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Cellulitis in chronic oedema of the lower leg: an international cross-sectional study

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What is already known on this topic?
• Chronic edema has many different causes, and is a frequent but neglected health care problem. • The association between chronic oedema and cellulitis is known, but few studies have clinically evaluated the size of the problem, and risk factors.

- Guidelines suggests that control of oedema is important to reduce the risk of recurrent cellulitis, but the evidence is limited.

What does this study add?

- Cellulitis in chronic leg oedema is common in all countries and types of health facilities.
- Wounds, obesity, midline swelling, male sex, and diabetes were independently associated to a recent episode of cellulitis (within the last 12 months). Severe stages of oedema were associated to cellulitis, while controlled swelling was associated with a reduced risk.
- Measures to improve the control of swelling may have a major effect on the incidence of cellulitis, being potentially preventable.

Summary

Background

Cellulitis and chronic oedema are common conditions with considerable morbidity. The number of studies designed to assess the epidemiology of cellulitis in chronic oedema are scarce.

Objectives

To investigate the prevalence and risk factors of cellulitis in chronic leg oedema, including lymphoedema.

Methods

A cross-sectional study, including 40 sites in nine countries, 2014–2017. Adults with clinically proven unilateral or bilateral chronic oedema (oedema >3 months) of the lower leg were included. The main outcome measures were frequency and risk factors for cellulitis within the last 12 months.

Results

Out of 7477 patients, 15·78% had cellulitis within the last 12 months, with a life-time prevalence of 37·47%. The following risk factors for cellulitis were identified by multivariable analysis: wounds [odds ratio (OR) 2·37, 95% confidence interval (CI) 2·03–2·78], morbid obesity (OR 1·51, CI 95% 1·27–1·80), obesity (OR 1·21, CI 95% 1·03–1·41), midline swelling (OR 1·32, CI 95% 1·04–1·66), male sex (OR 1·32, CI 95% 1·15–1·52) and diabetes (OR 1·27, CI 95% 1·08–1·49). Controlled swelling was associated with a reduced risk (OR 0·59, CI 95% 0·51–0·67). In a subgroup analysis, the risk increased with the stage of oedema [International Society of Lymphology (ISL), stage II OR 2·04, CI 95% 1·23–3·38, and stage III OR 4·88, CI 95% 2·77–8·56].

Conclusions

Cellulitis in chronic leg oedema is a global problem. Several risk factors for cellulitis were identified, of which some are potentially preventable. Our findings suggest that oedema control, is one of these. We also identified that advanced stages of oedema, with hard/fibrotic tissue, might be an important clinical indicator to identify patients at particular risk.

Introduction

Cellulitis is a common bacterial infection of the dermis and subcutaneous tissue,[1] and can occur in any body site, lower limbs being affected in 70-80% of cases.[2] It is a common medical emergency, often leading to hospitalization, long-term morbidity and recurrent disease.[1] In 2018-19 cellulitis accounted for 1·4% of all emergency admissions in the UK,[3] and it has been reported that it is one of the leading causes of potentially preventable hospitalizations.[4]

Chronic oedema is also frequent, with an estimated prevalence of 38% in European hospitals,[5] and 57% of patients cared for by community nurses in the UK.[6] Yet, it is a neglected health care disease.[7] Chronic oedema is defined as oedema present for more than three months.[8] Traditionally the term lymphoedema has been used for oedema resulting from a failure of the lymphatics, e.g. due to congenital malformation, cancer, injury or filariasis. However, recent research indicates the substantial role of the lymphatics in all chronic edema, leading to the introduction of this umbrella term. Chronic oedema is often multifactorial and covers a wide range of pathologies including, lymphoedema (primary and secondary) but also swelling due to venous insufficiency, immobility and obesity.[7]

A recent meta-analysis identified lymphoedema/chronic leg oedema as an independent risk factor for cellulitis (OR 6·77, CI 95% 3·46–13·27).[9] One of the reasons that the risk of cellulitis may be increased, is due to the important role of the lymphatics in immunity.[10, 11] Although both diseases are common, few studies have been designed to clinically examine the epidemiology of cellulitis in patients with chronic oedema. The objective of this study was to investigate the association of potential risk factors with the presence of cellulitis in patients with chronic leg oedema. The identification of preventable or modifiable risk factors could improve patient outcomes.

Patients and methods

Study design

This is an international, multicentre, cross-sectional study, performed as part of LIMPRINT*, an epidemiology study designed to prospectively determine the impact and prevalence of chronic oedema within health services. Forty sites from nine countries participated between June 2014 and August 2017. Both hospital (in- and outpatients) and community cases were included.

Ethical approval

Each country and study centre gained the appropriate approvals from the Ethical Review Committee and other research and service development committees.

Main outcome of interest

The presence of cellulitis (yes/no) in the sites affected by chronic leg oedema within the last 12 months, and its relation to potential risk factors.

* Lymphoedema IMpact and PRevalence- INTernational Lymphoedema Framework

Definitions

Chronic oedema: Defined as oedema, which had been present for more than three months and affected one or more areas of the body†.[8] Oedema was confirmed using the validated "Pitting Oedema Test" and Stemmer's sign‡ (patients with longstanding chronic non-pitting oedema with fibrosis were also included).[12] The duration was determined from medical records and through the patient or care giver. The severity was judged by palpation and clinical evaluation of the skin, using the ISL-staging (International Society of Lymphology)[13], originally developed for lymphoedema:

- Stage I: Early onset, with an accumulation of tissue oedema that decreases with limb elevation. The oedema may be pitting.
- Stage II: Limb elevation alone rarely reduces swelling and pitting is manifested.
- Stage III: The tissue is fibrotic (hard) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.

Cellulitis: Defined as an acute onset of soft-tissue erythema, warmth, and tenderness that rapidly resolved with antibiotics, most often caused by *Streptococcus pyogenes,* and/or *Staphylococcus aureus* (to a lesser extent). Erysipelas is a similar infection, but typically affects the more superficial part of the skin compared to cellulitis. The terms are often used interchangeably,[1] and are considered as one clinical issue in this manuscript. The current presence or a history of cellulitis were confirmed by a combination of physical examination, interview with the patient and/or review of the medical records by teams of clinicians which all included experts in lymphology.

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† Limbs, hands/feet, upper body (breast/chest wall, shoulder, back), lower body (buttocks, abdomen), genital (scrotum, penis, vulva), head, neck, or face.

‡ ‡ A positive Stemmer's sign: A skin fold cannot be pinched at the base of the second toe, and is diagnostic of lymphoedema.

Study population

Adults >18 years of age, with clinically proven unilateral or bilateral chronic leg oedema (regardless of the underlying cause), and able to understand the study and give informed consent according to ethical standard. Cases were excluded if unwilling or unable to participate, receiving end of life care or if judged as not in the patient's best interest.

Data collection

The methods has previously been published.[14] In brief, a standardized core tool was used in all participants, developed by an international expert panel and included both a questionnaire and a physical examination. An expert review deemed the tool as highly accurate.[14] Data were collected by trained health care professionals. Lymphoedema specialists confirmed the underlying chronic oedema classification, and the diagnosis of cellulitis. An additional tool was used in some centres with the appropriate expertise of undertaking the staging procedure (ISL). All sites followed the international study protocol and complied with standard operating procedures. In nine lymphoedema specialist centres, data using the LIMPRINT core tool were obtained from clinical records of all patients.[15]

Variables

There are no internationally agreed definitions on the outcome on chronic oedema management. In this study "control of swelling" was a subjective judgment by the investigator based on the clinical observation of the limb, clarified with the caregiver and if necessary with the lead physician within each service.[16] It was assessed as either present, absent or "don't know", at the time point of clinical assessment. The type (or absence) of treatment was noted including skin care, exercise, manual lymph drainage, types of compression, antibiotics, psychological support, and surgical treatments. Data included demography and relevant comorbidities. Body Mass Index (BMI) was estimated according to WHO categories as either underweight (BMI<20), normal weight (BMI 20-30), obese (BMI 30-40) or morbidly obese (BMI>40). Site of chronic oedema was collected using a body map where the upper and lower extremities, trunk including genitals (collectively termed midline swelling), face and neck were recorded. The oedema was further classified as either primary (congenital) or secondary (acquired), and whether related to cancer or not. Cancer related oedema was either classified as caused by treatment and/or due to metastatic disease. Non-cancer oedema was classified as due to clinically assessed venous disease (including confirmation by ultrasound), obesity, immobility, lymphatic filariasis and/or "other". Duration of oedema and leg mobility was documented. Wounds defined as "loss of intact skin" was made through clinical examination (wound classification will be published elsewhere). In selected centres, the severity of oedema was also assessed, ISL-staging tool.

Statistics

Statistical analyses were performed in Stata 12 (Statacorp, Texas). Due to the explorative study design, a formal sample size determination was not performed. A sample of over 5000 patients was expected to reveal the major factors associated with cellulitis. The principal analysis examined the binary outcome (history versus no history of cellulitis within the previous 12 months). Factors tested for an association with the outcome were broadly demographics, medical history and leg- and swelling characteristics. These variables were chosen as they were believed to be potentially associated to the outcome, and could be reliably collected in an international study like this. Principal analysis used logistic regression. Univariate comparisons were followed by a multivariable model, using a stepwise elimination until all factors remaining had an alpha of <0·05. Results were presented as OR and 95% confidence intervals. A similar analysis examined the severity of chronic oedema in a subgroup of 996 patients. Missing data were not imputed and therefore remained missing.

Results

Characteristics of countries, sites and patients

Of the 10,203 participants with chronic oedema, 7722 (75·68%) were identified with leg oedema and were included. In total 40 sites from nine countries participated, including Australia, Canada, Denmark, France, Ireland, Italy, Japan, Turkey and United Kingdom, table 1. These included specialist lymphoedema services (73·4%), out-patient acute hospitals (9·0%), hospitalized cases (8·6%), community nursing (1·2%), elderly care residential homes (0·3%), nursing homes (0·1%), and other (7·3%). Of the total, 7477 (96·8%) patients had information on the presence of a recent (<12 months) history of cellulitis. 61·87% of the cohort (with or without cellulitis) had well-controlled chronic oedema. Patient characteristics are presented in table 2.

[Table 1]

[Table 2]

Frequency of cellulitis

The number with chronic oedema of the lower leg experiencing at least one episode of cellulitis during their lifetime was 37·47%. In total, 15·78% (n=1180) had a history of cellulitis within the last 12 months of which 368 (31·2%) were hospitalized. Frequency of recent cellulitis ranged from 13·94% in the UK to 38·24% in Canada, table 1. The difference is likely explained by the type of facility.

In those assessed for the severity of the chronic oedema (n=966) the frequency of a recent history of cellulitis increased with the stage, affecting 9·70% with ISL stage I, 18·40% in stage II and 41·67% in stage III.

General risk factors

On univariate analysis statistically significant associations were found between recent cellulitis and diabetes (OR 1·56), male sex (OR 1·47), morbid obesity (OR 1·56), obesity (OR 1·19), chair bound patients (OR 1·39), peripheral arterial disease (OR 1·37) and heart failure/ischemic heart disease (OR 1·25). Age was weakly associated (P=0·12), table 3.

Local risk factors

On univariate analysis, wounds were identified as a statistically significant risk factor (OR 2·75). Secondary lymphoedema was associated with cellulitis when compared with primary lymphoedema (OR 1·25), but the risk was not related to whether the oedema was caused by cancer or its treatment or a non-cancer cause. Of the other factors only venous disease (OR 1·21) showed a positive association, and concomitant midline swelling (OR 1·30). Control of swelling was associated with a significantly lower risk (OR 0·51), table 3.

Independent risk factors

Factors remaining after multivariable analysis (logistic regression) were wounds (OR 2·37), morbid obesity (OR 1·51), obesity (OR 1·21), midline swelling (OR 1·32), male sex (OR 1·32) and diabetes (OR 1·27). Patients with controlled swelling had a markedly lower risk of cellulitis, OR 0·59 (CI 95% 0·51–0·67, P<0·001), table 4.

[Table 3-4]

Severity of oedema

Severity of oedema (n=966, table 5) was significantly associated with cellulitis: ISL stage II OR 2·10 and stage III OR 6·65 compared to stage I, by univariate analysis. An increased risk was also seen in hard (fibrotic) tissue vs. soft tissue (OR 2·85), and with a positive Stemmer's sign (OR 2·23). Even after adjustment for sex, obesity, diabetes, wounds, controlled swelling and midline swelling (n=889, table 5) ISL stage II yielded an OR 2·04, and stage III OR 4·88, by multivariable analysis.

[Table 5]

Discussion

This large study confirms that cellulitis is common in patients with chronic leg oedema. 15·78% of the patients experienced at least one episode of cellulitis within 12 months, with a life-time prevalence of 37·47%. The methodology adopted with a physical examination, access to lymphoedema experts, use of international definitions and standard operating procedures, strengthens the validity of our data. The life-time prevalence is higher than previously reported (7·95-35·7%) with direct comparison challenging due to methodological differences.[17-19]

Wounds, obesity, male sex, diabetes, midline swelling and, particularly, advanced stages of chronic oedema were independent risk factors for cellulitis, while control of swelling, was associated with a lower risk. Although risk factors in cellulitis have been studied in a meta-analysis (identifying previous cellulitis, concurrent wounds, leg ulcers, excoriating skin diseases, tinea pedis, obesity and lymphoedema/chronic oedema as risk factors),[9] only one single-centre study has been specifically designed in patients with chronic oedema/lymphoedema.[20] Independent risk factors were percentage difference of circumference of the limb, "food induced complications experiences", systolic blood pressure and primary lymphoedema. In contrast, we found that secondary lymphoedema was associated with cellulitis on univariate analysis, but it was not an independent risk factor.

Our most important findings were that control of swelling was associated with a significantly lower risk of cellulitis (OR 0·59) while advanced stages of chronic oedema were strong risk factors (ISL stage II; OR 2·04 and stage III; OR 4·88), indicating that cellulitis is preventable. Measures to control the swelling and halt the progression into advanced stages, e.g. with appropriate compression garment, should be mandatory.

Chronic oedema management is already widely recognized as an adjuvant to antibiotic prophylaxis for recurrent cellulitis.[21, 22] An RCT (n=84) in compression therapy significantly lowered the incidence of recurrence of cellulitis compared to conservative treatment, with a relative risk of 0·37 in favor of compression.[23] However, in our cohort only 48·2% of those with recent cellulitis had proper oedema control, highlighting the need to focus on this issue. A reduced incidence of cellulitis by implementation of compression therapy has been reported to decrease health care costs almost three fold over a 1-year period, mainly explained by a reduction of acute care costs.[24] Mechanisms of compression include reduced capillary filtration, increased lymphatic drainage, and a downregulation of pro-inflammatory cytokines. Warty skin, venous eczema, and occasionally fibrosis (especially seen in ISL stage III), can be reversed.[25, 26] These conditions are reservoirs or entry points for microbes.

It is hypothesized that the risk of cellulitis is increased due to a local immune deficiency, with an ineffective transport of antigens to the lymph node. Lymph stasis may also facilitate bacterial growth and impede bacterial and toxin clearance.[27] Cellulitis also seem to impair the lymphatics. A single MRSA infection has been shown to inhibit lymphatic vessel contraction and flow long after infection clearance.[27] As oedema predisposes to cellulitis and cellulitis can impair the lymphatics, potential prophylactic interventions should target all steps in this vicious cycle.[11]

As expected, wounds were associated with cellulitis, as was obesity. Increased fat deposition in primary lymphoid organs, leading to alterations of the leucocyte population might play a part.[28] Furthermore, decreased lymphatic transport, fewer lymphatic vessels, and changed architecture and smaller lymph nodes have been observed in obese mice.[29] We also found that males were 30% more likely to experience cellulitis than females, which has not been reported.[9] Male predominance may be due to behavioral and biological factors[30] with less efficient antigen presentation, lower phagocytic activity and lower antibody production.[31]

Diabetes as a risk factor for cellulitis could not be confirmed in the previously mentioned meta-analysis,[9] perhaps due to a too small sample size. However, our results are supported by a big matched cohort study (type I diabetes OR 2·84, CI 95% 2·48-3·25, and type II OR 2·03, CI 95% 1·97-2·08).[32] An abnormal neutrophil function and T-lymphocyte responses might come into play.[32] Proper foot care to prevent cellulitis is mandatory for all diabetics.

Being chair bound was also a risk factor, which might be explained by the increased hydrostatic pressure and lack of usage of the calf muscles, worsening the oedema. However, this association disappeared when correcting for other factors.

Limitations to our study needs to be noted. Cellulitis is known for being easily misdiagnosed; up to 30·7% of cases.[33] Observer bias was minimized by usage of international definitions of cellulitis, standard operating procedures, and training.[14] Recall bias was minimized by seeking information from the medical records.

Although recruitment was made from hospitals and community facilities, the majority of the patients were included from hospitals, potentially skewing our data towards more severe cases. Also, patients from developing countries were not included.

The assessment of "control of swelling" was open to personal interpretation. However, data were excluded where the decision was uncertain (n=465) and access to lymphoedema teams assisted in increasing the accuracy of the decisions.

The lack of correction for prophylactic antibiotics might also influence our data. Although antibiotic usage was recorded [in 194 (3·09%) with no cellulitis vs. 254 (21·64%) with cellulitis], this did not specify its use in prophylaxis. Lastly, one should keep in mind, that a cross-sectional study is limited to an assessment at only one time-point, indicating association but not causation.

In conclusion, our findings confirm that cellulitis in chronic leg oedema is a global problem. Although guidelines support the usage of oedema control to prevent cellulitis (e.g. with compression therapy), a substantial number of those recruited had uncontrolled swelling. This study adds epidemiological evidence of what has been known anecdotally for a long time: That oedema control is associated with a lower risk of cellulitis. Wounds, warty skin and eczema, as often seen in advanced stages of oedema, are potential entry points and/or reservoirs for microbes, and can be prevented and treated by compression therapy. Prevention

of deterioration of the oedema may have a significant effect on reducing the risk of cellulitis, and thereby reducing health care costs.

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Tables and figures

Table 1. Demographics of patients with chronic leg oedema (n=7477).	
Characteristic(s)	**Number of patients (%)**
Age, mean	65·05 (sd=16·36)
Missing	2
Female	5265 (70·42)
Missing	0
Weight	
Underweight	164 (2·20)
Normal weight	3120 (41·79)
Obesity	2631 (35·24)
Morbidly obesity	1551 (20·77)
Missing	11
Concomitant disease	
Diabetes	1379 (18·22)
Missing	0
Heart failure/ ischemic heart disease	1184 (15·65)
Missing	0
Facility	
Hospital based cases	7018 (93·86)
Community cases	125 (1·67)
Other	334 (4·47)
Missing	0
Classification of chronic oedema	

Primary	1396 (18·83)
Secondary	6016 (81·17)
Missing	65
Related to cancer or its treatment	1057 (17·63)
Non-cancer	4937 (82·37)
Missing	22
Venous disease	2421 (49·12)
Immobility	1847 (37·47)
Obesity	1478 (29·99)
Filariasis	8 (0·22)
Unilateral leg oedema	1861 (24·89)
Bilateral leg oedema	5616 (75·11)
Missing	0
ISL scale*	
I	237 (24·53)
II	549 (56·83)
III	180 (18·63)
Missing	0
Duration of leg oedema	
<1 year	833 (11·16)
1-2 years	739 (9·90)
2-5 years	1561 (20·91)
>5 – 10 years	1685 (22·57)
>10 years	2648 (35·47)
Missing	11
Mobility	

Normal	4203 (56·28)
Walking aid	2466 (33·02)
Chair bound	691 (9·25)
Bedbound	108 (1·45)
Missing	9
Concurrent swelling	
Upper limb	360 (4·81)
Missing	0
Midline	586 (7·84)
Missing	0
Presence of a leg wound	1129 (15·13)
Missing	0
Treatment with compression therapy	
Compression garment	5101 (68·41%)
Multilayer bandage	1888 (25·32)
Compression wrap	668 (8·96)
At least one of the above	5804 (77·83)
No compression	1653 (22·17)
Missing	20
Good control of swelling	4314 (61·87)
Missing	504
Antibiotics	448 (6·01)
Missing	20
Hospitalized cases due to cellulitis within the last 12 months	368 (4·95)
Missing	47

*ISL scale = International Society of Lymphology scale (assessment of severity of chronic oedema/lymphoedema). This was only performed in some centres with the appropriate expertise of undertaking the staging procedure, therefore missing data is regarded as = 0. ISL stage I: Early onset of the condition, with an accumulation of tissue oedema that decreases with limb elevation. The oedema may be pitting at this stage. ISL stage II:

Limb elevation alone rarely reduces swelling and pitting is manifested. ISL stage III: The tissue is fibrotic and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.

Table 2. History of lower leg cellulitis (<12 months) in patients with chronic oedema by country.

Country	Total number of patients with chronic oedema	History of cellulitis (<12 months)	Percentage
United Kingdom	4714	657	13·94
France	347	49	14·12
Japan	82	14	17·07
Denmark	859	149	17·35
Turkey	216	43	19·91
Italy	1065	211	19·81
Australia	108	26	24·07
Ireland	18	5	27·78
Canada	68	26	38·24
Total	7477	**1180**	**15·78**

Table 3. Explanatory variables for cellulitis in patients with chronic oedema of the lower leg, by univariate analysis (n=7477).

Risk factor	No cellulitis N (%)	Cellulitis N (%)	OR 95% CI	P-value
Sex				
Female	4517 (71·73)	748 (63·39)	1·00	
Male	1780 (28·27)	432 (36·61)	1·47 (1·29–1·66)	<0·001
Age				
<45 years	794 (12·61)	140 (11·87)	1·00	
45-64 years	1945 (30·89)	394 (33·42)	1·15 (0·93–1·42)	
65-74 years	1474 (23·41)	289 (24·51)	1·11 (0·89–1·38)	0·12
75-84 years	1389 (22·06)	251 (21·29)	1·02 (0·82–1·28)	
85+ years	694 (11·02)	105 (8·91)	0·86 (0·65–1·13)	
Obesity				
Normal weight	2694 (42·85)	426 (36·13)	1·00	
Under weight	136 (2·16)	28 (2·37)	1·30 (0·86–1·98)	
Obese	2213 (35·20)	418 (35·45)	1·19 (1·03–1·38)	
Morbidly Obese	1244 (19·79)	307 (26·04)	1·56 (1·33–1·83)	<0·001
Leg mobility				
Walks unaided	3570 (56·77)	633 (53·64)	1·00	
Walks with aid	2068 (32·89)	398 (33·73)	1·09 (0·95–1·24)	
Chair bound	554 (8·81)	137 (11·61)	1·39 (1·14–1·71)	0·007
Bedbound	96 (1·53)	12 (1·02)	0·70 (0·38–1·29)	
Diabetes				
Absent	5208 (82·71)	890 (75·42)	1·00	

Present	1089 (17·29)	290 (24·58)	1·56 (1·34–1·81)	<0·001
Heart failure/ ischemic heart disease				
Absent	5332 (84·68)	963 (81·61)	1·00	
Present	965 (15·32)	217 (18·39)	1·25 (1·06–1·46)	0·008
Neurological disease				
Absent	5729 (91·17)	1067 (90·81)	1·00	
Present	555 (8·83)	108 (9·19)	1·04 (0·84–1·30)	0·69
Peripheral arterial disease				
Absent	6088 (96·68)	1127 (95·51)	1·00	
Present	209 (3·32)	53 (4·49)	1·37 (1·01–1·86)	0·044
Swelling duration n=7466				
<1 year	654 (10·88)	149 (12·64)	1·00	
1-2 years	645 (10·26)	94 (7·97)	0·67 (0·51–0·88)	
2-5 years	1337 (21·27)	224 (19·00)	0·77 (0·61–0·96)	0·015
5-10 years	1399 (22·25)	286 (24·26)	0·94 (0·75–1·17)	
>10 years	2222 (35·34)	426 (36·13)	0·88 (0·72–1·08)	
Classification n=7412				
Primary	1208 (19·35)	188 (16·07)	1·00	
Secondary	5034 (80·65)	982 (83·93)	1·25 (1·06–1·48)	0·008
Secondary cause n=5994				
Cancer	897 (17·89)	160 (16·34)	1·00	
Non-cancer	4118 (82·11)	819 (83·66)	1·11 (0·93–1·34)	0·25
Cancer cause n=1053				
Cancer treatment				
Absent	125 (13·98)	13 (8·18)	1·00	

Present	769 (86·02)	146 (91·82)	1·83 (1·00–3·32)	0·046
Cancer metastatic				
Absent	789 (88·26)	149 (93·71)	1·00	
Present	105 (11·74)	10 (6·29)	0·50 (0·26–0·99)	0·042
Non-cancer n=4929				
Venous				
Absent	2125 (51·67)	383 (46·94)	1·00	
Present	1988 (48·33)	433 (53·06)	1·21 (1·04–1·40)	0·014
Immobility				
Absent	2585 (62·85)	497 (60·91)	1·00	
Present	1528 (37·15)	319 (39·09)	1·09 (0·93–1·27)	0·30
Obesity				
Absent	2952 (71·77)	499 (61·15)	1·00	
Present	1161 (28·23)	317 (38·85)	1·62 (1·38–1·89)	<0·001
Concomitant arm swelling				
Absent	5990 (95·12)	1127 (95·51)	1·00	
Present	307 (4·88)	53 (4·49)	0·92 (0·68–1·24)	0·57
Concomitant midline swelling				
Absent	5824 (92·49)	1067 (90·42)	1·00	
Present	473 (7·51)	113 (9·58)	1·30 (1·05–1·62)	0·015
Leg wound				
Absent	5490 (87·36)	841 (71·51)	1·00	
Present	794 (12·64)	335 (28·49)	2·75 (2·38–3·19)	<0·001
Control of swelling n=6973				
Not controlled	2082 (35·54)	577 (51·80)	1·00	

Controlled	3777 (64·46)	537 (48·20)	0·51 (0·45–0·58)	<0·001

Table 4. Logistic regression analysis: Independent risk factors associated with cellulitis of the lower leg in patients with chronic oedema (n=6947).

	OR 95% CI	P-value
Sex		
Female	1·00	
Male	1·32 (1·15–1·52)	<0·001
Weight		
Normal weight	1·00	
Under weight	1·17 (0·78–1·82)	<0·001
Obese	1·21 (1·03–1·41)	
Morbidly obese	1·51 (1·27–1·80)	
Diabetes		
Absent	1·00	
Present	1·27 (1·08–1·49)	0·003
Wound		
Absent	1·00	
Present	2·37 (2·03–2·78)	<0·001
Midline swelling		
Absent	1·00	
Present	1·32 (1·04–1·66)	0·020
Control of oedema		
Not controlled	1.00	
Controlled	0·59 (0·51–0·67)	<0·001

Table 5. Explanatory variables for cellulitis related to the severity of chronic leg oedema, a sub-group analysis (n=966).

	No cellulitis N (%)	Cellulitis N (%)	OR 95%CI	P-value
Pitting				
Non pitting	215 (28·0)	62 (31·2)	1·00	0·39
pitting	552 (72·0)	137 (68·8)	0·86 (0·61–1·21)	
Tissue quality				
Soft	576 (75·0)	102 (51·3)	1·00	<0·001
Hard (fibrotic)	192 (25·0)	97 (48·7)	2·85 (2·07–3·93)	
Stemmer's sign				
Negative	315 (42·0)	47 (24·5)	1·00	<0·001
Positive	435 (58·0)	145 (85·5)	2·23 (1·56–3·20)	
ISL scale*				
Stage I	214 (27·9)	23 (11·6)	1·00	<0·001
Stage II	448 (58·4)	101 (50·8)	2·10 (1·30–3·39)	
Stage III	105 (13·7)	75 (37·7)	6·65 (3·94–11·20)	
ISL scale* after adjustment for gender, obesity, diabetes, wound, control and midline swelling by logistic regression (n=889)				
Stage I			1·00	<0·001
Stage II			2·04 (1·23–3·38)	
Stage III			4·88 (2·77–8·56)	

*ISL scale = International Society of Lymphology scale (assessment of severity of chronic oedema/lymphoedema). ISL stage I: Early onset of the condition, with an accumulation of tissue oedema that decreases with limb elevation. The oedema may be pitting at this stage. ISL stage II: Limb elevation alone rarely reduces swelling and pitting is manifested. ISL stage III: The tissue is fibrotic and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.

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