

Lymphedema-associated comorbidities and treatment gap



Andrew Son, MD,^a Thomas F. O'Donnell Jr, MD,^a Jessica Izhakoff, BS,^b Julia A. Gaebler, PhD,^b Timothy Niecko, MS,^c and Mark A. Iafrati, MD,^a *Boston and Weston, Mass; and Tierra Verde, Fla*

ABSTRACT

Background: Lymphedema (LE) has been called the forgotten vascular disease, given such scant knowledge about LE-associated comorbidities or causes. Such knowledge of the comorbidities and treatment of LE may assist in diagnostic decisions and health care planning.

Methods: To determine the proportion of LE patients with various LE-associated comorbidities as well as the rate of associated treatment, deidentified Health Insurance Portability and Accountability Act-compliant commercial administrative claims from the Blue Health Intelligence (BHI) research database (165 million Blue Cross Blue Shield members) were queried. We analyzed a BHI study sample of 26,902 patients with LE who had been enrolled with continuous medical benefits for 12 months before and after the index date for the complete years 2012 through 2016. Patients were first identified by comorbidity and then grouped into those receiving no treatment for LE and those receiving any treatment for LE. Any treatment was defined as receiving manual lymphatic drainage, physical therapy, compression garments, or a pneumatic compression device. The purpose of this study was to determine the proportion of LE patients comorbid with various known LE-associated conditions and the treatment rates of LE patients with each comorbidity.

Results: Among the 84,579,269 BHI patients enrolled during the study window, 81,366 patients were identified with LE. From this LE group, our study focused on the 26,902 patients who were enrolled with continuous medical and pharmacy benefits for 12 months before and after the index date. Among these 26,902 LE patients, breast cancer was the most frequent comorbidity with LE (32.1%), and these patients almost universally received any treatment (94.2%); other cancer types, such as melanoma (2.1%) and prostate cancer (0.7%), were less frequent and received any treatment less often, 75% and 82% of the time, respectively. Venous leg ulcer was the most common non-cancer-linked comorbidity for LE (9.6%), but only 81.7% of venous leg ulcer patients received any treatment for LE.

Conclusions: To our knowledge, this is the largest study to date detailing the comorbidities associated with LE and LE treatment rates within each. Our findings suggest that a sizable proportion of cancer-related LE patients do not receive appropriate treatment. Furthermore, this study highlights the role of advanced venous disease as an LE comorbidity that is frequently untreated and its associated gap in treatment. (*J Vasc Surg: Venous and Lym Dis* 2019;7:724-30.)

Keywords: Lymphedema; Prevalence; Chronic venous insufficiency; Cancer

Lymphedema (LE) has been termed the forgotten vascular disease because in contrast to venous and arterial disease, there is limited awareness of this disease, its associated comorbidities, and treatment.¹ The importance of determining the causes of LE and the proportion of patients treated within each etiologic category may provide important information for diagnostic decisions and health

care planning. A review of the literature shows that most estimates of both the prevalence of LE and, in particular, the causes of LE are limited to a small number of observational case series associated with a specific LE cause, such as that of Kinmonth.²⁻⁴ Alternatively, there are even fewer epidemiologic studies.^{5,6} In the epidemiologic studies, the specificity of the cause may be lacking or lumped into a generalized category. The classic review of Rockson and Rivera, "Estimating the Population Burden of Lymphedema,"⁷ puts this problem in focus: "The data presented in this review represent, regrettably, only the aggregate of many small observations, often retrospective, and almost never rigorously undertaken."

Administrative databases, which contain collected health care data, have evolved from mere billing records into valuable research tools for studying and improving care.⁸ One application is to determine the distribution of disease in a population and its comorbidities and treatment. The Blue Health Intelligence (BHI) data set is an example of an administrative health care data set and is one of the largest health information data warehouses in

From the Cardiovascular Center, Tufts Medical Center, Department of Surgery, Tufts University School of Medicine, Boston^a; the Health Advances LLC, Weston^b; and the Niecko Health Economics, LLC, Tierra Verde.^c

Author conflict of interest: T.F.O. is a paid consultant for Tactile Medical, which provided support for statistical analysis for the study.

Presented orally at the Forty-fifth Annual Meeting of the New England Society for Vascular Surgery, Cape Neddick, Me, October 12-14, 2018.

Correspondence: Andrew Son, MD, Division of Vascular Surgery, Tufts Medical Center, 800 Washington St, Boston, MA, 02111 (e-mail: ason@tuftsmedicalcenter.org).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

Copyright © 2019 by the Society for Vascular Surgery. Published by Elsevier Inc. <https://doi.org/10.1016/j.jvsv.2019.02.015>

the United States. Ten years of claims for >165,000,000 members are available.⁹ As a result, this data set represents “real-world” clinical evidence. The purpose of this study was to determine the proportion of patients with LE in a real-world setting and to describe age and sex patterns; to define the etiology of LE by associating comorbidities known to be causes of LE (eg, breast cancer treatment); and to determine the rate at which patients with each comorbidity receive treatment for LE.

METHODS

Setting and data source. This study used deidentified Health Insurance Portability and Accountability Act-compliant commercial administrative claims data from the BHI research database for the complete years 2012 through 2016. The data set contained longitudinal information captured by commercial health insurance claims. The core BHI databases contain >165 million members of individual Blue Cross Blue Shield plans from across the United States. The study data were accessed by procedures compliant with the Health Insurance Portability and Accountability Act of 1996; therefore, informed consent or Institutional Review Board approval or exemption was not required.

Study population. As described in a previous publication,¹⁰ patients with a diagnosis of nonfilarial LE were first identified on the basis of one inpatient or two outpatient *International Classification of Diseases, Ninth Revision* (ICD-9) or *Tenth Revision* (ICD-10) diagnosis codes for primary or secondary LE (ICD-9: 457.0, 457.1, 757.0; ICD-10: I97.2, I89.0, Q82.0). Patients were then required to be continuously enrolled in the health plan with medical and pharmacy benefits for at least 12 months before and 12 months after the index date, which was defined as the earliest occurrence of LE and its treatment based on either the first occurrence of an inpatient or the second occurrence of an outpatient claim. Specific comorbidities were sought by ICD-9 or ICD-10 codes associated with LE. Patients within each comorbidity were then assigned to any treatment if they received at least one claim for active LE treatment, which included manual lymphatic drainage, compression garments, LE-related physical or occupational therapy, and intermittent pneumatic compression therapy with a simple pneumatic compression device (E0651) or an advanced pneumatic compression pump (E0652). If no claim was submitted for these forms of treatment or if only codes for education were submitted, the patient was categorized as receiving no treatment for LE. A schematic of the study protocol is shown in Fig 1.

Patients' demographic and clinical characteristics. The claims database included information on patients' demographic and socioeconomic characteristics, such as age, sex, commercial insurance type, and census region.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cross-sectional analysis of a prospectively collected Blue Health Intelligence research database
- **Key Findings:** Data of 26,902 lymphedema (LE) patients were analyzed, and breast cancer was the most frequent comorbidity (32.1%) with a treatment rate of 94.2%. Other cancers, such as melanoma (2.1%) and prostate (0.7%), were less frequent and received treatment less often (75% and 82%, respectively). Venous leg ulcers were comorbidities in 9.6%, but only 81.7% received any treatment.
- **Take Home Message:** This study found that breast cancer was the most frequent comorbidity of LE and that a sizable proportion of cancer-related LE patients do not receive appropriate treatment. Venous leg ulcer, an LE comorbidity, was frequently untreated.

Statistics. The proportion of patients receiving any treatment vs no treatment for each comorbidity was assessed by a χ^2 test. The proportion of patients who had received treatment by various clinical conditions was assessed by the binomial proportion test. All statistical tests were two sided with a significance level of $P < .05$. Analyses were performed using SAS version 9.4 software on a personal computer platform (SAS Institute, Cary, NC).

RESULTS

Proportion of patients with LE. Overall, 84,579,269 patients in the BHI data base were available for analysis, from which 81,366 (0.10%) were identified with LE as shown in Fig 1. Table I shows the proportion with LE by age and sex. From the total population (42,229,536) within the BHI data set for women, 74,807 (0.18%) women were identified with LE; from the total population of men in the BHI data set, 42,349,733, a lesser number of men, 28,358 (0.07%), had LE. The BHI data set contains only patients in the age groups ≥ 65 years who are covered by Medicare Advantage plans and as a result not the entire Medicare population. Subtracting the total number of patients >65 years in the BHI data and restricting the analysis to those patients <65 years reduces slightly the percentage of women in the age group <65 years with LE to 0.168% and the percentage of men to 0.059%. The greatest percentage of women with LE was in the 55- to 64-year age group, and a similar distribution was observed for men.

LE-associated comorbidities. Table II demonstrates the comorbidities associated with LE, which were selected for study on the basis of known causes of secondary LE. Based on an assessment of 26,902 eligible patients (determined by continuous enrollment criteria), breast

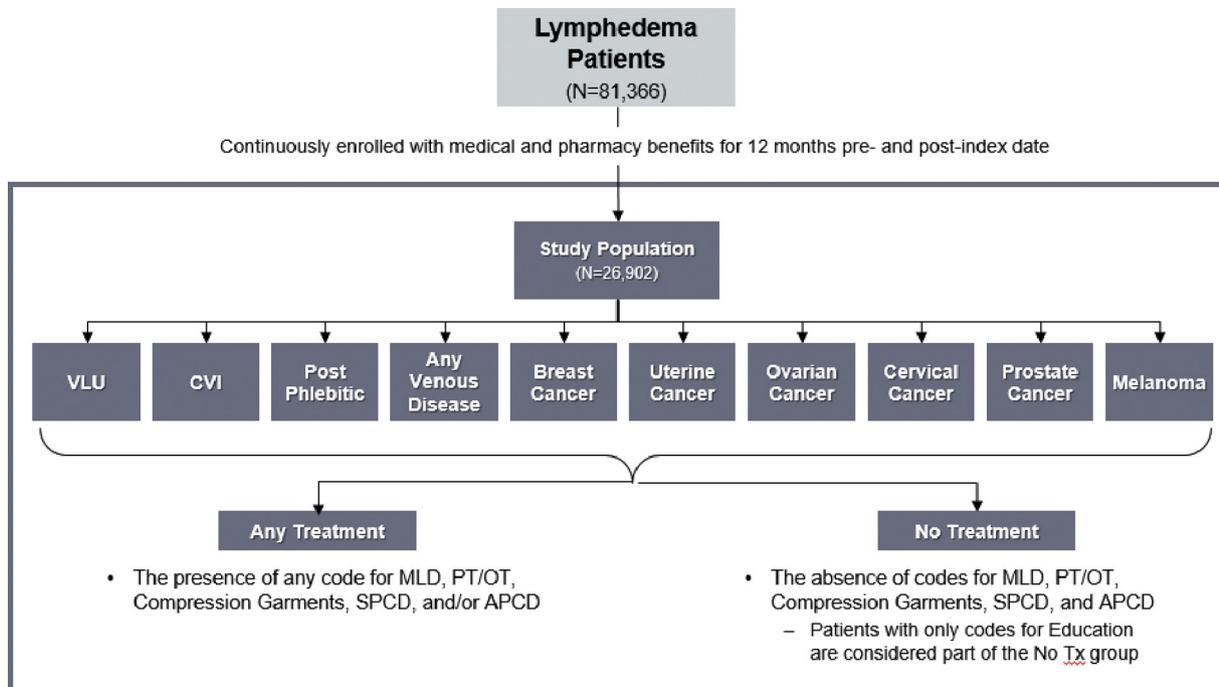


Fig 1. Lymphedema (LE) treatment gap analysis protocol. Among 81,366 patients identified in the Blue Health Intelligence (BHI) administrative data set with the diagnosis of LE, approximately a third qualified for the study. APCD, Advanced pneumatic compression device; CVI, chronic venous insufficiency; MLD, manual lymphatic drainage; PT/OT, physical or occupational therapy; SPCD, sequential pneumatic compression device; Tx, treatment; VLU, venous leg ulcer.

cancer, which occurred in 8636 patients (32.1%), was the most commonly diagnosed comorbidity associated with LE. The category of venous disease as a whole, which included patients with chronic venous insufficiency, venous leg ulcers (VLUs), postphlebitic syndrome, and iliac vein disorders, accounted for 10.4% of patients with LE. VLU specifically represented the majority of patients within the overall venous category as 9.6% of total LE patients were comorbid with VLU. Pelvic cancers, which included uterine, ovarian, and cervical cancer, accounted for 1.9%, 0.8%, and 0.6% of LE patients, respectively. Melanoma was observed in 2.1% of patients with LE. Prostate cancer was a less frequent LE comorbid condition, observed in only 188 patients (0.7%). Obesity, as an independent comorbidity, was identified in 3868 (14.2%) patients with LE.

Proportion treated for LE. Table III displays the association of the comorbidity with the proportion treated for LE. Across all comorbidities, between 75% and 94% of LE patients received any treatment. The highest rate of any treatment was among breast cancer patients, in which 94% of identified patients were treated. Patients with uterine, ovarian, and cervical cancer were treated 84%, 86%, and 82% of the time, respectively. Melanoma patients received any treatment 82% of the time. The lowest rates of any treatment were among prostate cancer patients (76%). Within breast cancer- and VLU-associated LE,

a greater proportion of patients with breast cancer received any treatment (94%) than did those with VLU (82%). This difference is shown to be statistically significant in Fig 2. Finally, patients were divided by the anatomic location of their LE into either upper or lower extremity. Because breast cancer predominates in the upper extremity (8636 cases) and its rate of treatment is 94%, the sum of lower extremity LE cases (4448 cases), which is half of the upper extremity cases, still averages a significantly lower 82% [3650/4448] treatment rate.

DISCUSSION

This study from a large health care administrative database demonstrates the comorbidities associated with LE and the number of patients treated for LE linked to the causes of LE.

LE-associated comorbidities. The two epidemiologic studies by Moffatt et al^{5,6,11} failed to provide specific details on the causes of LE. The causes of LE have traditionally been derived from clinical series, like that of Kinmonth,²⁻⁴ in which a large population of patients with LE were treated at a specialized center; as a result, there may be referral (selection) and diagnosis bias. Boccardo et al¹² compiled series from regions of Italy and also the rest of Europe. In their group of 945 patients, 57% of patients were classified with primary LE, of which 11% had upper limb involvement and a higher 72% had lower limb

Table I. Blue Health Intelligence (BHI) lymphedema (LE) prevalence data

Sex-age bracket	LE patients within BHI	Total BHI patients	BHI LE prevalence, %
Female	74,807	42,229,536	0.18
<1	40	472,636	0.01
1-4	77	1,762,390	0.00
5-9	82	2,357,255	0.00
10-14	220	2,521,208	0.01
15-19	436	2,770,669	0.02
20-24	625	3,634,864	0.02
25-29	1056	4,201,328	0.03
30-34	2127	3,482,181	0.06
35-39	3664	3,227,118	0.11
40-44	6397	3,174,881	0.20
45-49	9763	3,353,611	0.29
50-54	13,657	3,499,794	0.39
55-59	15,642	3,392,509	0.46
60-64	15,485	3,434,238	0.45
65-69	3795	666,944	0.57
70-74	932	147,168	0.63
75-79	364	62,848	0.58
80-84	445	31,207	1.43
85-89	0	19,409	0.00
90+	0	17,278	0.00
Male	28,358	42,349,733	0.07
<1	55	502,176	0.01
1-4	62	1,854,896	0.00
5-9	54	2,464,458	0.00
10-14	129	2,620,064	0.00
15-19	247	2,914,034	0.01
20-24	340	3,874,790	0.01
25-29	500	4,249,929	0.01
30-34	827	3,503,943	0.02
35-39	1290	3,258,708	0.04
40-44	2017	3,174,155	0.06
45-49	3061	3,286,947	0.09
50-54	4265	3,359,862	0.13
55-59	5889	3,201,574	0.18
60-64	6381	3,024,847	0.21
65-69	1946	742,914	0.26
70-74	703	184,190	0.38
75-79	310	75,379	0.41
80-84	282	31,920	0.88
85-89	0	15,665	0.00
90+	0	9282	0.00

Dividing BHI LE patients by 5-year sex-age bracket into total BHI patients yields the BHI prevalence of LE.

involvement. Secondary LE was described in 406 (43%) patients, in whom upper limb involvement was predominantly (98%) due to treatment of breast cancer. In lower

Table II. Lymphedema (LE) comorbidities

Comorbidity	No. of patients (%)
VLU	2577 (9.6)
CVI	162 (0.8)
Postphlebotic syndrome	18 (0.1)
Any venous disease	2808 (10.4)
Breast cancer	8636 (32.1)
Uterine cancer	603 (1.9)
Ovarian cancer	216 (0.8)
Cervical cancer	169 (0.6)
Prostate cancer	188 (0.7)
Melanoma	672 (2.1)

Total LE patients = 26,902.
CVI, Chronic venous insufficiency; VLU, venous leg ulcer.

limb cases, the most common secondary LE followed treatment of uterine cancer (46%), followed by urologic surgery for cancer (39%), such as prostate and seminoma of the testis. Treatment of melanoma accounted for (6%) of cases of secondary LE in this series. The problem with this series is that it is based on treatment patterns of >20 years ago, which have changed, and again, it reflects an analysis of patients in a specialty center.

By contrast, this study queried a *contemporaneous* large administrative database for the proportion of patients comorbid with known causes of LE. This analysis identified breast cancer as the leading comorbid condition associated with an LE diagnosis (32.1%). One of the major findings of this study is the previously underappreciated important role of phlebolymphe­dema as the second most common cause of LE (10.4%). Phlebolymphe­dema is a pathophysiologic consequence of venous hypertension and related lymphatic overload. Normally, excess interstitial fluid is effectively removed by lymphatic vasculature; but if the fluid load overwhelms the lymphatic capacity or if the lymphatics are defective through destruction of lymphatic vessels by episodes of cellulitis, interstitial fluid, macromolecules, and cytokines accumulate, which leads sequentially to edema, lipodermatosclerosis, and subsequent ulcer formation.¹⁰ Pelvic cancers were within the range of 0.6% to 1.9% of patients with LE. Melanoma and prostate cancer were less frequent at 2.1% and 0.7%, respectively. Similarly, however, these data may contain a referral and diagnosis bias, which can lead to under-reporting. Obesity, as an independent comorbidity for LE, was observed in 14.2% of patients, but this may be an underestimation of its true proportion because of the well-known unreliability of coding obesity in an administrative health care data set. Obesity and postoperative weight gain are well-recognized risk factors for the development of secondary LE, particularly with breast cancer treatment. Indeed, obesity alone can impair lymphatic function and has been associated with the development of primary LE.

Table III. Lymphedema (LE) comorbidities related to treatment rates

Patients, No. (%)	Patients with any treatment, No. (%)	Patients with no treatment, No. (%)	P value ^a
2577 (9.6)	2106 (82)	471 (18)	<.0001
162 (0.8)	134 (83)	28 (17)	<.0001
18 (0.1)	12 (75)	4 (25)	.0466
2808 (10.4)	2295 (82)	511 (18)	<.0001
8636 (32.1)	8139 (94)	497 (6)	<.0001
603 (1.9)	428 (84)	80 (16)	<.0001
216 (0.8)	185 (86)	30 (14)	<.0001
169 (0.6)	130 (82)	29 (18)	<.0001
188 (0.7)	142 (76)	46 (24)	<.0001
672 (2.1)	470 (82)	102 (18)	<.0001

^aP values were considered significant if <.05.

Comorbid conditions associated with LE and their relation to treatment. The goals of LE therapy, which currently are usually achieved through nonsurgical modalities, are to reduce edema, resulting in increased function, and to improve skin hygiene to prevent the development of infection, one of the major morbid complications of LE.¹³ This study further defined what proportion of patients within comorbidities associated with LE received any treatment and those who did not. Across these comorbidities, 6% to 25% of patients in the BHI database received no treatment, which represents a “treatment gap.” This health care metric is defined as the number of people with a condition or disease who do not receive treatment for that disease and is an important outcome measure in health care. According to the definition of the World Health Organization, “health is a state of complete physical, mental and social well-being

and not merely the absence of disease or infirmity.”¹⁴ Treatment refers to any intervention that is intended to restore health.¹⁴

Treatment gap. Once identified, steps can be taken to reduce the treatment gap. For example, the number of patients receiving no treatment for epilepsy is as low as 7% in the United States and approaches 0% in Sweden, but it is strikingly high in India (75%).¹⁵ The treatment gap assumes that the patient has already been diagnosed with the disorder, but the World Health Organization definition also includes the *lack of diagnosis of a disease* in the treatment gap.¹⁴ LE is an excellent example of the concomitant diagnosis gap. Historically, in contrast to arterial and venous disease, there has been no simple, noninvasive test accepted for the diagnosis of lymphatic dysfunction, so that lymphatic abnormalities are predominantly diagnosed by clinical means. Lymphoscintigraphy directly images the lymphatic system by intradermal injection of radionuclides into the interdigital space and has supplanted standard bipedal lymphography as the currently preferred method for *establishing* the presence of LE. This test has been recommended by both the International Society of Lymphology and the American Venous Forum guidelines with a grade 1 recommendation and B level of evidence as the initial test for the evaluation of patients with LE (guidelines 6.2.0. of the American Venous Forum).¹⁶

In general, there are multiple reasons for the existence of a treatment gap, which include physician-related, patient-related, and system-related causes. One major influential factor is that LE is a chronic disease; as such, there is no definitive cure, nor can the traditional acute care model of disease treatment be applied to the entire population of patients with LE. For surgeons, a patient with acute appendicitis undergoes appendectomy, and symptoms resolve. That is not the case with LE.

Once the patient has an established diagnosis of LE, the patient should undergo some form of therapy, which may be as simple as education on the management of LE and its potential complications. Most chronic diseases are treated with the benefit of evidence-based guidelines. Currently, there are no universally accepted guidelines for the management of LE to assist physicians in the recommendation of treatment. Randomized controlled trials, the basis for evidence-based guidelines, are few. Moreover, the physicians treating patients with LE vary from primary care physicians to oncologists, vascular surgeons, and vascular medicine specialists, which makes the transmission of education on the diagnosis and treatment difficult. Beyond the awareness of treatment options for physicians, the patients themselves, as with any chronic disease, must be involved in self-care. In chronic disease management, the physician must encourage or “coach” the patients to follow a treatment plan.¹⁷

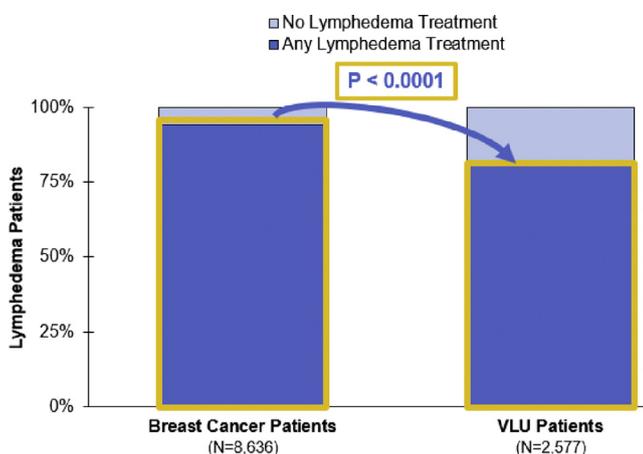


Fig 2. Lymphedema (LE) treatment rate among patients with breast cancer or venous leg ulcer (VLU). Among 26,902 eligible LE patients, a statistically significant greater proportion of LE patients with breast cancer received treatment for LE than did those with VLU.

The difference in treatment rates for the various causes of LE may provide some insight into the treatment gap. LE is a well-recognized complication of treatment for breast cancer by patients and their physicians, so that 94% of patients with LE underwent some form of treatment. By contrast, only 82% of patients with VLU received treatment for their limb swelling ($P < .0001$ vs breast cancer), as shown in Fig 2. This may be related to the lack of recognition of the critical role of the lymphatics in phlebolymphe dema .¹⁰ As a result, treatment for VLU may be directed toward reducing venous hypertension but not toward LE. Less well explained is the lower treatment rates for LE associated with pelvic cancers, melanoma, and prostate cancer, which are in the same range as VLU. That this gap in treatment is due to LE's being unrecognized in these cancers would seem unlikely because LE has been coded as a comorbidity of the disease in these individuals. Other factors may be operative in this situation, such as the severity of the LE and the patient's desire for treatment. A focus on both patient and physician education, however, may help improve the treatment gap in those disorders.

In addition to reducing limb volume and thereby improving functionality, prevention of cellulitis and its prompt treatment are key outcome measures for assessing the benefits of treatment. Previous studies have shown that treatment, particularly with advanced pneumatic compression devices, reduces the episodes of cellulitis in patients with LE, which is the major morbid complication of LE leading to further destruction of existing lymphatics and dramatically increased costs.¹³

Study limitations. Our study has several limitations. First, the identification of LE and associated comorbidities within the administrative claims relies on proper use of diagnosis coding. We can identify LE and other patients only so far as they are coded correctly. Second, the BHI database contains only commercially insured patients and thus may under-represent Medicare and Medicaid populations. LE is known to be more prevalent in older populations, so using the BHI data may bias our study toward treatment patterns and comorbidities that are more common among younger LE patients. Finally, severity of disease cannot be determined through claims data, so potential associations between LE severity and whether a patient receives treatment remain unknown.

CONCLUSIONS

To our knowledge, this is the largest study to date of LE treatment rates and comorbid conditions. Our findings confirm the major role of cancer associated with LE among those who receive treatment. However, this study also highlights the role of advanced chronic venous

disease—and of VLU in particular—as a comorbidity for LE. Whereas LE associated with breast cancer commonly receives treatment, a sizable proportion of other cancer-related LE patients do not receive appropriate treatment. Moreover, VLU, as a comorbidity, is associated with an 18% incidence of no treatment, further evidence of a treatment gap for LE.

AUTHOR CONTRIBUTIONS

Conception and design: AS, TO, MI
Analysis and interpretation: AS, TO, JI, JG, TN, MI
Data collection: TO, JI, JG, TN
Writing the article: AS, TO, JI, JG, TN
Critical revision of the article: AS, TO, JI, JG, TN, MI
Final approval of the article: AS, TO, JI, JG, TN, MI
Statistical analysis: AS, TO, JI, JG, TN, MI
Obtained funding: Not applicable
Overall responsibility: AS

REFERENCES

1. Adamczyk LA, Gordon K, Kholová I, Meijer-Jorna LB, Telinius N, Gallagher PJ, et al. Lymph vessels: the forgotten second circulation in health and disease. *Virchows Arch* 2016;469:3-17.
2. Kinmonth JB. *The lymphatics: surgery, lymphography and diseases of the chyle and lymph systems*. 2nd ed. London: Edward Arnold; 1982.
3. Kinmonth JB, Taylor GW, Tracy GD, Marsh JD. Primary lymphoedema. Clinical and lymphangiographic studies of a series of 107 patients in which the lower limbs were affected. *Br J Surg* 1957;45:1-10.
4. Kinmonth JB. Lymphangiography in man. *Clin Sci* 1952;11:13-20.
5. Moffatt CJ, Franks PJ, Doherty DC, Williams AF, Badger C, Jeffs E, et al. Lymphoedema: an underestimated health problem. *Q J Med* 2003;96:731-8.
6. Moffatt CJ, Vaughan K, Franks PJ, Rich A, Pinnington L. Chronic oedema: a prevalent healthcare problem for UK health services. *Int Wound J* 2017;14:772-81.
7. Rockson S, Rivera KK. Estimating the population burden of lymphedema. *Ann N Y Acad Sci* 2008;1131:147-54.
8. Huesch MB, Mosher TJ. Using it or losing it? The case for data scientists inside healthcare. *NEJM Catalyst*. Available at: <https://catalyst.nejm.org/case-data-scientists-inside-health-care/>. Accessed August 15, 2018.
9. Blue Health Intelligence. Available at: <https://bluehealthintelligence.com/about-us>. Accessed August 15, 2018.
10. Lerman M, Gaebler JA, Hoy S, Izhakoff J, Cullett L, Niecko T, et al. Health and economic benefits of advanced pneumatic compression devices in patients with phlebolymphe dema . *J Vasc Surg* 2019;69:571-80.
11. Williams AF, Franks PF, Moffatt CJ. Lymphoedema: estimating the size of the problem. *Palliat Med* 2005;19:300-13.
12. Boccardo F, Michelini S, Zilli A, Campisi C. Epidemiology of lymphedema. *Phlebolymphe dema* 1999;26:24-8.
13. Karaca-Mandic P, Hirsch AT, Rockson SG, Ridner SH. The cutaneous, net clinical, and health economic benefits of advanced pneumatic compression devices in patients with lymphedema. *JAMA Dermatol* 2015;151:1187-93.

14. World Health Organization definition. Available at: <http://www.who.int/>. Accessed August 15, 2018.
15. Meinardi H, Scott RA, Reis R, Sander JW; ILAE Commission on the Developing World. The treatment gap in epilepsy: the current situation and ways forward. *Epilepsia* 2001;42:136-49.
16. Gloviczki P. *Handbook of venous disorders: guidelines of the American Venous Forum*. 4th ed. Boca Raton, Fla: CRC Press; 2017.
17. Institute of Medicine Committee on Quality of Healthcare in America. *Crossing the quality chasm: a new health system for the 21st century*. Washington, DC: National Academy Press; 2001.

Submitted Dec 18, 2018; accepted Feb 15, 2019.