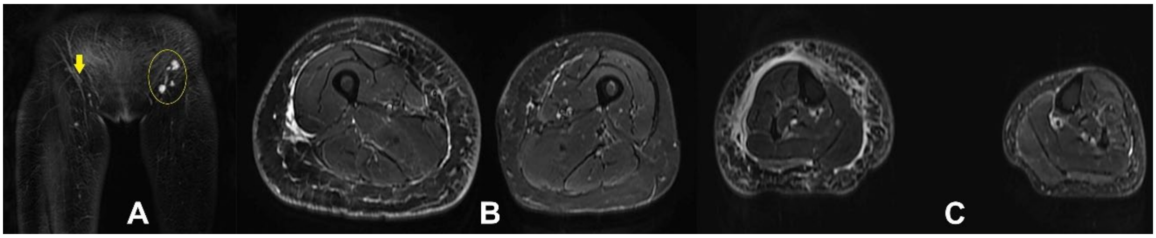

Fig. 2: *MR images from a 66-year-old female with primary lymphedema. Coronal section (A) shows a paucity of lymph nodes on the left side (arrow) relative to the right (circle). Axial sections of the thigh (B) and calf (C) show fat hypertrophy on the right side (left side of image) but minimal changes on the left side.*

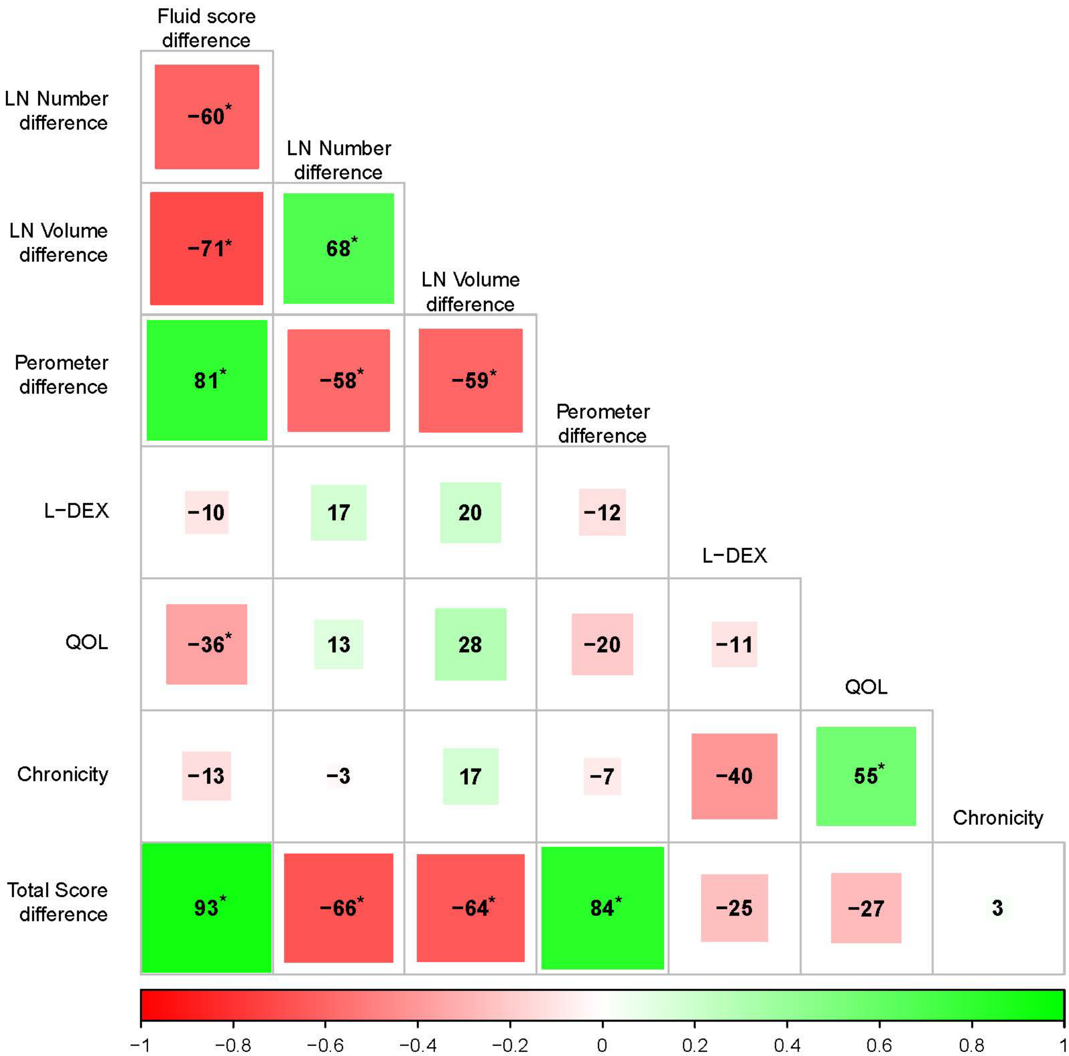

Fig. 3: *Correlation plot. The numbers represent the correlation coefficient determined by Spearman rank correlation method (ρ). Asterisk (*) represents statistically significant correlation ($p < 0.05$)*

both fluid and fat scores in secondary lymphedema patients. Similar trends were seen in primary lymphedema patients, though with the exception of the correlation between fat score and lymph node number, results were not statistically significant.

A role of lymph node in the pathophysiology of primary lymphedema has been suggested by histological studies demonstrating fibrotic nodes (17–21). This observation has been backed by MRI studies showing large variation in lymph node morphology between healthy and lymphedematous limbs (22). Moreover, Onoda et al (14) observed that greater affected limbs had fewer superficial groin lymph nodes and that there was an inverse correlation between ISL stage of a limb and the sum total size of inguinal lymph nodes of the ipsilateral side. Similarly, Hou et al (8) demonstrated a significant negative correlation between inguinal lymph node display and ipsilateral lower limb lymphedema while studying lymphoscintigraphy. However, these studies focused solely on secondary lymphedema and did not correlate their findings with radiologically observed severity.

The mechanism of lymph node hypoplasia/aplasia is not precisely known, though it is possible lymphatic and nodal pathologies reinforce each other. As the inguinal nodes serve as the primary collector of superficial lymph from the lower extremities, their reduction in overall volume may reflect atrophy secondary to chronic poor afferent flow, as noted in MR lymphangiography studies (22,23). On the other hand, fewer and smaller lymph nodes in the setting of reduced lymph flow could mean overall increased resistance to lymph flow, especially since lymph node resistance is higher at lower flow rates (24).Consequently, reduced lymph node function may limit the effectiveness of lymphatic repair strategies in the lower extremity, most notably lymph node transplants to the calf or thigh, as compromised downstream flow would continue to serve as a roadblock for lower extremity lymphatic drainage. Therefore, the number and volume of lymph nodes in an affected limb may be considered by surgeons in repair strategies, though this needs to be further explored.

The chronicity of lymphedema, L-DEX™ score, and quality of life scores did not significantly correlate with lymph node volume or number. These are less precise measures of lymphedema severity, and the quality-of-life metric is subjective. Chronicity is also based on the reported time of onset of symptoms and therefore does not consider subclinical disease where the lymphatic function may already be compromised. The absolute limb volume measurements (via the perometer) did not correlate with the lymph node number and volume; this is likely because limb volume can be affected by multiple factors including, notably, subcutaneous fat. On the other hand, the difference in limb volume measurement of the same individual, which controls for individual factors affecting limb volume, is indeed correlated with lymph node number and volume. This further highlights the role of MRI-based staging as a potentially more sensitive and quantitative technique to assess lymphedema severity.

This study has several limitations. These include a retrospective analysis and a small sample size, particularly of the primary lymphedema patients. This study also did not include an assessment of the lymph node function or the status of downstream central lymphatic channels.

The results of the study suggest that the number and volume of inguinal lymph nodes may add to the overall assessment of lower extremity lymphedema to guide surgical management, potentially being a determinant for the success of treatment options such as lymphovenous anastomosis or vascularized lymph node transfer (25). Future studies should further explore the relationship of nodal volume to lymphatic function and response to the lym-phatic repair.

CONFLICT OF INTEREST

All authors declare no competing financial interests exist.

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