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Lymphoedema and Complex Decongestive Therapy: data analysis and economical aspects

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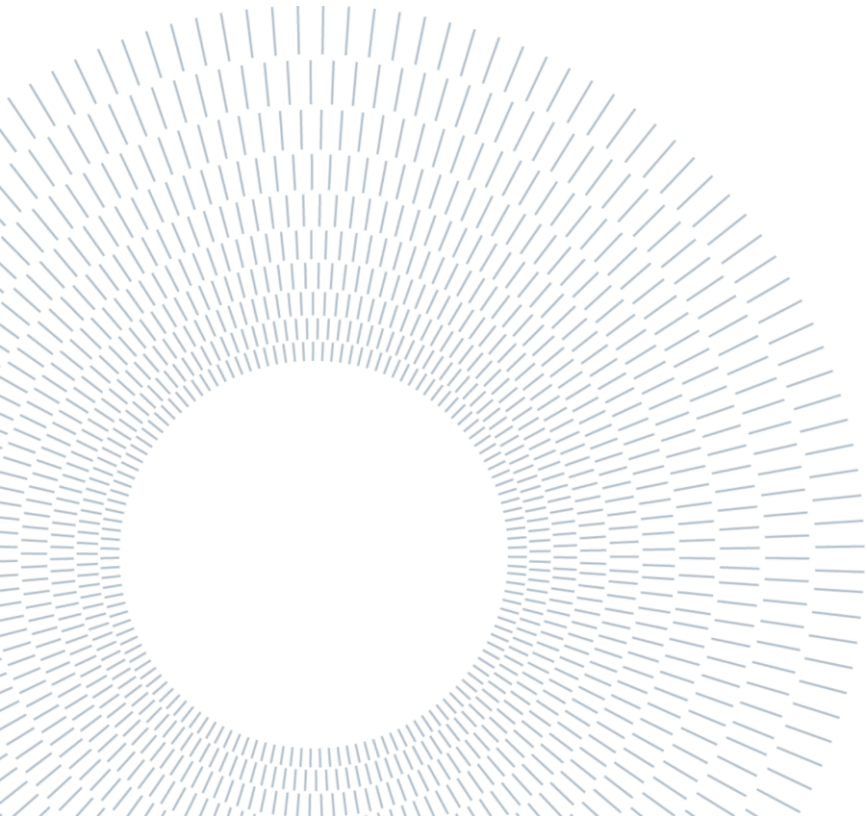

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My achievements are also yours.

Abstract

Lymphoedema is a chronic and degenerative disease caused by a partial inability to transport lymph. It differentiates into primary (genetic) and secondary (related to other diseases) and provokes an increase in volume of the affected limb (oedema). The treatment of lymphoedema, according to the guidelines, involves the application of Complex Decongestive Therapy in which circumferential measurements are taken on eight points in order to assess the progress of the oedema. Among the several techniques proposed in the literature, the so-called segmental technique was used in the study which, by identifying the eight points in a constant and proportional manner, allows comparison between subjects with different dysmorphic conditions.

A database containing data from 74 patients (38 lower and 36 upper) treated at the Istituto Clinico Città Studi in Milan was developed. Using statistical mixed-effects models, the variation of the edematous limb before and after treatment was quantitatively assessed in comparison to the healthy contralateral limb, showing how the oedema was distributed along the limb. Subsequently, centimetric measurements of the circumferences of the eight points were compared to study the efficacy induced by the treatment. The data were then re-analyzed by subdividing the patients according to clinical classifications such as etiology (primary and secondary), entity of lymphoedema (mild, moderate and severe), tissue consistency (soft, medium and hard) and dysmorphic pattern (LA1 and LA2).

The results of this thesis show that all points reported statistically significant differences (p-value < 0.05) between pre and post-treatment, resulting in a reduction, on average 7%, of the volume of the edematous limb even in the most compromised patients. In particular, the analysis revealed that lymph stagnation occurs at points B1 and C1, and it would therefore be advisable to pay more attention to them during the intensive phase of treatment. Moreover, for effective treatment it is not convenient to classify patients according to etiology and dysmorphic pattern, and the two entities, mild and moderate, being comparable, could be grouped into a single entity.

Through the implementation of an algorithm, the number of standard and custom-made braces to be prescribed to patients at the end of treatment and their costs were estimated. The custom-made brace was assigned to 89% of patients (37.6% primary and 62.4% secondary) and 96% (all secondary) with lower and upper limb lymphoedema, respectively. According to the regulations in force in the Lombardy Region, only patients with primary lymphoedema have the right to a free custom-made brace. This analysis, however, shows that secondary patients are the ones who most need this brace, which, moreover, costs significantly more than the standard one. The challenge is therefore to offer an equal level of care to all patients regardless of their medical history, which the study found to be irrelevant for the purpose of treatment.

Abstract in italiano

Il linfedema è una patologia cronica e degenerativa causata da una parziale incapacità di trasporto linfatico. Si differenzia in primario (genetico) e secondario (legato ad altre patologie) e provoca un aumento di volume dell'arto affetto (edema). Il trattamento del linfedema, secondo le linee guide, prevede l'applicazione della Terapia Decongestiva Complessa in cui vengono effettuate delle misure circonferenziali su otto punti al fine di valutare l'andamento dell'edema. Tra le diverse tecniche proposte in letteratura, è stata scelta per lo studio la cosiddetta tecnica segmentale che, individuando gli otto punti in maniera costante e proporzionale, permette il confronto tra soggetti con condizioni dismorfiche differenti.

È stato sviluppato un database contenente i dati di 74 pazienti (38 inferiori e 36 superiori) presi in cura dall'Istituto Clinico Città Studi di Milano. Attraverso l'impiego di modelli statistici ad effetti misti, è stata valutata quantitativamente la variazione dell'arto edematoso prima e dopo il trattamento rispetto a quello controlaterale sano, mostrando inoltre come l'edema si distribuiva lungo l'arto. In seguito, sono state confrontate le misure centimetriche delle circonferenze degli otto punti al fine di studiare l'efficacia indotta dal trattamento. I dati sono stati poi rianalizzati suddividendo i pazienti in base a classificazioni cliniche quali eziologia (primario e secondario), entità del linfedema (lieve, moderata e grave), consistenza tissutale (morbida, media e dura) e modello dismorfico (LA1 e LA2).

I risultati di questa tesi mostrano che tutti i punti hanno registrato delle differenze statisticamente significative (p-value < 0.05) tra il pre e il post trattamento comportando una riduzione, in media del 7%, del volume dell'arto edematoso anche nei pazienti più compromessi. In particolare, l'analisi ha mostrato che nei punti B1 e C1 si verifica un ristagno di linfa e pertanto sarebbe consigliabile prestare maggiore attenzione ad esse durante la fase intensiva del trattamento. Inoltre, per un trattamento efficace non è conveniente dividere i pazienti in base all'eziologia e al modello dismorfico, e le due entità, lieve e moderata, essendo comparabili, potrebbero essere raggruppate in un'unica entità.

Attraverso l'implementazione di un algoritmo, sono stati stimati il numero di tutori standard e su misura da prescrivere ai pazienti alla fine del trattamento e i relativi costi. Il tutore su misura è stato assegnato all'89% dei pazienti (37,6% primari e 62,4% secondari) e al 96% (tutti secondari), rispettivamente con linfedema all'arto inferiore e superiore. Secondo le norme vigenti in Regione Lombardia, solo i pazienti con linfedema primario hanno diritto ad avere gratuitamente un tutore su misura. Da quest'analisi però emerge che i pazienti secondari sono quelli che necessitano maggiormente di questo tutore, che per altro ha un costo nettamente superiore rispetto a quello standard. La sfida è dunque quella di offrire un livello di assistenza paritario a tutti i pazienti indipendentemente dalla loro storia clinica, che dallo studio è risultata irrilevante al fine del trattamento.

Key-words: Lymphoedema; Complex Decongestive Therapy; Detection points; Mixed-effects models; Statistical significance; Elastic compression braces.

Parole chiave: Linfedema; Terapia Decongestiva Complessa; Punti di rilevamento; Modelli a effetti misti; Significatività statistica; Tutori elasto-compressivi.

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1 Introduction

1.1. Lymphatic system

The lymphatic system (Figure 1) plays a major role in the formation of the body's immune defense. It is a complex of capillaries, lymph vessels and organs within the body that guarantee the circulation of lymph, which is a fluid that fills the interstices between body cells and has a different composition depending on the region from which it is drained [1]. It has an aqueous (fluid) part and a part composed of corpuscles, mostly represented by lymphocytes, a particular type of white blood cell.

Figure 1: *Lymphatic system.*

Circulating in the interstitial spaces, between one cell and another, the lymph has the purpose of reabsorbing plasma. The lymph capillaries have a very thin endothelial wall, and their confluence forms the lymphatic collectors, vessels with a larger diameter that obstruct the reflux of lymph in the opposite direction of circulation. The lymphatic collectors are characterized by a sequence of dilatations and constrictions and, in turn, flow into 12 vessels of greater caliber: the trunks or ducts; all lymphatic vessels flow into two ducts, the thoracic duct and the right lymphatic duct, which pour their contents into the left and right subclavian vein, completing the circulation of lymph in the blood.

The functions of the lymphatic system are:

- Draining: the lymphatic system performs the function of draining all excess liquids and waste substances from the tissues;
- Metabolic: concerns lipid metabolism, the lymph enables the absorption of triglycerides, it also plays a role in protein metabolism;
- Immune: within the lymphatic vessels, lymph is filtered by the lymph nodes, blocking the transmission of pathogens and in many cases cancer cells.

The tissue drainage function performed by the lymphatic system prevents the dangerous stagnation of fluid and it can be considered complementary to what the blood circulation does. Unlike the latter, the lymphatic system does not have a central motor organ, but the lymph flows in the vessels moved by the action of the muscles, in fact, by contracting and relaxing, these tissues function as a real pump. Excess fluids

are moved out of the tissues and into the lymphatic vessels, thus preventing stagnation. The exchange of fluids, across the capillary membrane, occurs in accordance with the principles enunciated by Starling (1896) [2], according to which the blood's hydrostatic pressure gradient pushes the fluid out of the capillaries towards the tissues, while the osmotic pressure gradient induces a passage in the opposite direction, i.e., from the blood into the capillaries (Figure 2).

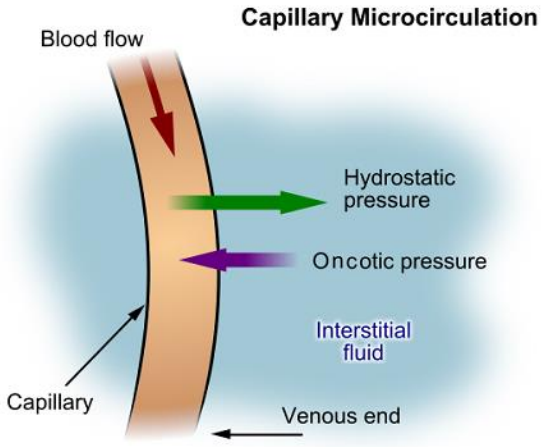

Figure 2: *Fluid exchange through the capillary membrane.*

The balance of these exchanges, under normal conditions, results in a net flow of fluid into the tissues that is subsequently drained by the lymphatic system. When the drainage function fails, due to injury or dysfunction of the lymphatic system, lymph tends to stagnate and accumulate in the tissues due to the unfavorable osmotic gradient. This condition is called **lymphoedema**, an oedema of lymphatic nature.

1.2. Lymphoedema

According to the most recent International Society of Lymphology (ISL) Consensus Document [3], "lymphoedema is an external (and/or internal) manifestation of lymphatic system insufficiency and deranged lymph transport" or, more simply, "a symptom or sign resulting from underlying lymphatic disease". Epidemiological data from the World Health Organization (WHO) [4], report that 300 million cases are registered worldwide, 1 in 20 people are affected by lymphoedema due to various causes. In Italy, about 350000 people suffer from lymphoedema and there are about 40000 new cases every year, mainly women between the ages of 30 and 40. It is therefore a widespread pathology, with an evolving, disabling, and progressive character. Lymphoedema is clearly manifested by chronic swelling of a limb, in 42% of cases the lower limb, involving the entire limb or only the proximal or distal portion. It also affects the upper limbs, face, genitals, and trunk. Generally, lymphoedema is asymmetrical, i.e., unilateral, in which case one limb appears visibly more edematous than the contralateral. Depending on the severity of the related pathological condition, this swelling may be more or less significant, ranging from mild to elephantiasis, i.e., when a limb becomes extremely large with severe hyperkeratosis and the appearance of elephant skin (Figure 3).

Figure 3: *Examples of persistent end-stage localized lymphoedema called elephantiasis.*

Lymphoedema can be etiologically primary or secondary [5, 6, 7]:

- **Primary** or congenital lymphoedema appears early in life and is a clinical manifestation of a defect in the lymphatic vessels or nodes, causing abnormal dilatation and valvular insufficiency. It is the least frequent cause of lymphoedema and occurs in individuals of varying ages with different phenotypic features [8].

- **Secondary** lymphoedema is mainly due to damage to the lymphatic system caused by neoplasia, surgery, trauma, infection, or radiotherapy, leading to obstruction or disruption of the system [6]. It is most often a consequence of malignancy or malignancy-associated treatments and a significant cancer survivorship problem [10]. It is absolutely the most frequent cause of the disease and an analysis of the data in the

literature shows that the incidence of secondary lymphoedema, despite improvements in surgical and radiotherapy techniques, remains high: about 20-30% of patients [4, 11], either immediately or a few years after surgery; this percentage can reach 60-80% [4, 11] when it is followed by radiation treatment on the satellite lymphatic stations.

Lymphoedema is thus manifested by an increase in the volume of the limb, which appears swollen. Other complications are associated with this pathology such as the alteration of skin color that tends to discolor and become shiny, the tissue consistency of the edematous limb from soft at the beginning can become hard if not adequately treated. Usually, the patient does not report pain but difficulty in moving or flexing the affected limb and a constant perception of heaviness and constriction that may increase to the level of becoming disabling in daily actions such as walking, driving, writing, etc.

The stages of lymphoedema can be classified according to various classifications (including the American, Italian, and Brazilian). The most common is that of the International Society of Lymphology (stages 0-III) [3].

Stage 0

The interval phase, or latent phase, describes a subclinical course. Although the lymphatic system is damaged, fluid removal is still normal. There is therefore no swelling. The symptoms of these patients are usually limited to a feeling of heaviness, indisposition, or early fatigue of the affected extremity. Lymphatic scintigraphy can already detect a pathological condition at this stage.

Stage I

At this stage, swelling has already occurred, but reversible. Here, no tissue changes occur yet. The oedema is soft, and a visible bruise remains under pressure. Patients at this stage benefit greatly from a conservative regimen. Elevation of the affected limb, or bandaging, usually provides sufficient therapy in the beginning.

Stage II

At this stage, the lymphoedema is no longer reversible with elevation. Upon pressure, no bruising remains, as fibrous remodeling of the subcutaneous tissue has already begun. The consistency of the oedema has already hardened, depending on the degree of fibrosis. A conservative therapy regimen is still applicable at this phase. In the event of resistance to conservative therapy, surgery is already indicated at this stage.

Stage III

The affected limb is severely swollen, and the patient's movements are severely restricted. Fibrotic and adipose deposits can cause impaired blood supply to the skin. Acanthosis and hyperkeratosis may occur, as well as ulcerations.

1.3. Diagnosis

An accurate diagnosis of lymphoedema is essential for appropriate therapy. In most patients, the diagnosis of lymphoedema can be readily determined from clinical history and physical examination. In other patients, confounding conditions such as morbid obesity, lipodystrophy, lipedema, endocrine dysfunction, venous insufficiency, unrecognized trauma, and repeated infection may complicate the clinical picture. Moreover, considering the basis of unilateral extremity lymphoedema, especially in adults, solid organ tumors (primary and/or metastatic), lymphomas, and soft tissue sarcomas which may obstruct or invade more proximal lymphatics need to be considered. For these reasons, a thorough medical evaluation is indispensable before starting the lymphoedema treatment. Co-morbid conditions such as congestive heart failure, hypertension, thyroid abnormalities, cerebrovascular disease including stroke, and vascular malformations may also influence the diagnosis and therapeutic approach undertaken [12].

The basics of the diagnosis are anamnesis, inspection, and palpation [13]. If the diagnosis of lymphoedema or its cause is unclear or needs better definition for prognostic or therapeutic considerations, imaging is necessary. It makes it possible to formulate the diagnosis and, if necessary, identify the underlying cause of the lymphoedema and monitor progress. The most common diagnostic procedures are lymphatic scintigraphy and fluorescence (indocyanine green) lymphangiography. These examinations can detect slowed lymphatic drainage at an early stage. Other techniques used are magnetic resonance imaging or computed tomography, which,

however, can only detect lymphoedema as early as stage II. Ultrasound examination is used for pre-operative planning.

Anamnesis

The anamnesis is divided into a general anamnesis and an oedema anamnesis. As part of the general anamnesis, family history must also be collected, in particular family diseases such as diabetes mellitus, chronic venous insufficiency or frequent lymphoedema. In addition, previous operations, infections and traumas, and the patient's pharmacological regimen must be clarified. If there is a tumor in the patient's history, relevant previous findings are needed to clarify whether there is a connection between lymphoedema and cancer. The specific oedema history mainly includes the onset and time course of the disease, as well as localization of the disease. Other points are concomitant pathologies such as pain swelling, skin symptoms such as erysipelas or an increased tendency to hematoma. The history should also contain information on possible prevention and improvement strategies (such as elevation of the affected limb in daily life).

Inspection

During the inspection, the patient should undress the affected part and be assessed both standing and lying down. Particular attention is paid to the location, swelling and the difference in circumference from the healthy limb (if the lymphoedema is unilateral). If the lymphoedema is bilateral, the circumference of both extremities must be reported as a separate value.

Palpation

During palpation, the affected extremities as well as inguinal and axillary lymph nodes are examined. Lymph nodes should be assessed for size, consistency, pain, and displacement. The nature of the oedema (soft, doughy, bulging, fibrotic, hard), as well as the persistence of a bruising on pressure are also examined. In addition to palpation, active and passive joint mobility, function (fist closure, pincer grip), sensitivity, scar quality, nail and hair growth, and skin temperature are assessed.

1.4. Complex Decongestive Therapy

Lymphoedema therapy is divided into conservative (non-operative) and operative methods. Conservative therapy is considered the gold standard and studies on operative methods, which require surgery, have not yet shown better results than conservative therapy and are only used if the latter has failed [14]. Conservative therapy aims to reduce interstitial fluid, thereby improving lymphatic drainage and preventing progression to higher stages. For this purpose, Complex Decongestive Therapy (CDT) or Complex Decongestive Physiotherapy (CDP) or Combined Physical Therapy (CPT), which consists of several interventions, was developed. It provides a two-stage programme that can be applied to both adults and children for most areas of the body. The first phase, also called '**intensive phase**', aims to reduce the volume and consistency of oedema while the second, called '**maintenance phase**' or 'optimisation phase', following the previous one, aims to prevent the reappearance of oedema [15].

The *intensive phase* is based on four steps:

1. **Skin care and hygiene**: These are essential because the skin of lymphoedema patients is often pathological, and if left untreated, could not tolerate treatment. The aim is to prevent bacterial and fungal infections, keeping the epithelial tissue well elastic, clean and without inflammation or redness.

2. **Manual lymphatic drainage (MLD)**: this consists of stimulating the healthy lymph node stations of the entire body, up to the treatment of the limb or edematous area with manual manoeuvres, which serve both to drain excess fluid and accumulated proteins outside the arterial, venous, and lymphatic capillaries. This step is the one that materially drains the excess lymphatic fluid and literally 'deflates' the lymphoedema, bypassing damaged or absent vessels or lymph nodes in the lymphatic system: its correct application, performed by highly experienced personnel, is therefore of crucial importance for the entire CDT [16].

3. **Compression bandage**: it has the characteristic of deeply compressing the newly treated tissues, and generally consists of overlapping layers of different material. Each layer has a precise and specific function, to make the bandage tolerable by the patient and above all not to limit the articulation of the bandaged limb.

4. **Decongestive gymnastics**: its purpose is to encourage lymphatic circulation by strengthening muscle work, to tone the muscles of the edematous limb, and to improve the action of other treatments. It is used to empty the lymphatic stations upstream of stasis and to promote lymphatic flow through muscle contraction.

If one of these four is lacking, the therapy is ineffective. Therefore, the application of just one of these elements is not enough, and all four must be used in synergy and synchronisation to achieve the intended benefits for the patient.

The *maintenance phase* follows the intensive phase and is based on medical compression with compression garments, skin care, exercise and manual lymph drainage repeated as needed. It aims to maintain and optimise the volume reduction achieved in the first phase. Lymphoedema therapy recognises the elastic brace as the key 'maintenance' tool for the results achieved with drainage therapies. Elastic compression does not act on the cause of the lymphoedema, but it is a treatment that improves the symptoms experienced by patients such as heaviness and tension in the limb and slows down the evolution of this disease over time. In general, the highest compression level tolerated by the patient is 20-60 mmHg and is probably the most beneficial.

It is important for prescribers to know how these are classified so that they can prescribe a brace that provides effective compression, fits the affected limb well, is comfortable and therefore tolerated by patients for prolonged periods of time. The

type of elastic brace and the level of compression prescribed depend on several factors including: site, extent, distribution, severity of oedema and the patient's ability to manage and tolerate the compression, considering patient preference [17].

Two types of braces can be prescribed for each patient: standard or custom-made.

- For **standard braces** there are size charts prescribed for patients with mild to moderate lymphoedema of the upper and lower limbs and with good maintenance of normal limb morphology.

- **Custom-made braces** are prescribed when the patient has lymphoedema that falls outside the measurement range of the standard one. They are best suited to the therapeutic needs of the individual patient and are described in particular for: obese patients, paediatric patients, patients with dysmetria and/or deformities of the upper and lower limbs, who require a specific pressure gradient in a particular segment of the limb, with oedemas in particular places (pubis, scrotum, breast, face).

The braces can be manufactured in two different weaves: flat-knit and circular-knit.

- **Flat knit** (with seams) is particularly suitable for its characteristics of high exercise pressure and low resting pressure, a special weave that also controls massive lymphoedema and provides a micro massage.

- The **circular knit** (seamless), produced in one piece, is suitable for small oedemas or for prevention and has the following characteristics: low exertion pressure, greater extensibility, and different compression classes.

A wide range of both standard and customised models can be found on the market; knee-highs, compression stocking (Figure 4), collant, for the lower limb, arm sleeve without hand (Figure 5) and a glove with fingers (Figure 6), for the upper limb.

Figure 4: *Example of compression stockings for lower limbs for the maintenance phase of lymphoedema.*

Figure 5: *Example of arm sleeve brace without hand for upper limb for the maintenance phase of lymphoedema.*

Figure 6: *Example of glove brace with fingers for upper limb for the maintenance phase of lymphoedema.*

To fulfil its therapeutic purpose, the brace must be replaced periodically, approximately every 6-8 months. Beyond this time limit it will tend to lose its tensile-elastic characteristic.

In this thesis work, standard and custom-made flat-knit braces were considered. For the lower limb, compression stocking was considered for all patients, which costs approximately 77 € + VAT if standard, or approximately 133.6 € + VAT if custom-made. For the upper limb, two braces were considered: arm sleeve without hand and glove with fingers. The brace pair costs approximately 190.2 € + VAT if standard or approximately 260.6 € + VAT if custom-made. VAT is 4% in the case of disability, exemption code RGG020 for rare disease or 048 oncology, or 22% when there are no exemptions. For both limbs, any optional extras such as: oblique foot, shaped heel, skin protectors etc. have not been considered.

Depending on the laws in force in the State or Region, the cost of the brace may be borne by the patient, the Health Service, or the insurance company.

1.4.1. Lymphoedema measurement techniques

After the doctor's admission visit, during the first day of treatment, the physiotherapist can begin the intensive phase by performing a series of assessments such as:

- volumetric measurement of limbs
- measurement of tissue consistency
- weight measurement and photographic detection

1.4.1.1. Volumetric measurements

The gold standard is a direct technique called water displacement (Figure 7), which directly measures the volume of the limb after immersion in water [18, 19]. It is based on Archimedes' principle, according to which the volume of water displaced by an object is equal to the volume of the object itself. The limb is immersed up to a certain level inside a container filled with water and the volume of water displaced by the limb is measured [20]; the measurement is made by calculating the rise in the level of water inside the container or by collecting and measuring the water that has come out of the container after the limb has been immersed. This technique is simple, repeatable, non-invasive, very accurate and has shown good reproducibility [18, 19, 20, 21, 22] and high accuracy [18, 21, 22]. Indeed, studies in the literature show high intra- and inter-operator reliability [21].

However, this method has some limitations: an accurate measurement requires a lot of time, adequate space, and a rather high cost; moreover, it requires considerable cooperation from the patient (especially in holding the limb still) and cannot be used in case of major functional limitations (positioning of the limb inside the container). It requires careful hygiene of materials and disinfection of the container between patients. It provides an estimate of the volume of the entire submerged limb segment but does not give an indication of the spatial distribution of oedema. Ultimately, these difficulties make water displacement unsuitable for routine use in clinical practice, although it is considered the gold standard [19, 23].

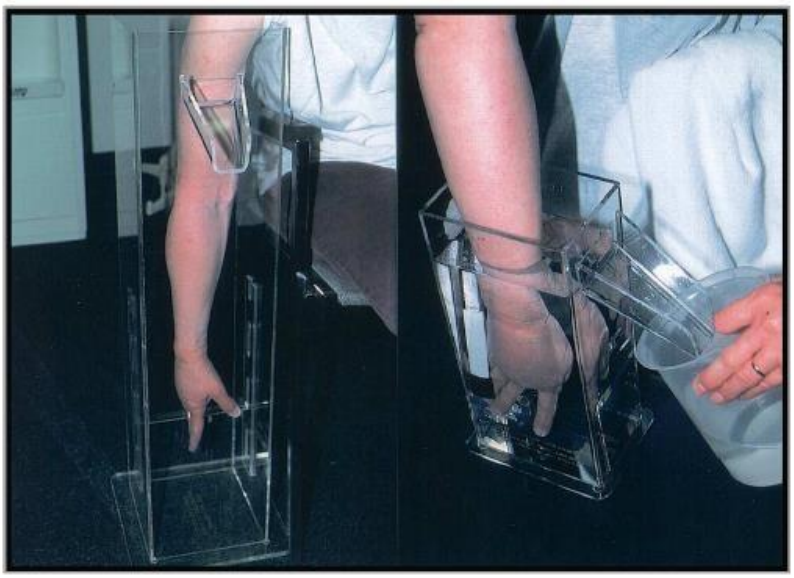

Figure 7: *Method for measuring volume by water displacement (WD)*

Indirect techniques [24] calculate limb volume with a small margin of error compared to direct volumetry by applying formulas for calculating the volumes of geometric solids, to which the various limb segments are assimilated. The more the shape of the various limb segments deviates from that of the theoretical limb on which the formula is based, the greater the error will be. Limb volume can be calculated from an accurate measurement of limb circumferences at various levels using a tape measure. This measurement has the advantage of being quick, cheap, and performed with readily available tools. It also has the advantage of highlighting the distribution of oedema by comparing measurements of different limb segments.

The most used measurement techniques at international level are:

- **Fixed heights**: limb circumferences are measured at intervals of 4, 8 or 10 cm, or considering anatomical reference points [25]. Although easy to use and self-comparable, the measurement points taken on patients at different heights do not maintain the same proportion when considered in relation to the length of a given segment (forearm-arm and leg-thigh). This does not fully satisfy practitioners of lymphoedema therapy, who require lymphoedema monitoring and assessment on constant measurement points in proportional terms, such as to facilitate the identification of recurring dysmorphic conditions on which a predefined compressive action can be developed.

- **Segmental Technique (ST**), referred to for this study, identifies the points on which to take circumferential measurements, constant in proportion, using a procedure for fractions of the various heights/lengths [26]. This procedure involves dividing the forearm into four equal parts, the arm, and the thigh into three equal parts. In this way, the points are always identified at 1/3, 2/3 and 3/3 in proportion to the length of the limb so that different individuals can be compared. There are 8 detection points identified for both the lower and upper limb as shown in Figures 8-9.

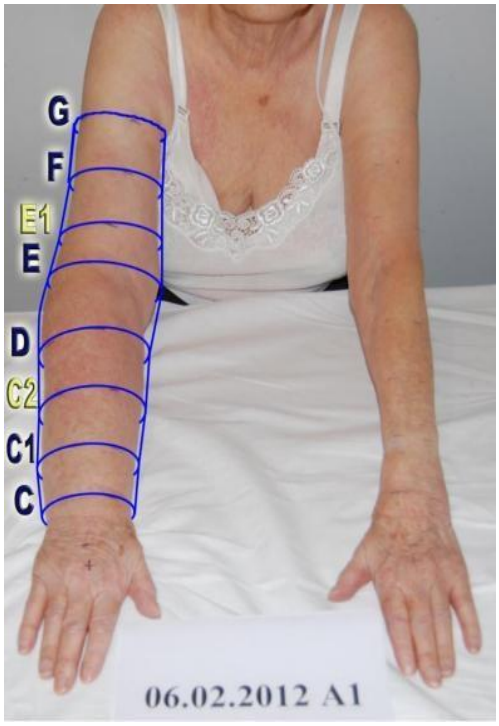

Figure 8: *Upper limb detection points identified using the segmental technique.*

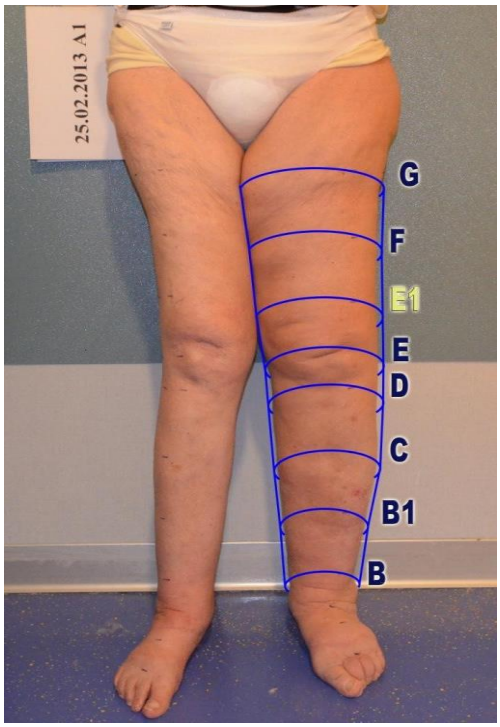

Figure 9: *Lower limb detection points identified using the segmental technique.*

Point detection procedure [26]

Lower limbs

The patient is laid on a couch in a supine position and, starting from the eumorphic limb, point measurements are taken using a tape measure. The first point measured is point B or the narrowest point at supramalleolar level. A mark is drawn over the tape measure on the side of the leg, as shown in Figure 10.

Point D, or the point below the styloid apophysis, is measured by bending the limb at 90° and, by placing the tape measure transverse to the longitudinal axis of the segment at the level of the superior-posterior III of the leg at the medial popliteal fossa, a mark is made below the tape measure on the side of the leg (Figure 11).

The E point or knee is measured by bending the limb to approximately 30° and placing the tape measure at the level of the inferior-posterior III of the thigh at the lateral popliteal fossa. Then extending the limb, a mark is made under the tape measure (Figure 12).

For the measurement of point C or the bulkiest point of the calf muscle, the patient is placed in an orthostatic position with the limbs extended and spaced at pelvic height as shown in Figure 13. The folding ruler is then placed parallel to the longitudinal axis of the leg with the initial part placed on the ground and the upper part placed along the boundary of the medial gastrocnemius from the lateral gastrocnemius. The distance between the lower support point at the gastrocnemius and the upper point at which the tape measure was separated from it is measured. Finally, the mean value of this distance is calculated, and a mark is drawn directly on the lateral part of the leg to correspond to this measurement.

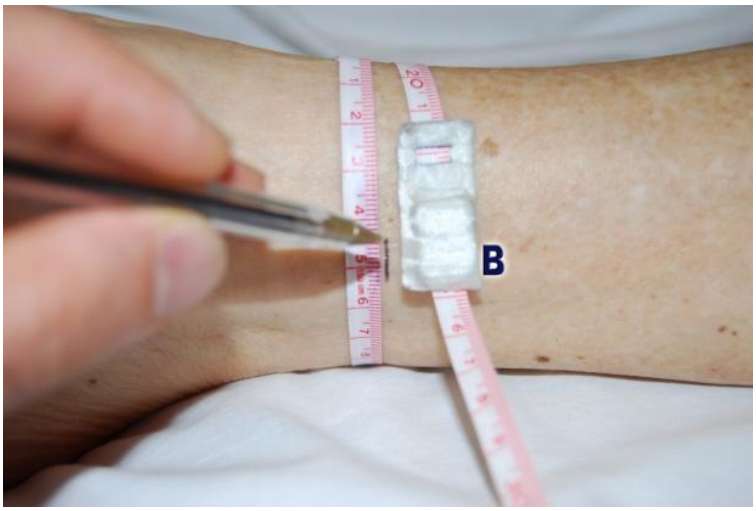

Figure 10: *Operator drawing the position of point B using the tape measure.*

Figure 11: *Operator drawing the position of point D using the tape measure.*

Figure 12: *Operator drawing the position of point E using the tape measure.*

Figure 13: *Operator drawing the position of point C using the folding ruler.*

Given the impossibility of objectively identifying the insertion of the gastrocnemius (unless assessed by ultrasound), point B1 or insertion point of the lower calf muscle, is identified as an intermediate point between point B and point C (Figure 14).

Once the leg measurement has been completed, the thigh height is measured, starting with the detection of point G or gluteal fold. To determine the latter, the tape measure is placed transverse to the axis of the segment at the gluteal fold (Figure 15), after which a mark is made under the tape measure in the lateral thigh area (Figure 16).

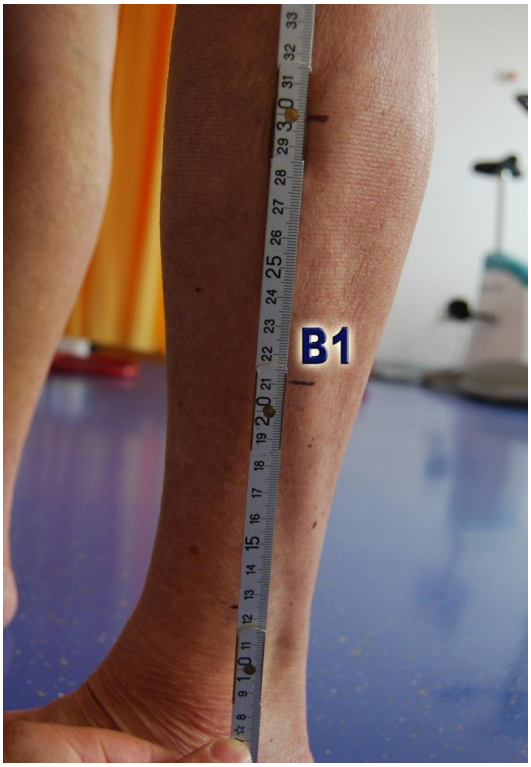

Figure 14: *Operator drawing the position of point B1 using the folding ruler.*

Figure 15: *Gluteal fold.*

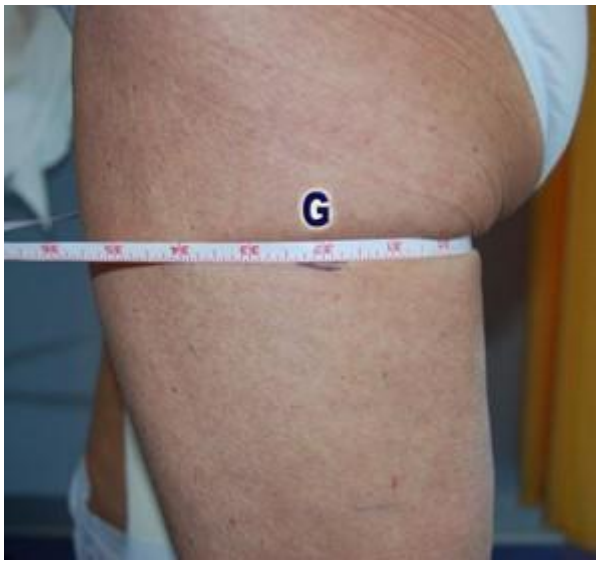

Figure 16: *Operator drawing the position of point G using the tape measure.*

Next, the thigh height is measured by placing the folding rule parallel to the axis of the segment, measuring the distance between point E and point G. Dividing this height into three equal parts, the intermediate points are identified and traced: F or intermediate thigh point, located at 2/3 of the thigh height starting from point E and E1 or intermediate point between point E and point F located at 1/3 of the thigh height starting from point E (Figure 17).

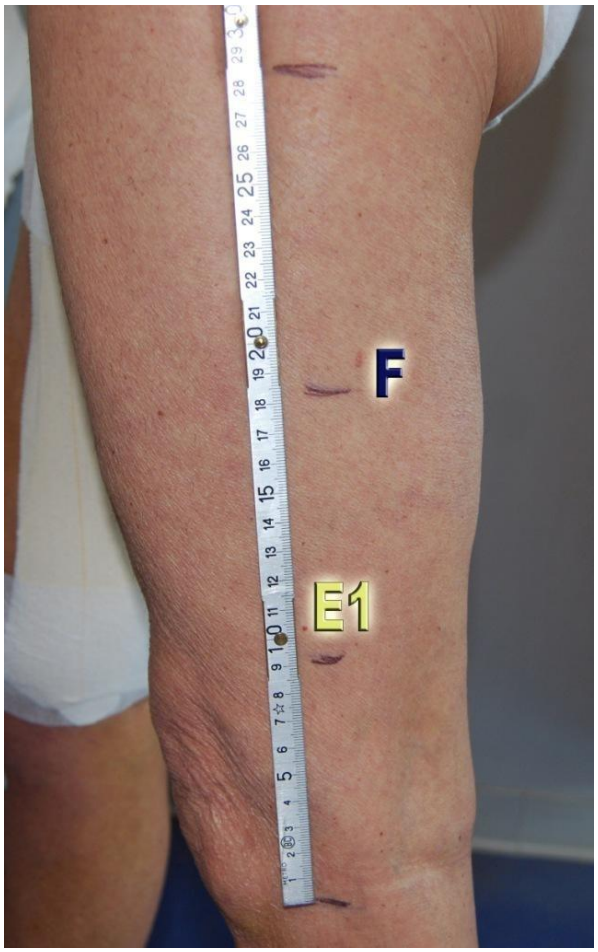

Figure 17: *Operator drawing the position of point E1 and F by dividing the thigh segment into three equal parts using the folding ruler.*

Once the operation on the pathological limb was completed, the heights are replicated on the healthy contralateral limb.

To measure the circumferences of the various measuring points, the patient is again laying on a couch in position A (Figure 18) with limbs extended and distanced at pelvis height. The circumference measurements are taken using the tape measure positioned transverse to the axis of the segment with its initial part placed below the mark and

with the weight attached to it positioned antero-medially and the other antero-laterally.

Figure 18: *The operator is taking centimetric measurements of the circumferences of the lower limb of patient placed in position A.*

Upper limb

Measurements of the upper limb are performed by first placing the patient in an orthostatic position with the eumorphic limb lying along the hip. The limb is then slightly abducted so that the tape measure could be placed inside the axillary cavity. By drawing a mark under the tape measure on the front of the arm, point G is identified as in Figure 19. Next, the patient assumes position A i.e., lying on a couch with the eumorphic upper limb abducted 45° fully extended and resting on the extensor surface (Figure 20).

Assuming this position, a point C or wrist is identified on the flexor surface of the forearm, between the hypothenar and thenar folds, at which a mark is traced with a pen (Figure 21). Once point C had been identified, point E or elbow is located, by flexing the forearm on the arm by approximately 90° and drawing a mark on the flexural surface at the cubital fold.

Figure 19: *Operator drawing the position of point G using the tape measure.*

Figure 20: *The operator is taking centimetric measurements of the circumferences of the upper limb of patient placed in position A.*

Figure 21: *Point C.*

Then the length of the forearm is measured from point C to point E by extending the limb again with the hand in line with the axis of the forearm and this length is divided into four equal parts to identify the following points: C1 placed at 1/4 the height of the forearm from point C, D or bulkiest point of the forearm placed at 3/4 the height of the forearm from point C, C2 or intermediate point between points C1 and D placed at 1/2 the height of the forearm (Figure 22).

Finally, the length of the arm is measured from point E to the previously measured point G and divided into three equal parts on which the points are drawn: F or intermediate point of the arm placed at 2/3 of the height of that district from point E, E1 or intermediate point between points E and F placed at 1/3 of the height of the arm from point E (Figure 23).

At the end, the same heights are taken on the healthy contralateral limb by placing the patient in position A.

For the measurement of the circumferences of both upper limbs, the patient's limb is rotated medially with the palm of the hand towards the ground.

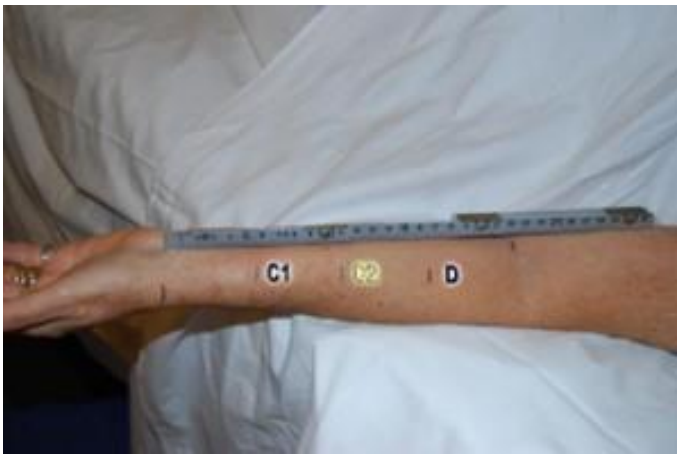

Figure 22: *Operator drawing the position of point C1, C2 and D by dividing the forearm segment into three equal parts using the folding ruler.*

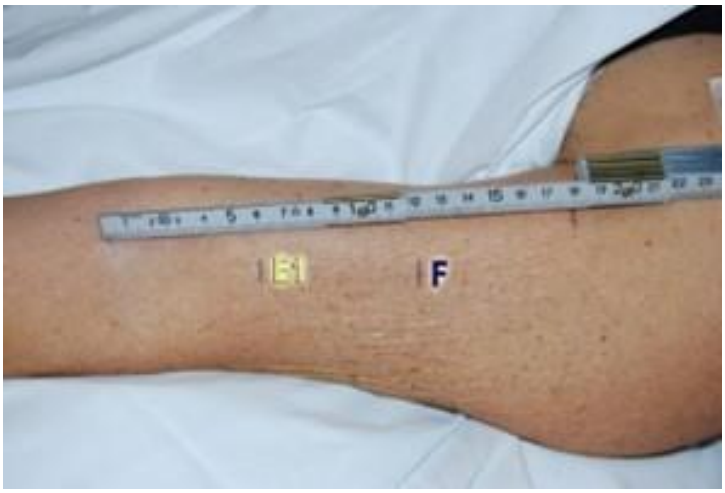

Figure 23: *Operator drawing the position of point E1 and F by dividing the arm segment into three equal parts using the folding ruler.*

1.4.1.2. Tissue consistency measurement

The assessment of oedema is based on inspection and palpation, which is expressed through the evaluation of two fundamental parameters: consistency and compressibility. Therefore, the clinical assessment of oedema is subjective and qualitative, but it is possible to make it objective and quantitative using the tonometer [27], a mechanical instrument developed in 1976 at Flinders Medical Centre (Figure 24). The tonometer is placed on the skin surface of the limb and held in a vertical position, without inducing pressure, measurements are taken at constant marker points. It is an accurate and repeatable method, useful for assessing tissue consistency by measuring tissue resistance to compression and its variation over time. The limitation of the method is the inability to take measurements in areas where it is not possible to position the instrument stably.

Figure 24: *Tonometer.*

For this thesis, it was deemed appropriate to refer to a medical instrumentation capable of objectively measuring tissue consistency even on concave and convex areas, and to monitor the effect of lymphoedema therapy at the end of treatment and over time in relation to this parameter. The instrumentation under investigation consists of a 7 mm high tape measure and two dynamometric elements attached to it (Figure 25). This instrument also allows an extremely precise measurement of body circumferences [26]. Thus, the intra- and inter-operator tolerance between the minimum measured circumference and the maximum circumference is reduced. This instrumentation is the result of a multicentre study (Ospedale L. Sacco, Istituto Clinico Città Studi e Politecnico di Milano) that is still in progress and soon to be published.

Figure 25: *Dynamometric tape measure- Italian patent number 1417397- European patent EP2.986.176 A1.*

1.4.1.3. Weight and photographic detection

For each patient, at the beginning and end of treatment, body weight and height are recorded in order to calculate the body mass index (BMI).

To further validate the results of the different treatments in qualitative terms, photographs are taken at the beginning and end of treatment, defined as follows [28]:

Lower limbs

In the anterior projection, the patient was positioned, as shown in the Figure 26, with:

- back and heels in support
- iliac crests aligned

- feet slightly separated
- toes pointing inwards

In the posterior projection the patient was positioned, as shown in the Figure 27, with:

- abdomen against the wall
- iliac crests aligned
- feet slightly separated
- toes against the wall and pointing inwards

Figure 26*: Photographic detection of lower limbs in anterior position.*

Figure 27: *Photographic detection of lower limbs in posterior position.*

Upper limbs

In the photographic detection of the upper limbs, the patient was positioned, as in Figure 28, with:

- straight back
- couch at navel height, shoulders relaxed and elbows in extension
- arms equal to shoulder width
- palms in support

Figure 28: *Photographic detection of upper limbs.*

Once the previously discussed evaluations have been performed, bandaging of the compromised limb takes place. The type of bandage is chosen according to the different clinical and dysmorphic conditions [29, 30]. Once the limb has been bandaged, applying the correct overlaps, the session is over, and the patient will not have to remove the bandage alone and must also be careful not to get it wet. After 24 hours (72 on weekends), the patient should undergo the second treatment session, during which, the limb will be unwrapped, the circumferences of each point re-measured, and the percentage centimetre reduction will be calculated for all points compared to the previous day. All updated data is recorded in the patient's medical record. The compression action is then measured again daily to establish the result

induced by the treatment. An intensive cycle includes ten sessions over a two-week period.

1.5. Aim of the thesis

In this thesis work we referred to the treatment of lymphoedema and in 74 patients treated at the Istituto Clinico Città Studi in Milan were analyzed.

The objectives of this study are to show the spatial distribution of oedema along the affected limb considering the clinical classifications indicated in the literature such as etiology and entity of lymphoedema and proposing new ones such as tissue consistency and dysmorphic pattern.

Another aim is to develop statistical models that quantitatively evaluate the effectiveness of Complex Decongestive Therapy.

In addition, another aspect considered was to highlight that in the therapy of lymphoedema, the segmental technique is appropriate to allow comparison between individuals with different characteristics in proportional terms.

This type of work is a consequence of the intention to characterize a sample population suffering from lymphoedema in order to assess the progress of the pathology considering the first and last day of the session.

Clearly, the need to address this issue depends on the fact that the incidence of the pathology is constantly increasing, and the implementation of a standard protocol is necessary.

Finally, the costs to be incurred during the maintenance phase are estimated.

2 Methods

The following chapter will present all the tools that were used for the thesis work.

The work is divided into three main sections.

In the first part, the digital database was developed for entering the data on the oedema treatment of the 74 patients treated at the Istituto Clinico Città Studi, Milano.

The second part deals with the analysis of all the information contained in the database. By using particular clinical factors, the efficacy of the Complex Decongestive Therapy is quantitatively evaluated and the distribution of oedema along the analyzed limb is shown.

In the third and final part, the number of patients needing a standard or custom-made brace and the respective costs were estimated.

2.1. Database development

The clinical record is an individual information document aimed at collecting all the clinical and therapeutic information. It is a fundamental tool for the hospital structure that allows the sharing of work between the medical staff involved in patient care and enables statistical and scientific studies such as this one to be carried out.

The sample that was examined consisted of 74 patients, 38 of whom had lymphoedema in the lower limb and 36 in the upper limb. Over the years, the same patients underwent treatment several times for a total of 220 records analyzed. Table 2.1 schematized the characteristics of the examined medical records.

Number of patients	Average age	Total number of files analyzed
74	67.5	220

Table 1: *Characteristics of the examined medical records.*

Each medical record consists of three sheets: the first concerns the patient's personal data, the second the daily measurements and the last the measurements at the start and end of treatment.

For the implementation of the database, it was decided to use Microsoft Excel® software [31]. The program allows the creation and management of spreadsheets that appear as tables consisting of thousands of cells in which numbers, text or formulas can be entered. The interface facilitates the recording, processing, and searching of data.

The need for this study was to create a database that could contain the data of lymphoedema patients and make clinical evaluations of these data.

For this reason, two worksheets were created: one for the lower limb and one for the upper limb. The following data were imported into each sheet:

- patient general information (name, treatment start date, weeks of treatment)
- dysmorphic pattern (lower limb only)
- entity of lymphoedema
- tissue consistency
- etiology
- point heights
- circumferences measurements of the healthy contralateral limb
- circumferences measurements of the edematous limb before treatment
- circumferences measurements of the edematous limb after treatment

The ID number uniquely defines a patient. He/she can make a variable number of treatments (each consisting of ten sessions), but the ID number will remain the same. This will allow the model developed later, to take into account the multiplicity of treatments associated with each patient.

The Istituto Clinico Città Studi in Milan provided a compressed folder within the medical records of individual patients were located. In each folder, named with the patient's surname, was an Excel file containing the measurements of interest. For this work, it was possible to automate the repeatedly performed operations by recording macros in Excel in order to compile the worksheet according to the type of data to be retrieved from other Excel files.

In the initial database, there was a column indicating the patients' surnames and with the implemented code, a path was created from this column to access the file relating to the various patients and the file concerning the lower or upper measurements. Having verified the existence of this path and the relevant file, all cells containing the data of interest were copied and imported into the final database for each patient.

Then, the following parameters were calculated:

- the centimetric percentage differences on all measuring points of the segmental technique of the edematous limb with respect to the same points of the healthy limb
- the daily percentage reductions in centimeters on all measuring points compared with the previous day
- daily, weekly, start and end of treatment centimetric percentage reductions
- the average of the percentage reductions per segment

2.2. Mixed effects models

2.2.1. Introduction to the mixed effects model

Considering the structure of the data, it was deemed appropriate to develop statistical models called mixed-effects models using Jamovi® software [32]. Mixed-effects model is an efficient tool for analyzing longitudinal or panel data, i.e., situations in which the observations are not independent of each other [33, 34, 35]. It has a regression form in which the coefficients are expressed as the sum of fixed effects and random effects: in particular, the random part collects the characteristics of each cluster (e.g., subject) for which several observations were measured. Fixed effects, on the other hand, describe the effect at the population level, i.e., the part common to all clusters.

This type of model allows to have a different number of observations for each cluster (unbalanced panel) and repeated measurements for each subject (through the inclusion of a time variable, concerning the instant of detection) [36, 37].

Estimations are made using the restricted maximum likelihood (REML) approach, that is a method for fitting linear mixed models. In contrast to the earlier maximum likelihood estimation, REML can produce unbiased estimates of variance and covariance parameters [38].

The goodness-of-fit of the model is analyzed using indices such as R-squared Marginal and Conditional. The model returns Fixed Effect Omnibus Tests and Fixed Effects Parameter Estimates as output. With omnibus tests, the statistical significance of the fixed effect at global level is assessed. The significance of the regression coefficient estimates is assessed using Student's t-tests.

For random effects, their variance is returned, which captures the variation between clusters. Next, Post Hoc Tests between fixed effects are performed, for which marginal means are also estimated and represented graphically. Finally, the normal distribution

of the residuals and their heteroskedasticity are observed, to assess how close they are to the model's optimal assumptions.

First, patients were divided according to the affected limb. The analyses, which will be explained in this chapter, were conducted separately for both upper and lower limb lymphoedema patients.

2.2.2. Pre and post-treatment analysis of the edematous limb compared to the healthy limb

The first analysis was developed to study the percentage variation between the pathological limb and the healthy limb, measured with respect to the latter. This variation was evaluated considering the measurements expressed in centimeters of both the pathological limb before and at the end of treatment, and the healthy limb measured on the first day and calculated as follows:

$$\Delta^{pre} = \frac{Pathological\ -Healthy}{Healthy} * 100 \tag{1}$$

$$\Delta^{post} = \frac{Pathological\ -Healthy}{Healthy} * 100 \tag{2}$$

$\Delta^{pre}$and Δ^{post} are the indices of asymmetry between pathological limb and healthy limb.

Measurements on the first day were classified as pre-treatment and those on the tenth day as post-treatment: measurements were collected for each of the eight detection points at each patient treatment session.

The dependent variable is Δ^{pre} or Δ^{post} calculated as (1) and (2).

The model uses, as fixed effects, the variable Time (referring to the measurement time before or after the treatment), the variable relating to the detection points (different depending on whether we are talking about the lower or upper limb) and their interaction. Random effects represent the characteristics of each subject, for whom different measurements (pre/post) were observed at different sessions for different detection points. The model predicts the estimation of a different random intercept component for each subject.

2.2.3. Treatment effect

In the second analysis, the percentage change between pre- and post-treatment measurement was examined and calculated by the following formula:

$$\Delta\% = \frac{Pre\_treatment - Post\_treatment}{Pre\_treatment} * 100 \quad (3)$$

Δ% defines the variation in terms of edema in pre-post treatment, used to characterize the effectiveness of treatment.

The model uses the variable Δ%, calculated as in (3), as the dependent variable. Measurement point variables are used as fixed effects, and a subject-specific intercept component is estimated as random effects.

2.2.4. Analysis of clinical factors

A further analysis was conducted to investigate the behavior of the various points in response to treatment by studying the clinical factors individually. The factors considered are: lymphoedema entity, tissue consistency, etiology, and dysmorphic pattern.

Regarding the entity, in the literature there is a scale defined by the "Consensus document of the International Society of Lymphology" [3] which, by defining thresholds, divides patients into groups according to the degree of lymphoedema.

The index evaluated is the Δ^{pre} and the three thresholds are:

- Δ^{pre} <= 20 % MILD oedema
- Δ^{pre} > 20 % and Δ^{pre} <= 40 % MODERATE oedema
- Δ^{pre} > 40 % SEVERE oedema

The tissue consistency of each patient was assessed by measuring the circumferences of the edematous limb with a 7 mm tape measure and two dynamometric elements attached to it. The patients were grouped according to three thresholds:

- > 0.5 mm SOFT tissue
- > -0.5 and < 0.5 mm MEDIUM tissue
- < -0.5 mm HARD tissue

As mentioned above, the main forms of lymphoedema are primary, due to malformations of the vessels of the lymphatic system, or secondary, due to external

adverse events that alter the normal function of the lymphatic system. For etiology analysis, patients were divided between primary and secondary.

Finally, the last factor of analysis was the dysmorphic pattern. It is proposed to distinguish patients according to the greater edematous point involved (LA1 for point B or LA2 for point B1).

Separately for each factor, two mixed effects models were developed. In the first, it was studied how the dependent variable, Δ^{pre} or Δ^{post} , changes depending on the detection points and the factor itself. In the second, $\Delta\%$ was considered as the dependent variable to be studied.

Both models include random effects for each subject detected, through the estimation of an intercept component, while the fixed effects are represented by the detection points, the clinical factors, and their interaction.

2.3. Analysis of elastic compression brace

To quantify the real cost of the maintenance phase of CDT caused by lymphoedema, considering the same sample of patients, the number of those needing a standard or custom-made brace was assessed. For the analysis, two datasets (one for the lower limb and one for the upper limb) were created using Microsoft Excel, from medical records provided by the Istituto Clinico Città Studi Milano. For each patient, centimetric measurements of the circumferences of some of the eight detection points were taken at the end of the treatment.

Tables 2 and 3 show the sizes of standardized braces for the lower limb and upper limb. For the lower limb, six sizes are available: 4, 6, 8, 10, 12, 14, and the points considered are B, C, E, and G; for the upper limb, 3 sizes are available: S, M, L, and the points considered are C, D, E, F, and G.

Depending on the point considered, each size is defined by a range of values expressed in centimeters within which it lies.

STANDARD ELASTIC COMPRESSION BRACES						
SIZE	**4**	**6**	**8**	**10**	**12**	**14**
G	44-48	47-51	50-55	54-59	58-63	62-68
E	35-35	34-37	36-39.5	39-42	41-45	44-48
C	30-33	32-35	34.5-37.5	37-40.5	40-44	43-47
B	18.5-20	20-22	22-24	24-26	26-28	28-30

Table 2: *Anatomical measurements for identifying the size of standard elastic compression braces for lower limb.*

STANDARD ELASTIC COMPRESSION BRACES			
SIZE	**S**	**M**	**L**
G	30.5-34.5	35-39	39-44
F	25.5-29	29-32	32-37
E	23.5-26	26-29	29-33.5
D	23-25	25-28	28-31
C	16-18	18-20	20-22.5

Table 3: *Anatomical measurements for identifying the size of standard elastic compression braces upper limb.*

Using an algorithm developed with R® software [39], the correct type of brace (standard or custom-made) was assigned to each patient. The algorithm also returned, in the case of the standard brace, the specific size provided that all circumferences fell

within the indicated ranges. If even one circumference was outside the range, the size was not assigned, and the brace was custom-made. The algorithm used for the lower limb, is shown below.

Algorithm 1 Assignment of elastic compression brace sizes for lower limb

```
dataset = dataset_punti_tutore
dataset$Tutore = “Tutore su misura”

for (i in 1: nrow(dataset)){
 if (dataset$B[i] >= 18.5 & dataset$B[i]  <= 20   &
    dataset$C[i]  >= 30 &  dataset$C[i]  <= 33   &
    dataset$E[i]  >= 32 &  dataset$E[i]  <= 35   &
    dataset$G[i]  >= 44 &  dataset$G[i]  <= 48) {
  dataset$Tutore[i] = "4"
 } else if (
    dataset$B[i]  >= 20 & dataset$B[i] <= 22   &
    dataset$C[i]  >= 32 & dataset$C[i] <= 35   &
    dataset$E[i]  >= 34 & dataset$E[i] <= 37   &
    dataset$G[i]  >= 47 & dataset$G[i] <= 51)
  {
  dataset$Tutore[i] = "6"
 } else if (
    dataset$B[i]  >= 22 & dataset$B[i]  <= 24       &
    dataset$C[i]  >= 34.5 & dataset$C[i]  <= 37.5   &
    dataset$E[i]  >= 36 & dataset$E[i]  <= 39.5     &
    dataset$G[i]  >= 50 & dataset$G[i]  <= 55){
    dataset$Tutore[i] = "8"
 } else if (
    dataset$B[i]  >= 24 & dataset$B[i]  <= 26     &
    dataset$C[i]  >= 37 & dataset$C[i]  <= 40.5   &
    dataset$E[i]  >= 39 & dataset$E[i]  <= 42     &
    dataset$G[i]  >= 54 & dataset$G[i]  <= 59){
    dataset$Tutore[i] = "10"
 } else if (
```

```
    dataset$B[i]  >= 26 & dataset$B[i]  <= 28   &
    dataset$C[i]  >= 40 & dataset$C[i]  <= 44   &
    dataset$E[i]  >= 41 & dataset$E[i]  <= 45   &
    dataset$G[i]  >= 58 & dataset$G[i]  <= 63){
    dataset$Tutore[i] = "12"
  } else if (
    dataset$B[i]  >= 28 & dataset$B[i]  <= 30   &
    dataset$C[i]  >= 43 & dataset$C[i]  <= 47   &
    dataset$E[i]  >= 44 & dataset$E[i]  <= 48   &
    dataset$G[i]  >= 62 & dataset$G[i]  <= 68){
    dataset$Tutore[i] = "14"
  }
}
```

3 Results & Discussion

This chapter will present the results obtained from the development of statistical models using the data contained in the database and from the economic analysis carried out on elastic compression braces.

The first part of the chapter is divided into three parts. The first relates to the evaluation of oedema between pre and post-treatment of the pathological limb compared to the contralateral healthy limb of a group of patients with unilateral lymphoedema. The second relates to the study of the percentage variation of oedema to quantify the effectiveness of the treatment performed on the edematous limb, comparing initial and final circumferential measurements. The third and final part studies deeply the data by implementing new models, focusing on the clinical classifications of lymphoedema.

The second part of the chapter calculates the number and typology, standard or custom-made, of elastic compression braces to be prescribed to the patients in the considered database, implementing an algorithm that assigns the correct typology following indications provided by the manufacturers. It also quantifies the amount of costs related to them.

3.1. Models results

3.1.1. Pre and post-treatment analysis compared to the healthy limb

This analysis was conducted to investigate the percentage change between the pathological and contralateral healthy limb by comparing the two measurement times of the circumferences (before and after treatment).

Considering 38 patients with 122 visits and with lymphoedema of the lower limb, the post hoc tests in the model described in section 2.2.2, showed a statistically significant difference between the marginal means before and after treatment for each point of at least 8.5%. All percentage values after treatment compared to the healthy limb were lower than those before treatment. Figure 29 shows that on average before treatment, the points most affected by pathology were D, C, B1 and B, which are located in the area below the knee. However, after treatment, they were reduced more than the other points, in particular points B1 (23.7%) and C (21.5%).

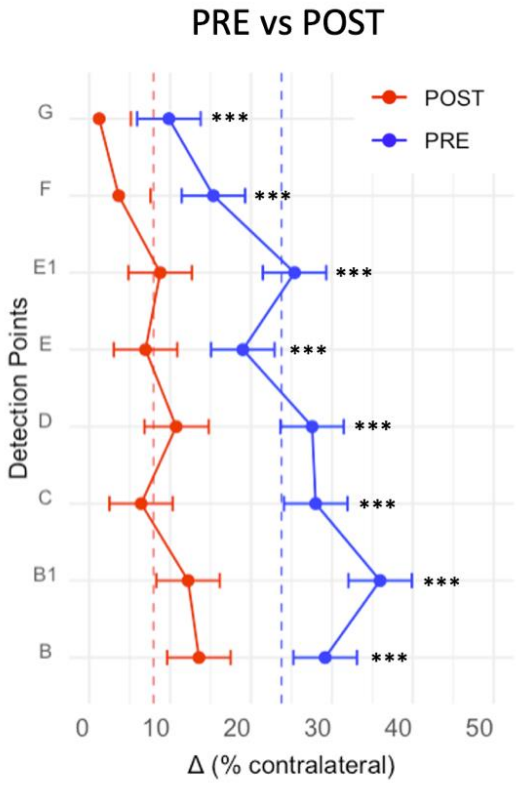

Figure 29: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (blue) and post-treatment (red) edematous lower limb circumference compared to healthy contralateral limb of all the detection points. *, **, ***: p<0.05, 0.01, 0.001 Pre vs Post.*

Furthermore, all points (B, B1, C, D, E, E1, F, G) were compared with each other before treatment and after treatment to assess whether a significant difference existed. In particular, Table 4 shows that the differences between adjacent points before treatment are all significant except between C-D. Moving along the limb from G to B there is an increasing difference, with the exception of the transition to point E and to point B. In the post-treatment, only the comparisons between B1-C, C-D and E1-F are significant and the trend of differences is almost similar to pre-treatment.

	PRE							POST						
	B1	C	D	E	E1	F	G	B1	C	D	E	E1	F	G
B	**-6.7**	1.1	1.6	**1.6**	3.7	**13.8**	**19.3**	1.3	**7.1**	2.8	**6.6**	**4.7**	**9.9**	**12.3**
B1	-	**7.9**	**8.4**	**16.9**	**10.5**	**20.6**	**26.1**	-	**5.8**	1.4	**5.2**	3.4	**8.5**	**10.9**
C	-	-	0.4	**9.0**	2.6	**12.6**	**18.1**	-	-	**-4.3**	-0.5	-2.3	2.7	**5.1**
D	-	-	-	**8.5**	2.1	**12.2**	**17.7**	-	-	-	3.7	1.9	**7.1**	**9.5**
E	-	-	-	-	**-6.4**	3.6	**9.1**	-	-	-	-	-1.8	3.3	**5.7**
E1	-	-	-	-	-	**10.0**	**15.5**	-	-	-	-	-	**5.1**	**7.5**
F	-	-	-	-	-	-	**5.4**	-	-	-	-	-	-	2.4

Table 4: *Difference of the estimated marginals means of the edematous lower limb circumference compared to the healthy contralateral limb. Comparison of the detection points in the pre-treatment (left) and post-treatment (right). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

In conclusion, being B1 (point near the ankle) the point that on average is most affected by the pathology and therefore more voluminous, the distal limb can be compared to the geometric figure of the cylinder as it does not tend to thin out as in the case of the healthy limb.

The same analysis was also conducted for the upper limb considering 36 patients with 98 visits. Also in this case, the differences between the marginal means estimated by the model for each point were all statistically significant with a value of at least 4.5%. All of the percentage values after treatment in relation to the healthy limb were lower than pre-treatment. Figure 30 shows that the most severely affected points are C1, C2 and D, which correspond to points identified on the forearm. As with the lower limb, for the upper limb the treatment was most effective on these points, reducing them by 17.3%, 15.2% and 13.4% respectively.

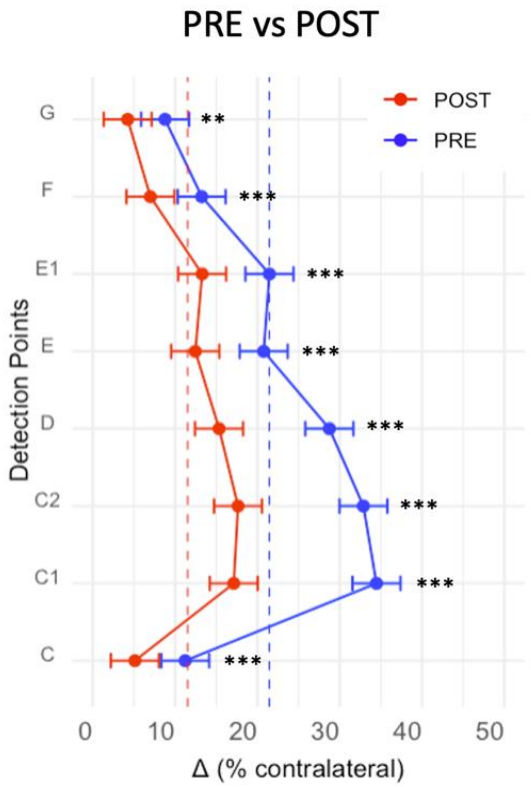

Figure 30: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (blue) and post-treatment (red) edematous upper limb circumference compared to healthy contralateral limb of all the detection points. *, **, ***: p<0.05, 0.01, 0.001 Pre vs Post.*

All points (C, C1, C2, D, E, E1, F, G) were compared with each other before treatment and after treatment to assess whether a significant difference existed. Table 5 shows that the only comparisons between adjacent points that are not significant are C1-C2 and E-E1 for pre-treatment. In post-treatment, however, only the comparisons between C-C1 and E1-F are significant. Furthermore, when moving along the limb both before and after treatment from G to C, the difference between the points is constantly increasing with the exception of E1-E and C1-C. In conclusion, it can be deduced that the treatment acts mainly on the area most affected by the pathology, the forearm, which nevertheless remains the most edematous.

	PRE							POST						
	C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G
C	**-23.2**	**-21.6**	**-17.5**	**-9.5**	**-10.2**	**-2.0**	**2.4**	**-12.0**	**-12.5**	**-10.2**	**-7.3**	**-8.1**	**-1.8**	**0.8**
C1	-	1.5	**5.7**	**13.7**	**13.0**	**21.2**	**25.6**	-	-0.5	1.7	**4.6**	**3.8**	**10.1**	**12.8**
C2	-	-	**4.1**	**12.1**	**11.4**	**19.6**	**24.1**	-	-	2.3	**5.1**	**4.3**	**10.6**	**13.4**
D	-	-	-	**7.9**	**7.2**	**15.5**	**19.9**	-	-	-	2.8	2.0	**8.3**	**11.1**
E	-	-	-	-	-0.6	**7.5**	**11.9**	-	-	-	-	-0.8	**5.4**	**8.2**
E1	-	-	-	-	-	**8.2**	**12.6**	-	-	-	-	-	**6.2**	**9.0**
F	-	-	-	-	-	-	**4.4**	-	-	-	-	-	-	2.7

Table 5: *Difference of the estimated marginals means of the edematous upper limb circumference compared to the healthy contralateral limb. Comparison of the detection points in the pre-treatment (left) and post-treatment (right). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

3.1.2. Treatment effect

The aim of the analysis was to examine the variation of the oedema by comparing the normalized measurements of the pathological limb on the last day with those on the first day, in order to quantify the effectiveness of the treatment.

Analyzing 38 patients with lymphoedema of the lower limb using the model developed as described in section 2.2.3, it was found that all points benefited from treatment with an average circumference reduction of 7%. In particular, as shown in Figure 31, the most reduced points are: C (10.3%), B1(13.3%) and B (10.7%).

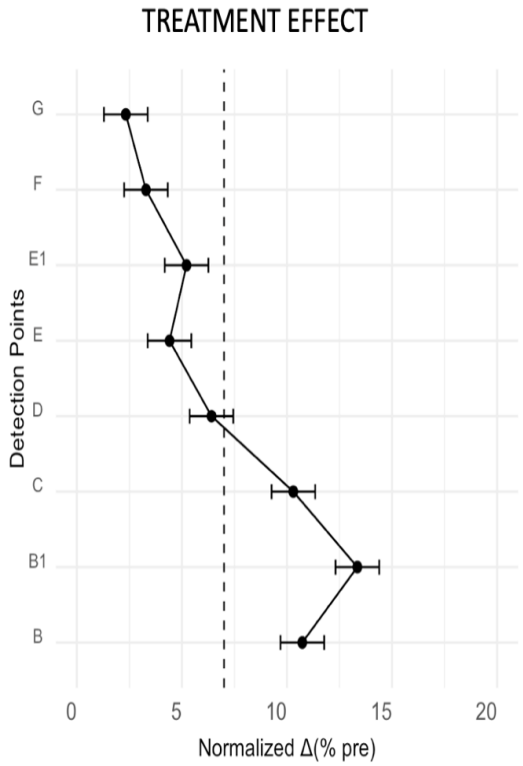

Figure 31: *Estimated marginals means (symbols) and 95% CI (whiskers) of normalized delta (pre-post/pre) of edematous lower limb circumference of all the detection points.*

All differences between the 8 detection points were calculated and evaluated the presence of statistical significance. Between the adjacent points, these differences are

all significant except in the comparisons between E-E1 and F-G and all positive except for B-B1 and E-E1, as is shown in Table 6.

	TREATMENT EFFECT						
	B1	**C**	**D**	**E**	**E1**	**F**	**G**
B	**-2.6**	0.4	**4.3**	**6.3**	**5.5**	**10.0**	**8.3**
B1	-	**3.0**	**6.9**	**8.9**	**8.1**	**10.0**	**11.0**
C	-	-	**3.8**	**5.8**	**5.0**	**7.0**	**7.9**
D	-	-	-	**1.9**	1.1	**3.1**	**4.0**
E	-	-	-	-	-0.8	1.1	**2.0**
E1	-	-	-	-	-	**1.9**	**2.8**
F	-	-	-	-	-	-	0.9

Table 6: *Difference of the estimated marginals means of the treatment effect. Comparison of the detection points in the normalized delta (pre-post/pre) of the edematous lower limb circumference. Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

From these results, it can be deduced that the therapeutic treatment succeeded in reducing the circumferences and the volume of all the points considered, acting particularly on the points that were most compromised before starting the treatment.

In addition, it can be concluded that from G to B the trend in the reduction of circumferences is always increasing with the exception of points E and B.

The analysis of 36 patients with lymphoedema of the upper limb, using the same statistical model (2.2.3), shows that all points also in this case benefited from the treatment, with an average circumference reduction of around 8%. In particular, as Figure 32 shows, the most reduced points are: D (9.9%), C2(10.7%) and C1 (12.1%).

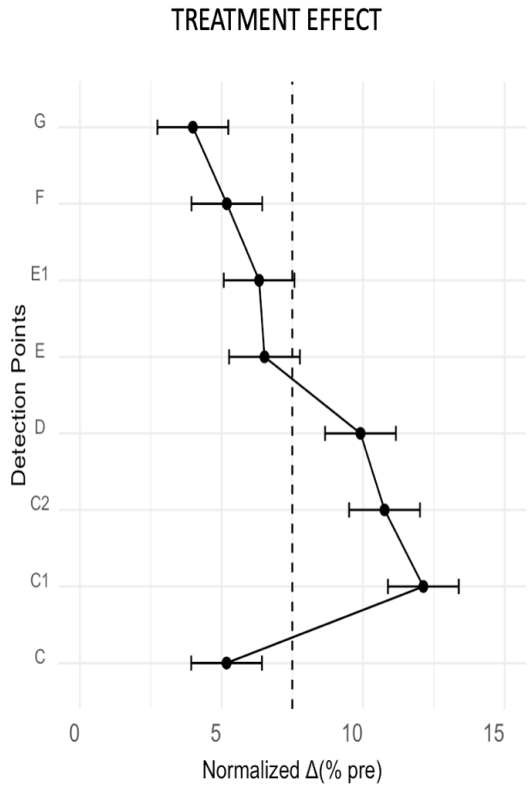

Figure 32: *Estimated marginals means (symbols) and 95% CI (whiskers) of normalized delta (pre-post/pre) of edematous upper limb circumference of all the detection points.*

All differences between the 8 detection points were calculated and the existence of statistical significance was assessed. Between adjacent points, the differences are only significant between C-C1 and between D-E and are all positive except when comparing points C-C1, as shown in Table 7.

	TREATMENT EFFECT						
	C1	**C2**	**D**	**E**	**E1**	**F**	**G**
C	**-6.9**	**-5.5**	**-4.7**	-1.3	-1.1	0	1.1
C1	-	1.3	**2.2**	**5.6**	**5.7**	**6.9**	**8.1**
C2	-	-	0.8	**4.2**	**4.4**	**5.5**	**6.7**
D	-	-	-	**3.3**	**3.5**	**4.7**	**5.9**
E	-	-	-	-	0.1	1.3	**2.5**
E1	-	-	-	-	-	1.1	**2.3**
F	-	-	-	-	-	-	1.2

Table 7: *Difference of the estimated marginals means of the treatment effect. Comparison of the detection points in the normalized delta (pre-post/pre) of the edematous upper limb circumference. Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

From these results, it can be deduced that the treatment succeeded in reducing the circumferences and volume of all the points considered, acting particularly on the points that were most compromised before starting the treatment (D, C2, C1).

3.1.3. Clinical factor analysis

Considering specifically the different clinical factors such as entity, tissue consistency, etiology and dysmorphic pattern, a further analysis was conducted to investigate the distribution of oedema, the percentage variation of circumferences before and after treatment, and the efficacy of the treatment itself by subdividing the patients according to these classifications. To achieve this goal, three mixed-effects models were implemented separately for each factor, described in section 2.2.4; the first for the analysis of data acquired before treatment, the second acquired after treatment (both in relation to the contralateral healthy limb), and the last used to compare the measurements of the edematous limb at the end of treatment with those at the beginning. The analysis was conducted separately for lower and upper limb.

Entity

In order to study this parameter, I'm referred to the scale indicated in the 'Consensus document of the International Society of Lymphology' [3], which, using as a parameter the percentage variation between the volume of the pathological limb compared to the healthy limb, defines three thresholds by dividing patients into groups according to the entity of the oedema: mild, moderate and severe.

<u>Lower limb</u>

For the lower limb, 38 patients were classified into 8 severe (39 visits), 18 moderate (70 visits) and 12 mild (13 visits). Each of the 8 points considered (B, B1, C, D, E, F, G) was compared between the different groups in order to assess whether or not there was a statistically significant difference (p-value < 0.05).

In the pre-treatment the differences among all points were not significant between mild and moderate. In fact, in Figure 33, it can be seen that the marginal means estimated by the model of mild patients for each point (symbols), do not deviate much from those of moderate patients and, moreover, the confidence intervals tend to overlap. Between moderate and severe patients, each point difference was significant. The only point where no significance is observed is point B1, although the p-value is not particularly high (0.06). Finally, mild and severe patients are compared, between whom a significant difference was recorded for all points.

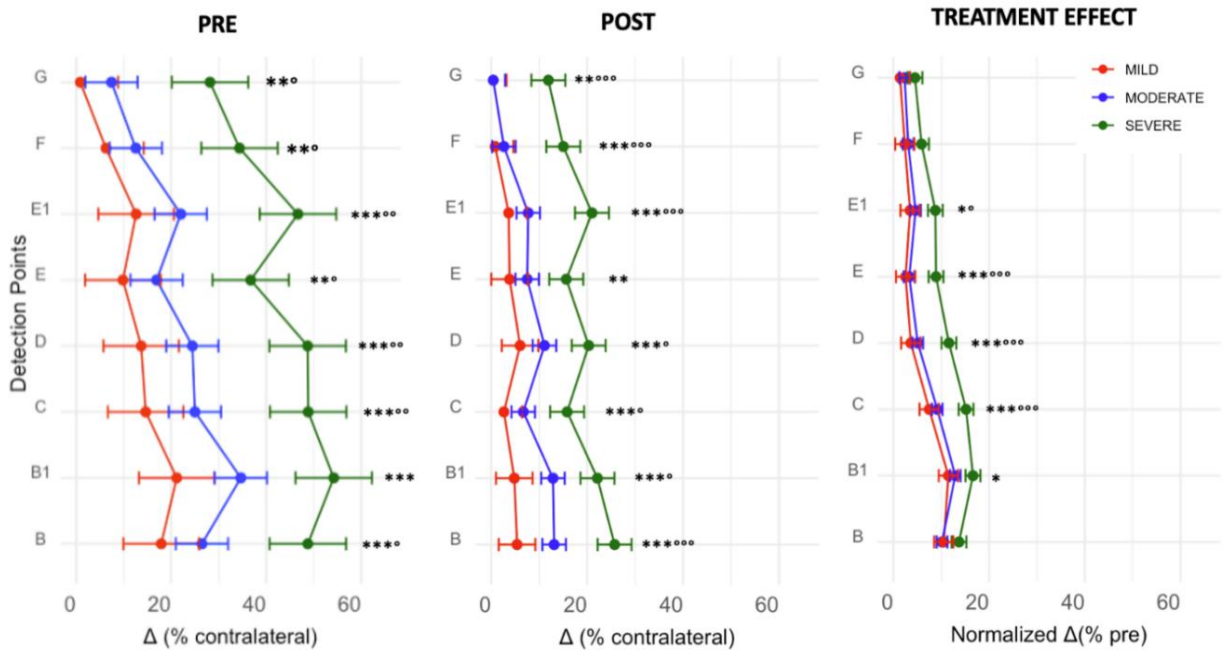

Figure 33: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous lower limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to lymphoedema entity: severe (green), moderate (blue) and mild (red). *, **, ***: p<0.05, 0.01, 0.001 Severe vs Mild; °, °°, °°°: p<0.05, 0.01, 0.001 Severe vs Moderate.*

In the post-treatment, there is an overall decrease in estimated point means in the three groups compared to pre-treatment. Among mild and moderate patients, the same scenario as described above is confirmed. All differences were statistically significant between mild and severe and between moderate and severe patients. The only point where no significance is observed is point E in the comparison between the latter.

Considering the normalized delta (pre-post/pre), shown in Figure 33 on the right, between the distinct groups, no significant improvements were observed at points G, F, B: the best treatment benefit of the severe group compared to mild and moderate (which are very similar) occurred in particular at points E, D, C. Overall, the smallest improvements were observed at points G and F for all entities and at point E for the mild and moderate categories.

Table 8 shows the differences between the marginal means estimated from the post-hoc tests in the statistical model between all point combinations.

		PRE							POST							TREATMENT EFFECT						
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
SEVERE	**B**	-5.4	-0.07	0.04	**12.0**	2.0	**14.3**	**20.5**	3.5	**9.9**	**5.4**	**10.0**	**4.7**	**10.7**	**13.8**	**-2.9**	-1.4	2.1	**4.8**	**4.9**	**7.8**	**9.2**
	B1	-	5.3	5.4	**17.4**	7.5	**19.8**	**26.0**	-	**6.3**	1.8	**6.4**	1.1	**7.1**	**10.2**	-	1.4	**5.0**	**7.7**	**7.8**	**10.7**	**12.1**
	C	-	-	0.1	**12.1**	2.1	**14.4**	**20.6**	-	-	-4.5	0.1	**-5.1**	0.7	3.9	-	-	**3.5**	**6.2**	**6.4**	**9.3**	**10.6**
	D	-	-	-	**11.9**	2.0	**14.3**	**20.5**	-	-	-	**4.6**	-0.6	**5.3**	**8.4**	-	-	-	2.6	**2.8**	**5.7**	**7.1**
	E	-	-	-	-	**-9.9**	2.3	**8.5**	-	-	-	-	**-5.3**	0.6	3.7	-	-	-	-	0.1	**3.0**	**4.4**
	E1	-	-	-	-	-	**12.3**	**18.5**	-	-	-	-	-	**5.9**	**9.1**	-	-	-	-	-	**2.8**	**4.2**
	F	-	-	-	-	-	-	6.2	-	-	-	-	-	-	3.1	-	-	-	-	-	-	1.3
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
MODERATE	**B**	**-8.1**	1.47	2.0	**9.5**	4.4	**13.9**	**19.0**	0.2	**6.4**	2.0	**5.6**	**5.3**	**10.4**	**12.6**	**-2.7**	0.9	**5.0**	**6.8**	**5.5**	**7.0**	**7.8**
	B1	-	**9.6**	**10.2**	**17.7**	**12.6**	**22.1**	**27.2**	-	**6.1**	1.7	**5.3**	**5.1**	**10.2**	**12.4**	-	**3.7**	**7.8**	**17.4**	**9.6**	**9.8**	**10.5**
	C	-	-	0.5	**8.0**	2.9	**12.4**	**17.5**	-	-	**-4.4**	-0.8	-1.0	**4.0**	**6.2**	-	-	**4.8**	**5.8**	**4.5**	**6.0**	**6.8**
	D	-	-	-	**7.5**	2.4	**11.9**	**17.0**	-	-	-	**3.6**	**3.3**	**8.4**	**10.6**	-	-	-	**1.7**	4.5	2.0	**2.7**
	E	-	-	-	-	-5.0	4.3	**9.4**	-	-	-	-	-0.2	**4.8**	**7.0**	-	-	-	-	-1.3	0.2	9.4
	E1	-	-	-	-	-	**9.4**	**14.5**	-	-	-	-	-	**5.0**	**7.2**	-	-	-	-	-	1.5	**2.2**
	F	-	-	-	-	-	-	5.1	-	-	-	-	-	-	2.2	-	-	-	-	-	-	0.7
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
MILD	**B**	-3.2	3.2	4.2	8.0	5.2	11.6	**17.0**	0.5	2.7	-0.6	1.5	1.7	4.5	6.0	-0.9	3.0	**6.9**	**7.9**	**7.0**	**8.1**	**9.1**
	B1	-	6.5	7.4	11.3	8.5	**14.9**	**20.3**	-	2.1	-1.2	0.9	1.1	3.9	5.4	-	4.0	**7.8**	**8.9**	**8.0**	**9.1**	**10.0**
	C	-	-	0.9	4.7	2.0	8.3	13.7	-	-	-3.3	-1.1	-0.9	1.8	3.2	-	-	3.8	**4.9**	4.0	5.0	**6.0**
	D	-	-	-	3.8	1.0	7.4	12.8	-	-	-	2.1	2.3	5.1	6.6	-	-	-	1.0	1.5	1.2	2.2
	E	-	-	-	-	-2.7	3.5	8.9	-	-	-	-	0.1	3.0	4.4	-	-	-	-	-9.2	1.7	1.1
	E1	-	-	-	-	-	6.3	11.7	-	-	-	-	-	2.8	4.2	-	-	-	-	-	1.0	2.0
	F	-	-	-	-	-	-	5.3	-	-	-	-	-	-	1.4	-	-	-	-	-	-	9.8

Table 8: *Difference of the estimated marginals means of the edematous lower limb circumference compared to the healthy contralateral limb and of the treatment effect. Comparison of the detection points in the pre-treatment (left), post-treatment (middle) and treatment effect (pre-post/pre) (right) according to the entity of lymphoedema: severe (green), moderate (blue) and mild (red). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

It can therefore be concluded that treatment is equally effective on the limbs of patients with mild and moderate lymphoedema, while limbs with severe lymphoedema, which deviate more from the healthy limb, benefit more from treatment. It could be proposed to unify the two entities mild and moderate as they are comparable in terms of both size and treatment effectiveness.

Upper limb

For the upper limb, 20 patients with severe (57 visits), 15 moderate (38 visits) and 3 mild (3 visits) were determined.

In the pre-treatment analysis, there is a marked significant difference between severe and moderate and between severe and mild patients at points C1, C2 and D, and to a lesser extent, but significant, at points E and E1 between severe and moderate. The difference between severe and moderate increases progressively from point G to point C1, while there is no difference at point C as shown in Figure 34.

In the post-treatment analysis, the same scenario is repeated, albeit with less marked differences between the different levels of entity: the greatest differences are always found at points C1, C2 and D.

Between the pre and post-treatment (Figure 34 on the right), significant differences are shown only in points C1, C2, D, E, in the comparison between severe and moderate.

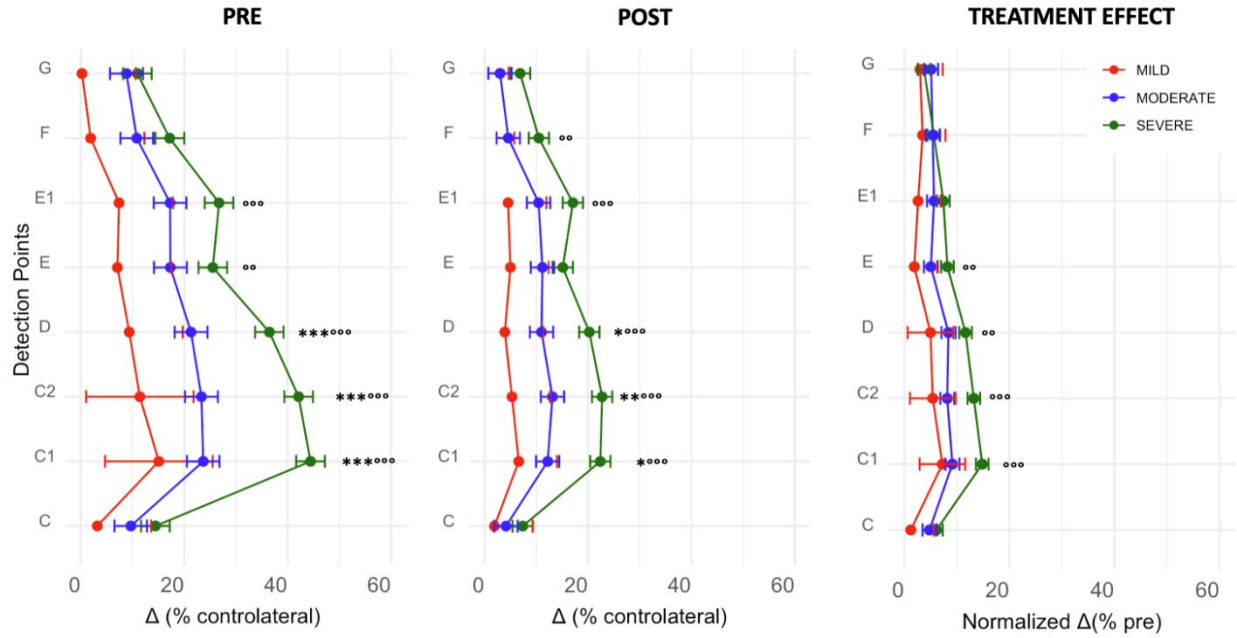

Figure 34: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous upper limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to lymphoedema entity: severe (green), moderate (blue) and mild (red). *, **, ***: p<0.05, 0.01, 0.001 Severe vs Mild; °, °°, °°°: p<0.05, 0.01, 0.001 Severe vs Moderate.*

Table 9 shows the differences between the marginal means estimated from the post-hoc tests in the statistical model among all combinations of points.

		PRE							POST							TREATMENT EFFECT						
		C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G
SEVERE	C	-30.0	-27.6	-22.0	-11.1	-12.3	-2.7	3.4	-15.0	-15.3	-12.8	**-7.7**	**-9.7**	-3.1	0.4	**-8.7**	**-7.1**	**-5.5**	**-2.0**	-1.3	5.0	**2.3**
	C1	-	2.3	**7.9**	**18.8**	**17.6**	**27.2**	**33.4**	-	-0.3	2.1	**7.2**	**5.3**	**11.8**	**15.5**	-	1.6	**3.1**	**6.6**	**7.3**	**9.2**	**1.1**
	C2	-	-	**5.6**	**16.5**	**15.3**	**24.9**	**31.1**	-	-	2.4	**7.6**	**5.6**	**12.2**	**15.8**	-	-	1.5	**5.0**	**5.7**	**7.6**	**9.4**
	D	-	-	-	**10.9**	**9.7**	**19.2**	**25.5**	-	-	-	**5.1**	3.1	**9.7**	**13.3**	-	-	-	**3.4**	**4.2**	**6.0**	**7.8**
	E	-	-	-	-	-1.2	**8.3**	**14.5**	-	-	-	-	-1.9	**4.6**	**8.2**	-	-	-	-	7.6	**2.5**	**4.4**
	E1	-	-	-	-	-	**9.5**	**15.7**	-	-	-	-	-	**6.5**	**10.1**	-	-	-	-	-	1.8	**3.6**
	F	-	-	-	-	-	-	**6.2**	-	-	-	-	-	-	3.6	-	-	-	-	-	-	1.8
		C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G
MODERATE	C	-13.9	-13.6	-11.6	**-7.6**	**-7.5**	-1.1	0.85	**-8.0**	**-8.9**	**-6.8**	**-7.0**	**-6.3**	-0.4	1.5	**-4.3**	**-3.3**	**-3.6**	-2.6	-8.6	-6.0	-3.1
	C1	-	0.3	2.3	6.3	6.4	**12.8**	**14.8**	-	-0.9	1.1	1.0	1.7	**7.6**	**9.2**	-	9.8	7.5	**4.0**	**3.4**	**3.7**	**4.0**
	C2	-	-	2.0	6.0	6.0	**12.5**	**14.5**	-	-	2.1	1.9	2.6	**8.5**	**10.1**	-	-	-2.3	**3.1**	**2.5**	**2.7**	**3.0**
	D	-	-	-	3.9	4.0	**10.4**	**12.4**	-	-	-	-0.1	0.5	**6.4**	**8.0**	-	-	-	**3.3**	**2.7**	**3.0**	**3.2**
	E	-	-	-	-	0.05	6.4	**8.4**	-	-	-	-	0.7	**6.6**	**8.2**	-	-	-	-	-5.9	-3.4	0
	E1	-	-	-	-	-	6.4	**8.4**	-	-	-	-	-	**5.8**	**7.4**	-	-	-	-	-	2.5	5.5
	F	-	-	-	-	-	-	2.0	-	-	-	-	-	-	1.5	-	-	-	-	-	-	2.9
		C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G
MILD	C	-11.8	-8.2	-6.1	-3.8	-4.2	1.2	2.9	-4.6	-3.3	-2.0	-3.0	-2.6	3.5	4.6	-6.0	-4.1	-3.7	-0.6	-1.3	-2.2	-1.7
	C1	-	3.6	5.7	7.9	7.6	13.1	14.8	-	1.2	2.6	1.6	2.0	8.2	9.3	-	1.8	2.2	5.3	4.6	3.7	4.2
	C2	-	-	2.0	4.3	4.0	9.5	11.1	-	-	1.3	0.3	0.7	6.9	8.0	-	-	4.4	3.5	2.7	1.9	2.4
	D	-	-	-	2.2	1.9	7.4	9.1	-	-	-	-1.0	-0.6	5.5	6.6	-	-	-	3.0	2.3	1.4	1.9
	E	-	-	-	-	-0.3	5.1	6.8	-	-	-	-	0.4	6.6	7.7	-	-	-	-	-0.7	-1.5	-1.0
	E1	-	-	-	-	-	5.4	7.1	-	-	-	-	-	6.2	7.2	-	-	-	-	-	-0.8	-0.3
	F	-	-	-	-	-	-	1.6	-	-	-	-	-	-	1.0	-	-	-	-	-	-	0.4

Table 9: *Difference of the estimated marginals means of the edematous upper limb circumference compared to the healthy contralateral limb and of the treatment effect. Comparison of the detection points in the pre-treatment (left), post-treatment (middle) and treatment effect (pre-post/pre) (right) according to the entity of lymphoedema: severe (green), moderate (blue) and mild (red). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

It can therefore be concluded that, as with the lower limb, mild and moderate patients respond to therapy in the same way and can therefore be grouped into a single classification. In severe patients, despite starting from a more compromised clinical situation, the therapy managed to reduce the volume of the affected limb overall.

Etiology

As described in the first chapter, there are two forms of lymphoedema: primary and secondary. The primary is congenital and is usually caused by incompletely formed lymphatic channels or lymph nodes, the secondary is not congenital but develops during life due to, for example, surgery, infection, or injury [5, 6, 7].

The patients in the database analyzed for this study were divided according to etiology (study not yet present in the literature). Due to a lack of data, only patients with lymphoedema of the lower extremity were examined, specifically 13 primary patients (49 visits) and 25 secondary patients (73 visits), to investigate the relevance of this distinction and the effectiveness of the treatment performed.

From the results of the implemented model, in general, no statistically significant differences emerged between the two groups. As is shown in Figure 35, in the pre-treatment the secondaries have on average higher values than the primaries at every detection point, except for point B. This means that statistically in secondary patients the edematous limb is more impaired than in primary patients. However, the differences between all points are not to be considered statistically significant. There

is a greater variation between the pathological and healthy limb when moving from point G to point B.

In post-treatment, the trends of the estimated marginal means of the two forms of lymphoedema overlap, thus generating a non-significance between them.

Also, in the analysis of treatment efficacy, there are no significant differences between the two groups studied, but for both a reduction in circumferences along the entire limb is estimated.

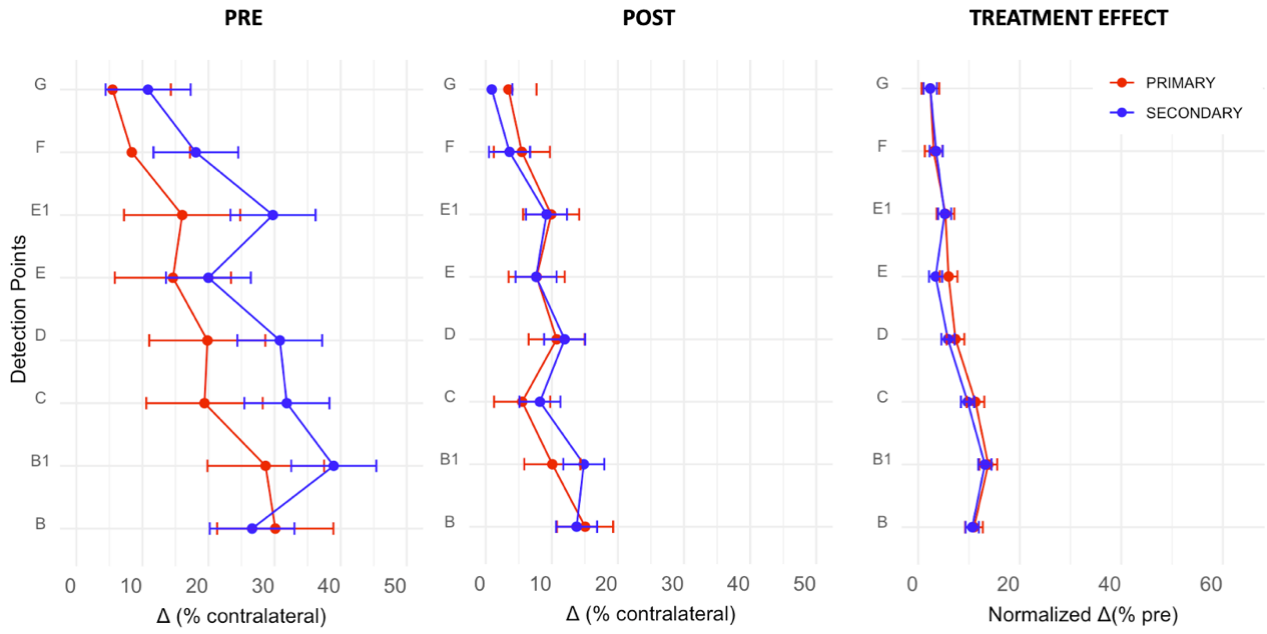

Figure 35: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous lower limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to lymphoedema etiology: primary (red) and secondary (blue).*

Table 10 shows the differences between the marginal means estimated from the post-hoc tests in the statistical model among all combinations of points.

		PRE							POST							TREATMENT EFFECT						
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
PRIMARY	**B**	1.4	**10.7**	**10.2**	**15.4**	**14.0**	**21.7**	**24.6**	**4.9**	**9.5**	**4.3**	**7.3**	**5.1**	**9.5**	**11.6**	**-2.8**	-0.2	**3.6**	**4.9**	**5.6**	**7.9**	**8.5**
	B1	-	**9.2**	**8.8**	**14.0**	**12.6**	**20.2**	**23.1**	-	**4.5**	-0.6	2.3	0.1	**4.6**	**6.6**	-	**2.5**	**6.4**	**7.8**	**8.4**	**10.7**	**11.4**
	C	-	-	-0.4	4.7	3.3	**11.0**	**13.9**	-	-	**-5.2**	-2.2	**-4.3**	0.04	2.0	-	-	**3.9**	**5.2**	**5.9**	**8.2**	**8.8**
	D	-	-	-	5.2	3.8	**11.4**	**14.3**	-	-	-	3.0	0.8	**5.2**	**7.2**	-	-	-	1.3	1.9	4.3	**4.9**
	E	-	-	-	-	-1.4	6.2	**9.1**	-	-	-	-	-2.1	2.2	**4.2**	-	-	-	-	6.2	**2.9**	**3.5**
	E1	-	-	-	-	-	**7.6**	**10.5**	-	-	-	-	-	**4.4**	**6.4**	-	-	-	-	-	2.3	**2.9**
	F	-	-	-	-	-	-	2.9	-	-	-	-	-	-	2.0	-	-	-	-	-	-	0.6
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
SECONDARY	**B**	**-12.3**	-5.2	-4.1	**6.6**	-3.3	**8.5**	**15.7**	-1.0	**5.5**	1.8	**6.1**	**4.5**	**10.1**	**12.8**	**-2.4**	0.9	**4.7**	**7.2**	**5.4**	**7.1**	**8.2**
	B1	-	**7.0**	**8.1**	**18.9**	**9.2**	**20.8**	**28.1**	-	**6.6**	2.9	**7.2**	**5.6**	**11.2**	**13.9**	-	**3.3**	**7.2**	**9.6**	**7.9**	**9.5**	**10.7**
	C	-	-	1.0	**11.8**	2.1	**13.7**	**21.0**	-	-	**-3.7**	0.5	-0.9	**4.5**	**7.2**	-	-	**3.8**	**6.2**	**4.5**	**6.1**	**7.3**
	D	-	-	-	**10.8**	1.0	**12.7**	**19.9**	-	-	-	**4.3**	2.7	**8.3**	**11.0**	-	-	-	**2.4**	0.6	**2.3**	**3.4**
	E	-	-	-	-	**-9.7**	1.9	**9.1**	-	-	-	-	-1.5	**4.0**	**6.7**	-	-	-	-	-1.7	-0.1	1.0
	E1	-	-	-	-	-	**11.6**	**18.8**	-	-	-	-	-	**5.5**	**8.2**	-	-	-	-	-	1.6	**2.8**
	F	-	-	-	-	-	-	**7.2**	-	-	-	-	-	-	2.6	-	-	-	-	-	-	0.6

Table 10: *Difference of the estimated marginals means of the edematous lower limb circumference compared to the healthy contralateral limb and of the treatment effect. Comparison of the detection points in the pre-treatment (left), post-treatment (middle) and treatment effect (pre-post/pre) (right) according to the etiology of lymphoedema: primary (red) and secondary (blue). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

In conclusion, it can be established from these analyses that the classification of patients by etiology in the diagnosis phase is relevant in order to investigate the causes that originated this disease, but in the treatment phase it is not, because all patients respond similarly to treatment.

Dysmorphic pattern

In this study the novel classification proposed by the Istituto Clinico Città Studi in Milan is investigated, whereby patients with lymphoedema of the lower limb are subdivided according to the greater edematous involvement of point B (LA1) or point B1 (LA2). The intention was to compare how the oedema is distributed in the two dysmorphic patterns and to discuss the relevance of this distinction for treatment purposes. 21 LA1 patients (64 visits) and 17 LA2 patients (58 visits) were analyzed.

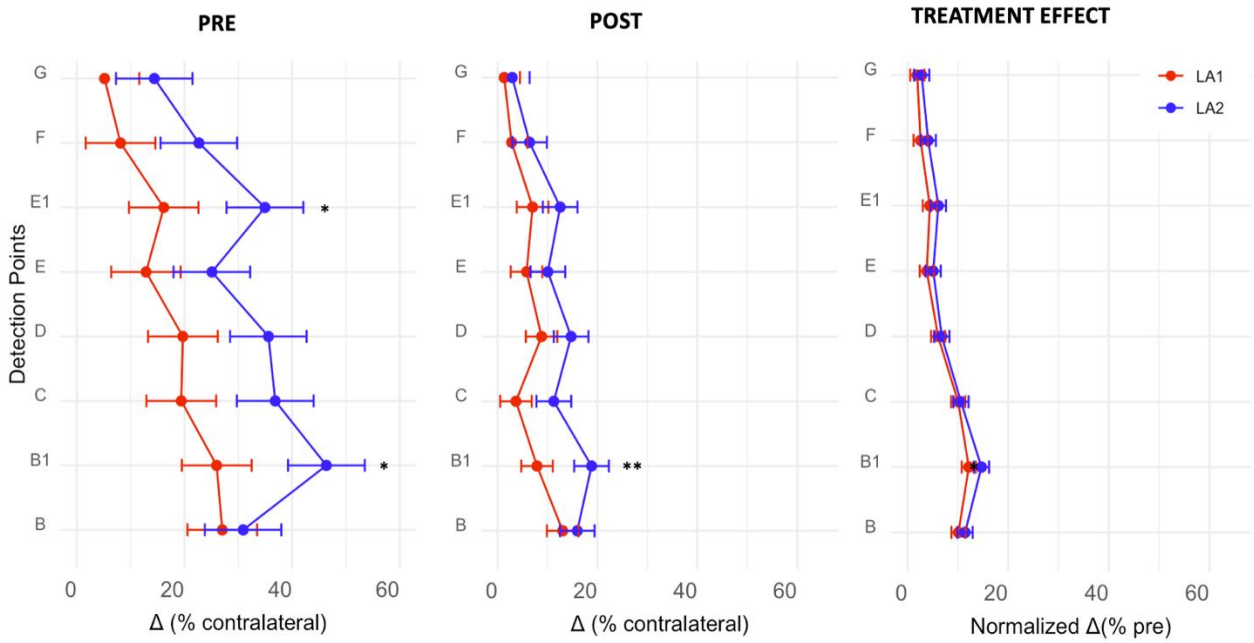

Figure 36: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous lower limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to dysmorphic pattern of lymphoedema: LA1 (red) and LA2 (blue). *, **, ***: p<0.05, 0.01, 0.001.*

As shown in Figure 36, the distribution of oedema along the limb is almost similar and no significant differences emerge at the various points except at B1 (both pre and post-

treatment) and E1 (pre-treatment). Overall, all the points of patients classified as LA2 deviate more from the healthy limb than those of LA1.

The differences between the various points for both LA1 and LA2 patients in the pre, post and delta normalized were also calculated, as shown in the following table.

		PRE							POST							TREATMENT EFFECT						
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
LA1	**B**	1.0	**7.6**	**7.3**	**14.1**	**10.8**	**18.9**	**21.8**	**5.1**	**9.3**	**4.2**	**7.2**	**6.0**	**10.2**	**11.7**	-2.0	0	**4.0**	**6.3**	**5.6**	**7.5**	**8.1**
	B1	-	**6.5**	**6.2**	**13.1**	**9.8**	**17.8**	**20.8**	-	**4.2**	-0.9	2.1	0.8	**5.0**	**6.5**	-	**2.1**	**6.1**	**8.3**	**7.7**	**9.5**	**10.2**
	C	-	-	-0.2	**6.5**	3.2	**11.2**	**14.2**	-	-	**-5.1**	-2.1	**-3.3**	0.8	2.3	-	-	**3.9**	**6.2**	**5.6**	**7.4**	**8.1**
	D	-	-	-	**6.8**	3.5	**11.5**	**14.5**	-	-	-	3.0	1.7	**6.0**	**7.4**	-	-	-	**2.2**	1.6	**3.4**	**4.1**
	E	-	-	-	-	-3.2	4.7	**7.7**	-	-	-	-	-1.2	2.9	**4.4**	-	-	-	-	-0.6	1.2	1.8
	E1	-	-	-	-	-	**8.0**	**11.0**	-	-	-	-	-	**4.2**	**5.6**	-	-	-	-	-	1.8	**2.5**
	F	-	-	-	-	-	-	2.9	-	-	-	-	-	-	1.4	-	-	-	-	-	-	0.6
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
LA2	**B**	**-15.4**	-5.9	-4.6	5.8	-4.0	**8.2**	**16.5**	8.0	**12.2**	7.1	**10.1**	**8.9**	**13.1**	**14.6**	**-3.2**	0.8	**4.6**	**6.3**	**5.3**	**7.3**	**8.6**
	B1	-	**9.4**	**10.7**	**21.2**	**11.4**	**23.6**	**31.9**	-	**7.5**	**4.0**	**8.7**	**6.2**	**12.4**	**15.8**	-	**4.0**	**7.8**	**9.5**	**8.5**	**10.5**	**11.8**
	C	-	-	1.2	**11.7**	1.9	**14.1**	**22.4**	-	-	**-3.4**	1.1	-1.2	**4.8**	**8.3**	-	-	**3.8**	**5.5**	**4.4**	**6.5**	**7.7**
	D	-	-	-	**10.5**	0.6	**12.9**	**21.2**	-	-	-	**4.6**	2.1	**8.3**	**11.7**	-	-	-	1.7	0.6	**2.7**	**3.9**
	E	-	-	-	-	**-9.8**	2.4	**10.7**	-	-	-	-	-2.4	**3.6**	**7.1**	-	-	-	-	-1.0	0.9	**2.2**
	E1	-	-	-	-	-	**12.2**	**20.5**	-	-	-	-	-	**6.1**	**9.6**	-	-	-	-	-	2.0	**3.3**
	F	-	-	-	-	-	-	**8.2**	-	-	-	-	-	-	**3.4**	-	-	-	-	-	-	1.2

Table 11: *Difference of the estimated marginals means of the edematous lower limb circumference compared to the healthy contralateral limb and of the treatment effect. Comparison of the detection points in the pre-treatment (left), post-treatment (middle) and treatment effect (pre-post/pre) (right) according to dysmorphic pattern of lymphoedema: LA1 (red) and LA2 (blue). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

In conclusion, it can be said that this distinction is not useful for the purpose of treatment, as at each detection point the percentage of circumference reduction is the same in LA1 and LA2.

Tissue consistency

As described in Chapter 1, one of the measurements taken during the first day of treatment is the tissue consistency of the edematous limb. This is generally assessed subjectively through palpation of the limb by the operator, or by using an instrument called tonometer that evaluates tissue consistency by measuring compressive strength and its variation over time. This instrument, however, is not capable of measuring concave and convex areas (present in tissues with lymphoedema) and for this reason, in this study, I am referred to a medical instrumentation described in section 1.4.1.2, the result of a multicenter study [26]. The tissue consistency of each patient was assessed by measuring the circumferences of the edematous limb and was divided into soft, medium, and hard. Patients were grouped according to three thresholds:

- > 0,5 mm soft tissue
- > -0,5 e < 0,5 mm medium tissue
- < -0,5 mm hard tissue

Considering the lower limb, 15 patients with soft (34 visits), 18 with medium (72 visits) and 6 with hard (16 visits) tissue were analyzed and compared. As shown in Figure 37, for none of the measured times under investigation were found statistically significant differences between the distinct groups except for the points E1 and D in the pre-treatment, B1 in the post-treatment and D in the normalized delta in the

comparison between medium and soft tissue. Generally, soft tissue has lower values for all points than the other tissue consistencies, and that the average of centimetric reduction in circumferences between patients with soft and medium tissue is the same (the trends overlap completely in the last graph on the right). Patients with hard tissue responded, albeit to a lesser extent than the other patients, to the therapy within a brief period of time.

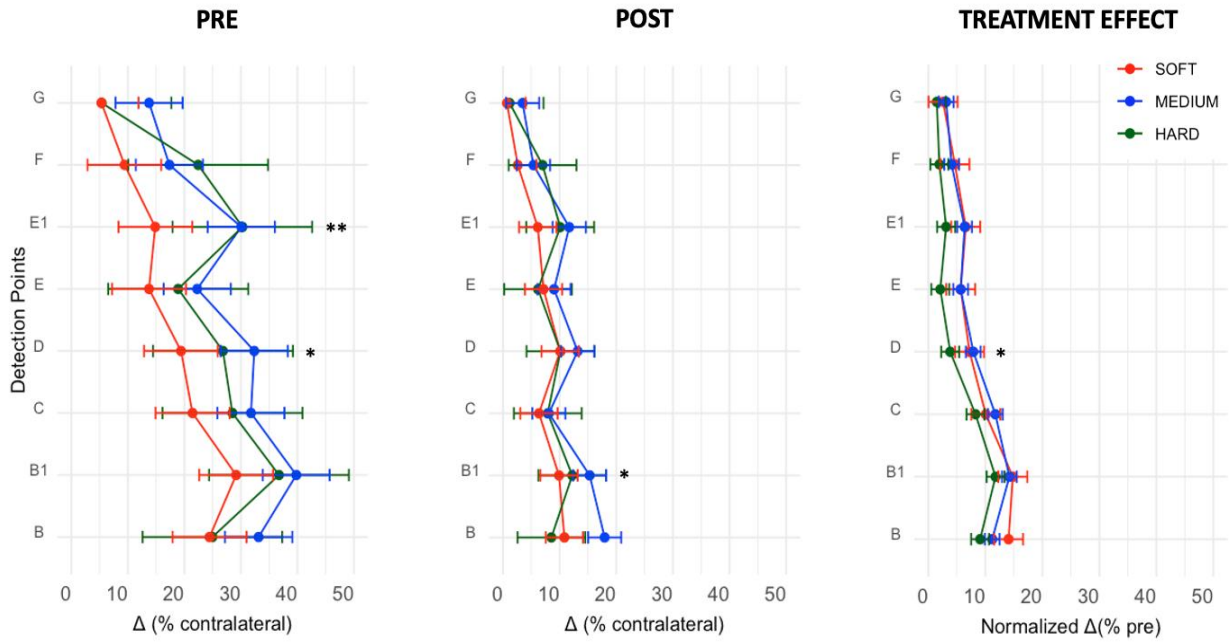

Figure 37: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous lower limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to lymphoedema tissue consistency: hard (green), medium (blue) and soft (red). *, **, ***: p<0.05, 0.01, 0.001 Medium vs Soft.*

In addition, post hoc tests were used to compare all points with each other according to the three tissue consistencies and calculate the differences in pre, post and normalized delta, as shown in the following table.

		PRE							POST							TREATMENT EFFECT							
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
HARD	**B**	-11.7	-3.5	-1.8	6.0	-5.3	2.5	**19.5**	-3.6	0.6	-1.5	2.3	-1.5	1.5	**7.3**	**-0.7**	4.0	**6.8**	**8.4**	**7.5**	**9.4**	**11.4**
	B1	-	8.2	9.9	**17.8**	6.4	**14.3**	**31.3**	-	4.3	2.0	6.0	2.1	5.2	**11.0**	-	**4.7**	**7.5**	**9.1**	**8.2**	**10.1**	**12.2**
	C	-	-	1.6	9.6	-1.7	6.0	**23.1**	-	-	-2.2	1.7	-2.1	0.9	6.7	-	-	2.8	4.3	3.5	**5.4**	**7.4**
	D	-	-	-	7.9	-3.4	4.3	**21.4**	-	-	-	3.9	0.04	3.1	**8.9**	-	-	-	1.5	0.6	2.5	**4.6**
	E	-	-	-	-	**-11.3**	-3.5	**13.5**	-	-	-	-	-3.9	-0.8	5.0	-	-	-	-	-0.8	1.0	3.0
	E1	-	-	-	-	-	7.8	**24.9**	-	-	-	-	-	3.1	**8.9**	-	-	-	-	-	**1.8**	3.9
	F	-	-	-	-	-	-	**17.0**	-	-	-	-	-	-	5.8	-	-	-	-	-	-	2.0
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
MEDIUM	**B**	**-6.6**	1.3	0.7	**10.8**	3.0	**15.7**	**19.3**	2.6	**9.8**	**4.7**	**8.9**	**6.2**	**12.5**	**14.4**	**-3.0**	-0.5	**3.3**	**5.5**	**4.8**	**7.1**	**8.0**
	B1	-	**8.0**	**7.4**	**17.5**	**9.7**	**22.4**	**26.0**	-	**7.2**	2.1	**6.2**	**3.6**	**9.9**	**11.8**	-	**2.4**	**6.3**	**8.5**	**7.8**	**10.1**	**11.0**
	C	-	-	-0.5	**9.5**	1.7	**14.4**	**18.0**	-	-	**-5.0**	-0.9	**-3.6**	2.7	4.6	-	-	**3.8**	**6.0**	**5.3**	**7.6**	**8.6**
	D	-	-	-	**10.0**	2.3	**15.0**	**18.5**	-	-	-	**4.1**	1.4	**7.8**	**9.7**	-	-	-	**2.2**	1.5	**3.8**	**4.7**
	E	-	-	-	-	**-7.7**	4.9	**8.5**	-	-	-	-	-2.6	**3.6**	**5.5**	-	-	-	-	-0.6	1.5	**2.5**
	E1	-	-	-	-	-	**12.6**	**16.2**	-	-	-	-	-	**6.3**	**8.2**	-	-	-	-	-	**2.2**	**3.2**
	F	-	-	-	-	-	-	3.5	-	-	-	-	-	-	1.9	-	-	-	-	-	-	0.9
		B1	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**	**B1**	**C**	**D**	**E**	**E1**	**F**	**G**
SOFT	**B**	-4.7	3.0	5.0	**10.7**	**9.5**	**15.0**	**19.1**	0.9	4.4	0.7	3.6	4.7	**8.2**	**10.1**	-2.7	0.8	**5.2**	**6.9**	**5.9**	**7.1**	**7.6**
	B1	-	7.7	**9.7**	**15.4**	**14.2**	**19.7**	**23.8**	-	3.5	-0.2	2.7	3.7	**7.2**	**9.1**	-	**3.5**	**7.9**	**9.6**	**8.6**	**9.8**	**10.3**
	C	-	-	2.0	7.6	6.5	**12.0**	**16.0**	-	-	-3.7	-0.8	0.2	3.7	**5.6**	-	-	**4.4**	**6.1**	**5.1**	**6.3**	**6.7**
	D	-	-	-	5.6	4.5	**9.9**	**14.0**	-	-	-	2.9	3.9	**7.4**	**9.3**	-	-	-	1.7	0.7	1.9	2.3
	E	-	-	-	-	-1.1	4.3	8.4	-	-	-	-	1.0	4.5	**6.4**	-	-	-	-	-1.0	0.1	0.6
	E1	-	-	-	-	-	5.4	9.5	-	-	-	-	-	3.5	**5.4**	-	-	-	-	-	1.1	1.6
	F	-	-	-	-	-	-	4.0	-	-	-	-	-	-	1.9	-	-	-	-	-	-	0.4

Table 12: *Difference of the estimated marginals means of the edematous upper limb circumference compared to the healthy contralateral limb and of the treatment effect. Comparison of the detection points in the pre-treatment (left), post-treatment (middle) and treatment effect (pre-post/pre) (right) according to lymphoedema tissue consistency: hard (green), medium (blue) and soft (red). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

The results obtained from the analysis conducted on the tissue consistency of the upper limb in 18 patients with soft (43 visits), 22 with medium (50 visits) and 3 with hard (5 visits) tissue, revealed no statistically significant differences between them (Figure 38).

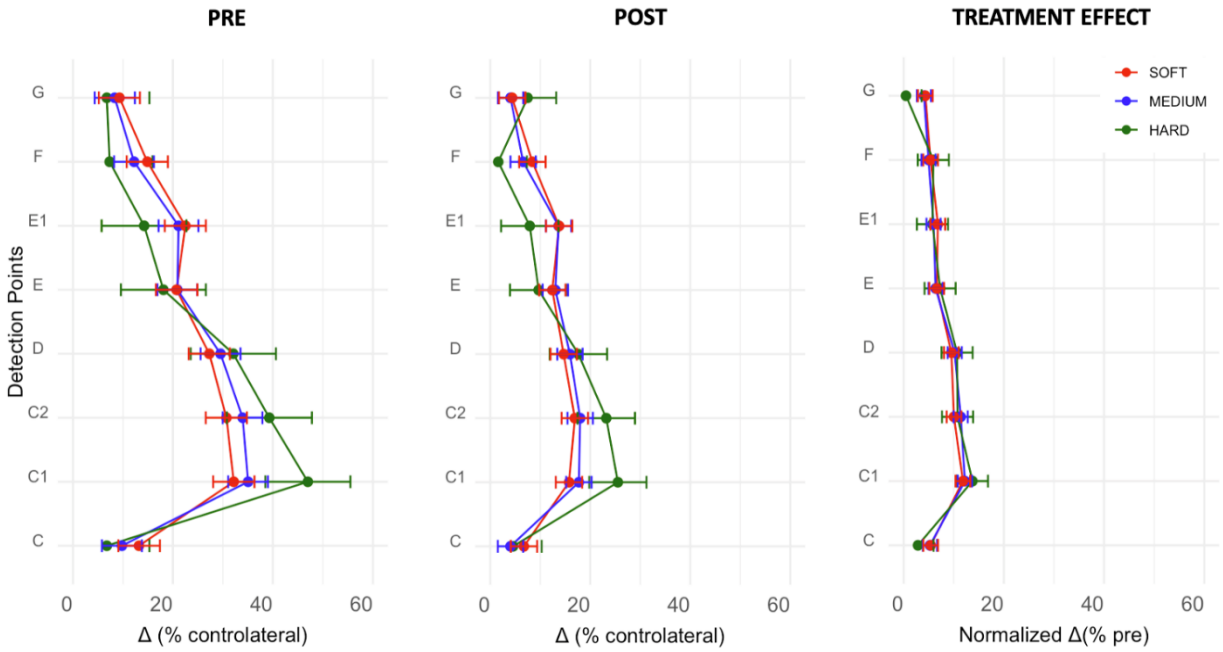

Figure 38: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous upper limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to lymphoedema tissue consistency: hard (green), medium (blue) and soft (red).*

In particular, they respond to treatment similarly, and despite the high degree of impairment, hard tissues also improve following Complex Decongestive Therapy.

Table 13 shows the calculated differences between all points of the different tissue consistencies in the pre, post and normalized delta.

		PRE							POST							TREATMENT EFFECT						
		C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G
HARD	C	**-40.1**	**-32.4**	**-25.2**	-11.3	-7.4	-0.5	0	**-20.9**	**-18.6**	-13.0	-5.1	-3.3	2.9	-2.9	**-10.8**	**-7.9**	**-7.8**	-4.4	-2.8	-3.0	2.3
	C1	-	7.6	14.9	**28.8**	**32.7**	**39.6**	**40.2**	-	2.3	7.8	**15.8**	**17.6**	**23.9**	**18.0**	-	2.9	3.0	6.4	**7.9**	**7.8**	**13.2**
	C2	-	-	7.2	**21.1**	**25.0**	**31.9**	**32.5**	-	-	5.5	13.5	**15.3**	**21.6**	**15.7**	-	-	0	3.4	5.0	4.8	**10.2**
	D	-	-	-	13.9	17.8	**24.7**	**25.2**	-	-	-	7.6	9.7	**16.0**	10.1	-	-	-	3.3	4.9	4.7	**10.1**
	E	-	-	-	-	3.8	10.7	11.3	-	-	-	-	1.7	8.0	2.2	-	-	-	-	1.5	1.3	6.8
	E1	-	-	-	-	-	6.8	7.4	-	-	-	-	-	6.3	0.4	-	-	-	-	-	-0.1	5.2
	F	-	-	-	-	-	-	0.5	-	-	-	-	-	-	-5.8	-	-	-	-	-	-	5.4
		C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G
MEDIUM	C	**-25.2**	**-24.1**	**-19.7**	**-11.1**	**-11.3**	-2.4	1.4	**-13.6**	**-13.9**	**-11.9**	**-8.9**	**-9.6**	-2.5	-0.01	**-6.9**	**-6.1**	**-4.9**	-1.1	-0.7	0.2	1.1
	C1	-	1.0	5.5	**14.1**	**13.9**	**22.8**	**26.6**	-	-0.2	1.7	**4.6**	4.0	**11.1**	**13.6**	-	**0.8**	**2.0**	**5.8**	**6.2**	**7.2**	**8.1**
	C2	-	-	4.4	**13.0**	**12.8**	**21.7**	**25.5**	-	-	2.0	**4.9**	4.3	**11.4**	**13.9**	-	-	**1.2**	**5.0**	**5.4**	**6.4**	**7.3**
	D	-	-	-	**8.6**	**8.3**	**17.2**	**21.1**	-	-	-	2.9	2.2	**9.3**	**11.8**	-	-	-	**3.8**	4.2	5.2	**6.1**
	E	-	-	-	-	-0.2	**8.6**	**12.5**	-	-	-	-	-0.6	**6.4**	**8.9**	-	-	-	-	0.4	1.4	2.3
	E1	-	-	-	-	-	**8.8**	**12.7**	-	-	-	-	-	**7.0**	**9.6**	-	-	-	-	-	1.0	1.9
	F	-	-	-	-	-	-	3.8	-	-	-	-	-	-	2.5	-	-	-	-	-	-	0.8
		C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G	C1	C2	D	E	E1	F	G
SOFT	C	**-18.9**	**-17.4**	**-14.0**	**-7.5**	**-9.2**	-1.6	3.9	**-9.0**	**-10.1**	**-7.9**	**-5.6**	**-7.0**	-1.6	2.3	**-6.4**	**-4.6**	**-4.1**	-1.2	-1.4	0	1.0
	C1	-	1.4	4.8	**11.4**	**9.6**	**17.2**	**22.8**	-	-1.1	1.0	3.3	1.9	**7.3**	**11.3**	-	1-7	2.3	**5.2**	**5.0**	**6.4**	**7.5**
	C2	-	-	3.4	**9.9**	**8.2**	**15.8**	**21.3**	-	-	2.2	4.4	3.1	**8.4**	**12.5**	-	-	0.5	**3.4**	**3.2**	**4.6**	**5.7**
	D	-	-	-	6.5	4.7	**12.3**	**17.9**	-	-	-	2.2	0.9	**6.2**	**10.2**	-	-	-	**2.9**	**2.6**	**4.1**	**5.2**
	E	-	-	-	-	-1.7	5.8	**11.4**	-	-	-	-	-1.3	3.9	**8.0**	-	-	-	-	-0.2	1.2	2.2
	E1	-	-	-	-	-	**7.6**	**13.1**	-	-	-	-	-	**5.3**	**9.3**	-	-	-	-	-	1.4	2.5
	F	-	-	-	-	-	-	5.5	-	-	-	-	-	-	4.0	-	-	-	-	-	-	1.0

Table 13: *Difference of the estimated marginals means of the edematous upper limb circumference compared to the healthy contralateral limb and of the treatment effect. Comparison of the detection points in the pre-treatment (left), post-treatment (middle) and treatment effect (pre-post/pre) (right) according to lymphoedema tissue consistency: hard (green), medium (blue) and soft (red). Negative value indicates that the value of the point in the row is smaller than the corresponding point in the column. Positive value indicates that the value of the point in the row is greater than the corresponding column point. Statistically significant differences (p-value <0.05) are highlighted in bold.*

3.2. Elastic compression braces results

At the end of each cycle of therapy, it is mandatory for the patient to wear the elastic brace daily, which then becomes the only serious and effective weapon to counteract the progression of the lymphoedema and preserve the benefits obtained from the intensive phase of Complex Decongestive Therapy [40-41-42]. The guidelines highlight the importance of compression therapy with an elastic brace, depending on the clinical case and at the discretion of the treating specialist. The brace should only be worn when the limb has reached its best condition, otherwise the patient cannot tolerate the high pressure on the edematous limb [43-44]. There are two types: standard or custom-made; the standard brace, which allows to reduce costs, can be prescribed only in lymphedema at the initial stage, but in the following clinical stages, due to the dysmorphic limb, it is necessary to prescribe the custom-made brace. In contrast to standard braces, custom-made ones fit perfectly to the patient's limb and have optimal characteristics that in some cases become a forced choice. The average lifespan of an elastic brace is approximately 6-8 months [45], because the material from which it is made, regardless of its nature and quality, tends to lose its elastic characteristics and properties over time with daily use. Braces, therefore, become less effective over time, eventually losing their usefulness, and forcing their replacement.

By developing an algorithm, each patient was assigned a more suitable (standard or custom-made) brace considering the status of the lymphoedema at the end of each treatment. The total number of braces examined for this analysis is 122 for the lower limb and 98 for the upper limb, assuming that each patient is classified as new at each treatment cycle. The results of the analysis showed that for the lower limb, 13 patients were prescribed a standard brace, while the remaining 109 patients were prescribed a custom-made brace, as shown in Figure 39. For the upper limb, 4 patients fell within the standard size, while the remaining 94 did not (Figure 40).

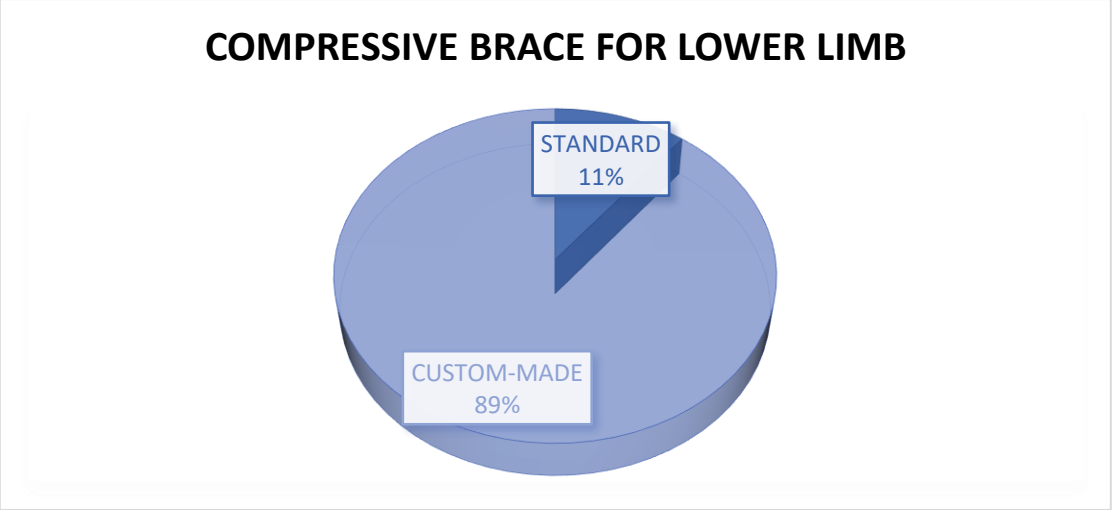

Figure 39: *Distribution of elastic-compression braces between standard and custom-made for the lower limb used in the maintenance phase of Complex Decongestive Therapy.*

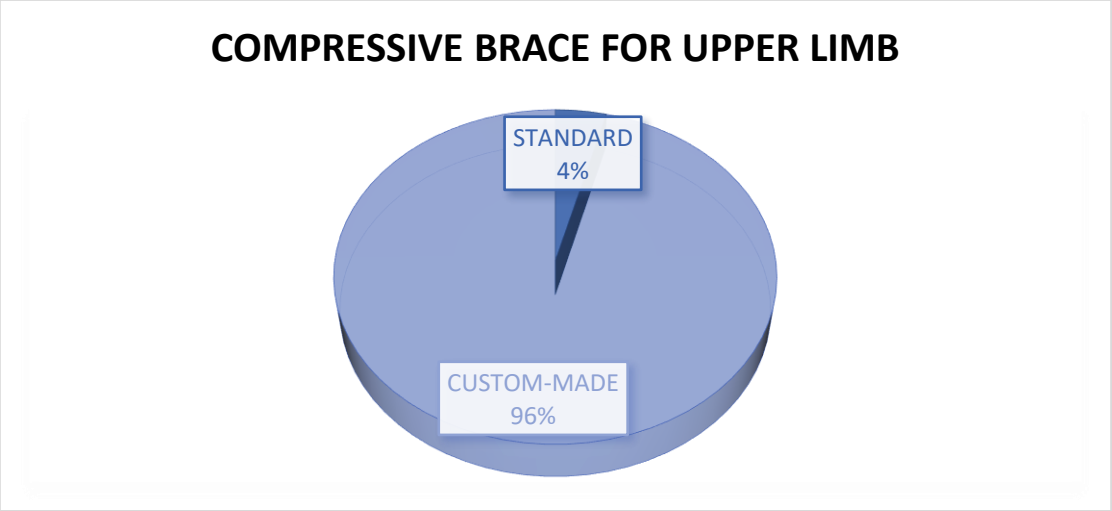

Figure 40: *Distribution of elastic-compression braces between standard and custom-made for the upper limb used in the maintenance phase of Complex Decongestive Therapy.*

In order to determine the average cost of each brace, for the lower limb it was assumed that all patients required a compression stocking and for the upper limb a brace consisting of an arm sleeve without hand + glove with fingers.

The average cost of a standard brace for a lower limb is approximately 77 € + VAT while for an upper limb it is approximately 190.2 € + VAT. In contrast, custom-made braces cost on average 133.6 € + VAT for the lower limb and 206.6 € + VAT for the upper limb. VAT is 4% in the case of disability or with exemption codes, and 22% in the absence of them.

As mentioned above, the brace must be replaced at least every six months to ensure the necessary compression and, therefore, the annual amount becomes:

- Standard lower brace: 154 € + VAT
- Standard upper brace: 380.4 € + VAT
- Custom-made lower brace: 267.2 € + VAT
- Custom-made upper brace: 413.2 € + VAT

The WHO has estimated the prevalence of lymphoedema in Italy at around 350 thousand cases. Epidemiological studies have shown that lymphoedema affecting the upper limbs is more frequent (58%) than the lower limbs (42%). Considering these data, an estimate of the annual costs at the national level was evaluated: about 147 thousand subjects have lymphoedema of the lower limb while 203 thousand of the upper limb. Assuming the same trend as in the analyzed database, it emerges that for the lower limb about 130830 patients need a custom-made brace for an annual amount of almost € 35 million + VAT and 16170 patients need a standard one for an annual cost of about € 2.5 million + VAT. For the upper limb, about 194880 patients need a custom-made brace for a total annual cost of € 80.5 million + VAT and 8120 patients need a standard brace for a total annual cost of over € 3 million + VAT. In summary, in Italy for patients with lymphoedema the total annual costs amount to approximately € 121 million + VAT.

In the Decree of the President of the Council of Ministers of 2017 defining the new Essential Levels of Care (Livelli Essenziali di Assistenza - LEA) in Annex 5, List 1,

under the heading "custom-made aids" [45], individual therapy aids are mentioned as "exclusively prescribable for patients with chronic primary lymphoedema (cod. RGG020) and for patients with secondary lymphoedema stabilized by oncological surgery, for whom compression therapy cannot be effectively conducted with similar standard aids (cod. 048)".

Here, a problem arises, since, due to the lack of implementing measures of the LEAs [45], patients with cod. 048 are forced to personally provide for the expenses related to the purchase and replacement of custom-made braces, expenses that they will have to bear for the rest of their lives.

Moreover, if some Regions, with their own measures and investments, have provided autonomously to give contributions to patients against proven expenses of custom-made elastic compression braces, in most Regions (including Lombardy), due to different availability of resources and re-entry plans, patients do not benefit from any assistance. In other words, in addition to the lack of the implementing decrees of the LEAs, there is an additional problem of territorial inhomogeneity in the assistance given to people with lymphoedema.

In this study, 68 braces for lymphoedema in the lower limb and 98 in the upper limb, prescribed to patients with cod. 048, were analyzed. Considering the costs just described the total amount for standard lower limb braces is 1001 € and 14562.4 € for custom-made ones. For standard braces for the upper edematous limb, the total cost is 760.8 € and 19420.4 € for custom-made ones.

In conclusion, it can be said that patients with secondary lymphoedema are those who most need a customized brace but for whom, according to the regulations in force in the Lombardy Region, no reimbursement is provided. This situation is becoming increasingly unacceptable, especially in the historical period in which we are living. For patients with lymphoedema, time is extremely precious, as it is a chronic condition characterized by a fast course and disabling outcomes. It is deemed incumbent on the

institutions to take action to make citizens' right to health and the right to a better quality of life a reality.

4 Conclusion

Lymphoedema, a disease that for a long time has received little attention from physicians and researchers, has obtained greater scientific interest especially since the last century, when there has been an increase in the number of cases of lymphoedema due to both the treatment of tumours (lymphadenectomy, radiotherapy, etc.) and the increased survival of these patients (with greater prevalence of the chronicity of lymphoedema itself).

For these reasons, the treatment of lymphoedema, although currently it has not achieved a definitive cure of the disease, has been complemented with various types of treatment and, among them, Complex Decongestive Therapy (CDT), managing to achieve important results with significant improvement of the affected limb, as recorded and published by several authors.

Analyzing the data reported in the literature, it emerges that there are 300 million cases worldwide, while in Italy 350 thousand people are affected by lymphoedema, with more than 40 thousand new cases every year. The high incidence demonstrates the importance of prevention, both in terms of early diagnosis and timely treatment, considering the heavy psychological, social, and physical disability implications of this pathology.

This thesis work arises from the need to characterize a sample population of subjects suffering from lymphoedema, to illustrate the course of the pathology along the affected limb over time, and to verify but mainly validate the effectiveness of the

treatments performed at the Istituto Clinico Città Studi in Milan. In addition, attention is focused on the need for intervention by the Public Health in the maintenance phase, characterized by the use of very expensive custom-made braces in most cases.

Medical records of 74 patients aged between 30 and 75 years treated at the clinic were collected. Over the years, the same patients have needed to undergo treatment again and, therefore, the total number of records analyzed is 220.

Initially, it was necessary to develop a database that contained all the medical records to be taken into account, and that was able to manage the data with which to make considerations of the change in oedema over time and to carry out statistical evaluations.

The first results obtained from the statistical analysis on the percentage change compared to the contralateral healthy limb between pre and post-treatment show that overall, all points responded positively to the therapy, decreasing by at least 8.5% for the lower limb and 4.5% for the upper limb. In particular, this percentage increased to 23.7% in the area below the knee and 17.3% at the forearm level, which corresponded to the most compromised areas before treatment.

In a second analysis, the percentage variation between pre and post-treatment measurements of the edematous limb was examined to characterize the effectiveness of the treatment. The data showed that the most compromised points, B1 for the lower limb and C1 for the upper limb, are the ones that are reduced the most (13%).

The effectiveness of therapy was also assessed by comparing patients divided according to different classifications: etiology (primary or secondary), entity (mild, moderate, or severe), tissue consistency (soft, medium, or hard) and dysmorphic pattern (LA1 or LA2). Regarding etiology, this distinction was not statistically significant. The analysis of the entity of lymphoedema showed that all entities can benefit from this treatment. However, there was no statistically significant difference between the response to therapy of mild and moderate patients, with severe patients

benefiting most. Statistically, it appears that even for patients with greater tissue impairment, margins of improvement can be achieved within a short period of time. However, these tissues are reduced in percentage terms to a lesser extent than the others. The statistical study on the dysmorphic pattern showed that this distinction is not significant for treatment purposes.

The last objective of this work was to quantify the number of braces to be prescribed to this sample of patients for the maintenance phase of therapy, distinguishing them between standard and custom-made, and evaluate the total cost. 220 braces were examined, and it was found that 203 were custom-made and 17 were standard. In general, the brace is the key tool for the optimisation of the results achieved in the first phase of CDT and avoids the aggravation of the pathology. The costs for this aid are very high, especially for those that have to be made specifically for the individual patient. The total amount can be borne by the patients themselves, by the National Health Service or by a health insurance company, also according to the regulations in force in the State or in the Region.

With respect to custom-made elastic compression braces, there is no uniformity of treatment in Italy. In fact, in some regional realities these are provided free of charge to secondary forms of lymphoedema resulting from neoplasms (code 048) and by payment of a ticket to primary forms (code RGG020). In others, such as in the Lombardy region, the problem of providing customised elastic compression braces for cancer patients remains unresolved. They are forced to pay for the purchase and replacement of the braces themselves (every 6-8 months).

The mixed effects models were used to conduct these analyses. They provide, through both qualitative and quantitative research methods, a more complete clinical overview that facilitates a wider and deeper understanding of the phenomenon.

In conclusion, the scientific research conducted has shown an overall and statistically significant improvement in the pathological condition of lymphoedema of the patients

after undergoing CDT. The use of the segmental technique for the identification of the points to be measured, allowed the comparison of patients with different characteristics in proportional terms.

Although these results are significant and promising, it is known that the sample analyzed came from a single clinical centre and that some of the categories examined had low numbers.

In order to confirm these results, further studies involving patients from multiple clinical centres could be considered.

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