PRACTICE-BASED EVIDENCE RESEARCH DESIGN

FOR LYMPHEDEMA MANAGEMENT

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by

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The undersigned, appointed by the Dean of the Graduate School, have examined the dissertation entitled

PRACTICE-BASED EVIDENCE RESEARCH DESIGN

FOR LYMPHEDEMA MANAGEMENT

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DEDICATION

This dissertation is dedicated to my family:

To my partner in life and my best friend: Avi

To my daughters: Yuval, Eynav, and Omer

To my parents: Amnon and Bracha

To my sister and brothers: Michal, Nadav, and Gal

Thank you all for believing in me and in this journey, for your support and love.

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ABBREVIATIONS AND DEFINITION

AD	Foot to knee length
AG	Foot to groin length
ALT	Aqua Lymphatic Therapy
BCRL	Breast cancer-related lymphedema
Cb	Circumference at the base of the segment
CDT	Complex Decongestive Therapy
CE	Chronic edema
CLT	Complex Lymphatic Therapy
CPT	Complex Physical Therapy
CT	Circumference at the top measurements of the segment
CVI	Chronic Venous Insufficiency
DASH	Disability of the Arm, Shoulder, and Hand questionnaire
Dist	Distal
DLT	Decongestive Lymphatic Therapy
Edu	Education
EMR	Electronic Medical Records
ES	Effect size
Exe	Exercise
FACT-B	Functional Assessment of Cancer Therapy Breast
FS	Functional status
GAR	Global assessment rating
GRC	Global rating of change
ICC	Intra-class correlation coefficient
ILF	International Lymphoedema framework
IR	Infection rate
ISL	International Society of Lymphology
LE	Lymphedema
LFLIE	Low-frequency low-intensity electrotherapy
LLL	Lower limb lymphedema
LLLT	Low-level laser therapy
LPT	Lymphedema physiotherapist
Lymph-ICF	Lymphoedema Functioning, Disability, and Health Questionnaire
Lymph-ICF-LL	Lymphoedema functioning, disability and health questionnaire-lower extremity lymphedema
LYMPHQOL	Lymph Quality of Life Questionnaire
MCID	Minimal clinically important difference
MDC	Minimal detectable change
Maccabi	Maccabi Healthcare Services

MLD	Manual lymph drainage
MLLB	Multi-layer lymphedema bandaging
MPQ	McGill Pain Questionnaire
MYMOP	Measure Yourself Medical Outcome Profile
PBE	Practice-based evidence
PPI	Present Pain Index
PROM	Patient-reported outcome measure
PT	Physical therapist
QOL	Quality of life
RLV	Relative limb volume
ROC	Receiver-operating characteristic curve
RTT	Rehabilitation Treatment Taxonomy
SEM	Standard error of measurement
SLD	Self-lymphatic drainage
SRD	Small real difference
ULL27	Upper-Limb Lymphedema 27
VS	Volume of a segment

ABSTRACT

Lymphedema (LE) is treated in Maccabi Healthcare Services (Maccabi) by LE physical therapists (LPTs). Until today, the knowledge of the extent of the problem in Israel, the interventions for patients with LE, and the effectiveness of these treatments were not well studied. The aims of this dissertation were to: (1) describe the treatment code documentation as part of the PBE process and to evaluate the accuracy of treatment code documentation by LPTs in Maccabi; (2) examine the known-group construct validity of functional status (FS) scores on patients with LE at Maccabi; and (3) describe characteristics of the patients with lymphedema treated at Maccabi between the years of 2010-2017. We used a Practice-based Evidence (PBE) research design to develop a new module for LE in the Maccabi electronic medical record (EMR) to support the gathering of data to address these gaps. The intra-rater reliability of arm and leg measurements by trained LPTs was found to be very high. The treatment code documentation system in the EMR was found to be clear and accurately used by most LPTs. Specific needs for improvement were identified. The computerized adaptive testing of FS score discriminated between patient groups in clinically logical ways both at intake into and discharge from LE treatments. Finally, descriptive analyses of the patients treated by LPT's in Maccabi revealed trends in physician diagnosis and referral, LPT classifications of LE, treatment interventions, co-morbidities, and more. This is the first time such a PBE research process was conducted in a large data set in a national health system for therapists treating patients with LE, laying the foundation for on-going research and application.

CHAPTER ONE: GENERAL INTRODUCTION

Lymphedema (LE) is a disorder of lymphatic vessels or lymph nodes identified in the International Classification of Diseases from the World Health Organization (2016). It is defined as the accumulation of protein-rich fluid in the interstitial tissue as a result of dysfunction of the lymphatic system (International Society of Lymphology [ISL], 2016). The causes of lymphedema are numerous and are divided into primary or secondary origin. (For more details, please refer to Chapters Two and Four of this dissertation). The decline of the lymphatic transport capacity below the ability for evacuating the interstitial load will cause imbalance and the accumulation of fluid in the interstitial tissue, such as is seen after trauma, oncology surgical and radiation treatments, or as a result of chronic venous insufficiency (CVI) (Rockson, 2016; ISL, 2016).

The incidence of lymphedema varies between 4% to 91% (Armer et al., 2009; Cormier et al., 2010; Moffatt, Keeley, Franks, Rich, & Pinnington, 2017). (For more information, please refer to Chapters Two, Four, Seven, and Eight of this dissertation.)

Complex decongestive therapy (CDT) is recommended as the conservative treatment for lymphedema (ISL, 2016). It involves two phases: an intensive therapy that aims to reduce maximum swelling and consists of skin care, manual lymphatic drainage (MLD), compression bandaging, and exercise; and a long-term phase that aims to maintain the results of the intensive phase and consists of compression garments, exercise, self-MLD, and skin care (ISL, 2016). Traditionally, the intensive therapy is done in the clinic by the physiotherapist, and the long-term therapy is

performed by the patient at home (International Lymphoedema Framework [ILF], 2012) .

Moreover, non-CDT treatments which have been found helpful and reported in the literature are: lower-level laser therapy, intermittent pneumatic compression therapy, and aquatic therapy (ISL, 2016). Lasinski et al. (2012) conducted a systematic review and found that several studies with CDT have demonstrated good outcomes in decreasing volume and improving symptoms. However, the quality of the methodology of these studies was critiqued as not standing at a high level of evidence and the contribution of each component of the bundled therapy was unclear. In a recent systematic review by Smile et al. (2018), compression therapy alone was found to be effective for lymphedema improvement. These findings raise the question about the necessity of a full course of CDT with all the components for all patients (Lasinski et al., 2012; McNeely et al., 2004). Thus, a modified approach that will include a different combination of the components personalized for the patient may be warranted for specific groups of patients.

Furthermore, breast cancer-related lymphedema (BCRL) is only one etiology for lymphedema, yet this is the most studied population in the literature of lymphedema research (Lasinski et al., 2012). Issues such as adherence to self-management, predictive factors for the success in maintaining results of therapy, and effectiveness of techniques are not properly addressed in the literature of BCRL and relatively few reports on lymphedema beyond breast cancer are in the literature (Lasinski et al., 2012). Moreover, in the real life of clinical practice, patients have other health problems that may influence the effectiveness of their coping with

lymphedema and consequently the outcome of their treatments. Randomized controlled trials (RCT) exclude patients who have co-morbidities such as metastatic disease, chronic heart failure, erysipelas infection, and more (Schmitz, Ahmed et al., 2009); as a consequence, clinicians find it hard to translate the knowledge from research lab to the bedside.

The next chapter (Chapter Two, a published manuscript) will discuss meaningful outcomes in lymphedema management. In order to be able to give the best treatment to the right patient, clinicians need to know how to assess and to precisely evaluate the outcomes of their intervention. Seeking what is clinically important is vital for true evaluation of the patient status, improvement, stability, and exacerbation.

Chapter Three discusses the practice-based evidence (PBE) research design, its goals and hallmarks, and the theoretical framework for this dissertation. Chapter Four is a published chapter in a book on the assessment of lymphedema; the detailed assessment that is described is the basis of the work of a physical therapist who treats people with lymphedema.

Reliability of measurements of front-line clinicians is a hallmark in PBE research. Chapter Five, a published manuscript, presents findings from a preliminary study on the reliability of measurements of physical therapists within the health system, Maccabi Health Services (Maccabi), in which the dissertation research was carried out. Volume is the main clinical outcome in lymphedema management; therefore, the physical therapist has to know what his/her measurement error is and how to use this information in routine practice.

Chapter Six presents a manuscript (under review) that describes the PBE process in the physical therapy department of Maccabi. Documenting the crucial participation by the Maccabi lymphedema physical therapists, findings from an accuracy test is presented, as well, in which the therapists had to accurately select treatment codes for 10 treatment vignettes.

Chapter Seven (manuscript under review) describes a construct-validity study for computerized adaptive test (CAT) functional scores (FS) in people who have lymphedema. This study was conducted to validate the use of a tool which is routinely used to measure function in Maccabi clinical practice but was never validated with people with lymphedema.

Chapter Eight (manuscript in preparation) describes the population of persons with lymphedema who were treated in the Maccabi; their proportion within the Maccabi members; and their demographic, health, and treatment characteristics over a period of eight years from 2010-2017.

Chapter Nine is a conclusion which briefly discusses and summarizes the findings reported in this dissertation, lessons learned, and conclusions with recommendations for future clinical, practice, education, policy and research.

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CHAPTER TWO: A MANUSCRIPT - WHAT IS CLINICALLY IMPORTANT IN LYMPHEDEMA MANAGEMENT – A REVIEW OF THE LITERATURE

Tidhar, D., Armer, J. M., & Stewart, B. R. (2018). What Is Clinically Important in Lymphedema Management? A Systematic Review. *Rehabilitation Oncology*, *36*(1):13-27.

Abstract

Objective: To summarize published reports on the clinical effectiveness of conservative lymphedema management by reporting on outcomes which use anchor-based and distribution-based approaches. Data Sources: MEDLINE and EBSCO databases from inception to April 2017. Study Selection: Articles were selected if they included an estimate for minimal clinically important difference (MCID). **Data Synthesis**: Twenty-four articles involving 938 patients met our inclusion criteria. Years of publication ranged from 1991 to 2016. Of these, 16 studies examined outcomes after the intervention was completed. The other 8 studies tested the reliability of measurement tools. Data were stratified according to different outcomes: limb volume (20 studies, 785 patients), symptoms (6 studies, 288 patients), skin changes (1 study, 28 patients), infection rate (5 studies, 255 patients), quality of life (4 studies, 148 patients), strength, function, endurance, fitness, and disability (3 studies, 89 patients). Most studies covered cancer-related lymphedema (22/23), especially as related to breast cancer (19/22). Large heterogeneity was found in the methods of estimations with regards to improvement, exacerbation, and stability of lymphedema. **Conclusion**: There is limited evidence to draw conclusions regarding the recommended MCID's for

different populations, outcomes, and periods of time. Further studies are needed to facilitate the process of improving clinical care of lymphedema.

Key words: lymphedema management, minimal clinically important difference (MCID) in lymphedema, clinically-significant meaningful change

Introduction

Lymphedema (LE) is defined as an accumulation of protein-rich fluid in the interstitial tissue and subcutaneous spaces due to insufficiency of the lymphatic system.(International Lymphedema Framework [ILF], 2012). Lymphedema can manifest as primary or secondary impairment of the lymphatic system, where the secondary origin is the most common. Secondary LE can develop due to various types of cancer and its treatments, trauma, venous problems, and other causes (International Society of Lymphology [ISL], 2013) that may lead to chronic morbidities such as physical and functional limitations, psychosocial disturbances, pain, and other symptoms (Fu et al., 2012; Hodgson et al., 2011; Quinlan et al., 2009). LE patients are more susceptible to skin infections which can become a life-threatening condition (Arsenault, Rielly, & Wise, 2011; Boneti et al., 2008). The incidence of LE varies according to its etiology and to differing definitions and measurement tools (Armer, Stewart, & Shook, 2009). Breast cancer-related LE (BCRL) incidence is reported to be 20% by Hayes et al. (2012). Cormier et al. (2010) reported an overall average of LE incidence of 15.5% that varied by malignancy other than breast cancer, where the incidence of head/neck LE was reported to be 4%, gynecologic origin 20%, genitourinary 10%, melanoma 16%, and sarcoma 30%.

It is common to define LE by stages and within each stage by its severity (which are elaborated in the consensus documents). In clinical practice, severity should be defined by the most severe segment (ILF, 2006; Stout et al., 2011). The common conservative treatment for LE is Complex Decongestive Therapy (CDT) (also known as Decongestive Lymphatic Therapy [DLT]) which includes several elements: skin care, compression bandaging, manual lymph drainage (MLD), and remedial exercises (Lasinski et al., 2012). Other conservative treatments that have been examined are the use of intermittent compression pumps (Feldman et al., 2012), low-level laser (Ridner et al., 2013), kinesio-taping (Rodrick et al., 2013), aqua lymphatic therapy (ALT) (McNeely, Peddle, Yurick, Dayes, & Mackey, 2011), low-fat diet (Shaw, Mortimer, & Judd, 2007), and upper limb and breathing exercises (Mosley, Piller & Carati, 2005).

Complex Decongestive Therapy is commonly administered in three phases: intensive; intermediate; and long-term. The purpose of the intensive phase is to reduce the affected limb to a normal size. Other goals may be improving range of motion, symptoms such as heaviness and pain, and function, and providing self-management tools for the long-term management of the condition (Larouche K & M-F, 2011; Stout et al., 2013). Substantial research has been conducted in studying CDT for the management of lymphedema. The results suggest an achievable reduction in limb volume between 17% to 60% (McNeely et al., 2011). Results vary due to different approaches of delivering this treatment (frequencies, session time), measurement tools (tape measurement, water displacement, bio-impedance spectroscopy, perometer), definitions of inclusion criteria (mild, moderate, severe),

and population diversity (Lasinski et al., 2012). The intermediate phase is administered when the patient has difficulty in maintaining the results of the intensive treatment, and needs further guidance on garment use, self-administered compression bandaging, and performing exercises. It has been recommended to limit this phase to 3 months. If the patient cannot control her/his LE, another intensive therapy is offered (ILF, 2006). The long-term management focuses on gaining long-term control on the condition; it consists of wearing a compression garment during the day, and (for some patients) bandaging overnight (Vignes, Porcher, Arrault, & Dupuy, 2007), skin care, self-manual lymphatic drainage, and exercises (ISL, 2013). A recent systematic review that examined the effectiveness of CDT found that there is sufficient evidence to recommend CDT for LE management, but not enough evidence regarding the contribution of each component of the treatment to the overall outcome (Lasinski et al., 2012).

The cost and burden of LE treatment are very high. Stout et al. (2012) reported an average cost of more than $3000 for an intensive series of 15 sessions for BCRL and another study (Arsenault et al., 2011) reported a cost of up to $1000 for the garment alone. Ryan et al. (2003) reported expenses of up to $2000 a month for women with lower limb LE (LLL) related to gynecologic cancer. In some countries, the costs are covered by the government, insurance, or other third-party payers, and in others the burden of the treatment costs lies on the patient's shoulders (Arsenault et al., 2011; Larouche K & M-F, 2011; Stout et al., 2013). McNeely et al.(2011) examined the supplementary effect that MLD has in addition to compression therapy and found that there was a small benefit. Whether adding MLD to the

treatment is cost-effective has yet to be determined. Health care providers need to act responsibly while making decisions for their patients' care. However, they need to be conscientious of the health system limitations, as well. To be able to accomplish these tasks, therapists need answers to the following questions: What should be expected from this treatment? What is considered to be a success or a failure? Is the intervention that we practice associated with the expected outcomes? For whom does this treatment work best? How do we measure success or failure? How do we know if the results of our treatment are clinically important?

Statistical significance of a treatment effect can depend on sample size and lacks the point of view of clinical importance. When clinical interpretation is not made clear, research data may be confusing to clinicians and may be misinterpreted. It is the authors' responsibility to make their results understandable to the readers and, in addition to providing the statistical significance, to interpret the clinical meaningfulness of the results (De Vet et al., 2006; Man-Son-Hing et al., 2002).

In statistical analysis, the researchers test their hypothesis. The statistical significance only represents the fact that the results were most likely not obtained by chance. It does not prove that the hypothesis which was generated by the researcher is true or false (Lydick & Epstein, 1993). For example, a study by Williams. (2002) examined MLD sessions and compared the results to a self-lymphatic drainage (SLD) intervention in BCRL for 3 weeks. This study found a statistically significant reduction of 71ml of arm LE in the MLD group, as compared to 30ml in the SLD group. The authors concluded that MLD should be recommended for clinical use over SLD based on the statistically significance of the results. However, the average

edema volume of the participants was over 700ml at the beginning of intervention. This amount is considered to be very severe by the Ramos et al. (1999) definition. The authors did not discuss whether a 10% reduction after a 3-week period is a meaningful enough outcome for patients who invest money and time in daily treatment.

To describe a meaningful change, researchers in medical studies use the term "minimal clinically important difference" (MCID) (Copay, Subach, Glassman, Polly, & Schuler, 2007). Minimal clinically important difference is the threshold value of a change in which its definition for each outcome is critical when assessing side effects, costs, and efforts, but, most importantly, success of an intervention (Man-Son-Hing et al., 2002). Researchers may disagree about what is considered a change, but they should make clear about their definition of MCID and let the readers decide for themselves. For example, Mosley et al. (2005) examined upper body and breathing exercises for BCRL and found an immediate statistically significant reduction of 52ml after 10 minutes of exercise. The authors did not report the MCID of volume reduction. Hence, clinicians have difficulties in deciding whether to recommend this exercise as a self-care measure for their patients, especially when we know that patients who administer self-care report a lower quality of life than those who have LE and do not engage in self-care (Ridner, Dietrich, & Kidd, 2011). Therefore, patients should invest their effort in an effective and meaningful intervention.

There are two approaches for defining MCID: distribution-based methods and anchor-based methods. The distribution-based method uses statistical

properties of the investigating tool without considering external measures (De Vet et al., 2006; Turner et al., 2010). This approach does not consider whether the change is important or meaningful to the patient or to the health system. Distribution-based methods include, for example, standard error of measurement (*SEM*), effect size (ES), minimal detectable change (MDC), and small real difference (SRD) (Copay et al., 2007). Anchor-based methods use an external anchor or indicator such as a patient response or a clinician opinion to validate a change as important (De Vet et al., 2006; Revicki, Hays, Cella, & Sloan, 2008). Examples include global rating of change (GRC) and receiver-operating characteristic curve (ROC) analysis (Lydick & Epstein, 1993; Revicki et al., 2008; Wright, Hannon, Hegedus, & Kavchak, 2012).

Distribution-based Methods

Standard error of measurement represents the error of measurement for a specific tool and is given in the same units as the measurement instrument. Standard error of measurement is directly correlated to the reliability of the test. Thus, the larger the *SEM* is, the smaller the reliability and the precision of the test. A result that is smaller than the *SEM* is possibly an error, rather than a real observed change that is obtained by a result that is larger than the *SEM* (Copay et al., 2007). Standard error of measurement has been found to correlate with anchor-based methods such that change experienced by a patient equates closely to a change of 1 *SEM* (De Vet et al., 2006).

Effect size describes a change that occurred from baseline to post treatment by the number of SDs. The score is a relative unit that can be compared with other outcomes. The numerator represents the mean change from baseline and the

denominator is the standard deviation. An example that was reported in studies defined ES as small when it is equal to 0.2, moderate when = 0.5, and large when = 0.8 (De Vet et al., 2006). The effect size can be used as a guide to assess the magnitude of the change (Lydick & Epstein, 1993).

The MDC represents the smallest change above the measurement error and is given with a level of confidence (MDC= 1.96X*SEM*X) where 1.96 represents the z value of a 95% confidence interval and is used, since there are 2 measurements involved: before and after the intervention (De Vet et al., 2006; Hart, Wang, Cook, & Mioduski, 2010). The disadvantages of distribution-based approaches are that, by themselves, they do not consider whether there was a clinically important change. For that reason, there is a need to explore the anchor-based methods.

Anchor-Based Methods

Global rating of change scales are commonly used in clinical studies (Kamper, Maher, & Mackay, 2009). Different scales for assessing the perceived change by the patient or clinician have been introduced over the years and found to be sensitive to both negative and positive changes (Copay et al., 2007). The areas of change can include quality of life, function, symptoms, general health, and more (Hart et al., 2010; Lydick & Epstein, 1993). Most studies used the global assessment rating (GAR) where the change was categorized into "better," "unchanged," and "worse." Numerous studies use continuous scales such as 15-point scales, such as -7 to +7, whereas 0 is considered as no change, -7 the worst change, and +7 the best change. Some investigators use cutoffs in GRC of mild (scored 2-3 on the scale), moderate

(respond 4-5 on the scale), and large change (absolute change of 6-7) (Lydick & Epstein, 1993; Turner et al., 2010).

Receiver-operating characteristic curve (ROC) analysis is used to discriminate between "improved" to "unchanged" and the patient response is dichotomized. Different cutoffs can be used to divide the population into two groups (Turner et al., 2010). In addition, the area under the curve represents the probability that the results will distinguish between "improved" and "unchanged." The scores that the ROC analysis provides range from 0.5-1. A score of less than 0.5 reflects the probability to distinguish between "improved" and "unchanged" to be low. A score of 0.7-0.8 is considered as acceptable, whereas 0.8-0.9 reflects an excellent ability to distinguish between "improved" and "unchanged."

Clinicians need reliable methods to detect patient improvement in relation to treatment cost, patients' effort and goals, and treatment side effects. The MCID should be provided in each study on each population and for every outcome (Copay et al., 2007). The MCID should be determined according to an anchor-based approach with the complement of a distribution-based method to provide its limits of error. If there is no accessible way to compare results to an anchor-based method, a distribution-based approach can be used (Turner et al., 2010). LE therapy has been criticized as time-consuming, very costly, and often non- effective (Lasinski et al., 2012). Nonetheless, it is being practiced all over the world, taught by LE schools, and considered the standard of care by health care systems (ISL, 2013; Levy et al., 2012; Stout et al., 2012). The effectiveness of CDT has been studied. However, the majority of studies do not include recommendations of what meaningful changes clinicians

should expect or aspire to. The objectives of this systematic review are to locate reports on the clinical effectiveness of conservative lymphedema management by reporting on outcomes which use anchor-based and distribution-based approaches.

Methods

The literature search was conducted through the EBSCO and MEDLINE databases, from inception to April 2017. The key words for the search were "lymphedema" or "lymphoedema" and "responsiveness" or "clinically significant" or "clinically important" or "measurement error" or "minimally clinical important change" or "minimal clinical change" or "small real difference." The focus of our search was for conservative interventions that led to clinically important outcomes and reliability studies that demonstrated clinical importance. After title and abstract screening, 416 of 483 articles were excluded where there was no report on conservative interventions. Articles that used imaging procedures as an outcome were excluded, as well, since they are used more as research tools than clinical assessment tools. The remaining articles (n = 67) were stratified into the outcomes of interest: volume, symptoms, skin changes, infection rate, quality of life, strength, function, and disability. Full-text articles were reviewed for each outcome. Then, 43 articles were excluded as non-relevant due to the use of the term "clinically important" without any discussion on clinically important definitions, outcomes, or recommendations (Figure 2.1). Therefore, 24 articles remained and are summarized in Tables 2.1-2.5.

Results

Volume as an outcome

Volume is the most reported outcome for LE management (Lasinski et al., 2012). There are different tools for measuring volume: water displacement, volume derived from calculations of circumferential measurements, and perometry. Bioelectrical impedance spectroscopy (BIS) is used to quantify extracellular fluid, but also provides estimation on volume. Basic circumferential measurements measured by a flexible tape are the most commonly used in clinical practices. Over the years, the definition of LE based on volume and ways to measure it had been debated (ISL, 2009; ISL, 2013). Armer et al. (2009) found that, for the same population with BCRL, different measurement definitions lead to different levels of LE incidence. For example, a definition of 2 cm difference between circumferential measurement was the most liberal that gave the highest estimation of LE incidence, and 10% difference in relative limb volume (RLV) the most conservative one that gave the lowest estimation (Armer et al., 2009). Twenty articles examined volume as their main outcome and defined MCID. These studies are reported in this review according to reliability (8 studies), immediate change after an intervention (2 studies), changes after intensive phase (3 studies), and changes in maintenance phase (7 studies).

Reliability studies (Table 2.1).

In clinical practice, decisions on patient's stability or change of status need to be made based on objective measurements. Eight studies examined reliability in volume measurements and gave a distribution-based characteristic to the outcome

(*SEM*, MDC). Taylor et al. (2006) conducted a study on BCRL and found that when an arm was measured according to anatomical landmarks and volume was calculated by the truncated cone method, the *SEM* was less than when compared to other methods of measuring such as measurement obtained from circumferential measurements based on distance from fingertips. Devoogdt et al. (2010) studied a new device for measuring BCRL. The device consisted of a steel bar with fixed measurement tapes in multiple sites (calculated for volume) and reported on MDC and % *SEM*. Tidhar et al. (2015) examined 41 physiotherapists and suggested 1% as a threshold for % *SEM* for assessing lower and upper extremity.

Katz-Leurer et al. (2012) assessed women in stable maintenance phase and measured them over an interval of 1 week. Their results take into consideration the time factor that is important in lymphedema, since lymphedema tends to change over the hours of the day, and from day to day. They reported on *SEM*'s for each segment of the arm and found the error of measurement to be less for each segment, than when summing these segments into a whole arm volume. Moreover, they reported on MDC from each segment and compared it to MDC of the whole arm. Their results emphasize the need to use segmental volumes in decision-making, rather than the volume calculations of the whole arm.

Chen et al. (2008) reported on *SEM* of circumferential measurements alone of BCRL (not calculated for volume). For those clinicians who do not calculate volume from the circumferential measurements, this study provides valuable clinical information with its estimation of what to expect using a flexible tape alone or when teaching patients self-measuring.

Lower limb lymohedema was tested by Sawan et al. (2009) in a study that examined a prophylactic use of compression garments. The researchers conducted a pilot reliability study on LLL. In their study, they reported on an intra-observer variable that measures repeatability and an inter-observer variable that measures reproducibility. In this case, the changes in leg volume can be reliably defined when taken by several observers only when it exceeds 1,000ml and beyond 270ml when taken by one observer. The author acknowledges that the MCID for reproducibility is large and presents a recommendation for further practice for decreasing it.

These studies give us estimations of what to expect when performing treatments and follow-ups on LE patients. Large differences in *SEM* were found between reports and these can be due to different training and experience of measurers, as well as different severities and locations of LE where *SEM* of a healthy arm will be smaller than *SEM* of a severe lymphedematous thigh; although Tidhar et al. (2015) didn't find significant difference between % *SEM* when healthy *vs.* LE arms or for legs were measured. It might be wise to look at the whole limb volume when trying to evaluate an effect of a series of sessions over a period of time; however, decisions after a single therapy or between sessions, where the changes can be small, should be evaluated according to segments since the *SEM* and MDC are smaller. Furthermore, when examining immediate effect of a technique or treatment, the clinician may choose to rely on results from studies that checked MCID at one time-point. However, when examining a patient over time (for example when measuring every sessions over a series of treatment sessions), results on MCID

from studies that took into consideration the time factor should be adopted (such as the Katz-Leurer and Bracha. (2012) study).

Immediate change (Table 2.2).

A few studies have examined the immediate effect of interventions and discussed their meaningfulness. McNeely et al. (2009) reported on a study that examined the immediate response of breast cancer survivors to a single 20-minute aerobic exercise event. They reported that this type of exercise didn't cause exacerbation of lymphedema as the increase in volume didn't exceed the cutoff point. Aqua Lymphatic Therapy was tested in a group of patients with BCRL. Tidhar et al. (2010) found reductions in volume after the first and last ALT session. The authors concluded that these were meaningful changes since they exceeded the *SEM* that was tested in a pilot study prior to the investigation (Tidhar & Katz-Leurer, 2010). Both studies demonstrate a cut-off point beyond which a change will be considered. However, no correlation or validation with an anchor-based method, such as the patient's response to the change, was reported. To be sure that a real change occurred, the patient needs to feel an improvement. This is true if the goal of the treatment is patient-centered. When the goal of treatment is solely maximum reduction of volume, a distribution-based method (such as *SEM*/MCD) that verifies statistically that a reduction had occurred may be sufficient.

Intensive therapy changes (Table 2.2).

Based on the findings that patients with a baseline volume difference between limbs of up to 500 ml reduced more than 50% of volume after a CDT

intervention, Ramos et al. (1999) concluded that a reduction of at least 50% will be considered a success. Two studies examined the effect of low level laser therapy (LLLT) (Carati, Anderson, Gannon, & Piller, 2003; Ridner et al., 2013). In Ridner et al. (2013) study protocol, all patients were wrapped with compression bandages after a session. The authors reported effect sizes which were not different between interventions; however, they were clinically meaningful when compared to baseline. Carati et al. (2003) reported 31% of participants exceeded the threshold of improvement. Although the changes demonstrated in these studies were large, the clinician will want to know whether, for example, a 50% reduction is sufficient for the patient to recognize improvement, or whether he/she will feels the difference between a 30% vs 40% change? These questions were not answered by the researchers in their studies. A comparison to an anchor-based method approach would have helped to answer these questions.

Maintenance phase (Table 2.2).

The purpose of the maintenance phase is to keep the volume of the limb(s) stable. Therefore, a meaningful change, for better or for worse, needs to be defined in order for clinicians to decide when to actively intervene. In this review, studies in which the intervention ended, but further reduction was expected as a long-term effect, were included, as well.

In 3 publications (Schmitz, Ahmed, et al., 2009; ISL, 2013; Katz et al., 2010), LE stability was defined as a prerequisite to participate in the programs (<10% increase in the past 3 months (Schmitz, Ahmed, et al., 2009), <10% increase in BCRL in the past 6 months (Jonsson & Johansson, 2013), and <15% increase in cancer-

related LLL in the past 3 months(Katz et al., 2010)). A threshold for exacerbation during the intervention was defined as an increase of ≥5% of RLV (Arsenault et al., 2011; Jonsson & Johansson, 2013; Katz et al., 2010; Schmitz, Ahmed, et al., 2009; Schmitz, Troxel, et al., 2009). In the weight-lifting results on BCRL, the proportion of women who demonstrated an exacerbation was similar in both the control and study groups (Schmitz, Ahmed, et al., 2009). The study on cancer-related LLL reported that no patient got worse after the study period; while two patients experienced skin infections during the intervention with increase of ≥ 5% of leg volume, they were referred to treatment and their volume subsided and did not reach the threshold at the end of intervention. This experience strengthens the decision that a 5% increase would be sufficient for intervention, since treatment delivery caused a decrease back to normal (Katz et al., 2010). In the pole-walking study, success was defined as a change of 3% decrease or greater than in RLV. When they found a decrease of 9% in RLV, the authors concluded that these women experienced a meaningful change in their LE (Jonsson & Johansson, 2013), since not only they didn't exacerbate, but reduced more than the 3% threshold. No study correlated their distribution-based results to an external anchor. Four studies in BCRL expected further improvement after intervention in the maintenance phase (Bertelli, Venturini, Forno, Macchiavello, & Dini, 1991; Carati et al., 2003; Gothard et al., 2010; Jeffs & Wiseman, 2013). Bertelli et al. (1991) examined an intervention of electrical stimulation added to use of a compression sleeve versus the use of a compression sleeve alone. They found that both groups did not change over 6 months; thus, adding electrical stimulation to the use of a sleeve showed no effect. Gothard et al. (2010) found that over 12 months, 9 of 21 (43%) participants reached

the threshold of meaningful changes; however, the mean reduction of the whole group did not reach the MCID. In this study, the mean percent RLV was 154% which is considered severe; hence, hyperbaric therapy may not stand alone in treating severe LE and may need an addition of compression therapy. Jeffs et al. (2013) reported on a home-based exercise intervention for 6 months in the maintenance phase. Despite the lack of information on the expected changes in excess limb volume in the self-management phase, the authors who conducted this study found that a difference of 2.5-6% change can be expected when adding an exercise program to standard self-management care. This is valuable information due to the fact that women with BCRL need to decide what to invest their valuable time in and often ask about what is useful. To determine whether this change is important to the patient will need further investigation with anchor-based approaches.

There is inconsistency between studies as to what is considered a change in volume and, moreover, what is meaningful change. Clinicians need to know what is the *SEM* and MDC for clinical use in order to be able to determine, first, if the technique they are delivering is working and, second, what is the trend of the volume over time. In case of improvement, they should continue with the same technique. In case of stabilization, it is important to examine whether the results match the patient's expectations and the therapist's prediction from the research that reported change. If stability is satisfactory, the patient can move into the next stage: the maintenance phase. Knowledge of what is considered to be a stable state and what is defined as deterioration can help the clinician advise correctly on how to maintain and when intervention might be necessary.

Symptoms (Table 2.3)

Several studies have addressed symptoms as an outcome of LE management, using symptoms as a sign for worsening or improvement. However, these studies did not describe what is considered to be a clinical change (Belmonte et al., 2012; Jonsson & Johansson, 2013; Katz et al., 2010; Mondry, Riffenburgh, & Johnstone, 2004; Ridner et al., 2013). Moreover, Letellier et al. (2014) measured pain with the short-form McGill Pain Questionnaire (MPQ). They reported improvement in the present pain index (PPI) change (Todd, Scally, Dodwell, Horgan, & Topping, 2008) for the study group. Although statistically significant, the PPI score did not reach the MCID. However, the ES was –0.7 which made the author question the fact that the MCID scores were not tested with lymphedema patients. Buchan et al. (2016) examined the mean number of symptoms experienced by persons with BCRL with the validated Norman lymphedema survey (Norman, Miller, Erikson, Norman, & McCorkle, 2001) and defined a meaningful change as a shift of 1 unit in overall number and in severity. Their study examined aerobic exercise versus resistance exercise and found that the aerobic group reported less symptoms from baseline. They concluded that this was meaningful change (Buchan, Janda, Box, Schmitz, & Hayes, 2016).

Schmitz et al. (2009) defined exacerbation in LE where there is a reported symptom that lasted more than a week. In this study where a weight-lifting program was introduced for women with BCRL, safety for the patient had to be defined. Such a definition can help a clinician try a new technique that is not necessarily

comfortable for the patient and be able to judge when to progress and when to retreat according to the patients' reports.

De Valois et al. (2012) conducted an intervention of acupuncture and moxibustion for BCRL and head and neck lymphedema. The main outcome was a "Measure Yourself Medical Outcome Profile" (MYMOP) questionnaire, in which the patient decides which symptoms are most troublesome for him/her. These authors used an anchor-based method for defining the success of their treatment in which a change in the MYMOP score of >0.5 was considered to be small; 1-1.5 moderate, and above 1.5 was considered a large change. Measuring symptoms burden in a sensitive way is important since therapists treat patients' symptoms (e.g. we don't cure lymphedema); it is reasonable that symptoms will be an outcome in therapeutic interventions. These outcomes can validate the results of treatment, especially where other objective variables, such as volume, do not respond to treatment.

Skin Changes (Table 2.3)

Skin hardening is a manifestation of the fibrosclerotic changes that happen in the tissue when LE progresses without proper care. To identify skin changes, clinicians use indentation ("pitting") and pinching the skin (Stemmer's sign) (ILF, 2006). The study by Gothard et al. (2010) was the only study which tried to define MCID of skin softening as a decrease of 2 grades of tissue hardening measured by an oncologist. The oncologist palpated the participants and quantified the amount of induration by a scale (0=none, 1=a little, 2=quite a lot, 3= very much). The authors concluded that this definition should be clinically meaningful since an improvement of 2 grades could not be due to a measurement error. Additionally, the patients

were asked to describe how their arm felt at the end of the follow-up period. Eight of 15 (53%) patients had a moderate lessening of induration in the examined areas. These findings were supported by the fact that 63% (12 of 19) participants reported that their arms felt softer (Todd et al., 2008). This is an example of a study that provides a patient perspective in addition to the objective outcome.

Infection Rate (Table 2.4)

Several studies have used infection rate (IR) as an outcome for safety (De Valois et al., 2012; Katz et al., 2010; Schmitz, Ahmed, et al., 2009; Tidhar & Katz-Leurer, 2010) or as an outcome of cost (Arsenault et al., 2011). The weight-lifting programs that are presented by the following researchers included patients that had stable LE. Infection rate was one of the parameters for stability (not more than one infection episode in the past 3 months) (Katz et al., 2010; Schmitz, Ahmed, et al., 2009). None of the studies that used IR as an outcome correlates this outcome to an external anchor. Moreover, Arsenault et al. (2011) performed a study in which they examined the influence of CDT on the infection-related hospitalization rate with a defined cut-off point of <29% annual incidence. They defined an estimate that termed NNT (number needed to treat) to be 0.13 (less than 1 patient who goes through CDT will need hospitalization due to cellulitis) which means that CDT can be considered as a method to prevent hospitalization for recurrent cellulitis. Since cellulitis is a life-threatening condition for LE patients, on one hand, it is important to define safety of intervention as IR of cellulitis. On the other hand, it is necessary to define expectations of reduction in IR when performing an intervention. Although LE management is very expensive, hospitalization due to cellulitis is costly, as well.[68]

More research is needed in this area to be able to guide the health care systems as to what kind of approach should be used in order to reduce IR in this population.

Quality of life (Table 2.5)

Quality of life (QOL) is an important outcome in LE management. Hence, several validated tools were developed for LE that consists of various domains: physical, function, social, appearance, and psychological. QOL is reportedly reduced in people who experience LE (Godoy, Braile, Godoy & Longo, 2002) and does not necessarily correlate to the severity or amount of volume (Launois et al., 2002). Furthermore, although several studies on BCRL found improvement in QOL with LE management (Kim & Park, 2008; Kim, Yi, & Kwon, 2007), no correlation was found between QOL and reduction of volume after intensive therapy (Tidhar & Katz-Leurer, 2010; Weiss & Spray, 2002), suggesting the importance of measuring QOL as a separate outcome for LE management. Although the studies suggested distribution-based MCID's for their outcomes and reported on true changes beyond *SEM* and RSD with large ES's, no study correlated the distribution-based outcome to an external anchor. This leaves clinicians with no recommendations as to what changes to expect that will be meaningful to the patient/health system (cost, for example) from the results of different questionnaires administered in clinical practice (Belmonte et al., 2012; Buchan et al., 2016; Devoogdt et al., 2014; Devoogdt, Van Kampen, Geraerts, Coremans, & Christiaens, 2011).

Ridner et al. (2013) reported low effect sizes for QOL questionnaires after three interventions (MLD, MLD+LLLT, LLLT). In their study, there was an improvement in symptoms burden and in volumetric measurements for all groups

which makes a researcher wonder, “If there is no change in QOL, what outcomes would be meaningful for a patient?”

Strength/endurance/fitness/function/disability (Table 2.5)

In the literature, there is no definition of the threshold for meaningfulness in change in grip strength, function, or disability in lymphedema patients (Boneti et al., 2008). A few studies reported improvement in outcome measures which exceeded the MCID. However, there was no correlation to an external anchor.

Since most of the tools were validated on musculoskeletal disorders, there is a need to investigate whether these tools can be validated for LE, and to define a cut-point for clinical significance which will enable measurement for meaningfulness, as well.

QOL, function, and disability are important outcomes in LE management, especially when volume is stable, in the maintenance phase, and when there are no changes in symptoms. Knowing what will be effective for patients in other aspects of their lives will enable clinicians to incorporate other modalities or therapies and consider cost-effectiveness, as well.

Conclusions

Lymphedema is a chronic condition which requires life-long management. Investing in interventions that will lead to meaningful changes is of great importance to people who live with LE. As clinicians, deciding whether to change our practices, adopt new devices or techniques, invest in education, and refer to new therapies, we need to have more information than statistical significance alone. We need to know whether our patients will be happier, or healthier, with the available intervention.

Will the change that they gain from the treatment make a difference for them? Furthermore, there is a need to correlate results to healthcare systems demands, as well, and find MCIDs which represents cost-effectiveness in the field of lymphedema management.

The purpose of this article was to review the clinical effectiveness of conservative lymphedema management outcomes by anchor-based and distribution-based approaches. Most of the studies examined volume as an outcome using different analytic approaches, of which *SEM* and MDC were the most frequently reported. Some of the studies did use cut-off points, especially when describing an intervention used during the maintenance phase when patients should be stable and there is a concern for exacerbation (Schmitz, Ahmed, et al., 2009) or hope for further improvement (Norman et al., 2001). Other outcomes such as symptoms, QOL, strength, endurance, fitness, function, and disability were assessed by a variety of tools with different MCID recommendations based on either anchor-and distribution-based approaches and combinations of both methods. Infection rate is a very important outcome and its MCID can help in decision-making regarding safety and cost in LE management.

The lymphedema population which is most researched is that of breast cancer survivors. Clinicians tend to generalize decision to their own patients based on the results of breast cancer studies. Lower limb lymphedema, head and neck LE, primary LE, and other types will respond differently to an intervention than BCRL and the expectations for success will be different, as well. Therefore, further research is needed on different populations of LE patients and on different tools. Ideally,

researchers should report on the estimated outcome, and on their definition of MCID using anchor-based methods, as well as distribution-based methods. In this way, researchers and clinicians will be able to understand and explore the findings and to transfer this new knowledge to practice.

Finally, MCID of a specific variable can be defined differently for/by the patient, the clinician, and the healthcare system. For example, with volume as an outcome, the clinician will aim for "maximum" reduction until stabilization to order a garment; the patient will want "just enough" so he can bend his knee, climb stairs, etc.; and the health care system will aim for "just enough" to reduce costs of hospitalization due to infection. The MCID "maximum" and "just enough" will be at different cut-off points for the same variable. Similarly, the clinician may desire the referral threshold to be mild LE to maximize outcomes with minimal treatments; the patient may desire relief from distressing symptoms, impaired function, or risk for recurrent infection, with a subjective definition for the threshold; and the health care system will desire later referral based on a higher limb volume difference to avoid unnecessary treatment in the event of transient or self-resolving swelling. Clinicians, as part of the health system, should be aware of the different interpretations of MCID that represent diverse expectations. Use and discussion of MCID in published articles should improve our understanding of what is clinically effective, thus leading to better use of resources and improved care for our LE patients.

Table 2.1: Characteristics of Included Reliability Studies

Study	Design	Sample	Intervention/ Follow-Up	Variable/tool	Distribution based – MCID
Chen (2008)	Reliability Study	14/BCRL	2 physical therapists conducted the measurements	Volume/ water displacement	Water displacement: *SEM* 27.2 (1.1%); SRD 75.4 (3.1%) SEMs for the circumference measurement ranged from 0.13 cm (*SEM*%= 0.5%) for intra-rater assessment of the forearm to 0.37 cm (*SEM*%= 1.3%) for the inter-rater assessment of the elbow; SRD Intra-rater upper arm 0.5 (1.5%), elbow 0.58 (2%) forearm 0.37 (1.5%). Inter-rater upper-arm, 0.8 (2.2%), elbow 1.02 (3.5%), forearm 0.7 (1.8%)
Devoogt (2010)	Validity and reliability	64/BCRL	1 assessor measured 64 women twice; 48 patients were measured twice by 2 assessors	Circumferential measurements/ measurement tape	MDC = 55ml; 1 cm at any site SEM = 0.8%-2% ICC intra = 0.942 inter = 0.998
Devoogdt (2011)	Reliability study	90/ 60 BCRL & 30 BC	Phase 1: Developing the questionnaire- by interviews followed by a pilot study on 29 patients, phase 2: Reliability completed questionnaire with an interval of 24-48 h	Volume/ measurement tape every 4 cm , using a cylindrical formula to calculate volume	Lymph-ICF total score: SEM=4.8, SRD=13.4; Physical function: SEM=7, SRD=19.4; Mental function: SEM= 9, SRD= 24.9; Household activities: SEM=7.7, SRD= 21.3; mobility activities: SEM= 7.7, SRD= 21.2 Life and social activities: SEM= 12.5, SRD 34.6
Devoogt (2014)	30/LLL	Reliability study	Phase 1: Developing the questionnaire- by interviews followed by a pilot study on 29 patients, phase 2: Reliability completed questionnaire with an interval of 24-48 h	Function, disability, health/ Lymph-ICF	SEM and SRD from 5.9 and 16.3 for physical function score to 12.6 and 35 for life and social activities score, respectively
Katz-Leurer (2012)	Reliability study	16/BCRL	Measurements were taken twice in a 1 week interval by 2 assessors at the same time of day	Volume/ self-developed measurement bar + tapes calculated by truncated cone method, Water displacement	Segmental SEMs in ml of affected arm: GF=14.7, EF=14, ED=20, DC=7.3, CB=3.4. Whole arm= 78.8, composite method=45ml; MDC: GF=40.7, EF=38.8, ED=55.4, DC=20.2, CB=9.4. whole arm=218.4ml composite method= 124.7
Sawan (2009)	Reliability study	8 for repeatability / LLL; 1 for reproducibility/healthy LL	Repeatability: 30 sets of 3 repeated measurements of a single observer; Reproducibility: 17 experienced lymphedema therapists measured 3 times a single lower limb of healthy volunteer.	Volume/circumferential measurement by tape- truncated cone method	Intra-observer variability (95% repeatability limit) r=270ml; Inter-observer variability (95% reproducibility limit) R=1000ml
Taylor (2006)	Cross-sectional comparison	66/ BCRL	5 raters measured circumferential measurements according to anatomical land marks twice	Volume/ measurement tape calculation of volume according to anatomical landmarks using the truncated cone method:	Anatomical land marks: SEM between 64.5 - 65.4 mL; MDC 150 ml
Tidhar (2015)	Reliability study	2BCRL, 3LLL	41 physical therapists measured 3 times an arm and a leg.	Volume/ measurement tape calculation of volume according to anatomical landmarks using the truncated cone method:	SEM arms 27.5 ml; mean % SEM 0.82% SEM legs 83.6 ml ; mean % SEM 0.64% SEM 83% of PTs measured > 1% SEM

Note. MCID= minimal detectable important change; BCRL= breast cancer-related lymphedema; *SEM*= standard error of measurement; MDC= minimal detectable change; LLL= lower limb lymphedema; LL= lower limb; ICC= intra-class correlation coefficient.

Table 2.2: Characteristics of Included Studies for Volume Outcome (MCID Represented by Anchor-Based or Distribution-Based Methods)

	Design/ Sample	Intervention/ Follow-Up	Phase	Variable/ Tool	MCID	Results
Arsenault (2011)	Prospective, case control, observational trial/ 21 secondary & primary LE	Control: medical records; Study: intensive phase of CDT then maintenance phase/24mos F/U	Maintenance	Volume with Circumferential measure	Anchor-based: ≥5% reduction in limb volume	4/10 participants demonstrated increase in 5% reduction over follow-up period; 3/10 stable; 3/10 worse.
Bertelli (1991)	RCT/ 74 BCRL	Control: elastic sleeve; Study: elastic sleeve + 10 sessions of 30min electric stimulation in 2 cycles of 2wks/6mos F/U	Maintenance	Sum of circumferences of 7 points with tape measure	Anchor-based: Success: decrease of >25% Unchanged: decrease of <25% Failure: increased of > 25%	no difference between groups. 17% reduction in both groups: unchanged.
Carati (2003)	RCT/ 28 BCRL	Study: 1 cycle or 2 cycles of LLLT to axillary region/3 mos; control: placebo/3 mos	Intensive and Maintenance	Volume with perometer	Anchor-based: Over 200 ml reduction in affected limb volume	No improvement immediately after intervention period. 31% of participants receiving 2 cycles of LLLT had more than 200 ml reduction compared to 3.8% in the placebo Group after 3 months
Gothard (2010)	Non-randomized phase II trial/ 21 BCRL (RLV >30%)	Hyperbaric therapy for 100min in 30 occasions for 6 weeks/12mos F/U	Maintenance	Volume with perometer	Anchor-based: Response: >20% improve-ment in %RLV	No clinically improvement. 7.51% mean reduction (p=0.005). However, 9/21 experienced >20% reduction.
Jeffs (2013)	RCT/ 23 BCRL	Study: exercise intervention with standard lymphedema self-care; control self-care alone/6mos F/U	Maintenance	Volume with perometer	Anchor-based: Expect improve-ment when exercise added to be between 2.5–6%	%change intervention: 95% CI –26.57 to –5.12; control improvement crossed the line of no effect (95 %CI –17.71 to 1.1)
Jonsson (2013)	Pre & Post pilot/ 23 BCRL	2wks control followed by Pole walking 3-5/wks. /8wks F/U	Maintenance	Volume with water displacement	Anchor-based: A change ≥3% RLV. An increase ≥ 5 considered exacerbation (intervention stopped)	9% reduction in LRV
Katz et al (2010)	Pre & Post pilot/ 10 cancer-related LLL	Observed weight-lifting for 2mos then unsupervised (2x/wks.) for 3mos/5mos F/U	Maintenance	Volume with perometer and circumferential measure	Anchor-based: >5% volume of affected leg >2cm circumferential measures clinically	No change from base line after 5 months
McNeely (2009)	Pre & Post/ 18 BC; 5 BCRL	20min aerobic exercise (arm crank)	Post-session	Volume with tape measure	Distribution based: SEM=0.2cm Anchor-based: >200ml diff between arms	Differences between limbs remained stable. Both limbs increased (not clinically) and decreased after 1 hour
Ramos (1999)	Retrospective/ 69 BCRL	CDT 30-60 min + Self- care 2-5 per week/ 6-8 week	Intensive	Volume with tape measure	Anchor-based: 50% reduction	Edema at baseline≤ 250 mL reduced 78%; 250 - 500 mL reduced 56%; ≥500ml reduced 38%
Ridner (2013)	RCT/ 46 BCRL	3 groups: LLLT 20min/ 10 sess; LLLT+MLD 40min/10 sess; MLD 40 min/ 8 sess	Intensive	Volume with tape measure; ECF/BIS	Distribution based: Effect Size of volume reductions. No indication for cut-off or desirable effect.	No differences were found between the groups over time. MLD=-0.42; LLLT= -0.64; MLD+LLLT = -0. 64 ES BIS:MLD= -0.54; LLLT = -0.55; MLD+LLLT = -0.53
Schmitz (2009)	RCT/ 141 BCRL	Study: 3mos observed weight-lifting (2x /wks.) then 39 wks., no obs (2x /wk.); Control: no change to exercise level over study /12mos F/U	Maintenance	Volume with water displacement	Anchor-based: possible exacerbation ≥5% of RLV	The proportion of women who had an increase of 5% or more in limb swelling was similar in the weight-lifting group (11%) and the control group (12%)
Tidhar (2010)	RCT/ 48 BCRL	Study: ALT + self-manage; Control: self-manage/ 3mos F/U	Post-session	Volume with water displacement	Distribution-based: SEM: 40.4 ml	Reduction of 52ml after 1st session and 98ml after last session

MCID= minimal clinically important difference; BCRL= breast cancer-related lymphedema; SEM= standard error of measurement; MDC= minimal detectable change; LLL= lower limb lymphedema; ml= milliliters; ALT= aqua lymphatic therapy; CDT= complex decongestive therapy; LLLT= lower level laser therapy; MLD=manual lymph drainage; ECF= extra cellular fluid; BIS=bio impedance spectroscopy; RLV= relative limb volume

Table 2.3: Characteristics of Included Studies for Symptoms/Skin Changes Outcomes (MCID Represented by Anchor- or Distribution-Based Methods)

	Design/Sample	Intervention/ Follow-Up	Phase	Variable/ Tool	MCID	Results
Buchan (2016)	RCT/41 BCRL	2 groups: Resistance exercise for 50min 2Xweek; aerobic exercise for 50min 2Xweek for 12 weeks; 12 weeks follow-up	Maintenance	Symptoms/self-report of severity and frequency	A shift of one unit	No differences between groups or over time Aerobic group reported less symptoms from baseline -1.5units
Carati (2003)	RCT/ 28 BCRL	Study: 1 cycle or 2 cycles of LLLT to axillary region; control: placebo/3 mos F/U	Intensive and Maintenance	Softening of skin clinical examination by oncologist self-report	Anchor-based: Improvement in 2 stages of tissue hardness as diagnosed by the Oncologist	8/15 pts with mod/ or marked decreased irradiated breast, pectoral fold &/or supraclavicular fossa induration 12/ 19 pts reported arms felt softer.
De Valois (2012)	1-arm observational/ 35 BCRL, head & neck LE	Acupuncture/ Moxibustion for 1 week/ 7-13 weeks with option for 6 more treatments	Intensive	Symptoms/ MYMOP	Anchor-based: On 0-6 scale: Mean changes: small: 0.5-1; moderate: 1.0-1.5; large >1.5	Changes in symptoms were moderate and large
Lettelier (2014)	RCT/ 25 BCRL	Study: ALT, Control: Home exercises with a DVD/ 3mos F/U	Maintenance	Pain/ MPQ	Distribution-based: SEM: total score =1.87 PPI=1.4 ES small=0.2, mod=0.5, large=0.8	PPI reduction of 0.5. ES=-0.7
Ridner (2013)	RCT/ 46 BCRL	3 groups: LLLT for 20min/ 10 sess.; LLLT+MLD for 40min/ 10 sess.; MLD for 40min/ 8 sess.	Intensive	Symptoms/ LSIDS-A	Distribution-based: Effect Size of symptom burden: MLD=-0.44; LLLT= -0.41; MLD+LLLT = -0. 46	No difference found between groups over time.
Schmitz (2009)	RCT/ 141 BCRL	Study: 3mos observed weight-lifting (2x /wks.) then 39 wks., no obs (2x /wk.); Control: no change to exercise level over study /12mos F/U	Maintenance	Symptoms/ Telephone survey of 14 items	Anchor-based: Possible exacerbation if women reported change in symptoms lasting ≥1wk	Improvement in severity of symptoms greater in study than control group

MCID= minimal clinically important difference; BCRL= breast cancer-related lymphedema; SEM= standard error of measurement; MDC= minimal detectable change; LLL= lower limb lymphedema; ALT= aqua lymphatic therapy; CDT= complex decongestive therapy; LLLT= lower level laser therapy; MLD=manual lymph drainage; LSIDS-A= lymphedema symptom intensity and distress scale–arm; MYMOP= Measure Yourself Medical Outcome Profile; MPQ= McGill Pain Questionnaire; PPI=present pain intensity

Table 2.4: Characteristics of Included Studies for Infection Rate Outcomes (MCID represented by Anchor- or Distribution-Based Methods)

	Design/Sample	Intervention/ Follow-Up	Phase	Variable/ Tool	MCID	Results
Arsenault (2011)	Prospective, case-control, observation-al trial/ 21 Secondary & Primary LE	Control: medical records; Study: intensive phase of CDT then maintenance phase/ 24mos F/U	Maintenance	Incidence of hospitalization for recurrent cellulitis/ CER; EER; ARR and NNT	Anchor-based: <29% annually of cases despite use of antibiotic therapy	ERR= 0.67 ARR=7.83 NNT = 0.13
De Valois (2012)	1-arm observational/ 35 BCRL & head/neck LE	Acupuncture/ Moxibustion for 1 week/ 7-13 weeks with option for 6 more treatments	Intensive	Infection rate/ # attacks during study period		2/35 cellulitis attack.
Katz et al (2010)	Pre & Post pilot/ 10 cancer-related LLL	Observed Weight lifting for 2mos then unsupervised (2x/wks.) for 3mos/ 5mos F/U	Maintenance	Infection Rate/ # attacks	Anchor-based: Pre-requisite to start intervention: no infection requiring antibiotics in 3 mos.	2/10 skin infections during study period
Schmitz (2009)	RCT/ 141 BCRL	Study: 3mos observed weight-lifting (2x /wks.) then 39 wks. (2x /wks., no obs.); Control: no change to exercise level over study/ 12mos F/U	Maintenance	Infection Rate/ # attacks	Anchor-based: Pre-requisite to start intervention. ≤ 1 infection in 3 mos.	No adverse events
Tidhar (2010)	RCT/ 48 BCRL	Study: ALT + self-manage; Control: self-manage/ 3mos F/U	Post-session	Infection rate/ # attacks during study period	Anchor-based: No infection will count for safety	No infections during the study period

MCID= minimal clinically important difference; BCRL= breast cancer-related lymphedema; SEM= standard error of measurement; MDC= minimal detectable change; LLL= lower limb lymphedema; ALT= aqua lymphatic therapy; CDT= complex decongestive therapy; LLLT= lower level laser therapy; MLD=manual lymph drainage LE= lymphedema; CER = Control Event Rate; EER= Experimental Event Rate; ARR =Absolute Risk Reduction; NNT= Number Needed to Treat

Table 2.5: Characteristics of Included Studies Quality of Life/Disability/Function/Strength/Endurance/Fitness Outcomes (MCID Represented by Anchor- or Distribution-Based Methods)

	Design/Sample	Intervention/ Follow-Up	Phase	Variable/ Tool	MCID	Results
Belmonte (2012)	Cross-over, single-blind randomized/ 36 BCRL	10 daily sessions of MLD followed by 10 sessions of LFLIET	Intensive	QOL/Fact B +4	Anchor-based: FACT-General changes: 5–6 pts; FACT-B: 7–8 pts; and trial outcome index: 5–6 pts.	FACT-General improved by 5.8 vs. 2.5 points (ctrl); FACT-B by 7.7 vs. 2.1; and trial outcome index 5.4 vs. 0.04
Buchan (2016)	RCT/ 41 BCRL	2 groups: Resistance exercise for 50min 2Xweek; aerobic exercise for 50min 2Xweek for 12 weeks; 12 weeks follow-up	Maintenance	1. QOL/ Fact B+4 2. Endurance/Squat test 3. Fitness test/ 6-min walk test	Distribution-based 1. Increase by ≥7 points 2. > 9 squats 3. >25m in 6-min walk	1. The resistance group +10 and aerobic-based exercise group +13.2 from baseline to 12 wks. and 14.6 and 14 at 24wk. 2. Resistance and aerobic group: 9.4, at 12 wks. and the resistance group 12.4 at 24wk (not statistically significant) 3. Resistance group 34.6 and aerobic group 26.9 at 24wk
Jonsson (2013)	Pre & Post pilot/ 23 BCRL	2wks control followed by Pole walking 3-5/wks. 8wks F/U	Maintenance	Disability/DASH	Anchor-based: 10 point change	2 point improvement
Lettelier (2014)	RCT/ 25 BCRL	Study: ALT 1/wks.; Control: Home exercises with a DVD/3mos	Maintenance	1. QOL/ Fact B+4 2. Strength/ Dynamo-meter 3.Disability/ DASH	For all outcomes ES small=0.2, mod=0.5 large=0.8 1. Combination of distribution-based and anchor-based methods 7-8 points 2. Distribution-based method. MDC=3.4kg 3. Combination of distribution- based and anchor-based methods. 10 points	1. FACT B+4= 5.8;ES=0.72 2. Control 2.1kg for healthy, 3.1kg for LE. Study: 3.2kg for healthy, 4.1kg for LE. ES 0.85-1.57 3. Study= 9 points; ES = -0.75, control=6.1points, ES=-0.33
Ridner (2013)	RCT/ 46 BCRL	3 groups: LLLT for 20min/ 10 sess.; LLLT+MLD for 40min/ 10 sess.; MLD for 40min/ 8 sess.	Intensive	QOL/ ULL27; FACT-B	Distribution-based: Effect Size of ULL27: MLD=0.13; LLLT= 0.52; MLD+LLLT = 0.42 Effect Size of ULL27: MLD=0.27; LLLT= 0.49; MLD+LLLT = 0.47	No difference between groups or within each group over time.

MCID= minimal clinically important difference; BCRL= breast cancer-related lymphedema; SEM= standard error of measurement; MDC= minimal detectable change; ALT= aqua lymphatic therapy; LLLT= lower level laser therapy; MLD=manual lymph drainage; QOL=quality of life; ULL27= upper limb lymphedema 27 questionnaire; FACT B+4=functional assessment of cancer treatment—breast cancer version 4 (plus 4 lymphedema items); DASH=Disability of the Arm, Shoulder and Hand questionnaire LE= lymphedema; LFLIET= low-frequency low-intensity electrotherapy.

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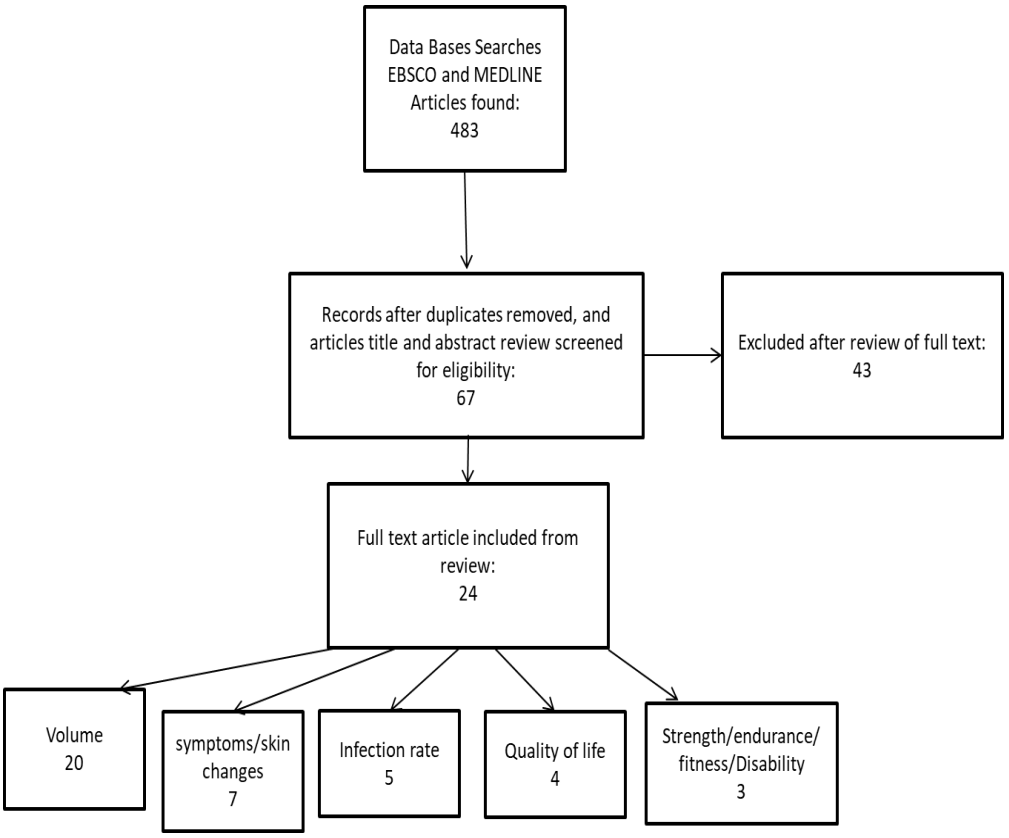
Figure 2.1: Chart Flow of the literature



Note. The majority of articles have more than one outcome

CHAPTER THREE: BACKGROUND

Practice-based Evidence (PBE)

When the evidence is a result of routine practice, we call it practice-based evidence (PBE) (Horn, DeJong, & Deutscher, 2012). Observational studies that take into consideration all the variables related to the patient (e.g., demographics and co-morbidities), the interventions (e.g., type and frequency), and outcomes (e.g., symptoms and volume change) may provide associations that could lead to more detailed recommendations as to what the right treatment is for a more focused group of patients (Deutscher et al., 2009; Horn, DeJong, Ryser, Veazie, & Teraoka, 2005). In PBE, there is no alteration in the process of care (Horn et al., 2012). The data are derived from computerized medical records that are in use in daily routine by clinicians. Since all data are captured, treatment interventions are documented as separate components and the potential of finding associations between clusters of techniques or non-conventional approaches is highly reasonable, as long as the documentation is detailed enough and reliable (Deutscher et al., 2009).

Goal of PBE: To identify associations between treatments and outcomes – to find the right treatment for specific patient group by reducing the effect of alternative explanations.

Hallmarks (Horn & Gassaway, 2007):

- All of the interventions that are offered are considered in the analyses.
- The hypotheses are not specific.
- No/minimal inclusion criteria to maximize generalization.

- Detailed characteristics of the patients (include demographics, illness, co-morbidities, etc.).
- The differences between patients are controlled by statistics and not by randomization.
- The research is done by the front-line clinicians in the field who are engaging in the process of care (after thorough process of identifying the data that are needed for documentation, implementation, and testing of professional documentation).
- Clinicians participate in all steps of study for well implemented knowledge translation and best practice.

Theoretical Framework

BioPsychoSocial model. Lymphedema has been studied for the past few decades and covers many areas from biology and physiology of the lymphatic system, through different and new interventions, and to newly-studied areas of genetics in LE (Miaskowski et al., 2013; Tidhar & Katz-Leurer, 2010); nevertheless, each study stands alone in the world of science. To have a continuum and growth, research needs a theoretical framework to work in and mature from (Armer, 2008).

Dr. Armer and colleagues were searching for a theoretical framework that would cover all aspects of lymphedema diagnosis, management, and risk-reduction (Armer, Radina, Porock, & Culbertson, 2003). Based on the literature that was scarce in the early 1990's, and on professional and clinical experience, no framework specifically for lymphedema was found (Armer, 2014). Originally, they discovered

that the biobehavioral model of cancer, stress and disease progression (Andersen, Kiecolt-Glaser, & Glaser, 1994), combined with models on coping with stress and the relationship between social support and problem-solving which were viewed as protective mechanisms, as Passik et al. (1998) reported, could be good foundations for a lymphedema model (Armer et al., 2003). Therefore, the BioPsychoSocial model for Secondary Lymphedema (Figure 3.1) is a theoretical framework that, first and foremost, concerns itself with the extent of lymphedema and ways to reduce the risk of developing lymphedema; by that, it specifies all the known predisposing factors that can put a woman who had gone through breast cancer treatments at risk for lymphedema. On the left side of the model are social support and problem-solving as protective mechanisms that influence the subjective and objective aspects of lymphedema and the outcomes of natural causes or interventions (functional, psychological overall QOL). In the middle of the model are objective measurements of volume change and subjective symptoms that influence the ability to cope in an effective way in the management of lymphedema, and also directly influence the outcomes. At the middle bottom of the model are coping effectiveness and symptom management that influence the objective and subjective aspects of lymphedema and the identified outcomes. On the right are the outcomes that are influenced by all the concepts in the model.

Relationships between the concepts are based on empirical studies and systematic reviews and are described below:

- Predisposing factors and their influence on outcome were studied by a few researchers; Bevilacqua et al. (2012) found that age, body mass index (BMI),

chemotherapy infusions on the arm in which a surgery was performed in the same axilla, the level of lymph node dissection at the axilla, location of radiotherapy, post-operative seroma, infection, and early onset of edema were predictive variables for the development of LE in 1054 women 60 months after surgery (Bevilacqua et al., 2012). Vignes et al. (2006) found that the time that passed since the onset of LE, and BMI were factors that predicted a success in the intensive therapy phase of CDT (which means women with shorter time since the onset of LE and lower BMI experienced the highest reduction in LE volume) (Vignes, Porcher, Champagne, & Dupuy, 2006).

- Prediction of outcomes by symptoms and volume was studied by Armer et al. (2003) who used a self-reported symptom questionnaire and found the feeling of "swelling now" and "heaviness in past year" to be predictive of detecting a ≥ than 2 cm difference between arms. Ramos et al. (1999) found that severity of lymphedema (that is present as a percentage of relative limb volume [RLV]) predicts the volume change at the end of intensive therapy, in such a way that those with severe lymphedema reduced up to 50% of RLV and those with mild lymphedema reduced more than 75% of their initial edema. Shigaki et al. (2013) reported results of a cross-sectional analysis of a 5-year longitudinal research, in which no matter what method of lymphedema diagnosis was used (10% RLV compared to base line or to the unaffected arm), a high correlation was found with functional limitations in the home environment (Shigaki, Madsen, Wanchai, Stewart, & Armer, 2013).

- Fu et al. (2013) reported on a relationship between staging of LE and psychological outcomes, where women with Stages 0 or 1 reported more anxiety than women with lymphedema Stages 2 and 3 (Fu et al., 2013).
- Problem-solving that predicted outcomes was studied by Heppner et al. (2009) who conducted a qualitative research in which they interviewed women with BCRL and found that taking action in seeking treatment and in talking freely about their lymphedema was helpful for reducing symptoms of stress, while avoiding seeking help was ineffective. However, their study did not examine the effectiveness of the coping strategies and they reported that some women's engagement in activities caused negative results (Heppner, Armer, & Mallinckrodt, 2009).
- Social support influence on outcomes and specifically on stress was investigated by Heppner et al. (2009) who found that support by family and friends helped these women deal with the stress involving LE; furthermore, lack of support by the health care system and insurance providers increased stress (Heppner et al., 2009). Mallinckrodt, Armer, and Heppner (2012) examined whether social support correlates linearly to outcomes of adjustment to illness and stress, and found that the relationship is curvilinear where women who are in the lowest quartile of support had high correlation between the level of support and the adjustment to illness and stress while the remaining three quartiles did not have significant correlation between level of social support and outcomes. Overall, women reported good coping when they had support by family members, friends, and also spiritual support which helped them be proactive in their LE management.

- Social support influence on coping effectiveness and symptom management was studied by Armer et al. (2009) and Armer, Brooks, and Stewart (2011) in a second analysis of survey data, where the researchers examined what influences women to practice self-care strategies to reduce the risk of developing lymphedema and concluded that education for self-care is important, although not sufficient for women to engage in self-care. There is a need for personal support such as empathy, confirmation, comfort, and clarification that can all be given by a devoted and understanding nurse. This support should be embedded in an educational program that will cover all aspects (Armer et al., 2009).
- Coping effectiveness and symptom management influence outcomes and have been reported in several systematic reviews and studies. Lasinski et al. (2012) reported a positive effect of CDT interventions on quality of life (QOL), function, symptoms, and volume (Lasinski et al., 2012). Kwan, Cohn, Armer, Stewart, and Cormier (2011) found a positive effect of exercise on LE outcomes such as strength, symptoms, QOL, and volume. Ridner et al. (2012) reported on lack of high quality studies that examined the effectiveness of self-management strategies on outcome; however Vignes, Porcher, Arrault, and Dupuy (2007) studied long-term lymphedema self-management and found that women who bandaged or use a compression garment sustained stability, while women who did not practice self-management exacerbated over time (Vignes, Porcher, et al., 2007). Lastly, in a case series of 30 patients, Tidhar, Hodgson, Shay, and Towers (2014) found that bandaging intensively by the patient or a care-giver with weekly follow-up sessions improved

volume reduction by 48%-92%, with mild lymphedema improving more than severe.

Overall there is good support for the relationships between concepts, besides the self-care effectiveness that was not well enough established. As mentioned before, this model was designed for BCRL and most of the evidence that was established is drawn from data from this population. PBE study should examine all patients who are referred to the physiotherapy clinics for LE management.

***Ways for the theory to guide a proposed research in Maccabi Healthcare Services (Maccabi)*:**

- Coping effectiveness with the focus on self-care and self-management is a concept that was found to be effective in only a few studies (Boris, Weindorf, Lasinski, & Boris, 1994; Tidhar et al., 2014; Vignes, Arrault, & Dupuy, 2007) which were not of high quality of evidence (e.g., case series and observational studies). A variety of tools are given to a patient: different types of exercise, self-massage, self-bandage, self-monitoring, skin care, compression bandaging, garments, compression devices, and weight-loss (Ridner et al., 2012). The concept of predisposing and covariate variables that influence diagnosis and outcomes may guide a PBE study by the fact that patients' characteristics, such as medication use, co-morbidities, demographics, surgery data, and more, are being collected routinely by the physiotherapists or automatically by the system (derived from the electronic medical records) and may be used in a multiple regression analysis of high

quality that takes into consideration every collected variable that can influence the outcome can be conducted.

- Selection of measurable independent and dependent variables are guided by the model. The physiotherapists routinely document volume, function, and symptoms which are the dependent variables. (They also document fear avoidance from movement that can be related to the adjustment concept.) Furthermore, all the interventions, including self-management (e.g., self-bandaging education by a care-giver or by the patient, self-massage, exercise education); therapist-delivered intervention (e.g., MLD, compression bandaging and more); co-morbidities, medication use, and demographics (age, gender) all may function as independent variables in a PBE study.
- Sample selection: The predisposing factors concept (including medication use, co-morbidities, and demographics) and the middle variables in the model (diagnosis and interventions) influence a multi-linear regression model that may be used in a PBE study.
- Based on recommendations by Armer et al. (2009) medical records should be used for data collection in a PBE study. In order to be sure that the documentation of intervention is conducted in a unified way, an accuracy test of documentation by the physical therapists should be conducted.
- Data analysis should be guided by the model as the influence of concepts one on the other. A multi-linear regression analysis should be performed and fit the model framework, if predisposing factors act as extraneous and covariate variables that could interfere with the outcome and bias the interpretation of the results.

- Interpretation of findings: The model refers to causality effects between some concepts and interactions between and among other concepts. However, as we see this model fit to a wider population (beyond breast cancer), it can be also referred as an exploratory framework. Strong relationships may be found between concepts that may be examined later on in experimental designs that can support causality.
- A PBE study should use the theoretical framework of the BioPsychoSocial Model (figure 3.1) for addressing the issues discussed above and should include all patients with all etiologies and co-morbidities that received a referral for lymphedema management and were treated in the physiotherapy clinics of Maccabi. The main outcome measures (dependent variables) could be volume change and functional scores (both documented on a regular basis through routine practice), as the model suggests. Other variables that are collected and could be analyzed in the future are cost (garment cost, number of sessions, etc,), fear avoidance of movement, and pain. Unfortunately, to this date we (Maccabi) do not have psychological status questionnaires or screening tests to assess our patients. Therefore, the concepts of outcome of psychological adjustments could not be evaluated through a PBE design in the near future. However, we do have evaluations on functional adjustments – ability (independently or not) to don a garment and to bandage; these could also perform as outcomes that can be analyzed with association to problem-solving and effectiveness of coping. For independent variables, as suggested above, predisposing factors that include co-morbidities, medication use, and interventions could be used and the association with

outcomes could be examined. The self-care interventions are included, as well, and may shed some light on the association with outcomes. If the results show strong association, further research can be performed to evaluate each strategy in an experimental design that may support a causal effect.

- A PBE study of lymphedema should be guided by the theoretical framework of the BioPsychoSocial Model of Secondary Lymphedema to examine all patients with all etiologies which demonstrates an extended version of what the model was intended to encompass. Hopefully, findings of such a study would be able to demonstrate that the model can fit people with lymphedema other than breast cancer survivors. The PBE is intended to focus on effectiveness of coping and symptom management with relation to outcomes, more on the physical outcomes (volume and function) than on psychological ones. However, there is no treatment for lymphedema that does not need patients' motivation and adherence: those are imbedded in the self-care interventions that should be addressed in such a study, as well. Finally, the PBE study is based on the foundations of the theoretical framework of the BioPsychoSocial Model and may be part of future research plans.

Rehabilitation Treatment Taxonomy.

The second theoretical framework is related to intervention: the conceptual framework of the Rehabilitation Treatment Taxonomy (RTT). This framework builds a rationale of using treatment intervention codes to describe an active procedure and

not a clinical reasoning process. Therefore, as described in Figure 3.2, the clinician is performing treatments (which could be a patient-delivered treatment, as well, such as education for self-management; treatments are presented as Rx#1, #2, #3 in the diagram) which aim to achieve specific outcomes (e.g., education for self-bandaging aims to reduce swelling). The specific outcomes are referred to as targets and presented as Tgt#1, Tgt#2, Tgt#3 in the diagram, and form the macro outcomes which are the aims of the rehabilitation (at the bottom of the diagram). There is a feedback loop that is created from the assessment through the interventions and outcomes which consists of the clinical reasoning process. However, this process is excluded from the taxonomy of the treatments, as the clinicians identify the treatment that results from the clinical reasoning process. In this way, we can understand better what the clinicians actually did with the patient to change the targets/outcomes (Dijkers, 2014). This conceptual model supports the need to use mutually-exclusive treatments that describe different interventions (Dijkers et al., 2014) and should be used in a PBE study.

The PBE is an on-going process in which the findings circle back to the physical therapists; a discussion will follow, and each one will decide whether to implement and change their practices accordingly. Thereafter, another study will be conducted to evaluate if the changes produced different outcome and so-forth, as a dynamic process. However, the basic foundation is still lacking a few steps, and the study on association between treatment processes and outcome will be a continuum of this dissertation (will not be covered in this dissertation). Therefore, the aims of the dissertation are presented here:

Aims of the dissertation

Aim # 1: To describe the treatment code documentation as part of the PBE process and to evaluate the accuracy of treatment code documentation by LPTs in Maccabi.

Aim # 2: To examine the known-group construct validity of functional status scores in patients with lymphedema treated at Maccabi.

Aim # 3: To describe characteristics of the patients with lymphedema treated at Maccabi between the years of 2010-2017.

Figure 3.1: BioPsychoSocial Model of Secondary LE (Armer, J. M., 2010)

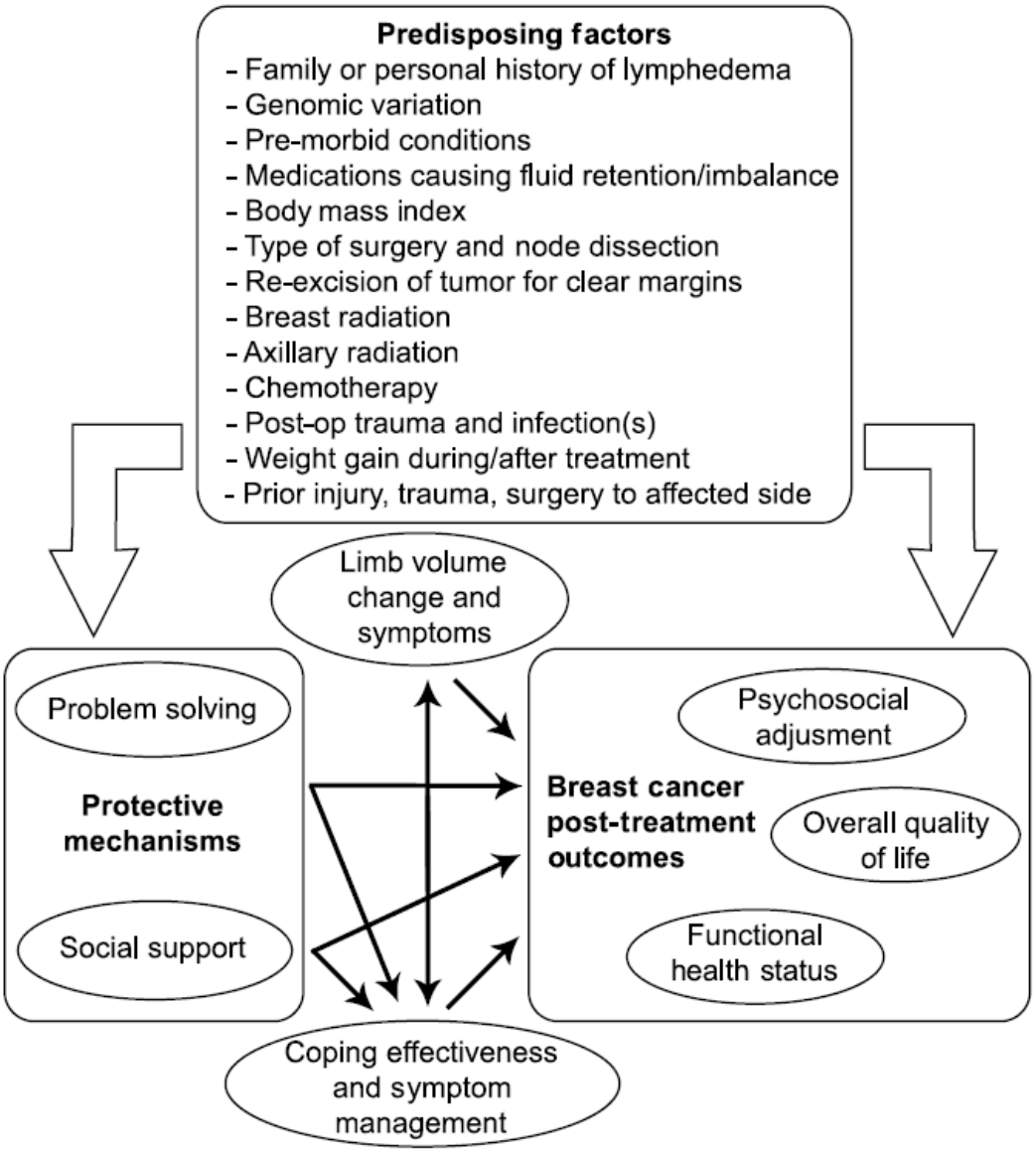
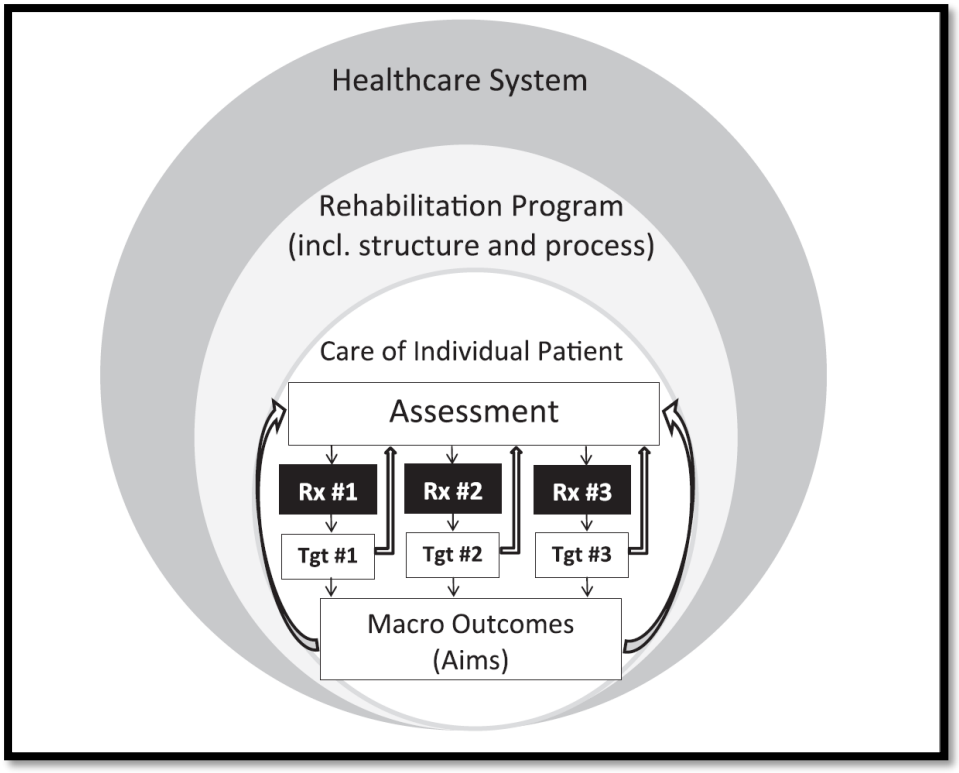


Figure 3.2: The Conceptual Framework of the Rehabilitation Treatment Taxonomy (RTT) (Dijkers, 2014)



Note. incl= include.

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CHAPTER FOUR: METHODS - A BOOK CHAPTER - CLINICAL EVALUATION OF LYMPHEDEMA

Tidhar, D., Armer, J.M., Bernas, M., Stewart, B. R., Feldman, J. L., Cormier, J. N. (2015). Clinical Evaluation of Lymphedema. In M-H. Cheng, D.C. Chang & K. Patel (Eds.), *Principles and Practice of Lymphedema Surgery* (pp. 51-59). Edinburgh, [Scotland]: Elsevier.

CLINICAL EVALUATION OF LYMPHEDEMA

Bullet Points

- Lymphedema (LE) severity may result in different treatment approaches. The indications for referral to conservative therapy are different from those for referral for surgery.
- The knowledge as to what extent the patient with LE is engaged with therapy helps focus the treatment approach and plan.
- Although LE is generally considered to be a 'non-painful' condition, a variety of symptoms, including pain, tenderness, heaviness, and firmness/tightness, can accompany this disorder and be quite distressing.
- Symptoms are important when setting goals for treatment, since what the patient will consider a successful outcome may differ from what is considered successful for the therapist, physician, or health care system.
- The main objective of lymphedema management is volume reduction and maintenance. Although limb volume is not the sole outcome, identifying when a patient enters volume stabilization is crucial for decision-making regarding further long-term management.

- Evidence in the literature supports the reliability of multiple approaches for the assessment of the swollen limb. It is important to note that while multiple measurement modalities are valid and reliable, they are not interchangeable; the selected method must be done repeatedly over time to assess for change.
- It is the clinician's role to provide the best diagnosis, treatment plan, and advice as to what will be the most appropriate management, taking into consideration the stage, severity, and psychosocial status that can help predict the amount of participation the patient (and/or caregiver) will be able to contribute to the process.

Introduction

Lymphedema (LE) is not a life-threatening condition in the majority of patients; however, it causes physical, functional, emotional, and social distress that can exceed the severity of the condition. The severity of lymphedema may result in different treatment approaches. Assessment should begin with a thorough history and physical examination to establish a correct diagnosis and care plan. Each phase of the clinical evaluation must be purposeful to ensure that the patient does not go through unnecessary expensive and time-consuming tests. LE is a chronic condition for which a cure has not yet been identified; nevertheless, when diagnosed early, intervention may reverse or reduce the condition to the pre-emergent state or minimize its debilitating effects. The indications for referral to conservative therapy are different from those for referral for surgery. This chapter will emphasize the phases that need to be addressed in the clinical evaluation.

Patient History and Assessment

The purposes of a thorough patient history are to identify risk factors for developing LE, identify the cause(s) of swelling, and to explore whether there are contraindications or precautions for treatment.

Medical history

Risk factors for developing LE for those who have no prior symptoms are outlined in Box 4.1: Patients may have undergone procedures or treatments that put them in a higher risk to develop lymphedema. The most investigated group is patients undergoing treatment for breast cancer; it had been shown that the extent of axillary operation, axillary radiation, high body mass index (BMI), post-operative infection, and seroma are all associated with a higher risk of developing LE (Bevilacqua et al., 2012). In a recent study, a small number of gene mutations/ haplotype that are associated with primary LE were found in women after breast cancer treatment, suggesting genomic risk factors for developing lymphedema (Miaskowski et al., 2013) in this population. Breast cancer survivors are at lifetime risk of developing LE and therefore need to undergo surveillance (Stout et al., 2012). Armer et al. (2013) reported that even women whose limb volumes were stable for 6 months after surgery prior to experiencing a 5% increase in volume, had a 94% chance of later developing LE (defined as =>10% limb volume increase) (Green et al., 2013). Another example is a study by Damstra et al. (2008) that found lymphatic dysfunction in patient's affected lower extremity after one episode of an erysipelas attack, a dysfunction which was evident in the non-clinical leg as well. These findings suggest that people who experience an erysipelas attack are at risk of developing LE

and should undergo surveillance and/or engage in risk-reduction activities (Damstra, van Steensel, Boomsma, Nelemans, & Veraart, 2008). Considering the importance of understanding risk factors for development of lymphedema and the limitations in our current knowledge, rigorous research with well-defined outcomes, adequate patient sample sizes, and prospective surveillance is imperative (Cemal, Pusic, & Mehrara, 2011).

Known Etiology of Lymphedema.

Primary lymphedema is due to dysplasia of the lymphatic system. Primary lymphedema can be clinically classified as congenital lymphedema which can manifest as swelling from birth to 2 years of age; lymphedema praecox: from 2 to 35 years of age; or lymphedema tarda, onset after 35 years of age. In most cases, a malformation of the lymphatic system will be evident in imaging (e.g. aplasia, hyperplasia, or hypoplasia) (Murdaca et al., 2012). Currently ten gene mutations have been identified that are associated with LE. These include VEGFR-3 that is associated with some Familial Milroy LE, first described in 1998, to, more recently, GJA1 in oculodentaldigital-LE and VEGF-C in Milroy-like LE, both described in 2013 (see reference 8 for more details) (Brouillard et al., 2017). Others still are yet to be identified and there are many more syndromes with lymphedema associated that have not been found (Brouillard et al., 2017; Greenlee, Hoyme, Witte, Crowe, & Witte, 1993).

Secondary lymphedema is associated with an extrinsic event (e.g. cancer, radiation, vascular disorders, trauma, skin infections, operation, etc.). The most researched etiology for LE is secondary due to breast cancer. This may be due to the

large numbers in which lymphedema occurs and the years of survivorship possible with modern treatment, as well as the high visibility of the swollen upper extremity. Lymphedema secondary to breast cancer can manifest itself in swelling of the whole upper quadrant of the truncal regions (front and back of the chest wall and arm); however, usually swelling (and sensation changes) will start in a specific region and in time will progress to other territories. Stanton et al. (2001) demonstrated in their study that the mechanism is not similar to a stopcock, rather the lymphatic change represents a regional swelling. Therefore, LE can start at the forearm or the hand and proceed proximally or at the upper extremity proximally and proceed distally. Another cause of secondary lymphedema is venous insufficiency in which the hypertension exceeds the lymphatic transport capacity (Bunke, Brown, & Bergan, 2009) leading to chronic edema , complicated frequently by chronic ulcers (Leidenius, Leivonen, Vironen, & von Smitten, 2005).

Co-morbidities.

This involves other conditions that may cause swelling or exacerbate LE (See Box 4.2: Differential diagnosis) or that may be considered contraindications for lymphedema treatment (Box 4.2) (International Lymphoedema framework [ILF],2006). An example is chronic heart failure in which both legs may be edematous. This type of swelling should be treated with the appropriate cardiac care. However, if swelling persists after elevation and medication for the cardiac condition, lymphedema compression bandaging (LBC) can shift fluid centrally and a cardiologist should be consulted as treatment begins and continues.

Medications.

Drugs that have a side effect of swelling (Box 4.3) (Keeley, 2008) can either

cause or exacerbate LE. Swelling will not always appear immediately after taking the drugs; therefore, establishing causality is difficult. However, when there are other drugs available which do not cause swelling, these patients may benefit from these alternatives. When there is no possibility to replace the drug and the edema is manageable (for example, when swelling disappears with elevation), compression stockings can be provided for LE care (Keeley, 2008).

Social situation and level of support. (Armer, 2005; Leidenius et al., 2005) Armer et al. (2010) published a model which showed that social support and coping style are protective mechanisms for outcomes of breast cancer-related lymphedema, such as quality of life and functional health status (Armer, 2010). In a clinical setting, a patient who has support from a family member may be able to adhere to the treatment regimen more readily than the patient who is coping alone.

Medical assessment and diagnosis

Screening tests.

The purpose of screening tests (Box 4.4) is to assist the physician to determine the etiology of the edema when clinical manifestation is not sufficient. For example, redness of the skin that accompanies swelling results from Erysipelas. However, Lymphangiosis Carcinomatosa can manifest in the same way. Laboratory assessment may demonstrate a pronounced leucocytosis, elevated CRP, and the blood cultures which are positive for Streptococci A or Staphylococcus aureus (Foldi M, Foldi E, & Kubik, 2006) indicating Erysipelas.

Lymphatic System Functional Assessment.

Lymphoscintigraphy is the current 'gold standard' imaging test for functional assessment that uses a tracer molecule linked to 99m technetium that is injected into the dermis in the foot and/or hand. This imaging test can evaluate dynamic response (reduced flow), areas of blockage, and dermal backflow (Bernas, 2013; Levy et al., 2012). It is indispensable in cases of complicated lymphedemas (i.e. chylous and non-chylous reflux, lymphangiodysplasia, etc.). Hwang et al. (2007) found that a baseline lymphoscintigraphy can predict a good response to Complex Decongestive therapy (CDT) in patients whose dominant lymphatics were imaged. For those patients who had a visualized collateral vessel without a main vessel, the response to CDT was poor. This important information can motivate people with a potential for a good CDT response to be actively invested in their treatment (Hwang et al., 2007). In addition to imaging helping to define the lymphatic problem and the possible response to treatment or direction of treatment, for most patients it is the only visual confirmation that can demonstrate the alterations in the function of their lymphatic system. These images can offer confirmation of their previously undiagnosed condition and can help focus their efforts on treatment with their clinicians.

ICG fluorescence Angiography uses indocyanine green and infrared fluorescent for imaging the lymphatic system. Although found to correlate with lymphoscintigraphy for superficial imaging, the system cannot detect lymph vessels and structures deeper than 2 cm. Therefore, ICG imaging lacks the ability to visualize and provide a complete image of the lymphatics (Bernas, 2013; Unno et al., 2008).

ICG imaging is not currently approved for clinical use worldwide. Although improved results and analyses continue to be reported (ILF, 2006), the lack of deeper lymphatic system imaging precludes its use for patients with more than superficial alterations in their lymphatic system.

Non-invasive MR imaging can assess lymph flow in vivo without administration of exogenous contrast agent (Rane et al., 2013). Several investigators have demonstrated high spatial-resolution imaging with the use of gadolinium contrast agents (Bernas, 2013).

Ankle-Brachial Pressure Index (ABPI).

As compressions influence microcirculation as well as venous and arterial flow, caution should be applied when vascular disturbances are detected. Compression is prohibited in the presence of critical ischemia (ABPI<0.5); however, in patients with low ABPI (0.5-0.8), compression may be applied for reduction of edema.

Color Doppler ultrasound.

This modality is used to assess deep vein thrombosis (DVT) and venous abnormalities (Levy et al., 2012). The existence of a DVT does not prevent referral for compression therapy. LCB are known to be safe in the acute phase of DVT with no long-term effect on the development of post-thrombotic syndrome, valve incompetency, or thrombus regression (Roumen-Klappe et al., 2009).

Computed tomography (CT) and magnetic resonance imaging (MRI).

These imaging techniques can be used to detect skin thickening and subcutaneous swelling (ILF, 2006). However, the 2-dimensional MRI gives limited information as to dilated lymphatics. A 3-D imaging study (versus lymphoscintigraphy) was found to be more informative. In this report, lymphatic anatomy and obstruction were identified, as well as the effect of obstruction on local structures and tissue composition (Liu, Wang, & Sun, 2005).

Lymphedema characteristics

These data are important for planning management according to patient goals, prognosis, expectations, and ultimately understanding of how to invest energy and effort.

Type (primary versus secondary).

This knowledge will not change the decision as to what conservative management will be offered to the patient. However, if surgical interventions are considered, this is important information (Lee & Villavicencio, 2010). An example is a patient who has primary LE of one limb, and may be at risk to develop LE in other limbs, especially if there are known anatomical defects; therefore, a holistic strategy that will target other areas, such as exercise, or even compression for prevention, can be addressed (Foldi M et al., 2006). Patients with familial primary lymphedema may also choose to undergo genetic evaluation for known genes if they have siblings who may also be at risk or they may wish to have children in the future.

Location.

Swelling can manifest in the extremities where compression bandaging and garments are more easily applied. However, areas such as face, neck, genital area, and chest (midline LE) are more challenging for application of compression (Leidenius et al., 2005). Swelling of these areas may benefit from the addition of other treatment modalities, such as aquatic lymphatic therapy and kinisio-taping, which have not yet been fully studied to provide high-level evidence (Rodrick et al., 2014).

Symptoms.

Although LE is generally considered to be a 'non-painful' condition, a variety of symptoms, including pain, tenderness, heaviness, and firmness/tightness (Cormier et al., 2009), can accompany this disorder and be quite distressing. Symptoms such as heaviness and swelling have been found to correlate with the physical findings of LE (Armer, Radina, Porock, & Culbertson, 2003; Carter et al., 2010). Symptoms are important when setting goals for treatment, since what the patient will consider a successful outcome (e.g. reduced symptoms), may differ from what is considered successful for the therapist (e.g. reduction of edema) or the health system (Weiss & Spray, 2002).

What makes the edema worse/better (e.g. response to elevation).

One of the main issues in deciding which lymphedema classification to choose is the response to elevation. For example, Stage 1 LE is when edema subsides after elevation (Katzel et al., 2014). Knowing what makes LE better helps in planning treatment and what advice to give to patients.

Presence of wounds.

Chronic ulcers of various etiology can occur when swelling is involved and can benefit from compression bandaging. However, proper wound care should be administered and all the information regarding chronicity, depth, size, and treatment should be obtained in order for a good collaboration between healthcare providers and the lymphedema therapies (Leidenius et al., 2005).

Self-management.

Adherence to compression garment or bandaging has proven to be the most effective means in maintaining the results of intensive therapy (Vignes, Porcher, Arrault, & Dupuy, 2011). The knowledge as to whether the patient with LE is engaged with therapy helps focus the treatment approach and plan. In addition, close adherence to management strategies using exercise Manual lymphedema drainage (MLD), and bandaging will aid prediction likelihood of success with certain other treatment protocols, including surgery.

Assessment Techniques

Observation

Every assessment starts with observation. A stepwise approach will help the clinician to perform a thorough assessment. Many important disease characteristics can be determined through the physical exam.

Functional status.

Functional status is observed from the moment a patient walks into the clinic. Examples of functional observation of the lower extremities include the following activities: Does the patient have a limp? Does he use an ambulation aid? Can he

bend his leg to a half-tailor position to take his shoes or socks off (may direct to restricted ROM in the hip joint)? Can the patient make a forward stride (the extended leg can be restricted by a scar in the groin area)? For upper extremities: Is the patient independent in donning/doffing a shirt or bra? Is there restricted shoulder motion/weakness? Patients with functional problems should be referred to physical therapy or occupational therapy services for evaluation and treatment (Levy et al., 2012).

Swelling.

Areas of indentation (bra, underwear, watch, jewelry, socks), asymmetry between limbs, or areas of swelling may be the first signs of swelling. Swollen segment(s) (e.g. hand, upper arm, genitals) can lead to more extensive swelling, or may be the only area of swelling. Nevertheless, swelling is an indication for treatment.

Skin condition.

Box 4.5 summarizes different skin conditions, including wounds that can accompany swelling. For example, dry skin can put a patient at risk for cellulitis or fungal infection. Infections need to be treated prior to the initiation of lymphedema therapy (Foldi et al., 2006). Stemmer's sign is present when the skin of a digit is fibrotic and cannot be lifted by the examiner's fingers (See Figure 4.1). The compliance of the skin will determine if the test is positive or negative; whereas the ability to grasp the skin and lift it will be a negative sign for LE. The absence of Stemmer’s sign does not rule out the diagnosis of lymphedema. Tissue changes (e.g. rubbery, pitting, non-pitting) help the clinician determine the classification of lymphedema (e.g. pitting edema); when edema resolves with elevation, LE will be

defined as Stage 1 (see Box 4.6) (Katzel et al., 2014).

Shape (normal versus distorted).

Shape is important since a compression garment cannot be properly fitted to a distorted shape without professional measurement, and, in most cases, there will be an effort to reduce the edema and normalize the limb shape and size prior to ordering a compression garment (ILF, 2006).

Measurement of swelling

The main objective of lymphedema management is reduction of volume and maintaining the results. Although limb volume is not the sole outcome (e.g. symptoms, function, etc, are also important), identifying when a patient enters into volume stabilization is crucial for the decision of when to order a garment for long-term management (the garment can be too big if ordered too soon; however, funding for treatment can be limited and sometimes therapy is discontinued before reaching stabilization). Figure 4.2 demonstrates a course of treatment.

A number of tools for measurement of limb volume are available. Table 4.1 summarizes the data available on each tool pertaining to specific recommendations for use (Lu, DeSouza, Armer, & Shyu, 2013). Each is discussed briefly here:

Water displacement.

Water displacement is considered to be the 'gold standard' for measuring limb volume. Using Archimede's law, the amount of water the limb displaced when immersed in a tank is equal to the volume of the limb. This technique has been shown to be highly reliable (ICC=0.99 and Standard Error of Measurement (*SEM*) of 27.2ml) (Chen, Tsai, Hung, & Tsauo, 2008). However, it has significant limitations

with respect to practicality of use: the procedure is limited to the arms and lower legs; big limbs may not fit into the tank; it requires high hygiene standards; it cannot be used for patients with open wounds; and it does not measure the proximal segment of the leg. Therefore, in practice it is less commonly used (Bernas, 2013).

Circumferential measurement.

Circumferential measurement with a flexible non-stretch tape is the most widely used clinical assessment with *SEM*s that range between 10 ml to 70 ml (Karges, Mark, Stikeleather, & Worrell, 2003; Taylor, Jayasinghe, Koelmeyer, Ung, & Boyages, 2006) with different protocols (measuring increments every 4 cm, every 10 cm, etc). Measuring according to anatomical landmarks (e.g. wrist, elbow) has been found to have the least measurement error with LE of the arm when volume is calculated with a truncated cone formula (Taylor et al., 2006) (Box 4.7). Reliability of this method was found to be high (ICC =0.99). Sander et al. (2002) found 6 cm increments (without anatomic landmarks) to be the most similar to water displacement. Katz-Leurer et al. (2012) found limb segment *SEM*s were lower than those for the whole limb, suggesting the use of segmental change for decision-making, rather than the whole arm volume. In the example in Figure 4.3 (Tidhar, unpublished data), the segments are in different severities that may lead to different approaches in treatment (e.g. the lower segment considered to be more severe and the upper segment moderate).

Perometry.

Perometry uses infrared light beams to estimate limb volume (excluding the foot and the hand for highest reliability). The advantages of perometry include high accuracy (measurement error for measuring lower extremities was found to be

121ml (Tan, Coutts, & Bulley, 2013), and upper limb 81ml) (Czerniec et al., 2010). The fact that the machine does not contact the skin enables measurement of limbs with wounds. This method has been used in several studies for early detection of LE. For example, Stout et al. (2012) used the cutoff of 3% as the threshold for initiation of an intervention (Stout et al., 2012). Furthermore, Stout et al. (2011) reported that the upper extremity limb segments at 10-20 cm and 20-30 cm measured using perometry to be highly correlated with total limb volume change (r^2= 0.845 and 0.952, respectively). Segmental measures were also predictive of later total limb volume change when LE was still in a subclinical stage (p=0.044 and <0.001, respectively), and thus an early indicator of emerging LE. Their work supports the use of segmental limb changes by perometry for decision-making, rather than the whole arm, as Katz-Leurer did with circumferential measurement technique.

Bioimpedance spectroscopy.

Fluid content can be measured using bioimpedance spectroscopy (BIS) which calculates the ratio of extracellular fluid by measuring the resistance to a painless electrical current in the body. This measurement had been used in assessing latent LE, in which fluid starts to accumulate, but before it may be noticeable by the patient or physician (Bernas, 2013). It also has been used in a study on breathing exercise where the trunk was measured with BIS (Moseley, Piller, & Carati, 2005).

Measurement summary.

Evidence in the literature supports the reliability of multiple approaches for the assessment of the swollen limb, as outlined in this section. It is important to note that while multiple measurement modalities are valid and reliable, they are not interchangeable. The chosen method (e.g. circumferences, perometry, BIS, water

displacement, etc.) must be done repeatedly over time to assess for change, such as either emergence of LE or progression of LE. Because of innate differences in the individual measures, comparisons are difficult to interpret when moving from one method or protocol to another.

Biometric measurements (weight/body mass index [BMI]).

Weight and BMI are important to measure since they are significant risk factors for developing arm LE (Bevilacqua et al., 2012; Paskett, Dean, Oliveri, & Harrop, 2012). When LE is present, a weight reduction program has been found to reduce LE (Shaw, Mortimer, & Judd, 2007). This clinical factor is important since a decision on when to fit a garment should take into consideration dietary plans, as well. This means that if a woman is starting a diet program at the end of therapy, she could reduce more of her limb size and therefore it will be wise to postpone the garment fitting until her weight stabilizes. In this situation, compression bandaging can be continued until weight and limb volume stabilize.

Decision on classifications

At the time of diagnosis and assessment, a classification of stage and severity (when a unilateral LE is present) of LE are required for management decisions (see Box 4.6). For example, a woman with stage 0 where no noticeable swelling exists is at risk of developing LE, and therefore should be offered advice on risk reduction strategies and begin regular surveillance of limb volume and symptoms. A man with severe LE who suffers from chronic wounds will be offered intensive CDT until the wounds are healed and the reduction of swelling stabilizes. For each classification,

there will be a different treatment plan offered based on evidence and expert clinical knowledge (Levy et al., 2012).

Summary

The assessment of uncomplicated LE is based primarily on clinical findings. It is the clinician's role to provide the best diagnosis, treatment plan, and advice as to what will be the most appropriate management, taking into consideration the stage, severity, and psychosocial status that can help predict the amount of participation the patient (and/or caregiver) will be able to contribute to the process. The clinician needs to exclude or identify other co-morbidities that can interfere with the success of therapy. Intensive therapy is time-consuming, labor-intensive, and costly. Treatment failure can lead to patient despair and lack of motivation for future attempts. In contrast, initiation of successful lymphedema therapy can lead to reduced risk of future complications, including cellulitis (Arsenault, Rielly, & Wise, 2011), improve quality of life (Kim, Yi, & Kwon, 2007), enhance function,(Jonsson & Johansson, 2009) provide tools for controlling this chronic condition (Vignes, Porcher, Arrault, & Dupuy, 2007), and set the foundation for ongoing success.

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Box 4.1: Risk Factors for Lymphedema of the Upper and Lower Limbs

Upper limb/trunk lymphedema

- Age
- Family or personal history of lymphedema
- Genetic predisposition to lymphedema
- Pre-morbid conditions
- Medications causing fluid retention/imbalance
- Body mass index
- Type of surgery and node dissection
- Re-excision of tumor for clear margins
- Breast radiation
- Axillary radiation
- Chemotherapy (e.g. taxane)
- Post-op trauma and infection(s)
- Weight gain during/after treatment
- Cording and seroma formation
- Congenital predisposition
- Insertion of pacemaker
- Arteriovenous shunt for dialysis*
- Living in or visiting a lymphatic filariasis endemic area
- Trauma in an 'at risk' arm (venipuncture, blood pressure measurement, injection)*

Lower limb lymphedema

- Inguinal, supra-femoral, para-aortic, pelvic, and iliac node dissection
- Postoperative radiotherapy
- Recurrent soft tissue infection at the same site
- Surgery or trauma to the limb (e.g., total knee replacement)
- Obesity
- Varicose vein stripping and vein harvesting
- Genetic predisposition/family history of chronic edema
- Advanced cancer
- Intra-pelvic or intra-abdominal tumors that involve or directly compress lymphatic vessels
- Poor nutritional status
- Thrombophlebitis and chronic venous insufficiency, particularly post-thrombotic syndrome
- Any unresolved asymmetrical edema
- Chronic skin disorders and inflammation
- Concurrent illnesses such as phlebitis, hyperthyroidosis, kidney or cardiac disease
- Immobilization and prolonged limb dependency
- Living in or visiting a lymphatic filariasis endemic area

Note. *Not based on evidence.

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Box 4.2: Differential Diagnosis of Lymphedema and the Contraindications (CI) or Precautions for Each Diagnosis

Unilateral limb swelling:

- Acute deep vein thrombosis (DVT) (CI for PIC)
- Post-thrombotic syndrome
- Arthritis
- Baker's cyst
- Presence /recurrence of carcinoma

Symmetrical swelling:

- Congestive heart failure (CI for PIC, LBC)
- Renal dysfunction (CI for PIC, MLD)
- Hepatic dysfunction
- Hypoproteinanemia
- Hypothyroidism/myxedema
- Lipoedema
- Idiopathic sodium retention
- Severe arterial insufficiency (ABPI <0.5) (CI for PIC, MLLB)
- Severe peripheral neuropathy (CI for PIC, MLLB)
- Pulmonary embolism (CI for PIC)
- Acute inflammations of the skin, e.g. cellulitis/erysipelas (CI for PIC, MLD)
- Pulmonary edema (CI for PIC)
- Active metastatic disease affecting edematous region (CI for PIC)
- Superior vena cava obstruction (CI for MLD)
- Tuberculosis and/or malaria (CI for MLD)
- Unstable hypertension (CI for MLD)
- Hepatic cirrhosis with abdominal fluid (ascites) (CI for MLD)

Note. CI=contra-indications, MLD=manual lymphatic drainage, MLLB= multi- layer lymphedema bandaging, PCI=pneumatic intermittent compression ABPI: Ankle-Brachial Pressure Index

Adapted with permission from:

International Lymphoedema framework (2006). Best practice for the management of lymphoedema international consensus. Retrieved April 20, 2018 from http://www.lympho.org/mod_turbolead/upload/file/Lympho/Best_practice_20_July.pdf

Box 4.3: Drugs that May be Associated with Lymphedema

1. Calcium channel blocker (Amlodipine, felodipine, Nifedipine, Diltiazem)
2. Corticosteroids (e.g. Prednisolone and Dexamethasone, Fludrocortisone)
3. Non-steroidal anti-inflammatories (e.g. Diclofenac, Ibuprofen, Naproxen, Celecoxib)
4. Alfa blockers (e.g. Doxazosin)
5. Sex hormones and related compounds (Estrogen (HRT), Anastrozole, Tamoxifen, Megestrol)
6. Antipsychotic (e.g. Risperidone, Fluphenazine, Olanzapine)
7. Antidepressant (e.g. Trazodone *)*
8. Anticonvulsants (e.g. Pregabalin, Gabapentin)
9. Antidepressants (e.g. Trazodone, Mirtazapine, Paroxetine)
10. Antidiabetics (e.g. Rosiglitazone, Pioglitazone)
11. Anti-parkinsonians (e.g. Amantadine, Cabergoline, Ropinirole)
12. Bisphosphonates (e.g. for cancer treatment: zoledronic acid, Risedronate, Tiludronate)
13. Cytotoxic chemotherapy (e.g. Docetaxel)
14. Sirolimus - decreases the action of the immune system
15. Potassium channel activator – diazoxide for hypoglycemia
16. Minoxidil *(*regaine) - alopecia androgenetica in both men and women.
17. Proton pump inhibitors (e.g. Esomeprazole,Omeprazole, Lansoprazole, pantoprazole)
18. Other drugs (Anagrelide, Atorvastatin, Cilostazol, Ciprofloxacin, Etretinate, Glatarimer acetate, Isosorbide dinitrate, Itroconazole, Metoclopramide, Nicotinic acid, Orlistat, Pentoxifylline, Tacrolimus, Voriconazole)

Adapted from:

Keeley, V. (2008). Drugs that may, exacerbate and those used to treat lymphoedema. *Journal of Lymphoedema, 3*(1), 57.

Keelley, V. (2012) Drugs and Lymphoedema: Those Which May Cause Oedema or Make Lymphoedema Worse. Reprinted from *LymphLink*. (Oct-Dec 2012);24(4):1-3.

Box 4.1: Screening Investigations for Differential Diagnoses

Blood tests:

- Full blood count (FBC)
- Urea and electrolytes (U&Es)
- Thyroid function tests (tfts)
- Liver function tests (lfts)
- Plasma total protein and albumin
- Fasting glucose
- Erythrocyte sedimentation rate (ESR)/Creactive protein (CRP)
- β-natriuretic peptide

Urine dipstick testing, including observation for chyluria

Ultrasound

Chest X-ray

Adapted with permission from:

International Lymphoedema Framework (2006). Best practice for the management of lymphoedema international consensus. Retrieved April 20, 2018 from http://www.lympho.org/mod_turbolead/upload/file/Lympho/Best_practice_20_July.pdf

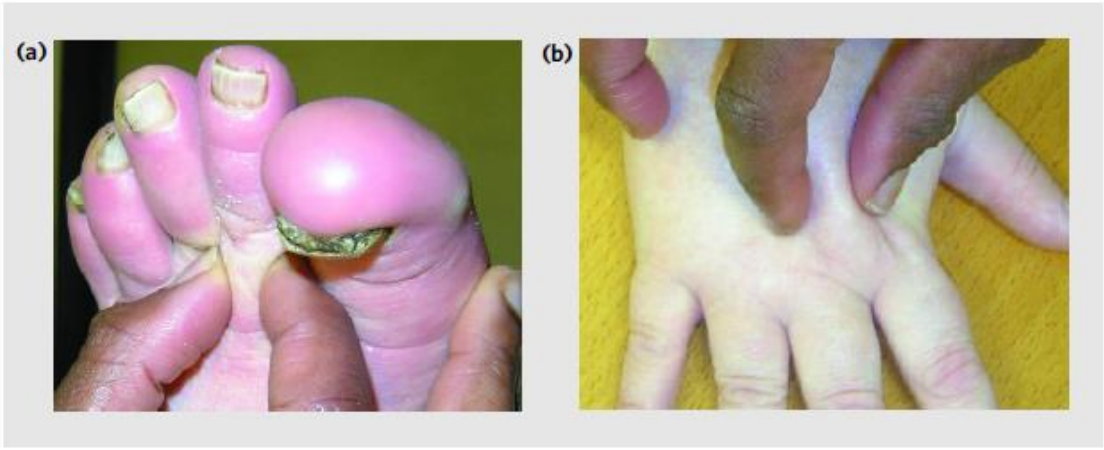
Box 4.5: Skin Conditions Potentially Associated with Lymphedema

- Dryness
- Broken
- Thickening
- Redness
- Pigmentation
- Brown
- Scars
- Warty
- Bumpy
- Blistered
- Fragile
- Dermatitis
- Cellulitis/erysipelas
- Fungal infection
- Hyperkeratosis (thickening of the outer layer of the skin)
- Lymphangiectasia (dilatation of lymph vessels; may appear as
- Blister-like protuberances on the skin)
- Lymphorrhoea (leakage of lymph from the skin surface)
- Papillomatosis (the development of warty growths on the skin consisting of dilated lymphatics and fibrous tissue)
- Lipodermatosclerosis (thickening and hardening of the subcutaneous tissues with brown discolouration of the skin; associated with chronic venous insufficiency
- Orange peel
- Deep skin folds
- Wound

Adapted with permission from:

International Lymphoedema framework (2006). Best practice for the management of lymphoedema international consensus. Retrieved April 20, 2018 from http://www.lympho.org/mod_turbolead/upload/file/Lympho/Best_practice_20_July.pdf

Figure 4.1: Stemmer's Sign as Diagnostic Tool for Lymphedema



Note. Stemmer's sign is a physical examination by pinching the skin. Stemmer's sign positive in (a) second toe or (b) middle finger.

Adapted with permission from:

International Lymphoedema framework (2006). Best practice for the management of lymphoedema international consensus. Retrieved April 20, 2018 from http://www.lympho.org/mod_turbolead/upload/file/Lympho/Best_practice_20_July.pdf

Box 4.6: Classification of Lymphedema

ISL Stages:

ISL stage 0: A subclinical state where swelling is not evident despite impaired lymph transport. This stage may exist for months or years before edema becomes evident.

ISL stage I: This represents early onset of the condition where there is accumulation of tissue fluid that subsides with limb elevation. The edema may be pitting at this stage.

ISL stage II: Limb elevation alone rarely reduces swelling and pitting is manifest.

ISL late stage II: There may or may not be pitting as tissue fibrosis is more evident.

ISL stage III: The tissue is hard (fibrotic) and pitting is absent. Skin changes such as thickening are seen.

Severity

Mild: <20% excess limb volume

Moderate: 20-40% excess limb volume

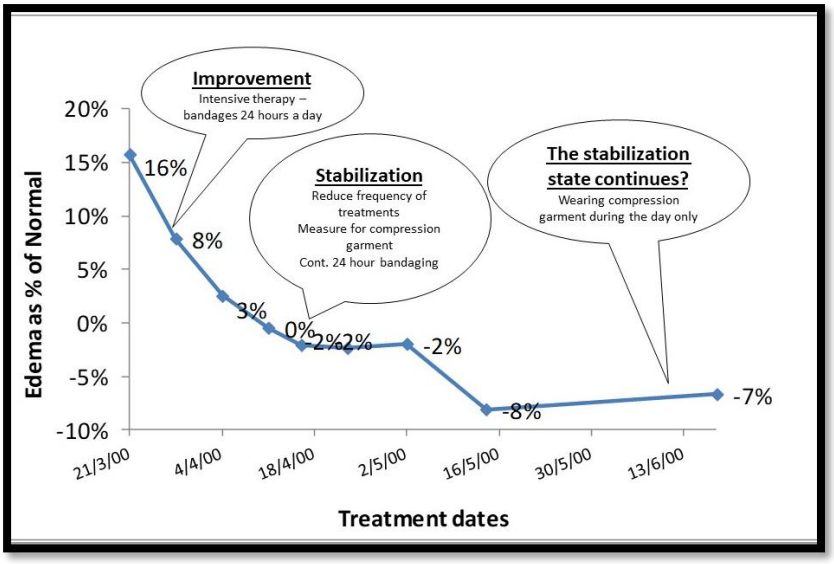
Severe: >40% excess limb volume

Note. Classification of lymphedema by the International Society of Lymphology.

Adapted with permission from:

International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. (2013). *Lymphology, 46*(1), 1-11.

Figure 4.2: Clinical Decisions for Lymphedema Management Based on Measurement Charts



Adapted with permission from D. Tidhar (unpublished data).

Table 4.1: ‘Gold Standard’ and Comparisons in Limb-volume Measurement

	Water Displacement	Circumference	Perometry	Electrical Impedance
Cost	Low	Low	High	High
Time to Operate	Moderate-High	High	Low	Low
Inter-rater Disparity	Low	High	Low	Low
Pre- and Post-Maintenance	High	Low	High	High
Local Measures	No	Yes	Yes	No
Self-monitoring Home/Travel	No	No	No	No

Note. Comparison of attributes of common tools in assessment of limb changes in lymphedema.

Adapted with permission from:

Lu, G., DeSouza, G., Armer, J., Shyu, C-R. (2013). Comparing Limb-Volume Measurement Techniques: 3D Models from an Infrared Depth Sensor versus Water Displacement. *Innovation and Research in Biomedical Engineering.* Proceedings of the 2013 International Conference on e-Health Networking, Applications and Services.

Box 4.2: Truncated Cone formula for Volume from Circumferences

Truncated cone formula

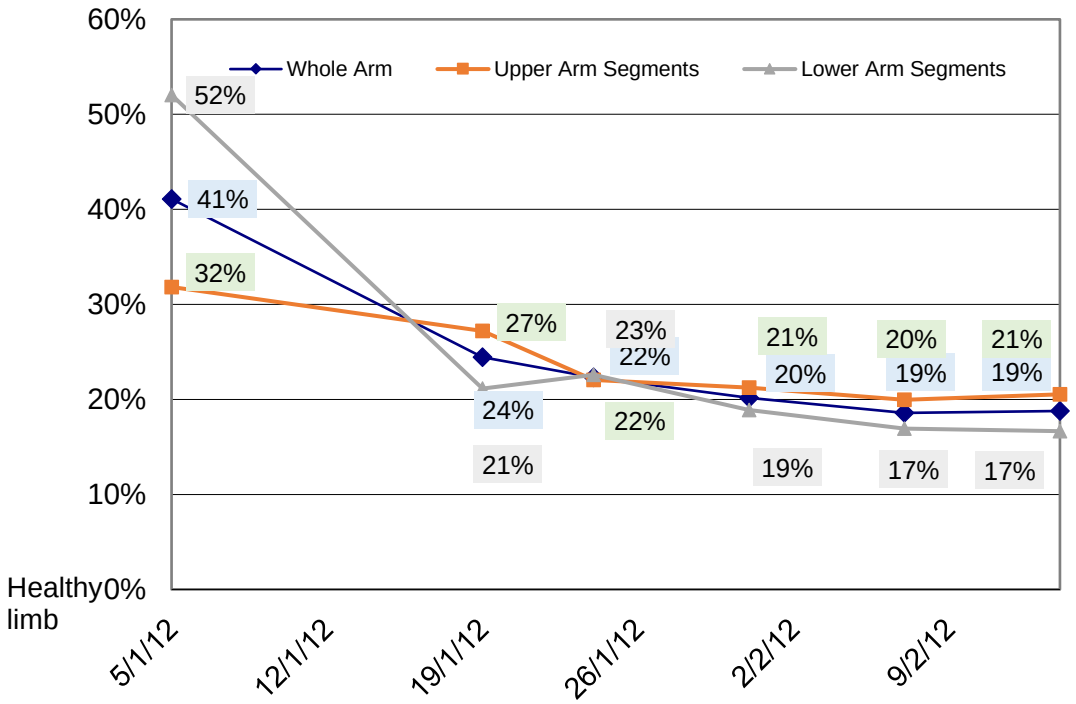
$V=h(C1*C1+C1*C2+C2*C2)/12*\Pi$

*Note.*Truncated cone formula for volume from circumferences where *V* is the volume of the segment, *C1* and *C2* are the circumferences at the ends of the segment, and *h* is the distance between them (segment length). Summing of the volume segments will add up to the estimated volume of the limb.

Adapted from:

Sander, A. P., Hajer, N. M., Hemenway, K., & Miller, A. C. (2002). Upper-extremity volume measurements in women with lymphedema: a comparison of measurements obtained via water displacement with geometrically determined volume. *Physical Therapy, 82*(12), 1201-1212.

Figure 4.3: Segmental Changes in Excess Limb Volume Over Time



Note. Percentage excess limb volume changes for upper and lower extremity segments and whole arms from baseline over a 5-week period.

Adapted with permission from D. Tidhar (unpublished data).

CHAPTER FIVE: METHODS – A MANUSCRIPT - PRELIMINARY WORK-MEASUREMENT ISSUES IN ANTHROPOMETRIC MEASURES OF LIMB VOLUME CHANGE IN PERSONS AT RISK FOR AND LIVING WITH LYMPHEDEMA: A RELIABILITY STUDY

Tidhar, D., Armer, J. M., Deutscher, D., Shyu, C. R., Azuri, J., & Madsen, R. (2015). Measurement Issues in Anthropometric Measures of Limb Volume Change in Persons at Risk for and Living with Lymphedema: A Reliability Study. *Journal of personalized medicine, 5*(4), 341-353. doi:10.3390/jpm5040341

Abstract

Understanding whether a true change has occurred during the process of care is of utmost importance in lymphedema management secondary to cancer treatments. Decisions about when to order a garment, start an exercise program, and begin or end therapy are based primarily on measurements of limb volume, based on circumferences taken by physiotherapists using a flexible tape. This study aimed to assess intra-rater and inter-rater reliability of measurements taken by physiotherapists of legs and arms with and without lymphedema and to evaluate whether there is a difference in reliability when measuring a healthy *versus* a lymphedematous limb. The intra-rater reliability of arm and leg measurements by trained physiotherapist is very high (scaled standard error of measurements (*SEM*s) for an arm and a leg volume were 0.82% and 0.64%, respectively) and a cut-point of 1% scaled *SEM* may be recommended as a threshold for acceptable reliability. Physiotherapists can rely on the same error when assessing lymphedematous or healthy limbs. For

those who work in teams and share patients, practice is needed in synchronizing the measurements and regularly monitoring their inter-rater reliability.

Keywords: decision-making; lymphedema; lymphedema management; minimal clinical; detectable change; reliability; standard error of measurement; tape measurement

Introduction

Lymphedema (LE) post cancer treatments is a chronic disease which has no cure (Cormier, Rourke, Crosby, Chang, & Armer, 2012); however, it can be managed successfully by reducing symptoms and maintaining that reduction (International Lymphoedema framework [ILF], 2006). LE early detection is performed by measuring volume and checking on symptoms and comparing them to baseline measurements (Stout, Binkley, et al., 2012). Management strategies vary and may include, for example, daily bandaging, performing exercises twice weekly, using a pneumatic compression device, or receiving manual lymph drainage. As long as patients improve by reaching their treatment goals, the treatment will be considered a success (Wright, Hannon, Hegedus, & Kavchak, 2012). Examples of treatment goals may be: improving a specific function, reducing symptoms such as pain or heaviness, preventing infection, improving body image, improving shape etc. Assessing LE outcomes only from the patient's perspective is not sufficient for therapists in their decision-making process; objective assessment such as volume measurement is needed, as well. Therefore, when resources are limited, and the question of adherence to treatment is considered, physiotherapists (PTs) are interested in

offering patients the most efficient tool or technique, one that will achieve successful outcomes.

One of the main outcomes for LE treatment is volume reduction that can be measured using different approaches. The Perometer™ is a device that uses infrared light beams to estimate the volume of a limb (Tan, Coutts, & Bulley, 2013). Water displacement is used to assess the volume of a limb by submerging the arm or leg in a water tank and measuring the water that is displaced. This method has been considered to be the 'golden standard' (Armer, 2005). A flexible measurement tape is a practical low-cost tool available in any clinic. Volume is derived from calculations of several circumferential measurements taken at predetermined points along the limb using a truncated cone formula (Taylor, Jayasinghe, Koelmeyer, Ung, & Boyages, 2006).

Knowing the minimum clinically important difference (MCID) of limb volume change is essential for the clinician in determining the existence of LE, its improvement, progression, or stability (Wright et al., 2012). There are numerous possible consequences to that decision. A garment ordered too soon may not fit and therefore result in a financial loss. Requiring a patient to wait longer than necessary and continue treatments may lead to reduced adherence to attend the therapy sessions as she/he may feel stable and resent wasting time and money coming to therapy. Prolonging treatment beyond what is needed could increase patient waiting lists to the detriment of lymphedema management services. When assessing patients' progress using the flexible tape method, the standard error of measurement (*SEM*) may be used by clinicians as a MCID (Tobbia et al., 2009). In a

case series by Tidhar et al. (2013), the clinical decision-making to order a garment was based on volume stability. The authors reported a *SEM* of 30ml for the therapist treating patients in a self-bandaging clinic, a threshold below which was considered stable and beyond was considered unstable (Tidhar, Hodgson, Shay, & Towers, 2014). Schmidt et al. (2009) defined the term "stable lymphedema" to help determine whether a woman with breast cancer-related LE (BCRL) could begin a weight-lifting program; one criterion was that women experience no more than 10% increase in arm swelling in the three preceding months. PTs who want to implement this weight-lifting program and who must decide whether to approve an individual's participation need to know their own scaled *SEM* in order to determine whether their patients are stable or not.

Few studies have examined the MCID of limb volume change: Katz Leurer et al. (2012) reported *SEM* of 78.8ml of the healthy arm vs 47.1ml of the affected arm in BCRL, Taylor et al. (2006) found the *SEM* of BCRL to be in a range of 64.5 – 65.4 ml (Taylor et al., 2006), and Devoogt et al. (2010) reported a minimal detectable change (MDC) of 55ml to detect a true change. One study by Sawan et al. (2009) reported a repeatability limit of 270 ml for leg volume; no other reports were found for *SEM* of leg volume. Devoogt et al. (2010) reported on scaled *SEM* that ranged from 0.8%-2% for measuring arms; no report was found on scaled *SEM* for leg LE measurement.

Some PTs work together in the same clinic and share patients' management. Knowing the inter-rater reliability of volume measurements is most important if they want to base their decisions on their colleague's assessment. Several studies have examined the inter-rater reliability in measuring arm volume and reported an intra-

class correlation (ICC) of more than 0.97 between raters (Sander, Hajer, Hemenway, & Miller, 2002; Taylor et al., 2006). Unfortunately, ICC cannot be translated to clinical practice as the dimensions are different from those used in practice. Sawan et al. (2009) reported on an inter-rater reliability and measured reproducibility of 1000ml when measuring one leg volume by 17 assessors. These findings have not been supported by any other study.

The aims of this study were: a) to determine the *SEM* for measuring volume of an arm and a leg with and without LE for the purpose of assessing and following up on patients with LE and surveying those who have not yet developed LE, b) to assess if there is a difference between *SEM* of healthy versus LE limbs and c) to examine the reliability between therapists when measuring an arm and a leg with and without LE.

Design and Methods

Sixty PTs who work in lymphedema management in Maccabi Healthcare Services and in private practice, received an invitation to attend the day of research, which contained the purpose and schedule of the day. Forty-one PTs volunteered and participated in the study that took place as part of a conference organized by the physiotherapy department of Maccabi Healthcare Services in Israel. All PTs were lymphedema specialists who had received 140 h of training and had more than one year's experience in measuring patients' limb volume (range from 1 to 20 years). This study was conducted as part of a practice-based evidence research process in which we test the reliability of PT's documentation before we start collecting data. In all, 41 PTs attend and volunteered to participate. The study was approved by the Ethics committee of Maccabi Healthcare Services.

Five patients were invited to participate in the study. Patients were asked to be present half an hour prior to the taking of measurements so they could lie supine to reduce any excess fluid that might have accumulated from commuting to the study venue. Prior to participation, consent was obtained from all patients. At the beginning of the conference, the primary author (DT) gave a short demonstration of the measuring procedure. Each physiotherapist (PT) left the conference for approximately 20 min throughout the day and measured one patient. Each patient volunteered his/her LE limb and a healthy limb (e.g., a woman with arm LE had her lymphedematous arm and a healthy leg measured). Both limbs were measured 3 times.

Circumferential measurements were taken at 6 points on an arm according to anatomical landmarks (Taylor et al., 2006) (mid palm, wrist, 10cm above the wrist point, elbow, 10cm above elbow and axilla), and 8 measurements for a leg using a measurement board (10cm from heel towards toes, 10cm from heel towards ankle, 20, 30, 40, knee, 55 and Groin).

The circumferences were then entered into a spreadsheet and a truncated cone formula (1) applied with each segment volume calculated:

$$Vs = \frac{h(Ct \times Ct + Ct \times Cb + Cb \times Cb)}{12\pi} \quad (1)$$

where *Vs.* was volume of a segment, *h* was the distance between two points of measurement, *Ct* represented the circumference at the top measurements of the segment, *Cb* represented the circumference at the base of the segment. Once each segment is calculated, a sum of five segments of an arm and seven segments of the leg are computed into a volume estimate (Casley Smith & Casley Smith, 1997). This

method was found to be valid (criterion validity) in several studies when compared to the gold standard of water displacement with intra class correlation coefficient (ICC) of >0.95 (Karges, Mark, Stikeleather, & Worrell, 2003; Taylor et al., 2006).

Data Analysis

SEM and Scaled *SEM* of limb volume were obtained by using the Formulas (2) and (3):

$$SEM = \frac{s}{\sqrt{3}} \tag{2}$$

where *s* as the standard deviation of 3 volume measurements of one PT.

Scaled *SEM* was calculated by the formula:

$$Scaled\ (\%)SEM = \frac{SEM}{\bar{v}} \times 100 \tag{3}$$

where the *SEM* is divided by the average of volume and multiplied by 100 to create a standard estimate that can be compared between leg and arm measurements. The data of both *SEM* and scaled *SEM* is presented as an average and confidence interval (CI) (for all PTs). As the definition for early detection of BCRL was set at 3% difference from baseline (Springer et al., 2010), a 1% scaled *SEM* seemed like an appropriate cutoff point for clinical use; therefore, the proportion of PTs whose scaled *SEM* did not exceed the 1% was calculated. Differences of scaled *SEM* between the groups were analyzed by Kruskal-Wallis nonparametric test to check whether one patient was more difficult to measure than others and resulted in significantly different outcome.

For analysis of the quality of the limb volume measurements made by different PTs, we used the difference between their first measurement from the true

mean (which was defined as the average of all measurements of the same limb) scaled by the true mean (formula 3). We then estimated the proportion of therapists whose measurements were within 5% of the true mean. As 10% difference between limbs is considered one of the definitions for LE (Armer, Stewart, & Shook, 2009; International Society of Lymphology [ISL], 2013), and was determined as defining stable LE as well (Schmitz et al., 2010), a 5% limit within the true mean seemed to be a reasonable cutoff point for a team of PTs treating the same patient.

The percentage difference (% diff) from the true mean for a single PT was calculated using the formula:

$$\%\text{diff} = \frac{v_1 - \bar{v}}{\bar{v}} \times 100 \quad (4)$$

where v_1 is the first volume measurement (out of three), $\bar{v}$ is the average of the volumes from all PTs who measured the same limb (only the first volume measurement was used since in clinical practice usually only one measurement is taken).

Differences between measurements from healthy and lymphedemadematous limbs were analyzed by Wilcoxon Rank Sum test. Statistical Package for Social Sciences (SPSS version 21.0, SPSS Inc., Chicago, IL, 2012) was used to analyze all data.

Results

Five patients with secondary lymphedema participated in the study. Two were women with upper extremity LE following breast cancer, one was a woman with

lower limb LE following treatment for sarcoma and two were men with phlebo-lymphedema of the lower extremity. The limbs to be measured included three healthy arms and two with LE (one severe and one mild), and two healthy legs and three with LE (one moderate and two severe). Forty-one PTs were divided into five groups of 6–11 each.

Aim 1: Intra-reliability

Average *SEM* for arm measurements was 27.5ml (CI 20.5-34.4ml). Figure 5.1 demonstrates the distributions of all *SEM*'s of the arm. Mean scaled *SEM* was 0.82% (CI 0.59%-1.05%). The proportion of PTs who had their scaled *SEM* less than 1% was 83% (Figure 5.2). From both Figures (5.1 & 5.2), an outlier is obvious with a *SEM* of 110ml and scaled *SEM* of 4.6%. Since all other PTs who had measured the same patient's arm had scaled *SEM* below 1%, it is obvious that this PT's technique needs improvement. The group who measured patient number 4 seemed to have fewer PTs who measured within the 1% cutoff point; however, when analyzing the differences between groups, no statistical differences were found in the scaled *SEM* (p=0.847).

Average *SEM* for leg measurements was 83.6 mL (CI 65–102 mL). Figure 5.3 demonstrates the distributions of all *SEM*'s of the leg.

Scaled *SEM* was 0.64% *SEM* (CI 0.5%–0.78%). The proportion of PTs whose scaled *SEM* was less than 1% was 83% (34/41) (Figure 5.4). There was no statistically significant difference of scaled *SEM* of legs (p = 0.598) between the groups measuring different patients.

Aim 2: *SEM* of healthy *vs.* lymphedema

There was no statistically significant difference between scaled *SEM* for healthy *vs.* LE arms ($p = 0.945$) or for legs ($p = 0.533$).

Figure 5.1: *SEM* in mL for 41 PTs measuring an arm; each symbol represents a patient

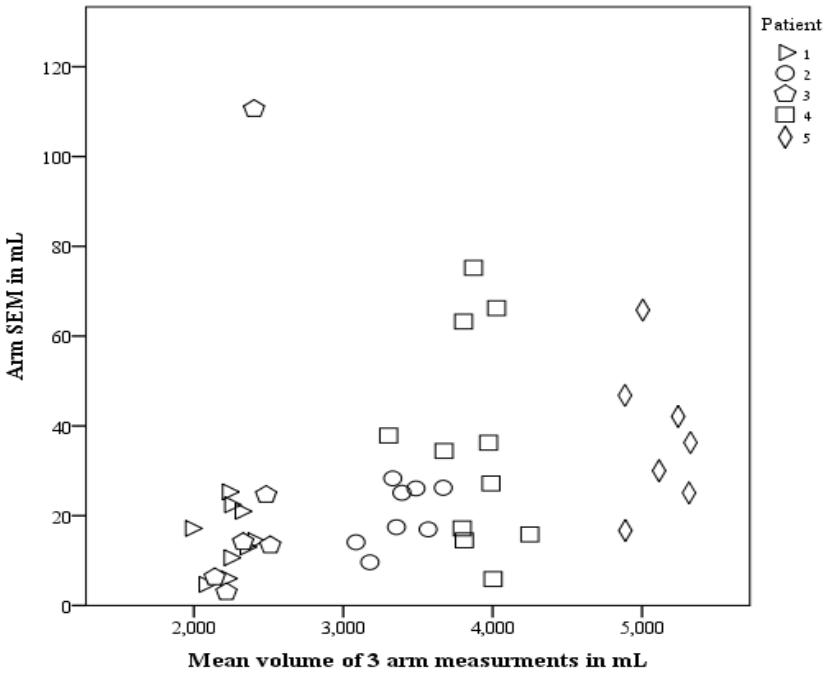


Figure 5.2: Scaled *SEM* presented in percentage, with the line at 1% cutoff

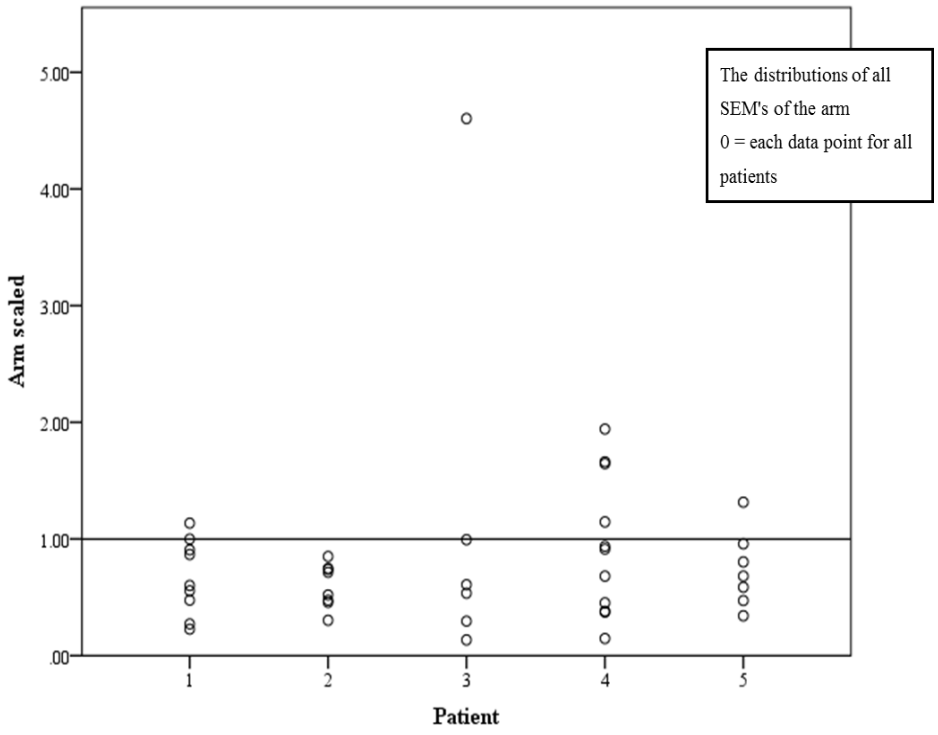


Figure 5.3: *SEM* in mL for 41 PTs measuring a leg, each symbol represents a patient

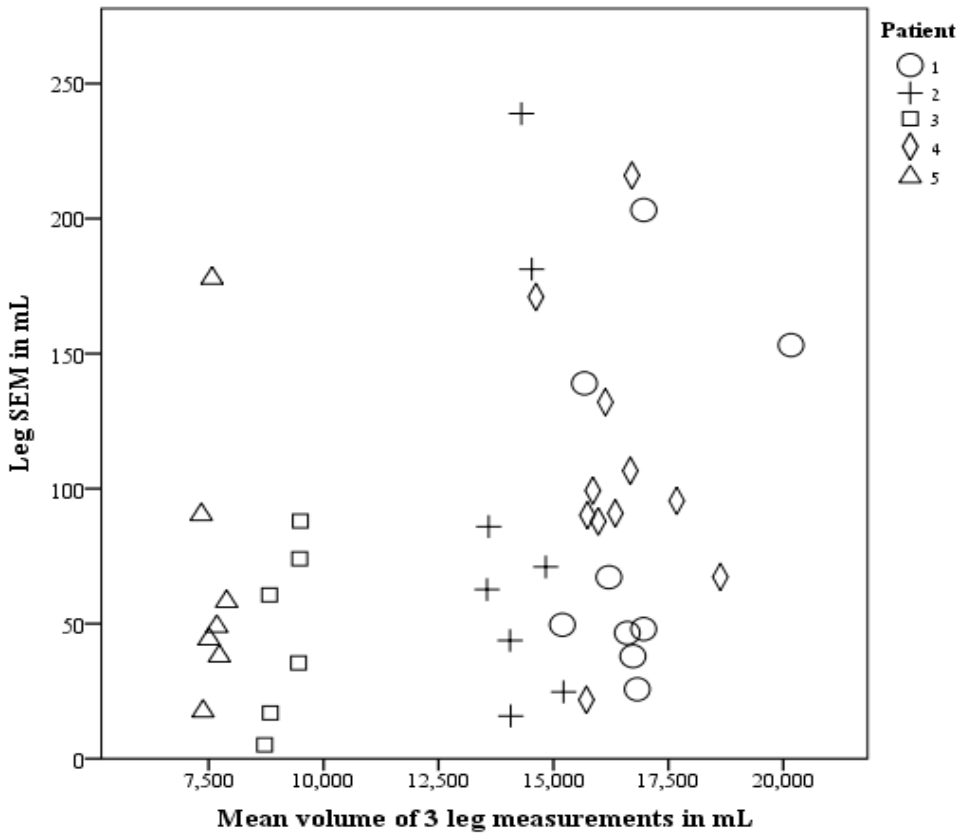
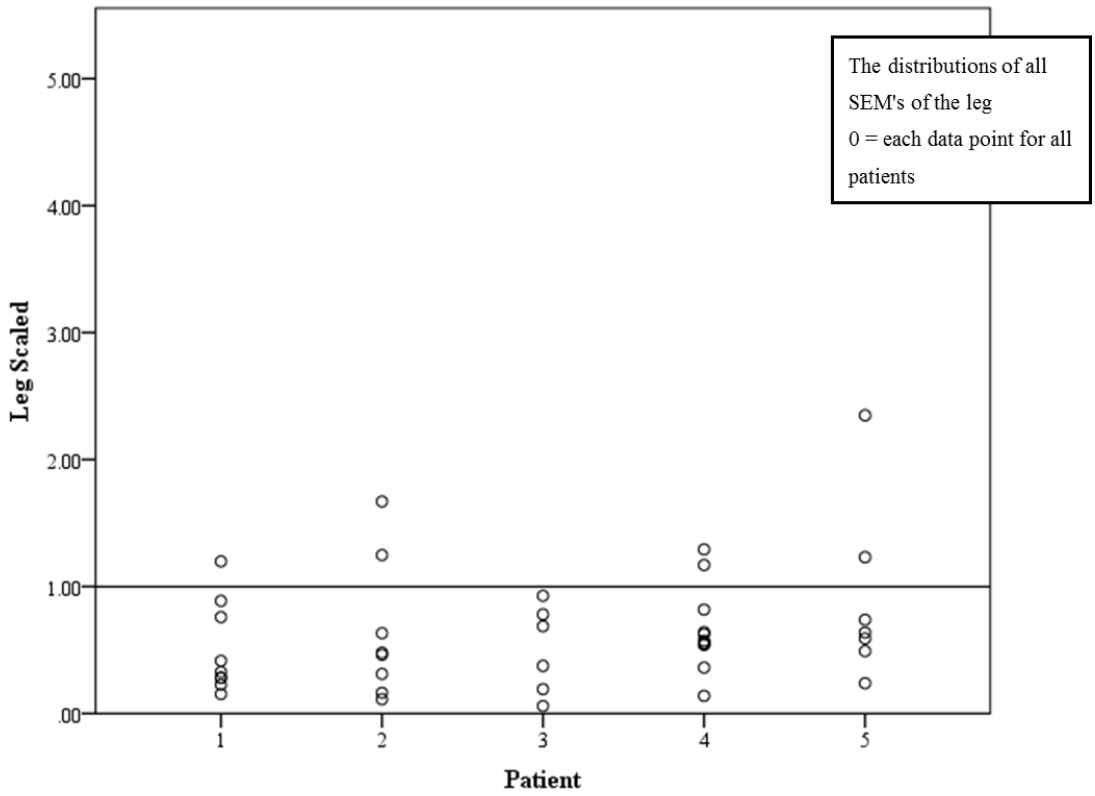


Figure 5.4: Scaled *SEM* presented in percentage, with the line at 1% cutoff



Fifty-six percent (23/41) of PTs' first measurement was within 5% of the true mean value for measuring an arm with CI of 42%–72% (Figure 5.5) and 80.5% (33/41) of PTs' first measurement was within 5% of the true mean value for measuring a leg with CI of 68%–93% (Figure 5.6).

Figure 5.5: Scaled difference from the true mean of arm measurements for each PT with cutoff points at ± 5%

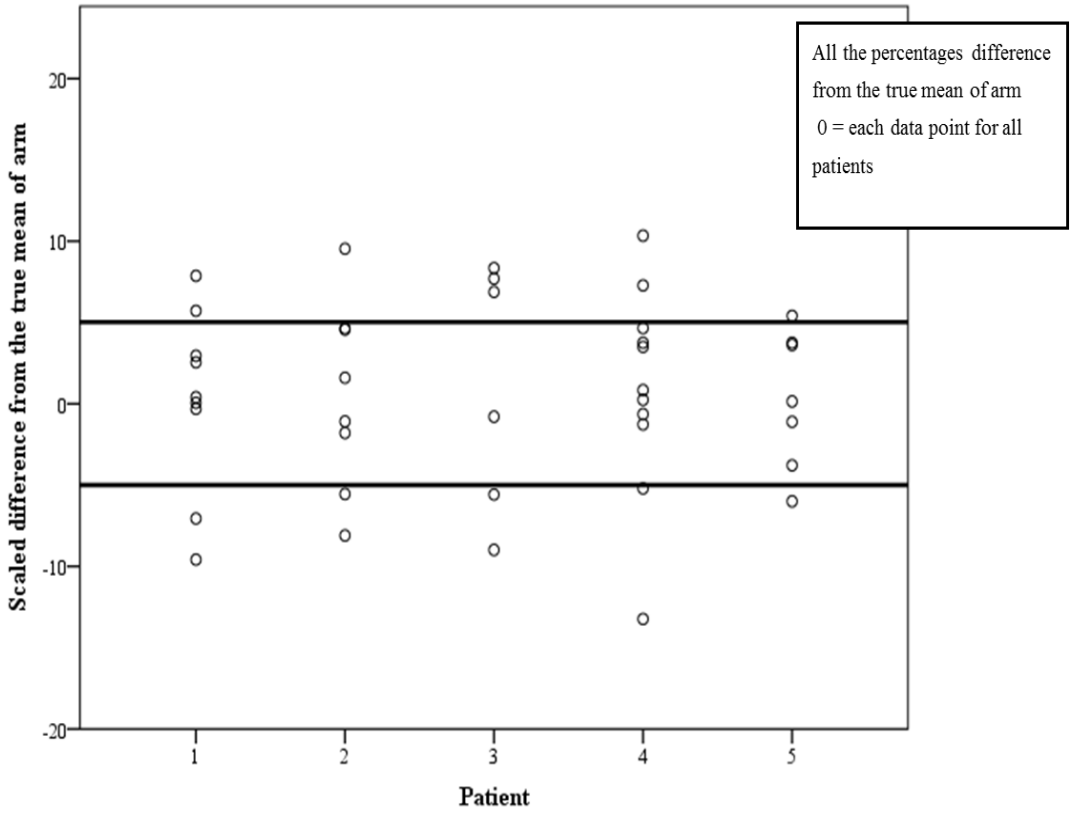
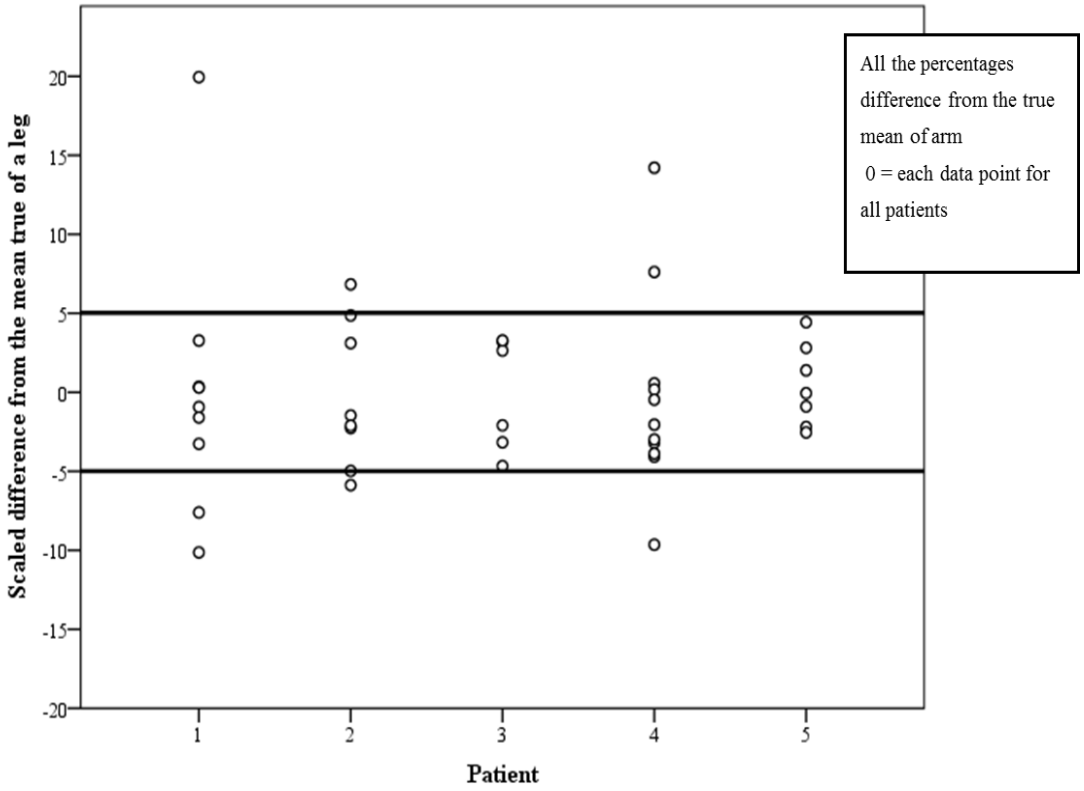


Figure 5.6: Scaled difference from the true mean of leg measurements for each PT with cutoff points at ± 5%



Discussion

The first purpose of the study was to examine intra-rater reliability of limb volume measurement for each PT. We found a mean *SEM* for an arm to be 27.5ml which is consistent with the study by Tidhar et al. (2010) who reported on 30ml *SEM* and with Bracha et al. (2012) who reported on 26.2 and 23.2ml for two raters in their study. For the leg, we found a mean *SEM* of 83.6 ml. The only study which reported intra-rater reliability of leg measurement was performed by Sawan et al. (2009) and found repeatability limit of 270 ml; however, the *SEM* was not reported which makes it difficult to compare to our findings. In our study, the mean scaled *SEM* for arm was 0.82% which is consistent with Devoogt et al. (2010) report of scaled *SEM* that

ranged from 0.8%-2%. The mean scaled *SEM* for leg was found to be 0.64% in our study; however, no report was found on scaled *SEM* for leg LE measurement in other studies. Since the majority (83%) of PT's measured below the 1% scaled *SEM* and as no recommendation regarding MCID for scaled *SEM* exists in the literature for legs or for arms, we recommend that a MCID of scaled *SEM* will be set at 1% by clinicians when assessing both arm or leg LE.

Furthermore, at the end of the analyses, a personal letter was sent to all PTs with information about their own *SEM* and scaled *SEM*. The PTs were encouraged to use their own *SEM* and scaled *SEM* as part of their practical reasoning process when treating patients with lymphedema, as was demonstrated in the study by Tidhar et al. (2014) regarding decisions that were made for ordering a garment. Deyes et al. (2013) reported a cost of $1500 for intensive therapy of 20 sessions in Canada. Stout et al. (2012) reported on only 15 sessions which cost $3000 in the USA. Using a personal *SEM* to detect when the patient's limb reaches a plateau may improve the cost effectiveness of LE treatments by optimizing the number of visits provided to the patient’s in accordance with the significance of in limb volume changes between visits. Beyond the purpose of this study, the anatomical landmarks method is being implemented for documentation in the clinical medical records in Maccabi healthcare services physiotherapy clinics. Therefore, PTs who are not accustomed to this method of measurement need to practice more to increase their confidence and reliability in the clinical routine. Hence, PTs who exceeded the 1% scaled *SEM* were recommended to practice and test their scaled *SEM* further until they reach the cutoff point of 1% or below.

Assessing whether there is a difference between scaled *SEM* of healthy vs lymphedema limbs was the second purpose of this study. We did not find any statistically significant difference in the scaled *SEM* between healthy vs affected arm or leg. Katz Leurer et al. (2012) found different *SEM* for healthy vs LE arms; however, they did not report whether these findings were significant. This information is important since the PTs who participated in our study now know that they may use the same scaled *SEM* when comparing affected limb to healthy one in detecting LE and as part of assessments and follow-ups in treatment routine.

The third aim of this study was to examine the reliability between therapists when measuring an arm and a leg with and without LE. In most reliability studies the protocol was for two measurers to assess several subjects; in our study 41 PTs each measured one arm and one leg. This design strengthens the external validity of the study as we have 41 PTs who work in lymphedema services all over the country. Furthermore, standardization of measurement technique is important for routine clinical documentation. The purpose of examining the inter-rater reliability is to ensure PTs who treat the same patients that they can rely on each other's outcomes. We examined the difference between the PT first measurements from the true mean and found that 56% and 80% of PT's who assessed an arm and a leg, respectively, measured within the ±5% range. No reported studies have used this method of assessing inter-rater reliability in limb volume measurement. However, we propose this method to be used clinically as it is a practical way of assessment which gives the team of PTs a tool for evaluating whether a group of PTs can work together. (e.g., if a PT got a score of 7% it means that he/she may have trouble relying on their

colleague's measurements when they share a patient management). If all PTs in a team obtained scores within the ±5% range, sharing patients' care can become more practical.

Results of the arm measurements from this study are not acceptable for clinical practice. They may be explained by the fact that the points of measurements were not constant; the PTs were instructed to measure at anatomical landmarks which are easy to detect but were not marked on the arms. Therefore, although the *SEM* that represents the consistency of an individual PT was very good, the agreement between 41 PT's was not. For the leg measurements, the instructions were to use a measurement board which enabled for more constant points and, therefore, the higher scores. Most of our PTs work alone in a clinic; however, for those who do work as a team, we recommend practicing their measurements with feedback from the person who is being measured for consistency of tape tension and points of measuring. Although not reported in the literature, from clinical experience, this is a useful way of improving consistency and when measuring an arm, a measuring board may be used to improve the inter-reliability.

Limitations

The study has a few limitations regarding the design. As we conducted the study as part of a conference day, it was not practical that all PTs measured all patients or even one patient. Therefore, we chose the design of dividing PTs into five groups and for each PT in a group to measure the same patient with the risk of finding differences in *SEM* and scaled *SEM* between limbs, at the cost of increased patient burden; however, no differences were found in the scaled *SEM* of the arm

and leg between limbs. Nevertheless, having PTs measure all patients would have increased the external validity of the study.

The results of the inter-rater reliability of the arm measurements raise another limitation. As only 56% of PTs measured within the limit of ±5% from the true mean, we question whether we could have changed the design of the study to prevent this from occurring. We could have expected that 41 PTs would not measure within the same inter-rater limit, even though intra-rater measurements were very constant. Usually lymphedema therapy is performed by a single PT; however, in some clinics there are teams of PTs who share patients' care. Therefore, we could have assigned PTs to their clinical teams, were possible, instead of randomly dividing them to groups. This way we would be able to provide a clinical tool for team work; however, this can still be achieved in clinical practice setting as well.

Conclusions

This study examined the intra- and inter-rater reliability of PTs measuring both arms and legs of patients with lymphedema. *SEM* and scaled *SEM* were analyzed and appear to be consistent with the literature with a mean *SEM* of 27.5 mL and 0.82% scaled *SEM* for an arm and a mean *SEM* of 83.6 mL and 0.64% scaled *SEM* for a leg. Most of the PTs measured below the 1% scaled *SEM*; therefore, the authors recommend that a 1% scaled *SEM* should be considered a threshold (MCID) of an arm and leg measurements; however, an anchor-based approach needs to be verified to assess whether this threshold is clinically meaningful as well. Our findings show that there was no difference between scaled *SEM* of healthy *vs.* LE limbs;

therefore, we suggest that the same scaled *SEM* can be used when measuring a healthy or LE limbs.

Furthermore, at the end of the analyses, a personal letter was sent to all PTs with information about their own *SEM* and scaled *SEM*. The PTs were encouraged to use their own *SEM* and scaled *SEM* as part of their practical reasoning process when treating patients with lymphedema, as was demonstrated in the study by Tidhar et al. [9] regarding decisions that were made for ordering a garment. Deyes et al. [23] reported a cost of $1500 for intensive therapy of 20 sessions in Canada. Stout et al. [24] reported on 15 sessions, l which cost $3000 in the USA. Using a personal *SEM* to detect when the patient's limb reaches a plateau may improve the cost effectiveness of LE treatments by optimizing the number of visits provided to the patient's in accordance with the significance of limb volume changes between visits. Beyond the purpose of this study, the anatomical landmarks method is being implemented for documentation in the clinical medical records in Maccabi Healthcare Services physiotherapy clinics. Therefore, PTs who are not accustomed to this method of measurement need to practice more to increase their confidence and reliability in the clinical protocols. Hence, PTs who exceeded the 1% scaled *SEM* were recommended to practice and test their scaled *SEM* further until they reach the cutoff point of 1% or below.

When working in the same clinic as a team, PTs who measure the same patients should practice together to reach acceptable agreement in their *SEM*. When a clinician needs to make decisions that involve resources such as time, money, adherence, and motivation, having a tool that will increase confidence in the decision-making process is important. *SEM* is such a tool.

Acknowledgments

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Author Contributions

All authors contributed equally to the study.

Conflicts of Interest

The authors declare no conflict of interest.

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CHAPTER SIX: FINDINGS - A MANUSCRIPT IN REVIEW- AIM ONE - TREATMENT DOCUMENTATION IN PRACTICE-BASED EVIDENCE RESEARCH FOR PATIENTS RECEIVING PHYSICAL THERAPY DUE TO LYMPHEDEMA

Tidhar, D., Deutscher, D., Armer, J. M., Horn, S. D. (2018). Known-groups Construct Validity of Functional Status Scores for Patients with Lymphedema. Manuscript submitted for publication.

Abstract

Objectives: To describe development and testing of a physical therapy treatment code documentation taxonomy within a practice-based evidence study framework for patients with lymphedema.

Method: Treatment codes for lymphedema physical therapy were developed within the electronic medical record and tested for accuracy of code selection amongst 43 lymphedema physical therapists (LPTs). LPTs were asked to accurately select 35 activity-intervention combination codes for 10 treatment vignettes representing real-life treatment scenarios. Accuracy was tested at a therapist level and a code level. An a priori criterion of 90% or more for a mean LPT or code score was defined as the targeted threshold for a successful implementation of the proposed treatment code documentation system.

Main outcome measures: The LPT score represented percentage of treatment codes accurately selected by each therapist. The code score represented percentage of LPTs who accurately selected each treatment code.

Results: The mean LPTs score was 91%, with 72% LPTs meeting the 90% criterion. Personal feedback was provided to each LPT. The mean code score was also 91%;

with 71% of treatment codes meeting the 90% criterion. We identified 9 low-score codes needing additional education or found to be redundant. These codes were either clarified or removed.

Conclusions: The proposed treatment code documentation system for lymphedema physical therapy was found to be clear and accurately used by most LPTs. Specific needs for improvement were identified. Follow-up testing is warranted to ensure ongoing accurate implementation of the treatment documentation system.

Key words: Lymphedema, practice-based evidence, rehabilitation treatment taxonomy

Abbreviation list

Complex decongestive therapy (CDT)

Electronic medical records (EMR)

International classification of functioning, disability, and health (ICF)

Lymphedema physical therapist (LPT)

Maccabi Healthcare Services (Maccabi)

Practice-based evidence (PBE)

Introduction

Lymphedema has been referred to as the hidden disease (Macdonald, 2001); it is still not recognized and treated like other chronic conditions (International Society of Lymphology [ISL], 2013). It is defined as the accumulation of protein-rich fluid in the interstitial tissue as a result of dysfunction of the lymphatic system (ISL, 2013). Complete decongestive therapy (CDT) is considered to be the accepted treatment for lymphedema. It is comprised of four elements: skin care, manual lymph drainage, compression bandaging, and exercise. This treatment is offered in two phases: intensive therapy to reduce maximum swelling and a long-term maintenance phase. Traditionally, the intensive therapy is provided by lymphedema physical therapists (LPTs) and maintenance is performed by the patient (International Lymphedema Framework [ILF], 2012); Lasinski, 2013). However, a comprehensive and concise taxonomy of lymphedema treatments to accurately describe and study lymphedema treatment effectiveness has not been developed, implemented, nor evaluated.

There has been progress in rehabilitation research in improving the description of the patient's characteristics and outcome. For example, the international classification of functioning, disability, and health (ICF) has been used as a reference to identify concepts of function in people who have lymphedema (P. Viehoff, Hidding, Heerkens, van Ravensberg, & Neumann, 2013; P. B. Viehoff et al., 2015). However, the Lymph-ICF, as reported by Devoogdt et al. (2011), does not describe the rehabilitation processes within LE management. Improvements in

reliable and valid methods used to describe treatment processes are still needed (Fasoli & Chen, 2014).

Rehabilitation treatment taxonomy is being developed to answer the needs presented above by developing a system of classification with the active ingredients of an intervention, their mechanisms of action, and their effects on patients (Fasoli & Chen, 2014). Recording of interventions improve the ability to study clinical practice differences and their effect on outcomes (Dijkers et al., 2014; Horn, DeJong, & Deutscher, 2012). Observational studies that take into consideration patient characteristics (e.g., demographics and co-morbidities), treatments provided (e.g., type and frequency), and desired outcomes (e.g., symptoms, volume change or functional status) may provide associations that could lead to more detailed recommendations as to what is the right treatment for a more focused group of patients (Deutscher et al., 2009; Horn, DeJong, Ryser, Veazie, & Teraoka, 2005) and suggest avenues for clinical studies. Practice-based evidence (PBE) has been proposed as a comprehensive and prospective observational study design that serves this purpose (Horn et al., 2012). In PBE, there is no alteration of the process of care and data are derived from routine practice. Associations between real-life interventions or clusters of techniques, sometimes non-conventional, with best outcomes, are identified, controlling for non-modifiable patient characteristics (Deutscher et al., 2009).

Here we describe the development of lymphedema treatment intervention codes in a large public healthcare service - Maccabi Healthcare Services (Maccabi). Maccabi is the 2nd largest public healthcare service in Israel and is fully computerized with each patient managed using a central electronic medical record (EMR)

(Deutscher, Hart, Dickstein, Horn, & Gutvirtz, 2008). Until 2009, CDT was the only included treatment code describing lymphedema physical therapy. The 2006 International Consensus Document for Best Practice Management of Lymphedema (ILF, 2006) recommended a more comprehensive description of lymphedema treatment. Nine treatment codes were identified and included the four components of CDT (MLD, skin care education, exercise, and compression), circumferential measurements, measurements of compression garments, education for self-massage, education for self-measurement, and education for self-bandaging.

Implementation of the new treatment codes in Maccabi took place during 2009, at which time 27 LPTs participated in a 4-hour workshop on best practice for the management of lymphedema. Then, new treatment codes were integrated into the EMR and the general CDT code was removed. An accuracy test of treatment code documentation was conducted to evaluate the ability of the LPTs to accurately select treatment codes using 10 treatment vignettes describing real-life treatment scenarios. Twenty-six (96%) lymphedema therapists participated in the accuracy test. The mean LPTs score was 77% and the mean code score was 79% (definitions of LPTs and code scores are given in details in the methods section of this manuscript). Results were presented to LPTs who provided feedback on missing treatment codes deemed necessary to fully represent lymphedema treatment (Tidhar et al., 2013). This lead to the development and testing of an updated treatment taxonomy for lymphedema treatment, proposed here. The aims of this study were to describe the new treatment taxonomy as part of a PBE study and assess the accuracy of treatment code documentation by LPTs in Maccabi.

Methods

Treatment taxonomy development

The lymphedema PBE process began in the summer of 2012 with a decision to update the lymphedema physical therapy module of the EMR. LPTs took an active part in the design of the new module that also took into consideration results from the 2009 treatment taxonomy testing described above.

LPTs participated in an active workshop in early 2013, designing the EMR to accurately and comprehensively represent the 3 basic components of PBE studies, i.e., patient characteristics, treatment interventions, and outcomes. Professional materials, including articles, textbooks, and referenced websites were used to guide the EMR design. Themes not extensively studied previously were discussed more thoroughly with the aim of reaching a consensus.

Studies on lymphedema treatment taxonomy available at that time were reviewed (ILF, 2006; ILF, 2012; ISL, 2009; ISL, 2013). There were a few debates among workshop participants. For example, documentation of level of pressure under the multi-layer lymphedema bandaging (mild, moderate, strong, and very strong) was recommended by some LPTs, in accordance with the 2012 Lymphedema Framework for Best Practice (ILF, 2012). However, it was argued that identifying how much pressure is applied is challenging; therefore, a compression bandage treatment code should not be divided into levels of pressure. Others suggested that documenting level of pressure was the best practice and that LPTs should learn to quantify the level of pressure they applied, so it could be accurately described in the

EMR. A consensus was achieved and the compression code was divided into three codes by level of pressure (mild, moderate, and strong).

Another debate example surrounded the amount of codes; some argued that specification was crucial to accurately describe the scope of management, and others thought having too many codes would increase burden and discourage LPTs from using the codes. Following this discussion, redundant codes were removed, reducing the final code list from 60 to 45.

In August 2016, the new treatment codes were launched and were divided into activity and intervention codes (Appendices 6.1 and 6.2), as suggested previously (Deutscher, Horn, Smout, DeJong, & Putman, 2010). The activity code is a main code that can stand-alone such as Lymph circumferential measurements, as it needs no further description or may represent a group of associated interventions. By contrast, Lymph bandage is an activity code that needs further description by an intervention code describing the level of pressure applied, e.g., Lymph bandage mild pressure. All LPTs were invited to implementation conference calls, offering the opportunity to present clinical decision-making processes on treatment plans. This led to the development of clinical scenarios used for the accuracy testing. LPTs used the new treatment code system in their routine practice for a period of one year followed by the accuracy test described below.

Accuracy testing of treatment code documentation

LPTs received an email including a link to a computerized survey system. They were asked to accurately select 35 activity-intervention combination codes using 10 treatment vignettes describing real-life treatment scenarios. An activity code was

selected first, and, if relevant, an intervention code was also selected, replicating the EMR recording method. Each activity-intervention combination code appeared only once.

The accuracy of the use of the proposed treatment taxonomy was tested on a LPT level and a code level. An a priori criterion of 90% or more for mean LPT and code scores was defined as the targeted threshold for a successful implementation of the proposed treatment code documentation system, as suggested previously (Deutscher & Horn, 2014; Horn et al., 2012). For the LPT level, LPTs scores were calculated as the percentage of treatment codes accurately selected by each LPT. At the code level, we calculated the percentage of LPTs who accurately selected each code.

This study was approved by Maccabi and the University of Missouri Health Sciences Institutional Review Boards for research for protection of human subjects; an exemption from informed consent from the LPTs was received.

Results

Forty-three LPTs (mean age 44.3; range 25-67 years) were asked to participate in the treatment coding accuracy test. Most LPTs were women (95.3%); 4.7% had a PT qualification certificate; 79.1% had a bachelor degree, 14% Master's degree, and 2.3% a PhD. LPTs had a mean of 18.5 years (range 1.2-42 years) of experience as physical therapists and 8.9 years of experience (range of 0.5-24 years) as a lymphedema therapist As described above, the treatment codes developed resulted in a list of activities and interventions listed in Appendices 1 and 2. Activities included five stand-alone codes with two administrative codes ("Lymph PT" and

"Lymph PT Complex") and three treatment codes ("Lymph Circum Measurements," "Lymph Garment Measurement," and “Manual Lymphatic Drainage”) (Appendix 6.1). Additionally, four activities had associated interventions (Appendix 6.2): "Lymph Compression Bandage" had seven associated interventions; "Lymph Education" had 11 associated interventions; "Lymph Exercise" had six associated interventions; and "Lymph Pump" had seven associated interventions. As an example, when educating about compression bandaging, the LPT can choose to teach a care-giver (the activity code the LPT will choose will be "Lymph Education" and the intervention code will be "Lymph Edu Caregiver Bandaging") or the patient (the activity code will be the same but the intervention code will be "Lymph Edu Self Bandaging"). An example of one vignette is presented in Box 6.1.

The mean LPT score was 91% (SD = 8%). Sixty-three percent of LPTs accurately selected more than 90% of activities/activity-intervention combination codes (Figure 6.1). Of the 16 who accurately selected fewer than 90% of the combinations, 14 accurately selected 90% of the activity codes and 10 accurately selected 90% of the intervention codes. Only one LPT selected fewer than 90% of both activities and intervention codes accurately.

The mean treatment code score was 91% (SD = 9.4%). All five stand-alone activity codes (presented in blue in Figure 6.2) were accurately selected by more than 90% of LPTs. Sixty-six percent of the activity-intervention combination codes were accurately selected by more than 90% of the LPTs (Figure 6.3). The activity-intervention combination codes that were selected by fewer than 90% of the LPTs are presented on the right side of the graph (the olive-green rectangle in Figure 6.2).

To further analyze these codes, we divided them into activity and intervention codes (Figure 6.3). Eight out of nine activity codes had scores higher than 90%. Out of these, 3 had also higher scores than 90% for the intervention codes ("Lymph Edu Self Bandaging," "Lymph bandage whole arm," and "Lymph Edu Caregiver Bandaging"). Five codes had intervention codes scores lower than 90% ("Lymph Pump Lymph Press," "Lymph Pump Pants Bilateral," "Lymph Pump Flebopress," "Lymph Edu Exe Tank Immersion," and "Lymph Exe Pumping Movement"). One code had both activity and intervention codes scores lower than 90% ("Lymph Exe Elevation").

Discussion

The first aim of this manuscript was to describe the development of a treatment taxonomy for lymphedema physical therapy as part of a PBE process. Activity and intervention codes were documented during routine practice of care. The definitions of activities and interventions within each activity were used previously in a study on patients post-stroke as part of a PBE study (Deutscher et al., 2010). Defining comprehensive, yet mutually exclusive, treatment definitions is essential to enable consistent and valid representation of rehabilitation ingredients (Dijkers, 2014), also referred to as the “black box” of rehabilitation (DeJong, Horn, Conroy, Nichols, & Healton, 2005; DeJong, Horn, Gassaway, Slavin, & Dijkers, 2004). However, in lymphedema management there are not yet accepted guidelines regarding treatment taxonomy. The activities and intervention codes that are described in this manuscript are based on consensus documents published by the International Lymphedema Framework (ILF, 2006; ILF, 2012) and the International Society of Lymphology(ISL, 2009; ISL, 2013). The additional treatment codes (which

are not described in the consensus documents) were developed as part of the PBE process, to enable a full description of what is clinically used in lymphedema physical therapy and are the product of years of experience of front-line clinicians. For example, "Lymph Edu Self Measurement" is used when patients are educated to measure the circumferences of their limbs. This code is not described as part of CDT (Lasinski, 2013); however, it is used for early detection of or exacerbation of lymphedema. Another example is "Lymph Edu Compress Garment Use," which is used when patients are educated on how to care for, don, and remove a compression garment. Adherence to lymphedema management is critical in order to achieve optimal outcomes (Ridner, 2009; Vignes, Porcher, Arrault, & Dupuy, 2007, 2011); documenting the fact that attention was given to education on how to use a garment is needed to examine its association with the targeted outcome.

The second aim of this manuscript was to evaluate the accuracy of treatment code documentation by LPTs. Sixteen LPTs (of 43) accurately selected fewer than the a priori quality threshold of 90% of activities or activity-intervention combination codes. Of them, 14 accurately selected more than 90% of the activity codes and 10 accurately selected more than 90% of the intervention codes. After a discussion on these results, a decision was made that each of these LPTs would be addressed individually and get personalized feedback on his/her performance. For example, one error was using "Lymph Compression" as an activity code and "Lymph Edu Caregiver Bandaging" as an intervention code, while there was a need to use "Lymph Education" as the activity code. This type of mistake could also be avoided using a

computerized algorithm enabling selection of only appropriate activity-linked interventions, a feature suggested for future development.

While trying to understand whether there were treatment codes that were problematic, we analyzed code level scores. Nine activity-intervention combination codes were accurately selected by fewer than 90% of LPTs. A discussion revealed that some of these codes were not being used on a regular basis. For example, only five LPTs have pneumatic compression pumps in their clinics. Therefore, the activity code "Lymph Pump" and intervention code "Lymph Pump Pants Bilateral " were not familiar to most LPTs. However, as some LPTs do use these codes, the decision was to retain these codes and enhance relevant therapist education. Two codes were found to be redundant ("Lymph bandage whole arm" and "Lymph bandage level AG"), which represented the same content – bandaging the arm from hand to axilla). Therefore, only "Lymph bandage level AG" was retained, as it is also used when bandaging a leg from the foot to the groin. The process of analyzing the results, discussing, and understanding what the reasons for mistakes were, and reflecting the conclusions back to the LPTs, while simultaneously receiving feedback from them, strengthened clinician involvement in the PBE process – a major characteristic of PBE studies.

The goal of PBE is to identify associations between treatments and outcomes – to find the right treatment for specific patient groups by reducing the effect of alternative explanations. One of the hallmarks of PBE is that the research is led by front-line clinicians who are engaged in the process of care (Horn & Gassaway, 2007). The results of the described accuracy tests were fed back during discrete conversations; the code changes were made in the new EMR lymphedema module;

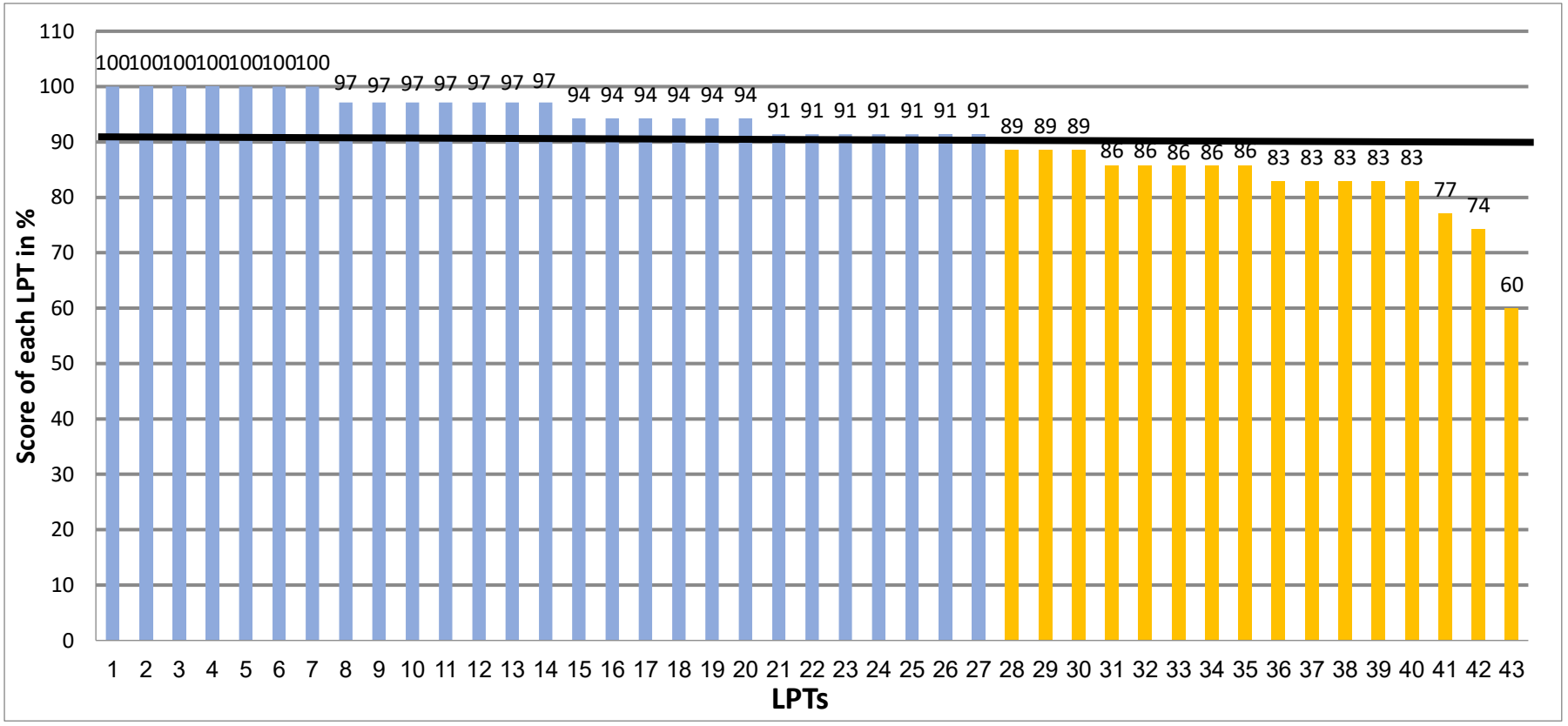
and the LPTs received a notification on that change. Finally, follow-up accuracy tests are needed until all LPTs and all treatment codes pass the a priori 90% accuracy threshold.

This study has several limitations. The procedure of testing could have over-simplified the process of clinical reasoning when selecting treatment codes, as not all vignettes may have accurately represented real-life scenarios. We do not yet know if success on the test translates to successful routine use of the coding system and improved patient outcomes.

Conclusions

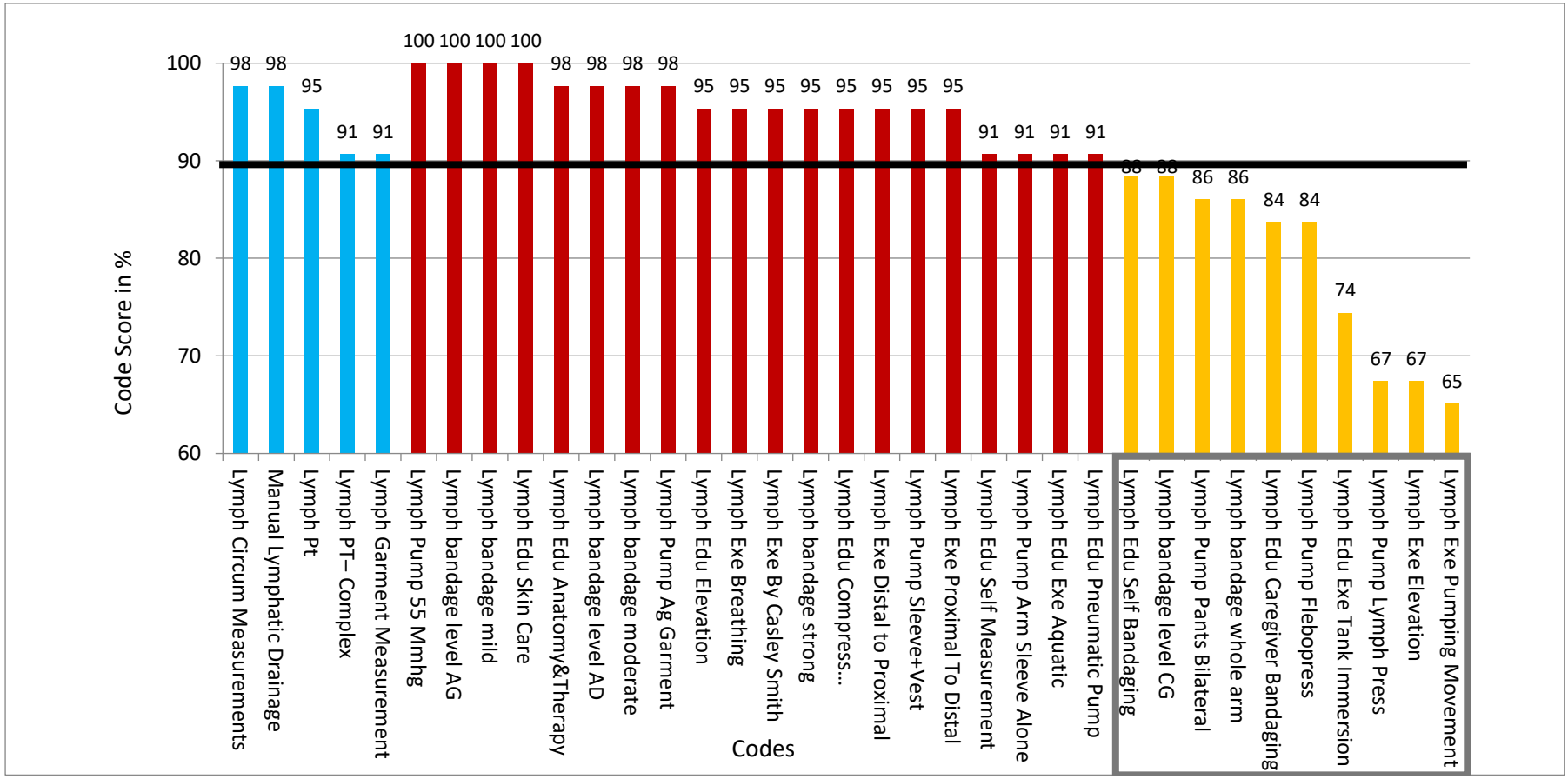
The new lymphedema treatment code taxonomy encompasses the codes that LPTs deemed relevant during routine care. An accuracy test revealed overall high scores on the LPTs and the code levels; however, we identified mistakes on the level of the LPT related to mismatching the right activity code with an intervention code. On the code levels, we identified codes that were redundant and codes that were used in an incorrect manner; modifications were made accordingly. A follow-up examination is needed to ascertain that the conclusions from the accuracy test were successfully implemented. The new proposed lymphedema treatment code system offers an accurate and comprehensive taxonomy that captures the most important treatment processes that may be studied for their associations with patient-centered outcomes within a PBE framework, an essential practice for the benefit of our patients.

Figure 6.1: Treatment Codes by Individual LPTs



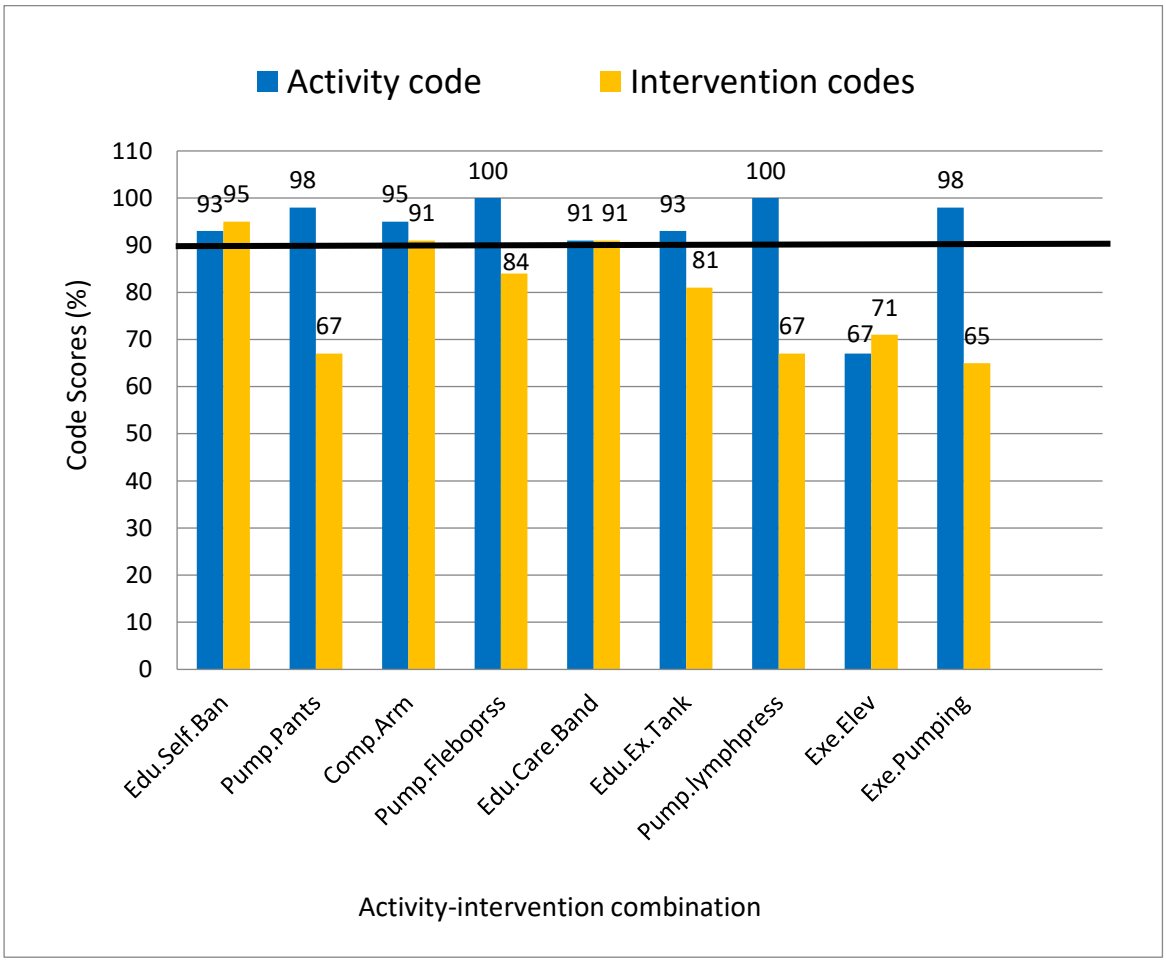
Note. in blue, LPTs who accurately selected more than 90% of codes; in orange, LPTs who accurately selected less than 90% of codes.

Figure 6.2: Code Scores for each Activity-Intervention Combination (%)



Note. in blue, activitiy stand-alone codes; in red, acitivity-intervention combinations selected by more than 90% of LPTs; and in orange, activity-intervention codes which were selected by less than 90% of LPTs

Figure 6.3: Codes with Low Activity-Intervention Combination Scores Presented by Activity and Intervention Codes



Interpretation of the graph: For example, for the code education for self-bandaging, 93% of LPT's accurately selected the activity code "education" and 95% accurately selected the intervention within the activity of self-bandaging.

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Table 6.1: **Stand-alone Activity Codes**

Activity codes	Description
Lymph PT Complex	Lymphatic physical therapy-complex: Therapist will choose this administrative code when the treatment will include all/some elements of the CDT/CPT/CLT (Complex Lymphatic/Physical/Decongestive Therapy). This type of session will last more than 30 minutes.
Lymph PT–	Lymphatic physical therapy: Therapist will choose this administrative code when the treatment will include some elements of the CDT/CPT/CLT (Complex Lymphatic/Physical/Decongestive Therapy). This type of session will last no longer than 30 minutes.
Lymph Circum Measurements	Lymph circumference measurements: Measuring the circumferences of the limb(s).
Lymph Garment Measurement	Lymph compression garment measurements: Lymphatic measurements for compression garments. The therapist will use this code when measuring for

	stockings, bra, sleeve, or glove by the therapist or by a fitter in the presence of the therapist.
Manual Lymphatic Drainage	The therapist will use this code when performing manual lymph drainage for the patient.

Table 6.2: **Activity Codes and Intervention Codes**

Activity codes	**Intervention codes**	**Description of activity-intervention combination**
Lymph Compression Bandage	Lymph bandage whole arm	Lymph compression bandaging of the whole arm: bandage from palm to axilla (with or without fingers)
	Lymph bandage level AD	Lymph compression bandaging up to the knee: bandaging below knee level
	Lymph bandage level AG	Lymph compression bandaging up to the groin: bandaging above knee level
	Lymph bandage level CG	Lymph compression bandaging from wrist to axilla (with or without fingers)
	Lymph bandage mild 1-layer	Lymph compression bandaging mild pressure: For AD level: 1-layer/1-2 bandages. Mild pressure is considered to be <20mmhg. In the absence of a way to measure pressure, the

		therapist should use this code when applying 1 layer/use of 1-2 bandages in an AD (up to the knee), 2-4 bandages in AG (up to the groin), and 1-2 for whole arm.
	Lymph bandage moderate 2-layer	Lymph compression bandaging moderate pressure: for AD level: 2-layers/3-4 bandages. Moderate pressure is considered to be >20-40mmhg. In the absence of a way to measure pressure, the therapist should use this code when applying 2 layers/ use of 3 bandages in an AD, 5-7 bandages for AG, and 4-5 bandages for the arm.
	Lymph bandage strong 3-layer	Lymph compression bandaging strong pressure: For AD level: 3-layers/>4 bandages. Strong pressure is considered to be >40-60mmhg. In the absence of a way to measure pressure, the therapist should use this code when applying 3 layers/ use of 4 bandages in an AD, more than 7 bandages for AG, and more than 5 bandages for the whole arm.
Lymph Education	Lymph Edu Self Measurement	Lymph education self-measurements: The therapist will teach the patient how to measure and document his/her limb circumferences.
	Lymph Edu Skin Care	Lymph education on skin care: The therapist will teach the patient the importance of skin hygiene and how to respond to signs of infection.

	Lymph Edu Anatomy & Therapy	Lymph education on anatomy and therapy options: The therapist will give the patient information about the lymphatic system and lymphedema therapy.
	Lymph Edu Elevation	Lymph education for elevation: The therapist will instruct the patient on elevation as a mean to reduce swelling.
	Lymph Edu Compress Garment Use	Lymph education on how to use the compression garment: The therapist will teach the patient how to don and doff the compression garment (including the use of wearing aids such as "easy slide", butler, etc.) and give the patient instructions about garment care (washing, drying etc.)
	Lymph Edu Exe Aquatic	Therapist will teach the patient water exercises.
	Lymph Edu Exe Tank Immersion	Therapist will teach the patient home exercise in a tank of water (proper height depends on the area of swelling, lukewarm temperature up to 32 C°).

	Lymph Edu Pneumatic Pump	Home use: The therapist will teach the patient how to use a compression pneumatic pump at home, instructing about position of treatment, frequency of treatment, duration, pressure applied, and percussion.
	Lymph Edu Self Bandaging	The therapist will teach the patient how to self-bandage, instructing about the duration of bandaging (23 hours/only at night/only during day time) and frequency of renewing the bandaging (twice a day, once a day, twice a week, etc.), bandage care (washing, drying, rolling, etc.) and warning signs (blueness, numbness, and tingling in the toes or fingers, pressure points, pain).
	Lymph Edu Caregiver Bandaging	The therapist will teach the patient how to self-bandage, instructing about the duration of bandaging (23 hours/only at night/only during day time) and frequency of renewing the bandaging (twice a day, once a day, twice a week, etc.), bandage care (washing, drying, rolling, etc.) and warning signs (blueness, numbness, and tingling in the toes or fingers, pressure points, pain). The therapist will also teach what to do in case of change in the appearance (move and try to loosen the bandage; remove one layer; remove the whole bandage; and re-bandage).

Lymph Exercise	Lymph Exe Breathing	The therapist will use this code when the patient is practicing breathing exercise during the treatment session.
	Lymph Exe By Casley Smith	The therapist will use this code when the patient is practicing Casley Smith's exercises according to the Casley Smith exercise booklet, during the treatment session.
	Lymph Exe Distal to Proximal	The therapist will use this code when the patient is practicing distal to proximal exercises, during the treatment session
	Lymph Exe Elevation	The therapist will use this code when positioning the patient in supine with the affected limb elevated.
	Lymph Exe Proximal to Distal	The therapist will use this code when the patient is practicing distal to proximal exercises, during the treatment session.
	Lymph Exe Pumping Movement	The therapist will use this code when the patient is practicing pumping exercise during the treatment session.

Lymph Pump	Lymph Pump 55 Mmhg	Applying 55 mmHg.
	Lymph Pump Arm Sleeve Alone	Using a pressure sleeve
	Lymph Pump Sleeve+Vest	Using a pressure sleeve + vest.
	Lymph Pump Pants Bilateral	Using a pressure pants bilateral.
	Lymph Pump Ag Garment	Using a pressure leg AG garment.
	Lymph Pump Flebopress	Using a flebopress machine with 4 compartments.
	Lymph Pump Lymph Press	Using a lymph press machine with 10-12 compartments.

Box 6.1: Treatment Vignette for the Agreement Test

A woman has lymphedema of the arm due to breast cancer surgery. She receives the following treatments on the first session:

1. The patient performs breathing exercises in the clinic with the guidance of the LPT

   - Which activity code will you choose from the list of activity codes?
   - Which of the intervention codes will you choose from the list of intervention codes?

2. The therapists explained and demonstrated how to bandage and the patient performed bandaging by herself:

   - Which activity code will you choose from the list of activity codes?
   - Which of the intervention codes will you choose for the list of intervention codes?

The answers for the first treatment:

- Activity: Lymph exercise
- Intervention: Lymph exe breathing

The answers for the first treatment:

- Activity: Lymph education
- Intervention: Lymph education self-bandaging

CHAPTER SEVEN: FINDINGS – A MANUSCRIPT IN REVIEW - AIM TWO - KNOWN-GROUPS CONSTRUCT VALIDITY OF FUNCTIONAL STATUS SCORES FOR PATIENTS WITH LYMPHEDEMA

Tidhar, D., Deutscher, D., Armer, J. M. (2018). Known-groups Construct Validity of Functional Status Scores for Patients with Lymphedema. Manuscript submitted for publication.

Abstract

During treatment of lymphedema, routine use of patient-reported outcomes measures (PROMs) is recommended to monitor patient progress; the validity functional status (FS) PROMs in these patients is unknown. Our aims were to examine known-groups construct validity of FS PROMs administered using computerized adaptive testing (CAT) at admission and discharge from physical therapy treatment due to lower and upper limb lymphedema. Upper and lower limb FS PROMs were measured using the shoulder CAT and the foot-and-ankle CAT, respectively. At admission (n=1600), patients who were younger, had more acute symptoms, had less severe lymphedema, had less co-morbidities, had no relevant surgical history, did not use medications for chronic conditions, and exercised regularly, had higher FS. At discharge (n=611), patients who were younger, had less advanced lymphedema, had less co-morbidities, had no relevant surgical history, had more acute symptoms, did not use medications for chronic conditions, and exercised regularly had higher FS change, after controlling for their baseline FS score. Low participation rates in FS outcomes data collection could have biased results. Overall,

the CAT-based FS PROMs used in this study discriminated between patient groups in clinically logical ways both at intake and at discharge from lymphedema treatment.

Key Words: Lymphedema, known-groups construct validity, function status, patient- reported outcomes measures, physical therapy rehabilitation

Introduction

Lymphedema is a progressive chronic disease that affects people's quality of life (Herberger et al., 2017; Karlsson, Wallenius, Nilsson-Wikmar, Lindman, & Johansson, 2015; Weiss & Daniel, 2015). Patients with lymphedema often experience deficits in daily tasks, work, sport, and leisure (Hidding, Beurskens, van der Wees, van Laarhoven, & Nijhuis-van der Sanden, 2014; Lee, Morris, Czerniec, & Mangion, 2018; Rowlands et al., 2014). Few studies have examined physical functional status (FS) as a patient-reported outcome measure (PROM), rather most used volume measures as the main outcome (Tidhar, Armer, & Stewart, 2018). Among those which assessed function, the Medical Outcomes Study Short Form-12 (SF-12) Health Survey (Rowlands et al., 2014); the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (Do, Choi, Ahn, & Jeon, 2017); or the Disabilities of the Arm, Shoulder and Hand (DASH) (Letellier, Towers, Shimony, & Tidhar, 2014) were used.

One way to assess construct validity of a measurement instrument is to examine whether it discriminates between different patient groups in known and logical clinical ways – the known-groups construct validity (Deutscher, Hart, Stratford, Dickstein, & Horn, 2011). For example, older patients or patients with a more severe conditions are expected to have lower FS than younger and healthier

patients (Gandek & Ware, 1998). Known-groups construct validity for assessing FS in lymphedema has been examined previously using several measures. Launois at al. (2002) examined construct validity of an upper limb lymphedema questionnaire (ULL27) and found significant and logical trends between four grades of lymphedema severity for the physical dimension (Launois et al., 2002). Lymphedema functioning, disability, and health were examined using the Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF) (Devoogdt et al., 2011) among women with and without lymphedema related to breast cancer; patients with lymphedema had lower function than those who had no lymphedema (Devoogdt, Van Kampen, Geraerts, Coremans, & Christiaens, 2011).

A few known trends have been found to be associated with FS related to lymphedema at admission to therapy. Severe lymphedema was associated with lower function (Herberger et al., 2017; Launois & Megnigbeto, 2001; Launois et al., 2002; Okajima et al., 2013). However, in other studies, severity was not found to be associated with level of function (Chachaj et al., 2010; Dawes, Meterissian, Goldberg, & Mayo, 2008; O'Toole et al., 2015). Higher pain levels were associated with lower function (Chachaj et al., 2010; Dawes et al., 2008; Herberger et al., 2017; O'Toole et al., 2015). Other factors associated with lower function in lymphedema were: no exercise history, cellulitis within the last 30 days, substance use (Okajima et al., 2013), and more co-morbidities (Dawes et al., 2008; Herberger et al., 2017).

We did not identify studies on factors associated with FS change in patients with lymphedema. Factors associated with a greater change in FS among patients with musculoskeletal disorders were: early age, acute conditions, less surgeries

related to the condition being treated, higher exercise history, and less co-morbidities (Deutscher et al., 2011; Hart, Cook, Mioduski, Teal, & Crane, 2006; Hart, Mioduski, & Stratford, 2005; Hart, Wang, Stratford, & Mioduski, 2008). Lower severity was associated with greater volume change in limb volume for patients with lymphedema (Ramos, O'Donnell, & Knight, 1999); younger age was associated with failure to maintain the results of volume change (Vignes, Porcher, Arrault, & Dupuy, 2011). No data were found to support these trends for FS outcomes of patients with lymphedema.

In physical therapy clinics in Maccabi Healthcare Services (Maccabi), a public healthcare organization in Israel, FS is examined during routine practice for all patients with musculoskeletal impairments using the patient-inquiry software developed by Focus on Therapeutic Outcomes, Inc. (FOTO) (Gozalo, Resnik, & Silver, 2016; Swinkels et al., 2007). Data are collected via computerized adaptive testing (CAT) (Hart, Deutscher, Werneke, Holder, & Wang, 2010), wherein patient's response of perceived ability to perform a functional task is transformed into a continuous score (0-100; low to high function) (Hart et al., 2006; Hart et al., 2005; Hart, Mioduski, Werneke, & Stratford, 2006; Wang et al., 2015) using an item-response theory model (Hays, Morales, & Reise, 2000; Lord, 1980). Since 2009, lymphedema therapists in Maccabi have started to administer FS CATs to patients with lymphedema. Two body-part specific CATs used most often were the foot-and-ankle (Hart et al., 2005) and the shoulder (Hart et al., 2006) CATs. The foot-and-ankle CAT was based on the Lower Extremity Functional Scale (LEFS) questionnaire (Binkley, Stratford, Lott, & Riddle, 1999) and was found to discriminate between

known-groups for patients with musculoskeletal impairments in clinically logical ways. Patients who had more chronic symptoms, were older, exercised less, had more co-morbidities, and underwent more surgeries reported less FS change (less improvement) at discharge (Hart et al., 2008). The shoulder CAT was developed from the validated Flexilevel Scale of Shoulder Function (FLEX-SF) questionnaire (Cook, Roddey, Gartsman, & Olson, 2003). It was found to have good known-groups construct validity for patients with musculoskeletal shoulder impairments, discriminating between groups by age, ethnicity, gender, limb dominance, and those who had had surgeries in clinically logical patterns (Wang, Hart, Cook, & Mioduski, 2010). To our knowledge, no published study has yet reported CAT-based FS scores for patients with lymphedema.

Before physical therapists started using FS-based PROMs for patients with lymphedema, a content validity examination was performed by a group of physical therapists trained in lymphedema therapy who compared the items from the foot-and-ankle and shoulder CATs with other questionnaires used in lymphedema studies (Keeley, 2008; Keeley et al., 2010; Launois et al., 2002). They concluded that the items were appropriate for patients with lymphedema, as they represented relevant levels of functional difficulties.

Therefore, our aim was to examine the known-groups construct validity of FS scores for patients treated due to lymphedema. Our hypotheses were that patients who were older, had more advanced lymphedema stage and severity, had more co-morbidities, had more chronic symptoms, purchased more medication for chronic

conditions, had surgeries related to their lymphedema, and exercised less will have lower FS scores at admission and lower FS change at discharge.

Methods

Design

This is a secondary analysis of longitudinal observational cohort data collected during 2009-2017 at Maccabi.

Sample

Data were captured from the integrated electronic medical records and electronic outcomes system (Deutscher, Hart, Dickstein, Horn, & Gutvirtz, 2008) from 51 clinics including 75 physical therapists treating patients for lymphedema during 2009-2017. Patient data were extracted if they received therapy for lymphatic disorders and were above 18 years of age. The baseline study cohort was identified as having received treatment for lymphedema of the foot-and-ankle or the shoulder using the electronic medical records. Participation rate was calculated as the percent of patients who had FS scores at admission from the baseline cohort (Deutscher et al., 2008). We analyzed each episode separately; therefore, we refer in the text to episodes of care for patients. To assess the potential for a systematic patient selection bias at intake, we compared patient characteristics between those with or without FS scores at admission. Completion rate was calculated as the percent of patients who had FS scores at both admission and discharge (complete), from those that had only taken the FS CAT at admission (incomplete) (Deutscher et al., 2008). To

assess the potential for a systematic patient selection bias at discharge, we compared characteristics of patients with complete or incomplete FS outcomes.

The eight patient variables of interest tested for known-groups constructs validity were: age-groups (18-44, 45-65 or >65), lymphedema stage classifications (0, 1, 2 and 3, with 3 being the most advanced stage); lymphedema severity classification (mild, moderate, severe); number of co-morbidities as the number of condition-specific health registries (0/1 registry, 2 or more registries) (Shalev et al., 2011); acuity of symptoms as days from the onset of the lymphedema (up to 21 days, 22-90 days, 91 days and more); number of chronic condition medications purchased (none, 1 or more); number of surgeries related to the lymphedema (none, 1 or more); and exercise history (at least 3 times a week, once or twice a week, seldom or never).

Data analysis

Descriptive analyses were used to report frequencies of categorical and nominal variables and means (standard deviation) for continuous variables. Comparisons were done using t-test for continuous variables and Chi-square analysis for nominal and categorical variables. To examine the known-groups construct validity, an analysis of covariance (ANCOVA) was used for each variable of interest, one at a time. The dependent variable for the known-groups analyses at admission was FS at intake, with age as a covariate for the assessment of variables other than age. The dependent variable for the known-groups analyses at discharge was FS change score, with FS score at intake as covariate. Analyses were performed using

the Statistical Package for Social Sciences (SPSS version 24.0, SPSS Inc., Chicago, IL, 2012). Approval for this study was granted by the ethics committee of Maccabi.

Results

Descriptive data: Figure 7.1 illustrates a sampling diagram of patients for the known-group construct validity study. After exclusions, out of 5545 patients, 1600 participated in FS survey at admission. A comparison of patients who participated or did not participate in FS outcomes at admission by body region (lower and upper extremities) is presented in Table 7.1. Participation rate for the lower limb was 34% (1318/3879), with no significant differences found on all variables except for co-morbidities and age. Patients who had FS scores at admission had less co-morbidities (0-1) and were younger compared to those without FS scores at admission. Participation rate for the upper limb was 17% (282/1666), with no significant differences found on gender and purchase of medications for chronic conditions between patients with and without FS at admission. However, patients with FS scores were younger, had less advanced and mild lymphedema, and had less co-morbidities (0-1), compared to those without FS scores at admission.

Completion rate was 37% (482/1318) for the foot-and-ankle CAT and 46% (129/282) for the shoulder CAT. The comparison of characteristics of patients with complete or incomplete outcomes data are presented in Table 7.2. No significant differences were identified between those with complete or incomplete outcomes data for all variables tested and for both body regions.

Estimated marginal means of 1600 patients who had FS scores at admission on the foot-and-ankle (n=1318) or shoulder (n=282) CATs are presented in Tables 7.3 and 7.4, respectively. For the foot-and-ankle CAT, seven of eight expected trends were observed, with higher FS scores at admission for patients who were younger, had lower lymphedema stages, had less severe lymphedema, had less co-morbidities, did not purchase medications for chronic conditions, had no relevant surgeries to the foot-and-ankle, and exercised regularly prior to admission. The expected trend for the acuity variable was not observed. For the shoulder CAT, five of eight expected trends were observed, with higher FS scores at admission for patients who had less co-morbidities, were treated for acute conditions, did not purchase medications for chronic conditions, had no relevant surgeries to the shoulder, and had exercised regularly. The expected trends for the variables of age, lymphedema stage and severity were not observed.

Estimated marginal means for the foot-and-ankle CAT and the shoulder CAT at discharge are presented in Tables 7.5 and 7.6, respectively. For patients who answered the foot-and-ankle CAT, seven of eight expected trends were found, with more FS change for patients who were younger, had less advanced lymphedema stage classification, had less co-morbidities, were treated for acute problems, did not purchase medications for chronic conditions, had no relevant surgery, and exercised regularly. The expected trend for the severity classification variable was not observed. For patients who answered the shoulder CAT, four of eight expected trends were found, with more FS change for patients who were younger, had less co-morbidities, were treated for more acute symptoms, and did not purchase

medications for chronic conditions. The expected trends for the variables of stage and severity classifications, and surgical and exercise history were not observed.

Discussion

This study aimed to examine the known-groups construct validity of FS scores derived from the foot-and-ankle and shoulder CATs for patients with lymphedema, and to explore whether known trends from other studies on FS scores at intake and FS change at discharge also exist among patients with lymphedema. We hypothesized that the FS scores tested would discriminate patient groups in clinically logical ways for eight variables of interest, including age, lymphedema stage and severity classifications, number of co-morbidities, acuity, purchase of medication for chronic conditions, surgical history, and exercise report.

The foot-and-ankle CAT scores at admission discriminated between patient groups in known and clinically logical ways for all variables tested, except for the acuity variable. No prior studies have reported construct validity of the foot-and-ankle CAT for patients with lymphedema. Our findings do not support Keeley et al.'s (2010) report; in their study, the FS scores on the LYMPHQOL questionnaire (a quality of life questionnaire with different dimensions) did not discriminate between different lymphedema severity stages (Keeley et al., 2010), The researcher thought that other factors such as co-morbidities and neurological problems could be associated with lower function and were not tested in their study; our findings support this notion as patients who had more co-morbidities had lower FS scores at admission. We expected people with more chronic symptoms to have lower FS scores at admission. However, the majority of patient who had lymphedema in our

study (96.7%) did not have acute symptoms, which made it unlikely to be able to identify the expected trend for this variable.

The shoulder CAT scores at admission discriminated between patient groups in clinically logical ways for five of eight variables assessed, partially supporting our hypothesis. Discrimination between severity and stages of lymphedema was not supported. However, a validity study on the ULL27 questionnaire examined FS scores and reported on logical discrimination between different grades of lymphedema severity at admission (Launois & Megnigbeto, 2001). It is clinically logical to expect that woman with more advanced stages of lymphedema will have lower FS scores. The fact that our shoulder cohort included very few patients with an advanced stage and severity (one with Stage 3 and six with severe lymphedema) might limit our ability to test the association between these factors and FS scores at admission.

On discharge, the foot-and-ankle CAT discriminated between patient groups in clinically logical ways on seven of the eight variables assessed. Although not all variables were statistically significant, possibly due to sample size limitations, the trend in each group was clinically logical. No published report on CAT FS at discharge on patients with lower limb lymphedema was found; however, a study by Hart et al. (2008) examined known-group construct validity on the foot-and-ankle CAT in patients who received musculoskeletal rehabilitation in outpatient clinics and found the same trends on the variables of age, acuity, co-morbidities, surgery history, and exercise history (Hart et al., 2008), supporting the construct validity of this CAT when answered by patients with lymphedema. In contrary to our expectations, no logical

trend was found for the variable of lymphedema severity, possibly due to the low sample size of this group with only seven patients with a severe classification.

On discharge, the shoulder CAT discriminated between patient groups in clinically logical ways on four of the eight variables assessed. Although not all variables were statistically significant, the trend in each group was clinically logical, adding to the previous support of the construct validity of this CAT when answered by patients with lymphedema. The study by Hart et al. (2006) which examined shoulder CAT among patients who received rehabilitation in outpatient clinics found the FS at discharge to discriminate groups of age (older people had lower discharge FS scores), gender (women had lower FS scores than men), and ethnicity (Caucasian had higher discharge FS than other ethnic groups). Our findings partially support these findings, as we found FS change at discharge to discriminate between age groups. Furthermore, no logical trend was found in other variables, such as stage and severity classifications of lymphedema, which can be explained as discussed above, by the low sample of severe lymphedema (three patients) with no patient in Stage 3 lymphedema classification. No trends were found on exercise history; however, we can observe that patients who exercise seldom have lower change in FS change scores than those who do exercise. We cannot provide an explanation why no trend was found on the surgical history variable.

Limitations

The potential for patient selection bias was a major concern in our study, as the overall participation rate was only 29%, possibly reducing generalizability of our results for patients with lymphedema. However, in an attempt to address this issue, we compared characteristics between those who had FS scores at admission and those who did not in both patient groups with lower and upper limb lymphedema. Our findings show that in the group with lower limb lymphedema, people who had no FS score at admission had more co-morbidities. No other differences were found between the groups reducing the overall concern for a potential patient selection bias at admission. In the upper limb group, patients with no FS scores at admission had no differences on the variables of gender and the use of medication; however, had more severe lymphedema, more advanced stages of lymphedema, more co-morbidities and were older. As the number of patients with more severe and advanced lymphedema was small, we may not know if these patients represent the population of people with lymphedema.

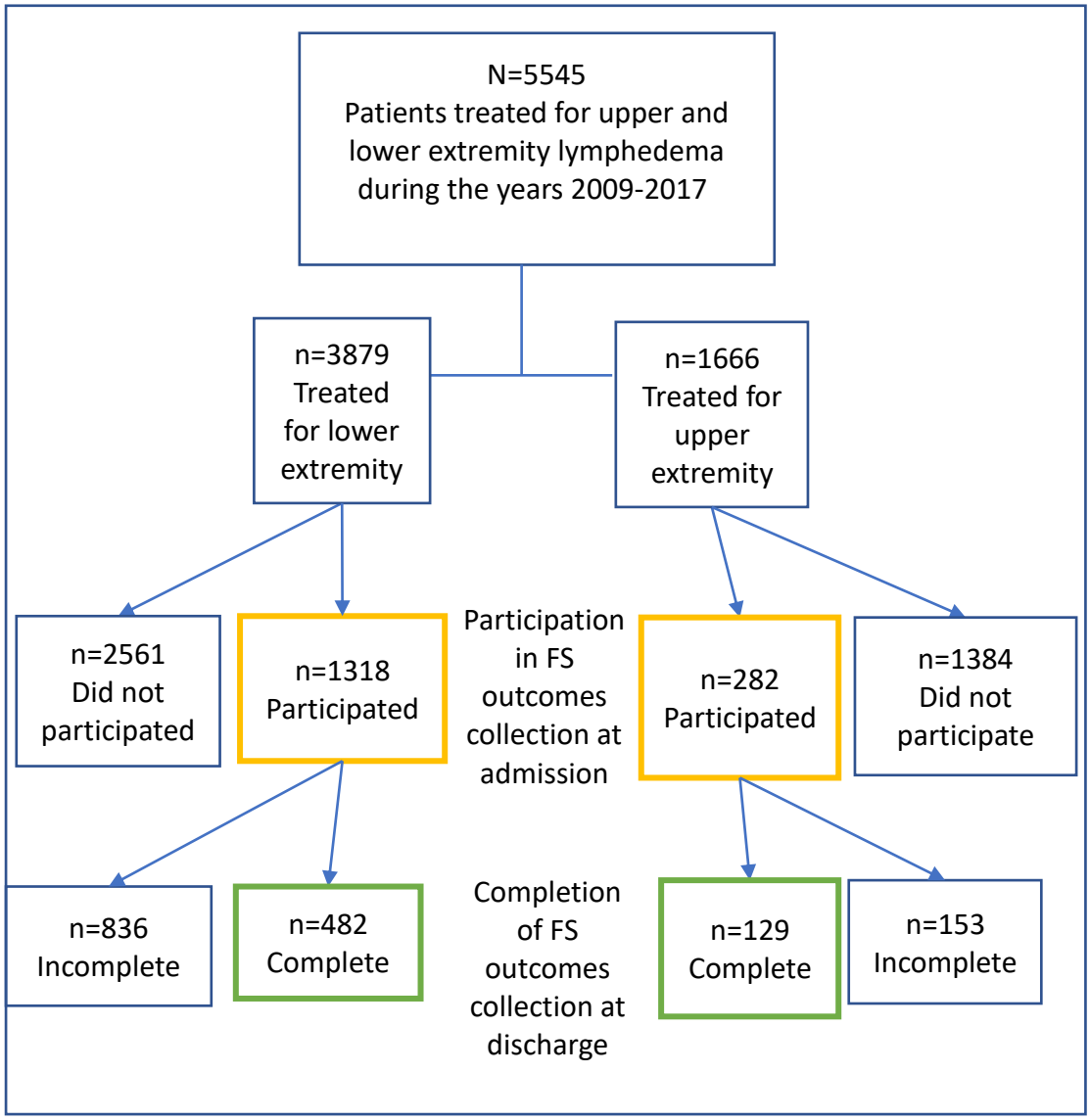
An overall low completion rate (38%) was another limitation in our dataset. We did not find any differences between patients with complete or incomplete outcomes data, reducing the concern for a systematic patient selection bias, although selection bias might still exist, as our findings are limited to the variables available to us. Improved participation and completion rates will help reduce concerns for a patient selection bias at admission. In addition to enhanced education and implementation efforts, it is also possible that participation and completion rates may be improved by developing a condition-specific FS-based PROM for

patients with lymphedema which might better address their most relevant functional limitations. Whether such a tool can help increase therapist and patient interest in the FS scores for clinical decision making and outcomes monitoring is yet to be studied.

Conclusion

Our findings suggest that FS estimated scores from the foot-and-ankle and shoulder CAT can discriminate between groups of patients in clinically logical ways on selected patient characteristics, supporting the known-group construct validity of the CAT FS in patients with lymphedema at admission and at discharge. We recommend further use of the foot-and-ankle and shoulder CAT for assessing perceived physical function for patients with lymphedema to enhance clinician's focus on functional goals in addition to swelling reduction. Improved participation and completion rates of routine use of FS outcomes at admission and discharge are important implementation goals that may increase both clinical and research applications of PROMs, for the benefit of our patients.

Figure 7.1: Participant Selection



Note. Patient selection diagram by participation and completion of functional status (FS) outcomes collection. Participation refers to having or not having completed FS surveys at admission. Completion refers to having completed or not completed FS surveys at discharge.

Table 7.1: Comparison of Patient Characteristics by Body Regions who Participated or did not Participate in Functional Status Outcomes Collection at Admission (N=5545)

		Lower Limb (n=3879)			Upper Limb (n=1666)		
		Participated (N=1318)	Did not participate (N=2561)		Participated (N=282)	Did not participate (N=1384)	
		%(n)	%	P	%	%	P
Age, Mean (SD)*		61.5 (14.9)	62.8 (14.8)	0.011	54.5 (12.4)	57.7 (12.8)	0.000
Age groups %				0.275			0.005
	18 to <45	14.1(186)	12.8 (329)		22.3 (63)	16.8 (233)	
	45 to <65	39.2 (516)	37.9 (970)		55.0 (155)	51.7 (715)	
	65 to highest	46.7 (616)	49.3 (1262)		22.7 (64)	31.5 (436)	
Gender	Women %	68.1 (897)	68.4 (1752)	0.823	97.2 (274)	95.6 (1323)	0.228
Stage, %**				0.248			0.008
	Stages 0 &1	26.1 (203)	24.3 (293)		71.3 (129)	60.3 (502)	
	Stage 2	58.3 (453)	57.3 (691)		28.2 (51)	36.6 (305)	
	Stage 3	15.6 (121)	18.3 (221)		0.6 (1)	3.1 (26)	
Severity, %**				0.109			0.005
	Mild	71.5 (313)	65.1 (433)		82.5 (94)	67.1 (349)	
	Moderate	21.5 (94)	26.1 (171)		12.3 (14)	21.0 (109)	
	Severe	7.1 (31)	8.7 (58)		5.3 (6)	11.9 (62)	

Co-morbidities count, %				<0.000			0.038
	0-1 co-morbidities	25.5 (336)	18.9 (485)		21.3 (60)	16.2 (224)	
	2 or more co-morbidities	74.5 (982)	81.1 (2076)		78.7 (222)	83.8 (1160)	
Purchase of medications for chronic conditions count, %				0.150			0.253
	No purchase of medications for chronic conditions	18.7 (247)	20.7 (530)		11.0 (31)	13.5 (187)	
	Purchase of medications for chronic conditions	81.3 (1071)	79.3 (2031)		89.0 (251)	86.5 (1197)	

Note. * independent t-test, otherwise Chi-square analysis, **Stage Foot & ankle n=1982, shoulder n=1014; Severity Foot & ankle n=1100, shoulder n=634.

Table 7.2: Comparison of Patient Characteristics by Body Regions Who Completed or did not Complete Functional Status Outcomes Collection at Discharge (N=1600)

		The Foot-and-Ankle CAT (N=1318)			**The Shoulder CAT (N=282)**		
		Complete (N=482)	Did not complete (N=836)		Complete (N=129)	Did not complete (N=153)	
		% (n)	% (n)	P	% (n)	% (n)	P
Intake		48.4 (17.9)	49.2 (17.2)	0.34	55.1 (12.8)	54.0 (11.9)	0.485
Age, Mean ±SD*		59.9 (15.2)	60.9 (14.1)	0.177	53.0 (11.7)	53.3 (13.5)	0.845
Age groups %				0.490			0.255
	18 to <45	12.7 (61)	15.0 (125)		21.7 (28)	22.9 (35)	
	45 to <65	39.0 (188)	39.2 (328)		51.2 (66)	58.2 (89)	
	65 to highest	48.3 (233)	45.8 (383)		27.1 (35)	19.0 (29)	
Gender	Women %	66.3 (319)	69.1 (578)	0.290	96.9 (125)	97.4 (149)	0.806
Stage, %**				0.394			0.223
	Stages 0 &1	23.4 (68)	27.7 (135)		66.7 (58)	75.5 (71)	
	Stage 2	61.0 (177)	56.7 (276)		33.3 (29)	23.4 (22)	
	Stage 3	15.5 (45)	15.6 (76)		0.0 (0)	1.1 (1)	
Severity, %**				0.153			0.882
	Mild	72.8 (123)	70.6 (190)		81.0 (47)	83.9 (47)	
	Moderate	23.1 (39)	20.4 (55)		13.8 (8)	10.7 (6)	
	Severe	4.1 (7)	8.9 (24)		5.2 (3)	5.4 (3)	
Co-morbidities count, %				0.979			0.405
	0-1 co-morbidities	24.7 (119)	26.0 (217)		9.3 (12)	12.4 (19)	
	2 or more co-morbidities	75.3 (363)	74.0 (619)		90.7 (117)	87.6 (134)	

Acuity				0.596			0.399
	Onset up to 21 days	3.30 (16)	4.4 (37)		11.6 (15)	17 (26)	
	Onset between 22-90 days	18.0 (87)	17.3 (145)		35.7 (46)	35.9 (55)	
	Onset more than 91 days	78.6 (379)	78.2 (654)		52.7 (68)	47.1 (72)	
Purchase of medications for chronic conditions count, %				0.246			0.246
	No use of medications for chronic conditions	17.0 (82)	19.7 (165)		17.0 (82)	19.7 (165)	
	Use of medications for chronic conditions	83.0 (400)	80.3 (671)		83.0 (400)	80.3 (671)	
Number of surgeries				0.144			0.94
	No surgeries at intake	74.5 (359)	78.1 (653)		22.9 (35)	23.3 (30)	
	1 or more	25.5 (123)	21.9 (183)		77.1 (118)	76.7 (99)	
Exercise History				0.330			0.769
	At least three (3) times a week	23.2 (112)	24.3 (203)		31.0 (40)	28.1 (43)	
	Once or twice a week	32.2 (155)	28.3 (237)		35.7 (46)	34.6 (53)	
	Seldom or never	44.6 (215)	47.4 (396)		33.3 (43)	37.3 (57)	

Note. * independent t-test, otherwise Chi-square analysis, **Stage for Foot-and-ankle CAT n=777, shoulder CAT n=181; Severity Foot-and-ankle CAT n=438, shoulder CAT n=114

Table 7.3: Estimated Marginal Means for Functional Status of Lower Limb at Intake (N=1318)

Independent variable		n	Estimated marginal means	Confidence Interval	F value	P value
Age-groups*					56.5	<0.000
	18 to <45	186	58.9	56.1-61.7		
	45 to <65	516	48.9	47.3-50.4		
	65 to highest	616	43.5	42.1-44.8		
Lymphedema Stage**					15.2	<0.000
	Stages 0 &1	203	52.4	49.9-54.8		
	Stage 2	453	46.2	44.6-47.8		
	Stage 3	121	42.5	39.4-45.7		
Lymphedema Severity***					7.6	0.001
	Mild	313	51.3	49.3-53.3		
	Moderate	94	49.3	45.6-52.9		
	Severe	31	37.7	31.1-44.3		
Co-morbidities count					13.0	<0.000
	0-1 co-morbidities	336	51.3	48.7-53.9		
	2 or more co-morbidities	982	46.1	44.9-47.3		
Acuity					1.6	0.195
	Onset up to 21 days	53	46.6	41.7-51.2		
	Onset between 22-90 days	232	49.6	47.2-51.8		
	Onset more than 91 days	1033	47.3	46.3-48.4		
Purchase of medications for chronic conditions count					16.5	<0.000
	No purchase of medications for chronic conditions	247	52.5	49.6-55.3		
	Purchase of medications for chronic conditions	1071	46.1	45.1-47.2		
Number of surgeries					45.1	<0.000
	No surgeries at intake	1012	49.5	48.4-50.5		
	1 or more	306	41.9	40.0-43.8		

Exercise History					9.2	<0.000
	At least three (3) times a week	315	50.1	48.2-52.1		
	Once or twice a week	392	49.5	47.7-51.2		
	Seldom or never	611	45.6	44.2-47.0		

Note. *ANOVA analysis; all other variables are controlled for Age-groups variable; **data are available on n=777, *** data are available on n=438

Table 7.4: Estimated Marginal Means for Functional Status of Shoulder at Intake (N=282)

Independent variable		n	Estimated marginal means	Confidence Interval	F value	P value
Age-groups*					2.10	0.123
	18 to <45	63	55.2	52.1-58.2		
	45 to <65	155	51.8	49.7-53.9		
	65 to highest	64	54.6	51.9-57.4		
Lymphedema Stage**					0.15	0.694
	Grades 0 &1	129	53.9	51.6-56.2		
	Grade 2	51	53.6	49.8-57.4		
	Grade 3	1	34.4			
Lymphedema Severity***					0.23	0.796
	Mild	94	54.9	52.2-57.6		
	Moderate	14	56.4	48.3-61.9		
	Severe	6	49.5	30.9-68		
Co-morbidities count					0.94	0.334
	0-1 co-morbidities	60	54.9	50.8-58.9		
	2 or more co-morbidities	222	52.7	51.0-54.5		
Acuity					0.72	0.488
	Onset up to 21 days	41	55.2	51.1-59.3		
	Onset between 22-90 days	101	53.9	51.3-56.5		
	Onset more than 91 days	140	52.5	50.4-54.5		
Purchase of medications for chronic conditions count					2.22	0.137

	No purchase of medications for chronic conditions	31	56.7	51.8-61.7		
	Purchase of medications for chronic conditions	251	52.8	51.2-54.4		
Number of surgeries					0.03	0.861
	No surgeries at intake	65	53.4	50.2-56.5		
	1 or more	217	53.1	51.3-54.8		
Exercise Adherence					3.894	0.021
	At least three (3) times a week	83	55.8	53.1-58.5		
	Once or twice a week	99	53.4	50.9-55.8		
	Seldom or never	100	50.6	48.1-53.1		

Note. *ANOVA analysis all other variables are controlled for Age-groups; **data are available on n=181, ***data are available on n=114

Table 7.5: Estimated Marginal Means for Functional Status for Lower Limb at Discharge, Controlling for Intake, (N=482)

Independent variable		N	Estimated marginal means	Confidence Interval	F value	P value
Age-groups					1.198	0.303
	18 to <45	61	10.9 (61)	7.0-14.8		
	45 to <65	188	7.8 (188)	5.9-9.8		
	65 to highest	233	7.6 (233)	5.7-9.4		
Lymphedema stage*					0.912	0.403
	Stage 0 &1	68	11.9	8.3-15.6		
	Stage 2	177	9.3	7.1-11.5		
	Stage 3	45	8.6	4.2-13.0		
Lymphedema Severity**					0.289	0.75
	Mild	123	8.8	6.5-11.2		
	Moderate	39	6.9	2.7-11.2		
	Severe	7	8.2	-3.5-19.9		
Co-morbidities count					5.060	0.025

	0-1 co-morbidities	119	10.9 (119)	8.3-13.6		
	2 or more co-morbidities	363	7.5 (363)	6.0-8.9		
Acuity					3.713	0.025
	Onset up to 21 days	16	12.5 (16)	5.6-19.4		
	Onset between 22-90 days	87	11.4 (87)	8.5-14.3		
	Onset more than 91 days	379	7.4 (379)	6.1-8.8		
Purchase of medications for chronic conditions count					2.555	0.111
	No purchase of medications for chronic conditions	82	10.8 (82)	7.5-14.2		
	Purchase of medications for chronic conditions	400	7.8 (400)	6.5-9.3		
Number of surgeries					0.520	0.471
	No surgeries at intake	359	8.6 (359)	7.1-10.0		
	1 or more	123	7.5 (123)	4.9-10.1		
Exercise History					0.330	0.716
	At least three (3) times a week	112	9.2	6.7-11.7		
	Once or twice a week	155	7.9	5.8-10.2		
	Seldom or never	215	7.9	6.1-9.8		

Note. *Data are available on n=290, **data are available on n=169

Table 7.6: Estimated Marginal Means for Functional Status for Shoulder at Discharge, Controlling for Intake, (N=129)

Independent variable		n	Estimated marginal means	Confidence Interval	F value	P value
Age groups					0.693	0.500
	18 to <45	28	13.4	8.6-18.3		
	45 to <65	66	10.3	7.2-13.5		
	65 to highest	35	9.9	5.5-14.4		
Lymphedema stage*					0.026	0.872
	Stage 0 &1	58	9.9	6.6-13.3		
	Stage 2	29	9.5	4.8-14.2		
	Stage 3	-	-			
Lymphedema Severity**					2.471	0.094
	Mild	47	8.5	4.8-12.2		
	Moderate	8	13.7	4.6-22.7		
	Severe	3	-5.6	-20.5-9.2		
Co-morbidities count					3.995	0.021
	0-1 co-morbidities	32	16.5	11.9-20.9		
	2 or more co-morbidities	97	8.7	6.2-11.3		
Acuity					6.283	0.030
	Onset up to 21 days	15	20.6	14.4-26.9		
	Onset between 22-90 days	46	10.8	7.2-14.3		
	Onset more than 91 days	68	8.3	5.4-11.2		
Purchase of medications for chronic conditions count					2.89	0.092
	No purchase of medications for chronic conditions	12	16.8	9.4-24.3		
	Purchase of medications for chronic conditions	117	8.3	7.7-12.5		
Number of surgeries					0.00	0.949
	No surgeries at intake	30	10.5	5.7-15.3		
	1 or more	99	10.7	80.1-13.3		
Exercise History					2.042	0.134

	At least three (3) times a week	40	10.2	6.2-14.3	
	Once or twice a week	46	13.6	9.7-17.4	
	Seldom or never	43	7.9	40.1-11.9	

Note. *Data are available on n=87, **data are available on n=58

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CHAPTER EIGHT: FINDINGS – A MANUSCRIPT IN PREPERATION- AIM THREE –LYMPHEDEMA, A SIGNIFICANT HEALTH PROBLEM IN ISRAEL - A COMMUNITY-BASED STUDY

Tidhar, D., Deutscher, D., Armer, J. M. (2018). Lymphedema, A Significant Health Problem in Israel - a community-based study. Manuscript in preparation for publication.

Abstract

Background: Lymphedema is recognized as a chronic disabling disease. In Israel, the knowledge regarding the extent of the problem and the treatment approaches is lacking. Aim: To describe the characteristics of people who were treated for lymphedema in the physical therapy department of Maccabi Healthcare Services in Israel over 8 years. Design: A retrospective cohort study. Method: Analyses of data extracted from automated databases (physical therapy database, electronic medical records, electronic appointment system, computerized adapting testing (CAT) for functional status (FS) scores, medication purchases, and chronic disease registries).

Results: In all, 6013 episodes were analyzed with high proportion (80%) of people having two or more co-morbidities and 85.6% using medications for chronic conditions. People were referred less from surgeons, less with oncology diagnoses, and more with non-specific diagnoses over the years. Stage 2 classification was the most frequent (45%); and more lower extremities (51%) than upper extremities (32%) were treated. Circumferential measurements and Education for self-management were the most frequent managements (73% and 70% respectively).

Discussion: The physical therapists need to be aware of the high rates of co-morbidities and medication use by their patients. They should continue measuring and assessing with the use of classifications to support safe and effective treatment.

Key words: lymphedema, co-morbidities, classification, treatment, physical therapy.

Introduction

Lymphedema occurs when the lymphatic system fails to remove the excess fluid from the interstitial space and an accumulation of the fluid occurs (International Society of Lymphology [ILF], 2017; Keeley, 2017). Studies on the incidence of lymphedema report 75% of people treated for head and neck cancer (Deng et al., 2012); 30% of women treated for vulvar cancer (Huang, Yu, Wang, & Long, 2017); and 29% of women treated for breast cancer (Zou et al., 2018) developed lymphedema . A prevalence of 1.33/1000 people with chronic edema (CE) (edema which presented for more than 3 months) was found in one study (Moffatt et al., 2003) and in a more recent one, a prevalence of 3.93/1000 people (Moffatt, Keeley, Franks, Rich, & Pinnington, 2017).

Lymphedema may manifest with other chronic conditions such as heart failure and venous insufficiency (Keeley, 2017); in a study on melanoma-related lymphedema, 29% had more than one co-morbidity and 28% had two or more co-morbidities (Gjorup et al., 2017). These co-morbidities can exacerbate lymphedema and/or may put these people at risk when they receive lymphedema treatment (Wilputte et al., 2005). An example is treating a person who has peripheral vascular

disease with compression bandaging, which could cause more ischemia to the limb (International Lymphedema Framework [ILF], 2012). On the other hand, if the ischemia is not severe (Ankle Brachial Pressure Index (ABPI) >0.5), compression therapy is indicated; therefore, obtaining data on co-existing conditions is essential for safety of treatment (ILF, 2012). When people with co-morbidities are excluded from studies, knowledge translation on the conclusions of well-designed studies is challenging, as the generalization is narrow (Horn, DeJong, & Deutscher, 2012).

As people get older they have more chronic diseases and they take medication for these diseases; the impact of medication on lymphedema is scantily discussed in the literature (Tesar & Armer, 2018). There are more than 900 medications which can potentially influence edema exacerbation or formation. An example of these medications is calcium channel blockers which may increase existing edema or create edema by disruption of capillary filtration flow, thereby causing an increase in plasma flow into the interstitium. If flow exceeds the lymphatic capacity to clear this fluid, this will cause edema. In people who are already at risk (e.g., after removal of lymph nodes), there could be a unilateral manifestation which will mask the underlying reason (Tesar & Armer, 2018).

Research for many years examined lymphedema related to cancer, specifically as related to breast cancer (BCRL), thus, upper limb, in all aspects of assessment and therapy (Kalda, 1999; Simonavice, Kim, & Panton, 2017; S. Vignes, Blanchard, Arrault, & Porcher, 2013; Zou et al., 2018). Nevertheless, lower limb lymphedemaseems to be more prevalent than upper limb (Iuchi et al., 2015), yet it is studied much less (Tidhar, Armer, & Stewart, 2018). In a community-based study

(n=129) in Sweden, 56% of the population had lower limb lymphedema and 38% upper limb LE, with head and neck lymphedema existing in 4% and genital lymphedema in 2% (Klernäs, Johnsson, Horstmann, & Johansson, 2017). The proportion of women with lymphedema was much higher than men, from 68.6% of women in one study (Moffatt et al., 2017) to 86% in another (Klernäs et al., 2017). The average age of those with lymphedema was reported to be 63 years (range = 58-68.6) (Abu-Rustum et al., 2006; Gjorup et al., 2017; Iuchi et al., 2015; Klernäs et al., 2017). In a cohort of primary and secondary lymphedema, 29% were under 21 years (Maclellan et al., 2015). The prevalence of CE increases with age; 5.4/1000 in people >65 years old (Moffatt et al., 2003) and 28.75/1000 for >85 years old (Moffatt et al., 2017).

In the past two decades, consensus documents were published (ILF, 2006; ILF, 2012; ISL, 2009; ISL, 2013; ISL, 2016) with recommendations regarding diagnoses, differential diagnosis, treatments, contraindications, and precautions in treatment for lymphedema. Recommendations for assessment included volume measurements, pain, function, and skin condition; furthermore, a classification of stage and severity was suggested for clinical decisions on treatment management. It is common to define lymphedema by stages (ISL, 2013). Stage 0 is characterized by a non-noticeable, sub-clinical swelling, in which the limb is at risk because of interference to lymph transport, but no symptoms are evident. In Stage 1, there is swelling that will resolve with elevation of the limb(s) and pressure on the skin (pitting) can leave an indent. In Stage 2 LE, the swelling does not resolve with elevation and the skin may or may not pit under pressure. Stage 3, known as

"elephantiasis," describes a limb which is very large and heavy, with hardening of the tissue, fibrosis, trophic skin changes, possibly leaking fluid, discoloration, and warts. When the other limb is healthy, it is common to classify lymphedema volume by its severity: mild is defined as a volume up to 20% greater than the healthy limb; moderate defines a volume between 20-40% above the healthy limb; and severe describes a volume 40% greater than the healthy limb.

The treatment techniques which were suggested in these documents included skin care, manual lymph drainage, education for self-lymphatic drainage, multi-layer lymphedema bandaging (compression bandaging), "remedial" exercises, Intermittent pneumatic compression, pain management, and psychosocial management. A recent consensus document included lower-level laser therapy, aquatic therapy, and resistance exercises, as well (ISL, 2016). Unfortunately, the level of evidence as to the effectiveness of these techniques is low (even for the more traditional treatments) and combinations of techniques are not studied enough (ISL, 2016; Lasinski et al., 2012). The International Lymphedema Framework recommended a more tailored plan of treatment regarding different classifications of lymphedema (for example, a person with Stage 1 lymphedema, should be treated initially with compression garment); these algorithms are not supported by scientific research, either (ILF, 2006; ILF, 2012). As we do not have published data in Israel on lymphedema prevalence, nor its diagnosis, assessment, and treatment processes, the aim of this manuscript is to describe characteristics of the people who were treated for lymphedema in the physical therapy (PT) department of Maccabi Healthcare Services (Maccabi) between the years of 2010-2017.

Methods

Settings and data source

A retrospective cohort study was conducted in Maccabi, a non-for-profit healthcare organization which according to the National Insurance Institute of Israel covers health for 2,219,638 people, consisting of approximately 25% of the total population of the country (National Insurance Institute [NII], 2017). The data for this study was obtained from the automated databases that are used routinely for gathering information in clinical practice; these include physical therapy database, electronic central medical file system, electronic appointment system, computerized adapting testing (CAT) for functional status (FS) scores (from the Patient Inquiry software developed by Focus on Therapeutic Outcomes, Inc. [FOTO] (Gozalo, Resnik, & Silver, 2016; Swinkels et al., 2008), medication purchases, and chronic disease registries (Chodick et al., 2010).

Dataset description

Patient characteristics on demographic data such as age and gender were retrieved from the medical dataset. Pain levels (rating out of 10 being the most pain experienced), language, and FS scores were retrieved from the FOTO system. Language was documented as the language that was selected for answering the FS survey. FS was examined in routine practice by CAT surveys; with perceived ability transformed to a scale 0-100 (low to high function). Administrative data such as waiting days from physician referral to lymphedema assessment, number of visits per episode, number of clinics and number PTs were retrieved from the physical

therapy dataset. In health data, body part retrieved from the physical therapy data on interventions. If a body part was reported in at least one of the interventions of lymphedema management, it was coded as "present". Moreover, we created six main body parts from the 18 treated body parts, for example: Lower limb included foot, ankle, knee, hip, right lower limb, left lower limb, two legs and a combination with central and general as well) The other five main body parts were: upper limb, head and neck, central, general and combinations of body parts (combinations of upper and lower limb, head and neck with central or with general body parts).

Co-morbidities were collected using computerized patient registries; the data were collected automatically using valid and reliable inclusion criteria (Bash et al., 2017; Chodick et al., 2010; Shalev et al., 2011). Two variables were used: the number of registries documenting a patient, and a dichotomous variable which reported "present," if the patient's identity existed in the following registries: hypertension, obesity, oncology, diabetes, renal insufficiency, blood clot, and chronic heart failure.

Use of medications for chronic conditions was collected from registries on medication purchases at the pharmacies. Two variables were used: the number of medications a patient purchased, and a dichotomous variable which reported "present" if the patient was identified as having purchased one of the following medication groups: cardio vascular, anti-thrombotic, anti-neoplastic, anti-depressant, anti-diabetic, anti-fungal, anti-convulsant, hormone replacement therapy, and anti-Parkinson.

Referring physician diagnoses were collected using the International Classification of Diseases (ICF, 9th edition) and were integrated and recoded into 14 categories by frequency: "lymphedema or swelling," oncology, administrative (such as "fill out forms" or "chronic medication refill" diagnoses), "vascular and ulcers," "overweight or obesity," breast surgeries, pain, trauma, skin infection, diabetes, renal disease, heart disease, lipedema, and other. The category of "other" contained all the diagnoses that were not related to edema or swelling and were less than 1% in frequency: for example, depression, diarrhea, spinal stenosis, vertigo, cough, and more. The variable was dichotomous and received a "present" score if the category existed in at least one out of four options in the electronic medical record (EMR). Specialties of referring physicians were collected from the physical therapy database and were included if the frequency was more than 1% of referrals; specialties with less than 1% were recoded to a variable "other."

Physical therapy assessment and treatment data

PT classifications were collected from the physical therapy dataset. At the end of the lymphedema assessment, the PT chose a classification and/etiology which would best describe the patient's condition. This list was integrated and combined into the most frequent classifications/etiologies: lymphedema stage (0,1,2,3), lymphedema severity (mild, moderate, severe), primary lymphedema, secondary lymphedema, "lymphedema or edema," BCRL, vascular, lipedema, erysipelas, and "other" (for etiologies that were not related to lymphedema). A dichotomous variable was created and a "present" score was given if the classification/etiology was present in at least one out of four options.

Lymphedema treatments were collected from the physical therapy database as dichotomous variables. A "present" score was given if the treatment was documented at least once in an episode. The treatments were: Circumferential measurements, Manual lymphatic drainage, Compression bandaging, Measuring for compression garments, Intermittent compression pump, and Education for self-management (which included education for reducing the risk of developing or exacerbating existing lymphedema, education for self-bandaging, self-massage, self-measurements and education for "remedial" exercises). In an update of the dataset a few years back, there was a technical mistake and a few codes integrated into one; to avoid exclusion of two years of data, we integrated these codes from 2010.

Population description

People with referral for lymphedema assessment were accepted in the physical therapy department in 43 clinics. Discharged episodes with treatment type of lymphatic therapy were included. Excluded were episodes with no visit records, no body parts recorded forlymphatic interventions, home visits, and group therapy episodes.

Data analysis

Proportions of patients with lymphedema treated in Maccabi were calculated using age groups from data from the Maccabi database with the denominator drawn from the Maccabi member's registry which was published at the beginning of 2018 (NII, 2017).

Continuous variables (age, pain, functional status, waiting days from referral to LE assessment) were presented as means (standard deviations [SD]) for normally distributed variables, and median (interquartile range [IQR]) for non-normal distribution variables. ANOVA analysis was used to find differences over the years. Frequency distributions were presented as % (n) and testing differences over the years and Chi-square analysis was used for categorical variables (gender, age groups, body parts, co-morbidities, medication use, physician diagnosis, PT classification and treatments). All analysis was performed by using Statistical Package for Social Sciences (SPSS version 24, SPSS Inc., Chicago, IL, 2018). Approval for this study was granted by the ethics committee of Maccabi institution, followed by a waiver from the University of Missouri Institutional Review Board committee.

Results

Over an 8-year period (2010-2017), 7,173 patients were treated for lymphedema by Maccabi PTs; a proportion of 3.2/1000 was found. We may estimate, based on data available on the number of the population in Israel at the end of 2017 of 8.5 million (NII, 2017), that 27,200 were treated for lymphedema nationally (as all citizens are obliged to be members of one out of four HMO's and lymphedema services are part of the national health insurance entitled to every citizen). The proportion increased with age: 10.9/1000 for 45-65 years old and 18/1000 for 75 or older (Table 8.1) and differs by gender, with 4.9/1000 for women vs 1.6/1000 for men.

For the purpose of description of the population who were treated for lymphedema, we used discharged episodes (and not patients); thus, overall, 6013

episodes were analyzed. Figure 8.1 demonstrates the increase in episode numbers from 10% increase in 2011 to 23% increase in 2017. Eighty-eight PTs documented lymphatic treatments over the years; with 29 treating in 2010, increasing to 46 in 2017. The mean age of the PTs was 43.2 years (SD=10.4). The majority were women (77%) with 7% having a PT qualification certificate, 77% having an education level of bachelor degree, 16% a Master's degree, and mean of 15 years(SD=14.9) of work experience in Maccabi.

The median waiting days from referral of the physician until the assessment in the physical therapy clinics was 22 days (IQR=29) with a mean of 32.1 days (SD=42.7) and increased over the years from 30 to 38 days. The median number of visits per episode was 5 (IQR=8); the mean number of visits per episode was 7.67 (SD=9.5), with 6.4 visits in 2010 increasing to 8.4 visits in 2017. The median number of visits when treating lower limb was 5 visits per episodes (IQR=7) vs 6 for upper limb (IQR=9), with a mean of 6.73 (SD=7.4) vs 9.6 (SD=12.5), respectively.

Table 8.2 demonstrates the demographic and health characteristics of the population. The mean age was 60.1 (SD=14.8) years, with 41% of people above the age of 65. Women received treatment more than men (78.2% vs 22.8%). From the FOTO system (n=2451), Hebrew was the most frequent (27.6%) language, as compared to Russian, English, Arabic and Spanish. Pain level was reported to be 5 (IQR=5), FS score was a mean of 53.2 (SD=12.7) for people who answered the shoulder CAT (n=240) at admission with 64.2 (SD=13.6) at discharge with an effect size of 0.82 between intake and discharge. For those who answered the foot/ankle

CAT (n=519), the mean score at admission was 47.2 (SD=17.3) and 56 (SD=14.7) at discharge, with an effect size of 0.45.

The most frequently treated body part was the lower limb (51%), followed by upper limb (32%), general (11.2%), combination of body parts (4%), head/neck (1.1%), and central body (0.3%). Lower limb and combinations of different body parts increased over the years: upper limb and "general" decreased, with no change in head/ neck and central body (Figure 8.2).

Most patients (80%) were recorded in 2 or more chronic disease registries, with an increase in records of people who were registered in 3 or more registries over the years (from 44% in 2010 to 68% in 2017). The most frequent chronic disease registry was hypertension (51.6%) (which remained stable over the years), followed by obesity (48.8%) (which increased over the years), and oncology (45.8%), which reduced over the years.

Most people (59.3%) took between 1-4 medications for chronic conditions, with 26.3% using more than 5 medications; this group increased over the years (from 20% in 2010 to 27% in 2017). The most frequent medications were cardiovascular (51.4%), followed by anti-thrombotic (36.9%), and anti-neoplastic (26.5%), with an increase of almost all medications over the years (except for anti-diabetic and anti-Parkinson which did not change) (Table 8.2).

The most frequent diagnostic group referred by physicians was "lymphedema or swelling" (54.2%), followed by oncology (17.5%), "vascular and ulcers" (11.2%), administrative (9.9%), pain (6%) and "other" (16%). During the 8-year period,

physicians referred less people with "lymphedema or swelling", oncology, and breast surgery diagnoses, and more with "vascular and ulcers", pain, administrative, and "other" diagnoses. Family physicians were the most frequent (41.4%) to refer, followed by surgeons (16.9%) and orthopedics (7.4%). Over the years there was a decrease of referrals coming from surgeons, and an increase in referrals from family physicians, and especially an increase in referrals with "vascular or ulcer" and "lymphedema or swelling" diagnoses categories, (Table 8.2).

At the end of the examination, the PTs at Maccabi need to decide on classification for treatment plan; the use of lymphedema classifications documented by the PTs is presented in Table 8.3. At the end of the assessment, in 59% of episodes (n=3521), classification of stage was documented, with or without severity. In 29% (n=1736), stage was present without severity. Combinations of both classifications (e.g., Stage 1 and mild LE) were present in 25% of cases (n=1505). In 34% of episodes (n=2043), severity was present with or without stage, and in 9% (n=538), severity was documented without stage. Altogether, in 68% of episodes (n=4059), classification of stage and/or severity was used. The PTs documented etiologies as an addition to classifications or alone, and over the years there was less use of etiologies in the documentation. However, secondary lymphedema as a sole etiology was present in 13.9%, primary lymphedema was present in 1.5%, edema/lymphedema in 8.4%, vascular in 1.4%, lipedema in 1.7%, BCRL in 0.9%, and other etiologies were less frequent.

When examining the classification group of lymphedema stage (n=3521), the most frequent classification was Stage 2 (45% of episodes) followed by Stage 1

(27%), Stage 0 (17%) and Stage 3 (12%). Within the upper limb, Stage 2 was documented in 34% of cases, Stage 1 and Stage 0 were equally represented (32% each), and Stage 3 in only 3% of episodes. In the lower limb, Stage 2 was present in 55% of cases, Stage 1 in 24%, Stage 3 in 17%, and Stage 0 in only 5%. Figure 8.3 demonstrates a reduction in the documentation of Stage 1, an increase in Stage 2 and stability of Stage 0 and Stage 3 over 8 years period. Stage 1 is significantly reduced in both lower and upper extremities. Stage 2 lymphedema didn't change in upper limb; however, it increased significantly in the lower limb (Figures 8.4 and 8.5).

Documentation of treatment for lymphedema: We examined six lymphedema treatment codes (Table 8.4). The most frequently used was Circumferential measurement code (73%), followed by Education for self-management (70%), Manual lymphatic drainage (54%), Measurements for a garment (46%), Compression bandaging (39%), and Intermittent compression pump (5%). Over the years, Manual lymphatic drainage and Compression bandaging codes decreased significantly, Circumferential measurement code reduced slightly, and Education for self-management, Measurements for a garment, and Intermittent compression pump codes increased (Figure 8.6). In 74% of episodes of the lower limb, Circumferential measurement code was documented, while in 46% of lower limb episodes, Compression bandaging was documented; both codes remained stable over the years (Figure 8.7). Manual lymphatic drainage was documented in 65% of upper limb episodes, and 78% of head and neck episodes and remained stable over the years (Figure 8.8). In head and neck episodes, Circumferential measurement, Measurements for a garment, and Compression bandaging codes

were rarely used (6%, 3% and 4%, respectively). In the body part "general," all intervention codes decreased over the years, except for Measurements for a garment which remained stable.

Intervention within stage classifications (elaborated in Appendix 8.1-8.5): Education for self-management was the most frequent in Stage 0 (79%), followed by Stage 1 (76%), Stage 2 (70%), and Stage 3 (64%). Circumferential measurement was used in 73% of Stage 0, 77% of Stage 1, 84% of Stage 2 and 64% of Stage 3. Manual lymphatic drainage was used in 43% of Stage 0, 50% of Stage 1, 52% of Stage 2, and 49% of Stage 3. Measurements for a garment was taken in 34% of Stage 0, 49% of Stage 1, 55% of Stages 2 and 3. Compression bandaging was the most frequent in Stage 3 (67%), followed by Stage 2 (52%), Stage 1 (25%), and Stage 0 (9%). Intermittent compression pump was used only in 2% of Stage 1, and 7% in Stages 2 and 3.

Interventions within different registries (Table 8.5): Documentation of the Circumferential measurement was highly frequent in all registries (69% in hypertension, up to 75% in obese) and was stable over the years. Education for self-management was highly frequent as well, with 66% in the blood clot registry and up to 73% in the oncology registry. Compression bandaging was present in 34% in people who were in the oncology registry and up to 48% in those who were in the nephrology registry, with no change over the years, except for oncology and obese with increase in use. Manual lymphatic drainage was performed mostly for people who were in the oncology registry (61%), with reduction for all registries over the

years, except for the people in blood clot registry. Measuring for a garment was frequent in 44%-50% of episodes, with increasing rates through all registries.

Discussion

Our aim was to describe the characteristics of people who were treated for lymphedema in the physical therapy department of Maccabi between the years of 2010-2017. The proportion of people who were treated in our study was 3.2/1000 and in another study was 2.7/1000 (Moffatt et al., 2017); the higher rates can be explained by the fact that our data are reported on people from birth and include acute stages vs CE, which is defined as edema present for at least 3 months. Furthermore, an overall prevalence estimation of 3.93/1000 for people who live with CE in the UK was found by the researchers (Moffatt et al., 2017). Therefore, we may estimate that the true prevalence of lymphedema in Maccabi and in Israel is higher than 3.2/1000, as our data were gathered only from the databases of people who got treated. The trend of higher prevalence with older age was supported by other studies. The mean age in our study was 60, with a higher proportion of women receiving treatment (77.8% vs 22.2%); these findings were similar to other studies (Maclellan et al., 2015; Moffatt et al., 2017).

There was an increasing number of new episodes every year which can be explained by the increase in the age of the population and older people being more likely to get treated for lymphedema. Furthermore, lymphedema is a chronic condition; people don't get cured in physical therapy and so they come back whenever they experience exacerbation or need further advice. The large increase in the past years may be due to an increase in awareness in the nursing population as

we conducted workshops all over the country, teaching wound care nurses how to use Compression bandaging with venous ulcers. Series of episodes lasted around 30 days with 6-9 sessions; these findings are similar to another study with a mean of 6 weeks with 6 sessions (Tidhar, Hodgson, Shay, & Towers, 2014). These findings support self-management, as treatment by the PT was not delivered every day (Douglass, Graves, & Gordon, 2016).

The majority of people were recorded in two or more chronic disease registries. Almost half (49%) were obese, similar to other study with a frequency of 48% meeting the criteria for obesity (Gutknecht et al., 2017). Being obese is a risk factor for developing or exacerbating lymphedema (Keeley, 2017; Mehrara & Greene, 2014). In Maccabi, over the years, people had more co-morbidities, reaching 85% in more than two registries in 2017. One of the reasons for the increase, beyond the fact that people get sicker and have more chronic diseases as they age, is the development of the registry to be more accurate and detect more people that fit the criteria.

The majority (85.6%) of the people who were treated for lymphedema used medications for chronic conditions, with cardiovascular being the most frequent medication group (51.4%). Amongst the medications used in this group are calcium channel blockers which potentially, depending on the dose and specific drug, may cause peripheral edema at the rate of 5%-70% (Tesar & Armer, 2018). The PTs should be aware of the high rate of medication use and specifically of those which have a side effect that could cause edema or exacerbate pre-existing lymphedema.

Over the years, physicians referred less with oncology diagnoses. An explanation for this trend can be that, historically, lymphedema was related to cancer and, specifically, to breast cancer (Keeley, 2017) and in moving to less invasive surgical procedures, the incidence of lymphedema from these procedures was reduced. To support this argument, we see that over the years, there are less referrals from surgeons (and, specifically, surgeons referring less with breast surgery diagnoses). We do feel that the referrals due to oncological etiologies should increase, as longer follow-up studies reveal higher prevalence of lymphedema ILF, 2006); there are still complications after breast cancer surgeries which need to be addressed; and, finally, more publications on recommendation for surveillance and early detection exist (ISL, 2016; Rafn et al., 2018; Stout et al., 2012).

Lymphedema is considered a painless disease. However, in our study 6% were referred with a diagnosis of pain with increasing rates over the years. People did report pain with a median of 5 (IQR=5) points, similarly to reports by Moffatt et al. (2017) on 50% of the participants who had pain or discomfort with a median of 4.2 (IQR=3.7) points (Moffatt et al., 2003). Administrative and "other" diagnoses categories were in almost third of the referrals; amongst them, 33% were referred as a stand-alone diagnosis (with no other lymphedema diagnosis), with increasing rates over the years. In a study by Maclellan et al. (2015), the proportion of patients who were referred with lymphedema and actually had a true diagnosis was 75%. In another study, the authors explained that lymphedema is overlooked by physicians, as 60% of patients are self-referred for lymphedema assessment (Keo, Gretener, & Staub, 2017). The true medical diagnosis of lymphedema in our study is unknown;

the trend over the years is of more referrals due to other diagnoses, which are not helping with the PT plan of treatment. Without a definite diagnosis of lymphedema, the PT is left to explore differential diagnoses, use of medication, co-morbidities, and every other aspect that could help with planning a safe and effective intervention. Patient self-referral to PT may be a solution for this trend in the future.

In the literature, several studies reported that people who suffer from lymphedema have reported reduced function (Bar Ad et al., 2012; Tiwari, Coriddi, Salani, & Povoski, 2013; Viehoff, Hidding, Heerkens, van Ravensberg, & Neumann, 2013). We examined function with the FOTO system using CAT FS. In our study the level of function of people who answered the shoulder CAT was similar to people with shoulder impairments receiving outpatient rehabilitation (not specifically for lymphatic disorders) in another study (Wang, Hart, Cook, & Mioduski, 2010). At discharge the score in our study was lower, however, reaching a good effect size. With people who answered the foot/ankle CAT, the intake score was similar to the report on people who came for foot/ankle rehabilitation in outpatient clinics (Wang, Hart, Stratford, & Mioduski, 2009). However, on discharge, the effect size in our study was much lower suggesting that the PTs in Maccabi should focus on improving function beyond the improvement in swelling.

Lower limbs were more frequently treated than upper limbs in different studies (Iuchi et al., 2015; Maclellan et al., 2015; Moffatt et al., 2003; Moffatt et al., 2017); these differences were found in our study, as well, with increasing rate of lower extremities over the years. This can be explained by an increase of referrals from family physicians, with an increase of venous and ulcers diagnoses, an

increased rate of people who were in the blood clot registry, and, as mentioned previously, the increase in awareness with the project of community wound care nurses education (Tidhar, Keren, Brandin, Yogev, & Armer, 2017). Upper limb proportions decreased over the years and may be due to the decrease in referrals with breast cancer surgeries, reduction of referrals from surgeons, and reduction in referrals with an oncology diagnoses, and less people who were treated recorded in the oncology registry.

The recommendations for best practice for treating lymphedema are based on the decision about lymphedema classification at the end of the physical therapy examination: skin condition, soft tissue hardening (pitting, Stemmer's sign), stage (response to gravitational changes), and severity (% difference from a healthy limb, if there is one) are all criteria for classification, regardless of the etiology (secondary or primary) (ILF, 2006; ILF, 2012; ISL, 2016). In the majority of episodes in our study, a stage and/or severity classification was used. The fact that a third of the stage classification is documented as a stand-alone classification is expected, as in bilateral lymphedema we don't have a healthy limb for comparison, thus, no severity. We should expect to find severity classification in every stage; however, almost a third of severity classification was documented as a sole classification. Implementation of the rationale of having both stage and severity for decision-making, is still needed, as each adds different information.

Within all classifications, the most frequent was Stage 2, similar to the findings of another study (Iuchi et al., 2015). In Maccabi the frequency of Stage 1 decreased over the years, and Stage 0 and Stage 3 remained the same (in both upper

and lower limb). Stage 2 increased and only in the lower limb; the increased rates of lower limb, the increase in referrals due to vascular/ulcers (which are mostly present in the lower limb), and the increase in awareness through education for nurses may all have contributed to the increase in Stage 2.

Stage 0 was present in third of cases within the upper limb vs only 5% in the lower limb. These differences may be due to the high awareness on surveillance, early detection, and programs for reducing the risk of lymphedema after breast cancer (ISL, 2016; Lacomba et al., 2010; Stout et al., 2012; Todd, Scally, Dodwell, Horgan, & Topping, 2008). Stage 3 was present in only 3% of the upper limb and 17% in the lower limb. These findings emphasize that people who were treated in Maccabi with lower limb had more advanced lymphedema stages (Stage 2 & 3 in 72% of cases) vs upper limb with the majority in early stages (Stage 0 & Stage 1 in 64% of cases).

The most frequent treatment code was Circumferential measurement; there is no description of the usage of this code in the literature. However, in almost every publication on clinical assessment of lymphedema, the recommendations are for using measurements and calculation of volume to assess severity and follow up on the progress, change, or stability of a patient condition (Iuchi et al., 2015; Taylor, Jayasinghe, Koelmeyer, Ung, & Boyages, 2006; Tidhar et al., 2018; Tidhar et al., 2014). Education for self-management was highly frequently used and increased over the years in all aspects; this trend may be due to the increase in knowledge about different types of exercise and different compression devices for self-

management use which may be of benefit to patients with lymphedema (McNeely et al., 2016; Williams, 2016).

Manual lymphatic drainage was present in more than half of episodes in our study, similarly to another study (Iuchi et al., 2015), while only 4% were treated with Manual lymph drainage in a study in the UK (Moffatt et al., 2003). The increasing knowledge about the relatively small contribution of Manual lymph drainage to a total successful outcome of treatment (Gradalski, Ochalek, & Kurpiewska, 2015; Maclellan et al., 2015; McNeely et al., 2004) may explain the reduction of this code over the years. Nevertheless, this code was stable in episodes with head and neck and the upper limb which could be due to the fact that Compression bandaging was not being used in head and neck lymphedema, and in the upper limb, with the majority being early stages (which don't require bandaging) it was used less, leaving more treatment time to spend on Manual lymphatic drainage.

Measuring for a garment was documented in almost half of the episodes; which was lower than what was reported in other studies (64%-82%) (Iuchi et al., 2015; Maclellan et al., 2015; Moffatt et al., 2003). Our data are underestimating the true number of people who got measured for a compression garment since, in some clinics, professional fitters measure instead of the PTs and thus less documentation is made.

Compression is the corner stone of lymphedema management, as recommended by the consensus documents (ILF, 2012; Stéphane Vignes, Porcher, Champagne, & Dupuy, 2006). Compression bandaging was documented in 39% of episodes, higher than what was documented in another study (13%) (Moffatt et al.,

2003). However, in our study, Stage 3 had 67% documentation and Stage 2 had 52%, conforming to the consensus recommendations (ILF, 2012; Vignes et al., 006).(Further examination into stage and intervention is presented in Appendix 8.1-8.5). Measuring for a garment code increased and the use of Compression bandaging decreased over the years. These trends may be related as more options for compression which the PTs are exposed to and use, and which are reimbursed by Maccabi for the patients (e.g., adjustable compression wrap devices) (McNeely et al., 2016; Williams, 2016).

Intermittent compression pump code was documented in 5% in our study compared to 31% use in another report (Maclellan et al., 2015). Till today, we have only 11 devices in Maccabi; therefore, the true potential of the use of this code is unknown. Furthermore, the Intermittent compression pump code increased over the years in both upper and lower limb, as new devices are purchased every year; this fact could be related to the increased number of studies finding it to be effective and safe (Feldman et al., 2012; Gurdal et al., 2012).

PTs used mostly lymphedema classification to describe their patients' conditions at the end of assessment, as being recommended in the literature. There were more advanced stages in lymphedema of the lower extremities than the upper extremities, with increasing rates of lower extremities. The most frequent classification was Stage 2, with increasing rates over the years. The most frequently used treatment codes were Circumferential measurements and Education for self-management in all classifications. Manual lymphatic drainage was frequently used more often in lymphedema Stage 1 and 2. Compression bandaging was more

frequently used in advanced stages than early stages. Measurement for a garment was highly used and increasing in all classifications. These findings are consistent with the recommendations in the literature

The data on FS, pain and language were available on 33% of our study population, and discharge scores of FS were available on 33% of these; therefore, these pose a problem of selection bias. The true prevalence of lymphedema cannot be calculated, as no knowledge regarding the reliability and consistency of documentation of medical diagnoses by the physicians exists and thus the true frequency of lymphedema is unknown. Finally, the integration of all educational codes into one code (Education for self-management) caused the loss of detailed information.

In the literature, there are conflicting recommendations or no recommendations at all regarding the treatment of people with lymphedema who have co-morbidities. For example, people who suffer from chronic heart failure (CHF) are usually excluded from studies; thus, no recommendation as how to treat lymphedema with heart disease is given (ISL, 2016). In contrast, the use of Manual lymph drainage was contraindicated in one document (ILF, 2006), while in another study was found to be safe in cardiac patients (Leduc et al., 2011). Furthermore, in a consensus document, the use of Compression bandaging was contraindicated in acute CHF (ILF, 2012), while in another study, avoiding Compression bandaging was recommended for stable cardiac patients (Wilputte et al., 2005). In our study population, 85% of patients had co-morbidities; the PTs were treating people with cardiovascular, nephrotic, blood clot, and diabetes diseases with Compression

bandaging and over the years did not reduce the use of this code. There are obviously risks in treating people with hemodynamic instabilities and the PTs who treat these people need to be aware and be educated about these risks.

Conclusion

Most people treated for lymphedema had more than two co-morbidities and took between one and four medications for chronic conditions with increasing rates over the years. Moreover, there was an increase in the referrals with administrative and other diagnoses from physicians which do not add information regarding the precautions the PT need to pay attention to when treating people with co-morbidities and high medication usage. This therefore strengthens a recommendation for patient self-referral in the PT department. Nevertheless, there is a need for physician education, as well as the collaboration of a multidisciplinary team to promote a safe and effective treatment plan.

To understand better what the consequences of these findings are, and whether these trends lead to better outcomes, a longitudinal observation study needs to be performed to examine associations between treatment-related variables, and limb volume and functional change in patients with lymphedema. Finally, all this data should be reflected back to the physical therapists so discussions may be carried out regarding the different trends that were observed; knowing where we are and what are the tendencies may increase the need to develop new programs, new interventions, and demand for research.

Table 8.1: An Accumulative Frequency of Number of Patients Over an 8 Year Period (2010-2017) who were Treated for Lymphatic Disorders in Maccabi Physical Therapy Clinics by Age Groups (N=7173)

Age groups	Maccabi members in 2017	People treated in PT	frequency
<15	604,383	28	0.005%
15-45	873,992	1050	0.12%
45-65	501,550	2834	0.57%
65-75	501,245	1645	1.09%
75+	89,713	1616	1.80%
Total	2,219,638	7173	0.32%

Figure 8.1: Description of the Lymphatic Discharged Episodes over the Years 2010-2017 (with the Difference in % From the Last Year) (N=6013)

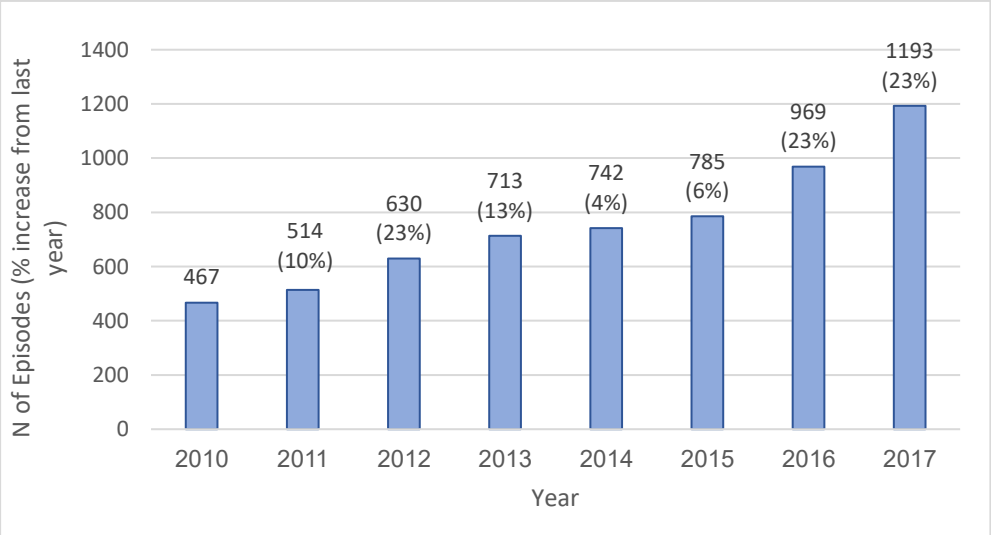


Table 8.2: Patient's Characteristics (N=6013)

Demographics		
Characteristic	Categories	%(n) / Mean(SD)
Age by groups, % (n)	0 to <18	0.6 (48)
	18 to <45	15.1 (1156)
	45 to <65	43.1 (3304)
	65 to <75	24.2 (1855)
	75 to highest	17.0 (1273)
Age, Mean, SD		60.1 (14.8)
Gender, % (n)	Female	77.8 (4681)
	Male	22.2 (1332)
Language selected for functional status PROM* % (n)	Hebrew	27.6 (2119)
	Russian	6.9 (533)
	English	1.4 (109)
	Arabic	0.7 (56)
	Spanish	0.3 (23)
	Missing	63 (4830)
Health Characteristics		
Body Part Treated, % (n)	Lower Extremity	51 (3122)
	Upper Extremity	32 (1873)
	Head AND Neck	1.1 (69)
	Central	0.3 (16)
	General	11.2 (671)
	Combination	4 (262)
Pain Level*, Median, IQR		5 (5)

Functional Status at Admission*, Mean, SD		48.6 (16)
Co-morbidities Presented as Chronic Disease Registries Count per Patient, % (n)	0 to 1 registries	20.6 (1240)
	2 registries	23.7 (1427)
	more than 3 registries	55.6 (3346)
Specific Disease Registry, % (n)	Hypertension	51.6 (3104)
	Obese	48.8 (2936)
	Oncology	45.8 (2751)
	Cardio-Vascular	22.8 (1372)
	Renal insufficiency	22.1 (1327)
	Diabetes	22 (1321)
	Blood clot	5.1 (306)
Total Number of Medications for Chronic Conditions % (n)	No chronic medication use	14.4 (868)
	1 to 4 medication use	59.3 (3563)
	5 and more medication use	26.3 (1582)
Medication Group % (n)	Cardio Vascular	51.4 (3091)
	Anti-Thrombotic	36.9 (2216)
	Anti-Neoplastic	26.5 (1595)
	Anti-Depressant	23.5 (1411)
	Anti-Diabetic	15.7 (946)

	Anti-Fungal	10.5 (631)
	Anti-Convulsant	10.5 (634)
	Hormone Replacement Therapy	4.3 (256)
	Anti-Parkinson	1.7 (105)
Referring Physician Diagnosis		
Diagnosis		At least %(n)
Lymphedema OR Swelling		54.2 (3260)
Oncology		17.5 (1054)
Vascular or Ulcers		11.2 (676)
Overweight or Obesity		10.4 (625)
Administrative		9.9 (596)
Breast Surgeries		6.4 (387)
Pain		6.3 (379)
Trauma		4 (238)
Skin Infection		3.2 (194)
Diabetes		2.4 (143)
Renal Diseases		0.3 (17)
Heart Disease		0.2 (11)
Lipedema		0.2 (14)
Other		18.2 (1092)
Specialties of the Referring Physician		
Family / internal medicine		41.4 (2487)
Surgery		16.9 (1014)
Orthopedics		7.4 (445)
Administrative		5.0 (300)

Traumatology	3.5 (208)
Pediatric	1.5 (90)
Other**	6.0 (340)
Missing	18.8 (1129)

Note. * frequency of less than 1%, ** Note: data were retrieved from a system of patient reported outcome measures (PROM) which had 2807 participants; SD Standard deviation, IQR inter-quartile range.

Table 8.3: Lymphedema Classification of Discharged Episodes for Decision on Treatment Plan (N=6013)

Classification of LE			
Stage	**Severity**	**n**	**%**
Stage 0	No severity	455	7.6%
	Mild	125	2.1%
	Moderate	1	0.0%
Stage 1	No severity	418	7.0%
	Mild	470	7.8%
	Moderate	44	0.7%
	Severe	3	0.0%
Stage 2	No severity	863	14.4%
	Mild	449	7.5%
	Moderate	229	3.8%
	Severe	51	0.8%
Stage 3	No severity	280	4.7%
	Mild	26	0.4%
	Moderate	43	0.7%
	Severe	64	1.1%
No staging	Mild	361	6.0%
	Moderate	113	1.9%
	Severe	64	1.1%

No Classifications of LE*			
Lipedema alone		105	1.7%
Edema alone		503	8.4%
Other alone or in combinations with each other		1346	22.4%

Note. *Include etiologies which are not used for treatment plan

Figure 8.2: Areas of Body Treated for Lymphedema over the Years (%) (N=6013)

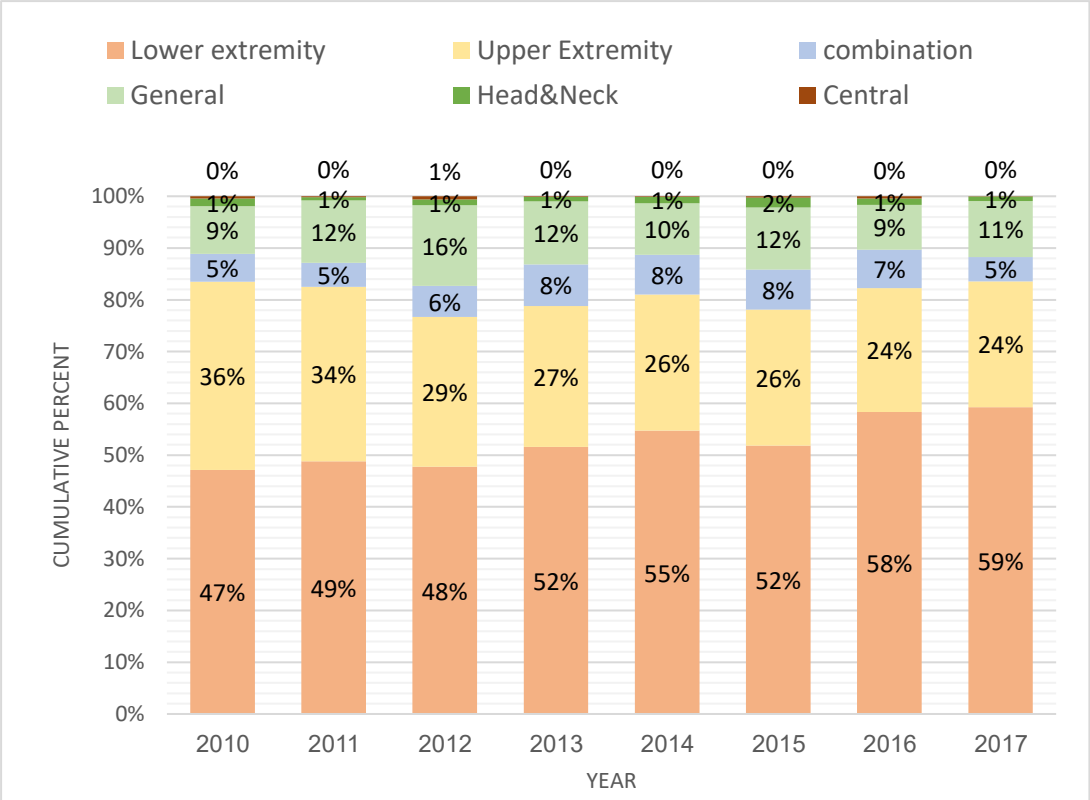


Figure 8.3: Stages of Lymphedema over the Years (%) (N=3521)

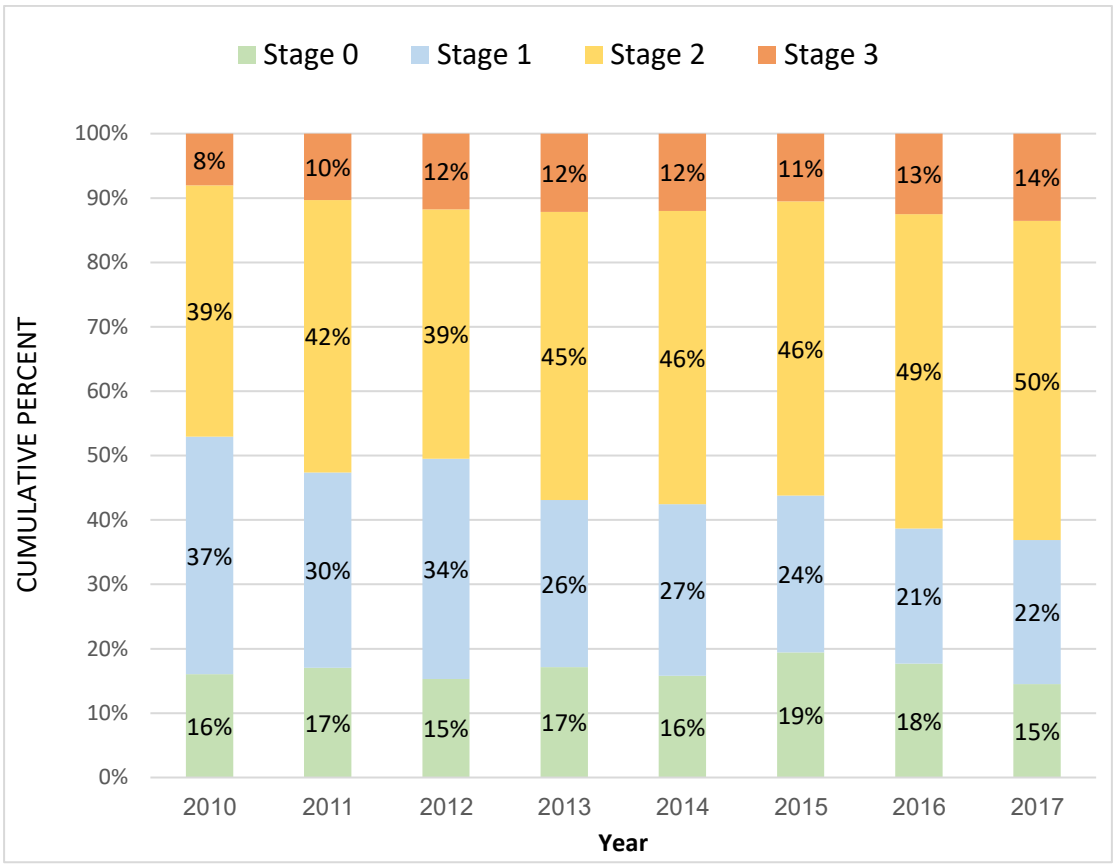
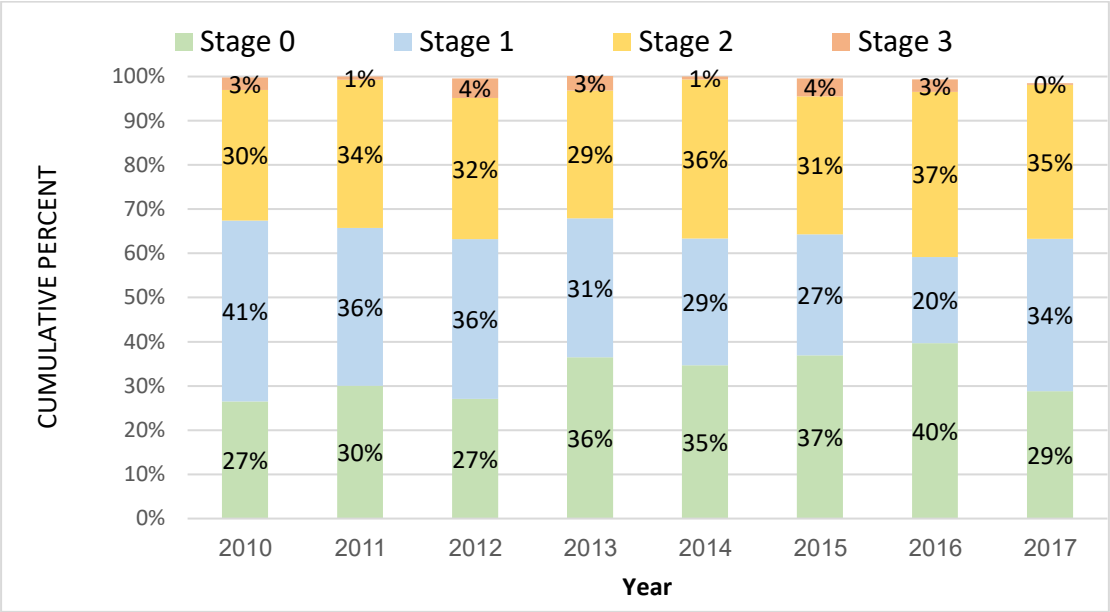
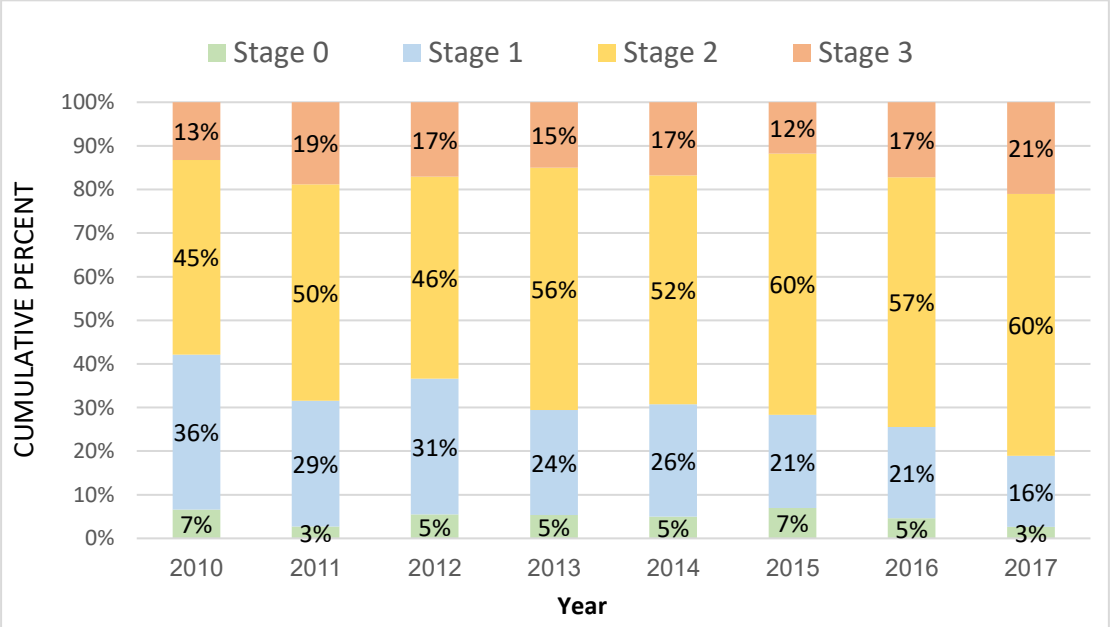


Figure 8.4: Different Stages of Lymphedema within the Upper Extremity of Discharged Episodes over the Years (N=1274*)



Note. *Upper extremity with classification of stage

Figure 8.5: Different Stages of Lymphedema Within the Lower Extremity Over the Years of Discharged Episodes (N=1676*)



Note. *lower extremity with a classification of stage

Table 8.4: Treatment Codes for Lymphedema Managements Presented by Different Body Parts Treated (N=6013)

Intervention	Lower extremity (n=3122)	Upper extremity (n=1873)	Head and neck (n=69)	Central (n=16)	General (n=671)	Combin-ation (n=262)	Total
Circumferential measurements	74% (2304)	77% (1450)	6 % (4)	25% (4)	60% (403)	85% (222)	73% (4387)
Education for Self-Management	69% (2145)	75% (1407)	59% (41)	44% (7)	55% (367)	89% (234)	70% (4201)
Manual Lymph Drainage	47% (1479)	65% (1226)	78% (54)	81% (13)	41% (274)	69% (182)	54% (3228)
Measurement for a Garment	49% (1533)	44% (826)	3% (2)	38% (6)	32% (217)	66% (173)	46% (2757)
Compression Bandaging	46% (1424)	32% (600)	4% (3)	13% (2)	28% (189)	55% (144)	39% (2362)
Intermittent compression pump	8% (247)	2% (42)	1% (1)	0% (0)	2% (13)	5% (14)	5% (317)

Note. Percentage out of the total n in each category; Combinations- treatment of different body parts together;

Figure 8.6: Documentation of Treatment Codes over Time (%) (N=6013)

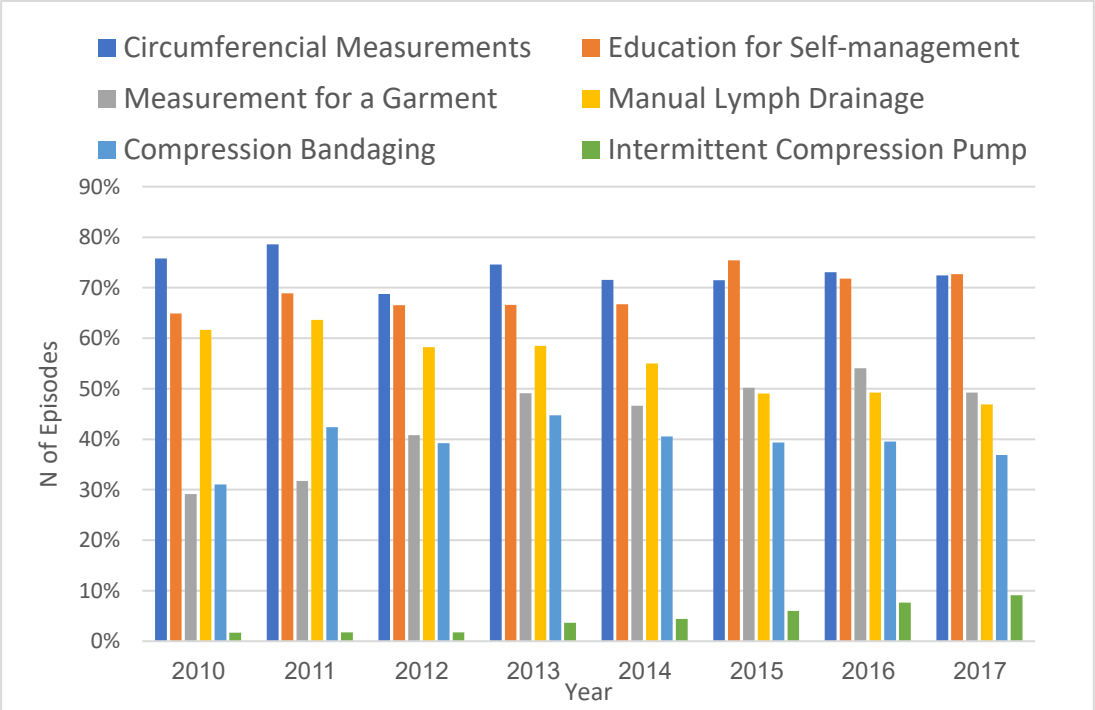


Figure 8.7: Documentation of Treatment Codes over The Years in the Management of the Lower Extremity (n=3122)

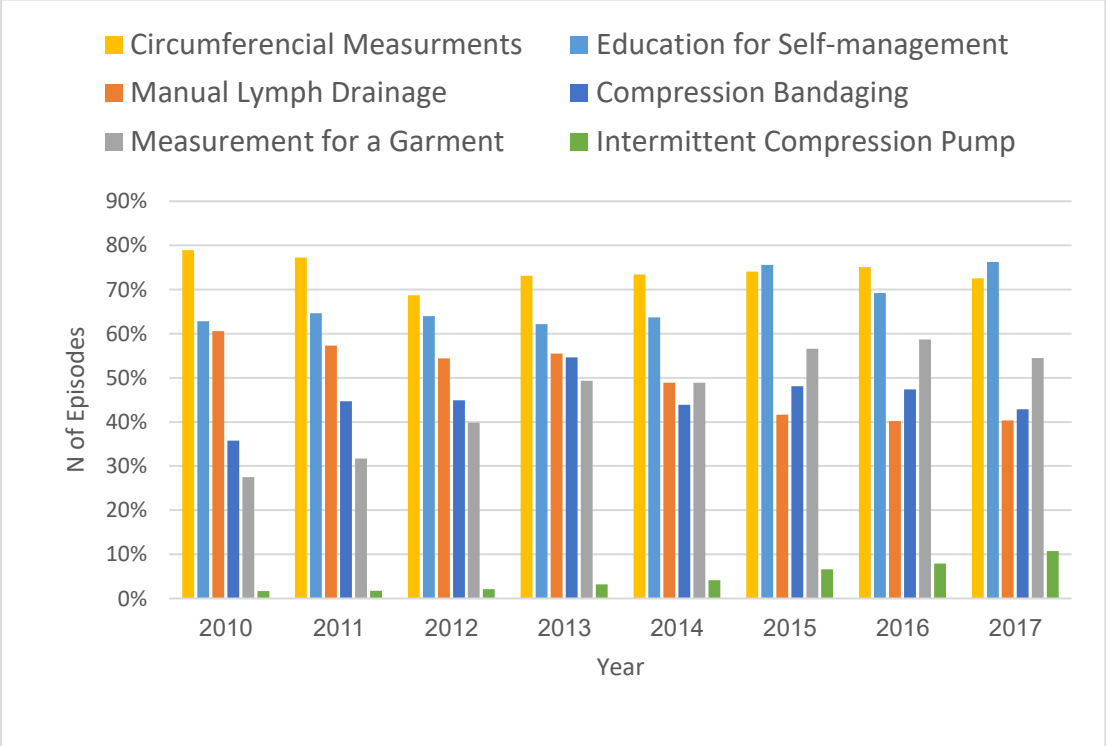


Figure 8.8: Documentation of Treatment Codes over The Years in the Management of the Upper Extremity (n=1873)

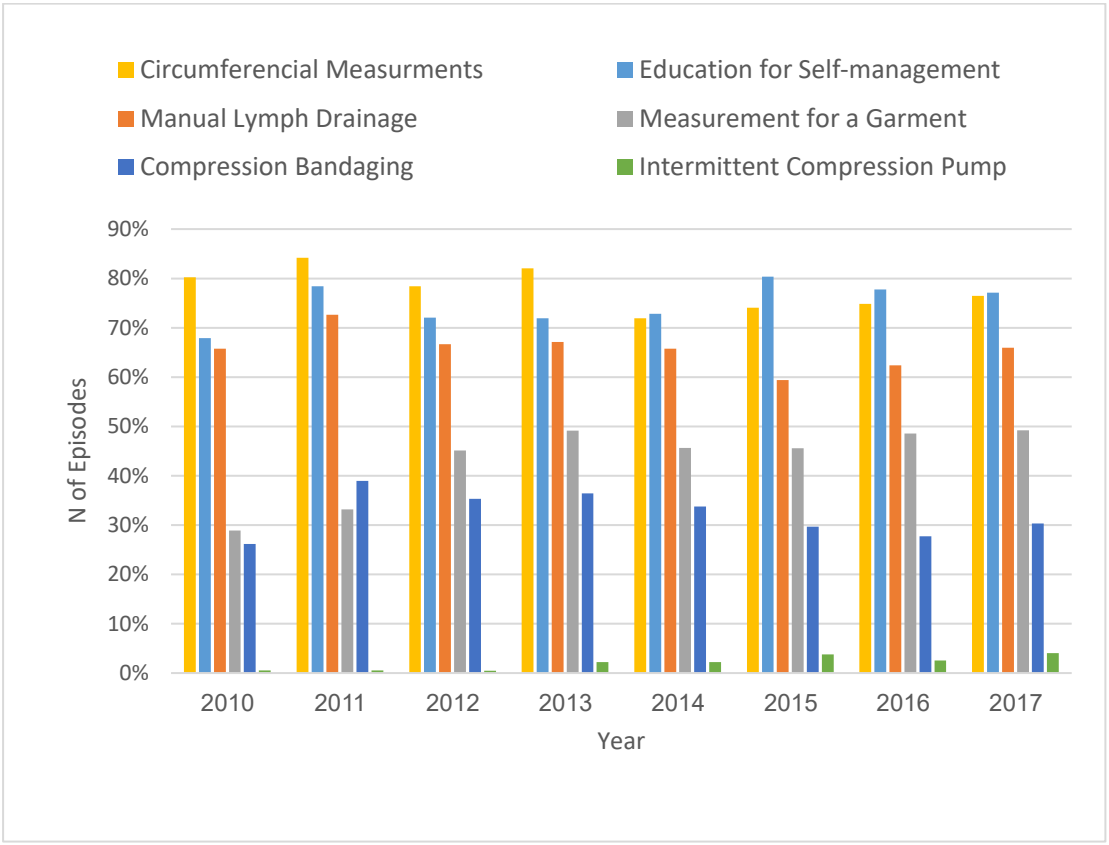


Table 8.5: Treatment Codes for Lymphedema Managements Presented by Different Co-morbidities (N=6013)

Intervention	Cardio-vascular (n=1372)	Nephrology (n=1327)	Oncology (n=2751)	Blood clot (n=306)	Obese (n=2936)	Diabetes (n=1321)	Hypertension (n=3104)
Circumferential Measurements	71% (971)	73%% (963)	74% (2022)	73% (223)	75% (2210)	73% (965)	69% (2144)
Education for Self-Management	67% (924)	69% (918)	73% (1995)	66% (202)	69% (2027)	67% (882)	70% (2712)
Manual Lymph Drainage	48% (664)	51% (677)	61% (1688)	48% (147)	50% (1467)	51% (60)	51% (1572)
Measurement for a Garment	46% (627)	49% (645)	44% (1224)	50% (152)	49% (1446)	49% (645)	48% (1493)
Compression Bandaging	45% (618)	48% (635)	34% (936)	51% (155)	46% (1344)	47% (617)	45% (1395)
Intermittent Compression pump	5% (75)	6% (78)	3% (95)	5% (16)	6% (189)	5% (65)	6.0% (176)

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Appendix 8.1

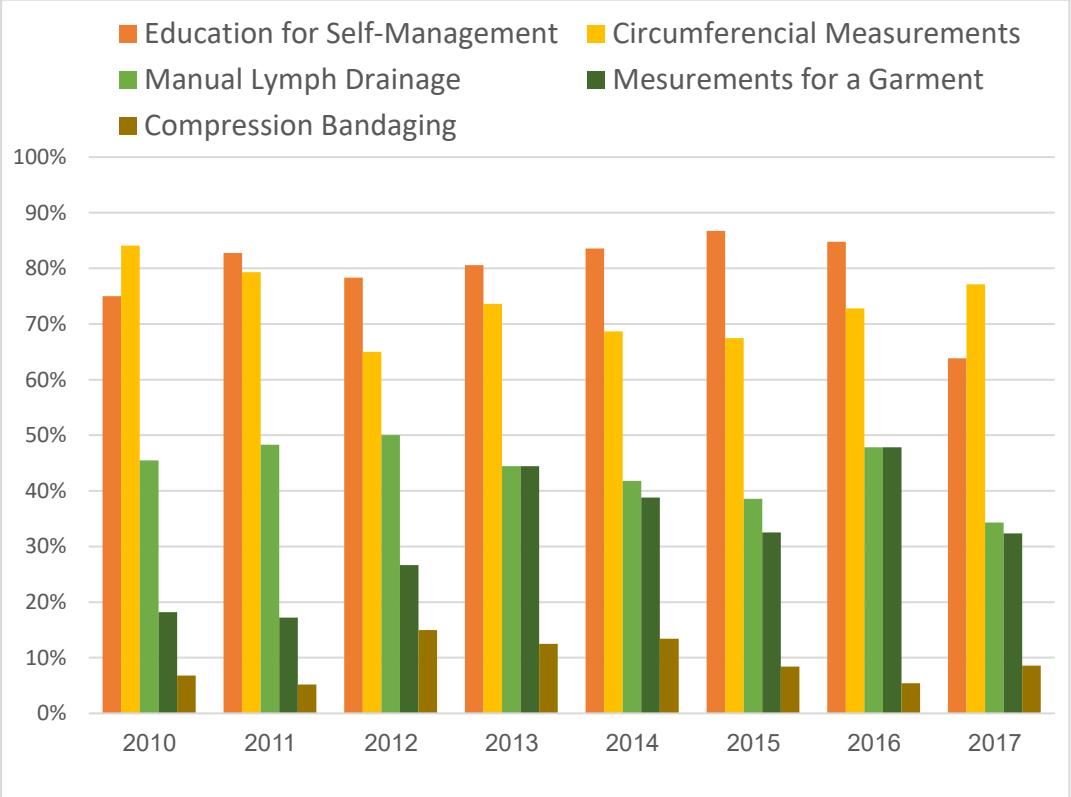
Treatment Interventions in Different Classifications of Lymphedema Presented in Percentages (N=6013)

Intervention	Stage 0 (n=581)	Stage 1 (n=935)	Stage 2 (n=1592)	Stage 3 (n=413)	Other (n=2492)	Total
Circumferential Measurements	73% (425)	77% (719)	84% (1343)	78% (323)	63% (1577)	73% (4387)
Education for Self-Management*	79% (459)	76% (712)	70% (1118)	64% (263)	66% (1649)	70% (4201)
Manual Lymph Drainage	43% (250)	50% (464)	58% (919)	49% (204)	56% (1391)	54% (3228)
Measurement for a Garment	34% (197)	49% (454)	55% (883)	55% (226)	40% (997)	46% (2757)
Compression Bandaging	9% (54)	25% (233)	52% (830)	67% (278)	39% (967)	39% (2362)
Intermittent Compression Pump	0.1% (1)	2% (20)	7% (114)	7% (29)	6% (153)	5% (317)

Note: Percentage out of the total n in each category.

Appendix 8.2

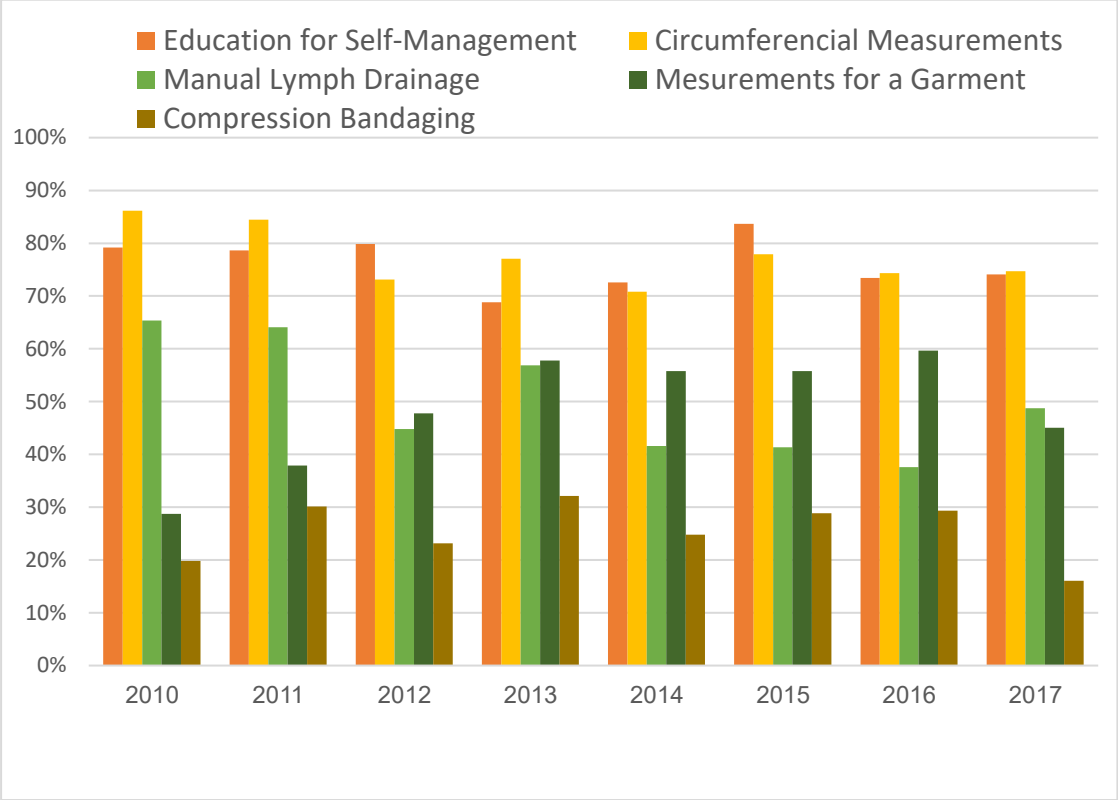
Lymphedema Management in Stage Zero Over the Years (n=581)



In Stage 0, the most frequent code used was Education for self-management (79%). This was followed by Circumferential measurements (73%), Manual lymph drainage in 43%, and Measurement for a garment (34%); In some episodes (9%), there was use of Compression bandaging code. Over the years, although overall Circumferential measurements, Manual lymph drainage, and Compression bandaging code documentations were declining, in Stage 0 they remained stable.

Appendix 8.3

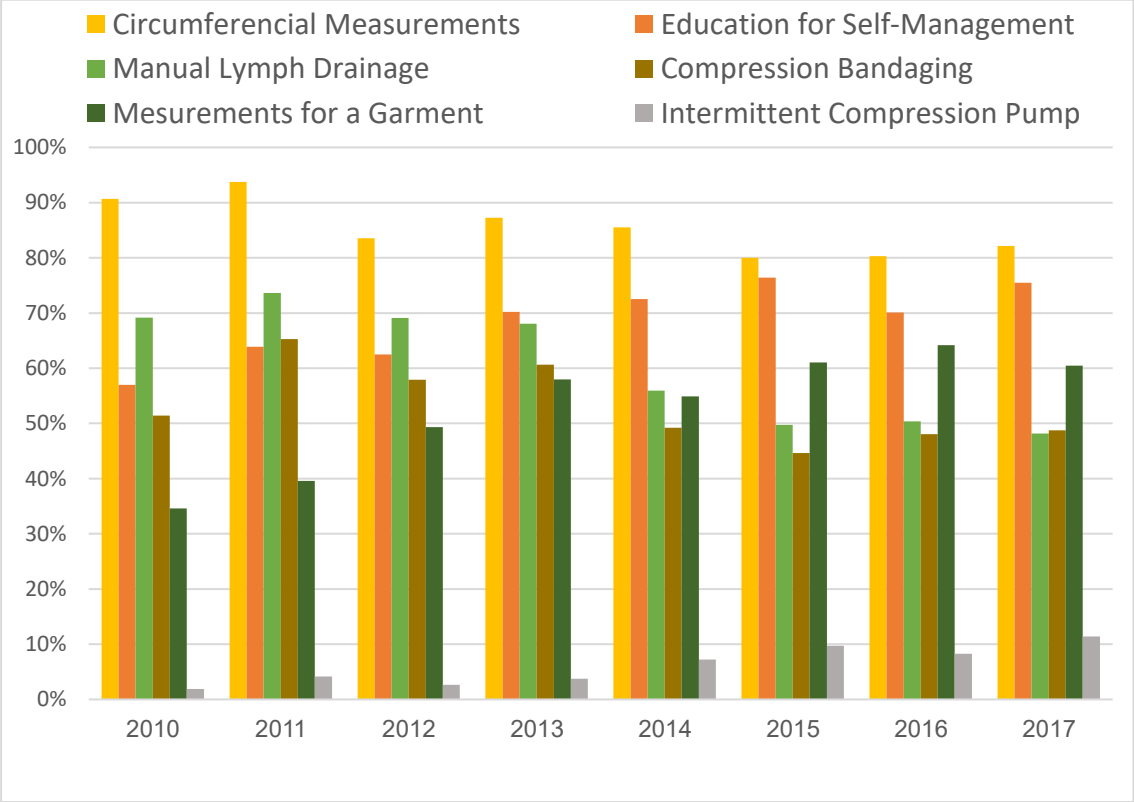
Lymphedema Management in Stage One Over the Years (n=1006)



In Stage 1, the frequency of code documentation was Circumferential measurements (77%), Education for self-management (76%), Manual lymph drainage (50%), Measurement for a garment (49%), Compression bandaging (25%), and Intermittent compression pump (2%). Over the years, although there was overall increase in Education for self-management and decrease in Compression bandaging with classification of Stage 1, the use of these codes didn't change.

Appendix 8.4

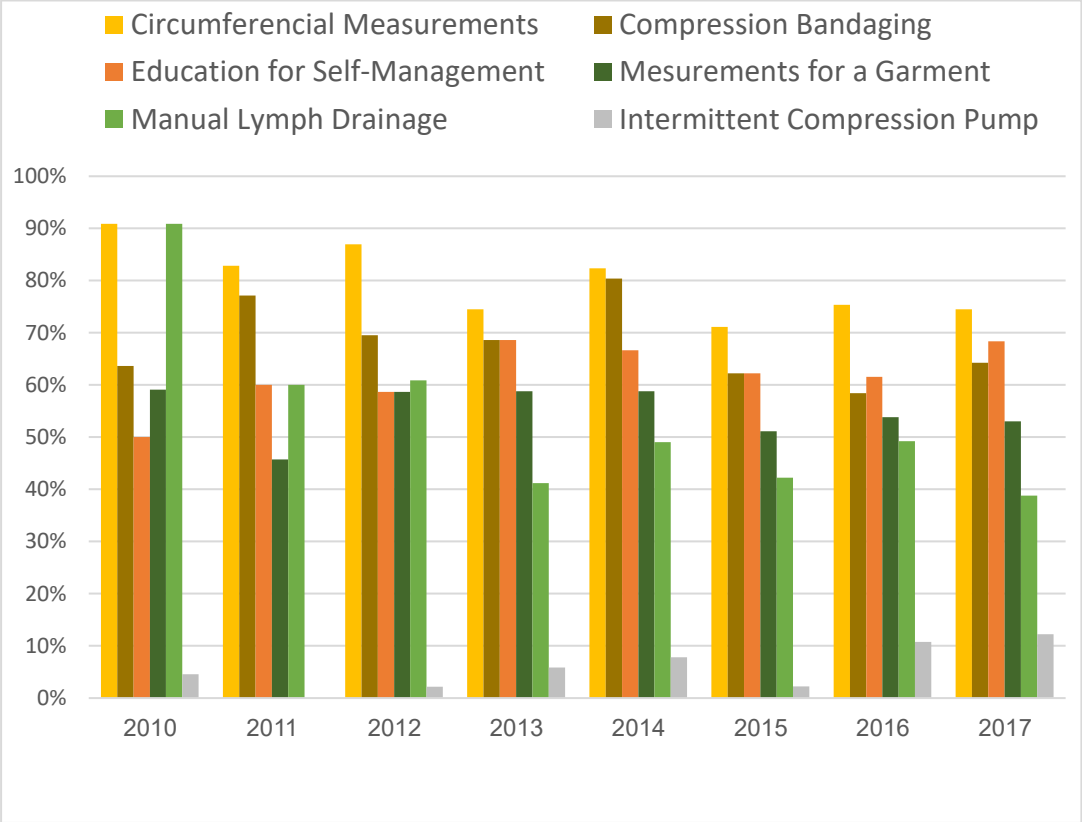
Lymphedema Management in Stage Two Over the Years (n=1592)



In Stage 2, the most frequently documented code was Circumferential measurements (84%), followed by Education for self-management (70%), Manual lymph drainage (58%), Measurement for a garment (55%), Compression bandaging (52%), and Intermittent compression pump (7%). Over the years, there was less use of the code for Circumferential measurements.

Appendix 8.5

Lymphedema Management in Stage Three Over the Years (n=413)



In Stage 3, the Circumferential measurements code was used in 78% of episodes, Compression bandaging in 67% of episodes, Education for self-management in 64%, Measurement for a garment in 55%, Manual lymph drainage in 49%, and Intermittent compression pump in 7% of cases. Over the years, although overall the use of Circumferential measurements and Compression bandaging was declining and the use of Measurement for a garment and Intermittent compression pump was increasing, the documentation of these codes in Stage 3 remained stable.

CHAPTER NINE: DISCUSSION

This dissertation covered the topic of practice-based evidence (PBE) research design in lymphedema management. After an introduction to lymphedema (Chapter 1), the next two chapters were: a published manuscript that discussed meaningful outcomes in lymphedema management (Chapter 2); and an introduction to the principles of the PBE, the theoretical framework, and the aims of the dissertation (Chapter 3). These aims were: 1) To describe the treatment code documentation as part of the PBE process and to evaluate the accuracy of treatment code documentation by LPTs in Maccabi; 2) To examine the known-group construct validity of functional status scores in patients with lymphedema treated at Maccabi; and 3) To describe characteristics of the patients with lymphedema treated at Maccabi between the years of 2010-2017. Chapter 4 was a published book chapter describing the assessment and examination of patients with lymphedema. Chapter 5 was a published manuscript with findings presented from a preliminary study in which measurement error was calculated for intra-rater reliability of physical therapists' assessment of patient circumferences. Addressing Aim 1, the PBE process was described in a submitted manuscript (Chapter 6) on code documentation with high accuracy in selecting treatment codes from a set of 35 activities and interventions. Codes which had lower scores than 90% were identified, redundant code was extracted, and a replacement new code was inserted instead. In another submitted manuscript, addressing Aim 2 (Chapter 7), the known-group construct validity test found that the computerized adaptive testing (CAT) of functional status (FS) scores was able to distinguish between known groups in trends that were clinically logical. Finally, Chapter 8, a submitted manuscript addressing Aim 3,

described the population with lymphedema, summarizing demographic, health, and treatment characteristics with trends over the years.

The physical therapists' involvement in the PBE process, from inception through the development of the lymphedema module within the Maccabi electronic medical record (EMR), was crucial, culminating in participation in the reliability study for measurements and accuracy testing for documentation of treatment codes. Even though the CAT FS was not validated specifically for patients with lymphedema, one-third of the physical therapists agreed to try and use it, enabling testing of the CAT FS for known-group construct validity.

The Maccabi EMR lymphedema module is being used in routine practice. After the reported tests, we can rely on the accuracy of treatment code documentation; however, we cannot know for a fact that the physical therapists are using these codes accurately in real-life with patients. Ways to deal with this challenge may be through: (1) educational sessions with discussions on real patients (with the EMR records); (2) developing workshops with scenarios in which therapists share patients' care and review the regime the last therapists used (e.g., if a therapists documented "compression bandaging" as an activity without describing the interventions within that activity [mild pressure, bandage up to the knee], do the records enable continuum of care?); (3) improving the technological capabilities of the EMR to connect activity codes to the associated interventions; and (4) developing reports that will provide data on the use of the different codes. Moreover, we would be able to reflect results back to the therapists, and

demonstrate the additive value of the content, where we did have detailed information.

Function and volume are the main outcome of lymphedema management. Unfortunately, for this dissertation, the Maccabi EMR data on volume outcome were not ready for use, and the CAT FS participation rates were low, leaving the research on the association between treatment interventions and outcomes, while controlling for patient characteristics, for a future study. This will become a post-doctoral study examining newly-available volume data. The challenges will be to improve the implementation of CAT FS use. We need to be aware that the low participation rate could be related to several reasons. It may be related to the beliefs of the physical therapists about the low sensitivity of the tool, as we saw that the effect size of the foot and ankle CAT FS at discharge was not high (no major functional improvement). Another explanation for the low improvement could be that the focus of treatment was to reduce swelling which does not necessarily cause a functional improvement response (Keeley et al., 2010). In either case, the low participation rate does not enable us to explore further, and, as the results of the known-group validity support the use of the CAT FS, we can now reflect these results to the therapists in an effort to reduce barriers (Deutscher et al., 2008), improve implementation, increase participation rates, and shift focus to function as a higher goal, beyond swelling reduction.

The description of the population who had lymphedema revealed interesting trends which may already help to re-enforce existing approaches and highlight others, as well as guide future research. The higher rate of the use of circumferential

measurement codes indicates that physical therapists consistently measure for assessment during treatment to detect change and to look for stability. However, over the years, there has been a slight decrease in use of circumferential measurements code. As this is a powerful implemented clinical tool for assessing swelling, we need to tackle this trend, either by reinforcing the therapists through positive feedback on its use, or through reflection of results from a PBE study (not yet conducted) that will show results of volume change with different interventions for different patient groups. A PBE process to try to capture the actual process of care is recommended; until we have results related to the associations between interventions and outcomes, only observations on the trends can be made.

Lymphedema classifications were used in the majority of Maccabi episodes, which has been supported by the lymphedema consensus documents over the years. However, the validation of these classification systems by the Maccabi physical therapists is lacking and this gap may be a problem in interpreting results from a PBE study. A way to overcome this challenge may be to compare correlations between the different severities (mild, moderate, and severe) and calculated EMR volume, as severity classification should be derived from the relative volume difference between limbs.

Moreover, reduction in referrals with oncology diagnoses is a trend that needs to be addressed. We need to increase awareness about lymphedema risk with the population who has cancer.

As the referrals from physicians with "lymphedema or edema" diagnoses decreased and referrals with "administrative" or "other" increased over the years,

leaving us with no reliable medical diagnosis of lymphedema and non-relevant information for planning a safe and effective intervention, educating physicians regarding the diagnosis of lymphedema is warranted. However, direct access to lymphedema assessment within the physical therapy department should also be created and encouraged. Lymphedema management should be a multidisciplinary work with each discipline contributing to the plan and management of care. The physical therapist plans the management according to the classification of lymphedema, amongst other factors; information regarding differential diagnoses, co-morbidities, and medication use is essential for a safe and effective program.

Communicating the results of the studies back to the physical therapists is the next step: discussing trends, frequencies, and scores; and leaving each physical therapist with the knowledge of what was found and the decision of whether they would like to change their practices accordingly. PBE is an on-going process which will not end, as we want to improve the care for our patients; the more detailed information we gather, the more the possibility of finding unique trends and associations which would otherwise not surface.

Finally, I find this dissertation to be a big step forward in the right direction, offering wide knowledge on different aspects of lymphedema. My patients often have lower limb swelling; chronic conditions, requiring multiple medications; personal problems; functional difficulties; and lots many other barriers to adherence to participate in a very demanding treatment plan. The knowledge that currently exist is often based on breast cancer-related lymphedema and rigorous studies often exclude patients with other conditions, leaving me and my colleagues with a lack of

information as how to treat our patients. I hope these dissertation findings will increase the awareness to the need for a wider knowledge in the field of lymphology and lymphedema management.

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2. Tidhar, D., Armer, J., M. , Deutscher, D., Shyu, C., Azuri, J., & Madsen, R. (2015). Measurement Issues in Anthropometric Measures of Limb Volume Change in Persons at Risk for and Living with Lymphedema: A Reliability Study. *Journal of personalized medicine, 5*(4), 341-353. doi:10.3390/jpm5040341

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INTERNATIONAL LYMPHOEDEMA FRAMEWORK

VITA

Dorit Tidhar was born and raised in central Israel. She received her B.PT from the Faculty of Health Sciences, Ben-Gurion University of the Negev (Israel), in 1997. Her MScPT was earned from the physical therapy department of Tel-Aviv University, Tel Aviv (Israel) in 2007. She has been a physical therapist since 1997. She was certified in the treatment of lymphedema by Prof. Casley-Smith in 1999 and has been a lymphedema therapist since then. She was certified by Prof. Casley-Smith as a teacher in Self-management and Exercise for Lymphedema in 2003. Dorit designed a program of Aqua Lymphatic Therapy to help people who suffer from lymphedema maintain and improve the results of conventional treatment. She has been working in Maccabi Healthcare Services since 1997 as a physical therapist and as the national coordinator of lymphedema therapy services since 2009. Dorit lives in Klachim (a small village in the south of Israel) with her husband, Avi, and their three daughters.