Reliability of Clinical Signs to Diagnose Lower Limb Lymphedema in Comparison to Immediate and Delayed Near Infrared Fluoroscopic Lymphangiography

Ahmed Sawaby, MD;[1] Rafik Mohamed, MD;[2] Islam Atta, MD[3]
[1]Lecturer of Vascular Surgery, Faculty of Medicine, Port Said University, Egypt
[2]Lecturer of Radiology, Faculty of Medicine, Alexandria University, Egypt
[3]Assistant Professor of Vascular surgery, Faculty of medicine, Kafr El-Shikh University, Egypt

Objective: Diagnosis of lower limb lymphedema depends on clinical signs in most health organization. One of the recent investigational tools for lymphedema diagnosis is near infrared fluoroscopy lymphangiogram. The aim of our study was to evaluate the accuracy of clinical signs in lymphedema diagnosis in comparison to fluoroscopic lymphangiography. Also, to know the value of immediate and delayed lymphangiography in clinically diagnosed lymphedema patients.

Patients and methods: Prospective Cohort study of 44 patients with 73 lower limbs swelling. All patients assessed by history, clinical examination. Body mass index has been measured. Immediate and delayed findings (After 24 hours) of near infrared lymphography of subcutaneous injection of Indocyanine Green has been documented.

Results: The sensitivity and specificity of clinical signs in predicting fluoroscopic -confirmed lymphedema were 77% and 58% respectively. The overall accuracy was 69 %. Forty six out of 73 limb swellings showed the classical clinical signs of lymphedema. Twenty five of them showed normal lymphatic pattern by immediate fluoroscopy. One half of this group showed changes of images of fluorescent lymphangiography after 24 hours of injection into dermal backflow pattern. The sensitivity of clinical signs in predicting lymphedema was 77%, specificity was 58%. The overall accuracy was 69%.

Conclusions: These results would suggest clinical signs of lymphedema unreliable in making a correct diagnosis of lymphedema in about one third of pateints. Also, we cannot rely on immediate lymphangiographic fluoroscopy to exclude lymphedema.

Key words: Lymphedema, Lymphangiography, Near Infrared Fluoroscopy.

Introduction

Lower-limb lymphedema is one of the disorders that must be distinguished from other causes of leg swelling. This is because the diagnosis of lymphedema, especially in its early stages, may be indistinguishable from those of other types of edema. In addition, early diagnosis of lymphatic insult is critical for changing the treatment regimen. The dorsal hump of the foot, square toes, Kaposi-Stemmer sign, and nonpitting edema are all typical manifestations used to diagnose lymphedema.[1]

These clinical indicators' accuracy in comparison to the current imaging modality, Indocyanine green (ICG) lymphangiogram, has not been fully determined. Since the late 1950s,[2-4] ICG has been used in medicine to assess cardiac output,[5,6] and to assess liver functional reserve prior to cirrhotic liver resection. ICG is a dye that may be injected into the human bloodstream with almost no side effects.[7] When activated with appropriate wavelength light in the near infrared spectrum,ICG becomes fluorescent.[8] The fluorescence is detected by a specialized camera and then transferred to a monitor, allowing for the identification of anatomical structures that contain the dye.[9,10]

We share our preliminary experience with a new imaging approach that leverages enhanced ICG fluorescence, injected subcutaneously, to show anatomical details of lymphedema of the extremities. Through a prospective evaluation of contemporaneously gathered data, this study assessed the diagnostic reliability of "traditional" clinical signs by comparing them to ICG near infrared fluoroscopic lymphangiography (NIRFL). Also, we study the role of immediate and delayed (After 24 hours) NIRFL in lymphedema group.

Patients and methods

Between January 1 and October 7, 2021, 73 extremities in 44 individuals were included in this study. 46 limbs (28 patients) out of them showed physical signs of lymphedema (Lymphedema

group). All patients were given a medical history and a physical examination. Patient gender, age, and body mass index (BMI) were among the demographic data collected.

During the study period, nurse practitioners or physicians noted the presence of clinical signs of lymphedema in all participants. These signs were the dorsal hump of the foot, square toes, Kaposi-Stemmer sign, and non-pitting edema **(Figure 1)**. The patients with clinical signs of lymphedema were classified into primary or secondary type according to their history.

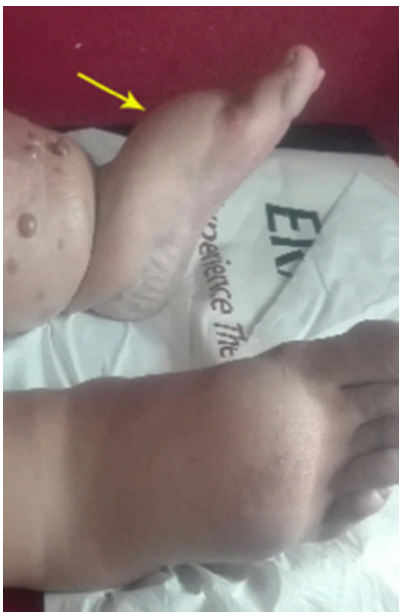


Fig 1: Humping of dorsum of foot with non-pitting edema in lymphedema patient.

Inclusion criteria: Chronic limb swelling more than three months.

Exclusion criteria: Acute limb infection, acute deep vein thrombosis, active ulcer, edema less than three months and allergy to iodine.

Fluorescence lymphography: Written informed consent has been approved. Ethical approval was granted by the local research and ethics committee. (NIRFL) was performed in all limbs.

Image interpretation: Without causing discomfort to the patient, we were able to capture real-time imaging of lymphatic drainage across the entire leg using our technique. The camera for acquiring images is a custom-made infrared camera that is portable and easy to use. In each webspace of the foot, just inferior to the medial and lateral malleoli,[11,12] 0.1 ml of ICG solution was injected subcutaneously. The near-infrared camera system was utilized to visualize fluorescence pictures of the lymphatic vessels immediately after the injections and after 24 hours. The fluoroscopic image was reported as normal linear pattern or abnormal dermal backflow pattern.[13]

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) The Kolmogorov- Smirnov was used to verify the normality of distribution of variables, Comparisons between the different stages for categorical variables were assessed using McNemar-Bowker, while Student t-test for normally distributed quantitative variables, to compare between two studied groups. Significance of the obtained results was judged at the 5% level ($p \leq 0.05$).

Results

Forty-four patients with seventy-three limb swelling were included in this study. The basic characteristic of patients involved showed that the median age was 54.0 years. The female (61.5%) was higher than male (38.5%). The majority of the patients was overweight or obese with mean BMI 48.64 **(Table 1).** Forty-six limbs out of 73 (lymphedema group) showed clinical signs of lymphedema with (30.4%) had dorsal hump of foot, (6.5%) square toes, (34.7%) non pitting edema and (10.8%) Kaposi -Stammer sign.

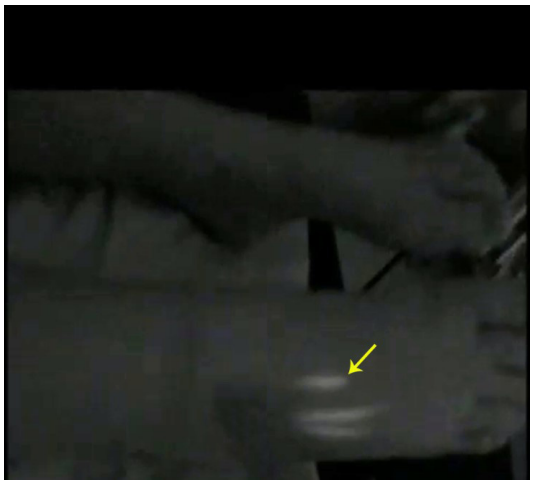
After careful history and clinical examination of lymphedema group (28 cases with 46 limbs), patients classified into primary and secondary lymphedema. Nine patients diagnosed as primary lymphedema as the swelling purely unilateral or one limb was huge than the other and there was no obvious secondary etiology in these young age group. The other nineteen patients diagnosed as secondary lymphedema. One woman had a history of hysterectomy with extended lymph node dissection and local radiation therapy for uterine cancer, and leg edema had manifested after surgery. Seven cases have past history of repeated attacks of cellulitis. One male patient suffering from lipodermatosclerosis with pigmentation of lower legs. Three female patients gave long history of leg swelling sparing the feet. After period of time (5-7 years), that the feet became humped and swollen. These patients diagnosed clinically as lipolymphedema. Seven patients had history of orthopedic surgery (Postoperative lymphedema).

All patients underwent ICG lymphangiography with immediate and delayed (After 24 hours) imaging. No complications were noted from the test.

Diagnostic testing analysis: The sensitivity of clinical signs in predicting lymphedema was 77%, specificity was 58%, the positive predictive value was 73% and the negative predictive value was 62%. The overall accuracy was 69% **(Tables 2,3)**.

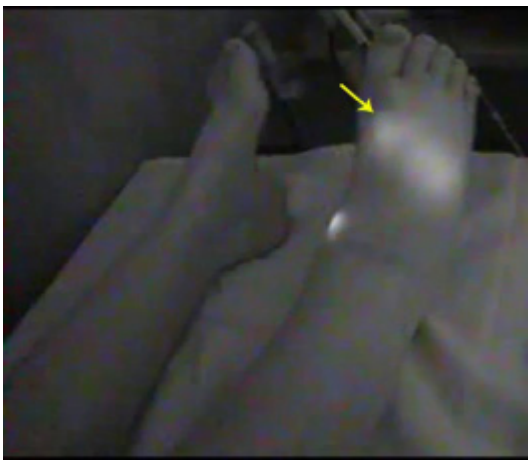
Regarding the finding of clinically diagnosed lymphedema group (46 limbs), twenty-five limbs showed immediate normal linear pattern. Thirteen limbs out of them changed to dermal backflow

after 24 hours of ICG injection (Five primary, two lipedema, and six cellulitis) **(Figure 2).** The rest of limbs (21) showed immediate dermal backflow that were not changed after 24 hours. The negative predictive value of immediate ICG fluoroscopy is 48 with statistically significant P value **(Table 4).** That means nearly half of the cases that experience normal linear pattern with immediate NIRFL changed into abnormal dermal backflow after 24 hours. According to our results, the sensitivity and specificity of immediate NIRFL for diagnosis of lymphedema are 63%% and 100% respectively with accuracy 71.74% **(Table 5).**



A

Fig 2A: NIRFL changes from normal linear pattern to abnormal dermal backflow pattern.



B

Fig 2B: NIRFL changes from normal linear pattern in patient suffering from repeated attacks of cellulitis.

Table 1: Basic patient characterization

	Number	Percent
Age (years)		
Range	0.75-77.0	
Mean±S.D.	48.63±19.25	
Median	54.0	
Sex		
Male	8	28.5
Female	20	71.5
BMI		
Normal weight	3	9.7
Over weight	9	29.0
Obese	11	35.5
Morbid obese	5	16.1
Not applicable (infants)	1	3.2
Range	23.2-45.7	
Mean±S.D.	48.64±5.93	

Table 2: 2x2 contingency table for diagnostic testing analysis

	Delayed		Total
	Negative	Positive	
Clinical signs			
Negative (non -lymphedema group)	17 (58.6%)	10 (22.7%)	27
Positive (lymphedema group)	12 (41.4%)	34 (77.3%)	46
Total	29	44	

Table 3: Results of diagnostic testing of clinical signs of lymphedema vs delayed NIRFL

Variable	%
Sensitivity	77.27
Specificity	58.62
PPV	73.91
NPV	62.96
Accuracy	69.86

Table 4: Comparison between immediate and delayed NIRFL (n = 46)

	NIRFL		^{McN}p
	Immediate	Delayed (After 24 hours)	
Linear pattern (No)	25 (54.3%)	12 (26.1%)	<0.001*
Dermal back flow (yes)	21 (45.7%)	34 (73.9%)	
Change	13 (28.3%)		
No change	33 (71.7%)		

^{McN}p: P value for McNemar test for comparing between immediate and delayed. *: Statistically significant at p ≤ 0.05.

Table 5: Agreement (sensitivity, specificity and accuracy) for immediate NIRFL

	NIRFL Delayed (After 24 hours)		Sensitivity	Specificity	PPV	NPV	Accuracy
	Linear pattern (No) (n = 12)	Dermal back flow (yes) (n = 34)					
Immediate NIRFL							
Linear pattern (No)	12 (100%)	13 (38.2%)	61.76	100.0	100.0	48.0	71.74
Dermal back flow (yes)	0 (0%)	21 (61.8%)					

PPV: Positive predictive value. NPV: Negative predictive value.

Discussion

One of the hallmark signs of lymphedema is lower-limb swelling. The edema becomes nonpitting as the disorder continues, despite the fact that it is pitting in the beginning. Other characteristics of lymphedema include sluggish swelling reduction with elevation and a lack of responsiveness to diuretics.[1] The dorsal hump of the foot, the Kaposi-Stemmer sign, square toes, and nonpitting edema are all skin abnormalities that have been documented and are considered classic. Unlike the dorsal hump of the foot, which is caused by swelling, the Kaposi-Stemmer sign is caused by the thickening of the skin at the base of the second toe.[14,15] This sign has been described as extremely specific but not particularly sensitive. Square toes are a symptom of lymphedema and are caused by a combination of swelling, skin thickening, and the compressive action of the surrounding toes. Hyperkeratosis causes horny, scaly skin, as well as a warty look of the skin. Non pitting edema is thought to be caused by significant tissue fibrosis and thickening. The increasing dilatation of the cutaneous lymphatics and deteriorating fibrosis induce papillomatosis and elephantiasis.[15] Many practitioners use the existence of these indicators to make a lymphedema clinical diagnosis and then recommend therapy.[16]

Diagnostic testing for lymphedema. Lymphedema can be diagnosed via nuclear medicine, radiology, and near-infrared fluorescence tests. Lymphocintigraphy and lymphangiography are nuclear medicine procedures, whereas magnetic resonance and computed tomography lymphangiography, as well as duplex ultrasound, are radiologic imaging procedures. Using fluorescent contrast agents and near-infrared fluorescence, a fresh technique for defining lymphatic function and anatomy has emerged.[17] Lymphoscintigraphy has been used for more than three decades, with sensitivity and specificity frequently reaching 90% in several investigations. The investigation is non-invasive and has few disadvantages.[18,19] Although it cannot be

utilized to confirm lymphatic bypass patency, the role of this study beyond making a diagnosis and assisting with surgical planning has been noted.[20,21] Because quantitative evaluation of nuclear isotope uptake has been demonstrated to be problematic, visual interpretation, semiquantitative evaluation, or a combination of the two (As utilized in this work) are frequently used instead.[21] While lymphangiography has historically played an essential part in the diagnosis of lymphedema, it now has a limited role due to a number of factors such as the danger of embolization, infection, and lymphatic damage. Its application is now restricted to the identification of thoracic, abdominal, and pelvic lymphatic disorders, as well as fistulas.[22] In fluorescent lymphangiography, ICG injected into the dorsum of the foot and drained to the groin along the medial portion of the thigh. Dermal backflow of lymph from collecting lymph veins to the skin surface is the most essential finding for lymphedema diagnosis. This method could be a better way to detect the presence or absence of lymphatic disease.[23] But another aspect to be considered is that although NIRFL is minimally invasive, there are still concerns for infection, local reactions, allergy to the ICG, and pain associated with the procedure. We consider imaging after 24 hours (Delayed image) as the staging systems relying on DBF patterns that time consuming, requiring up to 18 hours for recording.[24,25]

Our study showed that about half of the lymphedema patients with immediate normal pattern of NIRFL changed into dermal backflow after 24 hours. On the other hand, all cases with immediate dermal backflow persist as it is after 24 hours. This suggests that we couldn't relay on immediate images if it is normal but we should repeat imaging after long time to make sure lymphatic system is normal. Other finding noticed not all patients that diagnosed clinically with lymphedema manifesting abnormal lymphatic drainage. About 26% of cases showed lymphoedema free. These results highlight the importance of using objective testing to confirm diagnosis of lymphedema.

Jayaraj et al evaluate the accuracy of clinical signs in comparison to lymphoscintigraphy. It is hoped that the findings of this study, which show that nearly one-third of patients with clinical signs of lymphedema do not have lymphoscintigraphy-confirmed lymphedema and that only 17% of patients with lymphoscintigraphy-confirmed lymphedema have the classic clinical signs, will spur more research into this important topic. The shortcomings of the use of clinical signs in making a diagnosis of lymphedema are probably best highlighted by the positive and negative predictive values of 68% and 43%, respectively. Overall, the accuracy of 47% underscores the difficulty in depending on a clinical diagnosis of lymphedema.[26]

Another study conducted on 212 limbs demonstrates a weak correlation between clinical stages of lymphedema and imaging (ICG) staging. Therefore, we assert that physical examination findings alone should not be used in preoperative decision making for physiologic lymphedema surgery.[27]

This immediate linear pattern enabled the surgeon to delineate suitable lymphatics for lymphaticovenular anastomosis. In 2013, Chang et al. presented a simplified ICG lymphographic staging system that could be used immediately preoperatively to identify appropriate lymphatic channels for bypass.[14]

Also, we noticed from our study that most of patients were obese with high BMI. Obesity has been linked to an increased incidence of secondary lymphedema due to damage to the lymphatic system, according to several studies. It was discovered in 1957 that the heavier a patient was, the more likely to develop lymphedema following breast cancer therapy. Individuals with a body mass index greater than 30 had three times the probability of developing upper extremity lymphedema compared to patients with a body mass index less than 25 in a prospective level II trial of 137 patients with breast cancer.[28]

More research is needed to determine the sensitivity and specificity of ICG fluorescence lymphography in identifying lymphedema in patients with swollen legs on a bigger scale. However, we believe that this technology could eventually use as a method of lymphedema screening. We anticipate that once the utility of ICG fluorescence lymphography for the diagnosis of lymphatic disease is verified, it will be applied in other low-cost clinical testing.[29,30]

Conclusion

Fluorescence lymphangiography technique is safe and minimally invasive. Clinical signs of lymphedema appear to be unreliable in making a correct diagnosis of lymphedema in about 30 % of patients. Panoramic images of the leg after 24 hours of injection showed characteristic changes of patterns of lymph drainage in about fifty percent of patients suffering from clinically diagnosed lymphedema. These findings suggested that routine use of ICG fluorescence lymphography may be useful to differentiate lymphedema from edema resulting from other causes.

Acknowledgements: Special thanks for Takumi Yamamoto for his contribution in this research.

References

1. Burnand K, Mortimer P, Partsch H: Diagnosis and investigation of lymphedema. In: Browse N, Burnand K, Mortimer P, (eds.). Diseases of the lymphatics. London: *Arnold.* 2003; 100-51.

2. Baillif S, Wolff B, Paoli V, et al: Retinal fluorescein

and indocyanine green angiography and spectral-domain optical coherence tomography findings in acute retinal pigment epitheliitis. ***Retina.*** 2011; 31: 1156–63.

3. Mordon S, Devoisselle JM, Soulie-Begu S, et al: Indocyanine green; hysiochemical factors affecting its fluorescence in vivo. ***Microvasc Res.*** 1998; 55: 146–52.

4. Noura S, Ohue M, Seki Y, et al: Feasibility of a lateral region sentinel node biopsy of lower rectal cancer guided by indocyanine green using a near-infrared camera system. ***Ann Surg Oncol.*** 2010; 17: 144–51.

5. Desai ND, Miwa S, Kodama D, et al: A randomized comparison of intraoperative indocyanine green angiography and transit-time flow measurement to detect errors in coronary artery grafts. ***J Thorac Cardiovasc Surg.*** 2006; 132: 585–94.

6. Reuthebuch O, Häussler A, Genoni M, et al: Novadaq SPY: Intraoperative quality assessment in off-pump coronary artery by-pass grafting. ***Chest***. 2004; 125: 418–24.

7. Lim C, Vibert E, Azoulay D, et al: Indocyanine green fluorescence imaging in the surgical management of liver cancers: Current facts and future implications. ***J Visc Surg.*** 2014; 151: 117–24

8. Alander JT, Kaartinen I, Laakso A, et al: A review of indocyanine green fluorescent imaging in surgery. ***Int J Biomed Imaging.*** 2012; 2012: 940585.

9. Luo S, Zhang E, Su Y, et al: A review of NIR dyes in cancer targeting and imaging. ***Biomaterials.*** 2011; 32: 7127–38.

10. Daskalaki D, Fernandes E, Wang X, et al: Indocyanine green (icg) fluorescent cholangiography during robotic cholecystectomy: Results of 184 consecutive cases in a single institution. ***Surg Innov***. 2014; 21(6): 615-21.

11. Spinoglio G, Priora F, Bianchi PP, et al: Real-time near-infrared (NIR) fluorescent cholangiography in single-site robotic cholecystectomy (SSRC): A single-institutional prospective study. ***Surg Endosc.*** 2012; 27: 2156–62.

12. Yamamoto T, Narushima M, Doi K, et al: Characteristic indocyanine green lymphography findings in lower extremity lymphedema: The generation of a novel lymphedema severity staging system using dermal backflow patterns. ***Plast Reconstr Surg***. 2011; 127(5): 1979-86.

13. Bollinger A, Jäger K, Sgier F, et al: Fluorescence microlymphography. ***Circulation.*** 1981; 64(6): 1195-200.

14. Chang DW, Suami H, Skoracki R: A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. ***Plast Reconstr Surg***. 2013; 132: 1305–14.

15. Stemmer R: A clinical symptom for the early and differential diagnosis of lymphedema. ***Vasa***. 1976; 5: 261-2.

16. Browse N, Burnand K, Mortimer P: Diseases of the lymphatics. London: ***Arnold.*** 2003.

17. O'Donnell TF, Rasmussen JC, Sevick-Muraca EM: New diagnostic modalities in the evaluation of lymphedema. ***J Vasc Surg Venous Lymphat Disord.*** 2017; 5: 261-73.

18. Cambria RA, Gloviczki P, Naessens JM, et al. Noninvasive evaluation of the lymphatic system with lymphoscintigraphy: A prospective, semiquantitative analysis in 386 extremities. ***J Vasc Surg.*** 1993; 18: 773-82.

19. Lam MC, Luk WH, Tse KH: Lymphoscintigraphy in the evaluation of lower extremity lymphedema: Local experience. ***Hong Kong Med J.*** 2014; 20: 121-5.

20. Peller PJ, Friese JL, Lindgren EA, et al: Lymphoscintigraphy, lymphangiography and magnetic resonance imaging. In: Gloviczki P, (ed.). Handbook of venous and lymphatic disorders. 4th ed. Boca Raton: ***CRC Press.*** 2017; 712-24.

21. Vaqueiro M, Gloviczki P, Fisher J, et al: Lymphoscintigraphy in lymphedema: An aid to microsurgery. ***J Nucl Med.*** 1986; 27: 1125-30.

22. Gloviczki P, Calcagno D, Schirger A, et al: Noninvasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphic examinations. ***J Vasc Surg*** 1989; 9: 683-90.

23. Jager K, Isenring G, Bollinger A: Fluorescence microlymphography in patients with lymphedema. ***Int Angiol.*** 1983; 2: 129-36.

24. Yamamoto T, Narushima M, Yoshimatsu H, et al: Dynamic Indocyanine Green (ICG) lymphography for breast cancer-related arm lymphedema. ***Ann Plast Surg.*** 2014; 73(6): 706-9.

25. Yamamoto T, Yoshimatsu H, Narushima M, et al: Indocyanine green lymphography findings in primary leg lymphedema. ***Eur J Vasc Endovasc Surg.*** 2015; 49: 95–102.

26. Jayaraj A, Raju S, May C, et al: The diagnostic unreliability of classic physical signs of lymphedema. ***J Vasc Surg Venous Lymphat Disord.*** 2019; 7(6): 890-97.

27. Garza RM, Ooi ASH, Falk J, et al: The relationship between clinical and indocyanine green staging in lymphedema. ***Lymphat Res Biol.*** 2019; 17(3): 329-33.

28. Treves N: An evaluation of the etiological factors of lymphedema following radical mastectomy; an analysis of 1,007 cases. ***Cancer.*** 1957; 10: 444–59.

29. Mellor RH, Stanton AW, Azarbod P, Set al: Enhanced cutaneous lymphatic network in the forearms of women with postmastectomy oedema. ***J Vasc Res***. 2000; 37: 501-12.

30. Benson RC, Kues HA: Fluorescence properties of indocyaninegreen as related to angiography. ***Phys Med Biol.*** 1978; 23: 159-63.