EXECUTIVE SUMMARY OF THE THESIS

Lymphoedema and Complex Decongestive Therapy: data analysis and economical aspects

TESI MAGISTRALE IN BIOMEDICAL ENGINEERING – INGEGNERIA BIOMEDICA

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1. Introduction

According to the most recent International Society of Lymphology (ISL) consensus document [1], "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". It is classified as primary (genetic) or secondary (acquired) lymphoedema.
This pathology affects about 40000 Italians a year (20% to 40% are patients undergoing cancer treatment) [2]. The treatment protocol is based on a multidisciplinary-multimodal approach involving skin care, manual lymph drainage, compression therapy and decongestive exercise with a bandaged limb, called Complex Decongestive Therapy (CDT). The therapy is divided into two phases: the intensive phase, which aims to reduce the volume and consistency of oedema, and the maintenance phase, which aims to prevent the return of oedema using elastic compression braces. The technique, called 'Segmental Technique' (ST), identifies measurement points, that are always constant in proportional terms using a procedure for fractions of the various heights/lengths. By using this technique, it is possible to compare subjects with different dysmorphic conditions. Therefore, it can be determined, based on residual dysmorphisms, which of the different elastic compression braces (standard or custom-made) may be most suitable and compliant. In lymphology, elastic compression braces are unquestionably the mainstay of the maintenance phase of the disease. Custom-made elastic braces are indicated when the limb does not fit into the standard range of products on the market. The cost of a standard brace for a lower limb is around 77 € + VAT and for an upper limb around 190.2 € + VAT. Custom-made braces cost 133.6 € + VAT for lower limb and 206.6 € + VAT for upper limb. Depending on the laws in force in the state or in the region, the costs of elastic compression brace may be borne by the patient, the Health Service, or the insurance company.
The aims of this study were:

- to show the distribution of oedema along the limb based on clinical classifications;
- to quantitatively assess the effectiveness of Complex Decongestive Therapy using statistical models;
- to analyze the clinical costs of the elastic compression braces.

2. Materials and Methods

This thesis work was made possible by the collaboration between the Department of Electronics,

Information and Bioengineering (DEIB) of the Politecnico di Milano and the Istituto Clinico Città Studi, Milano.

2.1 Dataset and models

The clinical records of 74 patients (aged between 30-75 years) treated at the Clinical Institute were retrospectively reviewed. The medical records consisted of a biographical data sheet and a start-end treatment measurement sheet. Because of the chronic nature of lymphoedema, some patients underwent cycles of treatment over the years; making a total of 220 records.

For data management and processing, a database was created and implemented using Microsoft Excel ® software, to calculate volumes, centimetric differences and all useful indices for assessing lymphoedema before and after the treatment to quantitatively assess the effectiveness of CDT.

Patients were classified according to specific clinical characteristics, namely: 1) entity (mild, moderate, and severe classified according to International Society of Lymphology, [1]), 2) etiology (primary or secondary), 3) tissue consistency (soft, medium, or hard) and 4) dysmorphic pattern of lymphoedema according to the greater edematous point involved (LA1 for point B or LA2 for point B1, see the right panel of Figure 1). The analyses were conducted separately for both upper and lower limbs. However, only patients with lymphoedema of the lower limb could be further investigated according to etiology as lymphoedema of upper limb is extremely rare. The first analysis was the description of the lymphoedema within the limb by computing the percentage variation of the pathological limb with respect of the healthy limb, calculated as follows:

$$\Delta = \frac{Pathological - Healthy}{Healthy} * 100 \qquad (1)$$

The dataset contains the observations of 38 and 36 patients, for the lower and upper limbs respectively. Each patient underwent 10-days treatment. The measurements of 8 detection points, indicated in Figure 1 and 2, were collected the first day, that classified as pre-treatment and the tenth day, classified as post-treatment. Using the Jamovi ® software, mixed effects models were developed for unbalanced panel data: patient ID were used as random effects, while measurement time (pre/post treatment), detection points and their interaction as fixed effects. In addition to the point estimates of the coefficients and their 95% confidence intervals, post hoc fixed-effects comparison tests were returned. A statistical significance level of 5%, according to Bonferroni's correction, was considered. In addition, two mixed-effects models were developed, using the percentage change in pre- and post-treatment measurement as the dependent variable, calculated as follows:

$$\Delta\% = \frac{Pre\_treatment - Post\_treatment}{Pre\_treatment} * 100 \qquad (2)$$

By creating a mixed-effects model using detection points as the independent variable, it was intended to determine how Δ% varies across data points in order to characterize treatment efficacy. Similar specific and dedicated models were implemented according to 4 clinical factors (i.e.: entity, tissue consistency, etiology, and dysmorphic pattern) used as independent variables within the model. Separately for each factor, it was investigated how the percentage change with respect to treatment time, calculated as in (2), may change depending on the detection points and the factor itself. A mixed effects model was developed with this measure as the dependent variable and, as regressors in the model, detection points, the clinical factor, and their interaction. A further investigation was conducted by developing a model that uses the percentage difference with respect to the healthy limb as the dependent variable, calculated as in (1) maintaining the same regressors as the previous model. The research was conducted separately by measurement time (pre/post treatment).

2.2 Analysis of Elastic compression braces

At the end of the treatment (day 10), the percentage of patients requiring a standard or custom-made brace was assessed (based on standard table of elastic compression braces providers). For this analysis, two data sets (one for the lower limb and one for the upper limb) were created using Microsoft Excel, each consisting of the patient ID and circumference measurements at the end of treatment expressed in centimeters for all points. Using the R ® software, an algorithm was developed to indicate the type of brace to be prescribed. Each patient was assigned a size provided that all circumferences fell within the ranges indicated in the tables. If even one circumference fell outside the range, the size was not assigned, and the brace had to be custom-made. Then, the related costs were estimated.

3. Results

Overall data of lower limb: pre vs post

38 patients and 122 visits were analyzed. A statistically significant percentage reduction between pre- and post-treatment occurred for each detection point (at least 8.5%), particularly in points B1 and C. Figure 1 (left panel) represents the marginal means estimated by the model for each detection point, in the pre- and post-treatment, with a 95% confidence interval. An increasing trend can be seen along the G to C points of the limb, with the exception of point E and point C (for post-treatment) and point B (for pre-treatment). The difference between pre and post tends to be greater as points vary from G to B with a particular increase from points E to B1, while for point B there is a decrease with respect to point B1. There is also a slight decrease between point E1 and point E. Point B1 decreased more than the other points (13%) and the overall reduction it is concentrated in the area below the knee (above 10%) while in the thigh it is less than 6%.

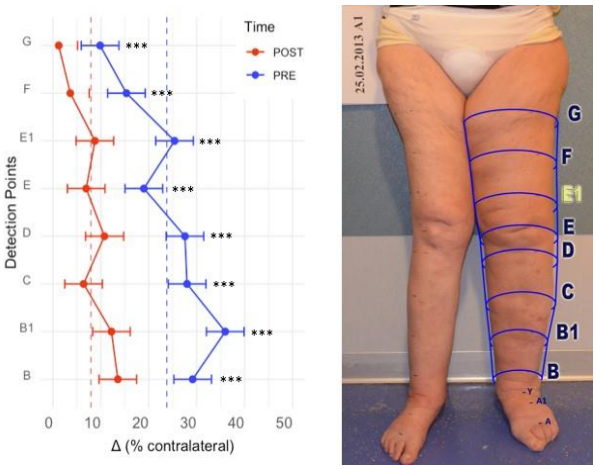

Figure 1: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (blue) and post-treatment (red) edematous lower limb circumference compared to healthy contralateral limb of all the detection points. *, **, ***: p<0.05, 0.01, 0.001 Pre vs Post.*

It was found that all points benefited from treatment with an average circumference reduction of 7% as shown in Figure 2. In particular the most reduced points are: C (10.3%), B1(13.3%) and B (10.7%).

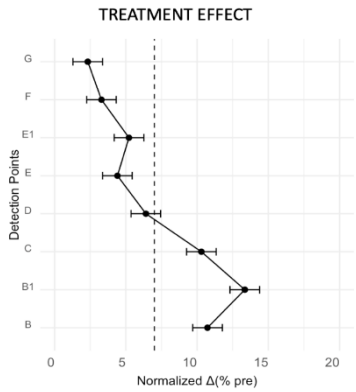

Figure 2: *Estimated marginals means (symbols) and 95% CI (whiskers) of normalized delta (pre-post/pre) of edematous lower limb circumference of all the detection points.*

Overall data of upper limb: pre vs post

36 patients and 98 visits were analyzed. A statistically significant difference is shown for each point between pre- and post-treatment, especially at points C1, C2, and D (corresponding to the forearm). A trend very similar to the lower limb can be observed for the upper limb (Figure 3), with even more marked differences between pre- and post-treatment for points D to C1. A relevant decrease in the difference with respect to the healthy limb from point C1 to point C can be noted, which coincides with a smaller difference between pre and post treatment.

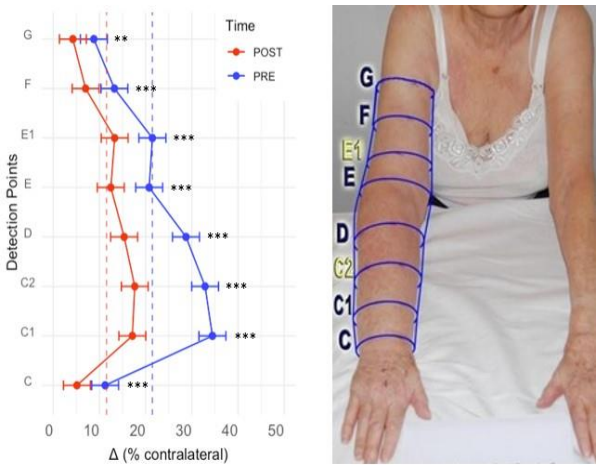

Figure 3: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (blue) and post-treatment (red) edematous upper limb circumference compared to healthy contralateral limb of all the detection points. *, **, ***: p<0.05, 0.01, 0.001 Pre vs Post.*

Figure 4 shows that all points also in this case benefited from the treatment, with an average circumference reduction of around 8%. In particular the most reduced points are: D (9.9%), C2(10.7%) and C1 (12.1%).

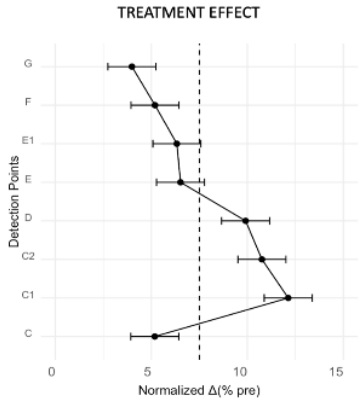

Figure 4: *Estimated marginals means (symbols) and 95% CI (whiskers) of normalized delta (pre-post/pre) of edematous upper limb circumference of all the detection points.*

Tables 1 and 2 represent the differences of the marginal mean of the detection points estimated by the models for the lower and upper limbs, respectively.

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

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 1-2: *Difference of the estimated marginals means of the treatment effect of lower and upper limb. Comparison of the detection points in the normalized delta (pre-post/pre). 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.*

Dysmorphisms pattern of lower limb

In general, few relevant differences emerged when comparing the different dysmorphic patterns. In the pre-treatment study, the estimated marginal means of LA2 were always greater than those of the LA1 at each detection point: these differences were only statistically significant at points B1 and E1. About the post-treatment analysis, the same overview of the situation was observed (LA2 greater than LA1), but with significant differences only at point B1.

Entity of lower limb

Using the variable entity as analysis factor, the mean percentage variation between pre- and post-treatment were estimated for the severe (8 patients, 39 visits), moderate (18 patients, 70 visits), and mild (12 patients, 13 visits) levels as shown in Figure 5.

While the moderate and mild levels were similar, they were significantly lower than the severe level. In particular, the differences were statistically significant for B1, C, D, E, E1 between severe and mild levels and for C, D, E, E1 between severe and moderate levels. Before treatment, the percentage variation between the healthy limb and the pathological limb classified as severe significantly differed at almost all points respect to those classified as mild and medium. No differences were observed for any point in the comparison between mild and medium. The same analysis was carried out at the end of the treatment, where these differences were found to be statistically significant for all points in the severe-mild and severe-medium comparisons, while no differences were observed between mild and medium.

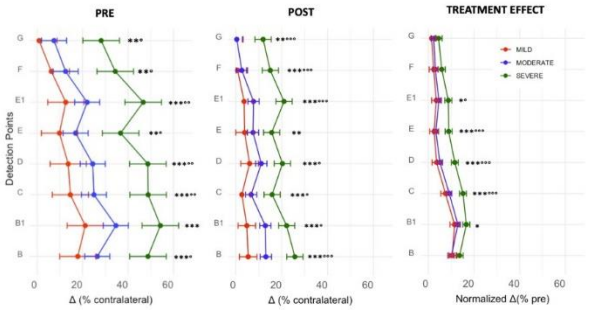

Figure 5: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous lower limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to lymphoedema entity: severe (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.*

Etiology and Tissue consistency of lower limb

From the point of view of etiology and tissue consistency, there were no statistically significant differences in percentage changes between pre- and post-treatment and in the comparison between pathological limb and healthy limb at any point analyzing 6 patients with hard tissue (16 visits), 18 medium (72 visits) and 15 soft (34 visits). Overall, the mean variation in 13 primaries patients (49 visits) was

not different from the 25 secondaries' one (73 visits), as well as the mean differences relative to the different tissue consistencies. The same results were achieved in the analysis of the tissue consistency of upper limb on 3 hard (5 visits), 22 medium (50 visits) and 18 soft (43 visits) patients.

Entity of upper limb

Using the variable entity as analysis factor, the mean percentage variation between pre- and post-treatment were estimated for the severe (20 patients, 57 visits), moderate (15 patients, 38 visits), and mild (3 patients, 3 visits) levels as shown in Figure 6. Similarly, differences were found between the mean of severe and mild patients, and between severe and moderate (only at C1, C2, D and E). In the pre-treatment analysis, differences between the pathological limb and the healthy limb were significant for all entity levels. Specifically, in the point comparison, differences were significant for points C1, C2, D in the comparison between severe and mild entity and for points C1, C2, D, E, E1 in the comparison between severe and moderate entity. Finally, in the post-treatment, only the mean differences with respect to the severe level were significant: in particular, for points C1, C2, D in the severe-mild comparison and in points C1, C2, D, E1, F in the severe-moderate comparison.

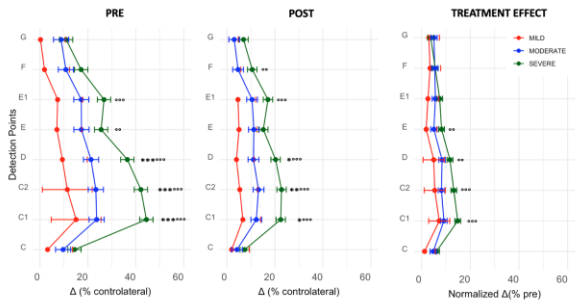

Figure 6: *Estimated marginals means (symbols) and 95% CI (whiskers) of pre-treatment (left), post-treatment (middle) edematous upper limb circumference compared to healthy contralateral limb and normalized delta (pre-post/pre) (right) of all the detection points according to lymphoedema entity: severe (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.*

Elastic compression braces

Assuming that each patient is classified as "new" at each treatment cycle, the total number of braces considered is 122 for the lower limb and 98 for the upper limb. The results of the analysis show that for the lower limb, 13 patients (10.6%) fit in the standard size, while the remaining 109 patients (89.4%) require a custom-made brace. For the lower limb, it is assumed that all patients require a compression stocking and therefore the total cost is 1001 € for standard braces and 14562,4 € for custom-made braces. For the upper limb, 4 patients (4%) fall into the standard size, while the remaining 94 (96%) do not. Therefore, if all patients need a brace consisting of an arm sleeve without hand and a glove, the total cost is 760,8 € for standard braces and 19420,4 € for custom-made ones.

4. Discussion

Lower limb

Pre vs Post: Pooling together the percentage change in relation to the healthy contralateral limb, regardless of classification, and comparing pre- and post-treatment, it can be stated that Complex Decongestive Therapy has been successful in reducing the volume of the limb at each detection point. The limb of a patient with lymphoedema can be compared to the geometric figure of the cylinder in that near the ankle (point B1), the diameter of the circumference does not tend to decrease but on the contrary in this point there is a greater difference in percentage compared to the healthy limb. Although the Complex Decongestive Therapy acts more on this area (13% reduction), the limbs with lymphoedema will never be able to return to a normal conformation.

Entity: Since patients with mild to moderate oedema have a similar distribution of oedema along the limb and since Complex Decongestive Therapy shows the same results in terms of percentage reduction, they can be unified in one class and treated in the same way. Complex Decongestive Therapy acts by reducing the volume of the limb significantly even in patients with severe lymphedema, despite the limb is very edematous.

Tissue consistency: The therapy can reduce the consistency of fibrotic tissue in a short time even on tissues classified as hard. However, the percentage reduction is lower than in other tissues.

Dysmorphism pattern: It has been shown that the distribution of the oedema and the efficacy of the treatment in the two dysmorphic patterns is almost similar as there are no significant differences in the various detection points. Therefore, for the purpose of the treatment, this distinction is not relevant.

Etiology: The analysis was conducted in order to answer the question of significance and difference in the classification between primary and secondary patients. The results show that this distinction is not relevant to the effectiveness of the treatment and that the patients respond similarly.

Upper limb

Pre vs Post: The pre- and post-treatment analysis compared to the contralateral healthy limb shows that all points responded positively to Complex Decongestive Therapy. The most compromised points before treatment are located at forearm level (C1, C2, D) and are those that reduced the most at the end of treatment. Although the therapy improves limb function by reducing physical and psychological suffering, the limbs of patients with lymphoedema can never return to the normal conformation of a healthy limb.

Entity: Like the lower limb, the treatment increases its effectiveness from mild to severe patients. In both the pre-treatment and post-treatment phases, there is a marked difference between severe versus moderate and mild lymphedema. On the contrary, no significant differences were found between the two mild and moderate entities and therefore the unification of the patients in a single entity is suggested.

Tissue consistency: Patients with edematous upper limbs with different tissue consistencies show no differences in the distribution of edema along the limb and additionally respond to therapy in a similar way. All patients benefited from therapy including patients with hard fibrotic tissue, despite the high degree of impairment.

Elastic compression braces

The new Essential Levels of Care (LEA), mention custom-made braces for the treatment of lymphoedema as prescribable for patients with both chronic primary lymphoedema (code RGGO20) and secondary lymphoedema stabilized after cancer surgery (code 048) [3]. However, the Lombardy region provides only the custom-made brace for free to patients with cod. RGG020, while patients with cod. 048 are obliged to pay for the purchase and replacement of the braces themselves. According to the data from the analysis of patients treated at the Milan Clinical Institute, the percentage of custom-made braces is extremely high. There are 68 patients with cod. 048 who are not entitled to a free custom-made brace, for the lower limb, and considering the costs of a single brace, this amounts to 9084.8 €. On the other hand, for the upper limb, all analyzed patients (98) have secondary lymphoedema and the total cost amounts to 19420.4 €.

Strength and Limitation

The mathematical research conducted has several notable strengths. Firstly, by using a mixed-methods approach, both qualitative and quantitative research methods were employed. Mixed-method approaches are likely to provide the most complete situation, as their integration facilitates a broader and deeper understanding of the phenomenon. Secondly, the database used had a large sample size that produced statistically significant results based on clinical subdivisions. Finally, it was possible to compare the various measurement points and assess the location of lymphoedema thanks to the segmental technique. The two main limitations of this study are that the patients came from a single clinical center (single-center study) and that some of the categories analyzed had low numerosity.

5. Conclusion

Lymphoedema is a chronic, disabling condition that usually evolves into a progressive worsening if it is neglected. Today, accurate early diagnosis, effective therapy and a solution for the maintenance phase are available to improve the patient's living conditions. Ultimately, lymphoedema leads to a cascade of interlinked problems, amplifying living and social costs, which may lead to the patient's abandonment of any interest in the treatment of his condition. The findings from this study have significant implications for the future clinical practice: they showed that the percentage change induced by the treatment on the sensitive points B1 for the lower limb and C1 for the upper limb have the same magnitude (13%). At these points, lymph stagnation occurs, probably due to body weight and the effect of gravity. It is advisable to pay more attention to them during the intensive phase of treatment. Furthermore, it is not recommended for successful treatment to divide patients according to etiology, and the two entities, mild and medium, being comparable, could be grouped into a single classification. The State determines the LEAs that must be guaranteed over the entire national territory. The Regions independently plan and manage healthcare within their territorial scope. Unlike in other regions, in Lombardy only patients with primary lymphoedema have free access to custom-made braces. However, it emerged from this thesis that it is secondary patients who need this type of brace in greater numbers. Only with the issuing of implementation decrees by the Minister of Health will it be possible to overcome the inequalities in care between patients, who will finally be able to use the same services free of charge.

6. Bibliography

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[3] Decree of the President of the Council of Ministers (DPCM) of 12 January 2017, GU n. 65 of 18 March 2017 (Ordinary Supplement n. 15).