International Journal of Surgery Publish Ahead of Print
DOI: 10.1097/JS9.0000000000003252

OPEN

The Pattern of Arm Lymphatic Drainage and Subclinical Lymphedema Progression after Axillary Lymph Node Dissection: A Prospective Cohort Study

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Running Head:

Lymphatic drainage patterns and the progression of subclinical lymphedema

Funding Source:

This work was supported by research funding from the Islamic Development Bank (IsDB) IDN 1031.

Conflict of Interest:

The authors have no competing interests.

Acknowledgments:

The authors wish to thank Faza Soelaeman MD and Adhitya Bayu Perdana for their encouragement and support on this project, especially for manuscript preparation.

Word count (Title): 18

Word count (Abstract): 247

Word count (Text body): 3187

Figures: 3, **Tables**: 5

"The Pattern of Arm Lymphatic Drainage and Subclinical Lymphedema Progression after Axillary Lymph Node Dissection"

Abstract

Background: Breast cancer treatment-related lymphedema (BCRL) is a chronic progressive morbidity for which a definitive cure has not yet been achieved. Since axillary lymph node dissection (ALND) is the main risk factor, we have studied the pattern of lymphatic drainage and subclinical lymphedema progression with ICG lymphography (ICG-L) after ALND as a part of our strategy to prevent BCRL.

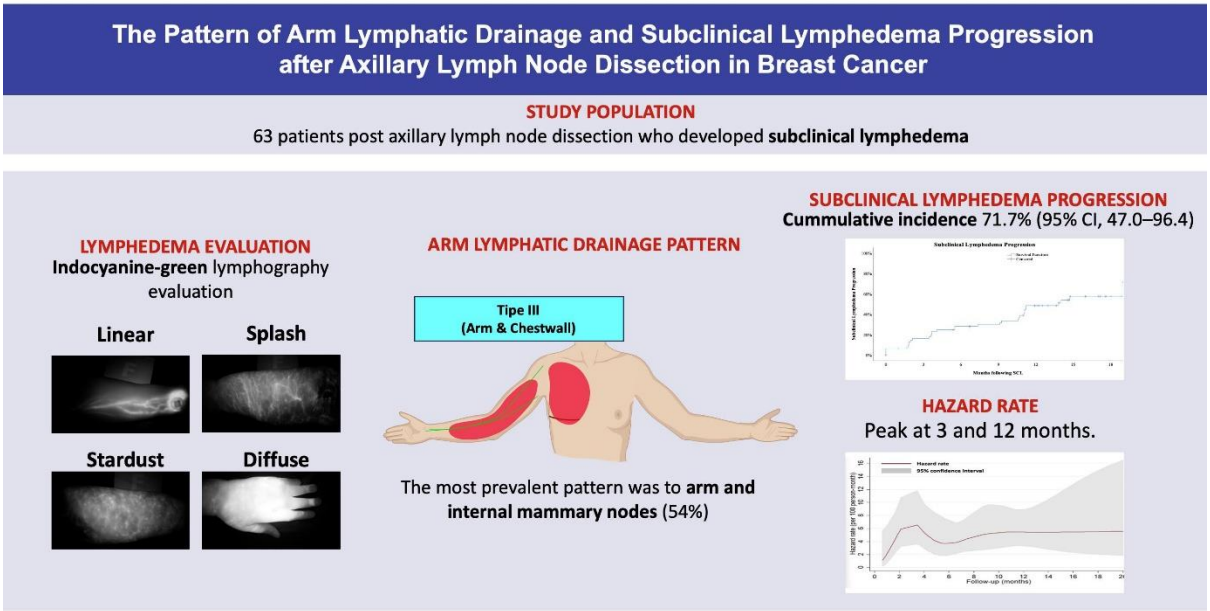
Methods: This study was a prospective cohort of breast cancer patients who underwent ALND between October 2022 and August 2024. We prospectively evaluated postoperative lymphatic drainage with ICG-L. Subclinical lymphedema progression to lymphedema was analyzed using the Kaplan-Meier method.

Results: Sixty-three patients were analyzed. Five classifications of lymphatic pathways were identified. The most prevalent pattern was arm and chest wall dermal backflow (DB), draining to internal mammary nodes or type III in 54% of cases, followed by arm DB and collateral drainage to clavicular nodes (type II) in 19.1%, and arm DB only (type I) in 14.3% cases. The cumulative incidence of subclinical lymphedema progression to BCRL was 71.7% (95% CI, 47.0–96.4) with a median BCRL incidence of 13.8 months (95% CI, 10.0–17.5). The hazard rate of BCRL reached its peak at 3 and 12 months.

Conclusion: The lymphatic drainage pattern of the arm will mainly drain into the internal mammary and clavicular nodes after ALND. A substantial number of subclinical cases progressing to early-stage BCRL can be detected by ICG-L within the first year. This finding could be used to develop strategies for BCRL prevention.

Keywords: breast cancer-related lymphedema, indocyanine green lymphography, axillary lymph node dissection, lymphedema prevention

Graphical abstract



Highlights

- Breast cancer-related lymphedema (BCRL) is a chronic progressive disease requiring screening and early detection as an important approach.
- A total of 63 patients were recruited to evaluate arm lymphatic drainage and progression of subclinical lymphedema after axillary lymph node dissection (ALND)
- Five lymphatic drainage patterns were identified using indocyanine green lymphography (ICG-L), with arm and chest wall dermal backflow draining to internal mammary nodes (type III) being the most prevalent (54%).
- The 18-month cumulative incidence of subclinical lymphedema progression to BCRL was 71.7%.

INTRODUCTION

Breast cancer treatment-related lymphedema (BCRL) causes significant morbidity in breast cancer patients[1]. Among several factors, axillary lymph node dissection (ALND) contributes to the main risk[2]. Indonesia is still facing challenges in reducing the prevalence of advanced-stage breast cancer among the population population[3]. Therefore, ALND is still commonly performed for axillary staging, which increases the risk of lymphedema. Once it progresses, an actual lymphedema cure is difficult to achieve with curative treatment[4]. So, a preventive strategy promoting early detection and intervention, i.e., secondary prevention, should be prioritized.

Numerous studies promote screening programs for secondary prevention[5–8], since it prevents lymphedema progression into the chronic phase[7]. Screening for subclinical lymphedema is essential since it is a sign that often precedes BCRL[9,10]. Bucci *et al*. concluded that patients with ALND who developed subclinical lymphedema were more likely to progress to BCRL[10]. Therefore, the key to screening BCRL is the capability to diagnose subclinical lymphedema[7].

As much progress has been made in lymphedema diagnostic modalities, and indocyanine green lymphography (ICG-L) is considered the most sensitive tool for detecting subclinical lymphedema[11–15]. ICG-L's ability to diagnose subclinical lymphedema by detecting alternative lymphatic pathways after ALND, i.e., dermal backflow patterns[9,15,16] and collateral pathways[17–21] is advantageous for secondary prevention.

Although the classification of lymphatic drainage changes after ALND has been well studied[17–21]. There are still no reports on its distribution in subclinical cases. Furthermore, limited data still exist on ICG-L screening to monitor subclinical lymphedema progression[9,16]. In this study, we aimed to determine the distribution of lymphatic patterns in subclinical lymphedema and evaluate the time it takes for BCRL progression. We anticipate that this study will be beneficial for BCRL's prevention strategy.

METHODS

Patients

The prospective cohort study was conducted from October 2022 to August 2024. The inclusion criteria were: 1). Breast cancer patients who underwent axillary lymph node dissection (ALND); 2. with subclinical lymphedema. We excluded patients with sentinel

node biopsy and pregnancy. The institutional review board approved the study (227/KEPK/IX/2022). Written informed consent was obtained from all participants,

Indocyanine Green Lymphography Evaluation

The ICG-L procedure was carried out before and after the surgery as per the scheduled time. The ICG was interpreted by the main researcher (BB) that was blinded by the patient identity and medical history. We used ICG dye (Premix Indocyanine Green USP 0.5%) that was injected subcutaneously (@0.1 ml) at the second and fourth web spaces of the hand and the ulnar border of the palmaris longus tendon at the wrist joint level[22,23]. Superficial lymphatic circulation was assessed at 5 minutes (transient phase) and 2 hours (plateau phase). At this point, we determined the arm dermal backflow (DB) using ICG-L stage which are classified as follows: stage 0, the linear pattern only; stage I, linear and splash patterns; stage II, linear and stardust/diffuse pattern in one region; stage III, linear and stardust/diffuse pattern in two regions; stage IV, linear and stardust/diffuse pattern in three regions; stage V, stardust and/or diffuse pattern[24].

Variable Definition

The subclinical lymphedema was defined by the presence of arm and/or torso DB. These criteria were specified by: 1. Arm DB with a splash and/or a stardust/diffuse pattern covering less than 30% of each arm region; 2. Torso DB was characterized by linear collateral lymphatic pathways to the clavicular, DB to ipsilateral or contralateral intramammary nodes; 3. No clinical symptoms and increasing upper extremity lymphedema (UEL) index < 10%[25]. Transient lymphedema was defined as the presence of subclinical lymphedema on initial ICG-L evaluation, followed by a subsequent return to a linear pattern on follow-up.

BCRL was defined by at least ICG-L stage II with a minimum 30% area in each upper limb region, with or without clinical symptoms and UEL index > 10%. The DB patterns were analyzed circumferentially with Fluoro 4000 XL near-infrared camera.

Surgery

All patients underwent surgery either as lumpectomy or mastectomy. ALND level I-II, if necessary, level III was performed according to the standard axillary surgical staging technique[26]. A sufficient length of afferent lymph vessels was taken to histopathology for metastasis and obstruction examination, as described in our previous study[27].

Follow-up and Outcomes

We evaluated the patients with clinical examination, lymphedema quality of life score (LeQOLiS)[28], UEL index, and ICG-L every two months in the first year and three months in the second year. Our study outcomes were: 1. The pattern of arm lymphatic drainage, and 2. Time for subclinical lymphedema progression to BCRL.

Statistical Analysis

Baseline characteristics were analyzed descriptively. To evaluate the time from subclinical lymphedema onset to the development of BCRL, we performed a time-to-event analysis using the Kaplan-Meier method. Patients were censored at the end of follow-up or if BCRL had not developed by the final visit. A flexible parametric survival model was also utilized to estimates hazard rates per 100 person-months at specific time points. Follow-up time in months was used as the time scale and the occurrence of BCRL was the outcome with 4 degrees of freedom[29]. Data analysis was performed with a 95% confidence interval (CI), and a p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 27.0 and Stata/MP version 17.0.

Sample size calculation was based on a one-arm survival analysis sample size[30]. The calculation was conducted using a two-sided α level of 0.05 and 80% statistical power. The work has been reported in line with the STROCSS criteria[31].

RESULTS

Table 1. Baseline characteristics

Variable		N = 63
Age (years)	Mean ± SD	48.1 ± 11.1
Gender, n (%)	Female	62 (98.4)
	Male	1 (1.6)
BMI (kg/m^2)	Mean ± SD	26.0 ± 4.6
Breast Cancer Stage, n (%)	II A	9 (14.3)
	II B	8 (12.7)
	III A	13 (20.6)
	III B	15 (23.8)
	III C	14 (22.2)
	IV	4 (6.4)
Surgery, n (%)	Mastectomy	50 (79.4)
	BCS	12 (19.0)
	Wide excision	1 (1.6)
Radiotherapy, n (%)	Yes	39 (61.9)
	No	24 (38.1)
Chemotherapy, n (%)	Yes	60 (95.2)
	No	3 (4.8)
Lymph nodes removed	Median (IQR)	18 (14-21)
Lymph vessel obstruction, n (%)	Yes	15 (23.8)
	No	47 (74.6)
	Missing	1 (1.6)
Afferent lymph metastasis, n (%)	Yes	0 (0)
	No	63 (100)
BCRL, n (%)	Yes	32 (50.8)
	No	31 (49.2)

*BMI = body mass index, BCRL = breast cancer-related lymphedema

Baseline Characteristics

Baseline characteristics are presented in Table 1. Among 63 patients with subclinical cases, the median (IQR) was 48.1 ± 11.1 years. There was one male patient (0.7%) in this study.

The BMI was obese with a mean ± SD of 26.0 ± 4.6 kg/m2. The locally advanced stage was found in 42 patients (66.7%). Regarding the type of surgery, mastectomy was conducted the most (79.4%). Radiotherapy was given to 39 patients (61.9%). Chemotherapy was delivered to 60 patients (95.2%). The details on the radiotherapy and chemotherapy given can be seen in **Supplementary Table S1**. The median (IQR) number of lymph nodes removed was 18 (14-21). We also found that lymph vessel obstruction had already occurred during surgery in 15 patients (23.8%). No afferent lymph vessel metastasis was found among all patients (0%). We found that more than half of the subclinical cases (50.8%) developed BCRL.

Subclinical Lymphedema Drainage Pattern and Classification

Among the 63 patients diagnosed with subclinical lymphedema, 57 (90.5%) exhibited arm dermal backflow, predominantly with the splash pattern (77.2%). Torso DB was observed in 54 patients (85.7%), with the chest wall being the most common site (62.9%). All are observed in Table 2.

Table 2. Subclinical lymphedema pattern

Variable		**N = 63**
Arm DB, n (%)	Yes	57 (90.5)
	No	6 (9.5)
Arm DB types (n=57)	Splash	44 (77.2)
	Stardust	13 (22.8)
Torso DB, n (%)	Yes	54 (85.7)
	No	9 (14.3)
Torso DB types (n=54)	Clavicular	16 (29.6)
	Chest wall	34 (62.9)
	Contralateral chest wall	4 (7.4)

*DB = dermal backflow

Based on the combination of arm and torso backflow patterns, we classified patients into five types: Type I (arm only), Type II (arm + clavicular), Type III (arm + chest wall), Type IV (arm + contralateral), and Type V (clavicular only) as shown in Table 3 and Figure 1. Type III was the most common, accounting for 54% of cases, followed by type II (19.1%), type I (14.3%), type IV (6.3%), and type V (6.3%). These classifications are visualized in Figure 1. Most patients had onset of subclinical lymphedema in 2 months after ALND (82.5%),

followed by 4 months (12.7%) **(Supplementary Table S2)**. At the onset of subclinical lymphedema, the median (IQR) of the UEL index percentage difference was -2.5 (-4.3–0.3) and LeQOLiS was 0 (0–3).

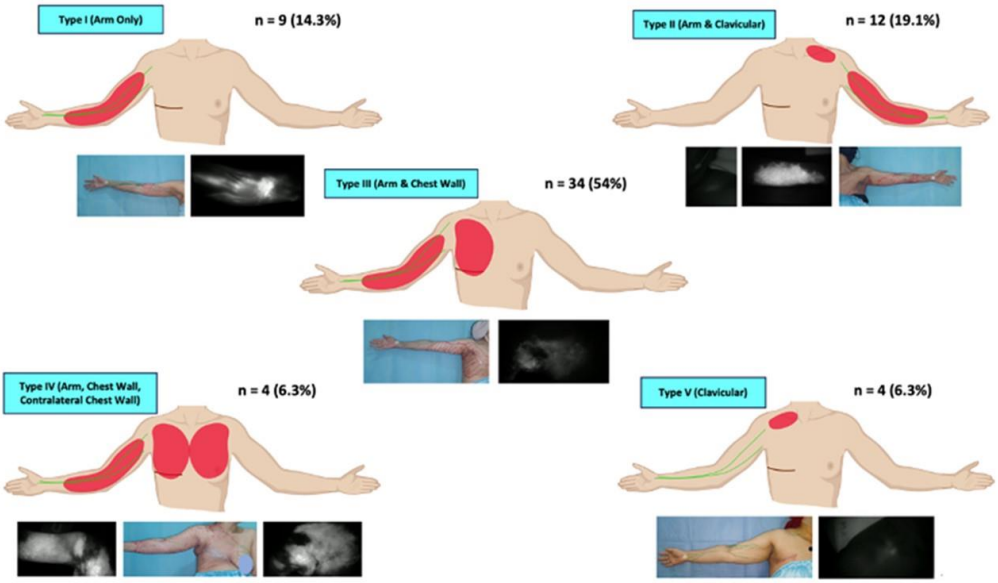


Figure 1. Subclinical Lymphedema Drainage Classification

Table 3. Subclinical lymphedema classification

Variable		**N = 63**
Classification, n (%)	Type I (arm only)	9 (14.3)
	Type II (arm + clavicular)	12 (19.1)
	Type III (arm + chest wall)	34 (54.0)
	Type IV (arm + contralateral)	4 (6.3)
	Type V (clavicular only)	4 (6.3)

Progression to Breast Cancer-Related Lymphedema

We found that more than fifty percent of BCRL patients were in the early stages. ICG-L stage II was among 17 patients (53.1%), ICG-L stage III was in 13 patients (40.6%), and ICG-L stage IV was among 2 patients (6.3%). During the onset of BCRL, the LeQOLiS score had a median (IQR) of 14 (6.3-20) and a mean UEL index percentage difference of 6.6 ± 7.0% as seen in **Supplementary Table S3**.

Lymphatic Drainage Pattern and Lymphedema Proportion

We found that the arm, clavicular, and chest wall regions had a higher proportion of involvement, each exceeding 50%. BCRL occurred in 66.7% of type I, 50% of type II, 52.9% of type III, 25% of type IV, and 25% of type V (**Table 4)**. In those who experienced BCRL, Type III had the highest proportion among all ICG-L stages, particularly in stage 2 (28.1%) and stage 3 (25%). In comparison, types I and II were the second most common group among the different ICG-L stages.

(**Supplementary Table S4)**.

Table 4. BCRL patients characteristics

Variable		**N = 32**
ADB stages, n (%)	Stage II	17 (53.1)
	Stage III	13 (40.6)
	Stage IV	2 (6.3)
LeQOLiS Score	Median (IQR)	14 (6.3-20)
UEL Index percentage difference	Mean ± SD	6.6 ± 7.0

*ADB = arm dermal backflow, BCRL= breast cancer-related lymphedema, LeQOLiS = Lymphedema quality of life score, UEL = Upper extremity lymphedema

Table 5. Lymphatic drainage classification and breast cancer-related lymphedema

Classification	**Total (n=63)**	
	BCRL (n=32)	**No BCRL (n=31)**
Type I (arm only)	6 (66.7)	3 (33.3)
Type II (arm + clavicular)	6 (50)	6 (50)
Type III (arm + chest wall)	18 (52.9)	16 (47.1)
Type IV (arm + contralateral)	1 (25)	3 (75)
Type V (clavicular only)	1 (25)	3 (75)

*BCRL= breast cancer-related lymphedema

Breast Cancer-Related Lymphedema Cumulative Incidence and Hazard Rate

Our study achieved a mean follow-up duration of 14.1 ± 3.2 months, which is deemed adequate, as prior research has identified the highest risk period for BCRL development to occur between 12 and 30 months postoperatively[2]. We observed that 32 subclinical lymphedema cases progressed to BCRL, while the remaining 31 patients were censored in the Kaplan-Meier analysis. One of the censored cases was classified as a transient lymphedema. This was a 25-year-old patient who was in stage IIA breast cancer, with a BMI of 20.2 kg/m², and received adjuvant radiotherapy.

The 18-month BCRL cumulative incidence was 71.7% (95% CI, 47.0-96.4). The median BCRL's cumulative incidence was 13.8 months (95% CI, 10.0-17.5) (Figure 2). It was also indicated in Figure 3 that the hazard rate of BCRL peaked at 3 and 12 months. The hazard rates were 7.0 (95% CI, 3.8-12.9) per 100-person month at 3 months and 5.4 (95% CI, 3.3-8.9) per 100-person month at 12 months.

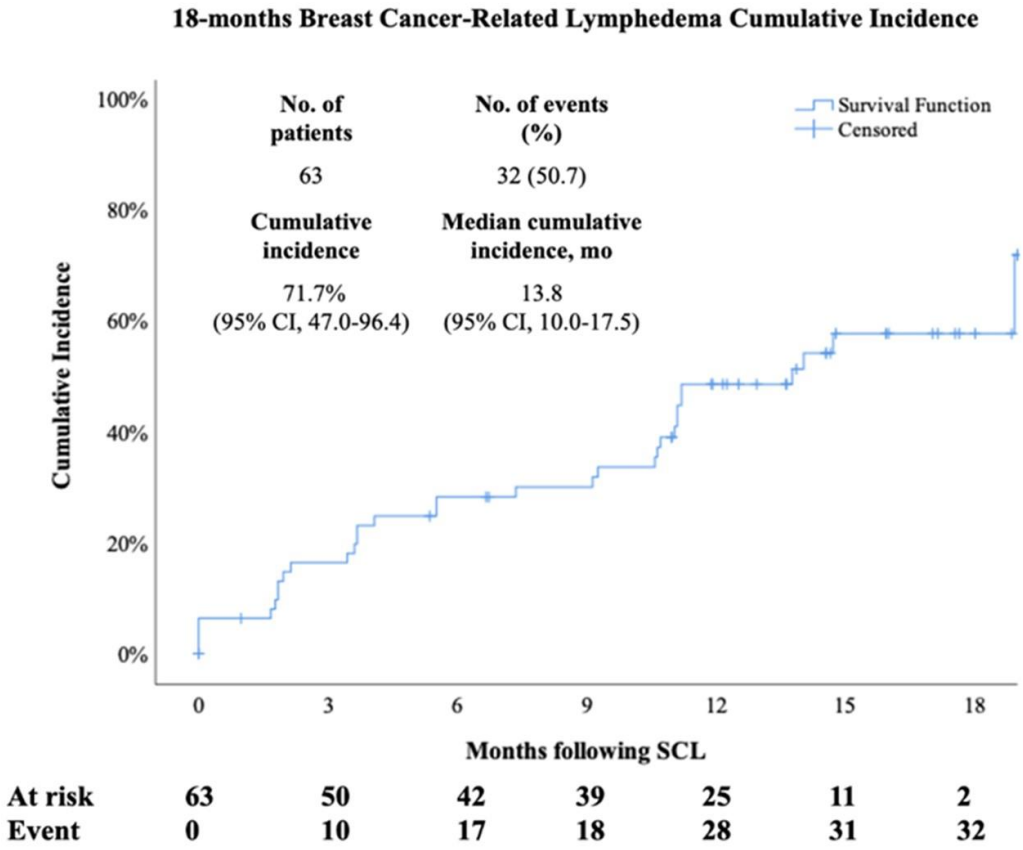


Figure 2. Breast Cancer-Related Lymphedema Cumulative Incidence

***Mo = Months, SCL = Subclinical lymphedema**

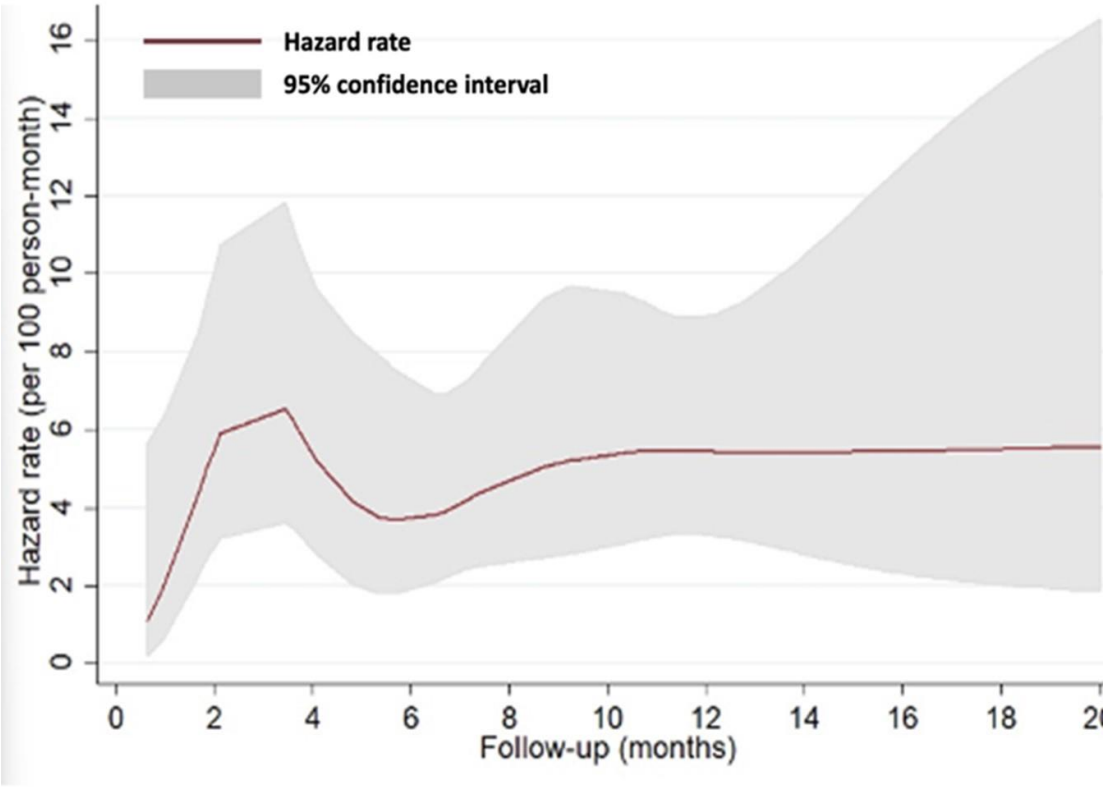


Figure 3. The Hazard Rate of BCRL

DISCUSSION

Nowadays, the trend for BCRL treatment has shifted from curative to preventive management. The reason lies behind that curative treatment has not achieved a "true" cure if lymphedema has developed and progressed[4]. Despite the need for more evidence to confirm its effectiveness[32], immediate lymphatic reconstruction has risen as an option for primary prevention[33–35]. Another way to prevent lymphedema is by employing secondary prevention to identify subclinical signs. This step is logical since the body creates alternative lymphatic drainage in response to lymphatic injury and manifests as subclinical lymphedema[17–21]. By earlier finding the changes in drainage, i.e., dermal backflow, communication with other collecting lymph vessels, and lymphangiogenesis, the subclinical lymphedema can be treated and prevented from progressing[9,10,16].

Locally advanced breast cancer constitutes the majority stage in Indonesia[3], with ALND, radiotherapy, and chemotherapy as the mainstay treatment[3,36]. Undoubtedly, these factors will increase the risk of BCRL to our patients[2]. Therefore, we think that the lymphedema screening program should be prioritized and included in our breast cancer management.

Many studies have reported methods for screening subclinical lymphedema but ICG-L is considered the most sensitive and reliable tool, specifically for subclinical lymphedema detection[11,13,15,37]. ICG-L has also previously been described to be able to map lymphatic pathways in the arm of patients who underwent ALND which serves as important knowledge to the development of lymphedema[38]. Splash pattern is the earliest ICG-L finding in asymptomatic patients and becomes the hallmark of subclinical signs[15]. Our data also shows that the splash pattern is the major subclinical sign (77.2%), followed by stardust (22.8%). These arm dermal backflow (DB) are one of the body's compensatory mechanisms of lymphatic obstruction by creating alternative pathways; the others are torso DB, connection with superficial or deep collecting lymph vessels, and lymphangiogenesis[17–21].

In our study, we used a three-injection site protocol for ICG lymphography that was modified from the Narushima et al that used two injection sites, and Suami et al at four locations[22,23]. This approach offers several practical advantages, including fewer needle punctures, which can help reduce the pain, anxiety, and patient complaints, particularly regarding swelling and temporary greenish discoloration at the injection site. Additionally, using fewer injection points reduces the total volume of ICG dye required, potentially lowering the overall procedural cost[39]. However, our injection method may pose a risk of underrepresenting the complete lymphosomal architecture, thereby decreasing the sensitivity of subclinical lymphedema detection[23]. Given this trade-off between patient comfort and diagnostic thoroughness, further research is warranted to evaluate the diagnostic accuracy of various injection techniques and their impact on early lymphedema detection. Ideally, future studies should assess whether a limited injection protocol sufficiently captures the relevant lymphatic pathways without compromising clinical sensitivity.

Based on our data, we found that most (82.5%) subclinical lymphedema had already occurred in 2 months post-ALND. This study aims to identify lymphatic system changes as early as possible following ALND. This approach is based on several previous studies that have reported that lymphatic changes occur within a few days after ALND. Lymphangiogenesis manifests rapidly after injury, as described in both studies by Nelson *et al.*[40] and Baluk *et al.*[41] According to these findings, lymphatic remodeling begins within weeks of lymphatic vessel damage, as early as 14-42 days. These timelines underscore that early molecular and structural changes in the lymphatic system can theoretically be detectable within 1–2 months.

The alternative lymphatic pathways after ALND have been classified based on seminal studies by Suami *et al*.[20] Based on their classification, firstly, we observe the combination of arm and chest wall DB (type III) carrying accumulating lymph fluid to internal mammary nodes, commonly found (54%) as subclinical cases. Fifty-three percent of this type has progressed to BCRL and type III represents the highest proportion of lymphatic drainage pattern among all stages of BCRL. Secondly, 19% of the accumulating lymph fluid was drained via regeneration or communication of lymphatic vessels to clavicular nodes (type II), and 50% progressed to BCRL.

The findings on internal mammary and clavicular node drainage have some essential points: first, the nodes serve as the main alternative routes after ALND; second, drainage to these nodes may indicate an ongoing process of severe afferent lymphatic obstruction. When the routes do not work for some reason, then lymphedema will develop[2]. We suggest that lymphatic drainage to internal mammary and clavicular nodes following ALND may indicate subclinical lymphedema with a potential risk of progressing to BCRL, which may not be detectable through clinical examination alone. Close follow-up is recommended when these signs appear for early BCRL detection and treatment.

Different methods are available to screen BCRL, starting from symptoms[42], circumferential measurement, water voluntary, perometry, bioimpedance spectroscopy, lymphoscintigraphy, and ICG-L. However, no universal diagnostic criteria are currently available since each study uses different methods[7]. Seeing that subclinical lymphedema is a risk factor for lymphedema development and progression[10], choosing the most sensitive tool to detect subclinical lymphedema is the key to BCRL screening[7]. ICG-L screening in our study provides evidence that BCRL can be diagnosed in an early stage. This was indicated by the following findings: 1. Fifty-three percent of the participants were diagnosed with stage II arm lymphedema; 2. BCRL was detected before the symptoms became severe as indicated by the lower LeQOLiS score; 3. The UEL index increased by less than 10%. Therefore, along with the other studies' results, we recommend ICG-L for BCRL screening since it is sensitive to detecting subclinical lymphedema before the onset of clinical symptoms and signs[15,16,43].

Our definition of BCRL was based on ICG-L findings that also included symptoms and UEL index differences. Hence it was not different from standard volume changes used commonly to diagnose BCRL. Furthermore, ICG-L-based evaluation for BCRL diagnosis is based on: 1) The stardust pattern observed in ICG-L is considered a sign of reversible lymphatic

abnormality[44]. 2) Additionally, our observations revealed that subclinical lymphedema with stardust pattern, despite the absence of clinical symptoms or measurable volume differences, exhibited dilated and sclerotic lymphatic vessels along with extracellular lymph fluid accumulation[45]. These insights highlight the importance of BCRL diagnosis based on ICG-L evaluation, as they may detect early lymphatic changes that are not evident through traditional volume-based definitions of BCRL.

The cumulative incidence (CI) of BCRL is reported to be between 9% and 54%. Differences in measurement methods (self-reported symptoms, objective tools evaluation, single or multiple diagnostic modalities), length of follow-up, and types of study design could explain the variability of the result[2,46–55]. Moreover, in several cohort studies, lymphedema is commonly diagnosed by self-reported swelling symptoms and measuring arm circumference[52]. The 18-month BCRL incidence in our study is 71%, with 50% of cases having lymphedema in 14 months. Our time-to-event BCRL analysis is different from that of other studies. It exhibits a higher BCRL cumulative incidence and median BCRL time that has never been reported in previous cohort studies[56–58]. The difference can be explained by the fact that the previous studies defined lymphedema by symptoms and arm volume measurement[56–58], which is less sensitive than ICG-L for detecting early changes in lymphatic circulation. Since ICG-L more frequently finds lymphedema[15,59], the cumulative incidence is high, and half of the patients experienced lymphedema in 14 months.

Another interesting finding is that the BCRL rate peaks at 3 and 12 months. It may imply that the first 3 months represent the early onset of lymphedema as an immediate response to lymphatic injury[60,61]. Following injury, tissue hypoxia and inflammatory response are triggered. Macrophages and CD4+ Th2 cells infiltrate the affected area, releasing mediators such as VEGF-C, IL-4, IL-13, IFN-γ, and LTB4. VEGF-C promotes lymphangiogenesis; however, the newly formed vessels are immature and leaky, resulting in ineffective drainage and exacerbation of edema. Th2 cytokines (IL-4, IL-13) inhibit lymphatic endothelial cell growth, and IFN-γ further suppresses lymphangiogenesis. LTB4 initially supports lymphatic repair but later shifts to an anti-lymphangiogenic role, exacerbating dysfunction[62]. This inflammation response will continue to occur, consequently resulting in obstruction of lymph flow and leading to fluid stasis. The increasing intraluminal pressure in the collecting superficial lymphatic vessels is transferred to the pre-collector vessels and capillaries. When it exceeds interstitial pressure, the contraction of filaments will open the channels between

lymphatic endothelial cells and lead to lymphatic fluid extravasation to interstitial tissue, causing early lymphedema [63,64]

This declining lymph function can be recovered. Several mechanisms could potentially reroute the obstructed lymphatic flow and prevent lymphedema development. The first is via dermal backflow; the second is via lymphangiogenesis; the third is by both mechanisms; the fourth is by rerouting to the lateral, deep, and lymphatic torso system[17,19]. However**,** this compensatory mechanism may fail, resulting in subsequent lymphatic dysfunction, leading to the delayed onset of BCRL at 12 months[40]. One of the possible contributing factors to this compensatory failure is adjuvant radiation, which may cause the delayed onset of lymphedema[40,65,66].

Radiotherapy causes apoptosis of cells, leading to fibrosis, which takes time to progress.[67] Fibrosis is a hallmark of chronic lymphedema and contributes to its irreversible and progressive nature. A key mediator is transforming growth factor-beta 1 (TGF-β1), which is secreted by macrophages and Th2 cells and promotes extracellular matrix (ECM) deposition by stimulating fibroblast activation, enhancing connective tissue growth factor expression, and inhibiting collagen degradation via the Smad signaling pathway. In addition, mast cells play a pivotal role by releasing chymase, which activates latent TGF-β1 stored in the extracellular matrix. This chymase-mediated activation of TGF-β1 further drives fibroblast proliferation and collagen accumulation, leading to sclerosis of lymphatic vessels and worsening lymphatic dysfunction[62]. Therefore, based on our findings, we recommend an initial ICG-L screening at 3 months after ALND, followed by a subsequent evaluation 12 months later for BCRL detection. However, further studies are necessary to confirm these findings to minimize the risk of getting the result by chance due to small sample size or single-center bias.

Equally important, our findings indicate that not all cases of subclinical lymphedema will progress to BCRL. When compensatory lymphatic mechanisms remain functional after lymphatic injury, some patients may not experience progression to BCRL. Abnormal lymphatic pattern such as splash observed on ICG lymphography may even revert to a normal linear pattern, as reported in a previous study[9]. These findings underscore the need for close monitoring of patients with subclinical lymphedema to support timely clinical decision and potential intervention.

We are aware that our study has limitations. Transient and subclinical lymphedema could be counted in our BCRL definition. But, the key to prevention is to find subclinical lymphedema as early as possible[10]. This can only be performed by ICG-L since it detects early changes in lymphatic circulation[15]. Our ICG-L depicts the splash pattern, which is the hallmark of the subclinical stage[15,59], and the stardust pattern that shows an irreversible state[15]. Another limitation is our short follow-up time; therefore, long-term delayed onset of BCRL due to radiotherapy cannot be evaluated yet. Longer follow-up time is needed. Moreover, our study was conducted in a single-center setting with a limited number of patients. As such, the findings should be interpreted with caution and may not be generalized to other populations with different characteristics. Future research with a more robust design, such as a larger sample size, multi-center involvement, and inclusion of a comparative arm, is recommended to validate these results

Despite this limitation, we have discovered new evidence that could be useful for BCRL prevention. First, ICG-L is a sensitive and reliable diagnostic tool for BCRL screening. The ability to find early change in lymphatic circulation has made it our preference for BCRL screening. Second, lymphatic drainage to clavicular and internal mammary nodes is a primary sign of subclinical lymphedema that should be closely followed due to a higher percentage of progression to lymphedema. Third, 3 and 12 months is the critical time for screening since the majority of subclinical lymphedema progresses to BCRL. Therefore, ICG lymphography may serve as a valuable tool to support clinical decision-making. Patients with these high-risk patterns may benefit from closer follow-up and earlier therapeutic intervention

Based on the above findings, we propose an algorithm for monitoring and treatment planning of subclinical lymphedema, with a minimum of two ICG-L evaluations **(Supplementary Figure S1).** Following ALND, an initial evaluation with ICG-L is performed at 3 months. When type I–III drainage patterns (the highest proportion to have BCRL) are detected, conservative management is recommended, as a prior study suggested that up to 32% of upper arm subclinical lymphedema may improve with conservative treatment[9]. These patients should then be reassessed 12 months afterwards (15 months post-ALND), as this is related to the second peak of the BCRL hazard rate in our findings. If there is improvement or stability in ICG-L findings, conservative measures can be continued. However, in cases of progression to BCRL, surgical treatment with supermicrosurgical lymphovenous bypass may be indicated.[68,69] Patients in this pathway remain under surveillance until 24 months.

For those presenting with type IV or V patterns, which are typically associated with a lower risk of progressing to BCRL, a more conservative approach involving routine clinical observation until 12 months (or 15 months postoperatively) is appropriate. If ICG-L findings remain stable or show signs of improvement, continued monitoring is sufficient. When progression to BCRL occurs, a conservative therapy is initiated[9]. These individuals also undergo follow-up care for up to 24 months. Although this framework may provide a practical foundation for clinical management, further studies are needed to optimize and validate the algorithm for broader application.

CONCLUSION

Based on the ICG-L analysis, the accumulation of arm lymph fluid after ALND will primarily drain into the clavicular and internal mammary nodes. This pattern could serve as a specific indicator of the subclinical stage, during which close monitoring of lymphedema progression is crucial, particularly within the 3 to 12-month period. We believe that this method enables early identification of patients at risk for BCRL, allowing timely interventions such as conservative treatment or preventive lymphedema surgeries to halt further progression.

Provenance and peer review:
Not commissioned, externally peer-reviewed.

REFERENCES

[1] Deban M, Vallance P, Jost E, McKinnon JG, Temple-Oberle C. Higher Rate of Lymphedema with Inguinal versus Axillary Complete Lymph Node Dissection for Melanoma: A Potential Target for Immediate Lymphatic Reconstruction? Current Oncology 2022;29:5655–63.

[2] McDuff SGR, Mina AI, Brunelle CL, *et al.* Timing of Lymphedema After Treatment for Breast Cancer: When Are Patients Most At Risk? International Journal of Radiation Oncology*Biology*Physics 2019;103:62–70.

[3] Setyawan IB, Kurnia D, Setiaji K, *et al.* Sociodemographic disparities associated with advanced stages and distant metastatic breast cancers at diagnosis in Indonesia: a cross-sectional study. Annals of Medicine & Surgery 2023;85:4211–7.

[4] Agarwal S, Garza RM, Chang DW. Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) for the prevention of secondary lymphedema. Breast J 2020;26:721–4.

[5] McLaughlin SA, Stout NL, Schaverien M V. Avoiding the Swell: Advances in Lymphedema Prevention, Detection, and Management. American Society of Clinical Oncology Educational Book 2020:e17–26.

[6] Heller DR, Killelea BK, Sanft T. Prevention Is Key: Importance of Early Recognition and Referral in Combating Breast Cancer–Related Lymphedema. J Oncol Pract 2019;15:263–4.

[7] Rafn BS, Christensen J, Larsen A, Bloomquist K. Prospective Surveillance for Breast Cancer-Related Arm Lymphedema: A Systematic Review and Meta-Analysis. J Clin Oncol 2022;40:1009–26.

[8] Shah C, Arthur DW, Wazer D, Khan A, Ridner S, Vicini F. The impact of early detection and intervention of breast cancer-related lymphedema: a systematic review. Cancer Med 2016;5:1154–62.

[9] Akita S, Nakamura R, Yamamoto N, *et al.* Early Detection of Lymphatic Disorder and Treatment for Lymphedema following Breast Cancer. Plast Reconstr Surg 2016;138:192e–202e.

[10] Bucci LK, Brunelle CL, Bernstein MC, *et al.* Subclinical Lymphedema After Treatment for Breast Cancer: Risk of Progression and Considerations for Early Intervention. Ann Surg Oncol 2021;28:8624–33.

[11] Mihara M, Hara H, Araki J, *et al.* Indocyanine Green (ICG) Lymphography Is Superior to Lymphoscintigraphy for Diagnostic Imaging of Early Lymphedema of the Upper Limbs. PLoS One 2012;7:e38182.

[12] Jørgensen MG, Toyserkani NM, Hansen FCG, Thomsen JB, Sørensen JA. Prospective Validation of Indocyanine Green Lymphangiography Staging of Breast Cancer-Related Lymphedema. Cancers (Basel) 2021;13:1540.

[13] Akita S, Mitsukawa N, Kazama T, *et al.* Comparison of lymphoscintigraphy and indocyanine green lymphography for the diagnosis of extremity lymphoedema. Journal of Plastic, Reconstructive & Aesthetic Surgery 2013;66:792–8.

[14] Chen WF, Lensing JN, Bowen M. Indocyanine green lymphography can be falsely negative in early extremity lymphedema. Journal of Plastic, Reconstructive & Aesthetic Surgery 2020;73:391–407.

[15] Yamamoto T, Matsuda N, Doi K, *et al.* The Earliest Finding of Indocyanine Green Lymphography in Asymptomatic Limbs of Lower Extremity Lymphedema Patients Secondary to Cancer Treatment. Plast Reconstr Surg 2011;128:314e–21e.

[16] Liu M, Liu S, Zhao Q, Cui Y, Chen J, Wang S. Using the Indocyanine Green (ICG) Lymphography to Screen Breast Cancer Patients at High Risk for Lymphedema. Diagnostics 2022;12:983.

[17] Suami H. Anatomical Theories of the Pathophysiology of Cancer-Related Lymphoedema. Cancers (Basel) 2020;12:1338.

[18] Suami H, Scaglioni M. Anatomy of the Lymphatic System and the Lymphosome Concept with Reference to Lymphedema. Semin Plast Surg 2018;32:005–11.

[19] Suami H, Koelmeyer L, Mackie H, Boyages J. Patterns of lymphatic drainage after axillary node dissection impact arm lymphoedema severity: A review of animal and clinical imaging studies. Surg Oncol 2018;27:743–50.

[20] Suami H, Pan WR, Taylor GI. Changes in the lymph structure of the upper limb after axillary dissection: Radiographic and anatomical study in a human cadaver. Plast Reconstr Surg 2007;120:982–91.

[21] Suami H, Taylor GI, Pan W-R. The Lymphatic Territories of the Upper Limb: Anatomical Study and Clinical Implications. Plast Reconstr Surg 2007;119:1813–22.

[22] Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I. Indocyanine Green Lymphography Findings in Limb Lymphedema. J Reconstr Microsurg 2015;32:72–9.

[23] Suami H, Heydon-White A, Mackie H, Czerniec S, Koelmeyer L, Boyages J. A new indocyanine green fluorescence lymphography protocol for identification of the lymphatic drainage pathway for patients with breast cancer-related lymphoedema. BMC Cancer 2019;19:985.

[24] Yamamoto T, Yamamoto N, Kageyama T, *et al.* Technical pearls in lymphatic supermicrosurgery. Glob Health Med 2020.

[25] Yamamoto T, Yamamoto N, Hara H, Mihara M, Narushima M, Koshima I. Upper Extremity Lymphedema Index. Ann Plast Surg 2013;70:47–9.

[26] Clough KB, Nasr R, Nos C, Vieira M, Inguenault C, Poulet B. New anatomical classification of the axilla with implications for sentinel node biopsy. British Journal of Surgery 2010;97:1659–65.

[27] Brahma B, Putri RI, Reuwpassa JO, *et al.* Lymphaticovenular Anastomosis in Breast Cancer Treatment-Related Lymphedema: A Short-Term Clinicopathological Analysis from Indonesia. J Reconstr Microsurg 2021;37:643–54.

[28] Yamamoto T, Yamamoto N, Sakai H, *et al.* Targeting Reflux-Free Veins with a Vein Visualizer to Identify the Ideal Recipient Vein Preoperatively for Optimal Lymphaticovenous Anastomosis in Treating Lymphedema. Plast Reconstr Surg 2018;142:804e–6e.

[29] Batyrbekova N, Bower H, Dickman PW, *et al.* Modelling multiple time-scales with flexible parametric survival models. BMC Med Res Methodol 2022;22:290.

[30] Nagashima K, Noma H, Sato Y, Gosho M. Sample size calculations for single-arm survival studies using transformations of the Kaplan–Meier estimator. Pharm Stat 2021;20:499–511.

[31] Agha R, Mathew G, Rashid R, *et al.* Revised Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery (STROCSS) Guideline: An update for the age of Artificial Intelligence. Premier Journal of Science 2025.

[32] Jørgensen MG, Toyserkani NM, Sørensen JA. The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphedema: a systematic review and meta-analysis. Microsurgery 2018;38:576–85.

[33] Boccardo F, Casabona F, De Cian F, *et al.* Lymphedema Microsurgical Preventive Healing Approach: A New Technique for Primary Prevention of Arm Lymphedema After Mastectomy. Ann Surg Oncol 2009;16:703–8.

[34] Johnson AR, Singhal D. Immediate lymphatic reconstruction. J Surg Oncol 2018;118:750–7.

[35] Coriddi M, Mehrara B, Skoracki R, Singhal D, Dayan JH. Immediate Lymphatic Reconstruction: Technical Points and Literature Review. Plast Reconstr Surg Glob Open 2021;9:e3431.

[36] Anwar SL, Raharjo CA, Herviastuti R, *et al.* Pathological profiles and clinical management challenges of breast cancer emerging in young women in Indonesia: a hospital-based study. BMC Womens Health 2019;19:28.

[37] Soran A, Bengur FB, Rodriguez W, Chroneos MZ, Sezgin E. Early Detection of Breast Cancer-Related Lymphedema: Accuracy of Indocyanine Green Lymphography Compared with Bioimpedance Spectroscopy and Subclinical Lymphedema Symptoms. Lymphat Res Biol 2023;21:359–65.

[38] Granoff MD, Pardo J, Johnson AR, *et al.* The Superficial and Functional Lymphatic Anatomy of the Upper Extremity. Plast Reconstr Surg August 2022.

[39] Jørgensen MG, Hermann AP, Madsen AR, Christensen S, Sørensen JA. Indocyanine green lymphangiography is superior to clinical staging in breast cancer-related lymphedema. Sci Rep 2021;11:21103.

[40] Nelson TS, Nepiyushchikh Z, Hooks JST, *et al.* Lymphatic remodelling in response to lymphatic injury in the hind limbs of sheep. Nat Biomed Eng 2019.

[41] Baluk P, Naikawadi RP, Kim S, *et al.* Lymphatic Proliferation Ameliorates Pulmonary Fibrosis after Lung Injury. Am J Pathol 2020;190:2355–75.

[42] Gursen C, Dylke ES, Moloney N, *et al.* Self-reported signs and symptoms of secondary upper limb lymphoedema related to breast cancer treatment: Systematic review. Eur J Cancer Care (Engl) 2021;30.

[43] Qin ES, Bowen MJ, Chen WF. Diagnostic accuracy of bioimpedance spectroscopy in patients with lymphedema: A retrospective cohort analysis. Journal of Plastic, Reconstructive & Aesthetic Surgery 2018;71:1041–50.

[44] Yamamoto T, Yamamoto N, Yoshimatsu H, Hayami S, Narushima M, Koshima I. Indocyanine green lymphography for evaluation of genital lymphedema in secondary lower extremity lymphedema patients. J Vasc Surg Venous Lymphat Disord 2013;1:400-405.e1.

[45] Brahma B, Yamamoto T, Agdelina C, *et al.* Immediate-delayed lymphatic reconstruction after axillary lymph nodes dissection for locally advanced breast cancer-related lymphedema prevention: Report of two cases. Microsurgery 2024;44:e31033.

[46] Paskett ED, Le-Rademacher J, Oliveri JM, *et al.* A randomized study to prevent lymphedema in women treated for breast cancer: CALGB 70305 (Alliance). Cancer 2021;127:291–9.

[47] Nguyen TT, Hoskin TL, Habermann EB, Cheville AL, Boughey JC. Breast Cancer-Related Lymphedema Risk is Related to Multidisciplinary Treatment and Not Surgery Alone: Results from a Large Cohort Study. Ann Surg Oncol 2017;24:2972–80.

[48] Zou L, Pei L, Hu Y, Ying L, Bei P. The incidence and risk factors of related lymphedema for breast cancer survivors post - operation : a 2 - year follow - up prospective cohort study. Breast Cancer 2018.

[49] Yamamoto T, Yamamoto N, Yoshimatsu H, Narushima M, Koshima I. Factors Associated with Lymphosclerosis: An Analysis on 962 Lymphatic Vessels. Plast Reconstr Surg 2017;140:734–41.

[50] Lin Y, Xu Y, Wang C, *et al.* Loco-regional therapy and the risk of breast cancer-related lymphedema: a systematic review and meta-analysis. Breast Cancer 2021;28:1261–72.

[51] Togawa K, Ma H, Sullivan-Halley J, *et al.* Risk factors for self-reported arm lymphedema among female breast cancer survivors: a prospective cohort study. Breast Cancer Research 2014;16:414.

[52] DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;14:500–15.

[53] Torgbenu E, Luckett T, Buhagiar MA, Chang S, Phillips JL. Prevalence and incidence of cancer related lymphedema in low and middle-income countries: a systematic review and meta-analysis. BMC Cancer 2020;20:604.

[54] Norman SA, Localio AR, Potashnik SL, *et al.* Lymphedema in Breast Cancer Survivors: Incidence, Degree, Time Course, Treatment, and Symptoms. Journal of Clinical Oncology 2009;27:390–7.

[55] Kilbreath SL, Refshauge KM, Beith JM, *et al.* Risk factors for lymphoedema in women with breast cancer: A large prospective cohort. The Breast 2016;28:29–36.

[56] Monleon S, Murta-Nascimento C, Bascuas I, Macià F, Duarte E, Belmonte R. Lymphedema Predictor Factors after Breast Cancer Surgery: A Survival Analysis. Lymphat Res Biol 2015;13:268–74.

[57] Hahamoff M, Gupta N, Munoz D, *et al.* A Lymphedema Surveillance Program for Breast Cancer Patients Reveals the Promise of Surgical Prevention. Journal of Surgical Research 2019;244:604–11.

[58] Ribeiro Pereira ACP, Koifman RJ, Bergmann A. Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. The Breast 2017;36:67–73.

[59] Yamamoto T, Yamamoto N. Indocyanine Green Lymphography for Evaluation of Breast Lymphedema Secondary to Breast Cancer Treatments. J Reconstr Microsurg 2022;38:630–6.

[60] Kilbreath SL, Lee M-J, Refshauge KM, *et al.* Transient swelling versus lymphoedema in the first year following surgery for breast cancer. Supportive Care in Cancer 2013;21:2207–15.

[61] Kim M, Shin KH, Jung S-Y, *et al.* Identification of Prognostic Risk Factors for Transient and Persistent Lymphedema after Multimodal Treatment for Breast Cancer. Cancer Res Treat 2016;48:1330–7.

[62] Sung C, Wang S, Hsu J, Yu R, Wong AK. Current Understanding of Pathological Mechanisms of Lymphedema. Adv Wound Care (New Rochelle) 2022;11:361–73.

[63] Brahma B, Yamamoto T. Breast cancer treatment-related lymphedema (BCRL): An overview of the literature and updates in microsurgery reconstructions. European Journal of Surgical Oncology 2019;45:1138–45.

[64] Olszewski W. The Pathophysiology of Lymphedema – 2012. Handchirurgie · Mikrochirurgie · Plastische Chirurgie 2013;44:322–8.

[65] Kwon S, Janssen CF, Velasquez FC, *et al.* Radiation Dose-Dependent Changes in Lymphatic Remodeling. International Journal of Radiation Oncology*Biology*Physics 2019;105:852–60.

[66] Komatsu E, Nakajima Y, Mukai K, *et al.* Lymph Drainage During Wound Healing in a Hindlimb Lymphedema Mouse Model. Lymphat Res Biol 2017;15:32–8.

[67] Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y, Thomas SM. Radiation-induced fibrosis: mechanisms and implications for therapy. J Cancer Res Clin Oncol 2015;141:1985–94.

[68] Chang DW, Dayan J, Greene AK, *et al.* Surgical Treatment of Lymphedema: A Systematic Review and Meta-Analysis of Controlled Trials. Results of a Consensus Conference. Plast Reconstr Surg 2021;147:975–93.

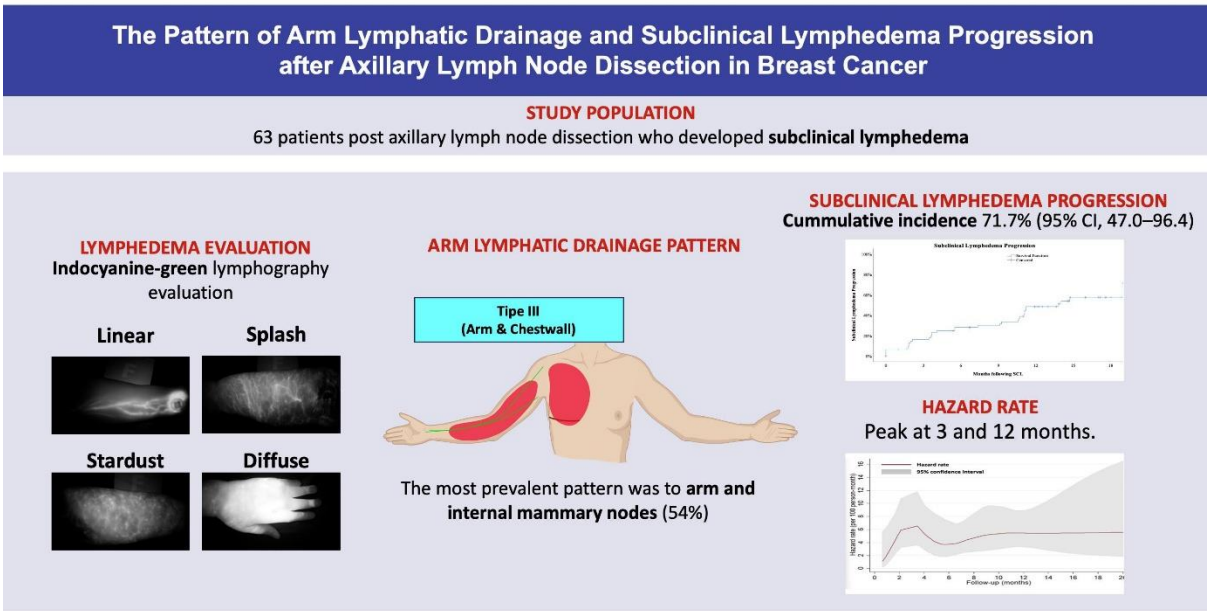
[69] Carl H, Walia G, Bello R, *et al.* Systematic Review of the Surgical Treatment of Extremity Lymphedema. J Reconstr Microsurg 2017;33:412–25.

CONTRIBUTION: BB and TY conceived and developed the motivation and need for the study. BB, TY, SSP, and KH developed the study design. BB, SJH, and AT conducted the literature search and data collection. Statistical analysis was conducted by BB. BB performed data interpretation in consultation with TY, SSP, SJH, PAY, PSP, KH, and AT. The manuscript was drafted by BB and TY. Critical editing of the manuscript was performed by BB and TY.

IJS-D-25-01041

Supplementary Figure/Table - http://links.lww.com/JS9/E898

Graphical abstract



Highlights

- Breast cancer-related lymphedema (BCRL) is a chronic progressive disease requiring screening and early detection as an important approach.
- A total of 63 patients were recruited to evaluate arm lymphatic drainage and progression of subclinical lymphedema after axillary lymph node dissection (ALND)

- Five lymphatic drainage patterns were identified using indocyanine green lymphography (ICG-L), with arm and chest wall dermal backflow draining to internal mammary nodes (type III) being the most prevalent (54%).
- The 18-month cumulative incidence of subclinical lymphedema progression to BCRL was 71.7%.