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1 **Cellulitis risk factors for patients with primary or secondary lymphedema**

2

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5

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13

14 **Table of Contents Summary**

15 Cellulitis occurred in almost 40% of 1,846 patients with primary or secondary lymphedema of
16 the upper or lower limb. Different risk factors for cellulitis were identified for primary and
17 secondary lymphedema. Knowing cellulitis risk factors for the different lymphedema forms
18 would help prevent this frequent complication, and enable practitioners to provide specific
19 advice and adapt management.

20

21

1 **Article Highlights**

2 **Type of Research:** Single-center cross-sectional study

3 **Key Findings:** Based on 1,846 patients, different risk factors were identified according to the
4 lymphedema form (primary or secondary, upper or lower limb). Awareness of those factors helps
5 physicians recognize lymphedema promptly and refer patients to specialized centers to optimize
6 management.

7 **Take home Message:** Awareness of risk factors for cellulitis in the different forms of
8 lymphedema may contribute to preventing this frequent complication, and enable practitioners to
9 provide specific advice and adapt management.

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12

1 **ABSTRACT**

2 **Background:** Limb lymphedema is a chronic disease with primary and secondary forms, the
3 latter essentially after cancer treatment.

4 **Objectives:** To analyze retrospectively cellulitis frequency and its associated risk factors in
5 patients with primary or secondary limb lymphedema.

6 **Methods:** Information from all 1,991 patients referred to a specialized lymphedema center, from
7 January to June 2018, was collected: previous cellulitis episode(s), clinical and lymphedema
8 characteristics.

9 **Results:** Among the 1,846 patients whose information could be analyzed, 695 (37.6%)
10 developed one or more cellulitis episodes and 23.3% had recurrent cellulitis. Cellulitis occurred
11 in 39.5%, 30.5% or 38.6% ($P = .02$) of the patients with secondary upper limb, secondary lower
12 limb or primary lower limb lymphedema, respectively; lymphedema had been present 106.5, 97
13 or 243.1 months. Lymphedema-onset-to-first-consultation (in our specialized center) interval,
14 age at lymphedema onset and radiotherapy were independently associated with cellulitis but not
15 axillary lymph-node excision, chemotherapy or lymphedema involvement. Lymphedema-onset-
16 to-first-consultation interval and lymph-node excision were associated with cellulitis, while body
17 mass index (BMI) or age at lymphedema onset for secondary lower limb lymphedema were not.
18 For primary lower limb lymphedema, male sex, BMI and age at lymphedema onset were
19 associated with cellulitis.

20 **Conclusion:** Different risk factors for cellulitis were identified for patients with lymphedema at
21 risk. Awareness of those factors is important for physicians to recognize lymphedema promptly
22 and refer patients to specialized centers to optimize management.

23 **Keywords:** Cellulitis; Frequency; Risk factors

24

1 INTRODUCTION

2 Lymphedema is a chronic, debilitating disorder responsible for enlargement of one or more
3 limbs. Lymphedema is divided into primary and secondary forms, the latter essentially after
4 cancer treatment. After breast cancer treatment including axillary lymph-node dissection,
5 lymphedema occurs in almost one out of five women and 5.6% after sentinel lymph-node
6 biopsy.¹ The main risk factors for developing upper limb lymphedema have been identified:
7 axillary lymph-node dissection, radiotherapy, obesity [body mass index (BMI) >30 kg/m²],
8 mastectomy and taxane chemotherapy.² For lower limb lymphedema, in industrialized countries,
9 pelvic cancer (cervical, ovarian, uterine, prostatic) and melanoma are the main causes. Lymph-
10 node excision combined with radiotherapy (external, brachytherapy) represents the main risk
11 factor for lymphedema after cancer treatment.³

12 Primary lymphedema reflects a constitutional lymphatic system defect. It mainly affects
13 young people, especially women, and is divided into non-syndromic forms: most frequently
14 isolated lymphedema (including familial forms (ie, Milroy disease, related to vascular
15 endothelial growth factor-receptor-3 (*VEGFR3*)-gene mutation) and syndromic forms, in which
16 lymphedema is a clinical sign of a more complex syndrome, sometimes with a genetic origin,
17 like Turner's syndrome.^{4,5} Primary lymphedema predominantly involves lower limb(s) and, very
18 rarely, upper limb(s), genitals or the face.

19 For our team, cellulitis (erysipelas), caused by β -hemolytic streptococcus, is an acute
20 dermohypodermatitis, ie, non-necrotizing cellulitis. Lymphedema is the most important risk factor
21 for developing cellulitis.^{6,7} Indeed, Dupuy et al⁶ found lymphedema to be the strongest
22 associated cellulitis risk factor (odds ratio (OR), 71.2), even preceding a break in the cutaneous
23 barrier (leg ulcer, wound, fissurated toe-web intertrigo, pressure ulcer, leg dermatosis; OR, 23.8),

1 chronic venous insufficiency (OR, 2.9), leg edema (OR, 2.5) or overweight (BMI ≥ 25 and < 30
2 kg/m²) (OR, 2.0). No data are available about cellulitis in the different lymphedema forms.

3 The aim of our study was to determine cellulitis frequencies in patients with upper and/or
4 lower limb primary or secondary lymphedema and to analyze the associated risk factors for
5 cellulitis in each patient subgroup.

6

7 **METHODS**

8 **Patients and methods.** From January to June 2018, we collected data from all consecutive
9 patients referred to our tertiary-care Department of Lymphology with a confirmed diagnosis of
10 upper or lower limb lymphedema. Since 2006, our unit has been designated a member of the
11 National Referral Centers for Rare Vascular Diseases dedicated to primary lymphedema. It also
12 receives and treats patients with secondary post-cancer lymphedema. It oversees consultations
13 and has a multidisciplinary team, trained in lymphedema management and comprised of
14 physiotherapists, nurses, psychologist, podiatrists, dietician and an orthopedic specialist to obtain
15 the detailed measurements needed to make the individually tailored elastic garments. Every
16 month, our specialized lymphedema consultation team sees about 330 patients.

17 We recorded the following characteristics during the consultation: sex, age, age at first
18 symptom, possible previous cancer and its treatment (surgery, lymph-node excision,
19 chemotherapy, radiotherapy, hormone therapy), symptom-onset-to-specialized-consultation
20 interval, lower-or-upper limb localization, limb involvement [complete: involving the entire
21 limb; distal: below the knee (calf, foot) or the elbow (forearm, hand); proximal: involving the
22 thigh, arm]; uni- or bilateral involvement; previous cellulitis (erysipelas) episode(s) (number),
23 BMI (body weight (kg)/height²/m²)).

1 Unilateral limb lymphedema was diagnosed when the affected-limb circumference was 2-cm
2 larger than that of the contralateral side. Lower limb lymphedema was confirmed clinically based
3 on increased limb volume, with mandatory pathognomonic Stemmer's sign (inability to pinch
4 the dorsal side of the skin of the second toe (or its base) confirming the diagnosis, except for the
5 very rare proximal form (only affecting the thigh) which required magnetic resonance imaging or
6 computed-tomography scan confirmation. Lower limb lymphoscintigraphy was obtained, when
7 necessary, to confirm the diagnosis. Other diagnoses, such as lipedema, chronic venous
8 insufficiency (regardless of clinical manifestations, etiological factors, anatomical distribution,
9 and pathophysiological (Clinical, Etiological, Anatomical and Physiological (CEAP) stage)⁸ and
10 various edema etiologies (cardiac, renal, hepatic) were excluded by physical examination and
11 appropriate testing, such as venous ultrasonography, if necessary. None of the patients had
12 previous venous or arterial ulcer(s), or had undergone surgical/endovascular venous treatment.

13 Cellulitis was defined as the association of systemic symptoms (fever (>38°C) of sudden
14 onset, chills) and local signs (erythema, pain, localized 'hot spot', increased volume) that
15 required antibiotics. Cellulitis was diagnosed only when those criteria were met. Isolated redness
16 on the lymphedematous limb without fever was not considered cellulitis. At each consultation,
17 every 6 to 12 months, patients were asked if cellulitis satisfying those defined criteria had
18 occurred during the interval since the last consultation. Moreover, at the first consultation, all
19 patients had been taught to recognize the clinical signs of cellulitis to become his/her own expert.
20 Recurrent cellulitis was defined as two or more episodes.

21 According to French law, Ethics Committee approval is not required because we conducted a
22 retrospective and descriptive – not interventional – study, with patients managed according to
23 our standard procedures and in respect of the Declaration of Helsinki. Informed written consent

1 for demographic, physiological and hospital-outcome data analyses was not obtained because
2 this observational study did not modify existing diagnostic or therapeutic strategies. None of the
3 patients was opposed to the use of their data.

4
5 **Statistical analyses.** Continuous variables are expressed as mean (\pm standard deviation, SD)
6 or median (interquartile range, IQR), and qualitative variables as number (%). Means were
7 compared using Student's *t*-tests. Percentages were compared using χ^2 tests. Lymphedema
8 characteristics were analyzed for their association with cellulitis in univariate and multivariate
9 models, using backward stepwise logistic-regression analysis to identify and retain independent
10 risk factors, respectively. Significance was defined as $P < .05$. All statistical analyses were
11 computed using RStudio v1.0.136 software (RStudio, Inc, Boston, Mass, USA).

13 RESULTS

14 Information from 1,991 lymphedema patients was collected over the 6-month period, and
15 1,846 patients, divided into subgroups according to the lymphedema location (lower vs upper
16 limb) and its form (primary vs secondary), were analyzed, as detailed in (Fig 1). Because
17 primary upper limb lymphedema is very rare (only three patients with four-limb involvement and
18 27 (1.4%) primary upper limb lymphedemas were excluded from this analysis), and because
19 secondary lymphedemas were exclusively post-cancer treatment, we analyzed three groups: post-
20 breast cancer upper limb lymphedema ($n = 1062$), post-cancer lower limb lymphedema ($n = 325$)
21 and primary lower limb lymphedema ($n = 459$). Patients and lymphedema characteristics for
22 these three groups are reported in Table 1.

23 Among the 1,846 patients, 695 (37.6%) developed one or more cellulitis episodes and 23.2%

1 had recurrent cellulitis. Cellulitis occurred in 39.5%, 30.5% or 38.6% ($P = .02$) of the patients
2 with secondary upper limb, secondary lower limb or, primary lower limb, respectively. Results
3 of univariate analysis of risk factors for cellulitis in patients with primary or secondary
4 lymphedema are given in Supplementary Tables.

5 **Secondary upper limb lymphedema after breast cancer treatment.** Among 1,692
6 women, 1,062 with upper limb lymphedema and mean BMI 27.8 kg/m^2 , mean lymphedema
7 duration was 106.5 months. Among them, 39.5% previously had cellulitis, which was recurrent
8 for 23.2%. Results of the multivariate analysis of risk factors for cellulitis in patients with
9 secondary upper limb lymphedema are given Table 2. Lymphedema-onset-to-first-consultation
10 interval (in our referral center), age at lymphedema onset and radiotherapy were independently
11 associated with cellulitis while axillary lymph-node excision, chemotherapy or segmentation of
12 the upper limb lymphedema were not.

13 **Secondary lower limb lymphedema after cancer treatment.** Three hundred and twenty-
14 five patients with secondary lower limb lymphedema (82.2% female; mean BMI, 27.3 kg/m^2),
15 most frequently after gynecological cancer treatment (49.8%), for a mean lymphedema duration
16 of 97 months, were included. Among them, 30.5% had previous cellulitis episodes, which were
17 recurrent for 21.2%. Multivariate analysis of these patients' risk factors for cellulitis are reported
18 in Table 2. Lymphedema-onset-to-first-consultation interval and lymph-node excision were
19 associated with cellulitis, while BMI or age at lymphedema onset were not.

20 **Primary lower limb lymphedema.** The 459 patients (79.1% female; mean BMI, 28.9
21 kg/m^2) had a mean age of 31.7 years at lymphedema (unilateral: 51.6%) onset. Among them,
22 38.6% had previous cellulitis episode(s), which were recurrent for 25.1%, with mean
23 lymphedema duration of 243.1 months. Male sex, BMI and age at lymphedema onset were

1 associated with cellulitis (Table 3).

2

3 **DISCUSSION**

4 Herein, we reported that cellulitis occurred in 37.6% of the 1,846 patients with primary or
5 secondary upper or lower limb lymphedema, whose lymphedema duration ranged from 97 to 243
6 months. Their recurrent cellulitis rate was 23.3%. Cellulitis was significantly associated with
7 BMI, lymphedema-onset-to-first-consultation (in our specialized center) interval, age at
8 lymphedema onset and radiotherapy for patients with secondary upper limb lymphedema after
9 breast cancer treatment; lymphedema-onset-to-first-consultation interval and lymph-node
10 excision for those with secondary lower limb lymphedema; and male sex, BMI and age at
11 lymphedema onset for patients with primary lower limb lymphedema.

12 The precise cellulitis rate in a large series of patients with clinically diagnosed lymphedema,
13 be it primary or secondary, or affecting upper or lower limbs, has not been analyzed previously.
14 One major potential difficulty is the definition of cellulitis. At each consultation, every patient
15 was asked whether cellulitis had occurred since the previous consultation. We considered a
16 cellulitis diagnosis only when sudden fever onset was associated with localized signs (redness,
17 increased volume of the lymphedematous limb, localized 'hot spot', pain). At the first
18 consultation, every patient had been taught to recognize the clinical signs of cellulitis to become
19 his/her own expert.

20 Mistry et al⁹ insisted that cellulitis was confirmed only in 31.9% of patients referred for
21 suspicion of lower limb cellulitis in an English university center. Other diagnoses included
22 venous eczema, chronic edema and lymphedema. Our cellulitis frequency confirmed previously
23 reported findings for upper limb after breast cancer and lower limb lymphedema.¹⁰⁻¹³ In the

1 multicenter LIMPRINT study¹² from four countries (United Kingdom, France, Italy and Turkey),
2 32.2% of patients with primary lymphedema and 35.1% of those with secondary lymphedema
3 had a history of cellulitis. Cellulitis frequencies in some studies^{14,15} were lower than herein,
4 without any clearly discernable explanation, meaning that more than one-third of lymphedema
5 patients developed one or more cellulitis episodes after lymphedema onset. Notably, bilateral
6 lymphedema involvement did not increase the risk of lower limb cellulitis. Patients are
7 prescribed measures to prevent cellulitis, such as meticulous skin care. Patients were instructed
8 to avoid cutaneous abrasions (eg, cuts, burns, insect bites, cat scratches and cracks in dry skins)
9 and to protect their skin during daily activities (using gloves for gardening, thimble when
10 sewing, not walking barefoot). Patients were taught self-examination to search for toe-web
11 intertrigo and its treatment.

12 Intriguingly, a long lymphedema-onset-to-first-consultation (in our specialized center)
13 interval and young age at lymphedema onset were associated with cellulitis for secondary but not
14 primary lymphedema. That is an important finding, with various consequences. Thus, for
15 secondary lymphedema, especially of the upper limb after breast cancer treatment, oncologists,
16 surgeons, radiotherapist need to be aware of this main complication so as to more rapidly refer
17 the patient to a lymphedema specialist (physician, physiotherapist). Unfortunately, for primary
18 lymphedema, the lymphedema-onset-to-first-consultation interval is often longer. Indeed,
19 patients with primary lower limb lymphedema experienced longer delays between symptom
20 onset and referral (14.0 vs. 3.5 years for secondary) in the study by Schallwani et al,¹⁴ which was
21 confirmed in another study on only new patients referred to our center.¹³ Cellulitis occurrence
22 could be a clinical factor heightening the awareness of other physicians of the need to consult a
23 specialist in a referral center, which precipitated the initiation of lymphedema management.

1 Cellulitis was more frequent in patients with secondary than primary lymphedema, while
2 the duration of follow-up was shorter. Those results suggest that underlying local immunological
3 mechanisms may differ between secondary (acquired) and primary lymphedema. Notably, for 35
4 women with upper limb lymphedema after breast cancer treatment, cutaneous cell-mediated
5 immunity, as assessed with dinitrochlorobenzene, was impaired.¹⁶ Lymphangiosarcoma
6 (Stewart-Treves syndrome) may develop in a lymphedematous limb, essentially after breast
7 cancer treatment, and only very rarely in primary lymphedema, suggesting an underlying
8 immune deficiency,¹⁷ probably distinct for primary and secondary lymphedema. Further studies
9 are required to explore immunological functions in patients with limb lymphedema, and
10 comparisons of primary and secondary forms. Pertinently, decongestive physiotherapy is able to
11 partially restore impaired cellular immune function (tuberculin skin test) in patients with upper
12 limb lymphedema after breast cancer treatment.¹⁸ In their case-control study, Teerachaisakul et
13 al¹⁹ found that the percentage circumference difference between the two limbs, primary
14 lymphedema and systolic blood pressure were risk factors for cellulitis, and suggested that
15 controlling lymphedema volume and systolic pressure might limit cellulitis frequency.

16 Based on this series, BMI was a risk factor only for primary lower limb lymphedema. That
17 finding led us to hypothesize that fat-tissue deposition in the lower limb during lymphedema
18 development might affect localized immunity, thereby facilitating infections. Obesity appears to
19 be an independent risk factor for cellulitis. Precise effects on the immune response are poorly
20 known. Adipose tissue is involved in inflammation and immunity, producing and secreting
21 adipokines, either pro-inflammatory or anti-inflammatory, such as adiponectin or leptin.^{20,21}
22 Moreover, fungal toe-web intertrigo is more common in obese than non-obese patients and
23 represents a portal of entry for cellulitis.²² Moreover, obese patients' skin tends to be dry (with

1 the risk of cracks), associated with altered repair of the skin barrier. Lymphatic flow might also
2 be damaged due to an inflammatory state.²³ Overweight and obese patients should have a
3 specific consultation with a dietician or nutritionist to incite them to lose weight, even though
4 weight loss seems to have little effect on lymphedema volume.²⁴ Hence, it is of interest to note
5 that obesity is a proven risk factor for developing upper limb lymphedema after breast cancer
6 treatment and its severity but not for favoring cellulitis once lymphedema is present.

7 **Limitations.** The main limitations of our study are its retrospective design, with the risk of
8 patient-memory bias (age at lymphedema onset, cellulitis definition or confused with other
9 dermatological diagnoses) and “survivor” bias, because we have the follow-up only for living
10 patients, which might select only those with good prognoses. Another limitation is the absence of
11 lymphedema-volume measurements, which is complicated for bilateral forms without a “normal”
12 limb for comparison. The lack of information on dates of cellulitis occurrence precluded
13 determining reliable frequency estimates. We did not include local risk factors, such as intertrigo,
14 in this retrospective analysis because the site of entry of cellulitis may have disappeared by the
15 time of the consultation during follow-up. None of the patients had present or previous limb
16 wound(s) or ulcer(s). Lastly, we could not analyze the impact of compliance (compression, low-
17 stretch bandage) as risk factor because cellulitis might modify lymphedema treatment and it is
18 impossible to establish the temporal sequence.

19

20 **CONCLUSION**

21 Cellulitis is a frequent complication of primary and secondary lymphedemas of the upper or
22 lower limb. Almost 40% of our patients had one or more cellulitis episode(s) with lymphedema
23 duration ranging from 8 to 20 years among the different forms. Although different risk factors

1 were identified for primary and secondary lymphedema, lymphedema-onset-to-first-consultation
2 interval (in our referral center), age at lymphedema onset and BMI appeared to be the most
3 important associated with cellulitis. A major improvement would be shortening the interval
4 between lymphedema onset and the first consultation in a specialized center to optimize and
5 adapt lymphedema management to each patient, and hopefully limit complications, like cellulitis.
6 Physicians, oncologists, surgeons and physiotherapists should be taught to recognize promptly
7 lymphedema and so as to refer the patient to specialists in a timely manner.

8 Knowing the cellulitis risk factors for the different lymphedema forms may contribute to
9 preventing this frequent complication, and enable practitioners to provide specific advice and
10 adapt management.

11

12 **Disclosures.** Conflicts of interest: none.

13

14

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22

23

1 **Table 1.** Patient and lymphedema characteristics for the three lymphedema populations.

| Characteristic | Upper limb after breast cancer treatment, n = 1062 | Lower limb after cancer treatment, n = 325 | Primary lower limb, n = 459 |
|--|--|--|-----------------------------|
| Sex, female | 1062 (100) | 267 (82.2) | 363 (79.1) |
| Age at lymphedema onset, years | 56.3 ± 11.8 | 56.6 ± 13.8 | 31.7 ± 18.6 |
| Body mass index, kg/m ² | 27.8 ± 6.1 | 27.3 ± 6.7 | 28.9 ± 7.7 |
| Cancer | | | |
| Breast | 1062 (100) | – | – |
| Gynecological ^a | – | 162 (49.8) | – |
| Melanoma | – | 65 (20) | – |
| Prostate | – | 12 (3.7) | – |
| Other | – | 86 (26.5) | – |
| Cancer treatment | | | |
| Surgery | 1057 (99.5) | 305 (93.8) | – |
| Tumorectomy | 494 (46.5) | – | – |
| Mastectomy | 558 (52.5) | – | – |
| Lymph-node excision | 1019 (96) | 242 (74.5) | – |
| Radiotherapy | 984 (92.7) | 184 (56.6) | – |
| Chemotherapy | 877 (82.6) | 140 (43.1) | – |
| Hormone therapy | 579 (54.5) | 15 (4.6) | – |
| Lymphedema-onset-to-1 st -consultation interval ^b , months | 45.1 ± 69.7 | 52.7 ± 78.3 | 182.1 ± 187.6 |
| Limb involvement | | | |
| Unilateral | 1049 (98.8) | 242 (74.5) | 237 (51.6) |
| Proximal | 104 (9.8) | 52 (16) | 6 (1.3) |
| Distal | 158 (14.9) | 52 (16) | 269 (58.6) |
| Whole | 800 (75.3) | 221 (68) | 184 (40.1) |
| Lymphedema duration, months | 106.5 ± 95.7 | 97.0 ± 94.6 | 243.1 ± 198.8 |
| Treatment | | | |

| | | | |
|-----------------------|------------|------------|------------|
| Elastic compression | 892 (84) | 280 (86.2) | 386 (84.1) |
| Low-stretch bandages | 381 (35.9) | 110 (33.8) | 136 (29.6) |
| Manual lymph drainage | 558 (52.5) | 125 (38.5) | 128 (27.9) |
| Past cellulitis | 419 (39.5) | 99 (30.5) | 177 (38.6) |
| >2 times | 246 (23.2) | 69 (21.2) | 115 (25.1) |

1 Results are expressed as n (%) or mean \pm SD.

2 ^a Uterine, cervical, ovarian.

3 ^b In our specialized center.

4

5

- 1 **Table 2.** Multivariate analysis of cellulitis risk factors for patients with secondary upper or lower
 2 limb lymphedema.

| Factor | Odds ratio (95% CI) | <i>P</i> value |
|---|---------------------|----------------|
| Upper limb lymphedema | | |
| Body mass index, kg/m ² | | .61 |
| For each 1 kg/m ² increment | 1.01 (0.98-1.03) | |
| For each 5 kg/m ² increment | 1.03 (0.91-1.17) | |
| Lymphedema-onset-to-1 st -consultation interval ^a | | <.0001 |
| For each 1-month increment | 1.007 (1.004-1.009) | |
| For each 12-month increment | 1.08 (1.05-1.12) | |
| Age at lymphedema onset | 0.98 (0.97-1.00) | .004 |
| Radiotherapy | 1.96 (1.01-4.0) | .05 |
| Tumorectomy (vs. mastectomy) | 1.26 (0.94-1.69) | .13 |
| Unilateral side | 0.62 (0.15-2.34) | .49 |
| Hormonotherapy | 0.78 (0.58-1.05) | .1 |
| Diabetes | 1.26 (0.64-2.45) | .51 |
| Lower limb lymphedema | | |
| Diabetes | 0.42 (0.02-2.95) | .44 |
| Body mass index (kg/m ²) | 1.02 (0.97-1.08) | .46 |
| Lymphedema-onset-to-1 st -consultation interval | 1.006 (1.001-1.012) | .01 |
| Unilateral lymphedema | 0.64 (0.30-1.38) | .25 |
| Lymph-node excision | 3.50 (1.28-11.62) | .02 |
| Chemotherapy | 0.98 (0.50-1.90) | .95 |

| | | |
|-------------------------|------------------|-----|
| Age at lymphedema onset | 0.99 (0.96-1.01) | .25 |
|-------------------------|------------------|-----|

1 ^a In our specialized center.

2

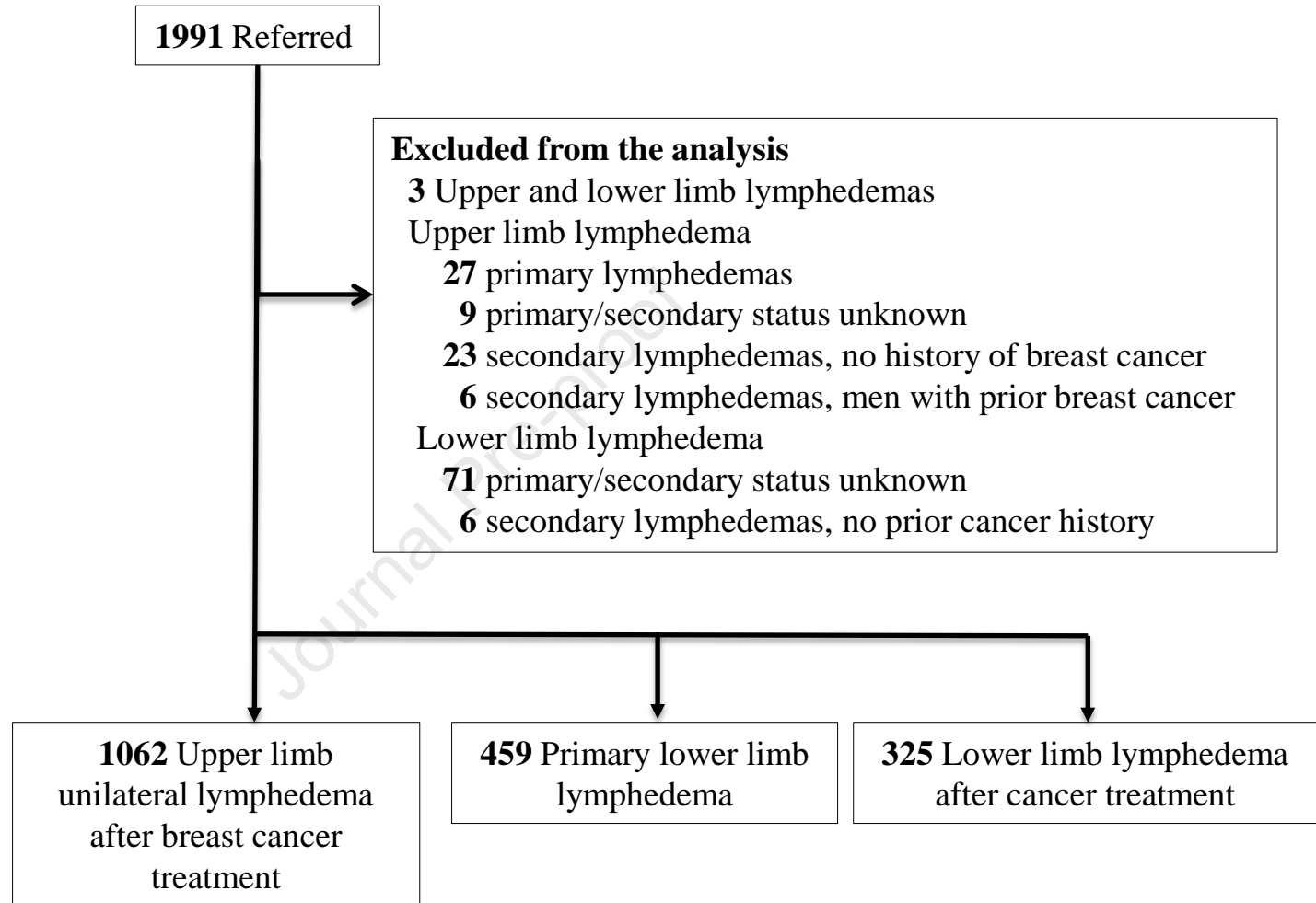
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- 1 **Table 3.** Multivariate analysis of cellulitis risk factors for patients with primary lower limb
2 lymphedema.

| Factor | Odds ratio (95% CI) | <i>P</i> value |
|---|---------------------|----------------|
| Sex male | 3.95 (2.15-7.46) | <.001 |
| Body mass index (kg/m ²) | 1.06 (1.02-1.09) | .002 |
| Lymphedema-onset-to-1 st -consultation interval ^a | 1.001 (0.999-1.002) | .33 |
| Age at lymphedema onset | 0.982 (0.967-0.999) | .04 |

- 3 ^a In our specialized center.

4



1 **Figure legend**

2 **Figure 1.** Flow chart of the patients included in the study seen in consultation in our specialized

3 lymphedema-dedicated center from January to June 2018.

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Supplementary Tables. Univariate analysis of cellulitis risk factors for patients with secondary and primary lymphedema.

Primary lower limb lymphedema

| Characteristic | OR (95% CI) | <i>P</i> value |
|--|---------------------|-------------------|
| Male sex | 2.8 (1.77-4.46) | <10 ⁻³ |
| Body mass index (kg/m ²) | 1.05 (1.02-1.08) | .001 |
| Lymphedema-onset-to-1 st -first consultation interval | 1.002 (1.000-1.003) | .004 |
| Age at lymphedema onset | 0.986 (0.975-0.996) | .009 |
| Diabetes | 1.34 (0.38-4.50) | .64 |

Secondary upper limb lymphedema

| Characteristic | OR (95% CI) | <i>P</i> value |
|--|---------------------|-------------------|
| Body mass index (kg/m ²) | 1.000 (0.977-1.023) | .98 |
| Diabetes | 1.30 (0.71-2.36) | .38 |
| Age at lymphedema onset | 0.97 (0.96-0.99) | <10 ⁻⁵ |
| Lymphedema-onset-to-1 st -first consultation interval | 1.006 (1.004-1.008) | <10 ⁻⁵ |
| Unilateral | 0.29 (0.08-0.88) | .04 |
| Hormonotherapy | 0.76 (0.59-0.98) | .03 |
| Radiotherapy | 1.94 (1.16-3.35) | .01 |
| Tumorectomy (vs mastectomy) | 1.29 (1.01-1.66) | .04 |
| Chemotherapy | 0.88 (0.64-1.22) | .45 |
| Lymph-node excision | 1.18 (0.63-2.29) | .62 |

Secondary lower limb lymphedema

| Characteristic | OR (95% CI) | <i>P</i> value |
|--|---------------------|----------------|
| Diabetes | 0.65 (0.09-2.73) | .59 |
| Body mass index (kg/m ²) | 1.02 (0.98-1.06) | .4 |
| Lymphedema-onset-to-1 st -first consultation interval | 1.005 (1.002-1.008) | .003 |
| Chemotherapy | 0.91 (0.55-1.49) | .71 |
| Lymph-node excision | 1.83 (0.89-4.05) | .11 |
| Unilateral | 0.95 (0.56-1.64) | .84 |
| Age at lymphedema onset | 0.97 (0.95-0.99) | .002 |
| Male sex | 1.25 (0.68-2.27) | .46 |
| Radiotherapy | 0.94 (0.57-1.56) | .8 |