Risk factors for lower extremity lymphedema after inguinal lymphadenectomy in melanoma patients: A retrospective cohort study

Tianzhe Chen, MM, BSc [a], Yue Lin, MM [b], Qian Tan, MD, PhD [a,b,*]

[a] Department of Burns & Plastic Surgery, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, China
[b] Department of Burns & Plastic Surgery, Nanjing Drum Tower Hospital, the Affiliated Hospital of Medical School of Nanjing University, Nanjing, China

ARTICLE INFO

ABSTRACT

Background: The aim of lymph node dissection for melanoma patients is to prevent metastasis. However, this procedure is accompanied by a long-term and impaired life-quality complication called *extremity lymphedema*. This condition involves long-term lower limb swelling, which causes discomfort and impaired function, and affects patients both physically and psychologically. Herein, we conducted a retrospective cohort study at a single center to investigate the risk factors associated with lower extremity lymphedema after inguinal lymphadenectomy.

Materials and Methods: We identified 136 inguinal lymphadenectomy melanoma patients treated between January 2010 and January 2021. The patients' demographic, clinical, and pathological data and postoperative outcomes were collected by electronic medical record review and patient follow-up. The patients' postoperative outcomes were defined as lower extremity swelling and lower extremity lymphedema. Univariate and multivariate analyses were used to determine the independent predictors of lower extremity lymphedema.

Results: The follow-up results from 85 melanoma patients who underwent inguinal lymphadenectomy were analyzed. Multivariate logistic regression analysis showed that number of lymph nodes removed ≥ 10 was the significant risk factor for postoperative lower extremity lymphedema (odds ratio = 6.468, P = .042, 95% confidence interval: 1.069 to 39.147). Moreover, 8 (100%) patients in the lower extremity lymphedema group and 32 (53.3%) patients in the normal group were female, which indicated that female patients might be more susceptible to postoperative lower extremity lymphedema (P = .012).

Conclusion: Our study found that number of inguinal lymph nodes removed ≥ 10 was associated with a significantly higher incidence of lower extremity lymphedema with a 6.5-fold increased risk in melanoma patients. Also, female patients were more likely to develop lower extremity lymphedema after inguinal lymphadenectomy.

BACKGROUND

Melanoma is a common yet aggressive skin cancer. In recent decades, the annual growth rate of melanoma incidence has been approximately 3%–5%. One clear etiology for melanoma is excessive ultraviolet exposure, which causes a very common pathological classification called *superficial spreading melanoma* in the white population. However, acral lentiginous melanoma is a low-morbidity type among all pathological classifications of melanoma and dominates in Asian and African populations. To standardize acral melanoma diagnosis and treatment in China, the Chinese Society of Clinical Oncology Melanoma Group revised many recommendations for clinical practice guidelines. Once a patient is pathologically diagnosed, wide lesion excision (WLE) and sentinel lymph node biopsy (SLNB) are necessary to obtain the Tumor, Node, and Metastasis stage for subsequent treatment. Also, patients with positive sentinel lymph node (SLN) or clinically evident regional LN metastases could receive complete LN dissections (CLNDs) to reduce the rate of distant metastasis. However, the Multicenter Selective Lymphadenectomy Trial 1 indicated that the clinical evidence for this procedure in SLN-positive patients is lacking [1]. The updated clinical guidelines and Multicenter Selective Lymphadenectomy Trial 2 recommended active surveillance or follow-up of SLN-positive patients as routine practice [2,3].

LN dissection, such as CLND, is associated with postoperative complications [4]. Inguinal LN dissection has resulted in significantly higher morbidity than axillary and cervical LN dissections. The prevalence of chronic lymphedema after axillary LN dissection is approximately 10%,

* Corresponding author at: Department of Burns & Plastic Surgery, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Department of Burns & Plastic Surgery, Nanjing Drum Tower Hospital, the Affiliated Hospital of Medical School of Nanjing University, 321 Zhongshan Rd, Nanjing 210008, China.
E-mail address: smmutanqian@sina.com (Q. Tan).

whereas it can be up to 35% after inguinal LN dissection [5]. However, studies have reported that the SLNB positive rate in patients with melanomas smaller than 1.0 mm (T1 stage) is only 8.9% [6], and the 10-year survival rate of the T1 stage is up to 93% [7]. Most patients with positive SLNs do not have further LN metastasis evidence after CLND [8]. In this case, the balance between the risk of complications from LN dissections and patient benefits remains controversial.

As one of the long-term complications after LN dissection, lymphedema is the most common physical disturbance in melanoma survivors. Histologic changes of cutaneous tissues include fibrosis, impaired function, and a life-long increased risk of limb inflammation [9]. Secondary lymphedema is viewed as an untreatable adverse effect after a beneficial therapy [10]. However, most previous studies involving lymphedema followed by LN dissections were in the breast or urogenital cancer populations [11,12]. Studies have concluded that groin dissection, diabetes, high body mass index (BMI), and peripheral vascular disease increase the risk of lymphedema [13–15]. A transverse incision, saphenous vein preservation, and videoscopic techniques have been shown to reduce the incidence of lymphedema [16–18]. A recent malignant melanoma study was conducted in the Danish population, which reported that surgical site infection (SSI) might mediate the onset of lymphedema following SLNB and CLND [19]. However, considering the racial differences of patients and the pathological differences of melanoma, our study is necessary. Given this, the purpose of this retrospective cohort study was to evaluate the clinical characteristics of LEL and explore their risk factors.

MATERIALS AND METHODS

Patients. Our study was conducted as a retrospective study and reported according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement. The study was conducted per the Declaration of Helsinki (as revised in 2013). This retrospective cohort study was Institutional Review Board approved. For this type of study, formal consent is not required. We performed a single-center retrospective cohort study using the medical records of the Nanjing Drum Tower Hospital from January 2010 to January 2021. We analyzed patients who were diagnosed with malignant melanoma and underwent inguinal LN dissection. The enrolled patients provided their postoperative outcomes during follow-up by telephone or return visit. Patients who received conservative treatment or WLE alone were not included in this study (Fig 1). In total, 136 patients were included.
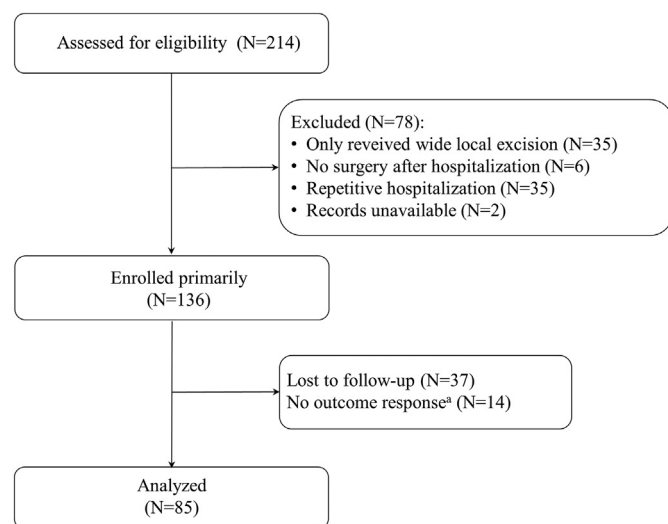

Fig 1. Flowchart of enrollment. Flow diagram of patients included in and excluded from the study. No outcome respond[a]: no patients' postoperative outcomes feedback because they had died and their family members did not respond to us either.

Patient outcome information included the chief postdischarge subjective physical complaint, subsequent visit physical examination and imaging materials, and the self-reported lower-extremity lymphedema screening questionnaire (SRLELSQ) score. The patients' demographic (sex, age, BMI), clinical (follow-up outcome, surgical method, length of stay, etc), and pathological (number and states of LNs removed, tumor marker, etc) characteristics were collected. All patients received early postoperative rehabilitation treatment during their hospitalization, and postoperative problems were handled positively.

Surgical Technique. The surgical technique was performed according to the Chinese melanoma clinical practice guidelines [20,21]. Patients were diagnosed with malignant melanoma by primary lesion biopsy. For first-visit patients, WLE and inguinal SLNB (for T1b–T4 patients) were recommended. Preoperative Doppler ultrasound SLN localization or intraoperative methylene blue staining methods were applied to assist in SLNB. If the postoperative pathological diagnosis reported SLN positivity, the patient could receive CLND or active surveillance. The minimum number of LNs retrieved in standard-quality inguinal LND was required to be ≥10. Intraoperatively, damage to blood vessels and nerves in the surgical area should be avoided, and lymphatic vessels should be ligated as completely as possible.

Follow-Up. Follow-up was performed by telephone, outpatient clinic visit, or online communication software (WeChat). Postoperative outcomes were reported by the patients themselves, except for 3 patients who had died. The patients were followed up in the first half-year after discharge from the hospital and every year subsequently. During follow-up, the information collected included the chief complaint, physical examination, postoperative imaging materials, and subsequent therapy protocols.

Self-Reported Lower-Extremity Lymphedema Screening Questionnaire. The Mayo Clinic developed a screening questionnaire to detect extremity lymphedema. The questionnaire includes 13 options and 5 degrees for each option (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much). The questionnaire options related to the leg, ankle, and foot sensation, including skin tightness, swelling, pain, or discomfort. The scores ranged from 0 to 32 points, and scores ≥5 points indicated a positive screen.

Outcome Evaluation and Grouping Criteria
Lower Extremity Swelling

Patients included in the LES group satisfied the following inclusion criteria: (1) LES complaint; (2) SRLELSQ score > 0; (3) limb swelling feeling was aggravated after lower limb activity and alleviated after rest; and (4) physical examination either showed or did not show a visible bilateral lower limb volume difference. Meanwhile, patients were excluded according to the following criteria: (1) those with cardiovascular, nephritic, or hepatic disease, which may result in tissue edema; (2) patients with malnutrition conditions; (3) those with endocrine diseases, such as hypothyroidism; (4) patients with lower limb vascular disease, such as venous thrombosis; (5) those with lower limb muscular dystrophy; (6) patients who were taking drugs, such as calcium antagonist and nonsteroidal anti-inflammatory drugs; (7) those with severe lower limb trauma; and (8) patients with other malignant tumors.

Lower Extremity Lymphedema

The limbs affected by lymphedema were evaluated according to the International Society of Lymphology criteria. Patients defined as having LEL were required to satisfy the LES group criteria. These patients were also required to meet the following criteria further: (1) visible bilateral lower limb difference or progressive surgical side limb volume enlargement; (2) unable to conduct outdoor activity, and (3) SRLELSQ score ≥5. Moreover, imaging materials, such as magnetic resonance imaging (MRI), computed tomography (CT), or Doppler ultrasound, were

considered to assist LEL diagnosis. MRI and CT were applied to display soft tissue thickness or fibrosis (Fig 2) [22], and ultrasonography was used to evaluate subcutaneous tissue thickness and blood vascular patency condition.

Statistical Analysis. Statistical analysis and graphing were performed using IBM SPSS version 26.0 (SPSS, Chicago, IL, USA, RRID: SCR_002865) and GraphPad version 8.0 (GraphPad Software, San Diego, CA, USA, RRID: SCR_002798). The distribution condition of measurement data was tested by skewness, kurtosis, a frequency histogram, and the Shapiro–Wilk test. Dichotomous variables were expressed as simple frequencies (n) or percentages (n%), and continuous variables (all presented non-normal distribution) were summarized as median or range (minimum–maximum). The Mann–Whitney U test (for cases of non-normal distribution) was used to test for significant differences between the measurement data of independent groups. The χ^2 test ($n \geq 40$) or Fisher Exact Test ($n < 40$) were used to assess the significant differences in enumeration data between 2 groups. Univariate logistic regression was carried out to determine the unadjusted association of clinical and operative characteristics with postoperative complications. Following univariate analysis, the surgery times and number of LNs removed ($P < .05$) were entered into a multivariate logistic regression model to predict lymphedema. Statistical tests were 2-tailed.

RESULTS

The final cohort study consisted of 85 patients who underwent lymphadenectomy and provided their postoperative outcomes. The postoperative follow-up results after surgery are shown in Tables 1 and 2 with different group criteria. According to LES evaluation criteria, patients were divided into LES and no LES groups (Table 1). The baseline demographic data and postoperative pathological characteristics exhibited no statistical difference between the groups. However, we identified 1 variable (length of stay) that showed a significant difference. The LES group displayed a longer hospital stay time than the no LES (or normal) group (25 [9–41] vs 18 [8–64] days, $P = .018$). Variables that did not satisfy the dichotomous variable conditions (eg, surgical treatment methods) were managed and analyzed later.

Patients were also divided into LEL and no LEL groups according to the LEL evaluation criteria (Table 2). Occasionally, we found 1 variable (sex) that showed a significant difference ($\chi^2 = 7.487$, $P = .006$). All 8 patients in the LEL group were female. We performed a pairwise comparison based on patients' sexes and the SRLELSQ scores (Fig 3). A score = 0 signified normal patients, scores 1–4 denoted LES but not LEL patients, and scores ≥5 represented LEL patients. The pairwise comparison results indicated that "score ≥ 5" patients were significantly different to "score = 0" patients ($\chi^2 = 6.347$, $P = .012$) or "scores 1–4"

Fig 2. Magnetic resonance imaging displayed a typical lymphedema patient with fibrosis and thickness in subcutaneous tissue. The T2-weighted images showed the stagnant water with a high signal.

Table 1
Clinical and pathological characteristics with LES grouping criteria

Patient characteristic	Total (N = 85)	LES (N = 25)	No LES (N = 60)	U/χ^2	P value
Sex				0.051	.822
Male	39 (45.9%)	11 (44%)	28 (46.7%)		
Female	46 (54.1%)	14 (56%)	32 (53.3%)		
Age (y)	61 (17–82)	62 (45–82)	61 (17–80)	−0.738	.460
BMI (WHO classification)	23.44 (16.53–34.42)	23.75 (19.05–30.8)	23.37 (16.53–34.42)	−0.661	.509
<18.5	4 (4.7%)	0 (0%)	4 (6.7%)		
18.5 ≤ BMI < 25	56 (65.9%)	18 (72%)	38 (63.3%)		
25 ≤ BMI < 30	19 (22.4%)	6 (24%)	13 (21.7%)		
30 ≤ BMI < 35	6 (7%)	1 (4%)	5 (8.3%)		
Primary melanoma localization					
Planta	31 (36.5%)	8 (32%)	23 (38.3%)		
Heel	19 (22.3%)	3 (12%)	16 (26.7%)		
Toe	19 (22.3%)	7 (28%)	12 (20%)		
Others	16 (18.8%)	7 (28%)	9 (15%)		
Surface area of lesion (cm²)	3.03 (0.09–34.1)	7.5 (0.09–23.4)	2.04 (0.09–34.1)	−1.765	.078
Surgical treatment methods					
SLND	34 (40%)	8 (32%)	26 (43.3%)		
CLND	33 (38.8%)	11 (44%)	22 (36.7%)		
SLND + CLND	11 (13%)	3 (12%)	8 (13.3%)		
Other lymph node dissection methods†	7 (8.2%)	3 (12%)	4 (6.7%)		
The number of LNs removed	5 (1–23)	7 (1–16)	4 (1–23)	−0.852	.394
Tumor status of LNs				1.199	.274
Positive	38 (44.7%)	14 (56%)	24 (40%)		
Negative	43 (50.6%)	11 (44%)	32 (53.3%)		
No report	4 (4.7%)	0 (0%)	4 (6.7%)		
Maximal diameter of LNs removed (cm)	2 (0.3–5.5)	2.2 (1–5.5)	2 (0.3–5)	−1.373	.170
Breslow thickness (mm)	4 (1.1–30)	4 (2–30)	3.5 (1.1–8)	−1.135	.257
1.1–2	14 (16.5%)	3 (12%)	11 (18.3%)		
2.1–4	20 (23.5%)	4 (16%)	16 (26.7%)		
>4	21 (24.7%)	6 (24%)	15 (25%)		
Unknown‡	30 (35.3%)	12 (48%)	18 (30%)		
Ulceration				0.366	.545
Present	27 (31.8%)	6 (24%)	21 (35%)		
Absent	20 (23.5%)	6 (24%)	14 (23.3%)		
Unknown‡	38 (44.7%)	13 (52%)	25 (41.7%)		
Stage (AJCC 8th)					
I	1 (1.2%)	0 (0%)	1 (1.7%)		
II	28 (32.9%)	7 (28%)	21 (35%)		
III	23 (27.1%)	6 (24%)	17 (28.3%)		
IV	1 (1.2%)	0 (0%)	1 (1.7%)		
Unknown‡	32 (37.6%)	12 (48%)	20 (33.3%)		
Length of stay (d)	20 (8–64)	25 (9–41)	18 (8–64)	−2.360	.018*
Tumor marker					
Ki67	−/+ (1:29)	−/+ (1:9)	−/+ (0:20)	Fisher	.333
HMB45	−/+ (12:20)	−/+ (7:5)	−/+ (5:15)	Fisher	.130
S100	−/+ (7:24)	−/+ (3:8)	−/+ (4:16)	Fisher	.676
A103	−/+ (8:16)	−/+ (4:5)	−/+ (4:11)	Fisher	.678

N, number.
* $P < .05$.
† Other lymph node dissection methods include popliteal fossa, iliac, and pelvic LN dissection.
‡ Denotes unknown information due to patients were not the firstly diagnosed in our hospital center.

Table 2
Clinical and pathological characteristics with LEL grouping criteria.

Patient characteristic	Total (N = 85)	LEL (N = 8)	No LEL (N = 77)	U/χ^2	P value
Sex				7.487	.006**
Male	39 (45.9%)	0 (0%)	39 (50.6%)		
Female	46 (54.1%)	8 (100%)	38 (49.4%)		
Age (y)	61 (17–82)	61 (53–82)	62 (17–80)	−0.475	.635
BMI (WHO classification)	23.44 (16.53–34.42)	23.50 (20.7–30.8)	23.44 (16.53–34.42)	−0.482	0.630
<18.5	4 (4.7%)	0 (0%)	4 (5.2%)		
18.5 ≤ BMI < 25	56 (65.9%)	5 (62.5%)	51 (66.2%)		
25 ≤ BMI < 30	19 (22.4%)	2 (25%)	17 (22.1%)		
30 ≤ BMI < 35	6 (7%)	1 (12.5%)	5 (6.5%)		
Primary melanoma localization					
Planta	31 (36.5%)	1 (12.5%)	30 (38.9%)		
Heel	19 (22.3%)	0 (0%)	19 (24.7%)		
Toe	19 (22.3%)	4 (50%)	15 (19.5%)		
Others	16 (18.8%)	3 (37.5%)	13 (16.9%)		
Surface area of lesion (cm²)	3.03 (0.09–34.1)	5 (0.09–14)	3.03 (0.09–34.1)	−0.374	0.708
Surgical treatment methods					
SLND	34 (40%)	1 (12.5%)	33 (42.8%)		
CLND	33 (38.8%)	3 (37.5%)	30 (39%)		
SLND + CLND	11 (13%)	2 (25%)	9 (11.7%)		
Other lymph node dissection methods†	7 (8.2%)	2 (25%)	5 (6.5%)		
The number of LNs removed	5 (1–23)	12 (1–15)	5 (1–23)	−2.012	0.044*
Tumor status of LNs				2.812	0.094
Positive	38 (44.7%)	6 (75%)	32 (41.6%)		
Negative	43 (50.6%)	2 (25%)	41 (53.2%)		
No report	4 (4.7%)	0 (0%)	4 (5.2%)		
Maximal diameter of LNs removed (cm)	2 (0.3–5.5)	2 (1.2–5.5)	2 (0.3–5)	−0.361	0.718
Breslow thickness (mm)	4 (1.1–30)	4.5 (2–5)	4 (1.1–30)	−0.169	0.867
1.1–2	14 (16.5%)	1 (12.5%)	13 (16.9%)		
2.1–4	20 (23.5%)	0 (0%)	20 (25.9%)		
>4	21 (24.7%)	2 (25%)	19 (24.7%)		
Unknown‡	30 (35.3%)	5 (62.5%)	25 (32.5%)		
Ulceration				1.379	0.240
Present	27 (31.8%)	0 (0%)	27 (35.1%)		
Absent	20 (23.5%)	1 (12.5%)	19 (24.7%)		
Unknown‡	38 (44.7%)	7 (87.5%)	31 (40.2%)		
Stage (AJCC 8th)					
I	1 (1.2%)	0 (0%)	1 (1.3%)		
II	28 (32.9%)	0 (0%)	28 (36.4%)		
III	23 (27.1%)	1 (12.5%)	22 (28.6%)		
IV	1 (1.2%)	0 (0%)	1 (1.3%)		
Unknown‡	32 (37.6%)	7 (97.5%)	25 (32.5%)		
Length of stay (d)	20 (8–64)	21 (9–32)	19 (8–64)	−0.324	0.746
Tumor maker					
Ki67	−/+ (1:29)	−/+ (0:2)	−/+ (1:27)	-	
HMB45	−/+ (12:20)	−/+ (2:1)	−/+ (10:19)	Fisher	0.540
S100	−/+ (7:24)	−/+ (0:2)	−/+ (7:22)	-	
A103	−/+ (8:16)	−/+ (1:1)	−/+ (7:15)	-	

* $P < .05$, ** $P < .01$.
† Other lymph node dissection methods include popliteal fossa, iliac, and pelvic LN dissection.
‡ Unknown information due to patients were not the firstly diagnosed in our hospital center.

To explore possible risk factors for LEL, 5 factors were considered, and continuous variables were transformed into binary variables owing to statistical reasons (Table 3). Between the LES and no LES groups, the univariate logistic regression showed that CLND (odds ratio [OR] = 1.966, $P = .190$), positive LN (OR = 1.697, $P = .276$), surgery >1 (OR = 1.263, $P = .681$), number of positive LNs removed ≥2
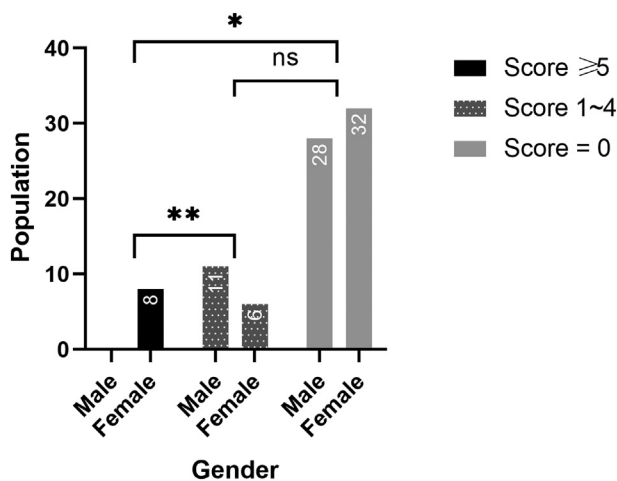
patients (Fisher Exact Tests, $P = .003$). No significant difference between "score = 0" and "scores 1–4" patients were observed ($\chi^2 = 1.725$, $P = .189$).

Fig 3. Pairwise comparison based on the patients' sexes and SRLELSQ scores. NS, nonsense. *P < .05, **P < .01.

(OR = 1.686, P = .295), and number of LNs removed ≥10 (OR = 1.833, P = .227) were not significant risk factors for LES. The univariate logistic regression model found that surgery >1 (OR = 4.500, P = .049) and number of LNs removed ≥10 (OR = 8.550, P = .012) might be risk factors for LEL. We then included these 2 potential risk factors into the multivariate logistic regression model for further analysis. The final result showed that number of LNs removed ≥10 (OR = 6.468, P = .042) was the significant risk factor for LEL, whereas surgery time > 1 (OR = 2.116, P = .376) was not. The area under the receive operating characteristic (ROC) curve was 0.716 (95% confidence interval [CI]: 0.533–0.900, P = .046) for the number of LNs removed and 0.718 (95% CI: 0.515–0.910, P = .044) for the number of positive LNs removed (Fig 4). For the best cutoff for the number of LNs removed at 9.50, the sensitivity was 75.0%, and the specificity was 77.8%.

DISCUSSION

Malignant melanoma is the most invasive skin cancer and has attracted the attention of researchers for decades. In the United States, the mortality of cutaneous melanoma mortality was up to 72% in 2017 [23]. Lymphatic metastatic spread can occur early or late during the disease process, which increases the number of factors that need to be considered during clinical treatment [24]. In this case, the updated clinical guidelines recommended that patients with clinically detected regional LN metastases should accept routine CLND [2]. However, inguinal LN dissection is always accompanied by LEL, which is a long-term complication that impairs patients' quality of life. Subsequent LES causes discomfort and impaired function, which affect patients both physically and psychologically [12,25]. Therefore, attention should be given to cancer-related lymphedema not only for cancer treatment but also to improve patients' quality of life.
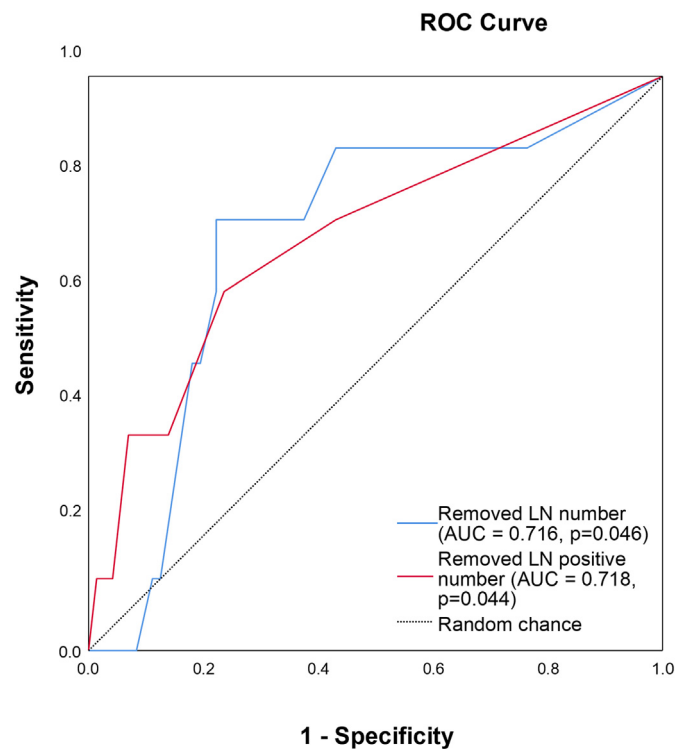

Fig 4. ROC curve for the number of LNs removed and the number of positive LNs removed. AUC, the area under the curve.

The criteria to define cancer-related lymphedema have not come from a well-established diagnostic system. The most common objective measurements are limb circumference and volumetric measurements via perometry, subjective assessments include patients' chief complaints and obviously increased limb size [12]. Other more accurate methods include noninvasive and invasive evaluation, such as MRI or lymphangiography, according to the International Union of Angiology and the Italian Society of Vascular Investigation consensus [26]. However, these advanced diagnostic instruments are not widely used for lymphedema identification because of the high cost. Moreover, the degree of limb swelling is also distinct in lymphedema patients, and moderate lymphedema is usually imperceptible. According to patients' postoperative outcome responses, patients diagnosed with LEL suffered a poor quality of life, and the costs were enormous. Meanwhile, patients with LES but not LEL indicated a small or no influence on daily life. So, we subdivided patients according to the severity of postoperative limb swelling, called the *LEL group*.

We found no statistical differences between the LES and no LES groups except for "length of stay." We found that postoperative

Table 3
Risk factors of LES/LEL using univariate or multivariate logistic regression model

	LES & no LES groups			LEL & no LEL groups					
	Univariate analysis			Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
CLND	1.966	0.715–5.406	.190	4.978	0.583–42.467	.142	–	–	–
LN positive	1.697	0.656–4.391	.276	3.844	0.727–20.332	.113	–	–	–
Surgery time >1	1.263	0.414–3.851	.681	4.500	1.002–20.209	.049*	2.116	0.403–11.115	.376
The number of positive LNs removed ≥2	1.686	0.634–4.482	.295	4.167	0.916–18.943	.065	–	–	–
The number of LNs removed† ≥10	1.833	0.686–4.903	.227	8.550	1.594–45.849	.012*	6.468	1.069–39.147	.042*

* P < .05.
† The number of LNs removed in 1 surgical process.

complications, such as SSI, seroma, and excessive drainage liquid, and a second operation led to the LES group's longer hospital stays. Previous researchers have verified that SSI was an independent risk factor for developing lymphedema, and seroma could increase the risk of developing SSI [19].

Besides melanoma, LEL is most commonly associated with oncologic therapies for gynecologic cancers, urologic cancers, and lymphomas [27]. We speculate that LEL can be caused by surgical procedures. To verify this hypothesis, we first reviewed evidence provided by previous studies and found that surgical methods might be a possible risk factor for developing lymphedema. Palmer et al showed that among pediatric melanoma patients in the United States, the addition of CLND significantly increased the risk of lymphedema [28]. Kretschmer et al reported a similar finding among the German population [29]. In an international multicenter cohort study of penile cancer, researchers reported that the number of LNs removed was an independent predictor of postoperative complications, including lymphedema [30]. We supposed that this conclusion might also apply to melanoma patients as they undergo similar inguinal LN dissection. We performed univariate and multivariate logistic regression analyses to investigate the surgical and pathology-related characteristics. Through the univariate analysis, we found that a second operation and ≥10 LNs removed could be risk factors for developing LEL. After including these 2 factors into the multivariate analysis, only ≥10 LNs removed were identified as an independent risk factor for LEL, with a 6.5-fold increased risk. In the ROC curve study, the number of LNs removed and the number of positive LNs removed were found to be significantly associated with LEL. However, we regard these as the same variable because the number of positive LNs removed correlates positively with the number of LNs removed.

All in all, the number of LNs removed ≥10 was found to be significantly associated with the development of lymphedema. Studies have shown that the number of dissected axillary lymph nodes was the risk factor for breast cancer–related lymphedema [31,32]. One explanation may be that having more LNs removed resulted in broader incisions to dissect LNs. Researches have shown that a minimally invasive technique contributes to fewer postoperative complications. Previous studies have shown that endoscopic radical LN dissection results in fewer LEL cases than open radical LN dissection for penile cancer (37% vs 3%, $P < .001$) [33]. Robotic inguinal LN dissection for melanoma was also reported to reduce postoperative complications significantly [34]. The anatomical explanation might be that more LN dissections lead to more widespread skin lymphatics and vasculature damage. However, this conjecture needs to be verified.

The number of excised lymph nodes is a quality assurance indicator in lymphadenectomy, so the association between the minimum number of LN yield and melanoma-specific survival is essential for clinical practice. A multicentric study identified that at least 10 LNs are required to stage melanoma patients after inguinal dissection, and a higher number of excised LNs had a better prognosis [35]. However, based on our study, number of inguinal LNs removed ≥10 was associated with a significantly higher incidence of LEL. Herein, the long-term and impaired life-quality complication is also needed to take into consideration when making a decision for melanoma patients.

Coincidentally, we noticed that the LEL group was predominantly female compared with the no LEL group. Other LN dissection-related neoplastic diseases, such as breast, gynecologic, and urologic cancers, exhibit distinct sex tendencies. However, there were few studies concerning the relationship between sex and LEL. Based on our results, we hypothesized that sex-related factors might affect lymphedema development in melanoma patients. The pairwise comparison indicated that female melanoma patients were more likely to develop LEL after surgery. One possible explanation may be that the lymphatic pressure in females is lower than that in males, according to Unno et al [36]. One factor supporting this explanation is that compression stockings slow down lymphedema progression. Unno et al also showed that the lymphatic pressure decrease with aging, but we did not verify this

finding. Another previous study reported that primary lymphedema is sex-linked, with a ratio of 1 male to 3 females; meanwhile, secondary lymphedema in breast cancer patients mainly occurred after patients underwent hormone therapy [37]. According to this, investigators proposed that sex hormones might play a role in the pathological etiology of lymphedema. However, this topic remains controversial.

The present retrospective cohort study is meaningful, as it included a number of Chinese postoperative melanoma patients unlike other retrospective studies. Also, we found that the number of LNs removed ≥10 increased LEL risk 6.5-fold, and identified that female patients were more likely to develop LEL after inguinal lymphadenectomy. Based on our findings, if patients are identified to have been exposed to these risk factors during treatment, physicians could emphasize the high potential to develop LEL and raise patients' awareness to have close monitoring during the following years. Meanwhile, preventive measures such as compression stockings and intermittent pneumatic compression should be introduced to patients as a routine intervention to avoid LEL. Nevertheless, there were several limitations in our study that should be noted. Firstly, the present LEL diagnosis criteria are a kind of qualitative, but not quantitative, standard. In most cases, lymphedema diagnosis is based on the initial chief complaint. However, lymphedema solely recognized by patient perception may present bias. There was significant discordance between the measured positive and patient-perceived lymphedema among postoperative cancer patients [38]. Also, CLND patients may present with a significantly lower swelling at 5 years postoperatively, and thus, the follow-up time should be sufficient. Lastly, considering that the sample in our study was not large, additional high-quality randomized controlled trials are needed to obtain more persuasive evidence.

In conclusion, our study found that the number of inguinal LNs removed ≥10 was associated with a significantly higher incidence of LEL with a 6.5-fold increased risk in melanoma patients. Meanwhile, female patients were more likely to develop LEL after inguinal lymphadenectomy.

Author Contributions

(I) Conception and design: TZ Chen, Y Lin; (II) administrative support: Q Tan; (III) provision of study materials or patients: TZ Chen, Y Lin; (IV) collection and assembly of data: TZ Chen; (V) data analysis and interpretation: all authors; (VI) manuscript writing: all authors; (VII) final approval of manuscript: all authors.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

This retrospective cohort study was Institutional Review Board approved. For this type of study, formal consent is not required. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

[1] Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014;370(7):599–609.

[2] Majem M, Manzano JL, Marquez-Rodas I, Mujika K, Muñoz-Couselo E, Pérez-Ruiz E, et al. SEOM clinical guideline for the management of cutaneous melanoma (2020). Clin Transl Oncol. 2021;23(5):948–60.

[3] Broman KK, Hughes T, Dossett L, Sun J, Kirichenko D, Carr MJ, et al. Active surveillance of patients who have sentinel node positive melanoma: an international, multi-institution evaluation of adoption and early outcomes after the Multicenter Selective Lymphadenectomy Trial II (MSLT-2). Cancer. 2021;127(13):2251–61.

[4] Hyngstrom JR, Chiang Y-J, Cromwell KD, Ross MI, Xing Y, Mungovan KS, et al. Prospective assessment of lymphedema incidence and lymphedema-associated symptoms following lymph node surgery for melanoma. Melanoma Res. 2013;23 (4):290–7.

[5] Arie A, Yamamoto T. Lymphedema secondary to melanoma treatments: diagnosis, evaluation, and treatments. Glob Health Med. 2020;2(4):227–34.

[6] Andtbacka RHI, Gershenwald JE. Role of Sentinel Lymph Node Biopsy in Patients with Thin Melanoma. 2009;7(3):308.

[7] Gershenwald JE, Ross MI. Sentinel-lymph-node biopsy for cutaneous melanoma. N Engl J Med. 2011;364(18):1738–45.

[8] Fife K, Thompson JF. Lymph-node metastases in patients with melanoma: what is the optimum management? Lancet Oncol. 2001;2(10):614–21.

[9] Rockson SG, Rivera KK. Estimating the population burden of lymphedema. Ann N Y Acad Sci. 2008;1131(1):147–54.

[10] Morgan PA, Franks PJ, Moffatt CJ. Health-related quality of life with lymphoedema: a review of the literature. Int Wound J. 2005;2(1):47–62.

[11] 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(6): 500–15.

[12] Shaitelman SF, Cromwell KD, Rasmussen JC, Stout NL, Armer JM, Lasinski BB, et al. Recent progress in the treatment and prevention of cancer-related lymphedema. CA Cancer J Clin. 2015;65(1):55–81.

[13] de Vries M, Vonkeman WG, van Ginkel RJ, Hoekstra HJ. Morbidity after inguinal sentinel lymph node biopsy and completion lymph node dissection in patients with cutaneous melanoma. Eur J Surg Oncol. 2006;32(7):785–9.

[14] Sars C, Gillgren P, Schultz I, Lindqvist EK. Risk factors for complications and long-term outcomes following completion lymph node dissection for cutaneous melanoma: a retrospective cohort study. J Plast Reconstr Aesthet Surg. 2020;73(8): 1540–6.

[15] Friedman JF, Sunkara B, Jehnsen JS, Durham A, Johnson T, Cohen MS. Risk factors associated with lymphedema after lymph node dissection in melanoma patients. Am J Surg. 2015;210(6):1178–84.

[16] Bertheuil N, Sulpice L, Levi Sandri GB, Lavoué V, Watier E, Meunier B. Inguinal lymphadenectomy for stage III melanoma: a comparative study of two surgical approaches at the onset of lymphoedema. Eur J Surg Oncol. 2015;41(2):215–9.

[17] Öztürk MB, Akan A, Özkaya Ö, Egemen O, Öreroğlu AR, Kayadibi T, et al. Saphenous vein sparing superficial inguinal dissection in lower extremity melanoma. J Skin Cancer. 2014.;2014:652123.

[18] Solari N, Gipponi M, Franco DSC, RÈ F, Sonia O, Bertoglio S, et al. Videoscopic inguinal-iliac-obturator lymph-node dissection: new videoscopic technique for regional lymphadenectomy in patients with melanoma. Anticancer Res. 2016;36(12):6579.

[19] Jørgensen MG, Toyserkani NM, Thomsen JB, Sørensen JA. Surgical-site infection following lymph node excision indicates susceptibility for lymphedema: a retrospective cohort study of malignant melanoma patients. J Plast Reconstr Aesthet Surg. 2018;71 (4):590–6.

[20] Chinese guidelines on standardized pathological diagnosis of melanoma (2021 version). Zhonghua Bing Li Xue Za Zhi. 2021;50(6):572–82.

[21] Chinese expert consensus on the surgical treatment of cutaneous/acral melanoma V1.0. Zhonghua Zhong Liu Za Zhi. 2020;42(2):81–93.

[22] Cellina M, Martinenghi C, Panzeri M, Soresina M, Menozzi A, Daniele G, et al. Noncontrast MR lymphography in secondary lower limb lymphedema. J Magn Reson Imaging. 2021;53(2):458–66.

[23] Schadendorf D, van Akkooi ACJ, Berking C, Griewank KG, Gutzmer R, Hauschild A, et al. Melanoma. Lancet. 2018;392(10151):971–84.

[24] Schadendorf D, Fisher DE, Garbe C, Gershenwald JE, Grob J-J, Halpern A, et al. Melanoma. Nat Rev Dis Prim. 2015;1(1):15003.

[25] Paskett ED, Dean JA, Oliveri JM, Harrop JP. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. J Clin Oncol. 2012;30(30):3726–33.

[26] Lee BBAP, Baroncelli TA, Boccardo FM, Brorson H, Campisi C, et al. IUA-ISVI consensus for diagnosis guideline of chronic lymphedema of the limbs. Int Angiol. 2015;34 (4):311–32.

[27] Garza R, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. BMC Cancer. 2017;17(1):468.

[28] Palmer III PE, Warneke CL, Hayes-Jordan AA, Herzog CE, Hughes DPM, Lally KP, et al. Complications in the surgical treatment of pediatric melanoma. J Pediatr Surg. 2013; 48(6):1249–53.

[29] Kretschmer L, Thoms K-M, Peeters S, Haenssle H, Bertsch H-P, Emmert S. Postoperative morbidity of lymph node excision for cutaneous melanoma-sentinel lymphonodectomy versus complete regional lymph node dissection. Melanoma Res. 2008;18(1).

[30] Gopman JM, Djajadiningrat RS, Baumgarten AS, Espiritu PN, Horenblas S, Zhu Y, et al. Predicting postoperative complications of inguinal lymph node dissection for penile cancer in an international multicentre cohort. BJU Int. 2015;116(2):196–201.

[31] Shah C, Wilkinson JB, Baschnagel A, Ghilezan M, Riutta J, Dekhne N, et al. Factors associated with the development of breast cancer–related lymphedema after whole-breast irradiation. Int J Radiat Oncol Biol Phys. 2012;83(4):1095–100.

[32] Kim M, Kim SW, Lee SU, Lee NK, Jung S-Y, Kim TH, et al. A model to estimate the risk of breast cancer-related lymphedema: combinations of treatment-related factors of the number of dissected axillary nodes, adjuvant chemotherapy, and radiation therapy. Int J Radiat Oncol Biol Phys. 2013;86(3):498–503.

[33] Kumar V, Sethia KK. Prospective study comparing video-endoscopic radical inguinal lymph node dissection (VEILND) with open radical ILND (OILND) for penile cancer over an 8-year period. BJU Int. 2017;119(4):530–4.

[34] Hyde GA, Jung NL, Valle AA, Bhattacharya SD, Keel CE. Robotic inguinal lymph node dissection for melanoma: a novel approach to a complicated problem. J Robot Surg. 2018;12(4):745–8.

[35] Rossi CR, Mozzillo N, Maurichi A, Pasquali S, Quaglino P, Borgognoni L, et al. The number of excised lymph nodes is associated with survival of melanoma patients with lymph node metastasis. Ann Oncol. 2014;25(1):240–6.

[36] Unno NTH, Suzuki M, et al. Influence of age and gender on human lymphatic pumping pressure in the leg. Lymphology. 2011;44(3):113–20.

[37] Morfoisse F, Zamora A, Marchaud E, Nougue M, Diallo LH, David F, et al. Sex hormones in lymphedema. Cancer. 2021;13:3.

[38] McLaughlin SA, Wright MJ, Morris KT, Sampson MR, Brockway JP, Hurley KE, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: patient perceptions and precautionary behaviors. J Clin Oncol. 2008;26(32):5220–6.