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The Qaly study: Quality of life and lower extremity lymphedema in 174 patients after inguinal lymphadenectomy

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ABSTRACT

Background: Lower extremity lymphedema (LEL) can develop in patients who undergo inguinal lymph node dissection (ILND) in the treatment of gynecologic, genitourinary, and skin and soft tissue malignancies. While LEL can negatively impact quality of life, the poorly documented prevalence and severity of lymphedema-related symptoms complicates the ability to identify high-risk patients and improve the selection of candidates for emerging microsurgical interventions.

Methods: This multicenter, cross-sectional study included patients who underwent ILND between 1990 and 2022 across three medical centers in the Netherlands. Retrospective clinical data, including demographic, surgical, and postoperative variables, were abstracted from medical records. Lymphedema prevalence and severity were assessed using the Lymph-ICF-LL questionnaire, while additional patient-reported outcome measures (PROMs) evaluated quality of life and lower extremity function. Statistical analyses included multivariate logistic and linear regression to identify predictors of lymphedema-related symptoms and their impact on PROMs.

Results: Among 174 patients who underwent ILND, 77 % reported lymphedema-related symptoms, which were associated with significantly lower quality of life. Multivariable analysis identified that younger age at time of surgery, medical history of cardiovascular disease, and postoperative complications such as surgical site infections (SSI) and prolonged wound healing were significant predictors of developing lymphedema-related symptoms. Additionally, the presence of lymphedema was strongly linked to poorer physical and mental health PROMs, with malignancy type and surgical factors influencing these outcomes.

Conclusion: This study emphasizes the significant burden of lymphedema-related symptoms following ILND, while highlighting the potential role of reconstructive microsurgery in reducing morbidity for high-risk patients.

1. Introduction

Lower extremity lymphedema (LEL) is a common condition that can develop following an inguinal lymph node dissection (ILND) in the treatment of gynecologic, genitourinary, and dermatological malignancies [1]. The accumulation of interstitial fluid from impaired lymphatic drainage often leads to functional disability, pain, and discomfort [2,3]. Limitations in normal range of motion, as well as psychological distress and social isolation in patients with LEL can significantly impact quality of life [4,5].

While meta-analyses have estimated the prevalence of LEL in patients who undergo inguinal lymphadenectomy to be 24 % (95 % CI: 17–31) [6], understanding the full scope of the problem has been complicated by a lack of consistent definitions and effective treatment methods [7]. Circumferential measurements and volume estimations of the lower extremity are among the primary means used to describe LEL severity. Such methods, however, are often incongruent with the degree of physical and psychosocial impairments attributed to LEL [8]. The ease

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of implementing conservative measures, such as physical therapy or compression therapy, to manage LEL symptoms has resulted in limited efforts to improve proper documentation of the condition's associated morbidity. Furthermore, the high costs and time-consuming trajectory associated with this approach undermine patient compliance, ultimately reducing its effectiveness in treating the LEL symptoms [9,10].

Contrary to conservative approaches, emerging microsurgical interventions that target the root cause of LEL open new opportunities for making informed prophylactic or therapeutic decisions with patients. Lymphaticovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT) show promising results in minimizing the degree of lymphedema progression [11]. Proper selection of patients who could benefit from microsurgical interventions could be improved if physicians were better guided by comprehensive data on LEL morbidity and associated characteristics.

This multicenter, cross-sectional study aims to determine the prevalence and severity of lymphedema-related symptoms in patients in the Netherlands who have undergone inguinal lymphadenectomy using comprehensive patient-reported outcome measures (PROMs). Furthermore, this study aims to assess impairments in function, activity limitations, and participation restrictions among those who report morbidity associated with LEL. With this data, this study intends to further clarify patient characteristics of those at greatest risk for LEL and for whom it poses a significant impact on quality of life. The findings from this research could in turn improve patient counseling and facilitate the proper selection of those who could benefit from microsurgical interventions.

2. Methods

2.1. Study design and participants

This multicenter, cross-sectional involved participants who underwent inguinal lymphadenectomy between 1990 and 2022 at three medical centers in the Netherlands: University Medical Center Utrecht (UMCU), The National Cancer Institute Antoni van Leeuwenhoek (AvL), and Maastricht University Medical Center (MUMC). Patients with a surgical procedure code for either unilateral or bilateral ILND in their electronic medical record were screened for eligibility before informed consent was gathered from those who met the inclusion criteria. Living patients who had undergone ILND were included if they were at least sixteen years-old at the time of informed consent, and if the surgery took place at least one year prior to the start of the study. Because all PROMs were gathered in an electronic questionnaire format written in Dutch, patients had to have a valid e-mail address and sufficient command of the Dutch language. Patients who were mentally and/or physically unable to read, understand, or complete the questionnaires employed in this study were further excluded from participating.

2.2. Data collection

Clinical and histopathological data were collected retrospectively from patients' electronic medical records. Abstracted variables included age at the time of surgery, sex, height and weight for calculating body mass index (BMI) at the time of surgery, comorbidities, intoxications, type and staging of malignancy for which ILND was indicated, the type of (neo)adjuvant therapy received, surgical laterality, the use of pre- or postoperative antibiotics, the number of inguinal lymph nodes dissected, as well as how many of which contained positive metastases. Additionally, data was collected on whether or not the great saphenous vein (VSM) was spared or ligated during surgery, and whether or not patients experienced any postoperative complications. Complications included any postoperative surgical site infections (SSI) for which antibiotics were administered, re-operations, the presence of wound dehiscence, wounds that required more than six weeks of postoperative therapy, as well as seroma development and, if applicable, the type of intervention required to treat it. The duration of follow-up was defined as the time from ILND until the date on which PROMs questionnaires were completed.

2.3. Patient-reported outcome measures

All versions of the questionnaires employed in this study were validated in a Dutch population and had consistent psychometric properties.

2.3.1. Lymphedema

Prevalence and severity of morbidity associated with lymphedema was assessed using the Lymphoedema Functioning, Disability and Health Questionnaire for Lower Limb Lymphoedema (Lymph-ICF-LL) [12]. The Lymph-ICF-LL consists of 28 questions, each of which is scored on an eleven-point scale (0–10), and spans five domains: physical function, mental function general tasks/household activities, mobility activities, and life domains/social life. The Lymph-ICF-LL is the first Dutch questionnaire with evidence of reliability and validity for assessing impairments in people with LEL (Cronbach alpha coefficient = 0.96 for the total score; 0.89–0.97 in each of the five domains). The total score of the Lymph-ICF-LL was calculated as follows: $(\text{sum of scores on questions} \div \text{total number of answered questions}) * 10$. Using the same formula, separate scores for each of the five domains were also determined. Scores range from 0 to 100 and the severity of impairments exacerbated by LEL was interpreted as follows: no problems (0–4), small problems (5–24), moderate problems (25–49), severe problems (50–95), and very severe problems (96–100). Participants with any degree of problems reflected in the total score (>4) of all five domains were considered to have lymphedema-related symptoms [12].

2.3.2. Quality of life

Self-reported state of health and quality of life were assessed with the 36-Item Short Form Survey (SF-36) and the EuroQol Five-Dimension Five-Level questionnaire (EQ-5D-5L) [13,14]. The SF-36 is composed of 36 questions with standardized response choices organized into eight multi-item scales: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. Scores for each of the eight sub-scales were linearly converted on a scale ranging from 0 to 100, with higher scores indicating greater levels of functioning or well-being. Two distinct higher-order summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), were aggregated from the eight SF-36 sub-scales using a standard scoring algorithm previously described [15].

The EQ-5D-5L questionnaire is a validated tool for assessing health-related quality of life across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension was rated on a five-point scale ranging from "no problems" to "extreme problems." Participants also rated their overall health on a visual analogue scale (VAS) from 0 (worst imaginable health) to 100 (best imaginable health). To calculate the EQ-5D-5L index score, responses were mapped to the EQ-5D-3L value set using the crosswalk methodology, as recommended for the Netherlands [16]. This approach aligns EQ-5D-5L data with the Dutch population's preferences for health states to ensure consistency and comparability of results.

Lower extremity function was assessed using the Lower Extremity Functional Scale (LEFS) [17]. The LEFS is a 20-item questionnaire designed to assess physical functioning among individuals with conditions affecting the lower extremity. Scores range from 0 to 80, with higher scores representing a greater degree of function.

2.4. Statistical analysis

Demographic variables, ILND surgical data, and PROMs were summarized using descriptive statistics. As previously outlined, the

prevalence of lymphedema-related symptoms was calculated as the proportion of participants who reported any degree of impairment (score >4) in each of the five domains of the Lymph-ICF-LL questionnaire [12]. Categorical variables between those who did and did not report lymphedema-related symptoms were analyzed using Pearson's Chi-squared test, while differences in means for continuous variables were compared using Welch's Two Sample *t*-test.

Multivariate logistic regression analysis was conducted to identify predictors of lymphedema-related symptoms in patients following ILND. All demographic, pre-operative, surgical, and post-operative variables abstracted from patients' medical records were included in the initial logistic regression model, ensuring that the effects of all variables were considered simultaneously. Backward stepwise regression using Akaike Information Criterion (AIC) was applied to refine the model. At each step, the predictor whose removal yielded the greatest reduction in AIC was eliminated. This process continued until no further removal improved model parsimony. In doing so, the trade-off between model fit and complexity was minimized by penalizing excessive parameters, effectively reducing the risk of overfitting while retaining the most informative predictors. Results were reported as odds ratios (ORs) with 95 % confidence intervals (CIs) and associated p-values.

Multivariate linear regression analyses were performed to assess the impact of variables extracted from patients' medical records, as well as the presence of lymphedema-related symptoms, on PROMs. Separate models were created for the mean scores of the SF-36, EQ-5D-5L, and LEFS responses. Backward stepwise regression was then applied, selecting variables based on AIC. The final models were summarized with regression coefficients, 95 % CIs, and p-values. All data analysis was conducted using R Statistical Software (v4.3.2; R Core Team 2023) [18]. A two-sided p-value of <0.05 was considered statistically significant. The full dataset and script used to perform analyses are available at: https://osf.io/kxucf/?view_only=689f176c75fa486289de81848231c18b.

2.5. Ethical consideration

The Institutional Review Board of the University Medical Center Utrecht approved this study (#23–242/DB). Prospective participants were informed about the purpose of the study, voluntary participation, confidentiality of the study process, as well as the right to withdraw at any time without repercussions. Written informed consent was provided by all participants before taking part in this study.

3. Results

3.1. Patient characteristics

Of the 813 patients who underwent an ILND between January 1990 and December 2022 at one of the three medical centers included in this study, 319 met the full inclusion criteria. Informed consent was obtained from 186 patients, and completed questionnaires were received from 174 patients, all of whom were included in the final analysis (Supplemental Fig. 1).

Of the 174 patients who participated in this study, 82 (47 %) were female and 92 (53 %) were male. The mean BMI was 27.01 ± 4.69 kg/m^2. The mean age of patients at the time of ILND and at the time of follow-up was 58.99 ± 12.71 years and 65.01 ± 12.51 years, respectively. The mean postoperative follow-up time was 72.23 ± 42.82 months. Complete patient characteristics including comorbidities, intoxications, preoperative characteristics, and (neo)adjuvant therapy are detailed in Table 1.

3.2. Surgical characteristics

Data on ILND performed on 192 groins was collected from 174 patients, including 156 who underwent unilateral and 18 who underwent

Table 1
Comparison of participant health characteristics.

	Total	Lymphedema-related symptoms, per patient		
Characteristic	N = 174[a]	Yes, N = 134[a]	No, N = 40[a]	p-value[b]
Demographics				
Sex				<0.001
Female	82 (47 %)	75 (56 %)	7 (18 %)	
Male	92 (53 %)	59 (44 %)	33 (83 %)	
BMI, kg/m^2	27.01 ± 4.69	27.06 ± 4.97	26.82 ± 3.69	0.91
Age at time of lymphadenectomy, years	58.99 ± 12.71	58.60 ± 12.61	60.29 ± 13.13	0.27
Age at time of follow-up, years	65.01 ± 12.52	64.70 ± 12.06	66.04 ± 14.06	0.30
Follow-up, months	72.23 ± 42.82	73.18 ± 43.46	69.05 ± 40.94	0.69
Comorbidities				
Diabetes				0.19
Yes	14 (8.0 %)	13 (9.7 %)	1 (2.5 %)	
Hypertension				0.94
Yes	53 (30 %)	41 (31 %)	12 (30 %)	
Cardiovascular disease				0.077
Yes	18 (10 %)	17 (13 %)	1 (2.5 %)	
Rheumatoid arthritis				0.59
Yes	5 (2.9 %)	5 (3.7 %)	0 (0 %)	
Inflammatory bowel disease				0.23
Yes	4 (2.3 %)	2 (1.5 %)	2 (5.0 %)	
Thyroid disease				0.21
Yes	9 (5.2 %)	5 (3.7 %)	4 (10 %)	
Intoxications				
Tobacco				0.77
Yes	17 (9.8 %)	14 (10 %)	3 (7.5 %)	
Alcohol				0.058
Yes	113 (65 %)	82 (61 %)	31 (78 %)	
Drugs				0.57
Yes	4 (2.3 %)	4 (3.0 %)	0 (0 %)	
Preoperative characteristics				
Medical center				0.79
Antoni van Leeuwenhoek	159 (91 %)	123 (92 %)	36 (90 %)	
Maastricht University Medical Center	8 (4.6 %)	6 (4.5 %)	2 (5.0 %)	
Utrecht University Medical Center	7 (4.0 %)	5 (3.7 %)	2 (5.0 %)	
Indication for lymphadenectomy				0.065
Angio sarcoma	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Basosquamous carcinoma	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Endometrium carcinoma	1 (0.6 %)	0 (0 %)	1 (2.5 %)	
Melanoma	110 (63 %)	90 (67 %)	20 (50 %)	
Merkel cell carcinoma	5 (2.9 %)	5 (3.7 %)	0 (0 %)	
Myoepithelioma	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Penile carcinoma	36 (21 %)	21 (16 %)	15 (38 %)	
Prostate carcinoma	5 (2.9 %)	3 (2.2 %)	2 (5.0 %)	
Squamous cell carcinoma	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Testicular carcinoma	3 (1.7 %)	3 (2.2 %)	0 (0 %)	
Urethral carcinoma	2 (1.1 %)	1 (0.7 %)	1 (2.5 %)	
Vulvar carcinoma	8 (4.6 %)	7 (5.2 %)	1 (2.5 %)	
TNM pathological stage				0.11
I	16 (9.2 %)	13 (9.7 %)	3 (7.5 %)	
II	26 (15 %)	15 (11 %)	11 (28 %)	
III	121 (70 %)	97 (72 %)	24 (60 %)	
IV	11 (6.3 %)	9 (6.7 %)	2 (5.0 %)	
Positive lymph nodes, preoperative				0.69
Yes	147 (84 %)	114 (85 %)	33 (83 %)	
Neoadjuvant therapy				

(*continued on next page*)

Table 1 (*continued*)

	Total	Lymphedema-related symptoms, per patient		
Chemotherapy				0.32
Yes	5 (2.9 %)	3 (2.2 %)	2 (5.0 %)	
Chemoradiotherapy				0.41
Yes	2 (1.1 %)	1 (0.7 %)	1 (2.5 %)	
Immunotherapy				0.86
Yes	41 (24 %)	32 (24 %)	9 (23 %)	
Radiotherapy				0.41
Yes	2 (1.1 %)	1 (0.7 %)	1 (2.5 %)	
Adjuvant therapy				
Chemotherapy				>0.99
Yes	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Chemoradiotherapy				>0.99
Yes	2 (1.1 %)	2 (1.5 %)	0 (0 %)	
Hormone therapy				>0.99
Yes	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Immunotherapy				0.41
Yes	48 (28 %)	39 (29 %)	9 (23 %)	
Immuno-radiotherapy				0.20
Yes	8 (4.6 %)	8 (6.0 %)	0 (0 %)	
Radiotherapy				0.83
Yes	28 (16 %)	22 (16 %)	6 (15 %)	

BMI, body mass index; TNM, tumor, nodes, metastases.
[a] n (%); Mean ± SD.
[b] Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test.

bilateral ILND. The mean number of inguinal lymph nodes resected from each patient was 9.67 ± 5.07, and the mean number of nodes with confirmed metastases was 1.57 ± 2.57. Ligation of the VSM was performed in 138 (79 %) patients but spared in 36 (21 %). Antibiotics were administered preoperatively to 69 (40 %) patients and postoperatively to 79 (45 %). Wound dehiscence occurred in 55 (32 %) patients and seroma development was observed in 118 (68 %), 104 of which required drainage. Wounds from 74 (43 %) patients required six weeks or more postoperative therapy, such as seroma drainage or postoperative antibiotics. Only five (2.9 %) patients required reoperation. No reconstructive LVA or VLNT microsurgery was performed on any of the patients during ILND. Complete surgical characteristics and other postoperative complications are detailed in Table 2.

3.3. Patient-reported outcome measures

3.3.1. Lymphedema

Based on the Lymph-ICF-LL questionnaire, 134 (77 %) patients reported experiencing some degree of lymphedema-related symptoms (Table 3.). Mean scores and distribution of categorical severity for each of the components of the Lymph-ICF-LL, including physical function, mental function, general tasks, mobility, and function in social life were significantly different between patients who reported lymphedema-related symptoms and those who did not. The mean total Lymph-ICF-LL score was 26.01 ± 17.29 for patients with lymphedema-related symptoms, and 1.41 ± 1.37 for those without ($p < 0.001$).

3.3.2. Quality of life

SF-36 scales measuring physical and social functioning, role limitations due to physical and emotional health, energy and fatigue, emotional well-being, pain, and general health were statistically significant between patients who did and did not report lymphedema-related symptoms (Table 4.). The summary measures of physical and mental component scores further reflected this difference. Patients with lymphedema-related symptoms had a lower mean physical and mental component score of 45.63 ± 10.43 and 49.19 ± 9.47, respectively, whereas those without lymphedema-related symptoms had a higher mean physical and mental component score of 56.28 ± 2.81 ($p < 0.001$) and 56.51 ± 3.44 ($p < 0.001$), respectively.

The level of severity distribution across all of the five health domains

Table 2
Comparison of lower extremity surgical characteristics.

Characteristic	Total N = 174[a]	Lymphedema-related symptoms, per patient: Yes, N = 134[a]	No, N = 40[a]	p-value[b]
Lymphadenectomy laterality				0.13
Bilateral	18 (10 %)	11 (8.2 %)	7 (18 %)	
Unilateral	156 (90 %)	123 (92 %)	33 (83 %)	
Number of inguinal lymph nodes resected	9.67 ± 5.07	9.81 ± 5.29	9.18 ± 4.28	0.83
Number of inguinal lymph nodes with confirmed metastases	1.57 ± 2.57	1.76 ± 2.85	0.95 ± 1.01	0.086
Great saphenous vein surgical technique				0.90
Ligation	138 (79 %)	106 (79 %)	32 (80 %)	
Sparing	36 (21 %)	28 (21 %)	8 (20 %)	
Reconstruction during lymphadenectomy				
No	174 (100 %)	134 (100 %)	40 (100 %)	
Preoperative antibiotic use				0.43
Yes	69 (40 %)	51 (38 %)	18 (45 %)	
Postoperative antibiotic use				0.95
Yes	79 (45 %)	61 (46 %)	18 (45 %)	
Wound dehiscence				0.89
Yes	55 (32 %)	42 (31 %)	13 (33 %)	
Seroma development				0.66
Yes	118 (68 %)	92 (69 %)	26 (65 %)	
Seroma requiring drainage				0.74
Yes	104 (60 %)	81 (60 %)	23 (58 %)	
Wounds requiring ≥6 weeks therapy				0.71
Yes	74 (43 %)	58 (43 %)	16 (40 %)	
Reoperations				>0.99
Yes	5 (2.9 %)	4 (3.0 %)	1 (2.5 %)	
Other complications				0.50
None	115 (66 %)	85 (63 %)	30 (75 %)	
SSI	50 (29 %)	42 (31 %)	8 (20 %)	
Seroma cavity exploration	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Hematoma exploration	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Postoperative bleeding	2 (1.1 %)	2 (1.5 %)	0 (0 %)	
Seroma excision	1 (0.6 %)	1 (0.7 %)	0 (0 %)	
Abscess	4 (2.3 %)	2 (1.5 %)	2 (5.0 %)	

SSI, surgical site infection.
[a] n (%); Mean ± SD.
[b] Fisher's exact test; Wilcoxon rank sum test; Pearson's Chi-squared test.

reported in the EQ-5D-5L were significantly different between patients who reported lymphedema-related symptoms and those who did not (Table 5.). Patients with lymphedema-related symptoms reported more moderate and severe problems with mobility, self-care, and usual activities, as well as greater degrees of pain, discomfort, anxiety, and depression. The mean index score was 0.81 ± 0.14 for patients with lymphedema-related symptoms and 0.98 ± 0.05 for those without ($p < 0.001$). The mean VAS score was also significantly different, in which patients with lymphedema-related symptoms reported lower scores of general health compared to those without (74.01 ± 14.36, 89.63 ±

Table 3
Impairments in function, activity limitations, and participation restrictions reported by participants with the Lymph-ICF-LL questionnaire.

	Lymphedema-related symptoms, per patient		
Lymph-ICF-LL Component	**Yes**, N = 134[a]	**No**, N = 40[a]	**p-value**[b]
Physical function			
Score	32.31 ± 19.81	2.67 ± 3.60	<0.001
Severity interpretation			<0.001
No problem	3 (2.2 %)	31 (78 %)	
Small problem	56 (42 %)	9 (23 %)	
Moderate problem	46 (34 %)	0 (0 %)	
Severe problem	29 (22 %)	0 (0 %)	
Mental function			
Score	19.79 ± 20.08	0.58 ± 1.87	<0.001
Severity interpretation			<0.001
No problem	33 (25 %)	37 (93 %)	
Small problem	54 (40 %)	3 (7.5 %)	
Moderate problem	32 (24 %)	0 (0 %)	
Severe problem	15 (11 %)	0 (0 %)	
General tasks/household activities			
Score	18.21 ± 22.55	0.08 ± 0.53	<0.001
Severity interpretation			<0.001
No problem	50 (37 %)	40 (100 %)	
Small problem	47 (35 %)	0 (0 %)	
Moderate problem	16 (12 %)	0 (0 %)	
Severe problem	21 (16 %)	0 (0 %)	
Mobility			
Score	29.17 ± 21.86	1.86 ± 3.36	<0.001
Severity interpretation			<0.001
No problem	12 (9.0 %)	32 (80 %)	
Small problem	54 (40 %)	8 (20 %)	
Moderate problem	39 (29 %)	0 (0 %)	
Severe problem	29 (22 %)	0 (0 %)	
Life domains/social life			
Score	27.24 ± 22.18	0.90 ± 2.09	<0.001
Severity interpretation			<0.001
No problem	20 (15 %)	36 (90 %)	
Small problem	53 (40 %)	4 (10 %)	
Moderate problem	35 (26 %)	0 (0 %)	
Severe problem	26 (19 %)	0 (0 %)	
Total			
Score	26.01 ± 17.29	1.41 ± 1.37	<0.001
Severity interpretation			<0.001
No problem	0 (0 %)	40 (100 %)	
Small problem	77 (57 %)	0 (0 %)	
Moderate problem	38 (28 %)	0 (0 %)	
Severe problem	19 (14 %)	0 (0 %)	

Lymph-ICF-LL, Lymphoedema Functioning Disability and Health Questionnaire for Lower Limb Lymphoedema.
[a] Mean ± SD; n (%).
[b] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

7.49; $p < 0.001$)

Patients who reported lymphedema-related symptoms scored significantly lower for each of the 20 items included in the LEFS questionnaire, indicating lesser degree of lower extremity function compared to those who did not report any lymphedema-related symptoms (Table 6.). Mean total LEFS scores were 57.80 ± 17.22 and 75.85 ± 6.79 for those with and without lymphedema-related symptoms, respectively ($p < 0.001$).

3.4. Predictors of lymphedema-related symptoms

A multivariable logistic regression analysis was performed to identify predictors of lymphedema-related symptoms based on demographic and surgical variables (Table 7.). Age at the time of ILND was a significant predictor of lymphedema-related symptoms, with those younger than 65 years-old at greater risk compared to those 65 years or older (OR = 2.56; 95 % CI: 1.08, 6.09; p = 0.033). Patients with cardiovascular disease, such as heart failure, hypercholesterolemia, and

Table 4
Comparison of 36-Item Short Form Health Survey health-related quality-of-life domains among participants with self-reported lymphedema.

	Lymphedema-related symptoms, per patient		
SF-36 Characteristic	Yes, N = 134[a]	No, N = 40[a]	p-value[b]
Scales			
Physical functioning	68.40 ± 26.55	93.50 ± 10.01	<0.001
Role limitations due to physical health	65.49 ± 42.46	100.00 ± 0.00	<0.001
Role limitations due to emotional problems	76.37 ± 36.98	100.00 ± 0.00	<0.001
Energy/fatigue	61.34 ± 19.04	86.00 ± 11.05	<0.001
Emotional well-being	75.91 ± 14.27	89.10 ± 8.30	<0.001
Social functioning	78.26 ± 22.94	97.19 ± 6.63	<0.001
Pain	78.32 ± 21.99	99.75 ± 1.58	<0.001
General health	58.81 ± 20.83	79.38 ± 17.69	<0.001
Summary measures			
Physical component score	45.63 ± 10.43	56.28 ± 2.81	<0.001
Mental component score	49.19 ± 9.47	56.51 ± 3.44	<0.001

SF-36, 36-Item Short Form Survey.
[a] Mean ± SD.
[b] Wilcoxon rank sum test.

Table 5
Comparison of EuroQol health domains and index values among participants with self-reported lymphedema.

	Lymphedema-related symptoms, per patient		
Characteristic	Yes, N = 134[a]	No, N = 40[a]	p-value[b]
EQ-5D Dimension			
Mobility			<0.001
No problems	67 (50 %)	38 (95 %)	
Slight problems	34 (25 %)	2 (5.0 %)	
Moderate problems	24 (18 %)	0 (0 %)	
Severe problems	9 (6.7 %)	0 (0 %)	
Self-care			0.014
No problems	112 (84 %)	40 (100 %)	
Slight problems	16 (12 %)	0 (0 %)	
Moderate problems	6 (4.5 %)	0 (0 %)	
Usual activities			<0.001
No problems	67 (50 %)	39 (98 %)	
Slight problems	44 (33 %)	1 (2.5 %)	
Moderate problems	20 (15 %)	0 (0 %)	
Severe problems	3 (2.2 %)	0 (0 %)	
Pain/discomfort			<0.001
No pain/discomfort	42 (31 %)	36 (90 %)	
Slight pain/discomfort	65 (49 %)	4 (10 %)	
Moderate pain/discomfort	22 (16 %)	0 (0 %)	
Severe pain/discomfort	4 (3.0 %)	0 (0 %)	
Extreme pain/discomfort	1 (0.7 %)	0 (0 %)	
Anxiety/depression			0.002
Not anxious/depressed	96 (72 %)	39 (98 %)	
Slightly anxious/depressed	30 (22 %)	1 (2.5 %)	
Moderately anxious/depressed	7 (5.2 %)	0 (0 %)	
Severely anxious/depressed	1 (0.7 %)	0 (0 %)	
EQ-Index			
Total index score	0.81 ± 0.14	0.98 ± 0.05	<0.001
EQ VAS			
Total VAS score	74.01 ± 14.36	89.63 ± 7.49	<0.001

EQ-5D-5L, EuroQol Five-Dimension Five-Level; VAS, visual analogue scale.
[a] n (%); Mean ± SD.
[b] Fisher's exact test; Wilcoxon rank sum test.

Table 6
Comparison of Lower Extremity Functional Scale scores among participants with self-reported lymphedema.

Activity	Lymphedema-related symptoms, per patient		
	Yes, N = 134[a]	No, N = 40[a]	p-value[b]
1. Any of your usual work, housework, or school activities	3.16 ± 0.93	4.00 ± 0.00	<0.001
2. Your usual hobbies, recreational, or sporting activities	3.04 ± 0.96	3.95 ± 0.22	<0.001
3. Getting into or out of the bath	3.08 ± 1.17	3.88 ± 0.46	<0.001
4. Walking between rooms	3.66 ± 0.65	4.00 ± 0.00	<0.001
5. Putting on your shoes or socks	3.34 ± 0.84	3.95 ± 0.22	<0.001
6. Squatting	2.47 ± 1.32	3.85 ± 0.43	<0.001
7. Lifting an object, like a bag of groceries from the floor	3.33 ± 1.01	3.90 ± 0.30	<0.001
8. Performing light activities around your home	3.49 ± 0.73	4.00 ± 0.00	<0.001
9. Performing heavy activities around your home	2.59 ± 1.26	3.70 ± 0.69	<0.001
10. Getting into or out of a car	3.41 ± 0.82	3.95 ± 0.22	<0.001
11. Walking two blocks	3.43 ± 1.02	3.98 ± 0.16	<0.001
12. Walking one mile	3.01 ± 1.36	3.93 ± 0.35	<0.001
13. Going up or down ten stairs (approximately one flight of stairs)	3.26 ± 1.07	3.95 ± 0.22	<0.001
14. Standing for 1 hour	2.31 ± 1.30	3.65 ± 0.58	<0.001
15. Sitting for 1 hour	3.52 ± 0.76	3.93 ± 0.27	<0.001
16. Running on even ground	1.74 ± 1.57	3.30 ± 1.07	<0.001
17. Running on uneven ground	1.60 ± 1.52	3.18 ± 1.26	<0.001
18. Making sharp turns while running fast	1.81 ± 1.58	3.28 ± 1.26	<0.001
19. Hopping	2.09 ± 1.42	3.58 ± 0.96	<0.001
20. Rolling over in bed	3.48 ± 0.85	3.93 ± 0.35	<0.001
LEFS total score (out of 80)	57.80 ± 17.22	75.85 ± 6.79	<0.001

LEFS, Lower Extremity Functional Scale.
[a] Mean ± SD.
[b] Wilcoxon rank sum test.

Table 7
Logistic regression model of predictors of secondary lymphedema following inguinal lymphadenectomy.

Predictor	Odds Ratio	95 % Confidence Interval		p-value
		Lower	Upper	
Age at time of ILND: **< 65**	2.564	1.079	6.092	0.033
Comorbidity: **Cardiovascular disease**	24.799	1.926	319.296	0.014
Postoperative antibiotics: **Yes**	0.064	0.008	0.532	0.011
Postoperative wounds[a]: **Yes**	6.813	1.016	45.688	0.048
Other postoperative complications: **SSI**	4.537	1.198	17.183	0.026

ILND, inguinal lymph node dissection; SSI, surgical site infection.
[a] Wounds requiring six weeks or more of postoperative therapy.

atherosclerosis were more than 24 times as likely to have lymphedema-related symptoms compared to those without (OR = 24.80; 95 % CI: 1.93, 319.30; p = 0.014). In contrast to patients who did not have any postoperative complications following ILND, those who developed SSI were more than four times as likely to have lymphedema-related symptoms (OR = 4.54; 95 % CI: 1.20, 17.18; p = 0.026), while those with wounds requiring six weeks or more postoperative therapy were nearly seven times as likely to have lymphedema-related symptoms (OR = 6.81; 95 % CI: 1.02, 45.69; p = 0.048). Patients who received postoperative antibiotics were significantly less likely to have lymphedema-related symptoms compared to those who did not (OR = 0.064; 95 % CI: 0.01, 0.53; p = 0.011). Neither (neo)adjuvant therapies or surgical characteristics, such as the number of lymph nodes resected during ILND and ligation of the VSM, were significant predictors of lymphedema-related symptoms.

3.5. Predictors of patient-reported outcomes

3.5.1. Lymphedema

Multivariable linear regression models were designed to predict quality of life and lower extremity function based on scores derived from corresponding PROMs (Supplemental Tables 1–3.). In all analyses, the presence of lymphedema-related symptoms was a significant predictor of lower mean SF-36 PCS (Estimate: −10.07; 95 % CI: −13.21, −6.93; p < 0.001) and MCS (Estimate: −6.93; 95 % CI: −9.81, −4.10; p < 0.001), EQ-5D-5L VAS score (Estimate: −13.99; 95 % CI: −18.55, −9.42; p < 0.001), and LEFS score (Estimate: −16.87; 95 % CI: −21.82, −11.91; p < 0.001).

3.5.2. Patient demographics

Age of patients ≥65 years-old at the time of follow-up was significantly associated with lower mean SF-36 PCS scores (Estimate: −3.33; 95 % CI: −6.19, −0.47; p = 0.023) (Supplemental Table 1.), while age of patients ≥65 years-old at the time time of ILND was a significant predictor of lower mean LEFS scores (Estimate: −6.27; 95 % CI: −10.57, −1.96; p = 0.005) (Supplemental Table 3.).

Comorbidities, such as BMI ≥30 kg/m^2 (Estimate: −5.35l 95 % CI: −10.57, −0.12, p = 0.045), hypertension (Estimate: −5.40; 95 % CI: −10.22, −0.58; p = 0.028), cardiovascular disease (Estimate: −10.00; 95 % CI: −17.17, −2.84; p = 0.007), and autoimmune disease (Estimate: −10.57; 95 % CI: −20.19, −4.23; p = 0.006) were significant significant predictors of lower mean LEFS scores (Supplemental Table 3.).

3.5.3. Malignancy

The type and staging of malignancy for which patients underwent ILND proved to be significant predictors of morbidity as measured by several PROMs (Supplemental Tables 1–3). Vulvar carcinoma was significantly associated with lower mean SF-36 PCS scores (Estimate: −11.22; 95 % CI: −18.09, −4.35; p = 0.002) and VAS scores (Estimate: −15.40; 95 % CI: −24.53, −6.27; p = 0.001). Metastasized myoepithelioma was also significantly associated with lower mean SF-36 PCS scores (Estimate: −21.60; 95 % CI: −39.10, −4.11; p = 0.016) and VAS scores (Estimate: −47.11; 95 % CI: −71.57, −22.66; p < 0.001). Basosquamous carcinoma was significantly associated with lower mean SF-36 PCS scores (Estimate: −23.05; 95 % CI: −40.00, −6.13; p = 0.008). Compared to patients with TNM stages I, II, and III, those with malignancies classified at stage IV were significantly associated with lower mean SF-36 PCS scores (Estimate: −11.05; 95 % CI: −18.77, −3.32; p = 0.005), and LEFS scores (Estimate: −14.77; 95 % CI: −25.31, −4.23; p = 0.006).

3.5.4. Surgical characteristics

Development of seroma for which postoperative excision was required was significantly associated with lower SF-36 PCS scores (Estimate: −29.47; 95 % CI: −52.31, −6.63; p = 0.012) (Supplemental Table 1.).

Adjuvant chemotherapy was a significant predictor of lower mean SF-36 PCS scores (Estimate: −12.82; 95 % CI: −24.72, −0.93; p = 0.035) (Supplemental Table 1.), and VAS scores (Estimate: −25.16; 95 % CI: −43.56, −6.76; p = 0.008) (Supplemental Table 2.). Compared with patients who received antibiotics postoperatively, the VAS scores of those who did not were significantly lower (Estimate: −4.80; 95 % CI: −8.65, −0.95; p = 0.015). All significant predictors of morbidity reflected in PROMs scores are detailed in Supplemental Tables 1–3.

4. Discussion

This study provides valuable insights into the prevalence, severity, and predictors of lymphedema-related symptoms, as well as their impact on PROMs following ILND. Of the patients in this cohort, 77 %

experienced lymphedema-related symptoms, which were significantly associated with quality of life reduction and lower extremity function impairment. While the prevalence of lymphedema-related symptoms identified in this study surpasses the 24 % reported in previous literature [6], estimations have been primarily based on objective outcomes, such as circumferential measurements and volume estimations of the lower extremities. This study not only recognizes the value of employing PROMs to quantify prevalence of lymphedema-related symptoms, but also highlights the disparity between patients' lived experiences and objective clinical measurements. Because new microsurgical interventions are aimed to treat symptoms and improve quality of life in patients with LEL, the perspective of patients remains paramount in determining degree of morbidity and the most appropriate therapeutic approach. The findings from this study underscore the necessity of integrating PROMs in the shared decision-making process.

Multivariable analysis identified patients who were younger at the time of surgery (<65 years), as well as those with a medical history of cardiovascular disease at significantly greater risk of reporting lymphedema-related symptoms. Blood stasis, as well as venous and lymphatic hypertension in patients with right-sided heart failure are known to exacerbate edema in the lower extremities [19]. Additional factors in this patient population, such as limited mobility, possible malnutrition, and hypoalbuminemia may further contribute to decreased oncotic pressure. Interestingly, data in this study revealed that other comorbidities related to cardiovascular disease, such as BMI $\geq$30 kg/m^2 and hypertension were not significant predictors of lymphedema-related symptoms. While the exact mechanism remains unclear, a proposed link between cardiovascular disease and lymphedema relies on the mobilization of cholesterol from macrophage stores that may depend on lymphatic vessels. Lymphatic dysfunction induced by inguinal lymphadenectomy, may contribute to elevated atherogenic lipoproteins and increased atherosclerotic plaque formation—key features of hypercholesterolemia and fundamental in the pathogenesis of atherosclerosis [20]. Congruent with previous literature [21], this study identified postoperative complications, such as SSI and wounds requiring prolonged therapy as significant predictors of lymphedema-related symptoms. While the prevention of SSI, seroma development, and other complications may be improved through proper postoperative wound drainage, the optimal duration remains inconclusive [22]. No data on the duration or use of postoperative wound drainage was collected from medical records in this study. Development of postoperative seroma, however, did not prove to be a significant predictor of lymphedema-related symptoms. Furthermore, postoperative antibiotics had a protective effect against lymphedema-related symptoms, suggesting that thorough therapy and infection prevention could reduce morbidity.

Several surgical factors previously described as having an impact on LEL pathogenesis following ILND, did not show statistical significance in this study [23,24]. Neither the number of lymph nodes resected nor the ligation of the VSM were significantly associated with the prevalence of lymphedema-related symptoms. These findings could impact the surgical technique applied during ILND, as previous studies have reported improved long-term survival attributed to the removal of micrometastatic disease from a greater number of inguinal lymph nodes harvested during the procedure [25]. Enhanced access to lymph nodes afforded by the ligation of the VSM, for which inconsistent impacts on LEL have been reported [6,26,27], may therefore be an important consideration in surgical technique. Nonetheless, findings from this study suggest that the pathophysiology of LEL is multifaceted, with patient-specific risk factors and postoperative care playing a prominent role.

4.1. Potentials for (prophylactic) reconstructive surgery

The findings of this study underscore the substantial burden of ILND-associated morbidity and the role that microsurgical reconstructive surgery could fill for patients who suffer from or are at risk for LEL. Estimates of clinical improvement in extremity circumference and volume change in patients with secondary LEL who undergo either LVA or VLNT range between 30 and 40 % [28]. Even in the absence of clinical improvement, patients who undergo reconstructive microsurgery in the treatment of LEL have reported improved quality of life outcomes with greater response to conservative therapies and in some cases a reduction in the overall use of compression garments to manage symptoms [29,30]. While more long-term studies are needed to better understand which patient characteristics contribute to improved clinical outcomes following LVA or VLNT in the treatment of LEL, this study identifies those at greatest risk for developing lymphedema-related symptoms following ILND. Patients younger than 65 years-old at the time of ILND or who have a medical history of cardiovascular disease had a significantly greater risk of developing lymphedema-related symptoms, and could, thus, stand the most to gain from prophylactic reconstructive microsurgery. Early studies conducted on LVA at the time of ILND show promising outcomes in the primary prevention of LEL [31,32]. Future research on long-term outcomes, as well as congruent studies with VLNT at the time of ILND are needed to better understand the impact of prophylactic reconstructive surgery in LEL prevention.

4.2. Strengths and limitations

This study comprises one of the largest and most comprehensive cohorts of patients who have undergone ILND for a diverse range of malignancy types and stages in the Netherlands. The inclusion of such an extensive cohort is of particular significance given the high mortality rate associated with malignancies for which ILND is indicated [1]. This has complicated the ability for patients to participate in long-term follow-up studies from which thorough analysis can produce meaningful data.

This study assesses multiple domains through the use of validated PROMs, the breadth and diversity of which have not been previously reported on in such a large cohort of patients following ILND. Findings on quality of life and lower extremity function provide a detailed and patient-centered understanding of ILND-associated morbidity. By including outcomes, such as functional impairments and psychosocial well-being, this study highlights the broader impact of ILND on patients' lives.

While the Lymph-ICF-LL is the first Dutch questionnaire with evidence of reliability and validity for assessing impairments in patients with secondary LEL, the scores from which the presence of lymphedema-related symptoms was derived are not an objective measure of lymphedema or its severity. This is an important distinction, as the presence of lymphedema-related symptoms does not always equate to clinically measurable lymphedema. Imaging modalities that better incorporate the physiologic features of lymphedema, such as indocyanine green (ICG) lymphangiography or lymphoscintigraphy can scan the layers of the collecting lymphatic channels and visualize lymphatic flow [33]. Previous studies have demonstrated a weak correlation between PROMs and functional imaging [34], underscoring the importance of using a multifaceted approach to evaluate lymphedema, particularly when guiding microsurgical decision-making. Implementing such methods in this study, however, was not feasible given the size of the cohort included. Nevertheless, the symptom-based approach employed by this study remains clinically relevant, as PROMs closely reflect patients' lived experiences and may be sufficient to determine eligibility for reconstructive microsurgery.

5. Conclusion

This study highlights the significant burden of lymphedema-related symptoms following ILND, demonstrating their prevalence, key predictors, and impact on patient-reported outcomes. Younger age at time of surgery, medical history of cardiovascular disease, and postoperative

complications, such as surgical site infections and prolonged wound therapy emerged as major risk factors for developing lymphedema-related symptoms. Postoperative antibiotics proved to have a protective effect, underscoring the importance of meticulous infection prevention. Surgical factors, such as the number of lymph nodes resected and ligation of the VSM did not significantly impact development of lymphedema-related symptoms, suggesting that pathophysiology of LEL is shaped more by patient-specific and postoperative care factors. Reconstructive microsurgery, such as LVA and VLNT, could offer a promising approach to reducing morbidity from lymphedema-related symptoms, particularly for high-risk patients identified in this study. Future research on long-term outcomes and studies investigating the effectiveness of prophylactic microsurgery performed at the time of ILND is needed to better understand its role in preventing LEL.

CRediT authorship contribution statement

Brett A. Hahn: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alieske Kleeven:** Writing – review & editing, Methodology, Investigation, Data curation. **Milan C. Richir:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Arjen J. Witkamp:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Anke M.J. Kuijpers:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Kristien B.M.I. Keymeulen:** Visualization, Validation, Supervision. **J. Henk Coert:** Supervision, Project administration, Methodology, Conceptualization. **Shan Shan Qiu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Data curation, Conceptualization. **David D. Krijgh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2025.102257.

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