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Mild symptoms matter: Results from a prospective, longitudinal study on the relationship between symptoms, lymphedema and health-related outcomes post-gynecological cancer

Melanie L. Plinsinga [a,*], Sheree Rye [a], Tamara Jones [a,b], Dimitrios Vagenas [c], Leigh Ward [d], Monika Janda [e], Andreas Obermair [f], Sandra C. Hayes [a,g]

[a] School of Health Sciences and Social Work, Griffith University, Nathan, Queensland, Australia
[b] Melbourne School of Psychological Sciences, The University of Melbourne, Parkville, Victoria, Australia
[c] School of Public Health and Social Work, Queensland University of Technology, Kelvin Grove, Queensland, Australia
[d] School of Chemistry and Molecular Biosciences, The University of Queensland, St. Lucia, Queensland, Australia
[e] Centre for Health Services Research, Faculty of Medicine, The University of Queensland, St Lucia, Queensland, Australia
[f] Queensland Centre for Gynaecological Cancer Research, The University of Queensland, Herston, Queensland, Australia
[g] Cancer Council Queensland, Fortitude Valley, Queensland, Australia

HIGHLIGHTS

- The most prevalent lower limb symptoms were pain, stiffness, and aching (prevalence >40 %).
- Lower-limb symptoms were associated with higher anxiety and depression, poorer overall quality of life and body image.
- Symptoms increase the odds of developing lymphedema, irrespective of symptom severity.

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ABSTRACT

Objectives. To describe lower-limb symptoms pre- through to 2-years post-surgery following newly diagnosed gynecological cancer; to explore relationships between lower-limb symptoms, lower-limb lymphedema, body image, quality of life, anxiety and depression; and to determine whether lower-limb symptoms predict lower-limb lymphedema.

Methods. Fourteen lower-limb symptoms, lymphedema, body image, anxiety, depression, and quality of life were prospectively collected in 408 women with gynecological cancer pre-surgery, and at 6-, 12-, and 24-months post-surgery. Point prevalence and cumulative incidence were calculated for symptoms. Cross-sectional relationships were explored between symptoms, lower-limb lymphedema and health-related outcomes at all timepoints, while regression analyses were used to assess the predictive relationships between lower-limb symptoms at 6-months post-surgery, and lymphedema at 12- and 24-months post-surgery.

Results. Participants were on average 59 (SD: 11) years of age, and 58 %, 28 %, 9 % and 5 % were diagnosed with endometrial, ovarian, cervical, and vulvar/vaginal cancer, respectively. Prevalence of any given lower limb symptom among all cancer types ranged between 11 and 59 %, with the most prevalent symptoms being pain, stiffness, and aching (prevalence >40 % across all time-points). The presence of symptoms was associated with higher anxiety and depression, poorer overall quality of life and body image ($p < 0.01$). Compared to those without symptoms, one or more lower limb symptoms of at least mild severity increased the odds of developing lymphedema up to 24 months post-surgery (OR > 1.3).

Conclusions. Self-reported symptoms are associated with adverse health-related outcomes. Assessment and management of symptoms, irrespective of symptom severity, has potential for improving health outcomes, including lymphedema, in those following gynecological cancer.

* Corresponding author at: School of Health Sciences and Social Work, Griffith University, Nathan, Queensland, Australia.
E-mail address: m.plinsinga@griffith.edu.au (M.L. Plinsinga).

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1. Introduction

Gynecological cancers, including ovarian, uterine, cervical, vaginal, and vulval cancer, account for 9 % of all new cancer diagnoses among Australian women [1]. They are also the third most common cancers for women in developed countries, including Australia and the United States of America [2]. The presence of symptoms, including pain, aching and heaviness, typically precede a gynecological cancer diagnosis, prompting initial medical exploration and subsequent diagnosis [3–5]. Subsequent treatment for malignant disease, which may include surgery, radiation, or chemotherapy, has the potential to resolve certain symptoms, or to further contribute to the progression and/or development of long term survivorship conditions, of which lower-limb lymphedema is one of the most common [6–8]. With an increasing 5-year survival rate for all gynecological cancers combined (currently at 67 %, and ranging from 43 % for ovarian cancer to 82 % for endometrial cancer) [1], there is a need to better understand symptoms and their relationship with other health-related outcomes.

Lower-limb lymphedema following gynecological cancer treatment is prevalent, although prevalence varies widely between cancer type [9–11]. Lymphedema typically presents within 12 months post-treatment [10], and in its early phase is characterized by an increase in extracellular fluid in the lower-limbs, ankles, feet, genital or pelvic region. As lymphedema progresses, visible and measurable size changes to the affected area occur, with later stages of lymphedema characterized by deposition of fatty and fibrotic tissue in the affected area [12]. Once lymphedema develops, it is intractable [12]. Best practice management includes prospective surveillance and early intervention through compression therapy; however, this is costly and time-consuming and does not form part of standard gynecological cancer care [13,14]. Lower-limb lymphedema adversely impacts all aspects of life, including body image, quality of life, and psychological and social wellbeing, and is a visible daily reminder of cancer [15–18].

The prevalence of symptoms including swelling, heaviness, and tightness have been reported in over 65 % of individuals with lower-limb lymphedema [19,20]. Anecdotally, clinicians report that changes in, or new lower-extremity symptoms are reported by patients prior to a lymphedema diagnosis. These reports are consistent with international lymphedema staging guidelines which define the first stage of lymphedema as being a subclinical or latent condition whereby symptoms, such as heaviness and tightness, are experienced in the absence of measurable swelling [12]. Subclinical stage 0 may be transitory, or exist for months to years before measurable swelling occurs and progresses to stage I-IV lymphedema Further, early intervention (at-subclinical stage 0 where there is a presence of symptoms, but no measurable swelling) through compression and exercise has been demonstrated to reduce and prevent development of chronic lymphedema [21].

It seems plausible that the presence of lower-extremity symptoms may predict lower-limb lymphedema, and be used to identify individuals who may benefit most from prospective surveillance and early lymphedema management strategies [22]. Therefore, the objectives of this study were to (i) describe lower-limb symptoms pre- through to 24-months post-surgery following newly diagnosed gynecological cancer, (ii) explore relationships between lower-limb symptoms, lower-limb lymphedema, body image, quality of life, anxiety and depression, and (iii) determine if the presence of lower-limb symptoms predicts lower-limb lymphedema.

2. Methods

2.1. Study design and subjects

The Lymphedema Evaluation in Gynecological Cancer Study (LEG) was a prospective, longitudinal cohort study that recruited women ≥18 years and newly diagnosed with gynecological cancer (International Classification of Diseases Codes C51–C58) between June 2008 and February 2011 at participating hospitals in Queensland, New South Wales, and Victoria, Australia [10,23,24]. The primary objective of the LEG study was to evaluate the incidence of lower-limb lymphedema and its associated risk factors [10,24]. Lower-limb symptoms, quality of life, body image, anxiety, and depression were assessed as secondary outcomes [24].

Ethical approval was obtained from hospital human research ethics committees (approval numbers: 2008000211, 2007/168, 200,842, 1189 A/P, 08/16, 10/14, 10/10/RPAH/28). Following provision of study information, all interested and eligible participants provided verbal and written consent pre-participation. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies [25].

2.2. Timing of data collection

Following informed consent, baseline assessment was performed approximately one week prior to diagnostic surgery and definitive gynecological cancer diagnosis. Follow-up assessments were coordinated with the participant's scheduled hospital follow-up visits between 6-weeks and 24-months post-surgery. Due to differences in scheduling between participants' follow-up appointments, follow-up assessments were conducted up to 10 times over the follow-up period (i.e., at 6-weeks, and 3-, 6-, 9-, 12-, 15-, 18-, 21- and 24-months post-surgery) per participant.

2.3. Data collection

Demographic, socioeconomic, and lifestyle behavioral characteristics were collected at baseline via a participant-administered questionnaire. Clinical information including diagnosis and treatment details were extracted by trained research nurses from medical records at baseline and at the 2-year follow-up.

2.4. Lower-limb symptoms

Participants self-reported the presence of 14 lower-limb symptoms within the last week using a five-point scale for severity: 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = extreme. The 14 lower-limb symptoms included: pain, pain performing any specific activity, tingling (pins and needles), weakness, stiffness, poor range of movement, numbness, tightness, ache, heaviness, reddish skin coloring, tenderness, thickened/hardened skin, and hot areas on the skin. Responses of ≥1 were used to indicate the presence of a symptom of at least mild severity, while responses of ≥2 indicated symptom presence of at least moderate severity.

2.5. Lymphedema

Lower-limb lymphedema was assessed via bioimpedance spectroscopy (BIS), and self-reported swelling. Lymphedema pertaining to the legs, as assessed by BIS, was considered present when the ratio of impedance at zero frequency of arm/leg (assessed separately for the dominant and non- dominant side; dominance determined by side used for writing) exceeded 1 standard deviation (sd) of the mean normative arm/leg ratios [26]. These cut-offs have been found to have a sensitivity of 0.75 and specificity of 0.85 [26].

Self-reported swelling was assessed by asking women if they "experienced any of the following: swelling of the right leg, left leg, both legs, between legs (vulva), lower abdomen, or pelvic region in the past three months". Anatomical sites were condensed into three regions of swelling: legs, vulva, and abdomen/pelvis. For the purpose of this study, only data for self-reported leg swelling are included as it coincides with lymphedema pertaining to the legs, as assessed by BIS.

2.6. Self-reported questionnaires

Quality of life (including physical, social, emotional and functional well-being domains of health-related quality of life) was measured using the 27-item Functional Assessment of Cancer Therapy – General, FACT-G questionnaire [27]. Final scores ranged from 0 to 108, with 108 reflecting high quality of life [28]. Body image was measured using the Body Image Scale [29], which assesses affective, behavioral and cognitive body symptoms specifically in cancer patients. Total scores range from 0 to 30, with higher scores indicating higher level of body image disturbance [29]. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) [30]. Total anxiety and depression scores ranged from 0 to 21, with higher scores indicating higher levels of anxiety and depression [31].

2.7. Statistical analyses

To account for differences in the number and timing of follow-up assessments between participants, follow-up assessments were grouped into time-phases for analysis; baseline (T1; pre-definitive diagnosis), 6-weeks to 3-months (T2), 6- to 12-months (T3), and 15- to 24-months post-surgery (T4). For T2-T4, outcome measures were averaged if multiple surveys were completed within each time-phase.

Point prevalence and cumulative incidence were calculated for lower-limb symptoms from baseline up to 24 months follow-up. Point prevalence was calculated by dividing the number of patients reporting symptoms by number of total participants providing data at each follow-up assessment (T1-T4). Cumulative incidence reflected the proportion of women with newly developed symptoms after baseline (that is, cases with the respective baseline symptom were excluded). These data were then used to calculate (i) the number of lower-limb symptoms of at least mild severity, and of at least moderate severity, and (ii) a dichotomous lower-limb symptom variable to report on the proportion of women with no symptoms versus those with one or more (mild or moderate) lower-limb symptoms, at each timepoint. Pearson Chi-Square analyses were used to explore the relationship between the presence of symptoms and types of cancer.

Medians (minimum, maximum and interquartile range) were used to describe non-parametric continuous outcomes. The relevant statistical tests (including Mann-Whitney tests, unpaired *t*-tests, chi-squared analyses) were undertaken to explore the cross-sectional relationships between lower-limb symptoms and lower-limb lymphedema, body image, anxiety, depression and quality of life at each time point. We also explored the number of symptoms reported by the presence of lymphedema.

To assess the predictive relationship between lower-limb symptoms at T2 (6 weeks to 3 months), and development of lower-limb lymphedema at T2-T4 (6 weeks to 24 months), our primary analyses involved adjusted logistic regression analyses with number of symptoms at T2 as the independent variable (using prevalence data). Women with evidence of lymphedema at T1 were excluded from these analyses. Potential confounding variables identified based on a priori knowledge included age and body mass index, cancer type, stage of disease at diagnosis, and number of lymph nodes removed. The analysis was run twice for the dichotomous variable of lower-limb symptoms; once for the presence of one or more *mild* lower-limb symptoms, and once for the presence of one or more *moderate* lower-limb symptoms. The effect size of the relationship was described using odds ratio's (ORs) and 95 % confidence intervals (CI) or beta values and standard errors.

Exploratory analyses involved evaluating the predictive relationship between newly developed lower-limb-symptoms and development of lower-limb lymphedema through adjusted logistic regression analyses using cumulative incidence symptom data. Further, as lymph node dissection is known to be the strongest risk factor for lymphedema development, we further explored its involvement in the predictive relationship between number of symptoms and lymphedema by conducting unadjusted, stratified analysis according to lymph node removal (yes/no). All statistical tests were two-sided and considered statistically significant at $P < 0.05$. Statistical analyses were performed in SPSS (Version 27.0, IBM Statistics, New York).

3. Results

Of 2121 potentially eligible participants, 408 women diagnosed with malignant disease were included. Recruitment, non-completion, and retention rates (including a flow diagram) have been described previously [24]. Table 1 presents patient descriptive statistics of the 408 women included in the LEG study. The majority of women were diagnosed with endometrial cancer (58 %). Pre-surgery, the average number of mild to extreme and moderate to extreme symptoms was 3.7 (SD 3.5) and 1.4 (SD 2.5), respectively.

3.1. Prevalence and cumulative incidence of lower-limb symptoms pre- through to two-years post-surgery

The prevalence of mild to extreme lower-limb symptoms, for all time-points across all gynecological cancer types is described in Table 2, and Supplementary Table 1 for moderate to extreme symptoms. Between 9 and 59 % of patients reported at least one lower-limb symptom up to 24-months post-surgery, irrespective of time-point assessed, cancer type and type and severity of symptoms. Specifically, prevalence

Table 1
Baseline characteristics for participants in the LEGS study ($n = 408$).

Characteristics	n (%)
Age (years)	
Mean (SD)	59 (11.4)
Body Mass Index Category	
< 25 kg/m^2	210 (51.5 %)
25–29.9 kg/m^2	74 (18.1 %)
30+ kg/m^2	122 (29.9 %)
Missing	2 (0.5 %)
Body Mass Index (kg/m^2)	
Mean (SD)	31.3 (8.4)
Cancer Type & Stage	
Endometrial cancer	235 (57.6 %)
Stage 1	*165 (70.2 %)*
Stage 2+	*66 (28.1 %)*
Missing	*4 (1.7 %)*
Ovarian cancer	114 (27.9 %)
Stage 1–2	*37 (32.5 %)*
Stage 3+	*68 (59.6 %)*
Missing	*9 (7.9 %)*
Cervical cancer	37 (9.1 %)
Stage 1	*33 (89.2 %)*
Stage 2+	*2 (5.4 %)*
Missing	*2 (5.4 %)*
Vulvar/vaginal cancer	22 (5.4 %)
Stage 1–4	*17 (77.3 %)*
Missing	*5 (22.7 %)*
Surgery Type	
Laparoscopy	152 (37.3 %)
Laparotomy	223 (54.7 %)
Surgery abandoned	3 (0.7 %)
Other	23 (5.6 %)
Missing	7 (1.7 %)
Lymph Node Dissection	
Yes	181 (44.4 %)
No	227 (55.6 %)
Evidence of Lymphedema	
Bioimpedance Spectroscopy	
Yes	76 (18.6 %)
No	212 (52.0 %)
Missing	120 (29.4 %)
Self-reported Leg Swelling	
Yes	55 (13.5 %)
No	290 (71.1 %)
Missing	63 (15.4 %)

Table 2
Proportions of lower-limb symptoms reported by participants at T1 (baseline), T2 (6 weeks – 3 months), T3 (6–12 months), and T4 (15–24 months) post-surgery for gynecological cancer.

	Symptoms Indicated as at Least Mild in Severity n (%)			
Lower-limb Symptoms	T1	T2	T3	T4
Pain	130 (39.9 %)	126 (41.9 %)	121 (44.8 %)	117 (47.8 %)
Pain during activity	107 (34.3 %)	115 (37.1 %)	116 (41.3 %)	101 (39.3 %)
Pins and needles	73 (22.1 %)	81 (26.1 %)	87 (31.5 %)	76 (30.0 %)
Weakness	105 (31.8 %)	119 (40.1 %)	103 (38.9 %)	92 (39.3 %)
Stiffness	156 (46.6 %)	137 (44.8 %)	152 (56.7 %)	143 (59.3 %)
Range of motion	100 (30.2 %)	109 (36.6 %)	120 (43.5 %)	99 (40.6 %)
Numbness	63 (19.0 %)	86 (27.7 %)	94 (33.5 %)	76 (29.1 %)
Tightness	88 (26.7 %)	88 (29.3 %)	92 (35.2 %)	79 (34.5 %)
Aching	161 (48.6 %)	153 (52.2 %)	146 (53.9 %)	130 (54.9 %)
Heaviness	85 (25.8 %)	72 (22.9 %)	77 (27.7 %)	71 (29.0 %)
Reddish skin	38 (12.5 %)	48 (14.6 %)	28 (9.2 %)	33 (11.6 %)
Tenderness	72 (23.9 %)	75 (25.0 %)	79 (28.4 %)	64 (25.0 %)
Thickness	34 (11.4 %)	34 (10.6 %)	30 (10.0 %)	33 (11.4 %)
Hotness	40 (13.2 %)	57 (17.4 %)	39 (13.3 %)	35 (12.5 %)
Number of Mild-Extreme Symptoms				
0	88 (25.9 %)	87 (25.1 %)	93 (27.2 %)	112 (35.2 %)
1 to 2	67 (19.7 %)	81 (23.4 %)	75 (21.9 %)	53 (16.7 %)
3 to 4	60 (17.7 %)	57 (16.5 %)	49 (14.3 %)	44 (13.8 %)
5 or more	125 (15.9 %)	121 (11.8 %)	125 (11.4 %)	109 (12.6 %)
Median (min, max)	3.0 (0, 14)	3 (0, 14)	3 (0, 14)	2 (0, 14)
Number of Moderate-Extreme Symptoms				
0	210 (61.8 %)	235 (67.9 %)	238 (69.6 %)	240 (75.5 %)
1 to 2	60 (17.6 %)	52 (15.0 %)	50 (14.6 %)	35 (11.0 %)
3 to 4	26 (7.6 %)	27 (7.8 %)	27 (7.9 %)	13 (4.1 %)
5 or more	44 (12.9 %)	32 (9.2 %)	27 (7.9 %)	30 (9.4 %)
Median (min, max)	0 (0,12)	0 (0, 12)	0 (0, 14)	0 (0, 14)

of any given symptom among all gynecological cancer types ranged between 11 and 49 %, 11–52 %, 9–57 %, and 11–59 % at baseline, 6-, 12-, and 24-months post-surgery, respectively. Incidence of mild to extreme symptoms ranged between 8 and 30 %, 11–42 % and 13–44 % at 6-, 12-, and 24-months post-surgery, respectively (Supplementary Table 2).

The majority of the sample (over 65 %) reported the presence of at least one *mild* symptom across all phases of assessment (Table 2). When we focused only on symptoms rated as moderate severity or higher, approximately 40 % of women reported at least one symptom pre-surgery, and by 24-months post-surgery, one in four women reported at least one symptom of moderate severity or higher (Supplementary Table 1). Incidence of moderate to extreme symptoms ranged between 1 and 11 %, 2–16 %, 3–18 % at 6-, 12-, and 24-months post-surgery, respectively (Supplementary Table 3).

Pain, stiffness, and aching were the most prevalent symptoms, reported by at least 40 % of the sample for mild to extreme symptoms, and by at least 11 % for moderate to extreme symptoms across all time-points (Table 2, Supplementary Table 1). At all post-surgery time-points, women with ovarian cancer reported higher prevalence of mild to extreme pins and needles (12 % – 15 %) and numbness (11 % – 15 %) compared with other cancer types. There were no other obvious differences between cancer types or across time.

3.2. The relationship between lower-limb symptoms, lymphedema and other health-related outcomes

The presence of one or more lower-limb symptom of at least mild severity was associated with higher prevalence of self-reported swelling ($p < 0.001$) at all timepoints, and with presence of lymphedema as measured using BIS at T1-T3 ($p < 0.05$, Table 3). Further, a higher number of lower-limb symptoms were reported in those with lymphedema compared with those without lymphedema (when measured with BIS: range $p < 0.01$ to $p = 0.17$; and self-reported leg swelling: all $p < 0.001$; Supplementary Table 4). The presence of one or more lower-limb symptoms of at least mild severity was also associated with lower body image, higher anxiety and depression, and lower overall quality of life and subscales ($p < 0.05$, Table 3). These relationships were consistently observed across all time points and for those with one or more symptoms of at least moderate severity ($p < 0.05$; Supplementary Table 5).

Outcomes of the unadjusted and adjusted logistic regressions can be found in Table 4 and Supplementary Table 6. Compared with women without lower-limb symptoms, those with 1+ mild to extreme lower-limb symptoms had 2.1 times higher odds of having lymphedema (95 % CI: 0.89, 5.19; $p = 0.10$), as assessed using BIS (Table 4). Predictive relationships were consistently observed for lymphedema assessed by self-reported leg swelling, with women who experienced 1–2 mild to extreme lower-limb symptoms having a 1.3 times higher odds of having lymphedema (95 % CI: 0.55, 2.81; $p = 0.60$), and those with 3+ mild to extreme symptoms a 3.6 times higher odds (95 % CI: 1.74, 7.43; $p < 0.001$) (Table 4). Findings remained consistent when replacing the symptom prevalence variable with symptom incidence variable within the model. That is, results suggest that the presence of symptoms, irrespective of whether symptoms are new (not present at baseline) or persistent or pre-existing (that is, present at baseline and T2 or present at baseline only), increased the odds of developing lymphedema (Supplementary Tables 7–8). In stratified analyses according to lymph node dissection, findings suggest that the predictive relationship between symptoms and lymphedema is only relevant for women who have had lymph nodes dissected. (Supplementary Table 9).

4. Discussion

Findings from this prospective, longitudinal cohort study show that lower-limb symptoms are prevalent up to 2-years post-surgery across all gynecological cancer types. Further, the presence of symptoms is associated with higher odds of developing lymphedema, poorer quality of life and body image, and higher anxiety and depression. Findings indicate that symptoms, including when self-reported as mild, are associated with adverse health-related outcomes. Our findings highlight the importance of assessing the presence of lower-limb symptoms, particularly when lymph nodes are removed as part of surgical treatment, and implementing strategies that may help prevent or alleviate their impact on health-related outcomes.

Our study found that for any of the 14 lower-limb symptoms assessed, prevalence per symptom across all cancer types ranged between 11 and 59 % up to 2-years post-surgery. Notably, lower-limb pain, weakness, stiffness, and aching were consistently reported by at least one in three women across all gynecological cancer types, irrespective of timing of assessment. To our knowledge, this represents the first report indicating how common lower-limb pain, weakness, stiffness, and aching are in gynecological cancers. Cancer-related pain – not specified as lower-limb pain – has also been highlighted in previous work as a common symptom in gynecological cancers. Findings from a review and meta-analysis of 52 studies across all cancer groups showed a 60 % (95 %CI 50 % to 71 %) prevalence of cancer-related pain (not specifically lower-limb pain) in gynecological cancers [32]. Also shown across all cancer types was that pain prevalence was higher for individuals *undergoing anticancer treatment* (59 %; 95 %CI 44 % to 73 %) compared with those *after curative treatment* (pain prevalence: 33 %, 95 % CI 21 % to 46 %) [32]. In contrast, findings from our study suggest a rise in lower-limb pain prevalence during the 15 to 24-month follow-up (e.g., after treatment) across all patients and specifically in those with endometrial and ovarian cancer. Nonetheless, findings from the review and this prospective, cohort study support that 'cancer-related' and 'lower-limb' pain in women with gynecological cancer is common across the cancer continuum and that pain is a treatment and survivorship symptom worthy of monitoring and management.

Although most symptoms assessed in this study showed similar prevalence rates across cancer types, our study revealed clear

Table 3
Cross-sectional relationship between self-reported one or more mild to extreme lower-limb symptoms with lymphoedema (BIS), self-reported leg swelling, anxiety, depression, quality of life and body image at T1 to T4.

	Self-reported Presence of 1+ Mild to Extreme Lower-limb Symptom (No/Yes)							
	T1 Baseline (pre-surgery)		T2 6 wks – 3 months (post-surgery)		T3 6–12 months (post-surgery)		T4 15–24-months (post-surgery)	
	No	Yes	No	Yes	No	Yes	No	Yes
Lymphoedema (BIS)								
Prevalence n (%)	13 (17.8 %)	56 (30.3 %)	3 (8.8 %)	35 (37.6 %)	12 (23.1 %)	57 (39.6 %)	30 (36.6 %)	54 (41.5 %)
Self-reported Leg Swelling (SRS)								
Prevalence n (%)	1 (1.1 %)	54 (21.4 %)	10 (11.5 %)	77 (29.7 %)	18 (19.4 %)	97 (39.0 %)	21 (18.8 %)	100 (48.5 %)
Anxiety (HADS)								
Normal (0–7)	61 (69.3 %)	158 (63.7 %)	84 (96.6 %)	192 (78.0 %)	84 (93.3 %)	182 (76.5 %)	98 (91.6 %)	143 (72.6 %)
Borderline (8–10)	13 (14.8 %)	44 (17.7 %)	2 (2.3 %)	33 (13.4 %)	6 (6.7 %)	31 (13.0 %)	5 (4.7 %)	28 (14.2 %)
Abnormal (11−21)	14 (15.9 %)	46 (18.5 %)	1 (1.1 %)	21 (8.5 %)	0 (0 %)	25 (10.5 %)	4 (3.7 %)	26 (13.2 %)
Mean (SD)	6.0 (4.2)	6.6 (4.2)	2.5 (2.6)	5.0 (3.8)	2.5 (2.9)	5.2 (3.9)	2.8 (3.2)	5.4 (4.2)
Depression (HADS)								
Normal (0–7)	83 (94.3 %)	208 (83.9 %)	85 (97.7 %)	217 (87.5 %)	91 (98.9 %)	215 (88.8 %)	109 (98.2 %)	170 (85.4 %)
Borderline (8–10)	1 (1.1 %)	26 (10.5 %)	2 (2.3 %)	20 (8.1 %)	1 (1.1 %)	21 (8.7 %)	2 (1.8 %)	20 (10.1 %)
Abnormal (11–21)	4 (4.5 %)	14 (5.6 %)	0 (0.0 %)	11 (4.4 %)	0 (0.0 %)	6 (2.5 %)	0 (0.0 %)	9 (4.5 %)
Mean (SD)	2.4 (2.9)	3.8 (3.4)	1.8 (1.9)	3.7 (3.2)	1.5 (1.7)	3.6 (3.2)	1.5 (1.9)	3.9 (3.4)
Quality of Life (FACT-G)								
Mean (SD)								
PWB (0–28)	24.6 (4.5)	22.0 (5.5)	24.8 (4.0)	21.7 (5.4)	26.7 (1.8)	23.4 (4.4)	26.7 (2.0)	23.5 (4.1)
SWB (0–28)	21.6 (5.5)	21.0 (5.4)	22.4 (4.6)	20.6 (5.1)	22.3 (4.4)	20.5 (5.6)	22.6 (5.0)	20.1 (5.9)
EWB (0–24)	17.2 (5.0)	17.6 (5.1)	20.8 (3.7)	19.4 (4.0)	21.1 (3.4)	19.5 (3.7)	21.2 (3.2)	19.3 (4.0)
FWB (0–28)	21.4 (5.9)	18.9 (6.4)	22.3 (5.6)	18.5 (5.9)	24.2 (4.1)	19.8 (6.0)	24.4 (4.0)	19.6 (5.7)
FACT-G (0–108)	84.1 (16.4)	78.6 (17.3)	90.0 (14.0)	79.7 (16.3)	93.9 (10.8)	83.0 (16.3)	94.7 (11.8)	82.0 (16.1)
FACT-G n	88	252	87	255	93	248	112	206
Body Image (0−30) [a]								
Median (Min, Max)	0.0 (0, 21.0)	2.0 (0, 23.0)	1.0 (0, 17)	3.0 (0, 28)	0.5 (0, 17)	3.0 (0, 26)	0.25 (0, 15.5)	4.0 (0, 24.8)
n	83	242	87	245	92	244	110	205

BIS: bioimpedance spectroscopy; SRS: Self-reported swelling; HADS: Hospital and anxiety depression scale; FACT-G: Functional Assessment of Cancer Therapy – General; PWB: Physical well-being; SWB: Social/family well-being; EWB: Emotional well-being; FWB: Functional well-being.
[a] Baseline Body Image Scale: 8 items included in summary score (range 0 to 24), two questions referring to effects of treatment were removed Q8 and Q10 as these were not applicable pre-surgery. Bolding denotes statistical significance at $p < 0.05$.

differences between gynecological cancer types for 'pins and needles', and 'numbness' from 6 weeks to 2 years post-surgery. Specifically, the highest prevalence rates were seen in women with ovarian cancer (42–50 %), compared to endometrial cancer (19–26 %), cervical cancer (19–47 %), and vulvar/vaginal cancer (12–44 %). The wide range in prevalence rates for cervical and vulvar/vaginal cancer is likely a reflection of the low number of cervical (5.4 %) and vulvar/vaginal cancer (9.1 %) participants in our cohort. The high prevalence of numbness, and pins and needles in ovarian cancer could be caused by the higher rates of chemotherapy and the more frequent use of taxane-based chemotherapy treatments received by women with ovarian cancer, which may damage the peripheral nerves [33].

Women with vulvar/vaginal cancer reported higher rates of reddish skin (42 %), tenderness (65 %) and thickness (31 %) during and shortly after treatment (6 weeks-12 months) in comparison with any other gynecological cancer type. This finding may be associated with higher rates of radiation treatment received by women with vulvar/vaginal cancer compared with other gynecological cancers. However, considering the symptoms in this study reflect the *lower-limbs* rather than the genital area, another possible explanation is the higher prevalence of

Table 4
Relationship between cumulative incidence of lymphoedema (BIS) and self-reported leg swelling at T2 to T4 (6 weeks to 24 months) with number of lower-limb symptoms reported at T2 (6 weeks to 3 months).

		Lymphoedema BIS Cumulative Incidence (T2 to T4)[a]					Self-Reported Swelling - LEG Cumulative Incidence (T2 to T4) [a]		
		Unadjusted Model	Adjusted Model[c]				Unadjusted Model	Adjusted Model[c]	
Number of Lower-limb Symptoms at T2[b]	n	OR (95 % CI)	OR (95 % CI)	*p*-value	Number of Lower-limb Symptoms at T2[b]	n	OR (95 % CI)	OR (95 % CI)	p-value
Mild-Extreme									
0	51	ref	ref		0	80	ref	ref	
1+	134	1.75 (0.76, 4.03)	2.12 (0.89, 5.19)	0.101	1 to 2	73	1.22 (0.63, 2.38)	1.25 (0.55, 2.81)	0.598
					3+	146	3.15 (1.78, 5.59)	3.60 (1.74, 7.43)	<0.001

[a] Excluding cases at baseline (T1).
[b] Due to restricted sample size and the absence of a linear relationship between number of symptoms and odds of lymphoedema, dichotomous results are presented for lymphedema measured with BIS (0, 1+ symptoms). Number of symptoms and self-reported leg swelling did show a linear relationship and therefore these results are presented in the categories of 0, 1 to 2, and 3+ symptoms.
[c] Model adjusted for baseline age (years), BMI (kg/m^2), cancer type (endometrial, ovarian, cervical, vulval/vaginal) cancer stage (I, II, III, IV and missing categories), and number of lymph nodes dissected. BIS: bioimpedance spectroscopy.

lower-limb lymphedema in women with vulvar and vaginal cancer compared with other gynecological cancer [34], with high association between lymphedema and reddish skin, and tenderness and thickness of the skin.

While the presence of any given symptom may have been as low as 10 %, the presence of at least one symptom graded as moderate severity was reported by at least one in four and up to 40 % of the sample across the 2-year follow up period. Further, when symptoms reported as being mild in severity are considered, the vast majority of women (>65 %) report at least one symptom. This is relevant since our findings also confirmed that the presence of lower-limb symptoms were associated with higher treatment-related morbidities (higher odds of having lymphedema) and poorer health-related outcomes (worse body image, poorer quality of life, higher anxiety, and depression) – morbidity that adversely influences life and concurrently have significant healthcare resource implications. Consequently, these findings support the surveillance and management of symptoms, even when reported as mild. These findings are also consistent with results from other survivorship studies involving other cancer cohorts, including breast, colorectal and lung cancer [35–37], that is to not disregard symptoms rated as mild, which are often reported to be distressful [36] and troublesome [35].

A limitation of this study was that only 59 % of the sample provided complete data (that is, self-reported symptom data at all 4 time points), and the absence of data on sentinel node versus lymph node dissection. It is likely that those with more advanced disease or higher treatment-related morbidity were more likely to be lost to follow up. However, the subsequent implications of this to the interpretation of our data is likely in the conservative direction. Authors recognize that there could be various underlying causes of symptoms which may differ pre- and post-treatment. Although the cause of symptoms in this study are unclear, a strong predictive relationship between symptoms and subsequent development of lymphedema was found, irrespective of whether symptoms were present at pre-surgery or newly developed post-surgery. A sample size of $n > 400$ enabled analyses to include adjustment for potential confounders. Nonetheless, power was more limited for stratified analyses by lymph node dissection, particularly when lymphoedema was classified according to BIS, highlighting the need for caution when interpreting these findings. The strengths of this study include its prospective, longitudinal design and 2-year follow-up, alongside the comprehensive assessment of lower-limb symptoms ($n = 14$). This study design supports the external validity and generalizability of our findings to the broader gynecological cancer population. Our study highlights the most common lower-limb symptoms in those with gynecological cancer and provides high-quality data to further explore these symptoms independently.

5. Conclusion

Lower-limb symptoms are prevalent up to 2-years post-surgery for gynecological cancers and are associated with higher treatment-related morbidity and poorer health-related outcomes. Future research that identifies strategies to mitigate symptoms and improve health-related outcomes is warranted.

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CRediT authorship contribution statement

Melanie L. Plinsinga: Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Sheree Rye:** Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Tamara Jones:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Dimitrios Vagenas:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Leigh Ward:** Writing – review & editing, Methodology, Conceptualization. **Monika Janda:** Writing – review & editing, Methodology, Conceptualization. **Andreas Obermair:** Writing – review & editing, Methodology, Conceptualization. **Sandra C. Hayes:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

Author Ward provides consultancy services to ImpediMed Ltd., a manufacturer of BIS devices. All other authors declare no conflicts of interest and no direct financial interest related to this manuscript.

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Appendix A. Supplementary data

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