

PREVALENCE OF LYMPHEDEMA USING LARGE DATA SETS; AN EPIDEMIOLOGICAL ANALYSIS IN THE UNITED STATES AND IN ITALY

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ABSTRACT

There is a lack of large epidemiological studies focusing on the prevalence of lymphedema. Vital registration data from the United States (US) (1999-2020) and Veneto, Italy (2008-2021) were analyzed. Lymphedema-related deaths were identified using disease-specific ICD-10 codes and served to estimate the burden of disease in the general population. We studied (i) the lymphedema-specific proportionate mortality as a proxy of the disease-specific prevalence, (ii) the prevalence of lymphedema in key patient subgroups, and (iii) age and sex-specific mortality rates. The prevalence of lymphedema increased over the last two decades with marked sex-specific differences: in the US, the estimated prevalence of lymphedema was 2.7 per 10,000 deaths for women and 1.5 per 10,000 deaths for men. In Veneto, the prevalence was 3.0 per 10,000 deaths for women and 1.1 per 10,000 deaths for men. The prevalence of lymphedema was 2- to 20-times in specific subgroups of patients, including those with obesity, skin infections, hyper-

tension, diabetes mellitus, breast/gynecological cancers, and venous thromboembolism. The estimated prevalence of lymphedema is 2- to 3-times higher than previously thought and has been increasing for the past two decades. These results will serve as a reference for future research in this field.

Keywords: lymphedema; mortality; epidemiology; trend; prevalence

Lymphedema is a chronic condition caused by the interstitial accumulation of excess of protein-rich fluid. Its clinical features include swelling, inflammation, recurrent infections, skin fibrosis, which may lead to a tightness feeling, discomfort and disability. Lymphedema is usually localized in the upper and lower extremities, but it can rarely manifest also in other body districts (1,2). It is classified in primary (inherited, congenital, or idiopathic) and secondary (acquired and driven by other disorders) disease. In developed countries, the leading cause of secondary lymphedema is an iatrogenic injury to the lymphatic

vessels, often caused by malignancy and trauma. In developing nations, filariasis caused by *Wuchereria bancrofti* is the most frequent cause of secondary lymphedema (2,3).

The diagnosis of lymphedema can be hampered by other causes of peripheral edema (e.g., chronic venous insufficiency or deep vein thrombosis). Thus, establishing the diagnosis could be delayed. In addition, evidence regarding its optimal treatment is still limited (4), and the lack of epidemiologic studies results in uncertainty of its prevalence and the proportion of disease-specific or complication-related mortality. Two older epidemiological studies have estimated the prevalence of lymphedema in two European countries to be between 1.3 and 1.4 per 1000 general population (3,5). Others estimated that roughly 140–250 million people being affected by lymphedema worldwide (6,7). It has to be expected that the actual prevalence of the disease is underestimated due to the fact that health care professionals are not sufficiently aware for this disease and may not recognize or correctly diagnose the primary or secondary lymphedema (5). Estimating its prevalence could enhance the process of diagnosis and treatment and helping policymakers to allocate resources more efficiently. Additionally, it would have implications for insurance and reimbursement issues, ultimately providing better coverage for patients and improving access to therapies (8).

In our study, we estimated the prevalence of lymphedema at death in the general population of the United States of America and of a large Italian region based on vital registration data.

MATERIALS AND METHODS

We studied lymphedema-specific proportionate-mortality across sexes and age groups and used this measure as a proxy of the disease-specific prevalence. We extracted data from the United States (US) from the publicly available Centers for Disease Control and Prevention, CDC WONDER database. Similarly, we obtained data from Veneto, an Italian region of 5 million, where all death

certificates are forwarded to the regional epidemiology department. In both countries, the causes of death are classified according to the International Classification of Diseases, 10th edition (ICD-10). We focused our analysis on the lymphedema as multiple causes of death (MCO), defined as either underlying or concomitant causes of death with ICD-10 codes been listed in any position of the certificates.

For the US data from January 1st, 1999 to December 31st, 2020 were extracted, while for the Veneto region all death certificates from January 1st, 2008 to December 31st, 2021 were investigated. Death certificates were considered to be lymphedema-related, if the following ICD-10 codes were present in any position (underlying or concomitant cause of death): I89.0 (lymphedema, not elsewhere classified) and Q82.0 (hereditary lymphedema). The codes I97.2 and I97.8 (cancer-associated lymphedema) were very rarely utilized during the study period and therefore not included in the present analyses. For each year, the number of deaths with lymphedema in any position (MCO) were calculated first. In addition, the time, age- and sex-specific proportionate mortality (share of lymphedema-related deaths out of all deaths) were calculated, as a proxy to estimate the prevalence at death of lymphedema in the general population over the two decades. The age and sex-specific lymphedema mortality rates (per 10,000 population) were also calculated in order to study the pattern of lymphedema related mortality by increasing age-group. The above-mentioned analysis has been calculated for both the Veneto region and the US. Finally, the association of the presence of lymphedema in any position on death certificates with the presence in any position of cancer (all cancers and specific cancer sites), and of selected circulatory, metabolic, respiratory, infectious, and degenerative diseases was investigated.

Data was analyzed with Stata (version 15.0) and RStudio (version 1.4). Data analyzed were anonymous and their use did not require ethics or institutional review board approval since data from the US were extracted from publicly available databases, and the analysis of causes of mortality in the Veneto

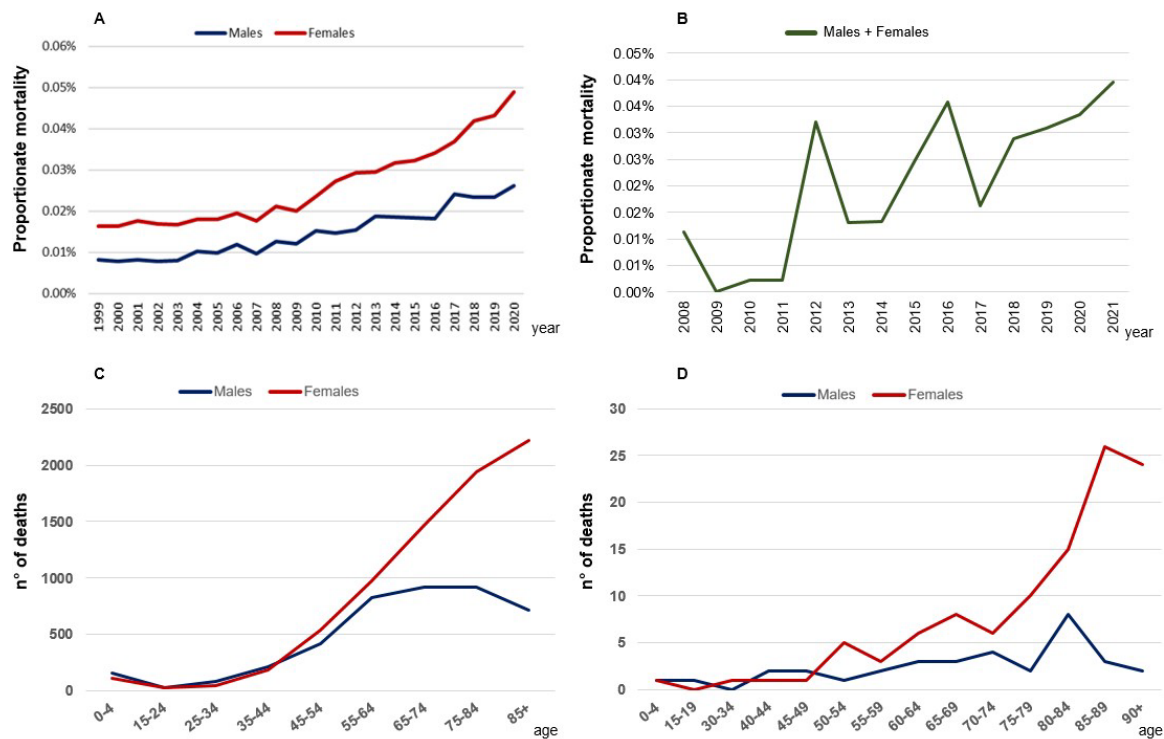


Fig. 1. Number of deaths with mention of lymphedema and estimated prevalence (proportional mortality) by sex and year in the United States and in Veneto region (Italy). Sex- and time-dependent lymphedema-specific proportional mortality (x100,000) in the US (Panel A); time-dependent lymphedema-specific proportional mortality (x100,000) in Veneto region (Panel B). Sex- and age-specific lymphedema death count in the US (Panel C) and Veneto region (Panel D).

region is included among mandatory activities of the Regional Epidemiology Department according to regional law. There was no financial support for this study.

RESULTS

Prevalence of Lymphedema – Comparison of US and Veneto Region (Italy)

In the United States, a total of 56,806,341 deaths from all causes have been recorded between the years 1999 and 2020. Of these patients, 28,319,495 (49.9%) were women and 28,486,846 (50.1%) were men. ICD-10 codes for hereditary lymphedema or lymphedema of unknown causes were mentioned in 11,948 deaths certificates: 7,604 patients (63.6%) were women and 4,344 (36.4%) were men. This led

to an estimated prevalence of 2.7 for women and 1.5 for men per 10,000 deaths, respectively.

In Veneto (Italy), 668,074 deaths were recorded in the period 2008-2021. 350,834 (52.5%) were women and 317,240 (47.5%) were men. Of these, 107 women and 34 men had lymphedema, corresponding an estimated prevalence of 3.0 and 1.1 per 10,000 deaths, respectively.

Figure 1 shows the sex-, time-, and age-dependent increase in the lymphedema cases and estimated prevalence at death (proportional mortality) in both the United States and in Veneto region. This was exponential especially in women. In men, the death count peaked around the age of 65-85 in the United States (Fig. 1, Panel C) and 80-85 in the Veneto region (Fig. 1, Panel D), and subse-

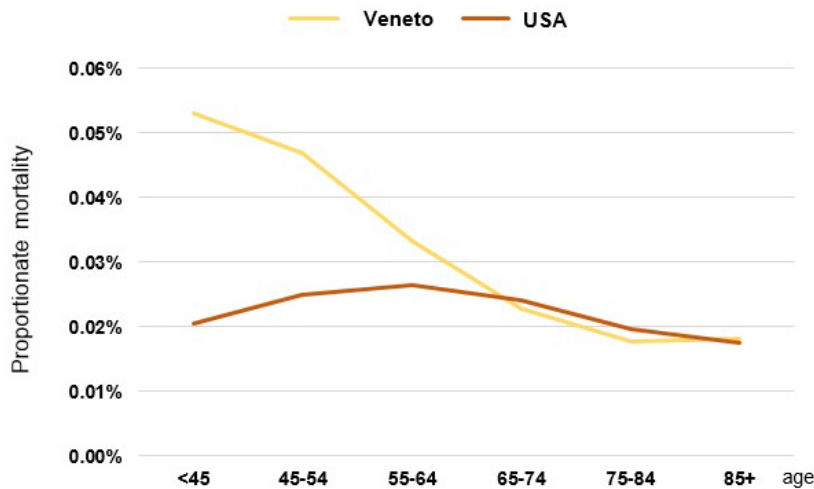


Fig. 2. Lymphedema-specific prevalence at death as estimated from proportional mortality across age groups.

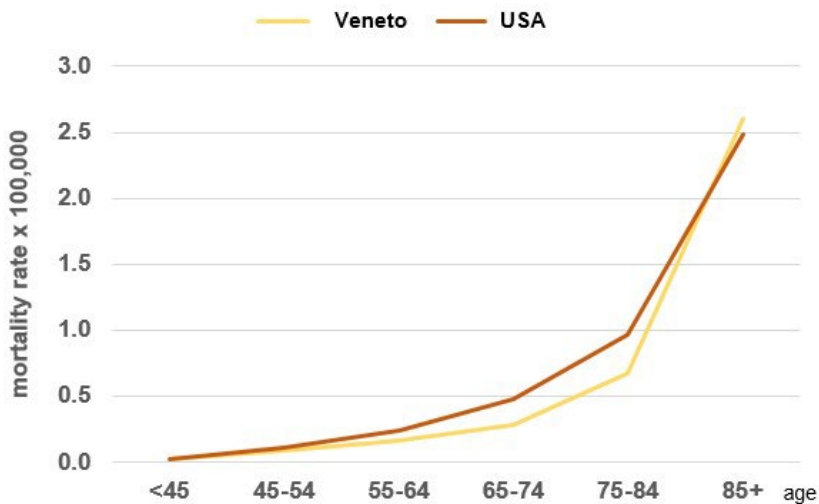


Fig. 3. Age-specific lymphedema mortality rate in the United States, 1999-2020, and in the Veneto region (Italy), 2008-2021.

quently the prevalence decreased over time. When accounting for the total number of deaths for other causes, the estimated prevalence (proportional mortality) of lymphedema in the United States remained stable across age groups, ranging between 2 and 3 per 10,000 in the general population. In Veneto, the prevalence was higher in younger patients

below the age of 45 years (5 per 10,000 general population) and then progressively decrease to 2 per 10,000 (Fig. 2).

The estimated prevalence (proportional mortality) of lymphedema increased in the United States and in Veneto over the past two decades. In the United States, the increase was from 1.6 in 1999 to 4.9 per 10,000 in women in

TABLE 1
Number of Deaths and Prevalence of Hereditary Lymphedema or Lymphedema of Unknown Causes by Mention of Selected Diseases in Death Certificates in the United States, 1999-2020

	Women		Men	
	N	Prevalence of lymphedema (x10,000)	N	Prevalence of lymphedema (x10,000)
All deaths for lymphedema (MCOB)	7,604	2.7	4,344	1.5
<i>Deaths with any mention of</i>				
Hypertensive diseases (I10-I15)	2,339	5.4	1,216	3.2
Ischaemic heart diseases (I20-I25)	1,207	2.1	856	1.2
Cerebrovascular diseases (I60-I69)	385	1.2	187	0.8
Venous thrombosis and pulmonary embolism (I80,I82,I26)	615	12.7	343	8.4
COPD (J40-J47)	927	3.0	585	1.9
Diabetes (E10-E14)	1,441	5.5	892	3.2
Obesity (E66)	1,355	41.8	1,002	28.9
Dementia, other organic mental dis (F00-F09)	550	2.0	178	1.2
Skin infections/ulcers (A46, L00-L08, L89, L97, L98.4, R02)	1,136	40.2	722	33.4
Any cancer (C00-C99)	2,242	3.4	1,006	1.4
Breast cancer (C50)	1,019	9.1	-	
Cancer of female genital organs (C51-C59)	437	6.2	-	
Prostate cancer (C61)			248	2.7
Colorectal cancer (C18-C21)	148	2.2	79	1.1
Lung cancer (C34)	124	0.8	98	0.5
Haematological malignancies (C81-C96)	166	2.5	164	2.0

Abbreviations: N = number of deaths; COPD = chronic obstructive pulmonary disease; MCOB = multiple cause of death

2020 and from 0.8 in 1999 to 2.6 per 10,000 in men in 2020 (*Fig. 1, Panel A*). In Veneto, it increased from 1.1 in 2008 to 3.9 per 10,000 in 2020: no sex-specific analysis was performed due to the low number of events in each sex group per year (*Fig. 1, Panel B*). When accounting for the cause- and age-specific mortality rate for lymphedema (*Fig. 3*), this was approximately linear by increasing age. Trends in age- and gender-specific lymphedema mortality rates also increased linear in

United States (*Supplemental Fig. S1*).

We studied the association between lymphedema and other diseases. In the USA the highest prevalence of lymphedema was observed in patients with obesity (41.8 per 10,000 women; 28.9 per 10,000 men), skin infections/ulcers (40.2 per 10,000 women; 33.4 per 10,000 men), concomitant venous thrombosis or pulmonary embolism (12.7 per 10,000 women; 8.4 per 10,000 men), breast cancer (9.1 per 10,000 women) (*Table 1*). In the Veneto

TABLE 2
Number of Deaths and Prevalence of Hereditary Lymphedema or Lymphedema of Unknown Causes by Mention of Selected Diseases in Death Certificates in the Veneto Region (Italy), 2008-2021

	Women		Men	
	<i>N</i>	<i>Prevalence of lymphedema (x10,000)</i>	<i>N</i>	<i>Prevalence of lymphedema (x10,000)</i>
All deaths for lymphedema (MCOB)	107	3.0	34	1.1%
<i>Deaths with any mention of</i>				
Hypertensive diseases (I10-I15)	41	5.5	9	1.8
Ischaemic heart diseases (I20-I25)	11	1.9	4	0.6
Cerebrovascular diseases (I60-I69)	7	1.2	2	0.5
Venous thrombosis/pulmonary embolism (I80,I82,I26)	5	6.6	0	-
COPD (J40-J47)	3	1.5	2	0.7
Diabetes (E10-E14)	14	3.4	7	1.7
Obesity (E66)	25	73.2	6	21.8
Dementia, other organic mental dis (F00-F09)	12	2.3	0	-
Skin infections/ulcers (A46, L00-L08, L89, L97, L98.4, R02)	19	22.0	3	5.8
All cancers (C00-C99)	37	4.0	14	1.2
Breast cancer (C50)	18	8.9	-	
Cancer of female genital organs (C51-C59)	8	9.3	-	
Prostate cancer (C61)	-	-	3	2.6
Colorectal cancer (C18-C21)	1	0.9	2	1.4
Lung cancer (C34)	1	0.8	5	1.8
Haematological malignancies (C81-C96)	3	3.0	2	1.7

Abbreviations: N = number of deaths; COPD = chronic obstructive pulmonary disease; MCOB = multiple cause of death

region, the highest prevalence of lymphedema was observed in obese patients (73.2 per 10,000 women; 21.8 per 10,000 men), skin infections/ulcers (22.0 per 10,000 women; 5.8 per 10,000 men) and breast cancers (8.9 per 10,000 women) (*Table 2*).

The crude relative risks of lymphedema in the presence of the above-mentioned diseases are displayed in *Supplemental Tables 1 and 2*. Due to the higher number of cases, risk estimates were more precise for the United States and showed that additional conditions

were characterized by a higher prevalence of lymphedema, including hypertensive disease, chronic obstructive pulmonary disease, diabetes, prostate, and gynecological cancers. In contrast, the prevalence of lymphedema appeared lower in patients with cerebrovascular diseases, ischemic heart disease, dementia, and lung cancer.

DISCUSSION

Lymphedema is a chronic disease long

recognized and commonly diagnosed in clinical practice. However, there is a lack of epidemiological studies in the current literature, especially concerning lymphedema not related to cancer. Our study provides insights into the prevalence at death (estimated by the proportionate mortality) of lymphedema from more than 340 million people. This data shows that the prevalence of lymphedema has been increasing over the last two decades with marked sex-specific differences, peaking almost 5 per 10,000 general population in women and 3 per 10,000 general population in men. The prevalence of lymphedema was 2- to 20-times in specific subgroups of patients, including those with obesity, skin infections, hypertension, diabetes mellitus, breast/gynecological cancers, and venous thromboembolism. In contrast, patients with cerebrovascular diseases and other types of cancers (i.e., lung cancer) had a lower prevalence of lymphedema. This study provides first large-scale estimate on the disease-specific prevalence and poses a solid basis for further research in this field.

One of the primary factors contributing to the increasing prevalence of lymphedema is the growing number of cancer survivors over the last 20 years (9-11). Lymphedema is a common complication of cancer treatment and the most common form of secondary lymphedema in developed countries. Some studies suggest that 25-50% of cancer survivors overall are at risk of developing secondary lymphedema, comprising lymphadenectomy and radiation as the most important predicting variables (12). Breast cancer treatment, including surgery and radiation therapy are significant contributor of breast cancer-related lymphedema (BCRL) in women, as it often involves the removal of axillary lymph nodes and the damage of the lymphatic system (13-16). Several studies suggest an estimated risk of developing BCRL of 14-40% after treatment completion (3,12). As the number of cancer survivors increased over the last two decades, so did the number of individuals at risk for developing lymphedema. This trend is further compounded by an ageing population, as older individuals are more susceptible to lymphedema due to weakened lymphatic

systems and have an increased risk for a new cancer diagnosis (17).

Lymphedema has been associated as a surgical complication of other malignancies: (i) melanoma, with a rate of lower extremity lymphedema ranging from 48.8-82.5% after inguinal lymph node dissection (18,19) and from 4.4-14.6% (18-20) of upper extremity lymphedema after axillary lymph node dissection; (ii) secondary lymphedema after gynecologic malignancy (cervical, endometrial and vulvar), with a rate of lymphedema after lymphadenectomy and/or radiation of approximately 18-42% (3) and (iii) urologic malignancy (penile and prostate), with a rate of lymphedema after lymphadenectomy and/or radiation of approximately 13-30% (3). In our study, we showed that lymphedema-prevalence was lower in patients with malignancies for which lymphadenectomy and/or radiation of specific body areas are uncommon.

Another significant factor contributing to the higher-than-expected prevalence of lymphedema is the pandemic of obesity, particularly in the US (21), as also highlighted in our results (*Tables 1 and 2*). Obesity has been shown to increase the risk of developing lymphedema by causing inflammation and damage to the lymphatic system with more metabolic waste products that need to be cleared from the body, leading to an increased lymphatic fluid production (22). The sedentary lifestyle typical of these patients with exceed weight further exacerbates the risk of lymphedema development. Several studies associated an elevated body mass index (BMI) with an increased risk of developing secondary lymphedema following damage to the lymphatic vasculature (23-25). Helyer et al found a three-time increased risk of developing lymphedema in patients treated for breast cancer and a BMI greater than 30 kg/m² (23). Werner et al demonstrated an incidence of lymphedema of 36% in patients with a BMI greater than 29 kg/m², compared to an incidence of 12% for patients with lower BMI (25).

Other studies suggested that obesity, without any antecedent surgery or injury of the lymphatic vessels, is a risk factor itself for developing lymphedema. In a study conducted

by Kwan et al approximately one-third of the analyzed obese patients had abnormalities of the lymphatic vessels on lymphoscintigraphy (26). As obesity rates continued to rise globally in the last two decades (27,28) and is termed as a pandemic with several health disadvantages (29,30), also the prevalence of lymphedema increased over the last two decades and will probably further increase in the following years.

In accordance with the literature, we demonstrated a strong association between skin infections/ulcers and lymphedema. On the one side, lymphedema can increase the risk of skin infections, such as erysipelas, cellulitis, lymphangitis, lymphadenitis, and acute inflammatory episodes, as the impaired lymphatic drainage, as well as the lymphedema-associated immune compromise, creates an ideal environment for bacterial and fungal growth (31). Dupuy et al showed that lymphedema was the major risk factor for a population of 167 patients hospitalized for cellulitis (32). On the other side recurrent skin infections can cause damage to the lymphatic vessels and therefore increasing itself the risk of lymphedema. Soo et al demonstrated in a cohort of 15 patients with recurrent episodes of leg cellulitis, an abnormality of the lymphatic system, suggesting an association with the infective episodes (33).

The increased use of antibiotics and the aging population has been associated with an increasing trend of skin infections over the last decades and total numbers will probably increase even more. Hersch et al showed that the total visits at health care facilities in the US for skin and soft tissue infections increased by 65% (from 8.6 million to 14.2 million patients) from 1997 to the year 2005 (34). Similarly, Lee and colleagues assessed trends regarding skin infections in the US and found a 40% increase (2.4 million to 3.3 million) in the overall incidence of skin infections (35). Lopez et al estimated an increase of lymphedema admissions from 26,625 to 28,105 during the period 2012-2017 in the US (36).

A higher awareness for this overlooked disease may also play a significant role for the increasing prevalence in both men and women

population, but it is also responsible for the sex-specific differences as lymphedema is often underdiagnosed in men, as men are less likely to seek medical attention for swelling in the limbs, leading to delayed diagnosis and treatment (37).

Other factors that might contribute to sex-specific differences regarding the trend of lymphedema include differences in anatomy, lifestyle factors, and environmental exposures. Women are more likely to develop lymphedema in the upper extremities due to the anatomical structure of the lymphatic system in this region. Lifestyle factors such as smoking and alcohol use also contribute to the development of lymphedema, and the frequency and the impact of these factors differ between men and women. Environmental exposures such as toxins and pollutants may also play a role in the development of lymphedema, and these exposures may also differ between men and women due to differences in occupation, cosmetics and/or hobbies. However, further research is needed to fully understand the role of these factors in the development of lymphedema.

This study has some limitations that should be mentioned: (i) the study analyses are related to ICD-codes of death certificates, which might be affected by either an underestimation or under-coding if the patient was affected by more severe diseases and the certifying physician did not consider that lymphedema significantly contributed to death, or an overestimation in case of swelling for other causes, i.e., obesity, deep vein thrombosis; (ii) all patients were classified having lymphedema not elsewhere classified. Cohort studies have shown that the number of patients with secondary lymphedema is greater than those with primary or hereditary lymphedema. As a result, it is difficult to draw any definite conclusion about this group of patients with lymphedema, and the possibility of misclassification cannot be ruled out; (iii) finally, estimation of disease prevalence in the general population from death certificates has obvious intrinsic limitations, which are primarily related to selective reporting and differences in the patient characteristics.

CONFLICT OF INTEREST AND DISCLOSURE

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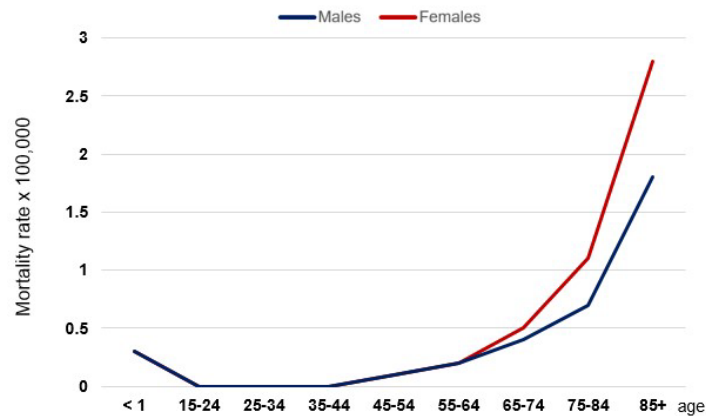


Fig. S1. Age- and sex-specific mortality rates related to lymphedema as multiple cause of death. US, 1999-2020.

TABLE S1
Number of Deaths and Relative Risk for Hereditary Lymphedema or Lymphedema of Unknown Causes by Mention of Selected Diseases in Death Certificates, United States, 1999-2020

	Women		Men	
	N	Relative Risk (95%CI)	N	Relative Risk (95%CI)
All deaths with lymphedema (MCOD)	7,604		4,344	
<i>Deaths with any mention of</i>				
Hypertensive diseases (I10-I15)	2,339	2.5 (2.3; 2.6)	1,216	2.5 (2.3; 2.7)
Ischaemic heart diseases (I20-I25)	1,207	0.7 (0.7; 0.8)	856	0.7 (0.7; 0.8)
Cerebrovascular diseases (I60-I69)	385	0.4 (0.4; 0.5)	187	0.5 (0.4; 0.6)
Venous thrombosis and pulmonary embolism (I80,I82,I26)	615	5.0 (4.6; 5.5)	343	5.9 (5.3; 6.6)
COPD (J40-J47)	927	1.2 (1.1; 1.2)	585	1.3 (1.1; 1.4)
Diabetes (E10-E14)	1,441	2.3 (2.2; 2.4)	892	2.4 (2.2; 2.5)
Obesity (E66)	1,355	18.7 (17.6; 19.8)	1,002	24.3 (22.7; 26.1)
Dementia, other organic mental dis (F00-F09)	550	0.7 (0.7; 0.8)	178	0.8 (0.6; 0.9)
Skin infections/ulcers (A46, L00-L08, L89, L97, L98.4, R02)	1,136	17.4 (16.4; 18.6)	722	26.1 (24.1; 28.2)
Any cancer (C00-C99)	2,242	1.4 (1.3; 1.4)	1,006	0.9 (0.8; 0.9)
Breast cancer (C50)	1,019	3.8 (3.5; 4.0)	-	
Cancer of female genital organs (C51-C59)	437	2.4 (2.2; 2.6)	-	
Prostate cancer (C61)	-	-	248	1.8 (1.6; 2.1)
Colorectal cancer (C18-C21)	148	0.8 (0.7; 1.0)	79	0.7 (0.6; 0.9)
Lung cancer (C34)	124	0.3 (0.2; 0.3)	98	0.3 (0.2; 0.4)
Haematological malignancies (C81-C96)	166	0.9 (0.8; 1.1)	164	1.3 (1.1; 1.5)

Abbreviations: N = number of deaths; COPD = chronic obstructive pulmonary disease; MCOB = multiple cause of death

TABLE S2
Number of Deaths and Relative Risk for Hereditary Lymphedema or
Lymphedema of Unknown Causes by Mention of Selected Diseases in
Death Certificates, Veneto Region (Italy), 2008-2021

	Women		Men	
	<i>N</i>	<i>Relative Risk (95%CI)</i>	<i>N</i>	<i>Relative Risk (95%CI)</i>
All deaths with lymphedema (MCOD)	107		34	
<i>Deaths with any mention of</i>				
Hypertensive diseases (I10-I15)	41	2.3 (1.6; 3.4)	9	1.9 (0.9; 4.0)
Ischaemic heart diseases (I20-I25)	11	0.6 (0.3; 1.1)	4	0.5 (0.2; 1.4)
Cerebrovascular diseases (I60-I69)	7	0.3 (0.2; 0.8)	2	0.4 (0.1; 1.8)
Venous thrombosis and pulmonary embolism (I80,I82,I26)	5	2.2 (0.9; 5.4)	0	
COPD (J40-J47)	3	0.5 (0.2; 1.5)	2	0.7 (0.2; 2.8)
Diabetes (E10-E14)	14	1.1 (0.6; 2.0)	7	1.8 (0.8; 4.1)
Obesity (E66)	25	31.0 (19.8; 48.5)	6	24.4 (10.1; 59.0)
Dementia, other organic mental dis (F00-F09)	12	0.7 (0.4; 1.3)	0	
Skin infections/ulcers (A46, L00-L08, L89, L97, L98.4, R02)	19	8.5 (5.2; 14.0)	3	5.9 (1.8; 19.2)
All cancers (C00-C99)	37	1.5 (1.0; 2.2)	14	1.3 (0.6; 2.5)
Breast cancer (C50)	18	3.3 (2.0; 5.5)		
Cancer of female genital organs (C51-C59)	8	3.2 (1.6; 6.6)		
Prostate cancer (C61)			3	2.5 (0.8; 8.2)
Colorectal cancer (C18-C21)	1	0.3 (0.0; 2.0)	2	1.3 (0.3; 5.5)
Lung cancer (C34)	1	0.3 (0.0; 1.9)	5	1.8 (0.7; 4.6)
Haematological malignancies (C81-C96)	3	1.0 (0.3; 3.1)	2	1.6 (0.4; 6.9)