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The critical role of phlebolymphedema in cellulitis associated with lymphedema: its incidence and economic impact in a large real-world population

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ABSTRACT

Objective: The aims of this study were: to define the incidence of cellulitis in patients with lymphedema (LED) overall and relate this to the etiology of LED; to determine how this rate might be affected by recurrence of cellulitis; and to quantify the contemporary economic burden of treatment. Understanding these factors is essential in developing targeted cellulitis prevention strategies and reducing health care costs.

Methods: The IBM MarketScan Research Database was examined from April 2013 to March 2019 for patients with a new diagnosis of LED (n = 85,601). Based on International Classification of Diseases (ICD)-9/ICD-10 diagnosis codes, the incidence and cost of cellulitis were ascertained during the 3-year follow-up period. Incidence rates (per 100 patient-years [PYs]) and cost (per patient per year) of cellulitis were evaluated among all patients with LED and within subgroups of LED etiologies.

Results: Among the three most common morbidities associated with LED (breast cancer-related lymphedema [BCRL], n = 17,954 [20.97%]; gynecological cancer-related LED [GCRL], n = 1256 [1.47%]; and phlebolymphedema [PLED], n = 8406 [9.82%]), rates of cellulitis were markedly lower for BCRL (8.9; 95% confidence interval [CI], 8.7-9.2) and GCRL (14.8; 95% CI, 13.4-16.4) vs PLED (47.7; 95% CI, 46.7-48.8). Patients with a history of cellulitis had markedly higher cellulitis rates during follow-up than those without—overall, 74.0% vs 16.4%; BCRL, 42.9%; 95% CI, 39.7%-46.3% vs 7.6%; 95% CI, 7.3%-7.9%; GCRL, 67.5%; 95% CI, 56.4%-80.8% vs 11.0%; 95% CI, 9.8%-12.4%; and PLED, 81.7%; 95% CI, 79.4%-84.1% vs 30.4%; 95% CI, 29.4%-31.4%, respectively. The mean $/patient/year of cellulitis-related costs for a patient with PLED ($2836; 95% CI, $2395-$3471) was significantly greater than that for BCRL ($503; 95% CI, $212-$1387) and GCRL ($609; 95% CI, $244-$1314).

Conclusions: The incidence of cellulitis associated with LED varies by the etiology of LED. PLED has the highest rates of both an initial cellulitis episode and recurrent cellulitis events. Additionally, PLED has one of the largest cellulitis-related total costs per patient per year. Prevention, as well as early identification and treatment of PLED-associated cellulitis, could significantly decrease health care costs and improve patient quality of life. (J Vasc Surg Venous Lymphat Disord 2023;■:101704.)

Keywords: Cellulitis; Lymphedema; Phlebolymphedema

Lymphedema (LED), an under-recognized and incurable disease, is defined as an excess of fluid in the interstitial space that accumulates due to a mismatch between the rate of fluid deposition via capillary filtration and the rate of fluid drainage via the lymphatics system.[1] Secondary LED, the most common form of LED, is associated frequently with oncologic treatment and damage to the lymphatic system, by either surgery, radiation, or a combination of both. LED associated with chronic venous insufficiency, however, is increasingly recognized as an important cause of secondary LED. Recently, the term phlebolymphedema (PLED), has been applied to describe LED from chronic venous insufficiency.[2] Elevated venous pressure due to valvular reflux, outflow

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obstruction, or a combination of both increase intracapillary pressure with further efflux of ultrafiltrate into the interstitial space. If lymphatic transport is unable to meet the increased demand, protein-rich fluid accumulates in the interstitial space.[3]

Edema has been cited as one of the major risk factors for cellulitis, an acute bacterial infection causing inflammation of the deep dermis and surrounding subcutaneous tissue. As a result, patients with LED are prone to this infection. Stagnation of this protein-rich fluid in the interstitial space, which is associated with lack of lymphatic transport, provides an excellent culture medium for bacteria.[4] As can often be seen in patients with LED, loss of protective skin integrity with hyperkeratotic, papillomatous skin and open ulcers provides entry for bacteria. Lymphatic dysfunction affects cell-mediated immunity, so that the traffic of host immune cells is blunted. This predisposition to cellulitis in patients with LED further exacerbates the problem by leading to inflammatory injury to the lymphatic vessels that can damage the capacity of the already insufficient lymphatic drainage system.[5] After one episode of LED-associated cellulitis, the risk for further subsequent episodes is greatly increased.[6]

Although LED is well-established as the major risk factor for developing cellulitis, the pathophysiology associated with the different causes of secondary LED may influence the risk of developing this complication. For example, the risk of cellulitis in breast cancer-related lymphedema (BCRL) may differ from PLED.

Several economic studies have shown treatments for LED-associated cellulitis are a significant burden to the health care system. Specifically, Challener and colleagues demonstrated that patients hospitalized with cellulitis spent a median of 4.7 days hospitalized at a median cost of $7341 per hospitalization.[7] Our previous Venous Ulcer Registry study showed both an increased medical resource utilization (MRU) and cost for patients with open venous ulcers hospitalized with cellulitis. Additionally, the cost in patients with both venous leg ulcers (VLUs) and cellulitis ($27,408 ± $10,859 per patient per year) was three-fold greater than those patients with VLUs without cellulitis ($11,088 ± $9343; $P < .0001$). A large portion of this increase was related to the cost of hospitalization ($9492) for the cellulitis cohort.[8]

There is a paucity of data, however, on the additional outpatient cost of cellulitis in patients with LED. In addition, the economic impact of patients with LED, who are at a significantly increased risk for readmission for episodes of cellulitis and increased risk for recurrent episodes of cellulitis, is critical to understand.

This study aims to investigate both the rates of cellulitis and recurrent episodes of cellulitis in patients with LED based on the etiology of LED. Specifically, this work compares BCRL, gynecologic cancer-related lymphedema (GCRL), and PLED. Additionally, the study aims to investigate the MRU and cost associated with cellulitis treatment related to these different etiologies of LED as well as those with previous episodes of cellulitis vs a de novo episode.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective review of large claims database
- **Key Findings:** The incidence of cellulitis in patients with phlebolymphedema (PLED) is significantly higher than the incidence of cellulitis in other etiologies of lymphedema (LED). Additionally, patients with PLED have significantly higher treatment costs per year for cellulitis compared with other etiologies of LED such as breast cancer-related LED and gynecologic cancer-related LED.
- **Take Home Message:** Clinicians should be aware of the significantly higher incidence of cellulitis in patients with LED, specifically PLED. These episodes and recurrent episodes of cellulitis come at a significant economic cost.

METHODS

Study design. A retrospective observational design was employed to obtain and analyze data from an integrated United States health care claims repository (IBM MarketScan Commercial Claims and Encounters [CCAE] and Medicare Supplemental and Coordination of Benefits [MDCR] databases). Informed consent was not obtained as this study was done through a commercial claims database, and no identifiable patient health information was collected. Additionally, institutional review board approval was not required as this data was de-identified claims data. The details of this process have been described in our previous publications, and only the relevant applications will be presented here.[9]

Study population. The study population included patients 18 years old or greater, who were first diagnosed with primary or secondary LED between April 1, 2013, and March 31, 2019. Patients were diagnosed with LED if they were assigned one diagnosis code for LED (International Classification of Diseases [ICD]-9: 457.0, 457.1, 757.0; ICD-10: I97.2, I89.0, Q82.0) in the acute care hospital setting, or at least two diagnosis codes, on two separate occasions, for LED in the ambulatory setting. The earliest incidence of an LED diagnosis code was deemed the "index date."

Exclusion criteria included patients without health care coverage during the 12-month period preceding the "index date" or a diagnosis of head or neck cancer. Head and neck cancer patients were excluded as their presentation differs significantly from LED of the extremity. Patients were categorized based on their disease etiology, as coded in the hospital or ambulatory setting.

Table I. Comparison of overall cellulitis rates to individual etiology cellulitis rates

Etiology of LED	Number	Rate/100 PYs with 95% CIs
Overall	85,601	25.4 (25.1-25.6)
BCRL	17,954	8.9 (8.7-9.2)
GCRL	1256	14.8 (13.4-16.4)
PLED	8406	47.7 (46.7-48.8)
Urologic cancer	1034	26.7 (24.5-29.1)
Melanoma	651	13.4 (11.7-15.5)
Morbid obesity	5771	44.8 (43.5-46.1)

BCRL, breast cancer-related lymphedema; *CI*, confidence interval; *GCRL*, gynecological cancer-related lymphedema; *LED*, lymphedema; *PLED*, phlebolymphedema; *PYs*, person-years.

Demographic information consisting of age, gender, comorbidities, and LED etiology were collected on each patient.

Study measures. Based on ICD-9 or ICD-10 diagnosis codes (a full listed of ICD codes is included in the Supplementary Appendix, online only), the incidence of upper or lower limb cellulitis was ascertained during the maximum 3-year follow-up period. These episodes of cellulitis were stratified by etiology of LED and care setting (hospital/ambulatory). This process was repeated for patients with or without a history of cellulitis. MRU was defined by the setting of care, either as an acute care hospitalization or in an ambulatory setting—physician's office, hospital outpatient, emergency room, or home health. Skilled nursing facilities were included as a non-acute care inpatient setting. The hospital admission or ambulatory visit was linked as due to cellulitis by the ICD code. The cost of each episode was captured to calculate both cost of each episode of cellulitis by etiology as well as cost of cellulitis per patient per year in both the ambulatory and inpatient setting, as expressed in 2019 United States dollars. Most importantly, the MRUs and costs were stratified by etiology of LED. This data was obtained from the MarketScan Medicare supplementary database, which provides detailed cost and use data for health care services performed for inpatients and outpatients.

RESULTS

Distribution of LED patients by etiology and baseline characteristics. A total of 85,601 patients with LED were included in the study (Table I). BCRL (n = 17,954; 21.0%) was the most common etiology of LED, followed by PLED (n = 8406; 9.8%) and then morbid obesity (n = 5771; 6.7%). GCRL accounted for 1.5% (n = 1256) of included patients. Patients without a specific etiology of LED entered as ICD-9-CM 457.1 or ICD-10-CM I89.0 (lymphedema, not elsewhere classified) comprised the vast majority of patients in the database (39,426; 46.1%). Because this was a health care claims data review, the analysis is dependent upon the coder designating a specific cause of secondary LED. In this category, no etiology of LED was assigned. Primary LED was defined as the etiology in only 59 patients (0.1%) (Table II). Because the diagnosis of primary LED is most frequently made in most patients under the age of 18, and under that age was an exclusion factor in this study, this figure does not reflect the proportion of primary LED in an entire population.

Patients with multiple causes of LED amounted to 9390 patients (11%). As it would be impossible to attribute the cause of the cellulitis to one specific etiology in the

Table II. Baseline characteristics of patients with lymphedema (*LED*)[a]

	All patients with LED (n = 85,601)	Patients with LED by etiology			*P* value
		BCRL (n = 17,954)	GCRL (n = 1256)	PLED (n = 8406)	
Age, years	61.2 (14.6)	56.7 (11.2)	61.0 (11.2)	66.9 (14.6)	<.0001
Sex					
Female	72.6	99.4	99.9	54.8	<.0001
Male	27.4	0.6	0.1	45.2	<.0001
Comorbidities					
Depression	28.2	31.5	24.7	25.6	<.0001
Diabetes	27.8	14.0	14.4	38.5	<.0001
Heart failure	10.3	1.9	2.1	18.8	<.0001
Hypertension	52.2	34.0	40.1	66.3	<.0001
Obesity	22.9	8.5	9.0	21.9	<.0001
Pulmonary hypertension	2.3	0.5	0.6	4.3	<.0001
Renal disease	15.2	3.9	8.0	22.6	<.0001

BCRL, breast cancer-related lymphedema; *GCRL*, gynecological cancer-related lymphedema; *PLED*, phlebolymphedema.
Data are presented as percent or mean (standard deviation).
[a]Baseline characteristics ascertained during 12-month history period.

Table III. Rates of cellulitis among patients with lymphedema (*LED*), overall and by etiology[a]

	All patients with LED	Patients with LED by etiology		
		BCRL	GCRL	PLED
All patients with LED	85,601	17,954	1256	8406
Rates, overall				
Rate (95% CI), per 100 PYs	25.4 (25.1-25.6)	8.9 (8.7-9.2)	14.8 (13.4-16.4)	47.7 (46.7-48.8)
Rates, by care setting hospital				
Rate (95% CI), per 100 PYs	2.8 (2.8-2.9)	0.7 (0.6-0.8)	1.6 (1.2-2.2)	5.7 (5.4-6.1)
Ambulatory				
Rate (95% CI), per 100 PYs	22.5 (22.3-22.8)	8.2 (8.0-8.5)	13.2 (11.8-14.6)	42.0 (41.1-43.0)
Patients with a history of cellulitis				
Rates, overall				
Rate (CI), per 100 PYs	74.0 (72.9-75.0)	42.9 (39.7-46.3)	67.5 (56.4-80.8)	81.7 (80.1-83.3)
Rates, by care setting hospital				
Rate (CI), per 100 PYs	10.5 (10.2-10.9)	6.7 (5.5-8.2)	9.6 (6.0-15.5)	10.8 (10.2-11.4)
Ambulatory				
Rate (CI), per 100 PYs	63.4 (62.5-64.4)	36.1 (33.2-39.3)	57.9 (47.6-70.2)	70.9 (69.4-72.4)
Patients without history of cellulitis				
Rates, overall				
Rate (CI), per 100 PYs	16.4 (16.2-16.6)	7.6 (7.3-7.9)	11.0 (9.8-12.4)	30.3 (29.6-31.0)
Rates, by care setting hospital				
Rate (CI), per 100 PYs	1.4 (1.4-1.5)	0.5 (0.4-0.5)	1.1 (0.7-1.6)	3.1 (2.9-3.3)
Ambulatory				
Rate (CI), per 100 PYs	15.0 (14.8-15.2)	7.1 (6.9-7.4)	9.9 (8.7-11.3)	27.2 (26.6-27.9)

BCRL, Breast cancer-related lymphedema; *CI*, Confidence interval *GCRL*, gynecological cancer-related lymphedema; *PLED*, phlebolymphedema; *PYs*, person-years.
[a]Rates ascertained during maximum 3-year follow-up period.

multiple cause group, these patients were not included in the analysis.

Patients with PLED were generally older (mean age, 66.9 years), compared with a mean of 56.7 years in patients with BCRL and 61.0 years old in patients with GCRL ($P \leq .0001$). Nearly all patients with BCRL (99.4%) and GCRL (99.9%) were female compared with 54.8% of female patients in the PLED group ($P \leq .0001$). Patients with PLED were more likely to have comorbidities such as diabetes, heart failure, hypertension, renal disease, and obesity, as demonstrated in Table I.

Overall rates (patients with and without a history of cellulitis) for comparative etiologies. The overall rate of cellulitis in all patients with LED (n = 85,601) was 25.4 per 100 person years (PYs) (95% confidence interval [CI], 25.1-25.6) (Table III). Compared with BCRL (8.9/100 PYs; 95% CI, 8.7-9.2) and GCRL (14.8/100 PYs; 95% CI, 13.4-16.4), PLED had a significantly increased rate of cellulitis (47.4/100 PYs; 95% CI, 46.7-48.8; $P \leq .0001$). This difference was seen in both hospital and ambulatory settings. In ambulatory settings, PLED (42/100 PYs; 95% CI, 41.1-43.0) had a significantly higher rate of cellulitis compared with both BCRL (8.2/100 PYs; 95% CI, 8.0-8.5) and GCRL (13.2/100 PYs; 95% CI, 11.8-14.6; $P \leq .0001$). In hospital settings, the rate of cellulitis for PLED (5.7/100 PYs; 95% CI, 5.4-6.1) was higher than BCRL (0.7/100 PYs; 95% CI, 0.6-0.8) and GCRL (1.6/100 PYs; 95% CI, 1.2-2.2; $P \leq .0001$).

Rates of cellulitis based on previous history of cellulitis. When patients were stratified based on a history of cellulitis, the overall rates (in all patients with LED) of cellulitis were higher in those with a history of previous cellulitis (74.0/100 PYs; 95% CI, 72.9-75.0) compared with those without a history of cellulitis (16.4/100 PYs; 95% CI, 16.2-16.6; $P \leq .0001$).

In patients with a history of previous cellulitis, patients with PLED (81.7/100 PYs; 95% CI, 80.1-83.83) had a significantly higher rate of cellulitis compared with patients with BCRL (42.9/100 PYs; 95% CI, 39.7-46.3; $P \leq .0001$) and patients with GCRL (67.5/100 PYs; 95% CI, 56.4-80.0; $P \leq .02$). Additionally, in patients without a history of previous cellulitis, patients with PLED (30.3/100 PYs; 95% CI, 29.6-31.0) had a significantly higher rate of cellulitis compared with patients with BCRL (7.6/100 PYs; 95% CI, 7.3-7.9) and patients with GCRL (11.0/100 PYs; 95% CI, 9.8-12.4; $P < .001$).

Table IV. Cellulitis-related health care expenditures among patients with lymphedema (*LED*), overall and by etiology[a]

	All patients with LED	Patients with LED by etiology		
		BCRL	GCRL	PLED
All patients with LED				
Cost of cellulitis per episode, mean (95% CI)[a]				
Hospital	$21,689 (20,562-23,006)	$15,034 (13,008-8262)	$17,555 (12,231-24,864)	$23,228 (20,842-26,751)
Ambulatory	$1085 (1025-1155)	$838 (704-1013)	$1269 (762-2226)	$1289 (1120-1498)
Cost of cellulitis per patient (per year), mean (95% CI)				
Total	$1776 (1498-2259)	$503 (212-1387)	$827 (402-1583)	$2836 (2419-3395)
Patients with history of cellulitis				
Cost of cellulitis per episode, mean (95% CI)[a]				
Hospital	$22,090 (20,667-23,786)	$12,809 (10,337-16,434)	$11,946 (8,090-18,741)	$24,948 (21,629-29,213)
Ambulatory	$1202 (1109-1318)	$836 (542-1293)	$1234 (549-2834)	$1295 (1108-1543)
Cost of cellulitis per patient (per year), mean (95% CI)				
Total	$7238 (5883-9809)	$1958 (1108-3489)	$3055 (1196-6192)	$5691 (4564-7131)
Patients without history of cellulitis				
Cost of cellulitis per episode, mean (95% CI)[a]				
Hospital	$21,091 (19,528-23,496)	$16,314 (13,587-20,259)	$21,222 (13,810-32,066)	$20,107 (17,366-23,617)
Ambulatory	$993 (913-1080)	$838 (704-1034)	$1284 (707-2724)	$1282 (1018-1615)
Cost of cellulitis per patient (per year), mean (95% CI)				
Total	$791 (669-1091)	$442 (155-1358)	$650 (262-1446)	$1261 (996-1595)

BCRL, breast cancer-related lymphedema; *CI*, confidence interval *GCRL*, gynecological cancer-related lymphedema; *PLED*, phlebolymphedema; *PYs*, person-years.
[a]Health care utilization and expenditures ascertained during maximum 3-year follow-up period.

Cellulitis-related medical resource utilization. The site of treatment, acute care hospital or in an ambulatory setting (doctor's office, hospital outpatient department, emergency room, home health), was compared. The ratio of ambulatory treatment to acute inpatient treatment was calculated for each of the causes of LED. When looking at overall rates of cellulitis irrespective of a history of recurrence, both BCRL (11.7) and GCRL (8.25) had higher ratios of ambulatory to hospital inpatient settings than PLED (7.4), which indicated that PLED was more frequently associated with acute care hospitalization for cellulitis.

In those with a previous history of cellulitis, the hospitalization rate was lower in the BCRL group (6.7/100 PYs; 95% CI, 5.5-8.2) compared with the PLED group (10.8/100 PYs; 95% CI, 10.2-11.4). The higher ratio of ambulatory to inpatient treatment seen in the overall group disappeared when looking at patients with a history of cellulitis (BCRL 5.38 vs PLED 6.6), indicating the impact of recurrent cellulitis shifting the treatment site toward inpatient hospitalization for both etiologies.

Cellulitis-related healthcare expenditure. For all patients with LED, the average cost per cellulitis episode, expressed as cellulitis-specific cost, in the ambulatory setting was $1085 (95% CI, $1025-$1155) and $21,689 (95% CI, $20,562-$23,006) in the hospital setting (Table IV). This averaged a mean cost of $1776 (95% CI, $1498-$2259) for cellulitis-related expenditure per patient per year regardless of etiology. The cost of cellulitis-related health care expenditures per patient per year for PLED ($2836; 95% CI, $2395-$3471) was higher than the cost of cellulitis-related health care expenditures per patient per year for BCRL ($503; 95% CI, $212-$1387) and GCRL ($827; 95% CI, $402-$1583). However, the cost of cellulitis-related health care expenditures per episode was comparable between PLED ($1289; 95% CI, $762-$2226) and GCRL ($1269; 95% CI, $762-$1690).

In all LED, regardless of etiology, patients with a prior history of cellulitis, the cost of cellulitis-related health care expenditures per patient per year ($7238; 95% CI, $5883-$9809) greatly exceeded that of those without a history of cellulitis ($791; 95% CI, $669-$1091). This difference was even greater in patients with PLED. In patients with both PLED and a history of cellulitis, the mean cellulitis-related health care expenditure was $5691 (95% CI, $4564-$7131) compared with $1261 (95% CI, $996-$1595) in those patients with PLED without a history of cellulitis.

When patients with a history of prior cellulitis by LED etiology were compared, patients with PLED ($5691; 95% CI, $4564-$7131) have a higher cost of cellulitis-related health care expenditure per patient per year than those with BCRL ($1958; 95% CI, $1102-$3489) or GCRL ($3055; 95% CI, $1196-$6192).

Table V. Comparison of patients with lymphedema (*LED*) with venous leg ulcers (*VLUs*) to patients with LED and chronic venous insufficiency (*CVI*) without VLUs[a]

	Patients with LED and VLUs	Patients with LED, CVI without VLUs
No.	4855	3551
Rates, overall		
Rate (95% CI), per 100 PYs	48.0 (46.7-49.3)	43.5 (41.8-45.2)
Rates, by care setting		
Hospital		
Rate (95% CI), per 100 PYs	6.2 (5.7-6.6)	4.8 (4.3-5.4)
Ambulatory		
Rate (95% CI), per 100 PYs	41.8 (40.7-43.0)	38.7 (37.1-40.3)
Patient with a history of cellulitis		
Rate (95% CI), per 100 PYs	79.6 (76.9-82.3)	79.9 (75.7-84.3)
Patients without history of cellulitis		
Rate (95% CI), per 100 PYs	29.6 (28.4-30.9)	28.8 (27.2-30.5)
Cellulitis-related cost (2019 US$)		
Total per patient per year	$3102 (2563-3813)	$2355 (1679-3354)

CI, Confidence interval; *PYs*, person years.
[a]Rates ascertained during maximum 3-year follow-up period.

The influence of venous ulcers. To determine the influence of VLUs on the incidence of cellulitis and the costs of treating cellulitis in patients with and without VLUs, we divided the PLED group into those with lymphedema and VLUs [VLU+] 4855 (58%) vs those with lymphedema and chronic venous insufficiency and no VLUs [VLU−] 3551 (42%) (Table V). The overall rate of cellulitis per 100 PYs among the VLU+ patients was higher than those without VLUs at 48.0/100 PYs (95% CI, 46.7-49.3) vs 43.5/100 PYs (95% CI, 41.8-45.2). No difference in the rate of cellulitis was observed between the two groups for the patients with a prior history of cellulitis or for those without a history of prior cellulitis. When the cellulitis-related health care expenditures between the two groups were examined, there was no significant difference in cost of cellulitis per patient per year between the two groups.

DISCUSSION

This analysis of a large health care claims data base of approximately 86,000 patients with LED showed a clear increase in the incidence of cellulitis in patients with PLED over LED associated with cancer treatment. As has been previously demonstrated, patients with a previous episode of cellulitis are at a greater risk of developing a recurrent episode. Furthermore, patients with PLED, in comparison to patients with BCRL or GCRL, had a higher rate of cellulitis episodes requiring hospitalization. This contributes to a greater cost for PLED.[10]

Relationship of the cause of secondary LED to the incidence of cellulitis. Edema has been long recognized as a major risk factor for developing cellulitis. In a study of patients with cellulitis carried out in 1995/1996 at seven centers in France, Dupuy and colleagues identified several independent risk factors for cellulitis. LED had the highest odds ratio (71.2), followed by disruption of the cutaneous barrier (23.8), venous insufficiency (2.9), and obesity (2.0).[11]

Vignes and colleagues conducted a retrospective study of nearly 2000 patients with LED referred to a specialized lymphedema clinic. The most common cause of LED, BCRL (58%), was associated with a nearly 40% occurrence of cellulitis, whereas primary lower limb LED had a comparable occurrence of cellulitis. Secondary lower limb LED had a lower 31% occurrence of cellulitis ($P < .02$).[12] It should be noted that Vignes excluded patients with venous disease and therefore differs significantly from our patient population.

Although LED is a defined risk factor for cellulitis, there is a paucity of studies showing how etiology of secondary LED may influence the incidence of cellulitis. One of the advantages of a large health care claims database is the size and spectrum of the population at risk for a disease or its complications (here, 86,000 patients with LED).[13] The current study clearly shows that patients with PLED are at a greater risk for cellulitis than those with BCRL or GCRL. A comparison of morbid risk factors for the groups indicates that PLED has a greater proportion of two important factors that can accentuate edema, heart failure, and renal disease. In addition, patients with advanced chronic venous insufficiency generally have loss of skin integrity either through an open ulcer or eczematous skin, which has been identified as a major factor promoting bacterial invasion.[6] The current study showed that VLUs increased the cellulitis rate for the

overall PLED population, but not when divided into a history of a previous cellulitis or no history of cellulitis. Finally, lower extremity LED has been shown to have a higher incidence of cellulitis than upper extremity LED due to potential perineal soilage and most importantly interdigital Tinea Pedis, which provides a site of invasion for bacteria.[14]

Recurrent cellulitis. A previous longitudinal study of 171 patients with a diagnosis of cellulitis examined their follow-up course. Nearly 50% of these patients had recurrent episodes of cellulitis, whereas a similar proportion had evidence chronic edema, leading to a strong association between these two factors, edema and cellulitis ($P < .0002$).[4] By contrast, a larger, recent health care claims-based analysis of nearly 6000 individuals with cellulitis showed a lower recurrence of 11% within 1 year.[14] Our study demonstrated a 4.5-fold increase in the rate of cellulitis for the overall group of patients with LED with a previous episode of cellulitis (74/100 PYs) over those without (16.4/100 PYs). Karpellin and associates observed that recurrent episodes of lower limb cellulitis can be more severe than the initial episode and result in a longer hospitalization.[15] The absolute increase in rate was greatest in the PLED cohort with a rate of 81.7/100 PYs in patients with a history of cellulitis and a rate of 30.3/100 PYs in PLED patients without a history of cellulitis.

Economic implications. Our economic analysis demonstrated that MRU and cost varied with the type of secondary LED as well as whether the cellulitis event was an initial one or a recurrent episode. The individual sites of service (MRU) vary in intensity (as will their cost), as inpatient hospitalization is more resource intensive than an outpatient visit. The ratio of ambulatory treatment to in-hospital treatment reflects the relative use of the lower intensity outpatient sites. This ratio varied with the type of secondary LED where the higher ratios for BCRL and GCRL than PLED indicates that a greater proportion of the lower intensity resources were utilized in the former than in the latter. In patients with a previous history of cellulitis, irrespective of the etiology, the site of service shifted to the more resource-intensive hospital site.

In a health care claims administrative database, "cost" represents what the insurer (either commercial or governmental) reimburses the provider (hospital or physician) for providing a service. Cost, what the insurer reimburses the provider, is usually described in the United States as dollars per patient per year ($PPY). Rather than employing the total cost of a hospitalization, which may be influenced by multiple factors, our analysis restricted the cost to that expended for cellulitis-related treatment. The cost for treating cellulitis ($PPY) was influenced by the etiology of the LED so that it was five-fold greater in PLED than in BCRL or GCRL. This cost was influenced by the greater rate of hospitalization incurred by PLED. Irrespective of the etiology of the LED, patients with a previous history of cellulitis had higher $PPY. Even within this subset of patients with a history of cellulitis, the $PPY of PLED predominated. These findings suggest that, from an economic point of view, the prime target population for prophylaxis should be patients with a previous history of cellulitis and, in particular, patients with PLED.

Several studies have examined the costs of hospitalization for treating cellulitis. Challener and colleagues reported the hospital costs incurred by patients with cellulitis in the Olmsted County (Minnesota) Epidemiology Project.[7] Of 195 patients diagnosed with cellulitis, 34 (17%) required hospitalization, where the median inpatient cost was $7341. Although cellulitis involving the lower extremity was more costly than upper extremity, no information was provided on the presence of LED or cellulitis recurrence. Our previously published analysis of a VLU registry demonstrated that nine of 78 patients (11.5%) with a VLU included underwent hospital admission for cellulitis over a 1-year period of follow-up.[8] In the previously published paper, the total cost for patients with cellulitis averaged nearly $30,000 and was threefold higher than those patients with VLU without infection.

LIMITATIONS

The limitations of this paper are largely related to the source of the data. This study is based on health care claims data, which relies on clinicians and coders to accurately input diagnosis and treatment codes. Additionally, the clinical severity of these disease states cannot be determined. Since the demographic characteristics including age, sex, and other comorbidities were not propensity-matched, this may influence the results.

Additionally, when calculating the cost of hospitalized episodes, this cost was derived from hospitalizations during which the principal discharge diagnosis was coded to be cellulitis. As this is the primary discharge diagnosis, the majority of the cost of the hospitalization is likely the result of the cost of the cellulitis; however, it is not possible to determine if all reimbursed amounts were for cellulitis-related services. As such, some of this cost may reflect the cost for other conditions.

CONCLUSIONS

The results of this study point to a significant area for improvement in patient care and reduction of health care expenditure. Given the greater risk of patients with PLED's cost of cellulitis, prevention, as well as early identification and treatment of PLED-associated cellulitis could significantly decrease health care costs and improve patient quality of life.

AUTHOR CONTRIBUTIONS

Conception and design: PS, AT, TO, DW
Analysis and interpretation: DW
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Writing the article: AT, TO
Critical revision of the article: PS, DW
Final approval of the article: PS, AT, TO, DW
Statistical analysis: DW
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Overall responsibility: TO

DISCLOSURES

T.O. was a consultant for Tactile Medical, Minneapolis, MN, when this study was performed. D.W. is the Senior Health Economist at Policy Analysis Inc (PAI), which received funding for this research from Tactile Medical.

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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table (online only). International Classification of Diseases (ICD), Tenth Revision (ICD-10) and Ninth Revision (ICD-9) Codes

Diagnosis	Code	Etiology
Cellulitis	L02511	**Cutaneous abscess of right hand**
Cellulitis	L02512	**Cutaneous abscess of left hand**
Cellulitis	L02519	**Cutaneous abscess of unspecified hand**
Cellulitis	L03011	Cellulitis of right finger
Cellulitis	L03012	Cellulitis of left finger
Cellulitis	L03019	Cellulitis of unspecified finger
Cellulitis	L03021	**Acute lymphangitis of right finger**
Cellulitis	L03022	**Acute lymphangitis of left finger**
Cellulitis	L03029	**Acute lymphangitis of unspecified finger**
Cellulitis	L03011	Cellulitis of right finger
Cellulitis	L03012	Cellulitis of left finger
Cellulitis	L03019	Cellulitis of unspecified finger
Cellulitis	L03011	Cellulitis of right finger
Cellulitis	L03012	Cellulitis of left finger
Cellulitis	L03019	Cellulitis of unspecified finger
Cellulitis	L02611	**Cutaneous abscess of right foot**
Cellulitis	L02612	**Cutaneous abscess of left foot**
Cellulitis	L02619	**Cutaneous abscess of unspecified foot**
Cellulitis	L03031	Cellulitis of right toe
Cellulitis	L03032	Cellulitis of left toe
Cellulitis	L03039	Cellulitis of unspecified toe
Cellulitis	L03041	**Acute lymphangitis of right toe**
Cellulitis	L03042	**Acute lymphangitis of left toe**
Cellulitis	L03049	**Acute lymphangitis of unspecified toe**
Cellulitis	L03031	Cellulitis of right toe
Cellulitis	L03032	Cellulitis of left toe
Cellulitis	L03039	Cellulitis of unspecified toe
Cellulitis	L03019	Cellulitis of unspecified finger
Cellulitis	L03029	**Acute lymphangitis of unspecified finger**
Cellulitis	L03039	Cellulitis of unspecified toe
Cellulitis	L03049	**Acute lymphangitis of unspecified toe**
ICD-9 CODES		
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68100		Cellulitis and abscess of finger, unspecified
68110		Cellulitis and abscess of toe, unspecified
68110		Cellulitis and abscess of toe, unspecified
68110		Cellulitis and abscess of toe, unspecified

(Continued)

Supplementary Table (online only). Continued.

ICD-9 CODES	
68110	Cellulitis and abscess of toe, unspecified
68110	Cellulitis and abscess of toe, unspecified
68110	Cellulitis and abscess of toe, unspecified
68110	Cellulitis and abscess of toe, unspecified
68110	Cellulitis and abscess of toe, unspecified
68110	Cellulitis and abscess of toe, unspecified
6819	Cellulitis and abscess of unspecified digit
6819	Cellulitis and abscess of unspecified digit
6819	Cellulitis and abscess of unspecified digit
6819	Cellulitis and abscess of unspecified digit

Boldface etiologies only in expanded analysis.