

The clinical characteristics of lower extremity lymphedema in 440 patients



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ABSTRACT

Background: Lower extremity lymphedema is frequently encountered in the vascular clinic. Established dogma purports that cancer is the most common cause of lower extremity lymphedema in Western countries, whereas chronic venous insufficiency (CVI) is often overlooked as a potential cause. Moreover, lymphedema is typically ascribed to a single cause, yet multiple causes can coexist.

Methods: A 3-year retrospective analysis was conducted of demographic and clinical characteristics of 440 eligible patients with lower extremity lymphedema who presented for lymphatic physiotherapy to a university medical center's cancer-based physical therapy department.

Results: The four most common causes of lower extremity lymphedema were CVI (phlebolympedema; 41.8%), cancer-related lymphedema (33.9%), primary lymphedema (12.5%), and lipedema with secondary lymphedema (11.8%). The collective cohort was more likely to be female (71.1%; $P < .0001$), to be white (78.9%; $P < .0001$), to demonstrate bilateral distribution (74.5%; $P < .0001$), and to have involvement of the left leg (bilateral, 69.1% [$P < .0001$]; unilateral, 58.9% [$P = .0588$]). Morbid obesity was pervasive (mean weight and body mass index, 115.8 kg and 40.2 kg/m², respectively) and significantly correlated with a higher International Society of Lymphology lymphedema stage (stage III mean weight and body mass index, 169.2 kg and 57.3 kg/m², respectively, vs stage II, 107.8 kg and 37.5 kg/m², respectively; $P < .0001$). Approximately one in three (35.7%) of the population sustained one or more episodes of cellulitis, but patients with stage III lymphedema had roughly twice the rate of soft tissue infection as patients with stage II, 61.7% vs 31.8%, respectively ($P < .001$). Multifactorial lymphedema was present in 25%. Approximately half of the patients with lipedema with secondary lymphedema (48.1%) or primary lymphedema (45.5%) had a superimposed cause of swelling that was usually CVI. Total knee arthroplasty was the most common cause of noncancer surgery-mediated worsening of pre-existing lymphedema.

Conclusions: In a large cohort of patients treated in a cancer-affiliated physical therapy department, CVI (phlebolympedema), not cancer, was the predominant cause of lower extremity lymphedema. One in four patients had more than one cause of lymphedema. Notable clinical characteristics included a proclivity for female patients, bilateral distribution, left limb, cellulitis, and nearly universal morbid obesity. (J Vasc Surg: Venous and Lym Dis 2020;8:851-9.)

Keywords: Lymphedema; Chronic venous insufficiency; Lipedema; Morbid obesity

Lower extremity lymphedema represents one of the most common clinical problems presenting to the vascular clinic. Long-standing doctrine posits that cancer and its

associated therapeutics represent the most common cause of lower extremity lymphedema in Western countries.¹⁻³ Conversely, chronic venous insufficiency (CVI) is often ignored as an important secondary cause of lymphedema or phlebolympedema (PhLE). In addition, the etiology of lower extremity lymphedema is typically attributed to a single or exclusive entity, yet multiple pathophysiologic causes often coexist. Unfortunately, there is a dearth of definitive studies that compare the frequency as well as important clinical characteristics of the most frequent causes of lower extremity lymphedema. The purpose of this study was to retrospectively document the prevalence and manifestations of the four most commonly encountered causes of lower extremity lymphedema in 440 patients who presented to an oncology-affiliated physical therapy lymphedema center in a large urban academic medical center.

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METHODS

Data collection and sample. The study was approved by the Institutional Review Board at The Ohio State University Wexner Medical Center, which included a patient

waiver of informed consent. A retrospective chart review was undertaken from January 2012 through December 2015 of patients (n = 524) with lower extremity lymphedema who underwent complex decongestive lymphatic physiotherapy. Patients were referred from a multitude of medical specialties, although they were predominantly oncology, vascular medicine, or vascular surgery based, and arrived with an established lymphedema diagnosis generated by their treating clinicians. The principal and hybrid causes of lymphedema and associated clinical characteristics were documented by a comprehensive electronic medical record review of data compiled from referring clinician and certified lymphedema physical therapist notations, limb photographs, and radiologic investigations (duplex ultrasound, lymphoscintigraphy, and ilio caval computed tomography venography). All data were reviewed and finalized by a physician board certified by the American Boards of Vascular Medicine and Internal Medicine.

Patients were excluded (n = 84) from the final analysis for the following reasons: infrequent or rare cause of lymphedema; and inadequate data to definitively substantiate the principal lymphedema cause as well as secondary lymphedema causes or associated clinical variables. After exclusion, 440 eligible patients were initially divided into the following four principal diagnostic categories reflecting the predominant cause of leg swelling: CVI-PhLE; cancer-related lymphedema (CRLE); primary lymphedema (PLE); and lipedema with lymphedema (lipolymphedema; LIPL). To be diagnosed with PhLE, a patient had to display limb swelling with or without skin changes (Clinical, Etiology, Anatomy, and Pathophysiology [CEAP] clinical class 3-6).⁴ The diagnosis of PhLE was exclusively reserved for patients with swelling that was *predominantly* mediated by venous hypertension. In contrast, patients with a principal diagnosis of PLE, LIPL, or CRLE subsequently complicated by CVI were not categorized with PhLE. All CRLE patients had undergone a lymph node dissection with or without adjunctive radiation. The diagnosis of lipedema required the classic diagnostic triad of disproportionate diet-resistant fatty leg swelling with a truncal-lower extremity "mismatch," easy bruising, and chronic leg pain or tenderness. Attendant modest transient or permanent dorsal foot swelling was required for the diagnosis of LIPL. A diagnosis of PLE was confirmed by suggestive physical findings in the absence of a secondary cause.

Patients within each of the four principal diagnoses were analyzed by demographic and baseline characteristics including age, sex, ethnicity, weight, body mass index (BMI), and anatomic distribution. Symmetric swelling was defined by a difference in comparative limb circumference of ≤ 1 cm. All patients were further classified by the lymphedema stage using the International Society of Lymphology criteria (Table 1).⁵ A history of cellulitis, coexistent massive localized lymphedema,

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** In 440 adults referred for lymphatic physiotherapy, chronic venous insufficiency and cancer-related lymphedema were responsible for 41.8% and 33.9% of lower extremity lymphedema cases, respectively.
- **Take Home Message:** Chronic venous insufficiency, not cancer-related therapy, may be the dominant cause of lower extremity secondary lymphedema in the United States.

and exacerbating noncancer surgery was recorded. All patients with a history of cellulitis had been previously diagnosed with lymphedema. Specifically, cellulitis was not the genesis of their lymphedema. A final lymphedema diagnosis was rendered that was defined by the principal diagnosis with or without additive secondary or tertiary causes.

Data analysis. Descriptive statistics were used to summarize characteristics of the study cohort. For categorical and ordinal variables, frequencies and percentages were calculated. For continuous variables, the number of patients, means, medians, standard deviations, and ranges were calculated. Null hypothesis testing used χ^2 test, t-test, analysis of variance, χ^2 test of trend, and other nonparametric tests as appropriate, with a two-tailed *P* value of $\leq .05$ to reject the null hypothesis. Multiple comparisons were adjusted using the method of Hochberg. All analyses were performed using R version 3.5.0 or later.⁶

RESULTS

The four principal diagnosis frequencies were PhLE (41.8%), CRLE (33.9%), PLE (12.5%), and LIPL (11.8%).

Demographic and clinical variables. Baseline and demographic data of the four principal lymphedema diagnoses are summarized in Table II. The mean age of the entire cohort was 57.3 years. Patients with CRLE, CVI-PhLE, and LIPL were significantly older than patients with PLE. Overall, lymphedema patients were significantly more likely to be female (71.1%; *P* < .0001). Although female sex statistically predominated in CRLE (78.5%; *P* < .0001), LIPL (100%; *P* < .0001), and PLE (83.6%; *P* < .0001), the proportion of women (46.1%) to men (39.7%) was relatively comparable in PhLE (*P* = .4174). Whereas the preponderance of enrolled patients was white (78.9%; *P* < .0001), the differential in incidence between blacks and whites was nonsignificant in PLE, 41.8% vs 58.2%, respectively (*P* = .2807). Thus, PLE was disproportionately represented in the black population.

Table I. Clinical stages of lymphedema according to the International Society of Lymphology⁵

Stage 0	Latent or subclinical; no evidence of swelling; subjective symptoms
Stage I	Early accumulation of fluid; usually pitting; subsides with elevation
Stage II	Swelling rarely reduced with elevation; pitting still present in early stage II, whereas pitting is absent in later stages as fibrosis and fat deposition begin
Stage III	Lymphostatic elephantiasis; nonpitting with trophic skin changes, further deposition of fat and fibrosis, and warty overgrowths

The mean weight and BMI of the combined cohort were 115.8 kg and 40.2 kg/m², respectively. The highest mean weights and BMIs were in the PhLE (136.4 kg and 45.6 kg/m², respectively), LIPLE (129.9 kg and 48.2 kg/m², respectively), and PLE (114.9 kg and 41.3 kg/m², respectively) groups and fulfilled the definition of morbid obesity. In contrast, the CRLE group was the lightest (85.8 kg and 30.2 kg/m², respectively). The intergroup comparisons were $P < .0001$ for both weight and BMI.

Only 6 of the 440 (1.4%) patients had stage I lymphedema and were exclusively represented in the LIPLE group. Stage II lymphedema was most common, occurring in 374 (85%), whereas stage III was present in 60 (13.6%). Patients with stage III lymphedema carried a significantly higher mean weight and BMI (169.2 kg and 57.3 kg/m², respectively) in contrast to patients with stage II disease (107.8 kg and 37.5 kg/m², respectively; $P < .0001$). Approximately one in five patients with PLE, LIPLE, or PhLE had stage III disease. All (100%) of the CRLE cohort were in stage II.

Significantly more patients presented with bilateral (74.5%) than unilateral (25.5%) lymphedema ($P < .0001$). Moreover, a high percentage of PhLE (89%) and PLE (80%) patients exhibited lymphedema of both limbs. As expected, 100% of LIPLE patients had bilateral involvement. The distribution of patients with bilateral (45.6%) or unilateral (54.4%) involvement was roughly equivalent in patients with CRLE. Symmetric bilateral lymphedema existed in 8.2% of all patients; it was most frequently observed in LIPLE (17.3%) and least likely in PhLE (4.9%).

The left leg was preferentially affected. In patients with bilateral lymphedema, the most swollen limb favored the left (208/301 [69.1%]) vs the right (93/301 [30.9%]; $P < .0001$). In patients with unilateral lymphedema, preferential left-sided involvement (66/112 [58.9%]) trended toward statistical significance ($P = .0588$). However, unilateral PhLE was more likely to involve the left side (15/20 [75%]; $P = .0253$). Although unilateral PLE was more likely to affect the left side (63.6%), this difference was

not significant ($P = .5465$), which likely reflected an inadequate sample size.

The majority of patients with isolated principal PhLE or hybrid forms of CVI had advanced venous hypertension as evidenced by CEAP clinical classes of 4 and 5/6 in 37.9% and 41.1%, respectively. CEAP clinical class 3 disease was rare (21%) and exclusively present in patients with a principal diagnosis of CRLE.

Five patients (PhLE, three patients; LIPLE, two patients) exhibited massive localized lymphedema of the medial thighs. They were significantly heavier (mean weight, 194.0 kg vs 114.7 kg [$P = .0152$]; mean BMI, 65.6 kg/m² vs 39.8 kg/m² [$P = .0008$]) than the remaining 434 patients without this complication.

Approximately one in three (35.7%) of the population sustained one or more episodes of cellulitis, but patients with International Society of Lymphology stage III lymphedema had a higher rate of soft tissue infection than patients with stage II, 61.7% vs 31.8%, respectively ($P < .001$). Cellulitis was significantly more likely to complicate patients with PhLE, LIPLE, or PLE (47.1%) than patients with CRLE (13.4%; $P < .0001$). Moreover, a history of soft tissue infection was noted in 49.1% and 48.9% of patients with PLE and PhLE, respectively.

A subset of patients ($n = 35$) with singular or hybrid PhLE, LIPLE, or PLE incurred worsening permanent swelling after undergoing subsequent noncancer surgery as outlined in [Table III](#).

Final lymphedema diagnosis. The final lower extremity lymphedema diagnoses in either a solitary or amalgamated fashion are outlined in [Table IV](#). With multifactorial lymphedema, the causes were enumerated in order of descending importance. Of the 440 patients, 102 (23%) had a subsequent nondominant secondary lymphedema diagnosis, whereas 7 (1.6%) had a tertiary lymphedema hybrid. Approximately half of the patients with LIPLE (48.1%) or PLE (45.5%) had a superimposed cause of lymphedema. The association of initial LIPLE and subsequent CVI was identified in 26 of 52 (50%) of the multifactorial lipedema cases. The second most common hybrid lymphedema was a combination of PLE with coincident CVI occurring in 20 of 55 (36%) cases.

DISCUSSION

This comprehensive study compares the occurrence and characteristics of the four most common causes of lower limb lymphedema referred to an oncology-based lymphedema physical therapy center in a large, urban academic institution. A literature review typically purports that the most common cause of lymphedema in Western countries is cancer and its treatment.¹⁻³ However, our analysis suggests that the most common cause (41.8%) is CVI or PhLE ([Fig 1](#)), followed by CRLE (33.9%). Our finding is in accordance with the few available studies,^{7,8} including a recent analysis of a large health

Table II. Demographic and clinical variables

	Intergroup comparisons					P value
	Total (N = 440)	CRLE (n = 149)	CVI-PhLE (n = 184)	LIPLE (n = 52)	PLE (n = 55)	
Age, years						
No.	440	149	184	52	55	
Mean ± SD	57.3 ± 15.0	57.8 ± 14.3	59.8 ± 14.9	56.3 ± 13.5	48.3 ± 15.5	<.0001
Minimum, maximum	18.0, 99.0	20.0, 90.0	20.0, 99.0	31.0, 89.0	18.0, 92.0	
Median (IQR)	58.0 (47.0-68.0)	58.0 (49.0-68.0)	61.0 (51.0-70.0)	56.5 (46.0-66.2)	49.0 (38.0-60.0)	
Sex						
Male	127/440	32/149	86/184	0/52	9/55	<.0001
95% CI	28.9 (24.8-33.3)	21.5 (15.6-28.7)	46.7 (39.7-53.9)	0.0 (0.0-6.9)	16.4 (8.9-28.3)	
Female	313/440	117/149	98/184	52/52	46/55	
95% CI	71.1 (66.7-75.2)	78.5 (71.3-84.4)	53.3 (46.1-60.3)	100.0 (93.1-100.0)	83.6 (71.7-91.1)	
Ethnicity						
White	347/440	138/149	141/184	36/52	32/55	<.0001
95% CI	78.9 (74.8-82.4)	92.6 (87.3-95.8)	76.6 (70.0-82.2)	69.2 (55.7-80.1)	58.2 (45.0-70.3)	
Black	85/440	7/149	43/184	12/52	23/55	
95% CI	19.3 (15.9-23.3)	4.7 (2.3-9.4)	23.4 (17.8-30.0)	23.1 (13.7-36.1)	41.8 (29.7-55.0)	
Hispanic	2/440	2/149	0/184	0/52	0/55	
95% CI	0.5 (0.1-1.6)	1.3 (0.4-4.8)	0.0 (0.0-2.0)	0.0 (0.0-6.9)	0.0 (0.0-6.5)	
Asian Indian	1/440	0/149	0/184	1/52	0/55	
95% CI	0.2 (0.0-1.3)	0.0 (-0.0 to 2.5)	0.0 (0.0-2.0)	1.9 (0.1-10.1)	0.0 (0.0-6.5)	
Indeterminate	5/440	2/149	0/184	3/52	0/55	
95% CI	1.1 (0.5-2.6)	1.3 (0.4-4.8)	0.0 (0.0-2.0)	5.8 (2.0-15.6)	0.0 (0.0-6.5)	
Weight, kg						
No.	440	149	184	52	55	
Mean ± SD	115.8 ± 49.9	85.8 ± 29.7	136.4 ± 54.7	129.9 ± 48.9	114.9 ± 36.3	<.0001
Minimum, maximum	13.0, 350.0	40.8, 273.0	39.5, 350.0	13.0, 268.0	60.3, 217.0	
Median (IQR)	102.6 (79.1-142.2)	79.7 (66.2-98.0)	121.5 (97.0-170.7)	127.7 (94.4-161.6)	107.8 (85.6-33.4)	
BMI, kg/m ²						
No.	440	149	184	52	55	
Mean ± SD	40.2 ± 14.8	30.2 ± 8.0	45.6 ± 15.7	48.2 ± 14.0	41.3 ± 11.9	<.0001
Minimum, maximum	15.0, 88.4	15.0, 65.0	19.2, 86.3	24.0, 88.4	20.8, 76.0	
Median (IQR)	36.6 (28.8-50.1)	28.4 (24.6-34.6)	42.8 (33.9-57.4)	46.0 (36.8-58.5)	38.3 (32.4-48.8)	
Lymphedema stage						
I	6/440	0/149	0/184	6/52	0/55	<.0001
95% CI	1.4 (0.6-2.9)	0.0 (-0.0 to 2.5)	0.0 (0.0-2.0)	11.5 (5.4-23.0)	0.0 (0.0-6.5)	
II	374/440	149/149	144/184	37/52	44/55	
95% CI	85.0 (81.4-88.0)	100.0 (97.5-100.0)	78.3 (71.8-83.6)	71.2 (57.7-81.7)	80.0 (67.6-88.4)	
III	60/440	0/149	40/184	9/52	11/55	
95% CI	13.6 (10.7-17.2)	0.0 (-0.0 to 2.5)	21.7 (16.4-28.2)	17.3 (9.4-29.7)	20.0 (11.6-32.4)	
Limb distribution						
Bilateral lower	328/440	68/149	164/184	52/52	44/55	<.0001
95% CI	74.5 (70.3-78.4)	45.6 (37.8-53.6)	89.1 (83.8-92.9)	100.0 (93.1-100.0)	80.0 (67.6-88.4)	
Unilateral lower	112/440	81/149	20/184	0/52	11/55	
95% CI	25.5 (21.6-29.7)	54.4 (46.4-62.2)	10.9 (7.1-16.2)	0.0 (0.0-6.9)	20.0 (11.6-32.4)	

BMI, Body mass index; CI, confidence interval (Wilson method); CRLE, cancer-related lymphedema; CVI, chronic venous insufficiency; IQR, interquartile range; LIPLE, lipedema with lymphedema (lipolymphedema); PhLE, phlebolympheidema; PLE, primary lymphedema; SD, standard deviation. Comparison of female vs male: CRLE: Hochberg adjusted P value <.0001; CVI: Hochberg adjusted P value = .4174; LIPLE: Hochberg adjusted P value <.0001; PLE: Hochberg adjusted P value <.0001; all: Hochberg adjusted P value <.0001.

Table III. Noncancer surgery associated with worsening lymphedema

Type of surgery	No.	%
Fasciotomies	1/35	2.9
Foot	3/35	8.6
Great saphenous vein harvest	3/35	8.6
Renal transplantation	1/35	2.9
Total hip arthroplasty	1/35	2.9
Total knee arthroplasty	20/35	57.1
Trauma	6/35	17.1

Patients with a principal diagnosis of cancer or cancer surgery were filtered from this table.

care administrative database in which CVI was indeed the most common cause of lower extremity lymphedema. In a 2014 editorial, Partsch and Lee⁹ highlighted that “CVI (CEAP C3 to C6) is always a chronic venous-lymphatic insufficiency.” Regrettably, clinicians often fail to recognize the lymphatic component with advanced CVI; consequently, PhLE tends to be unrecognized, leading to an underestimation of its prevalence. In a study by Rasmussen et al,¹⁰ diagnostic “dermal backflow” was demonstrated within the lymphatics in all patients with venous leg ulcers. More important, they showed lymphatic dysfunction with C0 through C4 disease, highlighting lymphatic impairment in earlier (even asymptomatic) clinical stages of chronic venous disease. In a 2014 publication, Brayton et al² illustrated that overall lymphedema prevalence among cancer survivors increased from 0.95% in 2007 to 1.24% in 2013. With a U.S. population of approximately 325 million, this

Table IV. Final lymphedema diagnosis (principal and hybrid)

Final diagnosis	No.	%
Cancer therapy	130/440	29.5
Cancer therapy + CVI	19/440	4.3
CVI	150/440	34.1
CVI + cancer therapy	15/440	3.4
CVI + surgery	19/440	4.3
Lipedema	22/440	5.0
Lipedema + cancer therapy	1/440	0.2
Lipedema + CVI	21/440	4.8
Lipedema + CVI + cancer therapy	1/440	0.2
Lipedema + CVI + surgery	4/440	0.9
Lipedema + surgery	3/440	0.7
Primary	28/440	6.4
Primary + cancer therapy	2/440	0.5
Primary + CVI	18/440	4.1
Primary + CVI + surgery	2/440	0.5
Primary + surgery	5/440	1.1

CVI, Chronic venous insufficiency.



Fig 1. Stereotypical example of the most commonly encountered lower extremity lymphedema, morbid obesity-mediated phlebolymphe- dema (PhLE). Characteristic abundant stasis hyperpigmentation along the calves exists and the feet and toes are only modestly swollen, consistent with a secondary cause of lymphedema.

suggests that the lymphedema prevalence due to cancer is approximately 4 million. In contrast, it has been estimated that 5% of the population have some skin changes associated with CVI,¹¹ which equates to a four-fold increase in PhLE prevalence of 16 million individuals.

Contemporary evidence negates the original Starling model of transcapillary fluid exchange. Specifically, the expected reabsorption of interstitial fluid through the venules does not occur; rather, interstitial fluid returns to the circulation primarily through the lymphatic system.^{12,13} This updated physiologic concept underlies the pathomechanism of venolymphatic hypertension. PhLE is initially mediated by increased venous filtration that spurs an initial increase in lymphatic transport. Ultimately, the increased filtration overloads lymphatic capacity, and “venous” lymphedema ensues. Unabated venous hypertension can permanently damage the lymphatic architecture, yielding traditional obstructive lymphedema that can eventuate in worsening swelling complicated by stereotypical skin changes.

In our analysis, women predominated in the PLE, LIPLE, and CRLE groups. Female predilection for patients with PLE (72%) was demonstrated >50 years ago in the classic series of Kinmonth et al.¹⁴ The most frequent form of PLE (>75%), lymphedema praecox, is strikingly more common in female patients, with an approximate 10:1 female to male ratio.¹⁵ In the study of Son et al,⁸ the female-specific pelvic cancers (cervical, uterine, ovarian) were the second leading cause of lower extremity lymphedema, accounting for 3.3% of secondary lymphedema cases. This proportion was greater than the prevalence of prostate CRLE. The lipedema sex findings are consistent with its well-recognized female predominance.

Ethnicity analysis showed a higher proportion of black patients with PLE (41.8%; Fig 2) than with CRLE, which differs from the earlier findings in the survey of Ridner et al¹⁶ of 1097 lymphedema patients. Specifically,

in their analysis of 571 patients with PLE, they noted a smaller proportion (14.6%) of black patients, which was in contrast to an even smaller proportion (4.2%) of black patients in the 526 with secondary lymphedema. Interestingly, the large proportion of black individuals in our PLE group (41.8%) was approximately 1.5 times their population percentage (28.3%) in the 2010 to 2018 census database for Columbus, Ohio, where the study was undertaken. Consequently, additional data are needed to confirm a unique potential susceptibility of the black population to PLE.

Morbid obesity was extremely prevalent in the CVI, LIPLE, and PLE cohorts as the mean BMI exceeded 40 kg/m² in all three groups. Remarkably, even the subgroup with CRLE exhibited mild obesity with a mean BMI of 30.2 kg/m². In a 2-year study of 482 patients with chronic venous disease and varying body weight, patients with advanced CVI were more likely to be obese (BMI >30 kg/m²).¹⁷ Danielsson et al¹⁸ documented a direct correlation between BMI and clinical severity of advanced CVI; however, this relationship was independent of reflux. Several studies have documented increased intra-abdominal and venous pressures in obese patients, which may explain the pathogenesis of obesity-mediated PhLE.^{19,20} Others have suggested that obesity-mediated PhLE may be provoked by intermittent popliteal vein compression.²¹ Finally, it has been shown that obese individuals are less active, taking fewer daily steps than people with a healthy body weight; thus, the calf muscle pump is not regularly activated, which begets venous hypertension.²²

Obesity has been cited as a major risk factor for development of secondary CRLE. In a prospective study of 277 patients with lower or upper extremity malignant melanoma, a BMI of ≥ 30 kg/m² was significantly correlated with development of secondary lymphedema (odds ratio [OR], 2.19; 95% confidence interval, 1.37-3.52).²³ In a 2014 study of 591 Mayo Clinic patients who underwent endometrial cancer surgery, multivariate analysis identified that an elevated BMI was a risk factor for development of lymphedema and that the risk was proportional to body weight. Specifically, a BMI of 30.0 to 39.9 kg/m² was associated with an adjusted OR of 1.45, whereas a BMI between 40.0 and 49.9/50+ kg/m² yielded an adjusted OR of 4.69.²⁴

Body weight was significantly correlated with lymphedema stage. Specifically, patients with stage III classification (elephantiasis) had a mean BMI (60 kg/m²) consistent with super obesity that was 1.6 times greater than in those with stage II disease. Similarly, in a 2011 analysis of 21 patients with elephantiasis, the mean BMI was 55.8 kg/m².²⁵ Stage III or elephantiasis lymphedema was equally distributed between PLE, LIPLE, and PhLE groups, in which approximately one in five patients were classified. Predictably, no patients with CRLE manifested stage III lymphedema. Five patients manifested



Fig 2. Bilateral limb swelling in a morbidly obese female patient with a principal diagnosis of primary lymphedema (PLE). The dramatically swollen dorsal feet and toes as well as exaggerated dorsal toe skin creases are typical manifestations of PLE. Hyperkeratotic papulonodular skin and abundant local fat deposition are consistent with International Society of Lymphology stage III lymphedema or “elephantiasis.” PLE was disproportionately represented in the black population.

an increasingly recognized complication of morbid obesity, massive localized lymphedema of the medial thighs. In a 2015 review of 65 cases of massive localized lymphedema, the average weight was 183 kg.²⁶ Our patients with massive localized lymphedema displayed a similar astounding mean weight of 194.0 kg with a BMI of 65.6 kg/m². In addition to the recognition that obesity can beget secondary lower extremity lymphedema, contemporary evidence illustrates that lymphedema can provoke dysfunctional adipocyte hypertrophy and hyperplasia with resultant secondary local fat deposition. Ultimately, both processes can sustain and fortify themselves through a positive feedback loop.²⁷

We observed that lymphedema preferentially affected the left side, both in distribution and in severity. For instance, in patients with bilateral involvement, the left side was more swollen in nearly 70% of the cases. Furthermore, patients within the bilateral PhLE subgroup had the highest percentage of swelling that was more severe on the left. In the combined patients with

unilateral lymphedema, the left limb (58.9%) was more likely to be affected and exhibited a trend near statistical significance. Individually, unilateral PhLE was statistically more likely to involve the left side, occurring in three-quarters of cases. Although unilateral PLE was also more likely to affect the left side in nearly two-thirds of the cases, an inadequate sample size probably negated statistical significance. Left-sided lymphedema proclivity is potentially explained by chronic left iliac vein compression by the overlying right common iliac artery or rarely by the ipsilateral internal iliac artery. It is conceivable that the omnipresent effect of abdominal obesity in our cohort accentuated chronic left iliac vein compression.

A preponderance (75%) of patients displayed bilateral lower extremity lymphedema. This was obviously an expected finding in the lipedema patients. However, a surprisingly high percentage of PhLE (89%) and PLE (80%) affected both limbs. Attendant morbid obesity in both groups likely increased the bilateral propensity. In the study of Deng et al²⁸ of 803 PLE patients, 67% had bilateral limb involvement.

Our analysis confirmed the association of lymphedema and soft tissue infection as 36% of the cohort had a history of one or more episodes of cellulitis. Moreover, approximately half of patients with PLE and PhLE had a history of soft tissue infection. Notably, 38.5% of our lipedema patients had a history of cellulitis, which was consistent with associated secondary lymphedema or lipolymphedema. The propensity for infection was increased by the severity of lymphedema as patients with stage III lymphedema were twice as likely to develop cellulitis as patients with stage II disease. In a multivariate analysis of 167 patients admitted to the hospital with erysipelas, underlying lymphedema was the most potent risk factor for infection with an OR of 71.2.²⁹

In early, uncomplicated stages of lipedema, the feet are spared of swelling. A distinct predominance of our lipedema patients (88.5%) manifested permanent foot swelling consistent with stage II or stage III secondary lymphedema (Fig 3). The high percentage of patients with permanent lipolymphedema can probably be explained by three factors: selection bias, whereby only severely affected lipedema patients were referred for aggressive therapy; disease duration, as the mean age of the lipedema cohort was 56.3 years, yet most cases arise in adolescence; and the permeating effect of underlying morbid obesity (mean BMI, 48.2 kg/m²). Magnetic resonance imaging contrasted the findings in pure lipedema vs lipedema with lymphedema. In pure lipedema, the lymphatic vessels are dilated but without reflux; whereas in lipedema with lymphedema, the lymphatic vessels are also dilated, but with morphologic signs of obstruction and dermal reflux. All 16 lower extremities (100%) with clinically manifested lipolymphedema



Fig 3. Classic case of relatively symmetric lipedema with secondary lymphedema (LIPLE) or lipolymphedema. Like most cases of secondary lymphedema, the feet and toes are only modestly swollen. Other notable findings of lipedema include a disproportionately smaller waist with a “mismatched” appearance, excessive skin laxity, infrageniculate erythrocyanosis, and bilateral distal medial thigh fatty lobules. Although small left calf varicose veins exist, the patient was not classified with concurrent chronic venous insufficiency (CVI) because of absence of axial venous reflux and characteristic skin changes.

exhibited abnormal high signal intensity areas on three-dimensional turbo spin-echo sequence.³⁰

We identified individuals with pre-established lymphedema who developed permanent swelling exacerbation after noncancer surgery. In the majority of these cases, total knee replacement arthroplasty was the surgical precipitant. Although total knee arthroplasty with subsequent postsurgical lymphedema is often encountered in the vascular clinic, there is a noteworthy absence of medical literature that documents this association.

Our final distinctive finding was the presence of additive or superimposed causes of lower extremity lymphedema

in 25% of the patients. PLE and lipedema were most likely to present in an amalgamated fashion. CVI was the disorder most likely to complicate pre-existing PLE, lipedema, and CRLE. The association of lipedema and subsequent CVI was particularly robust, occurring in half of hybrid lipedema cases (Fig 4). Although varicose or spider veins frequently complicate lipedema, secondary CVI with advanced skin changes is only rarely referenced in the literature. In a landmark 1949 lipedema article by Wold et al,³¹ 9% of the 119 patients had associated saphenous vein reflux, 5% displayed venous-mediated indurated skin discoloration, and 2.5% manifested stasis ulcerations. Our data suggest that the association of lipedema and CVI is not infrequent in a morbidly obese cohort; rather, it is unrecognized and under-reported.

The hybrid relationship of PLE with coincident CVI was also conspicuous, affecting one in three PLE patients. The affiliation of PLE and primary venous disease has been recognized in both Milroy disease and lymphedema-distichiasis syndrome as both disorders can manifest prominent saphenous and varicose veins.³² As true Milroy disease and lymphedema-distichiasis syndrome are rare, the majority of our PLE cases were likely complicated by superimposed morbid obesity-mediated CVI.

Limitations of the study center around its retrospective nature and potential misclassification of the lymphedema diagnoses. In cases of hybrid limb swelling, it can be potentially challenging to definitively ascertain the initiating and subsequent lymphedema risk factors and how they proportionately interact in the swollen limb. However, any diagnostic uncertainty resulted in exclusion from database enrollment. For instance, 71 of the 84 excluded patients were eliminated because of equivocation regarding the definitive cause of lymphedema. As our cohort was predominantly derived from a large metropolitan region, it is currently unclear whether the study results are generalizable to all Western lymphedema populations. Although CVI was the prevailing cause of lymphedema, it is possible that cancer therapy would be the most common cause if the study had been undertaken in a location with a significantly lower prevalence of obesity. Yet considering the rising obesity epidemic in the United States, we suspect our results portray the modern-day or "real-world" lymphedema clinic.

CONCLUSIONS

Although malignant disease is ubiquitously documented as the dominant cause of lower extremity lymphedema, our study challenges this doctrine by finding CVI the prevailing cause. Although lymphedema is typically ascribed to a single cause, we identified heterogeneous causation in one in four patients. CVI was the entity most likely to complicate pre-existing lymphedema and was especially prevalent in cases of lipedema and, unexpectedly, PLE. Morbid obesity was pervasive



Fig 4. Long-standing lipedema complicated by both chronic venous insufficiency (CVI) and secondary lymphedema. Although under-reported in the medical literature, we identified the hybrid of lipedema, lymphedema, and CVI in 50% of our patients. However, lipedema was the predominant or *principal* diagnosis, whereas secondary CVI and lymphedema played lesser roles in the genesis of the leg swelling.

and correlated with a higher lymphedema stage and likely the predisposition to bilateral limb involvement. Other notable findings included the predilection for left leg involvement, female sex proclivity, and confirmation of cellulitis susceptibility, which affected half of the PhLE and PLE subsets. Total knee arthroplasty was the most common cause of noncancer surgery-mediated worsening of pre-existing lymphedema. An unexpected finding was the higher proportion of black patients in the PLE cohort.

AUTHOR CONTRIBUTIONS

Conception and design: SD, EV

Analysis and interpretation: SD, EV, WA

Data collection: SD, EV, KH, JL, AC

Writing the article: SD, EV, KH, JL, AC, WA

Critical revision of the article: SD

Final approval of the article: SD, EV, KH, JL, AC, WA

Statistical analysis: SD

Obtained funding: SD

Overall responsibility: SD

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