Self-reported signs and symptoms of secondary upper limb lymphoedema related to breast cancer treatment : systematic review

TITLE PAGE

Title: Self-reported signs and symptoms of secondary upper limb lymphoedema related to breast cancer treatment: Systematic review

Running title: Signs and symptoms of lymphoedema

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Abstract

Introduction: Breast cancer survivors with secondary upper limb lymphoedema (ULL) may report a wide range of self-reported symptoms. At the moment, no overview of ULL-specific symptoms is available. The first aim, therefore, was to compare the prevalence rates of self-reported signs and symptoms in people with and without secondary ULL due to breast cancer treatment. The second aim was to determine whether symptoms of lymphoedema could be predictive for the development of ULL. The third aim was to describe the association between the presence/severity of symptoms and the presence/severity of ULL.

Methods: A systematic search was conducted in Medline, Scopus, CINAHL, and EMBASE databases, with key words related to breast cancer, symptoms, and ULL.

Results: Twenty-nine articles were eligible. The most frequently reported signs and symptoms were swelling (80.9%) and heaviness (66.7%) in the ULL group and tenderness (37%) and numbness (27%) in the non-ULL group. Perceived larger arm size, as well as feelings of arm tightness, stiffness, puffiness, pain, sensory disturbances, and functional changes were predictive for the development of ULL. Moderate correlations were found between the presence of swelling, firmness in the past year, and tightness now and severity of ULL. There was also moderate correlation between the presence of swelling and heaviness now and the presence of ULL.

Conclusions: Swelling and heaviness are the most commonly reported symptoms in patients with ULL. The presences of these two symptoms are moderately correlated with the presence and/or severity of ULL. Although limited information regarding the predictive self-reported symptoms for the development of ULL was found. Further research with standardized definitions of ULL and validated questionnaires for self-reported signs and symptoms are needed to confirm which signs and symptoms are related to ULL and which to other upper limb morbidities.

Keywords: Upper limb, lymphedema, breast neoplasms, self-report, signs and symptoms

Introduction

Lymphoedema is a life-long and debilitating condition and a significant health issue (Warren, Brorson, Borud, & Slavin, 2007). Lymphoedema has been defined as an abnormal accumulation of excess water, filtered plasma proteins, as well as extravascular blood and parenchymal cells in the interstitial space (Executive Committee of the International Society of Lymphology, 2016), as a result of lymphatic insufficiency and low transport capacity of the lymphatic system (Tiwari, Coriddi, Salani, & Povoski, 2013). Secondary upper limb lymphoedema (ULL) is a chronic disease that can occur as a result of disruption to the lymphatic surgery from trauma, infection, and cancer treatments (Hidding, Beurskens, van der Wees, van Laarhoven, & Nijhuis-van der Sanden, 2014). The incidence of secondary ULL after breast cancer treatment that involves axillary lymph node dissection ranges between 16% and 21% (DiSipio, Rye, Newman, & Hayes, 2013).

Breast cancer survivors with secondary ULL may experience multiple self-reported symptoms such as swelling, heaviness, tightness, firmness, fatigue, sensory changes such as numbness, tenderness, and pain, and limited range of motion (ROM), which may be due to increased lymph fluid and fibrosis as well as stretching of skin and interstitial tissue (Armer et al., 2019; Fu et al., 2015; Verbelen, Gebruers, Eeckhout, Verlinden, & Tjalma, 2014). However, it is unclear if these changes are strictly related to ULL. For example, functional changes, including limited ROM and decreases in strength, as well as increases in sensory symptoms, may occur due to breast cancer treatments themselves and, therefore, may not be uniquely associated with the presence of ULL (Armer & Fu, 2005; Armer, Radina, Porock, & Culbertson, 2003; Fu et al., 2015). Breast cancer surgery and radiotherapy may result in scar tissue formation, fibrosis, and myofascial dysfunctions such as adhesions and shortening of soft tissues and may contribute to limited ROM (Crosbie et al., 2010). Additionally, pain, numbness, and other sensory changes at the upper limb region may be caused by nerve damage during surgery, chemotherapy and/or radiotherapy (Armer & Fu, 2005; Baron et al., 2002; Ridner, Montgomery, Hepworth, Stewart, & Armer, 2007). Conversely, breast cancer survivors with ULL are suggested to have unique symptoms, such as feelings of swelling or heaviness, that are not present in women without ULL (Armer et al., 2003; Ridner et al., 2007). However, it is not known which symptoms are more associated in those with ULL secondary to breast cancer.

Early identification of ULL is important to alleviate the influence of lymphoedema on function and quality of life (Armer et al., 2019). Objective measurements are mainly used to monitor the presence or progression of ULL (Finlay, Ullah, & Piller, 2013). However, patients' own experience and self-perceived symptoms of ULL may be as important as objective severity of ULL in evaluating the presence of ULL, limb volume change and effectiveness of treatment (Finlay et al., 2013; Han, Heo, Lee, Jeon, & Yoo, 2010). Additionally, it has been stated that physiologic changes occur before visible physical alterations (Han et al., 2010). Thus, in the absence of physical changes, assessment of self-reported symptoms through questionnaires can be useful and cost-effective and would facilitate timely referral to lymphoedema therapists (Fu, 2014). Certain signs and symptoms including sensation (e.g. swelling, heaviness, tightness, redness, and tenderness) and functional changes (e.g. limited ROM) may be early indicators of secondary ULL and may therefore be useful for screening for the presence of ULL (Armer et al., 2003; Kosir et al., 2001). It has been revealed that up to 20% of at-risk breast cancer patients do not have objectively detectable ULL but do report symptoms of ULL (Fu et al., 2015) that may be an indicator of latent stage (Stage 0) of ULL, a subclinical oedema. Additionally, the number and/or severity of self-reported symptoms may be valuable to describe severity of ULL. It has been found that symptoms of swelling and heaviness are highly correlated with the diagnosis and severity of ULL (Han et al., 2010).

Studies investigating self-reported signs and symptoms of ULL have not been systematically reviewed. Understanding the prevalent symptoms of ULL and what symptoms appear to be predictive of or associated with the development of ULL, this could be incorporated more strongly in the clinical assessment for early detection of ULL. The first aim of this review, therefore, was to compare the prevalence rates of the commonly reported signs and symptoms of ULL, in people with and without secondary ULL, whose lymphedema status was determined using objective assessments (including circumference, water displacement, and bioimpedance spectroscopy (BIS)) and subjective assessments (including questionnaires and self-reported lymphoedema status). The second aim of this review was to determine whether symptoms of lymphoedema could be predictive for the development of ULL measured by objective and/or subjective outcomes in longitudinal studies. Lastly, the third aim was to investigate the association between the presence and/or severity of self-

reported symptoms and the presence and/or severity of ULL, determined by objective volume measurements.

Methods

Design

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009).

Research question and search strategy

The research question was determined using the Patient, Measurement/Instrument, Comparison, and Outcome (PICO) approach. It was formulated as: "What are the self-reported signs and symptoms of ULL assessed by objective and subjective measurements in people with secondary ULL related to breast cancer treatment?". A literature search was performed in the medical databases Medline, Scopus, CINAHL, and EMBASE, from their inception to December 5th, 2020. Additionally, other sources were searched (by hand) for records, including unpublished data. Search strategies were developed with the aid of the Health Sciences Library of the University of Sydney (Australia). The search strategy consisted of a combination of free text words and MeSH terms (only for searching Medline). Derivatives of 'breast cancer' and 'lymphoedema' were combined with self-reported signs and symptoms of ULL including 'swelling', 'puffiness', 'tiredness', 'thickness', 'pain', 'numbness', 'heaviness', and 'achiness'. The search strategy for Medline is given in Appendix A.

Eligibility criteria

Inclusion criteria were determined as follows: patients having secondary ULL due to breast cancer treatment for ULL group, breast cancer survivors/healthy volunteers for non-ULL group, an evaluation of self-reported signs and symptoms of ULL, and availability of published and/or ahead of print full-text articles in English or Dutch language. Animal studies, studies including adolescents or children samples, studies not evaluating

physical/self-reported signs and symptoms of ULL, and randomized controlled trials, reviews and meta-analysis were excluded.

Study selection

The study selection was performed in two phases. After removing duplicates, two researchers (ED and ADG) independently screened the titles and abstracts for inclusion in the first screening. Subsequently, full texts were independently screened by the same reviewers. When both reviewers did not agree, the article in question was discussed with a third reviewer (CG) to achieve consensus.

Risk of bias assessment and level of evidence

The quality of each included study was assessed by two researchers independently (ADG and CG) using the Newcastle-Ottawa Quality Assessment tools for cross-sectional, cohort, and case control studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) (Quigley, Thompson, Halfpenny, & Scott, 2018). This checklist is also recommended by the Cochrane Collaboration (Zeng et al., 2015). In all studies, a star rating system was applied to three dimensions including selection, comparability, and exposure/outcome (Stang, 2010). Explanations of all items are provided in Table 1. Based on the overall score (%) and consideration of the impact of missing items, two researchers (ADG and CG) independently rated the studies as low risk of bias (total score ≥70), moderate risk of bias (total score between >40 and <70), or high risk of bias (total score ≤40). Differences were resolved by discussion or consultation with a third reviewer (ED), if necessary. Additionally, based on the previous systematic reviews (Coppieters et al., 2016; DePauw et al., 2017), the level of evidence of each study was determined using the 2005 classification system of the Dutch Institute for Healthcare Improvement (Table 2).

Data extraction

Data extraction of the included studies was performed by two researchers (ADG and CG) and reported in the evidence tables (Table 3a-c). For all studies, the information of interest included: publication (author, year of publication, and country), number of participants, age, time point of data collection, ULL measurement, and measurement of self-reported signs and symptoms of ULL. Varying information was extracted to address each aim. For aim 1,

descriptive values of self-reported symptoms (extracted from total, subscale scores or the scores of single items of the questionnaires) were extracted. For aim 2, the ability of self-reported symptoms to predict the development of ULL, determined using the odds ratio [OR] or hazard ratio [HR], and the corresponding level of significance, was extracted from included longitudinal studies. For aim 3, the associations between the presence/severity of self-reported signs and symptoms of ULL and the presence/severity of ULL assessed by objective volume measurements, determined using the OR, point-biserial correlation coefficient (r), phi-coefficient (r_ϕ), Spearman's rho, coefficient of linear regression model [β], or area under curve (AUC) values and the corresponding level of significance were extracted.

Data synthesis

Because of the heterogeneity in the study designs and assessment methods of ULL and its signs and symptoms, meta-analyses were not feasible. However, results are summarized in different ways. For aim 1, the percentage of people with ULL (objectively or subjectively diagnosed) and the percentage of people without ULL reporting a certain symptom was calculated based on the indicated values (n, %). A ratio was, therefore, calculated of the number of people reporting this symptom to the total number of people with ULL (objectively or subjectively diagnosed) and people without ULL, respectively. No other quantitative analysis was carried out. For aim 2, predictive early symptoms for the development for ULL could not be synthesized and were reported study-by-study due to the limited numbers of studies and different statistical coefficients. For aim 3, associations were grouped based on the reported statistical values such as OR or correlation coefficient. Correlation coefficients were interpreted as <0.40 weak, between 0.41 and 0.74 moderate, between 0.75 and 0.90 strong, >0.90 very strong (Fleiss, 1986).

Results

Study Selection

Through the database search, 10081 records were identified. After the duplicates were removed, 5331 unique records were assessed on the basis of title and abstract. Seventy-eight records were screened for eligibility by full text review. Twenty-nine articles met the inclusion criteria and were retained for data synthesis. The identification and selection process of the articles are demonstrated in Figure 1. During the title, abstract, and full text screen, the percentage of agreement between two reviewers was 86%. The remaining 14% difference was resolved after consultation with the third reviewer.

Study Characteristics

In Tables 3a-c, study characteristics are presented for longitudinal cohort, cross-sectional, and case-control studies, respectively.

The designs of the included studies were as follows: 11 longitudinal cohort (Armer et al., 2019; Brunelle et al., 2020; Bundred et al., 2020; Cidon, Perea, & Lopez-Lara, 2011; Finlay et al., 2013; Gençay Can, Ekşioğlu, & Çakçı, 2019; Hayes, Janda, Cornish, Battistutta, & Newman, 2008; Hidding et al., 2019; Kosir et al., 2001; Norman et al., 2009; Suehiro et al., 2019) (Table 3a), 15 cross-sectional (Ahmed, Prizment, Lazovich, Schmitz, & Folsom, 2008; Armer & Fu, 2005; Armer et al., 2003; Bani et al., 2007; Flores, Nelson, Sowles, & Stephenson RG, 2020; Fu et al., 2015; Fu et al., 2018; Gartner et al., 2010; Kopec et al., 2013; Morris, Lee, Czerniec, & Mangion, 2017; Ridner & Dietrich, 2015; Ridner, Dietrich, & Kidd, 2011; Ridner et al., 2007; Sierla, Lee, Black, & Kilbreath, 2013; Svensson, Dylke, Ward, Black, & Kilbreath, 2020) (Table 3b), and three case-control studies (Honarvar et al., 2016; Korucu, Ucurum, Tastaban, Ozgun, & Kaya, 2020; Mak et al., 2009) (Table 3c). Studies were mainly from the USA (n=13, 45%) (Ahmed et al., 2008; Armer & Fu, 2005; Armer et al., 2019; Armer et al., 2003; Brunelle et al., 2020; Flores et al., 2020; Fu et al., 2015; Fu et al., 2018; Kosir et al., 2001; Norman et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2011; Ridner et al., 2007) and Australia (n=5, 17%) (Finlay et al., 2013; Hayes et al., 2008; Morris et al., 2017; Sierla et al., 2013; Svensson et al., 2020).

The sample sizes of the included studies varied from 25 to 3253 participants with or without ULL (12902 participants in total). Time since surgery/diagnosis of breast cancer or time since

ULL diagnosis ranged from 0 month (BC diagnosis/pre-surgery-immediately after surgery) to 17 years.

Self-reported signs and symptoms of ULL were evaluated using the Lymphedema and Breast Cancer Questionnaire (LBCQ) (Armer & Fu, 2005; Armer et al., 2019; Armer et al., 2003; Brunelle et al., 2020; Bundred et al., 2020; Ridner et al., 2007), the Norman Questionnaire (Ahmed et al., 2008; Norman et al., 2009), the Breast Cancer and Lymphedema Symptom Experience Index (BCLE-SEI) (Fu et al., 2015; Fu et al., 2018), the Lymphedema Symptom Intensity and Distress Survey-Arm (LSIDS-A) (Ridner & Dietrich, 2015; Ridner et al., 2011), the Lymphoedema Functioning, Disability and Health Questionnaire (Lymph ICF) (Hidding et al., 2019), the Arm Symptom Distress Scale (ASDS) (Mak et al., 2009), the Lymphoedema Self-Examination Survey (LYSES) (Morris et al., 2017), and the Functional Assessment of Cancer Therapy-Breast tool (version 4) (FACT-B) (Suehiro et al., 2019). The Norman Questionnaire was used for both diagnosis of ULL and self-reported symptoms in two included studies (Ahmed et al., 2008; Norman et al., 2009). 12 studies (Bani et al., 2007; Cidon et al., 2011; Finlay et al., 2013; Flores et al., 2020; Gartner et al., 2010; Gençay Can et al., 2019; Hayes et al., 2008; Honarvar et al., 2016; Kopec et al., 2013; Korucu et al., 2020; Sierla et al., 2013; Svensson et al., 2020) assessed self-reported symptoms by a self-developed questionnaire or questions. The assessment method for the signs and symptoms of ULL was not indicated in one study (Kosir et al., 2001).

Across these studies, several methods were used for the assessment of secondary ULL. For the objective volume assessments of ULL, two or more assessment methods were used in five studies (Bundred et al., 2020; Finlay et al., 2013; Honarvar et al., 2016; Ridner et al., 2007; Suehiro et al., 2019). Circumference measurements (Armer & Fu, 2005; Armer et al., 2003; Fu et al., 2015; Gençay Can et al., 2019; Hidding et al., 2019; Honarvar et al., 2016; Korucu et al., 2020; Kosir et al., 2001; Mak et al., 2009; Ridner et al., 2007; Suehiro et al., 2019), BIS (Bundred et al., 2020; Finlay et al., 2013; Hayes et al., 2008; Morris et al., 2017; Ridner et al., 2007; Suehiro et al., 2019; Svensson et al., 2020), as well as limb volume assessed by water displacement method (Honarvar et al., 2016; Kopec et al., 2013) and perometry (Brunelle et al., 2020; Bundred et al., 2020; Finlay et al., 2013; Ridner et al., 2007) were used to objectively define the presence of ULL. One study used ultrasound in order to measure skin and subcutaneous thickness, subcutaneous echogenicity, and subcutaneous-

echo-free space (Suehiro et al., 2019). The diagnostic threshold for ULL demonstrated large variability between the studies. ULL was determined to be present if the following inter-limb size or volume differences between the affected and unaffected limbs were reached: ≥1.5 centimeter (cm) (Mak et al., 2009), >/≥2 cm (Armer & Fu, 2005; Armer et al., 2003; Honarvar et al., 2016; Korucu et al., 2020), >200 milliliter (ml) (Fu et al., 2015), ≥5% (Brunelle et al., 2020), >/≥10% (Armer et al., 2019; Brunelle et al., 2020; Bundred et al., 2020; Gençay Can et al., 2019; J.T. Hidding et al., 2019; Kosir et al., 2001; Suehiro et al., 2019), or ≥20% (Armer et al., 2019) difference. Alternately, if BIS was used, the threshold used was an inter-arm ratio of impedance values >/≥ 3SD (Bundred et al., 2020; Hayes et al., 2008; Suehiro et al., 2019; Svensson et al., 2020) or >/≥ 2SD (Bundred et al., 2020; Svensson et al., 2020) above the mean of a normative population. One study (Suehiro et al., 2019) also used the tentative normal ranges (mean ± 2 SD) for the differences in circumferences and skin or subcutaneous thicknesses in order to diagnose ULL. The definition of ULL was not indicated in four studies (Finlay et al., 2013; Kopec et al., 2013; Morris et al., 2017; Ridner et al., 2007). Four studies based ULL diagnosis on a subjective assessment of ULL, namely the Norman Questionnaire (Ahmed et al., 2008; Norman et al., 2009; Sierla et al., 2013) and a self-developed questionnaire (Bani et al., 2007). Four studies also used patient-reported ULL status (Cidon et al., 2011; Flores et al., 2020; Fu et al., 2018; Gartner et al., 2010) based on the presence of subjective sensations of swelling, heaviness and/or tiredness (Cidon et al., 2011; Gartner et al., 2010) or a previous history of ULL diagnosis or treatment (Flores et al., 2020; Fu et al., 2018). The assessment method for the identification of the presence of ULL was not indicated in two studies (Ridner & Dietrich, 2015; Ridner et al., 2011).

In the present systematic review, all studies reported prevalence rates of self-reported signs and symptoms, of which nine studies (Ahmed et al., 2008; Armer & Fu, 2005; Bani et al., 2007; Fu et al., 2015; Korucu et al., 2020; Mak et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2007; Svensson et al., 2020) reported prevalence rates of self-reported sign and symptoms for participants with ULL and without ULL as well (aim 1). Five longitudinal studies investigated predictive symptoms for the development of ULL (measured using perometry, BIS, circumference measurement, or valid/reliable questionnaire) (aim 2) (Brunelle et al., 2020; Bundred et al., 2020; Hayes et al., 2008; Hidding et al., 2019; Norman et al., 2009). 12 studies indicated the associations between the presence/severity of self-reported symptoms

and the presence/severity of ULL as determined by objective measurements (Armer et al., 2003; Brunelle et al., 2020; Bundred et al., 2020; Finlay et al., 2013; Flores et al., 2020; Fu et al., 2015; Gençay Can et al., 2019; Hidding et al., 2019; Mak et al., 2009; Ridner et al., 2007; Suehiro et al., 2019; Svensson et al., 2020) (aim 3).

Risk of Bias within Studies and Level of Evidence

Risk of bias of the included studies ranged from 30% to 90%: a high risk of bias was found for seven studies (Ahmed et al., 2008; Fu et al., 2018; Kopec et al., 2013; Kosir et al., 2001; Morris et al., 2017; Ridner & Dietrich, 2015; Ridner et al., 2011), a moderate risk of bias for 13 studies (Armer et al., 2003; Bani et al., 2007; Finlay et al., 2013; Flores et al., 2020; Gartner et al., 2010; Gençay Can et al., 2019; Hidding et al., 2019; Honarvar et al., 2016; Mak et al., 2009; Norman et al., 2009; Ridner et al., 2007; Sierla et al., 2013; Suehiro et al., 2019), and a low risk for bias for nine studies (Armer & Fu, 2005; Armer et al., 2019; Brunelle et al., 2020; Bundred et al., 2020; Cidon et al., 2011; Fu et al., 2015; Hayes et al., 2008; Korucu et al., 2020; Svensson et al., 2020) (Table 1). Based on the 2005 classification system of the Dutch Institute for Healthcare Improvement, the level of evidence was determined to be "B" for 17 studies with a comparative design (Ahmed et al., 2008; Armer & Fu, 2005; Armer et al., 2019; Armer et al., 2003; Bani et al., 2007; Brunelle et al., 2020; Bundred et al., 2020; Flores et al., 2020; Fu et al., 2015; Fu et al., 2018; Honarvar et al., 2016; Korucu et al., 2020; Mak et al., 2009; Norman et al., 2009; Ridner et al., 2007; Sierla et al., 2013; Svensson et al., 2020) and "C" for 12 non-comparative studies (Cidon et al., 2011; Finlay et al., 2013; Gartner et al., 2010; Gençay Can et al., 2019; Hayes et al., 2008; Hidding et al., 2019; Kopec et al., 2013; Kosir et al., 2001; Morris et al., 2017; Ridner & Dietrich, 2015; Ridner et al., 2011; Suehiro et al., 2019). For the "ascertainment of exposure" item, patient-reported ULL status as a ULL diagnosis used by three studies (Cidon et al., 2011; Flores et al., 2020; Fu et al., 2018; Gartner et al., 2010) and no information on the assessment method of the presence of ULL in two studies (Ridner & Dietrich, 2015; Ridner et al., 2011) may be related to the moderate/high risk of bias. Additionally, although the objective assessment method for the assessment of ULL was indicated in four studies, definition of ULL was not described properly (Finlay et al., 2013; Kopec et al., 2013; Morris et al., 2017; Ridner et al., 2007).

Synthesis of Results

A total of 35 self-reported signs and symptoms of ULL were extracted from the different questionnaires used in the 29 included studies. The numbers (%) of studies reporting each self-reported ULL symptom are listed in Table 4. Additionally, minimum and maximum prevalence rates of each ULL symptom across all studies reporting that ULL symptom were extracted when available.

Differences between ULL and non-ULL groups (AIM 1)

Data (the presence of each symptom in ULL and non-ULL patients; n or %) of nine studies reporting 16 symptoms of participants with and without ULL were collated (n=2849) (Ahmed et al., 2008; Armer & Fu, 2005; Bani et al., 2007; Fu et al., 2015; Korucu et al., 2020; Mak et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2007; Svensson et al., 2020) (Table 3b-c). The non-ULL group comprised of breast cancer survivors without ULL in eight studies (Ahmed et al., 2008; Armer & Fu, 2005; Bani et al., 2007; Fu et al., 2015; Korucu et al., 2020; Mak et al., 2009; Ridner & Dietrich, 2015; Svensson et al., 2020). Only one study (Ridner et al., 2007) included healthy volunteers as a comparison group.

Based on the data in nine studies, prevalence rates were calculated by the first author (CG) for the following self-reported symptoms: swelling, heaviness, tightness, firmness, tingling, perceived larger limb size, aching, limited ROM, tenderness, pain, paresthesia, numbness, stabbing, redness, increased arm temperature, and burning (Figure 2) (Ahmed et al., 2008; Armer & Fu, 2005; Bani et al., 2007; Fu et al., 2015; Korucu et al., 2020; Mak et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2007; Svensson et al., 2020). For participants with ULL, the most prevalent symptoms were swelling (80.9%) and heaviness (66.7%). Burning sensations were reported the least frequently in only 15.4%. In the non-ULL group, tenderness was reported most frequently (36.6%) followed by numbness (27.1%). Sensations of increased arm temperature were reported least frequently (3.4%) in the non-ULL group.

Five out of nine studies performed a statistical comparison of prevalence rates between participants with and without ULL. Significant differences between groups were found for the prevalence of nine self-reported symptoms (Bani et al., 2007; Fu et al., 2015; Mak et al., 2009; Ridner et al., 2007; Svensson et al., 2020) and three patient detected physical signs (Svensson et al., 2020). Swelling in the arm, breast/chest now or in the past year (Fu et al.,

2015; Mak et al., 2009; Ridner et al., 2007; Svensson et al., 2020), arm tightness/firmness (Fu et al., 2015; Ridner et al., 2007; Svensson et al., 2020), arm heaviness (Fu et al., 2015; Ridner et al., 2007; Svensson et al., 2020), limited arm ROM (Bani et al., 2007; Fu et al., 2015; Ridner et al., 2007), pain (Bani et al., 2007; Mak et al., 2009) and sensory disturbances including paraesthesia and/or tingling in the axilla/arm (Bani et al., 2007; Fu et al., 2015; Mak et al., 2009) or aching (Fu et al., 2015) in the arm were found more frequently in the ULL group than non-ULL group (comprising of breast cancer survivors and/or health volunteers). Regarding patient detected physical signs, the positive pinch test on forearm and upper arm and pitting oedema were more prevalent in the ULL group when compared to the non-ULL group (comprising of breast cancer survivors) (Svensson et al., 2020). Additionally, two studies indicated that ULL group reported significantly worse severity in the symptoms of swelling, pain, tingling, limited arm ROM (Mak et al., 2009), and heaviness (Korucu et al., 2020) than the non-ULL group (comprising of breast cancer survivors).

Predictive self-reported signs and symptoms for the development of ULL (AIM 2)

A total of 14 self-reported symptoms were found as a predictor for the development of ULL in three studies (Brunelle et al., 2020; Hayes et al., 2008; Norman et al., 2009) with longitudinal design (Table 3a). A third longitudinal study (Hidding et al., 2019) reported measures of accuracy of certain signs and symptoms for the prediction of ULL. The presence of ULL was determined by objective volume assessments such as perometry (Brunelle et al., 2020), BIS (Hayes et al., 2008), and circumference measurements (Hidding et al., 2019). The other study assessed ULL with the Norman Questionnaire (Norman et al., 2009). It was found that perceived arm size larger was a predictor for the development of ULL (for RVC ≥ 10%, HR 3.09 95% CI 1.61 to 5.89 and for RVC ≥ 5%, HR 1.91 95% CI 1.21 – 3.04) within the first 5 years post-surgery (Brunelle et al., 2020). Hayes et al. (Hayes et al., 2008) reported that the presence of general upper extremity symptoms on the affected side (including stiffness, pain, tingling, numbness, weakness, and limited ROM) at 6 months after surgery (baseline) was predictive for the development of ULL between 9 and 18 months after surgery (OR 3.1, 95%CI 0.9 to 10.7). Norman et al. (Norman et al., 2009) revealed that several symptoms, which were present before the first identification of ULL, were predictors of later ULL, namely, tightness for clothing or jewelry (HRs 5.47 and 7.37, respectively), altered skin sensation in the affected arm (HRs 3.12), firmness in skin (HR 3.52), puffiness

(HR 4.20), swelling after exercise (HR 3.45), pain (HR 2.42), indentations in skin (HR 1.88), and difficulty in writing (HR 1.35). Heaviness and swelling had Area Under the Curve (AUC) of 0.78 and 0.82, respectively, for the detection of an arm volume difference of > 10% (Hidding et al., 2019).

Association between self-reported symptoms and objective ULL (AIM 3)

In four cross-sectional/case control studies (Armer et al., 2003; Fu et al., 2015; Mak et al., 2009; Svensson et al., 2020) (Table 3b-c), (n=535) the following symptoms were found to be associated with the presence of objectively detected ULL using circumference measurement (Armer et al., 2003; Fu et al., 2015; Mak et al., 2009; Svensson et al., 2020) and BIS (Svensson et al., 2020), reported as odds ratios for ULL. The highest odds were found for: swelling now (ORs 47.40 to 561) (Armer et al., 2003; Fu et al., 2015; Mak et al., 2009; Svensson et al., 2020), heaviness now/in past year (ORs 5.0 to 17.49) (Armer et al., 2003; Fu et al., 2015; Svensson et al., 2020), arm firmness (OR 10.33) (Fu et al., 2015), increased arm temperature (OR 9.07) (Fu et al., 2015). Other signs and symptoms show lower but significant odds for ULL: numbness (OR 2.19 to 9.90) (Armer et al., 2003; Fu et al., 2015; Mak et al., 2009), limited ROM in arm/elbow/wrist/finger (OR 2.23 to 5.86) (Fu et al., 2015; Mak et al., 2009), tightness (OR 5.7) (Svensson et al., 2020), pain in breast, chest, or arm (ORs 1.99 to 2.81) (Fu et al., 2015; Mak et al., 2009), tingling (OR 5.54) (Fu et al., 2015), aching (OR 5.14) (Fu et al., 2015), burning (OR 2.86) (Fu et al., 2015), tenderness (OR 2.47) (Fu et al., 2015), redness (OR 2.47) (Fu et al., 2015), and stiffness (OR 3.55) (Fu et al., 2015). Additionally, one study (n=100) reported the associations between self-reported physical signs and the presence of objectively detected ULL using BIS (Svensson et al., 2020). There were significant associations between positive pinch test on the upper arm (OR 22.9) and forearm (OR 45.7), and skin pitting (OR 44.9) and the presence of ULL.

Three studies (n=61) reported correlation coefficients. Two studies described the associations between the presence of symptoms including feeling of tightness, numbness, swelling and skin firmness and the severity of objectively detected ULL (Gençay Can et al., 2019; Ridner et al., 2007) (Table 3a-b). Another study reported associations between the presence of swelling and heaviness and the presence of ULL (Hidding et al., 2019) (Table 3a). Ridner et al. (Ridner et al., 2007) described moderate correlations between the presence of

swelling in the past year and severity of ULL measured with circumference measurements (r=0.45; p≤0.001) and BIS measurement (r=0.62; p≤0.001). Furthermore, the presence of firmness in the past year was found to be moderately correlated with severity of ULL measured with Bioimpedance measurements (r=0.68; p≤0.001) (Ridner et al., 2007). Gençay Can et al. (Gençay Can et al., 2019) found moderate correlation between tightness now and the severity of affected arm volume measured by circumference measurements (r=0.45; p=0.02). A week correlation was found between the feeling of numbness now and the severity of affected arm volume (r=0.37; p0.04) (Gençay Can et al., 2019). Hidding et al. (Hidding et al., 2019) described a moderate correlation between the presence of feelings of swelling currently and heaviness with the presence of ULL (defined as an arm volume difference of >10% using the data from circumference measurements) (phi correlation coefficient, r_{ϕ}=0.64, p<0.05).

In two longitudinal studies, the associations between the presence of self-reported symptoms and the progression to ULL (RVC ≥ 10%) measured by perometry (Brunelle et al., 2020; Bundred et al., 2020) and/or BIS (Bundred et al., 2020) (Table 3a). The presence of five self-reported symptoms such as perceived larger arm size (HR 6.44), tighter sleeve fit (HR 4.17), tighter sleeve cuff fit (HR 6.11), tighter ring fit (HR 1.82), and swelling (HR 3.24) was found to be significantly associated with the presence of ULL (RVC ≥ 10%) (Brunelle et al., 2020). Additionally, Bundred et al. (Bundred et al., 2020) indicated that self-reported feeling of swelling at pre-surgery was significantly associated with the presence of ULL at 36 months post-surgery (OR 2.06).

Lastly, two longitudinal studies (Finlay et al., 2013; Gençay Can et al., 2019) indicated a decrease in self-reported symptoms after a 4-week intervention. Finlay et al. (n=80) reported that an improvement in ULL (measured with BIS and/or perometry) after a 4-week intervention was associated with a decrease of symptoms including heaviness (βs ranged from 17.5 to 54.1), tightness (βs 13.8 and 33.4), pain (β 37.8), and perceived limb size (βs ranged from 29.0 to 47.9). Additionally, there was a significant decrease in the percentages of self-reported swelling (from 88% to 24%), tightness (from 72 % to 12%), heaviness (from 60% to 8%), and numbness (from 40% to 4%) in a study of Gençay Can et al. (n=25) (Gençay Can et al., 2019) (Table 3a).

Discussion

To our knowledge, the present study is the first systematic review summarizing the signs and symptoms of ULL. The present study provided a structured overview of prevalence rates of self-reported signs and symptoms in participants with and without secondary ULL. Additionally, we aimed to determine whether self-reported symptoms of lymphoedema could be predictive for the development of ULL over time by the longitudinal studies. Lastly, we investigated the associations between the presence or severity of self-reported symptoms and the presence or severity of ULL assessed by objective volume measurements. The present systematic review has revealed a total of 35 signs and symptoms of ULL described in the literature. Collated data showed average percentage rates of these symptoms ranging between 15.4% (burning) and 80.9% (swelling) in patients with ULL. Swelling (80.9%) and heaviness (66.7%) were the most prevalent symptoms in patients with ULL, whereas breast cancer patients without ULL most commonly reported tenderness (36.6%) and numbness (27.1%). Moreover, prevalence rates of nine self-reported symptoms (e.g. swelling, limited ROM, tightness/firmness, heaviness, and sensory disturbances including pain, paresthesia, tingling, and aching) and three patient detected physical sign (e.g. positive pinch test on upper arm and forearm and pitting oedema) were higher in people with ULL than those without ULL. The presence of perceived larger arm size, as well as arm tightness, stiffness, puffiness, pain, sensory disturbances (numbness and tingling), and functional changes (weakness, limited ROM, swelling after exercise, and difficulty in writing) were identified as predictors for the development of ULL. Furthermore, the highest odds of the associations between the presence of objectively detected ULL and self-reported symptoms were found for swelling now, heaviness now/in the past year, firmness, and feelings of increased arm temperature. There were also strong odds of associations between the presence of pitting oedema and patient reported differences in tissue texture of affected and unaffected limbs. Moderate correlations were found between severity of ULL and swelling in the past year, firmness in the past year, and tightness now. There were also moderate correlations between the presence of swelling and heaviness now and the presence of ULL.

In the literature, self-reported symptoms are considered as important data to discriminate patients with and without ULL and to detect ULL at an early stage of development (Armer et

al., 2008; Armer et al., 2003). In the present systematic review, not surprisingly, self-reported symptoms including swelling and heaviness are the most commonly reported symptoms in patients with ULL. Based on the evidence obtained from the literature, swelling and heaviness are unique self-reported symptoms for patients with ULL as higher prevalence rates have been presented in ULL patients than in those without ULL. However, we found limited information regarding the predictive self-reported symptoms for the development of ULL (Brunelle et al., 2020; Hayes et al., 2008; Norman et al., 2009; Svensson, Dylke, Ward, Black, & Kilbreath, 2019), in particular symptoms of perceived larger arm size, tightness, firmness puffiness, and pain may be predictor of ULL. However, in two studies investigating the predictive signs and symptoms for the development of ULL (Hayes et al., 2008; Norman et al., 2009), time frames between the predictor and diagnosis of ULL are not very wide or even not specified. One study (Brunelle et al., 2020) indicated that 58% of people who developed ULL had the symptom of perceived larger arm size approximately 6 months before ULL onset (range= 68 months before to 50 months after ULL onset). Median time to report symptoms related to increased size of body part (e.g. perceived larger arm size, tightness or heaviness) was ≥12 months post-surgery (from 12 to 21 months post-surgery).

In addition to identifying the presence of specific symptoms, Fu et al. (Fu et al., 2015) suggest that the number of symptoms experienced may be used as an early diagnostic indication for the detection of ULL as well. To discriminate breast cancer survivors with ULL from healthy women, diagnostic cut-off value of three symptoms (sensitivity of 94% and specificity of 97%) is suggested. Additionally, diagnostic cut-off of nine symptoms (sensitivity of 64% and a specificity of 80%) was recommended for the discrimination between survivors with ULL and at-risk survivors (Fu et al., 2015). Furthermore, not only the number of symptoms but also symptom severity and distress related to certain signs and symptoms may be relevant. Symptom distress entails the patient's complex emotional responses evoked by physical symptoms in the context of patients with ULL (Fu & Rosedale, 2009). It has been reported that it is vitally essential to evaluate symptom distress encompassing temporal, situational, and attributive dimensions in patients with ULL (Fu & Rosedale, 2009). In the present systematic review, two studies (Korucu et al., 2020; Mak et al., 2009) compared the differences in severity of symptoms between patients with ULL and non-ULL. Patients with ULL indicated more severe ULL symptoms including heaviness (Korucu et al.,

2020), swelling, pain, tingling, and limited arm ROM (Mak et al., 2009) when compared to those without ULL. Additionally, symptom distress was worse in patients with ULL than in those without ULL (Mak et al., 2009).

An interesting finding of this review is the common report of pain and other sensory symptoms e.g. paraesthesia, aching, numbness, tingling, and tenderness in people with ULL (Bani et al., 2007; Fu et al., 2015; Mak et al., 2009). Included studies demonstrated that the sensation of pain increased the odds of ULL by twofold (Fu et al., 2015; Mak et al., 2009). However, the debate on pain as a sign of ULL or not remains due to the use of different questionnaires for the assessment of signs and symptoms of ULL and different diagnostic tools and definitions for the diagnosis of ULL. Based on previous data, it is possible that pain, sensory changes (e. g. aching, numbness, and tenderness) and ULL coexist. Potentially, they may both be products of more involved treatment regimens such as mastectomy, axillary lymph node dissection, and/or radiation therapy (De Groef et al., 2017; Hidding et al., 2014; Kootstra et al., 2013; Wang et al., 2016). Included studies investigating differences in pain and sensory changes in people with and without ULL found that mastectomy (Bani et al., 2007; Fu et al., 2015), axillary lymph node dissection (Fu et al., 2015), and radiotherapy (Bani et al., 2007; Fu et al., 2015) were more frequent in the ULL group than in the non-ULL group. Pain and sensory changes, therefore, may be associated with ULL but may also be explained by other possible causes, including nerve damage during surgery, chemotherapy or radiotherapy and local structural impairments associated with shoulder pain due to more invasive breast cancer treatments. The damage of the intercostal brachial and thoracodorsal nerve occurring during axillar lymph node dissection has been considered as a major cause of axillary paresthesia and pain (Gartner et al., 2009; Hayes et al., 2012). Additionally, in breast cancer survivors, musculoskeletal disorders related to shoulder pathology and altered upper quadrant biomechanics may be sources of limited ROM and nociception (Crosbie et al., 2010; Stubblefield & Keole, 2014). Nociceptive pain characteristics may also include symptoms such as heaviness, pain, and tightness. In addition to the nociceptive and neuropathic problems described above, sensitization of the central nervous system (including widespread pain hypersensitivity, enhanced temporal summation, and efficacious endogenous descending pain inhibition) may contribute as well to the wide range of self-reported signs and symptoms, in particular ‘pain’ (Edwards et al., 2013). It was found that

38% of breast cancer survivors with pain more than one year after breast cancer surgery had self-reported symptoms of central sensitization (De Groef et al., 2018). For these reasons, clinically, to determine if an individual's pain and other signs and symptoms are primarily associated with ULL, a thorough assessment by clinicians who have experience in both pain and lymphoedema is needed. An exploration of possible peripheral (e.g. nociceptive and/or neuropathic problems) or central (e.g. hypersensitivity of central nervous system) causes should be considered for further examination and treatment, regardless of limb difference. Furthermore, the contribution of psychological factors (e.g. body vigilance and catastrophizing) should be considered.

Limited arm ROM has been generally considered as an impairment resulting from more invasive breast cancer treatments rather than a specific symptom of ULL (Hidding et al., 2014). However, the present systematic review demonstrated that people with ULL experienced limited arm ROM more frequently than those without ULL (Bani et al., 2007; Fu et al., 2015; Ridner et al., 2007). Specifically in patients with ULL, increased limb volume and adaptations in mechanical properties of soft tissue including hypertrophy and pathological fibrotic changes (Hashemi et al., 2018) may further enhance the emergence and persistence of limited arm ROM. Similar as for the symptom 'pain', clinical examination should seek to differentiate between the exact cause of these impairments.

This systematic review highlighted several issues in the assessment of self-reported signs and symptoms of ULL. Firstly, there is a lack of uniformity in the use of measurement tools for the assessment of self-reported signs and symptoms of ULL. In the present systematic review, self-reported signs and symptoms of secondary ULL were measured by the LBCQ (19 symptoms) in six studies (Armer & Fu, 2005; Armer et al., 2019; Armer et al., 2003; Brunelle et al., 2020; Bundred et al., 2020; Ridner et al., 2007), and by the Norman Questionnaire (10 items) (Ahmed et al., 2008; Norman et al., 2009), BCLE-SEI (24 symptoms) (Fu et al., 2015; Fu et al., 2018), or LSIDS-A (14 symptoms) (Ridner & Dietrich, 2015; Ridner et al., 2011) in two different studies. Beyond the presence of symptoms of ULL, symptom intensity and distress are evaluated using the Norman Questionnaire, BCLE-SEI, and LSIDS-A. Although it has been indicated that these questionnaires are comprehensive, time-efficient, and cost-effective outcome measures (Ridner & Dietrich, 2015), they are not well studied in terms of all psychometric properties (internal consistency, test-retest reliability, diagnostic accuracy, and

content, construct, and/or discriminant validity) and have been generally assessed in a single population or the same population in which the development study was performed. For these reasons, it should be questioned if they have acceptable validity and reliability and the consistency in the results between different populations. However, a significant proportion of the studies (41%) in the present systematic review still use self-developed questionnaires or measures, which were developed based on the opinions of the research teams without reliability and validity testing. Additionally, the vast majority of studies included in the present systematic review were undertaken in Western populations, which may decrease generalizability. It has been reported that the descriptions of sensory symptoms may convey different meanings among different ethnicities and cultures (Apfel et al., 2001). In accordance with the cross-cultural differences in the language of sensory symptomatology, the translations of "tingling" and "needles" sensations may be difficult for the target population (Shaikh, Bentley, & Kamerman, 2013). Furthermore, the terms "numbness", "tingling", and "needless" can be used interchangeably when describing the sensory symptoms (Crawford, Bouhassira, Wong, & Dukes, 2008). Thus, content validity of the assessment tools investigating the signs and symptoms of ULL may be lower than the original questionnaire (Shaikh et al., 2013).

Limitations

The findings of the present systematic review should be interpreted in the light of some limitations. The first limitation was the high to moderate risk of bias of the majority of the included studies (20 studies of 29) mainly depending on the items "ascertainment of exposure" and "comparability" of Newcastle-Ottawa Scale. Following characteristics of included studies lead high to moderate risk of bias: 1) the presence of patient-reported ULL rather than objective diagnosis of ULL, 2) a lack of ULL definition for the diagnosis even if objective assessment for ULL was used, 3) not controlled for type of surgery and/or time since surgery, and 4) a lack of sample size calculations for case-controlled studies. Additionally, studies were from low levels of evidence since they were designed as cross-sectional or case control studies.

Suggestions for further research and clinical implications

According to the results of the present systematic review, there is a clear gap, with limited high quality studies with longitudinal design to prospectively investigate whether certain signs and symptoms of ULL are accurate predictors for the development of ULL. In addition, more studies are needed to investigate the underlying physiological mechanisms (e.g. musculoskeletal/nociceptive, neuropathic, central, and/or the lymphoedema itself) of the symptoms of ULL to avoid confusion with signs and symptoms of other side effects of breast cancer treatments (Fu et al., 2015).

We suggest that assessments may include both objective methods for volume differences and subjective methods, such as valid and reliable questionnaires for ULL related symptoms for the evaluation of different aspects of ULL. It is noted that pre-operative volume and symptom assessments are essential to determine the changes after breast cancer surgery more accurately (Armer et al., 2003). Based on the recent studies, the presence of key symptoms of lymphoedema such as swelling and heaviness, and perceived arm size larger and patient detected physical signs such as pitting oedema and differences in inter-limb texture may be important criteria for follow-up assessments by a lymphoedema physiotherapist (Brunelle et al., 2020; Svensson et al., 2020). Furthermore, in the absence of an objective ULL but presence of self-reported signs and symptoms, other musculoskeletal, neuropathic, and central processing related causes should be further investigated. However, in the present systematic review, the majority of included studies have moderate/high risk of bias, they use different self-reported or validated questionnaires and various definitions and methods for the diagnosis of ULL. It is difficult, therefore, to make firm suggestions for clinical practice, particularly regarding pain as a sign of ULL.

Additionally, it may be difficult to evaluate some symptoms, including heaviness, tightness, pain, and sensory symptoms such as numbness, tingling, and needles since people may describe these symptoms in different ways (Finlay et al., 2013) based on the differences in their definitions and various cultural backgrounds on the perception of sensory symptoms (Apfel et al., 2001; Crawford et al., 2008; Shaikh et al., 2013). Thus, the validity and reliability of the measurement tools for assessing the signs and symptoms of ULL should be tested in different cultures and cross-cultural adaptations should be performed before using them. Additionally, high-quality studies with proper case definitions, including pre-surgery

evaluations for the presence of objective ULL and its symptoms, controlled for important factors, such as the type of surgery and time since surgery, and performed in different cultures and ethnicities are needed.

In conclusion, based on the studies included in the present systematic review, subjective feelings of swelling and heaviness are the most commonly reported symptoms in people with ULL and these two symptoms have the strongest associations with the presence of ULL. Additionally, the presence of swelling and heaviness are moderately correlated with the presence and/or severity of ULL. The symptom of perceived larger limb size might be a potential predictor for the development of lymphoedema in people at-risk ULL. Evaluating self-reported swelling, heaviness, and perceived larger arm size may facilitate early diagnosis, in addition to using diagnostic measurements for ULL. In addition to key symptoms, patient detected physical signs (pitting oedema and/or tissue texture differences between limbs) may be included in the screening process. Furthermore, the underlying cause of the presence of pain and sensory symptoms such as paraesthesia, aching, numbness, tingling, and tenderness may be investigated in order to start appropriate treatment. Unfortunately, high to moderate risk of bias of the majority of the studies, high variations in the assessment methods for symptoms of ULL, and limited numbers of studies made it difficult to draw firm conclusions on the predictive symptoms for the development of ULL and the association among the self-reported symptoms and ULL. Furthermore, the link between pain and ULL cannot be clarified and requires future investigation. To bring more clarity on the predictive symptoms for the development of ULL and the highly associated symptoms with ULL, prospective and longitudinal studies including preoperative assessment of limb volume and symptoms, using valid and reliable questionnaires tested in different population, and also investigating symptom intensity and distress are warranted. Lastly, to increase generalizability, we suggest that further studies should be conducted in non-Western populations taking into account multisite enrollment and data collection.

Conflict of Interest:

The authors declare that they have no conflict of interest. Authors have full control of all data and they agree to allow the journal to review the data if requested.

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Table 1. The methodological quality of cross-sectional, cohort, and case control studies.

COHORT STUDIES										
	SELECTION				COMPARABILITY	OUTCOME				
	Representativeness	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration outcome of interest was not present at baseline	Controlled for **type of surgery** and **time since surgery**	Assessment of the outcome	Follow-up long enough **(12 months)**	Adequacy of follow-up **(>85%)**	**Total score (%)**	**Total Risk of Bias**†
Armer, 2019 (Armer et al., 2019)	+	+	+	+	-/-	++	+	-	70	**Low**
Brunelle, 2020 (Brunelle et al., 2020)	+	+	+	-	-/-	++	+	+	70	**Low**
Bundred, 2020 (Bundred et al., 2020)	+	+	+	+	+/+	++	+	-	90	**Low**
Cidon, 2011 (Cidon et al., 2011)	+	+	+	+	-/+	+	+	-	70	**Low**
Finlay, 2013 (Finlay et al., 2013)	+	+	+	-	-/-	+	-	+	50	**Moderate**
Gençay Can, 2019 (Gençay Can et al., 2019)	+	+	+	-	-/-	+	-	+	50	**Moderate**
Hayes, 2008 (Hayes et al., 2008)	+	+	+	-	-/+	+	+	+	70	**Low**
Hidding, 2019 (Hidding et al., 2019)	+	+	+	-	-/-	++	-	+	60	**Moderate**
Kosir, 2001 (Kosir et al., 2001)	+	+	+	-	-/+	-	-	-	40	**High**
Norman, 2009 (Norman et al., 2009)	+	+	+	-	-/-	+	+	-	50	**Moderate**
Suehiro, 2019 (Suehiro et al., 2019)	+	+	+	-	-/-	++	+	-	60	**Moderate**
CROSS-SECTIONAL STUDIES										
	SELECTION				COMPARABILITY	OUTCOME				
	Representativeness	Sample size	Non-respondents	Ascertainment of exposure	Controlled for **type of surgery** and **time since surgery**	Assessment of the outcome	Statistical test		**Total score (%)**	**Total Risk of Bias***
Ahmed, 2008 (Ahmed et al., 2008)	+	-	-	+	-/-	++	-		40	**High**
Armer, 2005 (Armer & Fu, 2005)	+	-	+	++	-/-	++	+		70	**Low**
Armer, 2003 (Armer et al., 2003)	+	-	-	++	-/-	++	+		60	**Moderate**
Bani, 2007 (Bani et al., 2007)	+	-	-	+	+/-	+	+		50	**Moderate**
Flores, 2020 (Flores et al., 2020)	+	-	-	+	+/+	+	+		60	**Moderate**
Fu, 2018 (Fu et al., 2018)	+	-	-	+	-/-	++	-		40	**High**
Fu, 2015 (Fu et al., 2015)	+	-	+	++	-/-	++	+		70	**Low**

Table 1. The methodological quality of cross-sectional, cohort, and case control studies (continued).									
	Representativeness	Sample size	Non-respondents	Ascertainment of exposure	Controlled for **type of surgery** and **time since surgery**	Assessment of the outcome	Statistical test	**Total score (%)**	**Total Risk of Bias***
Gartner, 2010 (Gartner et al., 2010)	+	-	+	+	-/-	+	+	50	**Moderate**
Kopec, 2013 (Kopec et al., 2013)	-	-	-	++	-/-	+	-	30	**High**
Morris, 2017 (Morris et al., 2017)	+	-	-	++	-/-	+	-	40	**High**
Ridner, 2015 (Ridner & Dietrich, 2015)	+	-	+	-	-/-	++	-	40	**High**
Ridner, 2011 (Ridner et al., 2011)	+	-	-	-	-/-	++	-	30	**High**
Ridner, 2007 (Ridner et al., 2007)	+	-	-	++	-/-	++	+	60	**Moderate**
Sierla, 2013 (Sierla et al., 2013)	+	-	-	+	+/-	+	+	50	**Moderate**
Svensson, 2019 (Svensson et al., 2020)	+	-	+	++	-/+	+	+	70	**Low**
CASE-CONTROL STUDIES									
	SELECTION				COMPARAILITY	EXPOSURE			
	Adequate Case definition	Representativeness	Selection of controls	Definition of controls	Controlled for **type of surgery** and **time since surgery**	Ascertainment of exposure	Same method of ascertainment in cases and controls	Non-response rote	**Total score (%)**	**Total Risk of Bias***
Honarvar, 2016 (Honarvar et al., 2016)	+	+	+	+	-/-	+	+	-	60	**Moderate**
Mak, 2009 (Mak et al., 2009)	+	-	-	+	-/+	+	+	+	60	**Moderate**
Korucu, 2020 (Korucu et al., 2020)	+	-	-	+	+/+	+	+	+	70	**Low**

†The studies were rated as low (total score is ≥70), moderate (total score is between >40 and <70), or high risk of bias (total score is ≤40).

Table 2. Level of evidence, according to the 2005 classification system of the Dutch Institute for Healthcare Improvement CBO (www.cbo.nl).

	Intervention
A1	Systematic review of at least 2 independent from each other conducted studies of evidence level A2
A2	Randomized double-blinded comparative clinical research of good quality and efficient size
B	Comparative research, but not with all characteristics as mentioned for A2. This includes also patient-control research and cohort research
C	Not comparative research
D	Opinion of experts

Table 3a. Evidence table of **longitudinal studies on** self-reported ULL symptoms in people with and without ULL, predictive symptoms for ULL and measures of association for the relationship between symptoms and ULL.

Author, Year, Country	**Participants (n), Age [mean±SD, median (min-max), %], (y)**	**Time since surgery**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence/Incidence n (%) or % (95% CI)**	**Predictors OR/HR [95% CI]**	**Association β [95% CI] /HR [95% CI]**
Armer, 2019 (Armer et al., 2019), USA	BC patients at risk for ULL (n=486), 50.1±10.8	From pre-surgery (after completion of NAC) to 36 months post-surgery[a]	- Circumference measurement (ULL definition= ≥10% and ≥ 20% difference compared to baseline and/or contralateral limb) - Self-reported (swelling and heaviness)	LBCQ	At 3 years: - ULL symptoms (swelling and/or heaviness): 37.8% (33.1% - 43.2%) - ULL incidence by ≥10% difference: 59.4% (53.2% - 64.1%) - ULL incidence by ≥20% difference: 36.9% (31.9% - 42.6%)	-	-
Brunelle, 2020 (Brunelle et al., 2020), USA	BC patients at risk for ULL (n=647), 56.6, range: 27-83	From pre-surgery to 5 y post-surgery[a]	Perometry (ULL definition= ≥5% and ≥ 10% difference compared to baseline and/or contralateral limb)	LBCQ	Incidence (n=647): - Non-ULL (<5%): 393 (60.7%) - ULL (≥5%): 254 (39.3%) - ULL (≥10%): 64 (9.9%) Patients with symptoms (n=547): - Non-ULL (<5%): 313 (79.6%) - ULL (≥5%): 234 (92.1%) - ULL (≥10%): 61 (95.3%) Non-ULL (<5%) (n=313): Median no of symptoms: - 2 (range 0 – 10) Median time of symptom report: - 12.1 mo (range 0.2 – 86.4) Tenderness: 58.7% Aching: 43.2% Tightness/firmness: 35.9%	*Multivariate analysis* **For ULL (≥5%)** - Perceived larger arm size: HR 1.91 [1.21 – 3.04], p=0.006 **For ULL (≥10%)** - Perceived larger arm size: HR 3.09 [1.61 – 5.89], p=0.001 *Median time to report symptom* **For ULL (≥5%) (n=254)** - Perceived larger arm size: At ULL (≥5%) onset (range 68.8 mo before to 51.1 mo after ULL onset) **For ULL (≥10%) (n=64)** - Perceived larger arm size: 6.1 mo before ULL onset (range 68.9 mo before to 50.2 mo after ULL onset)	*Univariate analysis* **For ULL (≥5%)** - Perceived larger arm size: HR 2.20, p<0.01 - Tighter sleeve fit: HR: 1.67, p<0.20 - Heaviness: HR: 0.58, p<0.20 - Stiffness: HR: 0.61, p<0.05 - Aching: HR: 0.80, p<0.20 **For ULL (≥10%)** - Perceived larger arm size: HR 6.44, p<0.01 - Tighter sleeve fit: HR: 4.17, p<0.01 - Tighter sleeve cuff fit: HR: 6.11, p<0.05 - Tighter ring fit: HR: 1.82, p<0.20 - Swelling: HR: 3.24, p<0.01

Table 3a. Evidence table of **longitudinal studies on** self-reported ULL symptoms in people with and without ULL, predictive symptoms for ULL and measures of association for the relationship between symptoms and ULL (continued).

Author, Year, Country	Participants (n), Age [mean±SD, median (min-max), %], (y)	Time since surgery[a]/ diagnosis of ULL[b]	Measurement method for ULL	Measurement of self-reported ULL symptoms	Prevalence/Incidence n (%) or % (95% CI)	Predictors OR/HR [95% CI]	Association Mean (SD) / β [95% CI] /HR [95% CI] /r
Bundred, 2020 (Bundred et al., 2020), UK	BC patients at risk for ULL (n=1100) 55.7 (12.4)	From pre-surgery to 5 y post-surgery[a]	- Perometry (ULL definition= >10% difference compared to baseline and/or contralateral limb) - BIS (ULL definition = BIS inter-arm ratio > 2 or 3SD mean of a normative population)	LBCQ	Incidence of ULL (24 mo post-surgery) - 22.4% by perometry - 45.2% and 57.6% by BIS (2 or 3 SD) Swelling/heaviness: Before surgery: 8% At 6 mo post-surgery: 43% At 24 mo post-surgery: 66% Numbness: At 24 mo post-surgery: 73%	-	*Relative volume increase from 6 to 24 mo* - Swelling: 2.0 (8.0) p < 0.001 - Heaviness: 1.7 (7.5) p = 0.001 *Univariate analysis* ULL (> 10%) - Swelling pre-surgery (yes): OR 2.06 [1.22 – 3.49] p=0.007
Cidon, 2011 (Cidon et al., 2011), Spain	BC (n=127), 58.0 (28.0-79.0)	5y[a]	Patient-reported ULL status	Self-reported (Severity=mild, moderate, and severe; identified by participants)	Symptoms: 67% mild, 25% moderate, 8% severe $Swelling_{hand/arm}$: 37% (13% at post-surgery, 24% at 1-2y[a]) Heaviness: 33% Tiredness: 27% Tightness: 25% Indentations in skin: 9% Difficulty in writing: 6%	-	-
Finlay, 2013 (Finlay et al., 2013), Australia	ULL (n=80); Intervention 1 (n=24), NI Intervention 2 (n=21), NI Yoga group (n=35), NI	NI	Perometry BIS (ULL definition=NI)	Self-reported	-	-	*Intervention 1* Changes in perometry Heaviness: β =17.5 [2.8-32.2] p=0.02 Tightness: β =13.8 [0.7-26.9] p=0.04 Limb size: β =29.0 [10.0-48.1] p<0.01 *Intervention 2* Changes in BIS Pain: β = 37.8 [5.7-69.9] p=0.02 Heaviness: β =54.1 [21.9-86.2] p<0.001 Tightness: β =33.4 [6.8-59.9] p<0.01 Limb size: β =47.9 [7.3-87.5] p=0.02 Changes in perometry Heaviness: β =43.1 [14.4-71.8] p<0.01 Limb size: β =46.2 [11.1-81.2] p <0.01
Gençay Can, 2019 (Gençay Can et al., 2019), Turkey	Subclinical ULL (n=25), 51.1±10.4	19.4±10.4 mo[b]	Circumference measurement (subclinical ULL definition=<10% difference between limbs) At least one symptom (swelling, heaviness, tightness, or numbness)	Self-reported	*Before treatment* Swelling: 88% Tightness: 72% Heaviness: 60% Numbness: 40%	-	*Univariate analysis* Affected arm volume -Tightness: r=0.45, p =0.02 -Numbness: r=0.37, p=0.04

Table 3a. Evidence table of **longitudinal studies on** self-reported ULL symptoms in people with and without ULL, predictive symptoms for ULL and measures of association for the relationship between symptoms and ULL (continued).

Author, Year, Country	Participants (n), Age [mean±SD, median (min-max), %], (y)	Time since surgery	Measurement method for ULL	Measurement of self-reported ULL symptoms	Prevalence/incidence n, %	Predictors OR/HR [95% CI]	Association AUC [95% CI]
Hayes, 2008 (Hayes et al., 2008), Australia	BC (n=287), 55.0±10.0	6-18 mo[a]	BIS (ULL definition = BIS inter-arm ratio ≥ 3SD mean of a normative population)	Self-reported	ULL and non-ULL participants: ROM ↓: 34% Numbness: 62% Pain, stiffness, weakness, numbness: ULL > non-ULL p<0.05	ULL symptoms$_{baseline}$: OR 3.1 [0.9-10.7]	-
Hidding, 2019 (Hidding et al., 2019), The Netherlands	BC patients at risk for ULL (n=48), 51.3±8.5	NI	Circumference measurement (ULL definition=>10% difference between limbs)	Lymph-ICF	-	-	Heaviness and swelling – ULL: moderate correlation (r_{ϕ}=0.64), p<0.05 *Symptoms compared to total volume* Heaviness: AUC=0.78 [0.68-0.88] p <0.001 Swelling: AUC=0.82 [0.71-0.93] p <0.001
Kosir, 2001 (Kosir et al., 2001), USA	BC (n=30), 51.7±12.0	Pre-surgery[a]	Circumference measurement (ULL definition=>10% difference between limbs)	NI	At 3 mo[c]: ULL (n=1), 13.5% volume ↑ Pain, numbness, aching, needling, tingling: n=7 No ULL symptoms: n=13 At 6 mo[a]: ULL (n=1), 10.0% volume ↑ ULL symptoms: n=3 No ULL symptoms: n=6	-	-
Norman, 2009 (Norman et al., 2009), USA	BC (n=631), ≤50 y: 61%, 50-79: 62%, ≥80: 30%	2 mo[a]	Norman Questionnaire[a] (At 3 locations: hand, lower arm, and upper arm; 1=only participant would notice, 2=someone close to participant would notice, 3=anyone would notice)	Norman Questionnaire[a]	Symptoms (n/mo): Moderate/severe ULL=7 symptoms Mild ULL=3 symptoms Non-ULL=0 symptoms Severity and distress of symptoms: moderate-severe ULL > no/mild ULL $ULL_{mod./severe}$; ULL_{mild}; $non\text{-}ULL_{current}$; $non\text{-}ULL_{ever}$ $Tightness_{jewelry}$: 80.0%; 44.0%; 27.4%; 6.7% $Tightness_{clothing}$: 57.3%; 33.3%; 10.2%; 1.2% Puffiness: 87.8%; 58.5%; 21.2%; 2.9% Cannot see veins: 55.6%; 14.3%; 5.2%; 0.2% Different skin: 56.5%; 28.6%; 13.3%; 3.25%	$Tightness_{jewelry}$: HR 7.37 [4.26-12.76] $Tightness_{clothing}$: HR 5.47 [1.95-15.10] Puffiness: HR 4.2 [1.66-10.62] Different skin: HR 3.12 [1.24-7.82] Skin thickness: HR 3.52 [1.97-6.27] Pain: HR 2.42 [1.36-4.32] Indentations in skin: HR 1.88 [0.46-7.71] $Swelling_{after\ exercise}$: HR 3.45 [1.08-11.05] Difficulty in writing: HR 1.35 [0.41-4.49]	-

Table 3a. Evidence table of **longitudinal studies on** self-reported ULL symptoms in people with and without ULL, predictive symptoms for ULL and measures of association for the relationship between symptoms and ULL (continued).							
Author, Year, Country	**Participants (n), Age [mean±SD, median (min-max), %], (y)**	**Time since surgery**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence/incidence n, %**	**Predictors**	**Association**
					$ULL_{mod./severe}$; ULL_{mild}; non-$ULL_{current}$; non-ULL_{ever} Thickness: 81.2% 48.6% 30.8% 11.2% Pain: 66.7% 39.7% 31.3% 15.1% Indentation in skin: 71.4% 20.1% 9.3% 1.2% $Swelling_{exercise}$: 46.0% 15.5% 8.4% 1.5% Difficulty writing: 21.9% 10.8% 10.4% 4.7%	-	-
Suehiro, 2019 (Suehiro et al., 2019), Japan	BC (n=97), Non-ULL: 61 (range 34-87) ULL 63 (range 51-75)	From pre-surgery to 24 mo post-surgery[a]	- Circumference measurement (ULL definition= >tentative normal range, mean±2 SD) - BIS (ULL definition = BIS inter-arm ratio > 3SD mean of a normative population) - US (ULL definition: skin/ subcutaneous thickness > tentative normal range)	FACT-B	ULL (n=4, 4.1%) Non-ULL (n=93, 95.8%) Pre-surgery: - Arm swelling: 9% - Intensity: mild (1-2) At 3 mo: - Peak intensity in patients with swelling + tenderness - Intensity: Swelling + tenderness > swelling p<0.05 At 6 mo: - Swelling: 17% - Peak intensity in patients with swelling During study period: - Swelling/tenderness: 30%	-	Swelling & Objective parameters= p>0.05

Abbreviations: [a]= Time since surgery; [b]=Time since ULL diagnosis [c]=self-report measure of ULL diagnosis and ULL symptoms; cm=centimeter; n=amount of participants; mo=months; y=years; ↓=decreased; ↑=increased; <=less than; >= greater than; ≤= less than or equals to; ≥=greater than or equals to; AUC=Area under the curve; BC=Breast cancer; BIS=Bio-impedance Spectroscopy; CI: Confidence Interval; FACT-B= Functional Assessment of Cancer Therapy-Breast Tool; LBCQ= Lymphedema Breast Cancer Questionnaire; Lymph-ICF=Lymphoedema Functioning, Disability, and Health Questionnaire; NAC= Neoadjuvant Chemotherapy; NI=Not indicated; OR=Odds Ratio; ROM=Range of Motion; ULL=Upper limb lymphoedema; USA=United States of America.

Table 3b. Evidence table of **cross-sectional studies on** self-reported ULL symptoms in people with and without ULL, and measures of association for the relationship between symptoms and ULL.						
Author, Year, Country	**Participants (n), Age [mean±SD/SE, (min-max), %], (y)**	**Time since surgery[a]/ diagnosis of breast cancer[b] or ULL[c]**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence n, %**	**Association**
Ahmed, 2008 (Ahmed et al., 2008), USA	Total (n=1287) ULL (n=104), 70.8±0.5 Non-ULL + with symptoms (n=475), 71.1±0.2 Non-ULL + no symptoms (n=708), 71.1±0.3	8.1 y[b]	Norman Questionnaire[d]	Norman Questionnaire[d]	**Total sample** 43% ULL symptoms (>3 mo) Swelling: 30.3% Pain/discomfort: 21.3% ROM ↓/difficulty in writing: 17.6% **Participants with ULL** Swelling: 64.4% Pain/discomfort: 39.4% ROM ↓/difficulty in writing: 31.7% **Participants non-ULL + with symptoms** Swelling: 68.0% Pain/discomfort: 50.3% ROM ↓/difficulty in writing: 40.8% **Participants non-ULL + no symptoms** Swelling: 0% Pain/discomfort: 0% ROM ↓/difficulty in writing: 0%	-
Armer, 2005 (Armer & Fu, 2005), USA	Total (n=100), 58.7±12.8 ULL (n=36), 57.5±12.2 Non-ULL (n=64), 59.4±13.1	28 mo[a]	Circumference measurement (ULL definition=>2 cm difference between limbs)	LBCQ	**ULL** **<60 y** **≥60 y** $Swelling_{now}$: 62% 59% p>0.05 $Swelling_{past\ year}$: 65% 50% p>0.05 $Tightness_{clothing}$: 38% 50% p>0.05 $Firmness_{now}$: 62% 53% p>0.02 $Numbness_{now}$: 70% 33% p=0.03 $Numbness_{past\ year}$: 68% 27% p=0.01 $Tenderness_{past\ year}$: 68% 27% p=0.01 $Aching_{now}$: 57% 13% p=0.007 $Aching_{past\ year}$: 75% 20% p=0.001 Temperature $_{arm\text{-}now}\uparrow$: 24% 0% p=0.01 **Participants non-ULL** **<60 y** **≥60 y** $Swelling_{now}$: 31% 15% p>0.05 $Swelling_{past\ year}$: 31% 29% p>0.05 $Swelling_{breast\text{-}now}$: 21% 3% p=0.02 $Tightness_{clothing}$: 13% 18% p>0.05 $Firmness_{now}$: 39% 15% p=0.02 $Heaviness_{now}$: 24% 3% p=0.01 $Heaviness_{past\ year}$: 31% 9% p=0.02 $Numbness_{now}$: 79% 35% p<0.001	-

Table 3b. Evidence table of **cross-sectional studies on** self-reported ULL symptoms in people with and without ULL, and measures of association for the relationship between symptoms and ULL (continued).						
Author, Year, Country	**Participants (n), Age [mean±SD/SE, median (min-max or IQR), %], (y)**	**Mean/Median time since surgery[a]/ diagnosis of breast cancer[b] or ULL[c]**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence n, %**	**Association OR/AUC [95% CI]**
					Non-ULL **<60 y** **≥60 y** $Numbness_{past\ year}$: 85% 39% p<0.001 $Tenderness_{now}$: 55% 27% p=0.02 $Aching_{now}$: 34% 9% p=0.01 $ROM_{shoulder}$ ↓: 31% 9% p=0.02	-
Armer, 2003 (J. M. Armer et al., 2003), USA	*STUDY A:* HV (n=40), 41.2±13.1, ULL (n=40), 59.4±10.3 *STUDY B:* non-ULL (n=103), 59.0±12.6	STUDY A: 6.4 y[a], STUDY B: 3.3 y[a]	Circumference measurement (ULL definition=>2cm difference between limbs)	LBCQ	-	*STUDY A* Heaviness: OR 7.995 [1.116-54.726] Swelling: OR 96.889 [9.865-951.611] Numbness: OR 9.902 [1.819-53.918] *STUDY B* $Heaviness_{past\ year}$: p=0.02 $Swelling_{now}$: p=0.0007
Bani, 2007 (Bani et al., 2007), Germany	Total (n=742), 53.0±10.9 ULL (n=235), 52.9±10.2 Non-ULL (n=507), 53.0±11.2	4.3 y[b]	Self-developed questionnaire	Self-reported	**ULL** **Non-ULL** $Pain_{breast/chest}$: 44% 36% p=0.01 $Pain_{axilla}$: 55% 31% p<0.001 $Pain_{arm}$: 57% 28% p<0.001 ROM ↓: 63% 31% p<0.001 $Paresthesia_{axilla}$: 60% 36% p<0.001 $Paresthesia_{arm}$: 47% 23% p<0.001	-
Flores, 2020 (Flores et al., 2020), USA	Total (n=587), 64 White (n=266), 64.9±8.4 *African-American (n=262), 62.2±8.1	White= 12.7±7.4 y[b] African American = 12.5±7.2[b]	Patient-reported ULL status	Self-reported	ULL sign/symptoms→ n=156 (29.5%) women >50% women with ULL symptoms →no ULL diagnosis **White** **African-American** $Swelling_{breast}$: 6.4% 14.9% p=0.001 $Swelling_{axilla}$: 11.7% 21.0% p=0.003 $Swelling_{arm}$: 22.9% 36.2% p<0.001 $Swelling_{hand}$: 14.7% 21.8% p=0.03 Hardness: 8.3% 17.9% p=0.001 Skin pitting: 7.5% 11.1% p=0.31 Skin darkening: 4.9% 19.8% p<0.0001 Heaviness: 17.3% 30.9% p=0.0005	*Total Population (n=195)* Diagnosis of ULL & ULL symptoms: p>0.05 *White (n=72)* Diagnosis of ULL & ULL symptoms: Kappa=0.11, p=0.33 African-American (n=123) Diagnosis of ULL & ULL symptoms: Kappa=0.25, p=0.06
Fu, 2018 (Fu et al., 2018), USA	Total (n=355), ULL (n=208), 21-39 y: 14.4%, 40-59 y: 48.1%, 60-80 y: 37.5%, non-ULL (n=147), 21-39 y: 4.8%, 40-59 y: 60.0%, 60-80 y: 35.4%	4.6 y[b] 6 mo-10 y[c]	Patient-reported ULL status	BCLE-SEI	-	Symptom report: ULL vs. non-ULL: AUC= 0.751 P<0.001 Eight symptom features: AUC=0.742 [0.688–0.795] Sensitivity=0.731 [0.49–0.77] Specificity=0.660 [0.655–0.860]

Table 3b. Evidence table of **cross-sectional studies on** self-reported ULL symptoms in people with and without ULL, and measures of association for the relationship between symptoms and ULL (continued).						
Author, Year, Country	**Participants (n), Age [mean±SD/SE, median (min-max or IQR), %], (y)**	**Mean/Median time since surgery[a]/ diagnosis of breast cancer[b] or ULL[c]**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence n, % or mean**	**Association OR [95% CI], AUC**
Fu, 2015 (Fu et al., 2015), USA	Total (n=250) ULL (n=42), 58.0±10.7 At risk for ULL (n=148), 55.8±11.6, HV (n=60), 36.5±12.8	5 y[a]	Circumference measurement (ULL definition=>200 ml difference between limbs)	BCLE-SEI	ULL symptoms: ULL > At risk ULL/HV F=117.53, p <0.001 **ULL** **At risk ULL** $Swelling_{arm}$: 100.0% 17.3% p<0.001 $Tightness_{arm}$: 71.4% 34.7% p<0.001 $Heaviness_{arm}$: 71.4% 15.4% p<0.001 $Firmness_{arm}$: 69.0% 24.0% p<0.001 $Aching_{arm}$: 61.9% 30.0% p<0.001 Tingling: 59.5% 27.3% p<0.001 ROM_{arm} ↓: 57.1% 24.0% p<0.001 $Tenderness_{arm}$: 52.4% 47.3% p=0.60 $Pain_{arm}$: 45.2% 40% p=0.59 $Numbness_{arm}$: 45.2% 34.2% p=0.20	**ULL vs. At risk ULL** 9 symptoms: AUC=0.72 [0.64 - 0.80] Sensitivity=0.64 [0.49 - 0.77] Specificity=0.80 [0.73 - 0.86] **ULL vs. HV** 3 symptoms: AUC=0.96 [0.95-0.98] Sensitivity=0.94 [0.83-0.98] Specificity=0.96 [0.88-0.99] $Swelling_{arm}$: OR=561 [76.04-71644.4] p<0.0001 $Heaviness_{arm}$: OR=17.46 [8.22-39.25] p<0.0001 $Firmness_{arm}$: OR=10.33 [5.04-22.16] p<0.0001 $Temperature_{arm}$ ↑: OR=9.07 [2.98-29.94] p=0.0001 $Tightness_{arm}$: OR=7.78 [3.84-16.84] p<0.0001 ROM_{arm} ↓: OR=5.86 [2.94-11.93] p<0.0001 $Tingling_{arm}$: OR=5.54 [2.79-11.26] p<0.0001 $Aching_{arm}$: OR=5.14 [2.60-10.46] p<0.0001 ROM_{finger} ↓: OR=4.56 [1.92-10.66] p=0.0008 ROM_{elbow} ↓: OR=4.39 [1.53-12.21] p=0.006 ROM_{wrist} ↓: OR=4.23 [1.58-10.99] p=0.004 Burning: OR=2.86 [1.11-6.93] p=0.02 Redness: OR=2.47 [1.02-5.66] p=0.04
Gartner, 2010 (Gartner et al., 2010), Denmark	ULL and non-ULL (n=3253), 18-70 y	26 mo[a]	Patient-reported ULL (Severity on NRS, 1-3 mild, 4-7 moderate, 8-10 severe)	Self-reported	Swelling/heaviness: 38% (mild: 50%, moderate: 38%, severe: 12%) Pain: 47% $Heaviness_{arm}$: 3.9 (mean score) $Heaviness_{forearm\text{-}hand}$: 4.0 (mean score) ULL symptoms: 50% everyday, 25%: 1-3 d/w, 24% rarely	-

Table 3b. Evidence table of **cross-sectional studies on** self-reported ULL symptoms in people with and without ULL, and measures of association for the relationship between symptoms and ULL (continued).

Author, Year, Country	Participants (n), Age [mean±SD/SE, median (min-max or IQR), %], (y)	Mean/Median time since surgery[a]/ diagnosis of breast cancer[b] or ULL[c]	Measurement method for ULL	Measurement of self-reported ULL symptoms	Prevalence n, % or median (IQR)	Association r
Kopec, 2013 (Kopec et al., 2013), Canada	BC (n=744), <50 y: 21.6% ≥50 y: 78.4%	6 mo[a]	Water displacement (ULL definition=NI)	Self-reported	ULL: 34% participants At 6 mo[a]: Tenderness, pain, tightness: **ULL > non-ULL** p=NI	-
Morris, 2017 (Morris et al., 2017), Australia	ULL (n=54), 63.2±13.2	1.5 y[a]	BIS (ULL definition=NI) ISL classification: ULL severity	LYSES	Symptoms: Elevation improves swelling Indentations in skin Skin firmness/changes	-
Ridner, 2015 (Ridner & Dietrich, 2015), USA	ULL (n=236), 58.9±11.0	4.8 y[a]	NI	LSIDS-A	Swelling: 90.2% Fatigue: 75.7% Heaviness 74.0% Tightness: 66.8% Difficulty in sleeping: 61.3% Aching: 60.2% Appearance: 59.6% PA ↓: 56.0% $Pain_{arm}$: 51.9% $Burning_{chest}$: 14.9% Flakey skin: 14.4 %	-
Ridner, 2011 (Ridner et al., 2011), USA	ULL (n=51), NI	0-199 mo[c]	NI	LSIDS-A	9 symptoms= >50 % ULL participants Heaviness tightness, coldness, achiness, swelling, hardness, appearance, fatigue, difficulty in sleeping Symptom burden Sleep: 30% Body image: 20% $Symptoms_{number}$: 11 (8-17) Symptom burden: 2.7 (1.1-9.5)	-
Ridner, 2007 (Ridner et al., 2007), USA	Total (n=25), ULL (n=11), 53.6±8.9 HV (n=14), 46.2±16.3	NI	Circumference measurement, Perometer, BIS (ULL definition=NI)	LBCQ	**ULL (n) HV (n)** $Swelling_{arm\text{-}now}$: 10 1 p=0.001 $Swelling_{arm\text{-}past\ year}$: 9 0 p=0.001 $Swelling_{pitting\text{-}now}$: 7 0 p=0.001 $Swelling_{pitting\text{-}past\ year}$: 5 0 p=0.01 $Swelling_{chest\text{-}now}$: 4 0 p=0.03 $Swelling_{chest\text{-}past\ year}$: 4 0 p=0.03	$Swelling_{pitting\text{-}past\ year}$ IM → r=0.62 Circumferential → r=0.76 p≤0.001 $Firmness_{past\ year}$ IM → r=0.68 p≤0.001

Table 3b. Evidence table of **cross-sectional studies on** self-reported ULL symptoms in people with and without ULL, and measures of association for the relationship between symptoms and ULL (continued).						
Author, Year, Country	**Participants (n), Age [mean±SD/SE, median (min-max or IQR), %], (y)**	**Mean/Median time since surgery[a]/ diagnosis of breast cancer[b] or ULL[c]**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence n, % or mean ± SD**	**Association OR [95% CI]**
					ULL (n) HV (n) $Swelling_{breast\text{-}now}$: 4 0 p=0.03 $Swelling_{breast\text{-}past\ year}$: 5 0 p=0.01 $Firmness/tightness_{now}$: 7 1 p=0.01 $Firmness/tightness_{past}$: 8 0 p=0.001 $Tenderness_{arm/now}$: 5 6 p=1.0 $Heaviness_{now}$: 8 1 p=0.01 $Heaviness_{past\ year}$: 8 1 p=0.01 $Numbness_{arm/now}$: 7 3 p=0.05 $Aching_{arm/now}$: 6 5 p=0.43 $Temperature_{arm}\uparrow$: 3 0 p=0.07 $Symptoms_{past}$: 6.15 ± 3.53 / 1.05 ± 1.29 $Symptoms_{present}$: 6.58 ± 1.88 / 1.38 ± 1.88	-
Sierla, 2013 (Sierla et al., 2013), Australia	Total (n=444), ULL (n=154), <40 y: 8%, 40-55 y: 49%, 56-70 y: 36%, >70 y: 3% Non-ULL (250), <40 y: 8%, 40-55 y: 41%, 56-70 y: 48%, >70 y: 2% Unsure (n=40), <40 y: 10%, 40-55 y: 53%, 56-70 y: 33%	< 1y[a]: 1%, 1-5 y[a]: 63%, 5-10 y[a]: 22%, >10 y[a]: 9%, no response: 5%	Norman Questionnaire[d] (mild=only participant would notice; moderate=someone close to participant would notice; severe=anyone would notice)	Self-reported	ULL severity Mild: 52%; moderate: 36%; severe: 5%; no response: 10% Self-reported discomfort Mild: 46%; moderate: 35%; severe: 7%; no response: 12% $ULL_{breast/chest}$: moderate-severe discomfort $\uparrow$ χ^2=8.64; p=0.003	-
Svensson, 2020 (Svensson et al., 2020), Australia	Total (n=100) 61.8±10.6 ULL (n=48), 63.7±11.1 Non-ULL (n=52), 60.1±10.0	ULL: 1041 (402.3-2248) d Non-ULL: 928 (331.3-4004) d	BIS (ULL definition = BIS inter-arm/segmental ratio ≥ 2 or ≥3SD mean of a normative population)	Self-reported on VAS (0-10 cm)	*Symptoms* ULL non-ULL Swelling: 95.8% 32.7% p<0.01 Tightness: 60.4% 21.2% p<0.01 Heaviness: 77.1% 40.4% p<0.01 *Physical signs* $Pinch\ test_{forearm}$: 93.8% 25.0% p<0.01 $Pinch\ test_{upper\ arm}$: 72.9% 23.1% p<0.01 Pitting: 91.7% 23.1% p<0.01	*Univariate analysis* Swelling: OR 47.4 [10.3-218.7] Tightness: OR 5.7 [2.4-13.7] Heaviness: OR 5.0 [2.1-11.9] *Physical signs* $Pinch\ test_{forearm}$: OR 45.0 [11.9-169.6] $Pinch\ test_{upper\ arm}$: OR 9.0 [3.6-22.2] Pitting: 36.7 [10.9-123.0] *Multivariate analysis* Swelling: OR 58.8 [4.9-709.4] p=0.001 $Pinch\ test_{forearm}$: OR 73.5 [7.3-736.9] p<0.001 $Pinch\ test_{upper\ arm}$: OR 23.9 [2.8-201.7] p=0.003

Table 3b. Evidence table of **cross-sectional studies on** self-reported ULL symptoms in people with and without ULL, and measures of association for the relationship between symptoms and ULL (continued).						
Author, Year, Country	**Participants (n), Age [mean±SD/SE, median (min-max or IQR), %], (y)**	**Mean/Median time since surgery[a]/ diagnosis of breast cancer[b] or ULL[c]**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence n, % or mean ± SD**	**Association**
						Swelling and/or Pinch test$_{forearm}$: Sensitivity: 1.00 [92.6 - 100] Specifity: 0.62 [0.47 – 0.75]

Abbreviations: [a]= Time since surgery; [b]=Time since breast cancer diagnosis; [c]=Time since ULL diagnosis; [d]=self-report measure of ULL diagnosis and ULL symptoms; cm=centimeter; d=days; d/w: day(s) a week; n=amount of participants; mo=months; y=years; ↓=decreased; ↑=increased; <=less than; >= greater than; ≤= less than or equals to; ≥=greater than or equals to; AUC=Area under the curve; BC=Breast cancer; BCLE-SEI=Breast Cancer and Lymphedema Symptom Experience Index; BMI= Body Mass Index; BIS=Bio-impedance Spectroscopy; CI: Confidence Interval; HV=Healthy volunteers; IM=Impedance measures; ISL=International Society of Lymphology; LBCQ= Lymphedema and Breast Cancer Questionnaire; LYSES=Lymphoedema Self-Examination Survey; LSIDS-A=Lymphedema Symptom Intensity and Distress Survey-Arm; NI=Not indicated; NRS=Numeric Rating Scale; OR=Odds Ratio; PA=Physical activity; ROM=Range of Motion; SAI=Symptom-associated interference; SD=Standard deviation; SE=Standard error; ULL=Upper limb lymphoedema; USA=United States of America; VAS=Visual Analog Scale

Table 3c: Evidence table of **case-control studies on** self-reported ULL symptoms in people with and without ULL, and measures of association for the relationship between symptoms and ULL.								
Author, Year, Country	**Participants (n), Age [mean±SD], (y)**	**Time since surgery**	**Measurement method for ULL**	**Measurement of self-reported ULL symptoms**	**Prevalence n, % or mean±SD or median (IQR)**			**Association OR [95% CI]**
Honarvar, 2016 (Honarvar et al., 2016), Iran	ULL (n=400), 52.3±11.0; Non-ULL (n=283), 50.1±10.9	NI	Circumference measurement (ULL definition=>2 cm difference between limbs) Water displacement	Self-reported	Symptoms in ULL: edema, heaviness, body image, pain, paresthesia **ULL > non-ULL;** p=NI Swelling: 36.4 times ↑ Paresthesia: 5.6 times ↑ Heaviness: 5.5 times ↑ $Pain_{moderate-severe}$: 4.7 times ↑ ROM ↓: 1.3 times ↑			-
Korucu, 2020 (Korucu et al., 2020), Turkey	Total (n=107), age range 25-65 ULL (n=50), 54.34±9.08 non-ULL (n=57), 53.68±9.41	ULL: 4.24±2.97 y non-ULL: 3.19 ±1.76 y	Circumference measurement (ULL definition= ≥2 cm difference at least 2 points)	Self-reported on VAS	Heaviness/discomfort:	**ULL**	**non-ULL**	
					Prevalence:	28%	10.5%	
					VAS score (rest):	1.0 (1.0-2.0)	1.0 (1.0-1.0) p=0.018	
					VAS score (activity):	3.0 (1.0-5.2)	2.0 (1.0-3.0) p=0.009	
					VAS score (night):	1.0 (1.0-3.0)	1.0 (1.0-3.0) p=0.71	
Mak, 2009 (Mak et al., 2009), China	Total (n=202), ULL (n=101), 53.0±9.6 non-ULL (n=101), 50.3±7.7	ULL: 3.7 y non-ULL: 3.5 y	Circumference measurement (ULL definition=≥1.5 cm difference between limbs) <3cm=mild ULL, 3-5cm=moderate ULL, >5cm=severe ULL)	ASDS		**ULL**	**non-ULL**	Swelling: OR=49.21 [18.85-128.50] Pain: OR=2.81 [1.34-5.88] Numbness/tingling: OR=2.19 [1.08-4.47] ROM_{arm} ↓: OR=4.66 [2.28-9.54] $ASDS_{total}$: OR=0.86 [0.82-0.91] SS subscale: OR=0.63 [0.55-0.74] SAI subscale: OR=0.82 [0.76-0.88]
					Swelling:	68.3%	1% p<0.0001	
					Pain:	31.7%	7.9% p<0.006	
					Numbness/tingling:	30.7%	12.9% p=0.02	
					ROM_{arm} ↓:	40.6%	11.9% p<0.0001	
					$ASDS_{total}$:	20.0±7.8	11.3±5.6 p<0.0001	
					SS subscale:	10.9±3.1	7.5±2.0 p<0.0001	
					SAI subscale:	9.1±4.9	3.8±3.8 p<0.0001	
						Severe ULL >	**Mild ULL**	
					SS subscale:	12.1±2.6	9.7±2.6 p<0.005	

Abbreviations: cm=centimeter; n=amount of participants; y=years; ↓=decreased; ↑=increased; <=less than; >= greater than; ≥=greater than or equals to; ASDS=Arm Symptom Distress Scale; CI: Confidence Interval; IQR=Interquartile range; NI=Not indicated; OR=Odds Ratio; ROM=Range of Motion; SAI=Symptom-associated interference; SD=Standard deviation; SS=Symptom severity; ULL=Upper limb lymphoedema; VAS=Visual Analog Scale.

Table 4. Self-reported ULL symptoms and corresponding number of studies reporting this symptom. (Total number of studies =29)

ULL Symptom (n studies (%) reporting on this symptom)	**References**[†]	**Range in prevalence rate of the symptom reported**
Swelling (n=19, 65%)	(Ahmed et al., 2008; Armer & Fu, 2005; Armer et al., 2019; Armer et al., 2003; Brunelle et al., 2020; Bundred et al., 2020; Cidon et al., 2011; Flores et al., 2020; Fu et al., 2015; Gartner et al., 2010; Hidding et al., 2019; Honarvar et al., 2016; Mak et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2011; Ridner et al., 2007; Sierla et al., 2013; Suehiro et al., 2019; Svensson et al., 2020)	0%-100% (Ahmed et al., 2008; Armer & Fu, 2005; Armer et al., 2019; Bundred et al., 2020; Cidon et al., 2011; Flores et al., 2020; Fu et al., 2015; Gartner et al., 2010; Mak et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2007; Sierla et al., 2013; Suehiro et al., 2019; Svensson et al., 2020)
Heaviness (n=17, 58%)	(Armer & Fu, 2005; Armer et al., 2019; Armer et al., 2003; Brunelle et al., 2020; Bundred et al., 2020; Cidon et al., 2011; Finlay et al., 2013; Flores et al., 2020; Fu et al., 2015; Gartner et al., 2010; Hidding et al., 2019; Honarvar et al., 2016; Korucu et al., 2020; Ridner & Dietrich, 2015; Ridner et al., 2011; Ridner et al., 2007; Svensson et al., 2020)	3%-77% (Armer & Fu, 2005; Armer et al., 2019; Bundred et al., 2020; Cidon et al., 2011; Fu et al., 2015; Gartner et al., 2010; Korucu et al., 2020; Ridner & Dietrich, 2015; Ridner et al., 2007; Svensson et al., 2020)
Pain (n=12, 41%)	(Ahmed et al., 2008; Bani et al., 2007; Finlay et al., 2013; Fu et al., 2015; Gartner et al., 2010; Hayes et al., 2008; Honarvar et al., 2016; Kopec et al., 2013; Kosir et al., 2001; Mak et al., 2009; Norman et al., 2009; Ridner & Dietrich, 2015)	0%-66% (Ahmed et al., 2008; Bani et al., 2007; Fu et al., 2015; Gartner et al., 2010; Mak et al., 2009; Norman et al., 2009; Ridner & Dietrich, 2015)
Tightness (n=11, 37%)	(Armer & Fu, 2005; Brunelle et al., 2020; Cidon et al., 2011; Finlay et al., 2013; Fu et al., 2015; Kopec et al., 2013; Norman et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2011; Ridner et al., 2007; Svensson et al., 2020)	0%-80% (Armer & Fu, 2005; Brunelle et al., 2020; Cidon et al., 2011; Fu et al., 2015; Norman et al., 2009; Ridner & Dietrich, 2015; Ridner et al., 2007; Svensson et al., 2020)
Firmness/hardness (n=9, 31%)	(Armer & Fu, 2005; Brunelle et al., 2020; Flores et al., 2020; Fu et al., 2015; Hayes et al., 2008; Morris et al., 2017; Norman et al., 2009; Ridner et al., 2011; Ridner et al., 2007)	0%-81% (Armer & Fu, 2005; Brunelle et al., 2020; Flores et al., 2020; Fu et al., 2015; Norman et al., 2009; Ridner et al., 2007)
Sensory changes		
Numbness (n=9, 31%)	(Armer & Fu, 2005; J. M. Armer et al., 2003; Brunelle et al., 2020; Bundred et al., 2020; Fu et al., 2015; Hayes	3%-73% (Armer & Fu, 2005; Bundred et al., 2020; Fu et al., 2015; Hayes et al., 2008; Mak et al., 2009; Ridner et al., 2007)

	et al., 2008; Kosir et al., 2001; Mak et al., 2009; Ridner et al., 2007)	
Aching (n=7, 24%)	(Armer & Fu, 2005; Brunelle et al., 2020; Fu et al., 2015; Kosir et al., 2001; Ridner & Dietrich, 2015; Ridner et al., 2011; Ridner et al., 2007)	6%-61% (Armer & Fu, 2005; Brunelle et al., 2020; Fu et al., 2015; Ridner & Dietrich, 2015; Ridner et al., 2007)
Tingling (n=4, 13%)	(Fu et al., 2015; Hayes et al., 2008; Kosir et al., 2001; Mak et al., 2009)	5%-59% (Fu et al., 2015; Mak et al., 2009)
Increased arm temperature (n=3, 10%)	(Armer & Fu, 2005; Fu et al., 2015; Ridner et al., 2007)	0%-27% (Armer & Fu, 2005; Fu et al., 2015; Ridner et al., 2007)
Paraesthesia/needless (n=3, 10%)	(Bani et al., 2007; Honarvar et al., 2016; Kosir et al., 2001)	23%-47% (Bani et al., 2007)
Burning arm/chest (n=2, 6%)	(Fu et al., 2015; Ridner & Dietrich, 2015)	0%-19% (Fu et al., 2015; Ridner & Dietrich, 2015)
Arm redness (n=2, 6%)	(Fu et al., 2015; Ridner et al., 2007)	1%-36% (Fu et al., 2015; Ridner et al., 2007)
Stabbing (n=1, 3%)	(Fu et al., 2015)	0%-23% (Fu et al., 2015)
Coldness (n=1, 3%)	(Ridner et al., 2011)	NA
Skin symptoms		
Indentations in skin (n=3, 10%),	(Cidon et al., 2011; Morris et al., 2017; Norman et al., 2009)	1%-71% (Cidon et al., 2011; Norman et al., 2009)
Altered skin sensation (n=2, 6%)	(Morris et al., 2017; Norman et al., 2009)	11%-56% (Norman et al., 2009)
Cannot see knuckles/veins of the hand (n=1, 3%)	(Norman et al., 2009)	0%-55% (Norman et al., 2009)
Flakey skin (n=1, 3%)	(Ridner & Dietrich, 2015)	14% (Ridner & Dietrich, 2015)
Skin darkening (n=1, 3%)	(Flores et al., 2020)	12% (Flores et al., 2020)
Skin pitting (yes) (n=2, 6%)	(Flores et al., 2020; Svensson et al., 2020)	8% - 91% (Flores et al., 2020; Svensson et al., 2020)
Functional symptoms		
Limited ROM (n=6, 20%)	(Ahmed et al., 2008; Armer & Fu, 2005; Bani et al., 2007; Fu et al., 2015; Hayes et al., 2008; Mak et al., 2009)	0%-63% (Ahmed et al., 2008; Armer & Fu, 2005; Bani et al., 2007; Fu et al., 2015; Hayes et al., 2008; Mak et al., 2009)
Fatigue (n=3, 10%)	(Cidon et al., 2011; Ridner & Dietrich, 2015; Ridner et al., 2011)	27%-75% (Cidon et al., 2011; Ridner & Dietrich, 2015)
Difficulty in writing (n=3, 10%)	(Ahmed et al., 2008; Cidon et al., 2011; Norman et al., 2009)	0%-40% (Ahmed et al., 2008; Cidon et al., 2011; Norman et al., 2009)
Difficulty in sleeping (n=2, 6%)	(Ridner & Dietrich, 2015; Ridner et al., 2011)	61% (Ridner & Dietrich, 2015)
Weakness (n=1, 3%)	(Hayes et al., 2008)	NA
Decreased physical activity (n=1, 3%)	(Ridner & Dietrich, 2015)	56% (Ridner & Dietrich, 2015)
Swelling after exercise (n=1, 3%)	(Norman et al., 2009)	15-46% (Norman et al., 2009)
Elevation improves swelling (n=1, 3%)	(Morris et al., 2017)	NA
Discomfort (n=1, 3%)	(Sierla et al., 2013)	86% (Sierla et al., 2013)
Pain related disturbances		
Tenderness (n=6, 20%)	(Armer & Fu, 2005; Brunelle et al., 2020; Fu et al., 2015; Kopec et al., 2013; Ridner et al., 2007; Suehiro et al., 2019)	1%-58% (Armer & Fu, 2005; Brunelle et al., 2020; Fu et al., 2015; Ridner et al., 2007; Suehiro et al., 2019)
Discomfort (n=2, 6%)	(Ahmed et al., 2008; Korucu et al., 2020)	0%-50% (Ahmed et al., 2008; Korucu et al., 2020)

Other signs/symptoms		
Body image/appearance (n=3, 14%)	(Honarvar et al., 2016; Ridner & Dietrich, 2015; Ridner et al., 2011)	59% (Ridner & Dietrich, 2015)
Perceived larger limb size (n=3, 10%)	(Armer & Fu, 2005; Brunelle et al., 2020; Finlay et al., 2013)	14%-58% (Armer & Fu, 2005)
Tighter sleeve/sleeve cuff/ring fit (n=1, 3%)	(Brunelle et al., 2020)	NA
Puffiness (n=1, 3%)	(Norman et al., 2009)	2%-87% (Norman et al., 2009)
Pinch test forearm/upper arm (n=1, 3%)	(Svensson et al., 2020)	6%-93% (Svensson et al., 2020)

NA=Not available.

[†]Studies indicating each symptom with/without certain numbers or percentages.

Figure Legends

Figure 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow chart.

Figure 2. Average prevalence of self reported signs and symptoms of lymphoedema and non-lymphoedema groups.

Appendix 1. Search strategy

Search Combination	Medline	EMBASE	CINAHL	Scopus
SEARCH #1 “Breast cancer Lymphedema” OR “Lymphedema” OR “Upper Limb Lymphedema”	14177	18 996	2 476	16 952
SEARCH #2 “Puffiness” OR “Tiredness” OR “Thickness” OR “Pain” OR “Numbness” OR “Swelling” OR “Heaviness” OR “Achiness”	1 480 198	1 639 991	199 397	2 898 580
SEARCH #3 #1 AND #2	3065	3126	566	3324

Search strategy of Medline

((Puffiness[All Fields] OR ("fatigue"[MeSH Terms] OR "fatigue"[All Fields] OR "tiredness"[All Fields]) OR thickness[All Fields] OR ("perception"[MeSH Terms] OR "perception"[All Fields] OR "perceptions"[All Fields]) OR ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "signs"[All Fields] OR "diagnosis"[MeSH Terms] OR "signs"[All Fields]) OR ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "symptoms"[All Fields] OR "diagnosis"[MeSH Terms] OR "symptoms"[All Fields]) OR ("pain"[MeSH Terms] OR "pain"[All Fields]) OR ("hypesthesia"[MeSH Terms] OR "hypesthesia"[All Fields] OR "numbness"[All Fields]) OR ("edema"[MeSH Terms] OR "edema"[All Fields] OR "swelling"[All Fields]) OR heaviness[All Fields] OR tightness[All Fields]) AND ("lymphoedema"[All Fields] OR "lymphedema"[MeSH Terms] OR "lymphedema"[All Fields])) AND (("upper extremity"[MeSH Terms] OR ("upper"[All Fields] AND "extremity"[All Fields]) OR "upper extremity"[All Fields] OR ("upper"[All Fields] AND "limb"[All Fields]) OR "upper limb"[All Fields]) OR ("breast"[MeSH Terms] OR "breast"[All Fields]) OR ("arm"[MeSH Terms] OR "arm"[All Fields]) OR ("upper extremity"[MeSH Terms] OR ("upper"[All Fields] AND "extremity"[All Fields]) OR "upper extremity"[All Fields]) OR ("torso"[MeSH Terms] OR "torso"[All Fields] OR "trunk"[All Fields]))