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# Natural History of Subclinical Lower Limb Lymphedema After Gynecologic Cancer Surgery Using Indocyanine Green Lymphography

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**Background:** Subclinical lymphedema is characterized by abnormal lymphatic findings in the absence of clinical symptoms or edema. However, the natural history of subclinical lymphedema after gynecologic cancer surgery remains unclear.
**Methods:** In this observational cohort study, the asymptomatic lower limbs of patients treated for gynecologic malignancies were evaluated using indocyanine green (ICG) lymphography between April 2021 and June 2024. Subclinical lymphedema was defined as asymptomatic limbs with abnormal ICG findings (stage ≥ 1). Patients were followed up at approximately 6-month intervals without therapeutic intervention until objective edema developed. Time-to-event outcomes were analyzed using the Kaplan–Meier method and Cox regression. Longitudinal changes in the lower extremity lymphedema index were assessed using a mixed-effects model.
**Results:** Eighty asymptomatic lower limbs were included, of which 26 were classified as subclinical. During a median follow-up of 24 months, objective edema developed more frequently in the subclinical group than in the nonsubclinical group (50% versus 5.6%, $P < 0.001$). Subclinical lymphedema was independently associated with objective edema development (hazard ratio, 8.57; 95% confidence interval, 2.36–31.2; $P = 0.0011$). Subjective symptoms also occurred earlier in the subclinical group ($P = 0.021$). Mixed-effects modeling demonstrated significantly greater longitudinal increases in the lower extremity lymphedema index in the subclinical group ($P = 0.023$).
**Conclusions:** Asymptomatic abnormalities detected using ICG lymphography are associated with an increased risk of subsequent lower limb lymphedema after gynecologic cancer surgery. However, not all subclinical cases progress, which supports the need for risk-based surveillance. *(Plast Reconstr Surg Glob Open 2026;14:e7998; doi: 10.1097/GOX.0000000000007998; Published online 5 August 2026.)*

## INTRODUCTION

Lymphedema remains a common and debilitating complication following cancer treatment, particularly after lymph node dissection and radiotherapy.[1] Traditionally, the diagnosis of lymphedema has relied on clinically apparent findings such as limb edema and measurable increases in limb circumference or volume.[2] However, these manifestations typically represent relatively advanced stages of the disease, by which time irreversible tissue changes may have already occurred.[3]

To address this limitation, the International Society of Lymphology (ISL) introduced the concept of latent lymphedema, also described as subclinical lymphedema and classified as stage 0, denoting impaired lymphatic transport in the absence of clinically detectable edema.[4] Although this classification provides an important conceptual framework, the ISL definition does not specify concrete methods for demonstrating lymphatic transport impairment.

The development of imaging and measurement technologies has led to attempts to operationalize

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this concept.[3,5–9] Indocyanine green (ICG) lymphography has demonstrated abnormal lymphatic flow patterns, such as dermal backflow, in limbs without overt edema or symptoms.[10] Based on these observations, abnormal ICG findings in asymptomatic patients have been proposed to represent subclinical lymphedema. Subsequently, bioimpedance analysis and other quantitative methods have been used to identify subtle fluid changes in the absence of clinical edema.[6,7,11–13] As a result, the term "subclinical lymphedema" has been increasingly used to describe a test-positive but clinically negative state.

However, the increasing use of test-based definitions of subclinical lymphedema has highlighted several important areas that remain unexplored. In previous studies, abnormalities detected by imaging or quantitative measurements have frequently been used to characterize subclinical disease. However, the subsequent clinical course of these findings has not been fully elucidated.[10,14,15] Additionally, many investigations have been cross-sectional in nature or have included early therapeutic interventions, thereby limiting the evaluation of the natural history of subclinical lymphedema and the clarification of its prognostic implications.[7,16,17]

The clinical relevance of subclinical lymphedema is closely associated with its longitudinal course. Whether test-positive, asymptomatic states consistently precede the development of clinically overt lymphedema remains unclear. If such subclinical abnormalities remain stable over time without progressing to measurable edema or patient-reported symptoms, their clinical significance may differ from that of a true preclinical disease state. Conversely, if they can reliably predict subsequent clinical deterioration, early identification may offer meaningful opportunities for risk stratification and patient management.

Most existing studies on subclinical lymphedema have focused on breast cancer–related upper limb lymphedema.[6,7,12,13,15–17] Conversely, relatively little is known about the natural history of subclinical lymphedema in the lower extremities, particularly after gynecologic cancer surgery. Lower limb lymphedema differs fundamentally from upper limb disease owing to constant gravitational load, interactions with the venous system, and a higher prevalence of bilateral involvement, all of which may influence disease progression.[2]

The present study investigates the natural course of subclinical lymphedema in patients with lower limb lymphatic abnormalities identified by ICG lymphography in the absence of clinical edema or subjective symptoms at baseline. By longitudinally evaluating limb circumference, clinical signs of edema, and patient-reported symptoms without therapeutic intervention, we sought to determine whether subclinical lymphedema represents a true preclinical stage of lymphedema or a nonprogressive, compensated condition. Using this approach, we aimed to clarify the clinical significance of subclinical lymphedema and contribute to a more evidence-based framework for its diagnosis and management.

### Takeaways

**Question:** Does an asymptomatic abnormality on indocyanine green (ICG) lymphography predict the subsequent development of clinical lower limb lymphedema after gynecologic cancer surgery?

**Findings:** In this longitudinal observational study, asymptomatic patients with abnormal ICG findings were more likely to develop clinical lymphedema over time. However, not all subclinical cases progressed to overt disease.

**Meaning:** Asymptomatic ICG abnormalities indicate an increased risk, but not inevitable progression, and provide a basis for risk stratification and postoperative surveillance.

## MATERIALS AND METHODS

This observational cohort study was conducted at the National Defense Medical College (Saitama, Japan) between April 2021 and June 2024, and was approved by the institutional review board and institutional ethics committee (approval no.: 5087). All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent to participate in this study was obtained from all participants before enrollment. We reviewed consecutive patients who presented to our department for evaluation of unilateral lower limb edema after treatment for gynecologic malignancies.

In this study, subjective symptoms were defined as the presence of heaviness, tightness, pain, or swelling in the lower extremities, whereas objective findings were defined as pretibial or dorsal foot pitting edema on physical examination. Limbs with neither subjective symptoms nor objective findings were classified as asymptomatic and included in the study.

Bilateral lymphoscintigraphy and ICG lymphography were performed in all patients, regardless of symptoms. For lymphoscintigraphy, 40 MBq of technetium-99m diethylenetriamine pentaacetic acid–human serum albumin (POOLSCINTI Injection; Nihon Medi-Physics Co., Ltd., Tokyo, Japan) was subcutaneously injected into the first and fourth interdigital spaces of the lower extremities. Simultaneously, 0.2 mL of 0.25% ICG (Diagnogreen; Daiichi Sankyo Co., Ltd., Tokyo, Japan) was injected into the same sites.

After injection, patients were instructed to ambulate for 1 hour. Whole-body imaging was performed 2 hours after injection using a computerized gamma camera (NM 830; GE Healthcare Technology Inc., IL).

Following lymphoscintigraphy, circumferential fluorescent images of both lower extremities were obtained using a near-infrared camera system (Photodynamic Eye; Hamamatsu Photonics K.K., Shizuoka, Japan). Imaging was performed in a room without natural light. Patients were positioned supine, and the imaging head of the Photodynamic Eye system was held at a distance of 20–40 cm above the skin. Fluorescent images were recorded as photographs and videos. (**See Video [online]**, which demonstrates a representative ICG lymphography examination.)

The lymphoscintigraphy findings were graded according to a previously reported staging system[5] (Table 1). The ICG lymphography findings were evaluated using a dermal backflow staging system[10] (Table 2). In this system, stage 0 is defined as negative for lymphedema, whereas stages 1 and above are defined as positive. All imaging evaluations were independently performed by 4 board-certified plastic surgeons (I.Y., Y.I., K.M., and H.F.) using the recorded videos and photographs, and the evaluators were blinded to the patients' clinical information.

The diagnosis of lymphedema in symptomatic limbs was established based on clinical and imaging findings. After diagnosis, appropriate conservative management, including the prescription of compression garments, was initiated according to institutional protocols.

Based on the ICG lymphography findings, asymptomatic limbs were classified into 2 groups. Subclinical lymphedema was defined as asymptomatic limbs showing abnormal lymphatic patterns corresponding to stage 1 or higher on ICG lymphography, whereas limbs with stage 0 findings were classified as nonsubclinical.

Patients were excluded if they had medical conditions that could cause nonlymphatic lower extremity edema, including heart failure, renal failure, liver cirrhosis, deep vein thrombosis, or hypothyroidism. Patients who had received prior treatment for lymphedema at other institutions, including compression therapy and surgery, were also excluded.

The following clinical characteristics were recorded for all included patients: age, body mass index (BMI), type of gynecologic malignancy, details of cancer treatment (including surgery, lymphadenectomy, chemotherapy, and radiotherapy), duration from cancer treatment to the initial visit, and ISL clinical stage in the symptomatic limb. The lower extremity lymphedema (LEL) index was calculated as a quantitative severity measure based on circumferential measurements at the suprapatellar border, 10 cm above and 10 cm below the patella, the lateral malleolus, and the dorsum of the foot, adjusted for BMI.[18] The incidence of subjective symptom development, occurrence of objective edema, and longitudinal changes in the LEL index were compared between the subclinical and nonsubclinical groups.

**Table 1. Lymphoscintigraphy Type**

| Type | Description |
|---|---|
| 0 | Inguinal lymph nodes stain normally; no dermal backflow pattern is seen |
| I | The number of visible inguinal lymph nodes is reduced |
| II | Few or no inguinal lymph nodes are seen; dermal backflow is seen in the thigh |
| III | No inguinal lymph nodes are detected; dermal backflow is seen in the thigh and leg |
| IV | Dermal backflow and lymph stasis are seen in the leg |
| V | No dermal backflow is seen; no tracer migration is seen |

**Table 2. ICG Lymphography Stage**

| Stage | Description |
|---|---|
| 0 | No dermal backflow pattern |
| I | A splash pattern around the groin |
| II | A stardust pattern extending proximally to the superior border of the patella |
| III | A stardust pattern extending distally to the superior border of the patella |
| IV | A stardust pattern extending to the entire limb |
| V | The existence of a diffuse pattern with a stardust pattern in the background |

Patients were followed up at approximately 6-month intervals. During follow-up, patients who reported subjective symptoms without objective evidence of pitting edema were managed with observation alone, and compression therapy was not initiated. The development of objective edema, defined as pretibial or dorsal foot pitting edema on physical examination, was considered a clinical event, after which compression therapy was initiated. Follow-up data after event occurrence were not included in the longitudinal analysis. No lymphedema-specific intervention was provided to asymptomatic limbs unless objective edema developed.

Continuous variables were summarized as mean ± SD or median (interquartile range [IQR]), as appropriate, and compared between groups using the Mann-Whitney *U* test. Categorical variables, including the type of gynecologic malignancy, details of cancer treatment, site of lymphadenectomy, dermal backflow stage, lymphoscintigraphy stage, and ISL clinical stage in the symptomatic limb, were analyzed using the Fisher exact test. The time to the development of objective edema and subjective symptoms was estimated using the Kaplan–Meier method, calculated from the date of the initial imaging examination. Comparisons between the subclinical and nonsubclinical groups were performed using the log-rank test in the overall cohort and in subgroups stratified by para-aortic lymphadenectomy status. The proportional hazards assumption was assessed using log–log survival plots. When this assumption was satisfied, Cox proportional hazards regression analysis was performed with adjustment for para-aortic lymphadenectomy. A post hoc power analysis was performed using the Schoenfeld formula to evaluate the statistical power of the Cox regression analysis.

Longitudinal percentage changes in the LEL index from baseline were analyzed using a mixed-effects model for repeated measures (MMRM), with group (subclinical versus nonsubclinical), visit, and group-by-visit interaction as fixed effects and subjects as a random effect, using a compound symmetry covariance structure. The baseline LEL index and lymphadenectomy site were included as covariates. Missing data were handled under the assumption that data were missing at random. Statistical significance was defined as a *P* value less than 0.05. All statistical analyses were performed using SPSS version 31.0.1 (IBM Corp., Armonk, NY).

## RESULTS

A total of 87 patients were screened during the study period. Seven patients were excluded for the following

reasons: deep vein thrombosis (n = 3), prior lymphedema treatment at another institution (n = 3), and heart failure (n = 1). The remaining 80 asymptomatic lower limbs were included in the final analysis. Among these, 26 limbs were classified as having subclinical lymphedema, and 54 limbs were classified as nonsubclinical. The median follow-up duration was 24 months (IQR, 16.5–36 mo) in the subclinical group and 24 months (IQR, 12–30 mo) in the nonsubclinical group.

The baseline demographic and clinical characteristics are summarized in Supplemental Digital Content 1. (**See table, Supplemental Digital Content 1**, which describes baseline demographic and clinical characteristics of the study cohort, **https://links.lww.com/PRSGO/F136**.) No significant differences were observed between the subclinical and nonsubclinical groups in age, BMI, causative cancer type, radiotherapy, chemotherapy, duration from cancer surgery to ICG lymphography, or baseline LEL in either the symptomatic or asymptomatic limb. However, the distribution of lymphadenectomy sites differed significantly between the 2 groups. Notably, para-aortic lymphadenectomy was more frequent in the subclinical group ($P = 0.0057$).

Kaplan–Meier analysis demonstrated a significantly higher cumulative incidence of objective edema development in the subclinical group than in the nonsubclinical group in the overall cohort ($P < 0.001$; Fig. 1A). Objective edema developed in 50% and 5.6% of patients in the subclinical and nonsubclinical groups, respectively. When stratified by para-aortic lymphadenectomy status, the subclinical group remained at significantly higher risk, both among patients who underwent para-aortic lymphadenectomy ($P = 0.028$; Fig. 1B) and those who did not ($P < 0.001$; Fig. 1C). The proportional hazards assumption was satisfied for objective edema. In Cox proportional hazards regression analysis adjusted for para-aortic lymphadenectomy, subclinical lymphedema was independently associated with the development of objective edema (hazard ratio, 8.57; 95% confidence interval, 2.36–31.2; $P = 0.0011$). Post hoc power analysis confirmed that the 16 observed events provided a statistical power of 98.1% to detect the observed hazard ratio of 8.57 at a 2-sided significance level of 0.05. A representative case demonstrating progression from subclinical to clinically apparent lymphedema is shown in Figure 2.

Kaplan–Meier analysis showed a significantly higher cumulative incidence of subjective symptom development in the subclinical group than in the nonsubclinical group in the overall cohort ($P = 0.021$; Fig. 3A). Subjective symptoms developed in 57.7% and 22.2% of patients in the subclinical and nonsubclinical groups, respectively.

When stratified by para-aortic lymphadenectomy status, no significant difference was observed between groups among patients who underwent para-aortic lymphadenectomy ($P = 0.267$; Fig. 3B), whereas a significant difference persisted among those who did not undergo para-aortic lymphadenectomy ($P = 0.029$; Fig. 3C). The proportional hazards assumption was not satisfied for subjective symptoms; therefore, Cox proportional hazards regression analysis was not performed for this outcome.

Longitudinal changes in the LEL index differed significantly between the subclinical and nonsubclinical groups (group-by-visit interaction, $P = 0.023$; Fig. 4). At 24 months, the adjusted mean percentage change in the LEL index was higher in the subclinical group than in the nonsubclinical group (8.48% versus 1.18%, respectively).

## DISCUSSION

In this study, we evaluated the natural history of subclinical lower limb lymphedema following gynecologic cancer surgery and examined its clinical significance during a median follow-up of 24 months. Our results demonstrated that subclinical lymphedema was strongly associated with the subsequent development of objective edema, with a hazard ratio of 8.57 in the adjusted Cox proportional

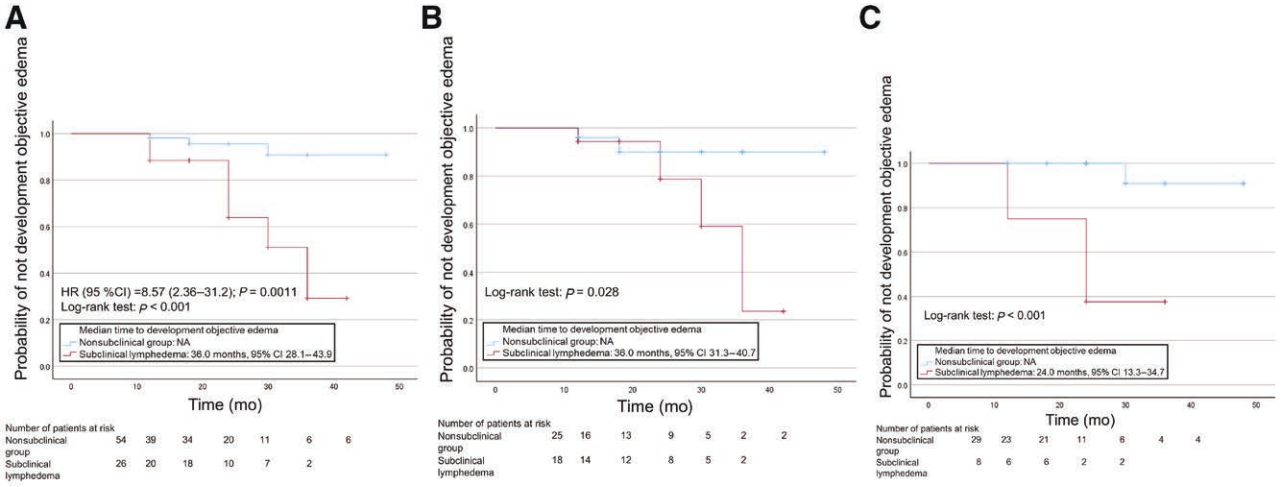


**Fig. 1.** Kaplan–Meier curves for the development of objective edema. A, Cumulative incidence of objective edema in the overall cohort, comparing the subclinical and nonsubclinical lymphedema groups. B, Cumulative incidence stratified by para-aortic lymphadenectomy status among patients who underwent para-aortic lymphadenectomy. C, Cumulative incidence stratified by para-aortic lymphadenectomy status among patients who did not undergo para-aortic lymphadenectomy. Differences between groups were assessed using the log-rank test. HR, hazard ratio; CI, confidence interval; NA, not applicable.

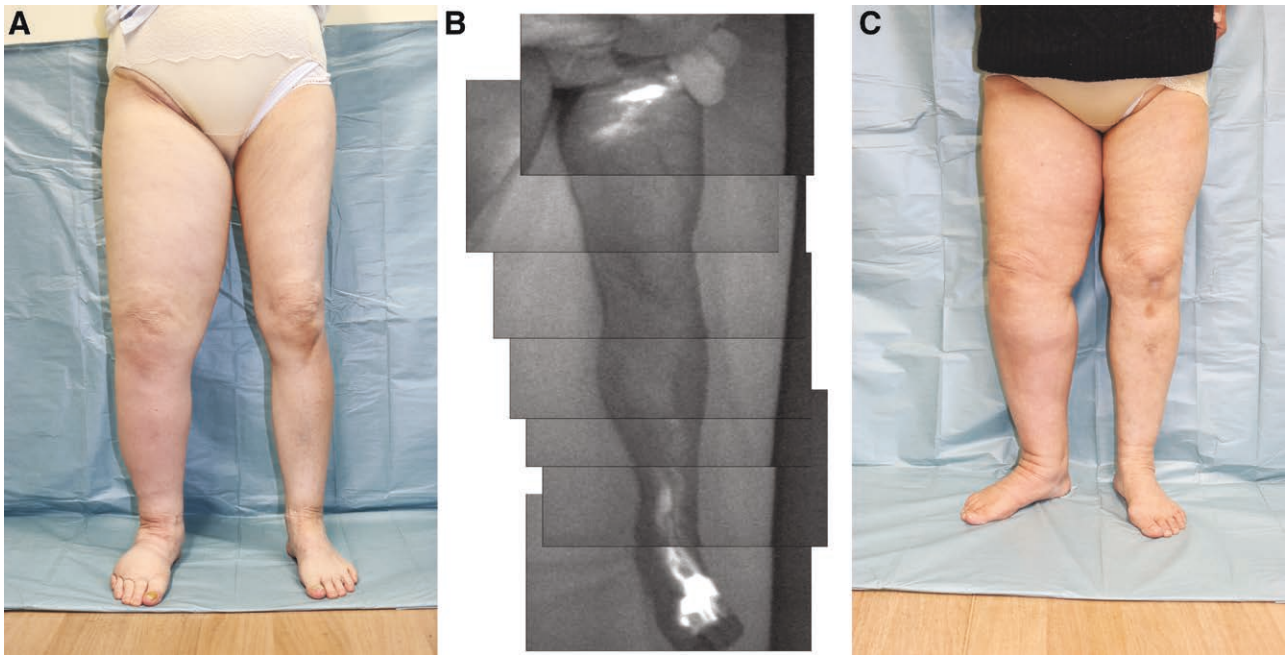


**Fig. 2.** Clinical progression from subclinical to clinically apparent lymphedema. A, Clinical photograph at the initial visit. Objective edema is observed in the right lower limb, whereas the left lower limb seems clinically normal. B, ICG lymphography of the left lower limb at the initial visit. Despite the absence of clinical symptoms, a splash pattern is observed in the groin region, consistent with subclinical lymphedema. C, Clinical photograph at 12 months after the initial visit. Objective edema has developed in the left lower limb, demonstrating progression from subclinical to clinically apparent lymphedema.

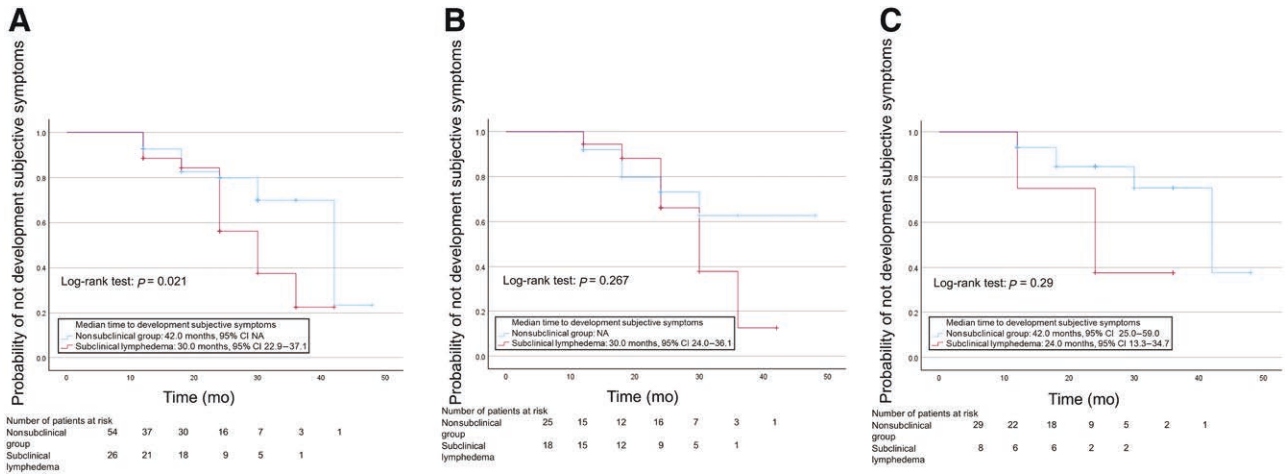


**Fig. 3.** Kaplan–Meier curves for the development of subjective symptoms. A, Cumulative incidence of subjective symptom development in the overall cohort, comparing the subclinical and nonsubclinical lymphedema groups. B, Cumulative incidence stratified by para-aortic lymphadenectomy status among patients who underwent para-aortic lymphadenectomy. C, Cumulative incidence stratified by para-aortic lymphadenectomy status among patients who did not undergo para-aortic lymphadenectomy. Differences between groups were assessed using the log-rank test. CI, confidence interval; NA, not applicable.

hazards analysis. A longitudinal assessment using an MMRM revealed a significant group-by-time interaction, indicating divergent LEL index trajectories between patients with and without subclinical findings. Collectively, these findings suggest that subclinical lymphedema may represent a precursor stage preceding clinically apparent edema.

Subclinical lymphedema is generally defined as a condition in which patients have no subjective symptoms or clinically detectable edema despite abnormal findings on lymphatic imaging or functional assessments. In this context, subclinical lymphedema has previously been defined as the presence of dermal backflow patterns on ICG lymphography in asymptomatic limbs in patients with secondary LEL.[10] Several studies have investigated whether early interventions at this stage can prevent progression to clinically apparent lymphedema.[4,7,10] However, relatively few

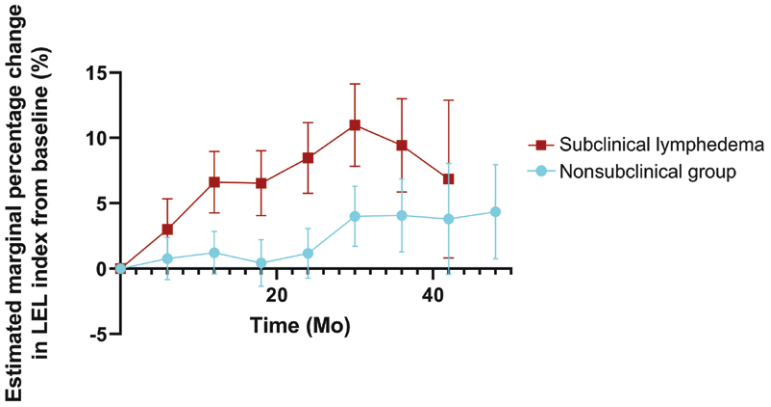


**Fig. 4.** Longitudinal changes in the LEL index. The estimated marginal mean percentage change in the LEL index from baseline over time in the subclinical and nonsubclinical lymphedema groups was analyzed using an MMRM. Error bars represent 95% confidence intervals. A significant group-by-visit interaction was observed ($P = 0.023$), indicating divergent trajectories between groups.

observational studies have examined the natural course of untreated subclinical lymphedema and quantified its risk of progression.[19]

In this context, a previous study demonstrated dermal backflow patterns in 19 of 28 asymptomatic limbs in patients with unilateral secondary LEL, indicating that ICG lymphography can detect early lymphatic dysfunction.[10] However, subsequent clinical outcomes have not been evaluated; therefore, it remains unclear whether such subclinical imaging abnormalities consistently progress to overt lymphedema or instead represent changes that do not inevitably lead to clinical disease. In the present study, we addressed this issue by demonstrating that asymptomatic lower limbs with dermal backflow on ICG lymphography were at significantly higher risk of developing subjective symptoms, objective edema, and increased limb circumference and volume.

Regarding patient characteristics, para-aortic lymphadenectomy was performed significantly more frequently in the subclinical group. Extensive lymph node dissection, particularly para-aortic lymphadenectomy, has been recognized as a risk factor for postoperative lymphedema in patients with gynecological cancer.[20,21] Our findings are consistent with this concept and suggest that para-aortic lymphadenectomy may contribute to early lymphatic dysfunction. Conversely, no significant differences were observed between the groups in other established risk factors, including BMI and adjuvant radiotherapy.[22–24]

Kaplan–Meier analysis demonstrated that patients in the subclinical group had a significantly higher incidence of progression to objective edema, with approximately half developing objective edema within 36 months. This association remained consistent even after adjusting for the extent of lymph node dissection. These findings suggest that subclinical lymphedema can independently predict the risk of progression to clinically apparent lymphedema.

Conversely, subjective symptoms appeared significantly earlier in the subclinical group; however, the magnitude of this difference was less pronounced than that observed for objective measures. The symptoms assessed in this study, including heaviness, tightness, pain, and swelling, are not specific to lymphedema. In particular, taxane-based chemotherapy, which is commonly used as an adjuvant treatment for gynecologic malignancies, is known to cause peripheral neuropathy.[25–27] In our cohort, chemotherapy was administered to 56 of the 80 patients, and the proportion did not differ significantly between the 2 groups ($P = 0.443$). Because chemotherapy is typically administered as adjuvant therapy in the early postoperative period, most patients are considered to have completed treatment before study enrollment, given the mean intervals of 59.2 and 72.6 months from cancer surgery to the initial assessment. Furthermore, taxane-induced peripheral neuropathy most commonly develops within 30 days of treatment initiation,[28] suggesting that its influence on subjective symptom evaluation during the follow-up period was likely limited. However, it remains possible that some patients were undergoing or initiated chemotherapy around the time of enrollment, and in such cases, treatment-related adverse effects may have influenced subjective symptom evaluation.

Longitudinal modeling using MMRM demonstrated a significant group-by-time interaction, indicating distinct trajectories between the groups in the LEL index, a composite indicator of limb circumference and volume. The estimated percentage change in the index increased progressively in the subclinical group from 6 to 30 months, whereas changes in the nonsubclinical group remained modest during the same period. Beyond 36 months, the estimated values in the subclinical group seemed to decline, and the confidence intervals widened. This is more likely attributable to reduced precision resulting from a smaller number of observations at later time points, rather than reflecting true stabilization or regression of disease progression. Overall, these findings suggest that subclinical lymphedema follows a progressive course, with sustained increases in the LEL index over time.

This study demonstrated that asymptomatic patients with abnormal findings on ICG lymphography were more likely to progress to clinically overt lower limb lymphedema over time. However, some of the patients with subclinical findings did not develop lymphedema during the study period. A previous study also reported that mild ICG abnormalities may spontaneously resolve.[29] Taken together, these findings suggest that asymptomatic ICG abnormalities do not necessarily predict progression to lymphedema. Based on these findings, closer surveillance may be warranted for asymptomatic limbs with abnormal ICG findings to enable timely detection of disease progression. Future studies should aim to identify additional risk factors beyond ICG findings to more accurately stratify patients at high risk of disease progression and establish appropriate management and treatment strategies during the asymptomatic phase. These findings provide an important foundation for the development of risk-based approaches.

This study had some limitations. First, this was a single-center study with a relatively small sample size, which may have limited the generalizability of the findings. Second, the follow-up period was relatively short, and late-onset progression may not have been fully captured. Third, repeat ICG lymphography was not routinely performed at the time of symptom onset, which precluded a detailed evaluation of the longitudinal changes in imaging findings in relation to clinical progression. Fourth, all patients in this study had preexisting unilateral symptomatic lymphedema, and the findings may not be directly generalizable to patients who remain bilaterally asymptomatic after gynecologic cancer surgery.

In conclusion, asymptomatic abnormalities detected by ICG lymphography are associated with an increased risk of subsequent clinical lower limb lymphedema. However, not all subclinical cases progress, highlighting the need for refined risk stratification. These findings provide a foundation for future studies that aim to develop risk-based management strategies.

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## DISCLOSURE

*The authors have no financial interest to declare in relation to the content of this article.*

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