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A Prospective Study on the Safety and Efficacy of Vascularized Lymph Node Transplant

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Abstract

PURPOSE: While vascularized lymph node transplant (VLNT) has gained popularity, there is a lack of prospective long-term studies and standardized outcomes. The purpose of this study was to evaluate the safety and efficacy of VLNT using all available outcome measures.

METHODS: This was a prospective study on all consecutive patients who underwent VLNT. Outcomes were assessed with two patient-reported outcome metrics, limb volume, bioimpedance, need for compression, and incidence of cellulitis.

RESULTS: There were 89 patients with the following donor sites: omentum (73%), axilla (13%), supraclavicular (7%), groin (3.5%). Mean follow-up was 23.7 ±12 months. There was a significant improvement at 2 years post-op across all outcome measures: 28.4% improvement in the Lymphedema Life Impact Scale (LLIS), 20% average reduction in limb volume, 27.5% improvement in bioimpedance score, 93% reduction in cellulitis, and 34% of patients no longer required compression. Complications were transient and low without any donor site lymphedema.

CONCLUSION: VLNT is a safe and effective treatment for lymphedema with significant benefits fully manifesting at 2 years post-op. Omentum does not have any donor site lymphedema risk making it an attractive first choice.

Mini Abstract

Vascularized lymph node transplant provides satisfactory reduction in limb volume, bioimpedance, and improved quality of life. Vascularized omentum transplant is a reliable alternative to peripheral VLNT with no risk of donor site lymphedema and particularly significant impact in reducing the incidence of cellulitis.

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INTRODUCTION

Lymphedema is a common, debilitating, and often misunderstood disease. The primary treatment is lifelong compression and manual lymphatic drainage. While these therapies are essential for managing swelling, they do not treat the underlying disease. It is not uncommon to see a young breast cancer survivor with lymphedema who is 100% compliant with compression still experience increased limb swelling over time. This is because chronic lymphedema is immunologically-mediated fibroproliferative disorder. Stagnant lymph leads to an inflammatory response causing fibrosis of the lymphatic vessels which causes even more lymph stasis spiraling into fulminant lymphedema.(1–6) This inflammatory response also leads to fibroadipose deposition.(7) Compression may mitigate swelling, but its effectiveness is limited by the lack of an exit for lymph. Consequently, vascularized lymph node transplant has been used to both restore immunologically active lymph nodes and provide a portal for lymph egress.

Vascularized lymph node transplant (VLNT) is now routinely used at an increasing number of academic centers. (8–12) VLNT involves transplanting vascularized lymph nodes to the affected limb with an arterial and venous anastomosis. A lymphatic anastomosis is not typically performed as the transplanted lymph nodes stimulate lymphangiogenesis via VEGF-C signaling.(13, 14) Ingrowth of new lymphatics into transplanted lymph nodes has been confirmed in both animals and humans.(15) The proposed mechanism for VLNT is that the lymph entering the transplanted lymph nodes is shunted into the venous system via interconnections between the lymphatic sinuses and venules within the transplanted nodes. (9) Initial concerns of donor site lymphedema have been addressed using reverse lymphatic mapping which minimizes this risk.(16) While a variety of donor sites have been utilized for VLNT (Table 1), the authors' first choice is the omentum and gastroepiploic lymph nodes which eliminate any risk of donor site lymphedema.(17, 18) These advances in safety have led to increased use of VLNT.

While VLNT is being performed at higher rates, there are limited prospective outcomes studies. Most studies are retrospective and rely on a single outcome measure—limb circumference—often with limited follow-up. Limb circumference or limb volume is only a snapshot of the limb that is in flux throughout the day. Often patients are placed in postoperative compression which can confound the outcome data. The purpose of this study was to address gaps in our knowledge of outcomes following VLNT by using all available outcome metrics: limb volume, bioimpedance, and two different patient reported outcome metrics with long-term follow-up.

METHODS

This was a prospective study conducted at Memorial Sloan Kettering Cancer Center between November 2014 and July 2020, under IRB #17–377. Inclusion criteria consisted of patients aged 18–80 years with secondary lymphedema of the upper or lower extremity, International Society of Lymphology (ISL) Stage 0, 1, 2, or 3 lymphedema, and a BMI of less than 30. Patients who underwent combined VLNT and either lymphovenous bypass or liposuction were excluded. Preoperative assessment included: BMI, history of cellulitis,

use of prophylactic antibiotics, lymphedema stage, and compression regimen. All patients underwent preoperative decongestive therapy prior to baseline measurements. Lymphedema evaluation included limb volume measurements, bio-impedance, and two lymphedema-specific validated quality of life (QOL) questionnaires. (19) Preoperative imaging included indocyanine green (ICG) lymphangiography, lymphoscintigraphy and magnetic resonance angiography (MRA) to assess the lymphatic system, fluid and fat composition, vein stenosis, and rule out cancer recurrence.

Limb Volume

Limb volume was assessed using a perometer and manual measurements. In order to minimize the confounding factor of postoperative lymphedema therapy on limb volume outcomes, preoperative baseline measurements were taken *after* each patient was optimized with preoperative decongestive therapy. Limb volumes were then recorded at 6 months, 12 months, and annually thereafter. Manual limb volumes were calculated by measuring limb circumferences at 4 cm intervals from the wrist to 44 cm proximally (19) then using the truncated cone formula used by Brorson for volume calculation.(20). A limb volume difference of 10% or greater is traditionally the threshold for lymphedema although this is an arbitrary and historical cutoff.(21) A perometer (Pero-system model 1000NT, Wuppertal, Germany) was used for automated limb volume measurements. A conversion formula previously described by our group was used for manual measurement conversion to perometer measurements, for a unified limb volume scale.(19)

Bioimpedance

Bioimpedance was recorded using the L-DEX model U400 (Impedimed, Brisbane, Australia). Bioimpedance spectroscopy extrapolates the extracellular fluid content by measuring electrical impedance across each limb which is then normalized resulting in an L-DEX score. The lower the L-DEX score, the less fluid in the limb. Historically, an L-DEX score of 10 or greater was consistent with a diagnosis of lymphedema but more recently a score of 6 or higher has been accepted as the new threshold. (22, 23)

Patient-reported Outcomes (PROMs)

Patient-reported outcomes were measured using two validated lymphedema-specific questionnaires with different look-back periods at each follow-up. These included the Lymphedema Life Impact Scale (LLIS version 2) and the Upper Limb Lymphedema-27 (ULL27).(24) The LLIS questionnaire includes 18 questions measuring physical, psychological and functional domains with a look back period of 1 week. Scores are presented for each domain and for overall impairment (%). ULL-27 is an upper-extremity lymphedema-specific questionnaire, which includes 27 questions, measuring physical, emotional and social domains with a look back period of 1 month. Similar to LLIS, ULL-27 scores are generated for each domain as well as for overall impairment.

Surgical Technique

Donor site selection for VLNT was tailored to each patient. In general, the authors' first choice was omentum using an open approach.(11) However, if the patient required skin

replacement or had a hostile abdomen, peripheral lymph nodes from the lateral thoracic system, groin, or supraclavicular region were harvested. This was always performed using reverse lymphatic mapping to minimize the risk of donor site lymphedema.(9) The recipient site selection was also patient-specific. In the upper extremity, if there was axillary vein compression or axillary contracture, then lymph nodes were placed in the axilla after vein decompression and scar excision. If the axilla was asymptomatic and the majority of swelling was in the forearm, distal heterotopic lymph node transplant was performed.(25) A similar approach was used for the lower limb.

A few technical details regarding the omentum harvest are worth highlighting. A nasogastric tube was placed temporarily during surgery to decompress the gut and was removed prior to extubation. An open approach for omentum harvest was used for precise bipolar dissection around the proximal pedicle and lymph nodes, which is not possible using laparoscopic instruments. The gastroepiploic nodes and omentum were based on the right gastroepiploic vessels. Whenever possible, two venous anastomoses were performed to both the proximal and distal end of the gastroepiploic vein. This restores the normal bidirectional venous drainage of the omentum and eliminates venous hypertension.(26) The thoracodorsal and circumflex scapular vessels were most commonly used as recipients.

For the lower extremity, the most common recipient sites were the calf using medial sural vessels, or the ankle used posterior tibial vessels. When going proximal, the descending branch of the lateral circumflex femoral vessels were most commonly used. Intraopeorative perfusion of the omentum in all cases was confirmed with ICG angiography. Post-operative viability of the omentum was confirmed with MRA at 1-year post-op.

Postoperative Care

All patients resume a regular diet after presence of flatus typically within 24 hours. Nasogastric tubes are not used postoperatively. Patients with upper extremity lymphedema are typically discharged on post-operative day 3. Patients with lower extremity lymphedema are typically out of bed by post-operative day 3 but remain non-weight bearing with a walker for 2 weeks. Compression is resumed at two weeks post-operatively and then patients gradually resume full weight bearing over the next 5 days. 40 mg of subcutaneous enoxaparin is given daily for 1 month to reduce the risk of venous thromboembolism. Two weeks postoperatively, both upper extremity and lower extremity patients begin compression wrapping and manual lymphatic drainage of the entire limb without restriction by a certified lymphedema therapist. Once the limb has plateaued in volume, the patient is placed in a compression garment.

Statistical Analysis

Statistical analysis was conducted using the GraphPad Prism software v.9.2.0. Continuous variables were presented as averages and standard deviations and were compared using paired student *t*-test. A p value of <0.05 was considered significant.

RESULTS

Demographic and Clinical Data

All demographic and intake data is listed in Table 2. A total of 89 patients, 88 females (98.9 percent) and 1 male (1.1%), with an average age of 58.8±10.6 years were included in this study. The mean BMI was 25.8±3.4 kg/m^2. Mean follow-up time was 23.7±12 months (Table 2). All 89 patients were diagnosed with secondary lymphedema due: to breast cancer (73%), gynecological cancer (20%), melanoma (2%) or other (5%). The majority of patients had ISL stage II lymphedema (n=79, 89%). A total of 65 patients (73%) were diagnosed with upper extremity lymphedema, and 24 patients (27%) were diagnosed with lower extremity lymphedema. The mean preoperative duration of lymphedema was 55.1 months.

35 patients experienced cellulitis preoperatively (39.3%) and the mean number of episodes per year was 3±3.4. 10 patients (11%) were on prophylactic antibiotics. 45 patients (51%) were in compression around the clock, 22 patients used daily compression (25%), 13 patients used occasional compression (15%), and 9 patients (10%) did not use any form of compression.

VLNT donor site breakdown was: omentum (n=65, 73%), lateral thoracic (n=12, 13%), supraclavicular (n=6, 7%), groin (n=3, 3.5%) and other (n=3, 3.5%). A total of 110 omentum transplants were performed including 68 single lymph node transplants and 21 double omentum transplants with both a proximal and distal recipient site in the same limb.

Clinical Outcomes

VLNT Decreases Limb Volume—Volume differential outcomes are outlined in Figure 1 and Table 3. The mean preoperative volume differential for patients diagnosed with lymphedema was 31.4% ± 14.7. All patients at 1 year postoperatively had a mean reduction in limb volume differential of 8.6 percent (p=0.0954) although this was not significant. However, there was a statistically significant difference by two years postop with a mean reduction of 20% (p=0.0239). At 2 years after treatment with VLNT, 51.6 percent of patients demonstrated improved volume differential. A similar trend was noted in a subgroup analysis of upper extremity lymphedema patients (Figure 7, Table 4). A 14.9 percent decrease was demonstrated 1 year after treatment with VLNT (p=0.0704) and a 15.6 percent decrease in volume differential was recorded 2 years after VLNT (p=0.0239). 60.6 percent and 55.6 percent of patients had an improved volume differential 1 year and 2 years postoperatively, respectively.

VLNT Reduces Bioimpedance Score and Need for Compression—The mean preoperative L-DEX score was 34.0±29.5. The mean L-DEX score at 1 year postoperatively was 31.1±25.9 which was not statistically significant. However, at two years postop, there was a statistically significant 27.5% reduction in the L-DEX score. 58.6 percent of patients had decreased L-DEX scores 2 years after VLNT (Figure 2, Table 3). Sub-group analysis of upper extremity lymphedema patients was similar to the overall cohort (Figure 8, Table 4), demonstrating 24.0 percent and 31.1 decrease in LDEX scores 1 year (p=0.0400) and 2

years (p=0.0696) after VLNT, with 62.6 percent and 57.9 percent of patients demonstrating improved L-DEX scores 1 year and 2 years after VLNT, respectively. Finally, out of all patients that were using some form of compression pre-operatively, 34.4% of these patients no longer used compression following VLNT.

VLNT improves Quality of Life—Overall, lymphedema patients had a significant and sustained improvement in LLIS scores which manifested as 29.3 percent (p=0.0003) significant decrease recorded 1 year after treatment and 28.5 percent (p=0.0322) significant decrease recorded 2 years after treatment (Figure 3, Table 3). Interestingly, improvement in QOL 1 year after VLNT was demonstrated in each of the LLIS components alone, demonstrating an improvement in both Physical (p<0.0001), Psychological (p=0.0830) and Functional (p=0.0104) subscales (Figure 4–5, Table 3). Improvement in Physical LLIS score was shown to be persistent 2 years after VLNT (p = 0.0117), while the psychological and functional domains did not show to be significantly improved at that time point (p = 0.1230, p = 0.5763, respectively). 84 percent of patients demonstrated improved LLIS scores 1 year after treatment, a trend which persisted in 72.7 percent of patients 2 years after surgery.

LLIS scores analyzed for upper extremity patients (Figure 9–14, Table 4) demonstrated similar results with improved LLIS scores 1 year (p=0.002) and 2 years (p=0.0781) postoperatively, and 89.4 percent and 75 percent of patients demonstrating improvement 1 year and 2 years after surgery, respectively.

These findings were corroborated by the ULL-27 questionnaire results, demonstrating significantly improved scores across all domains (physical: p=0.0011, emotional: p=0.0054, social: p=0.0008), as well as significantly improved total scores 1 year after surgery (p=0.0006). 89.4 percent of upper extremity lymphedema patients demonstrated improved ULL-27 scores 1 year after surgery, which persisted in 85.7 percent 2 years after surgery. 34.4 percent of patients included in this study stopped wearing compression by 2 years post-VLNT.

VLNT Decreases Incidence of Cellulitis—Overall, patients with secondary lymphedema showed an 85 percent decrease in the total number of cellulitis episodes by 1 year after VLNT from 3.0±3.4 to 0.5±1.2 total episodes (p=0.0002). This finding was confirmed by a significant 82 percent (p=0.0008) decrease in average number of cellulitis episodes per year from 1.1±1.3 to 0.2±0.4 episodes per year (Figure 6, Table 3). These findings were supported by the subgroup analysis for upper extremity lymphedema patients demonstrating 78 percent decrease in cellulitis episodes per year after VLNT. (Figure 15, Table 4)

VLNT is Safe—Complications after treatment with VLNT were recorded in 14 patients resulting in a 15.7 percent complication rate (Table 5). Donor site complications included 1 hernia (1.1 percent) and 1 episode of transient pancreatitis (1.1 percent). This was during our first omentum harvest and we have since limited our pedicle dissection without any further issues. None of the patients in this series developed donor site lymphedema. Recipient site complications included 2 cases of total flap loss (1.8 percent), and one partial flap loss (0.9 percent). Other complications included hematoma (3.4 percent), seroma (3.4 percent),

postoperative infection (2.2 percent) and wound dehiscence (1.1 percent). 4 patients (4.5 percent) experienced cancer recurrence (Table 3).

Case Studies

Case 1—This is a 68-year-old patient who developed severe right upper extremity lymphedema following axillary dissection and radiation for breast cancer. The patient had an axillary contracture and limited range of motion. Despite full compliance with compression, her lymphedema progressed. The patient underwent a free omentum transfer to the right axilla and a second free omentum transfer to the right forearm. Her manual volume differential significantly improved from 39.4% preoperatively to 21.4% 1 year after surgery and 13.1% 2 years after surgery (Figure 16), which has been reflected in significant improvement in her range of motion and quality of life scores. She was in daily compression both pre- and post-operatively.

Case 2—A 49-year-old patient with a history of right breast cancer developed lymphedema following axillary dissection and radiation. Despite all conservative measures and physiotherapy, she continued to have progressive and intractable right upper extremity lymphedema. She has also had cellulitis resulting in sepsis and an ICU stay. The patient underwent vascularized omentum lymphatic transplant to right forearm. Her manual volume differential has significantly improved from 79.6% preoperatively to 47.8% 1 year after surgery and 44.9% 2 years after surgery (Figure 17), which has been reflected in significant improvement in her quality of life scores. Her cellulitis episodes have also decreased from 0.7 episodes per year to none 2 years after surgery. She was in occasional compression prior to surgery, but optimized preoperatively and remains in compression postoperatively.

DISCUSSION

Vascularized lymph node transplant is one of several surgical techniques we use to address different stages of lymphedema. When a patient first connects with our team, potential surgical candidates are those with a BMI of less than 30, are compliant with lymphedema treatment, and do not have significant venous disease. The reason for a BMI cutoff for physiologic surgery is that elevated BMI impairs lymphatic function. (27, 28) In our experience, these patients have had poorer outcomes with higher complication rates. Consequently, patients with a BMI over 30 are first referred to for weight loss or bariatric surgery as appropriate.

All patients have MRA preoperatively and indocyanine green (ICG) lymphangiography performed in the office. If a linear lymphatic vessel is visualized on ICG, then a lymphovenous bypass is attempted. If there are no bypassable lymphatic vessels identified, then VLNT is offered. Patients with axillary contracture, pain, or axillary vein compression are offered VLNT to the axilla upfront as there is an opportunity to improve range of motion and decompress the vein. Omentum is typically our first choice because of the abundance of lymphatic tissue and no risk of donor site lymphedema. However, patients who require skin replacement or have had significant abdominal surgery or omentectomy are not candidates. In such cases we will use a lateral thoracic, supraclavicular, or groin lymph node flap. Currently there is no data comparing the efficacy of omentum to peripheral lymph node

flaps and we did not have enough patients in each group to adequately power a subgroup analysis. However, approximately one-third of all patients had uptake of technetium in their transplanted lymph nodes on lymphoscintigraphy at one year postop, confirming lymphangiogenesis into the VLNT.

Finally, liposuction is reserved only for those patients with advanced lymphedema that is fat-dominant, with minimal to no pitting edema who are committed to lifelong compression around the clock. While we will combine these procedures in series when indicated, we do not perform them simultaneously so that we can measure the effect of lymph node transplant alone.

Vascularized lymph node transplant has evolved considerably in the past decade. VLNT was initially met with justifiable concerns of donor site lymphedema. The description of reverse lymphatic mapping by Dayan and colleagues significantly reduced this risk.(16) More recently, donor sites such as the omentum and supraclavicular flap have virtually eliminated the risk of donor site lymphedema. These improvements in safety have led to more widespread adoption.

Of equal importance was the efficacy of VLNT, where studies were limited in early years with varying outcome measures. There are now a total of 15 prospective studies to date on VLNT which report significant improvements in limb circumference or volume, quality of life, cellulitis, and compression. (25, 29–40) While these results appear positive across the board, they do not reflect the consensus of the lymphatic surgery community: VLNT does work but not everyone experiences an improvement. It is difficult to obtain a clear picture of the outcomes of VLNT because current publications focus on mean and standard deviation, and outcomes do not always follow a standard distribution. For example, a mean limb volume reduction of 20% does not tell you if every patient improved or if some patients did not respond. This study aimed to provide the trajectory of each individual patient by publishing the estimation plots, and by using all available outcome measures with long-term follow-up.

Summarizing the findings in this study, statistically significant improvements following VLNT fully manifest at 2 years post-op. 75% of patients reported a significantly improved quality of life. Approximately half of all patients had an average of a 20% reduction in their limb volume differential. This finding was paralleled by an average improvement in the bioimpedance score of 27 percent. There was also a highly significant reduction in the incidence of cellulitis. Finally, one-third of patients who were using a compression garment preoperatively were no longer using compression post-operatively.

One might ask why 75% of patients had an improvement in quality of life while only about 50% of patients had a significantly reduced limb volume. The reason for this discordance is multi-factorial. Limb volume differentials are often the primary focus in outcomes but do not reflect the full reality of the patient. There are several points to highlight: (1) baseline measurements in this study were recorded *after* patients were first optimized with lymphedema therapy, (2) limb volume is an isolated snapshot of a moving target and often misleading, and (3) limb volume outcomes are of limited use in patients who do not have

significant limb volume differentials. Regarding the first point, most studies record the baseline limb volume measurement when the patient first presents to the office, prior to any preoperative lymphedema therapy. The major confounding issue with this baseline is that it is standard of care for patients to undergo postoperative lymphedema therapy. This leaves one wondering whether it was the surgery or the therapy that led to an improved measurement. To minimize this issue, baseline measurements in this study were taken only after each patient was optimized with preoperative lymphedema therapy. The average volume reduction would otherwise have been more impressive if our baseline measurements were taken at the patient's initial consult.

Secondly, limb volume measurements are limited because they do not represent the totality of the condition of the limb. This is because swelling fluctuates due to a wide array of conditions: time of day, diet, temperature, and activity all impact measurements and are in constant flux. Using two isolated limb volume measurements to determine efficacy of an intervention is like using two single blood glucose measurements in a diabetic to determine if a new drug was effective. There is nothing that exists that is analogous to a hemoglobin A1C in lymphedema. Only multiple limb volume measurements over time will provide a higher resolution picture of any significant changes in the limb.

Furthermore, limb volume differential is only a useful metric in patients who have a significant difference in limb volume. Many of these patients still have a poor quality of life which does not correlate with limb volume as previously published. (41) One specific reason for poor quality of life in a patient with minimal volume difference is the need for compression. In this study, one-third of patients no longer required compression—even though their modest limb volume difference never changed, their quality of life significantly benefitted from doing away with compression.

The results in this study and other studies demonstrate that VLNT does work. What we struggle to figure out is who will respond and who will not respond to VLNT. At this time, we cannot adequately power a subgroup analysis of responders and non-responders to VLNT. However, as patient recruitment continues to increase, we hope to determine those independent variables that may predict both success and failure with VLNT. Based on what we know now, our ideal candidate for VLNT is someone who already has axillary contracture or axillary vein compression, rapid progression of lymphedema, thin body habitus and compliant with conservative treatment.

VLNT Effect on Limb Volume

This study demonstrates the efficacy of VLNT treatment with 8.6 percent excess volume reduction in patients treated with VLNT for secondary lymphedema with 61 percent of patients demonstrating improvement in volume reduction 1 year after VLNT. A statistically significant 20 percent excess volume reduction was demonstrated 2 years after VLNT, with 51.6 percent of patients demonstrating improvement. These findings were confirmed by 8.5 percent decrease in L-DEX scores 1 year after VLNT, and a statistically significant 27.2 percent decrease 2 years after VLNT. Taken together, these findings support the results demonstrated in previous studies showing a correlation between L-DEX scores and limb volume reductions at different time points (11, 42, 43).

Significant limb volume and circumference reductions after VLNT have been consistently reported in the literature (11, 25, 44, 45). A recent meta-analysis by Basta *et al* (46) showed a 48.8 percent reduction in excess limb circumference and 56.6 percent reduction in volume following LVA and VLNT. Another recent meta-analysis of randomized and nonrandomized clinical trials found 17 studies that examined the role of VLNT in the treatment of lymphedema.[5, 9, 10, 12, 14, 16, 40–50] Based on this analysis, the authors concluded that 'there is evidence to support that VLNT can be effective in reducing severity of lymphedema (grade 1B), however, there is no evidence that VLNT can cure lymphedema'. (12) A systematic review of 10 studies pooling 185 patients treated with VLNT, showed an average of 39.55 percent excess circumference reduction and 26.4 percent excess volume reduction after VLNT. However, follow-up periods were variable. (47) Patel et al. and Ho et al. (40, 48) demonstrated a significant reduction in excess limb volume by an average 9.60 percent, as calculated in a recent meta-analysis. (12)

Nguyen et al. (17) reported a mean volume reduction of 22% in 42 patients who underwent VOLT. However, p value was not provided and the mean follow-up consisted of 14 months. (17) Several additional studies reported limb volume reductions following VLNT treatment, however, results were presented as volumes (49, 50) or absolute volume reduction (as opposed to excess volume reduction). Other studies demonstrated significant circumference reductions after treatment with VLNT utilizing different donor sites (14, 25, 35, 51–55), including the omentum (56–59), however, volumes were not calculated.

While several systematic reviews (12, 44, 47, 60–63) have demonstrated a reduction in circumference and volume for both upper and lower extremities (8, 43, 64–67), the high heterogeneity of the included studies in terms of both the methods and outcome measures used to assess limb changes pre and post-VLNT limits the conclusions that can be drawn in the aggregate and precludes the development of substantial quantitative conclusions and precise estimates of the effects of VLNT on limb volume/circumference. Volume measurements were used to depict limb changes in this study due to their consistently demonstrated superiority over circumference measurements and higher sensitivity and specificity. (19) Volume changes were presented as "volume differential" or "volume excess reduction", utilizing three different objective modalities including perometer, manual measurements and bio-impedance (L-DEX scores).

The consistently significant excess volume reduction 2 years after treatment demonstrated in our study, supports the assumption that the effects of VLNT are delayed compared to other treatments.(68) This could be explained by the proposed mechanism by which VLNT improves lymphedema; While the exact mechanism by which VLNT improves lymphedema has yet to be fully deciphered, our lab has shown that in addition to assisting in absorbing local lymphatic fluid and redirecting it into the vascular system (44), the transplanted lymph nodes produce vascular endothelial growth factor-C (VEGF-C) which induces local lymphangiogenesis by formation of spontaneous connections between the transferred nodes and the recipient site.(15) Lymphangiogenesis induction and connections formation with the systemic circulation might require more time for optimal function, compared to other surgical management strategies. These findings stress the importance of longer follow

up periods in lymphedema patients to fully characterized and quantify VLNT effects on lymphedema, for better selection criteria and improved outcomes.

VLNT Effect on QoL

In addition to significant improvements in objective measures after treatment with VLNT reported in the literature, VLNT has been shown to improve overall quality of life and functional status in lymphedema patients.(25, 69) This study demonstrated durable improvement in all quality of life domains—physical, psychological, and functional. These outcomes support the findings of previous studies that demonstrated significant improvements in LLIS scores after VLNT treatment.(11, 70–72) Having a long-term improvement after 2 years is more compelling that results reported at one year post-op when many patients are still in the post-operative “honeymoon” period where optimism and hope can result in a more positively skewed result.

This finding supports previous studies showing that limb volume excess and QOL scores are not correlated.(19) This finding also justifies using PROMs as the primary outcome metric for lymphatic surgery as there are lymphedema patients with minimal limb volume differences that do not meet the conventional 10% volume differential in diagnosing lymphedema.

There are a variety of patient-reported outcome metrics for lymphedema that are used, some validated and some arbitrary that have been reported. This makes comparison of outcomes between the results in this study and other published studies unfortunately difficult. A recent systematic review and meta-analysis concluded that patients who underwent VLNT and physiotherapy had significantly reduced pain and heaviness and significantly improved overall function.(12) The Lymphoedema Quality of Life (LYMQOL) score also demonstrated significant improvement after VLNT for both upper and lower extremity lymphedema patients. (40) Ciudad et al. (56) demonstrated a 2.7-fold quality-of-life improvement ($P < 0.01$) using the LYMQOL tool in 16 patients undergoing combined gastroepiploic VLNTs and modified RRPP. Mousavi et al. (59) reported a ‘significant improvement, satisfaction, function and appearance’ as well as non-significant ‘improvements in symptoms and mood domains’ in 24 VOLT patients, however, no validated tools were used for QoL estimation.

VLNT Effect on Cellulitis

Reducing the risk of infection is an imperative component in the effectiveness of lymphedema management. About a third of patients with lymphedema develop recurrent soft tissue infections (73, 74), which often require hospitalization for intravenous antibiotics resulting in substantial costs on patients and healthcare systems (73, 75–77). Several studies have demonstrated an interplay between bacteria and the lymphatic system on a molecular level, suggesting a direct role of bacteria in generating lymphatic dysfunction which impairs the host immune mechanisms leading to a vicious cycle. (78–81) Therefore, reducing the incidence of infections is of paramount importance to lymphedema patients, both clinically and financially. (11, 76, 82)

This study demonstrated a significant 85 percent reduction in total cellulitis episodes and an 82 percent reduction in cellulitis episodes per-year after treatment with VLNT (mean difference of −2.5 total episodes, p=0.0002 and −0.9 episodes per-year, p=0.0008). These findings support other studies that have shown a decrease in skin infections including erysipelas, lymphangitis, and cellulitis.(25, 52, 69, 83–85) Becker et al.(86) showed a 2 percent reported infection recurrence in a series of 1,500 patients who underwent VLNT over a period of 20 years. A more recent study investigating a combined double VLNT and modified radical reduction with preservation of perforators (RRPP) reported no episodes of infection postoperatively, compared to an average of two infections per year preoperatively (87). According to a recent meta-analysis, a pooled analysis of two studies with a total of 56 patients showed a nonsignificant reduction in the number of infections per year in patients after VLNT with a mean difference of −0.48 episodes per year (p = 0.22).(12) Eight case series with a total of 248 patients reported a significantly reduced mean number of cellulitis infections per year after surgery with a mean difference of −2.34 episodes per year (p < 0.00001). (35, 40, 48, 88–92) Six case series with a total of 233 patients reported on the proportion of patients with pre- operative and postoperative cellulitis. Cellulitis was significantly reduced by 35 percent after vascularized lymph node transfer (p < 0.0001).(17, 39, 43, 50, 57, 93). Mousavi et al. (59) reported a significant 95.7% reduction in cellulitis episodes per-year after VOLT in 24 patients (p=0.04). Nguyen et al. (17) reported that postoperative cellulitis episodes occurred in 2 lower-extremity patients, compared to history of cellulitis in 31 patients. However, the number of cellulitis episodes, and reduction in cellulitis episodes were not recorded.

Safety of VLNT

The results in this study demonstrate a satisfactory safety profile for VLNT. There was no donor site lymphedema observed in this study. Donor site complications, particularly for the omentum were isolated and largely mild. Most prior publications on the omentum demonstrate higher complication rates, but these are largely for pedicled flaps which necessitate the creation of a hernia when transposed into the subcutaneous layer. (94, 95), (96) The results in this study report a lower complication rate than published in the literature (30.1 percent), according to a recent systematic review. This finding challenges the widely held assumption that VLNT should be reserved for only severe forms of lymphedema due to high complication rates. (53, 58, 97, 98) Nguyen et al. (17) reported a 16% complication rate in a series of 42 patients after VOLT, including one episode of pancreatitis and one case of flap loss. Ciudad et al. (56) reported a 37.5% recipient site complication rate in 16 patients after VOLT, including paresthesia, hyperesthesia, seroma and lymphatic leakage. No donor site complications were recorded.

Strengths and Limitations—This study possesses a number of limitations. All VLNT procedures were performed by a single lymphedema surgical team, potentially limiting the generalizability of the findings despite the considerable number of patients. Second, the use of consistent selection of omentum lymphatic transplants as donor sites (73 percent of cases) potentially limits the conclusions that can be drawn in the aggregate.

Secondly, there was no control group of patients undergoing lymphedema therapy alone. While we have a control group in our study protocol, it has been difficult to recruit patients and maintain consistent follow-up for measurements without providing them with any therapeutic benefits. This was compounded by COVID restrictions which minimized any non-essential office visits. We expect to recruit more patients into the control group in the future for comparison.

The present study represents the accumulated experience of a tertiary cancer center specializing in the treatment of secondary lymphedema and is the largest single-center series with the longest follow-up period investigating the effects of VOLT to date. (17, 18, 56–59) Both objective (perometer, manual and L-DEX) and subjective (LLIS, ULL-27) measurements were independently taken by a single trained clinical research coordinator, independent of the surgical team. Multicenter studies with longer follow-up are needed to better understand different disease patterns (fluid-dominant versus fat-dominant), and unlock the pathophysiological mysteries behind the variability in patient presentation and disease progression to select the best candidates for VLNT. Additional studies are needed to examine the effect of different donor sites (99) and combined approaches that utilize adjunctive procedures such as liposuction and excisions (47, 49, 52–54, 68, 85, 100) on VLNT outcomes.

CONCLUSION

VLNT is a safe and effective treatment for patients with lymphedema who face a relentlessly progressive and proliferative disease. The findings of the present study demonstrate the benefits of VLNT across multiple outcome measures. The lack of donor site lymphedema risk is a significant advantage of the omentum. Larger studies are needed to further refine patient selection

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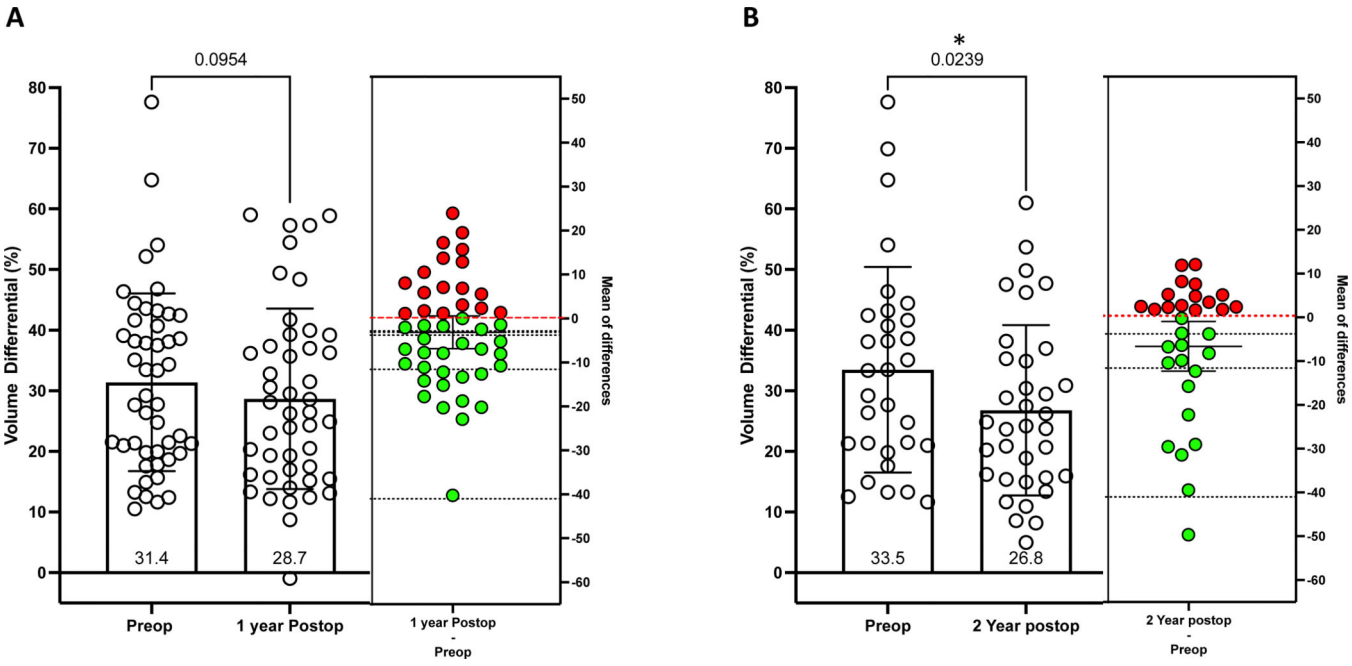

Figure 1 -
Volume Differential (%) 1 year and 2 years post-VLNT

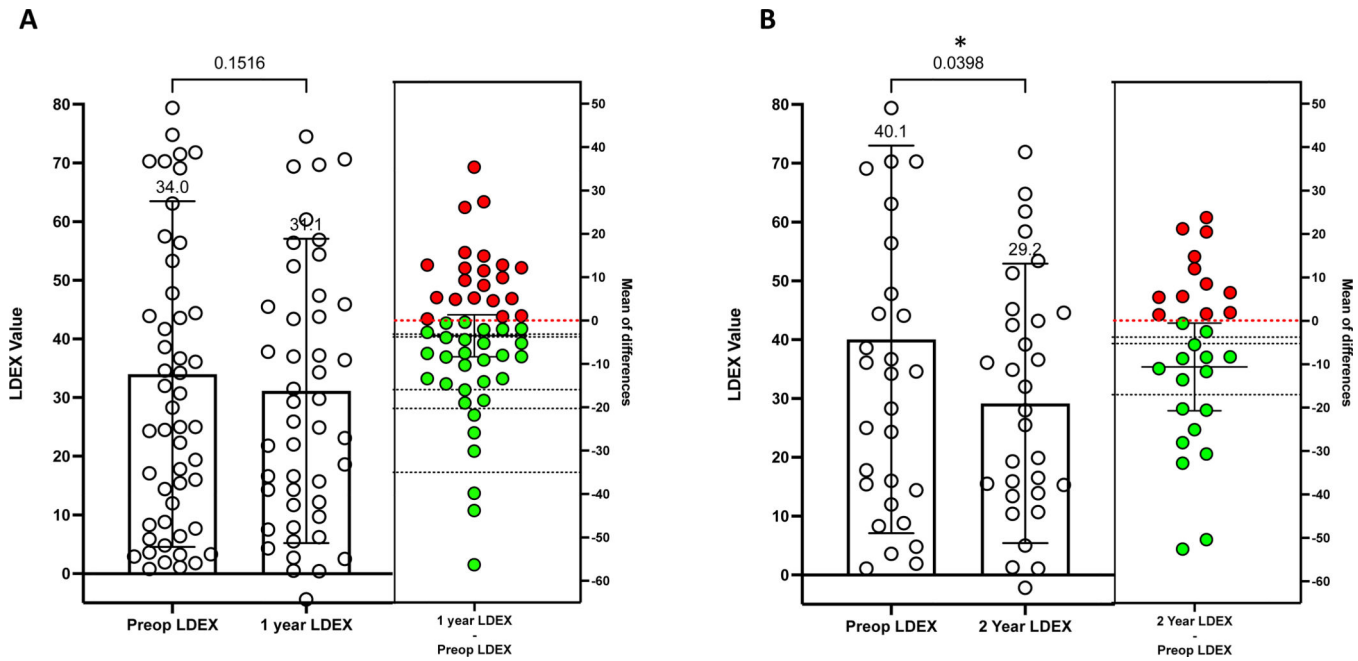

Figure 2 -
LDEX scores 1 year and 2 years post-VLNT

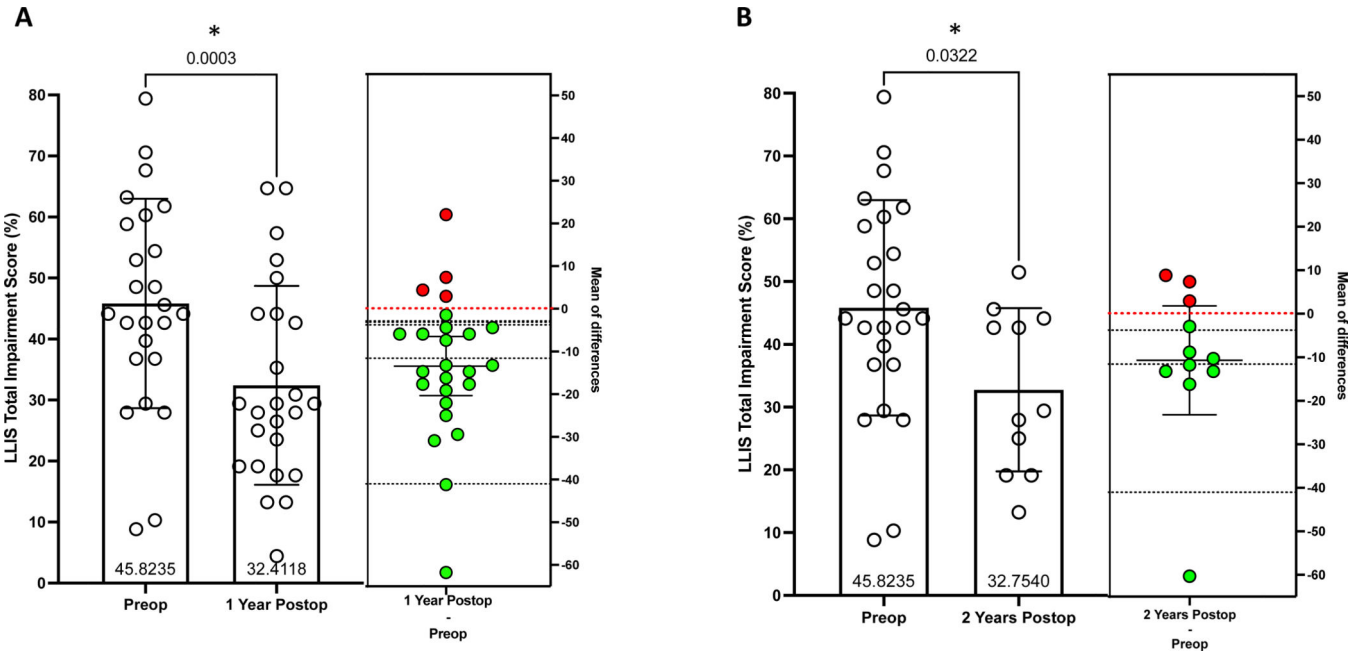

Figure 3 -
LLIS Total Impairment Scores 1 year and 2 years post-VLNT

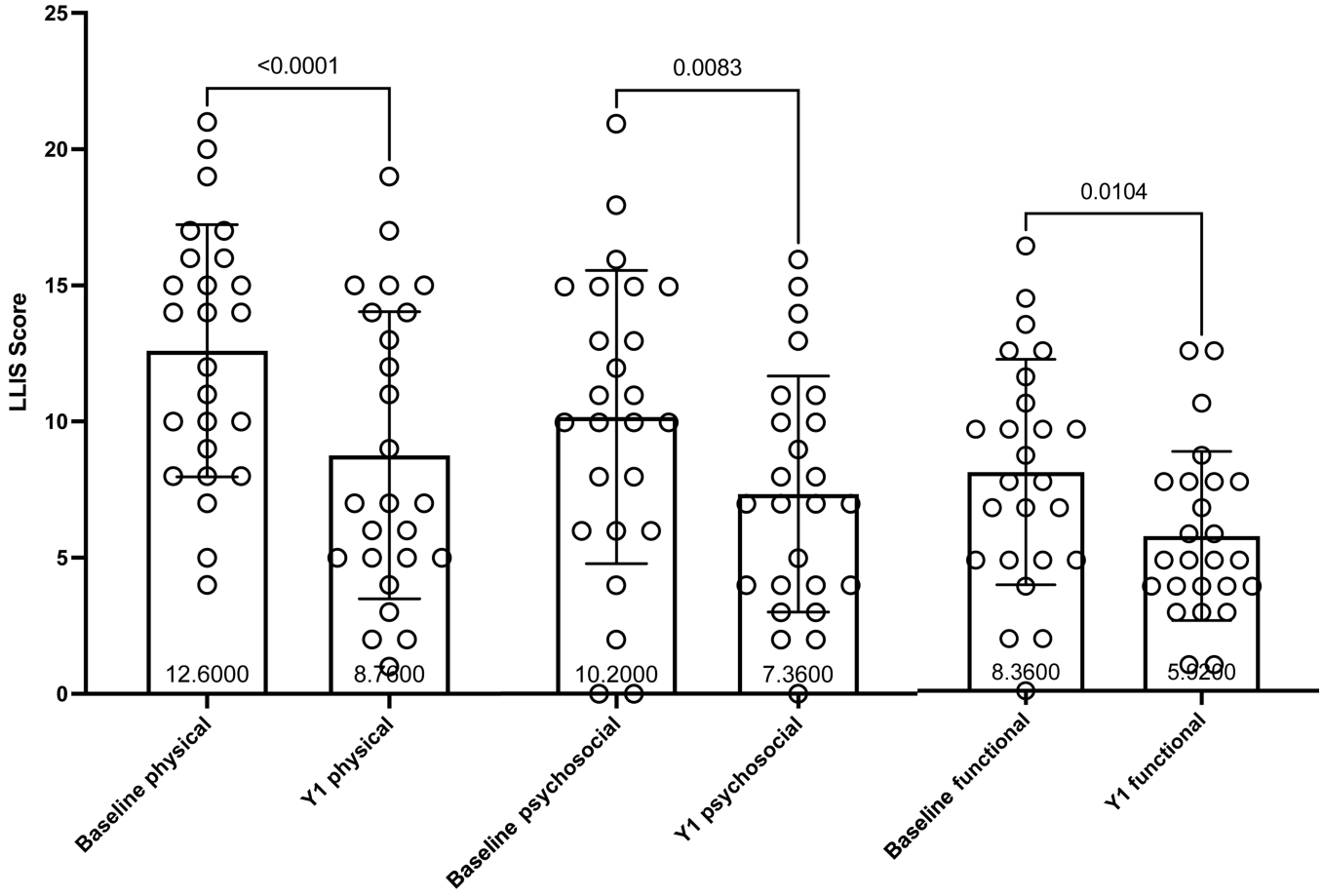

Figure 4 -
LLIS Physical, Psychological and Functional Scores 1 year post-VLNT

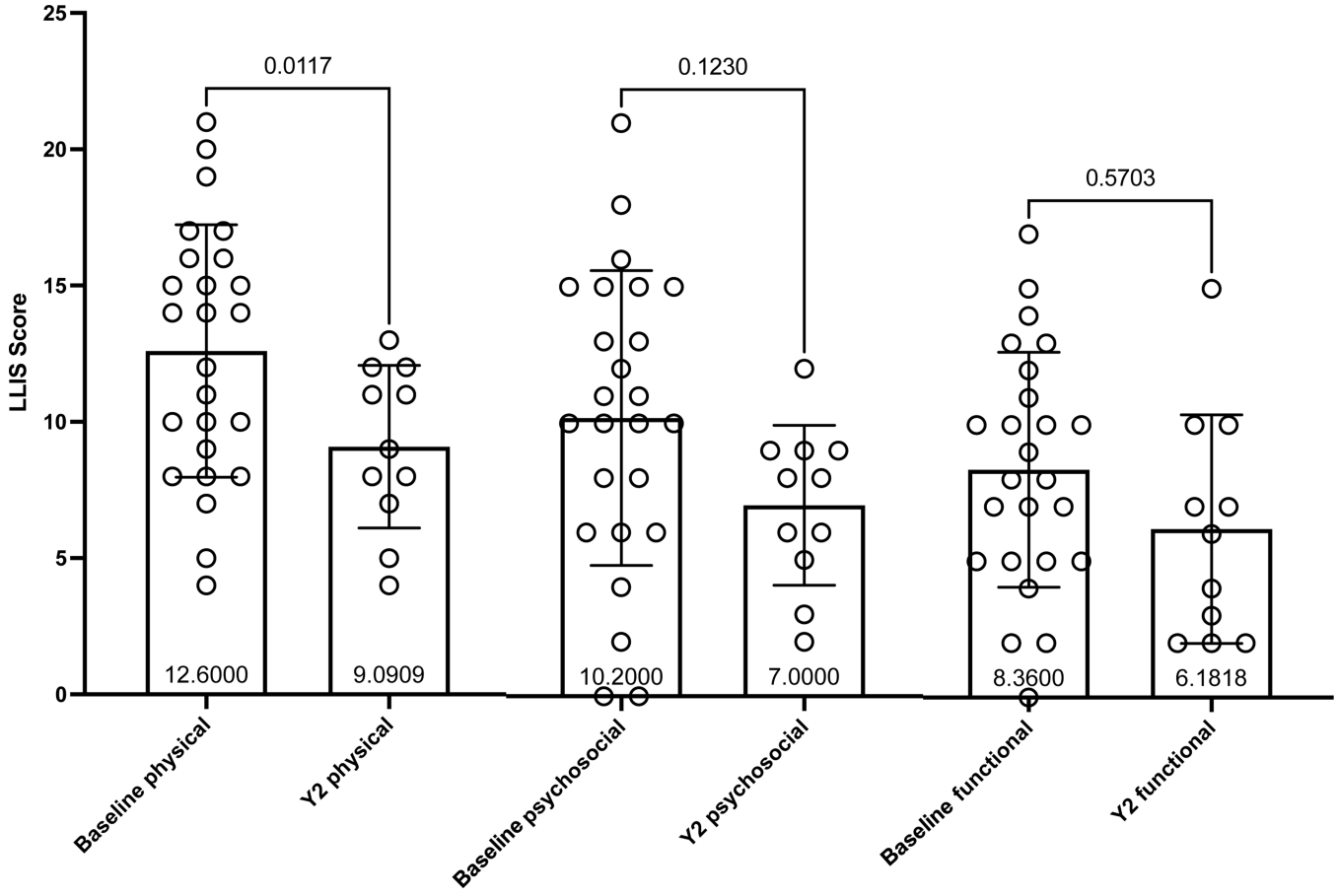

Figure 5 -
LLIS Physical, Psychological and Functional Scores 2 years post-VLNT

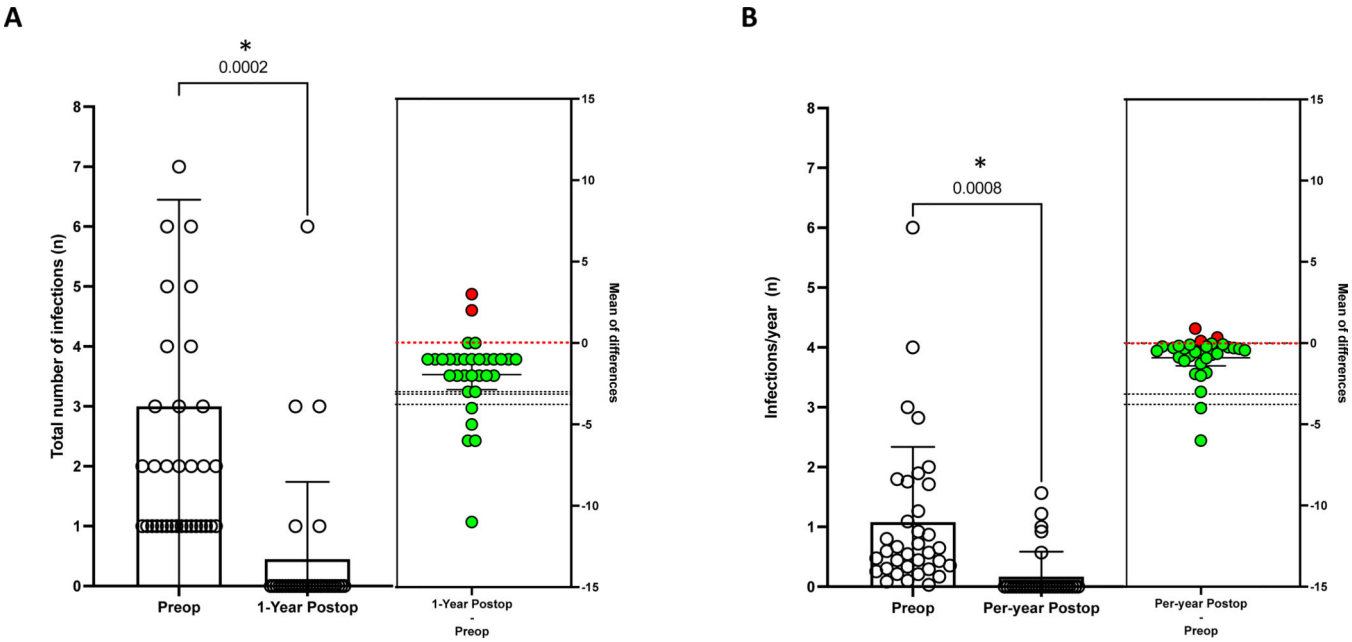

Figure 6 -
cellulitis episodes post-VLNT

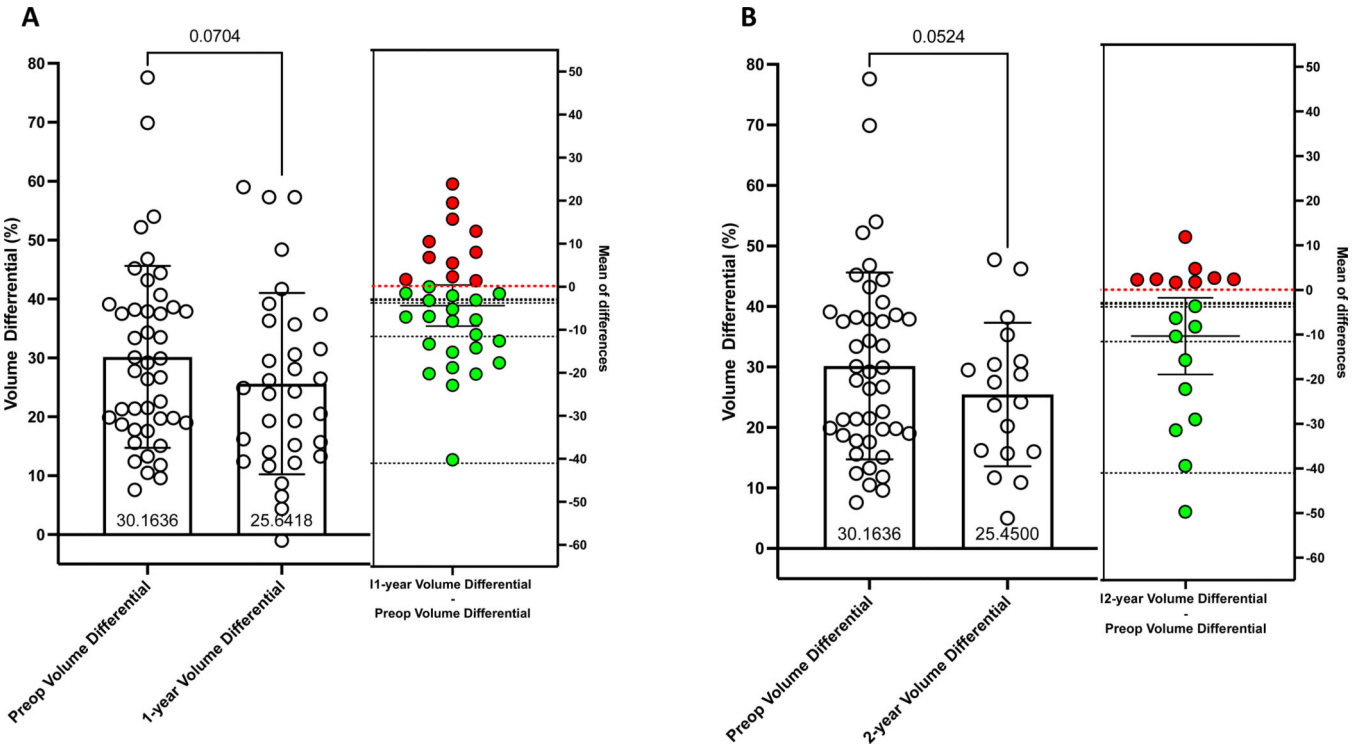

Figure 7 -

Volume Differential)%) 1 year and 2 years post-VLNT in upper extremity lymphedema patients

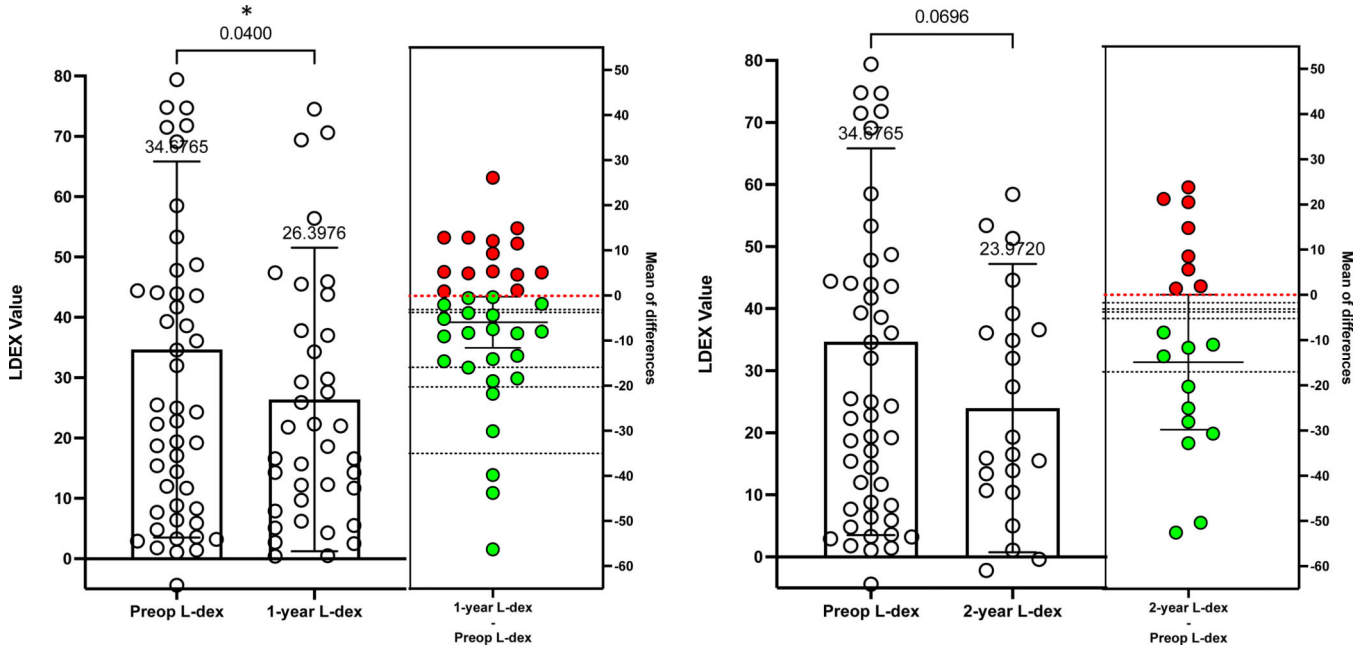

Figure 8 -

LDEX scores 1 year and 2 years post-VLNT in upper extremity lymphedema patients

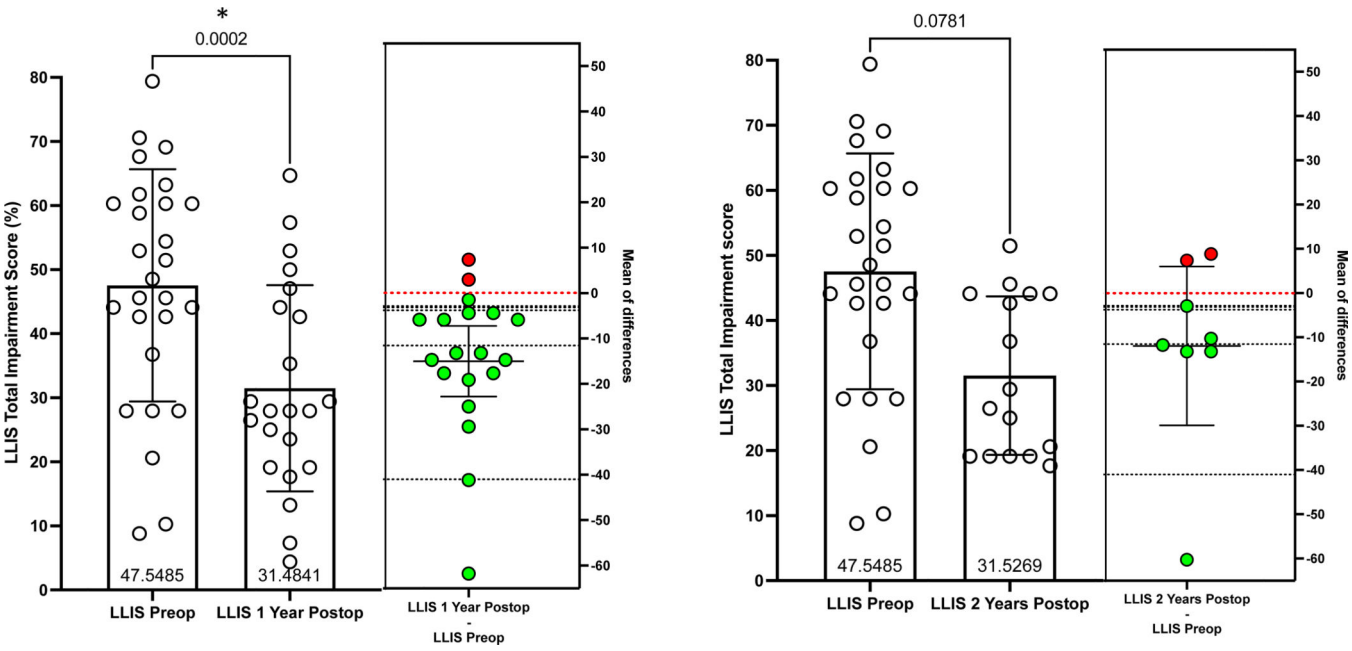

Figure 9 -

LLIS Total Impairment scores at 1 year and 2 years post-VLNT in upper extremity lymphedema patients

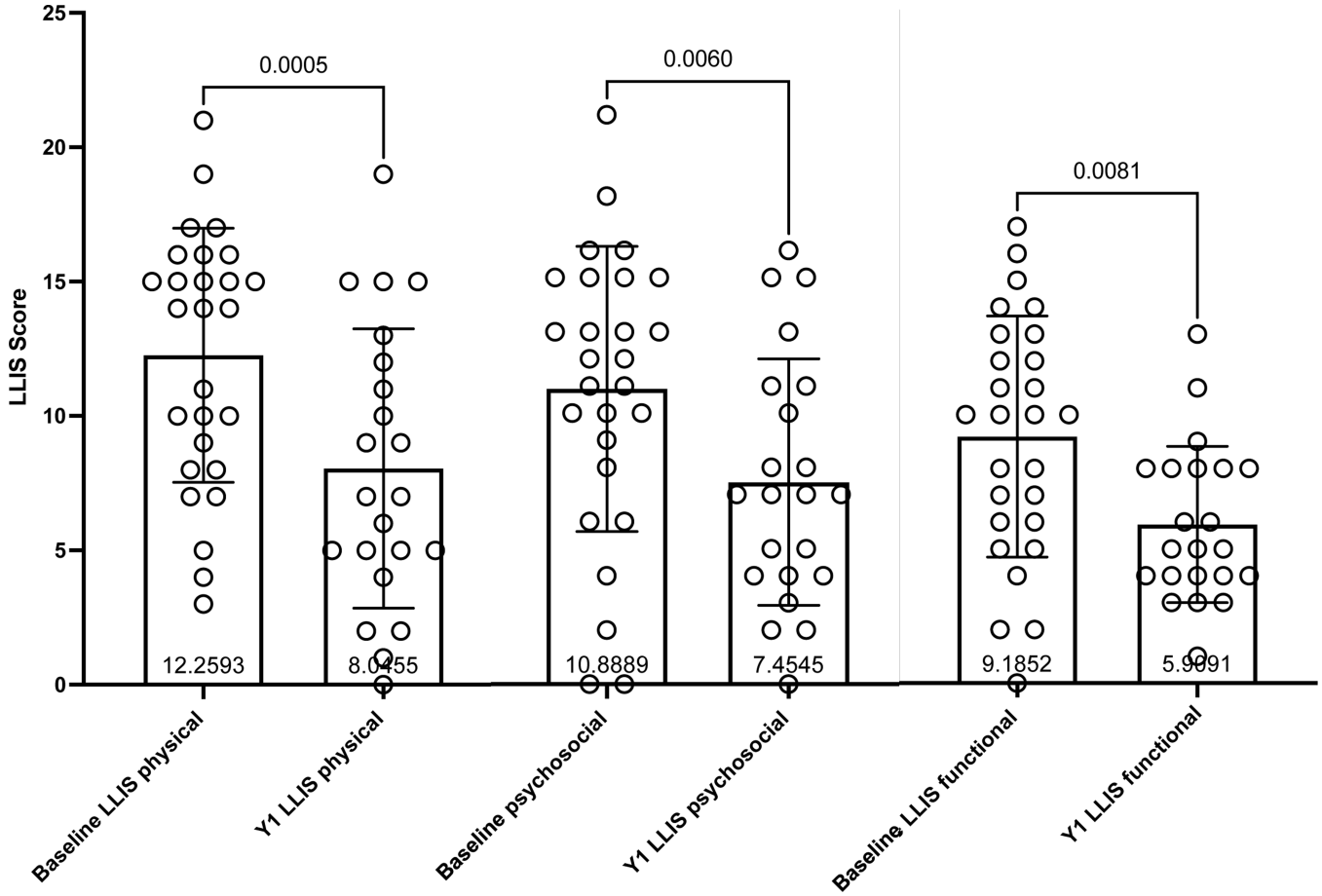

Figure 10 -
LLIS Physical, Psychological and Functional Scores 1 year post-VLNT

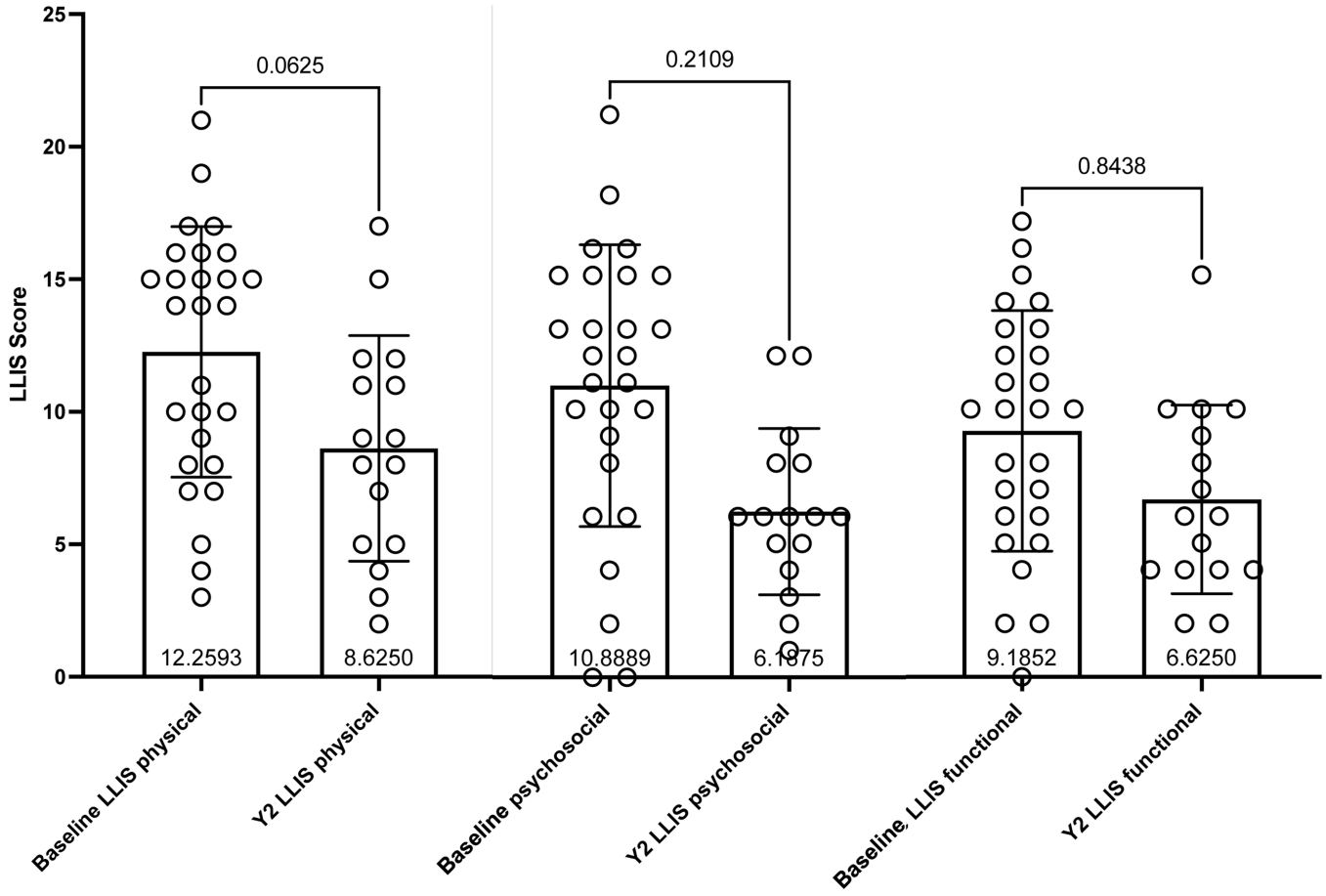

Figure 11 -
LLIS Physical, Psychological and Functional Scores 2 years post-VLNT

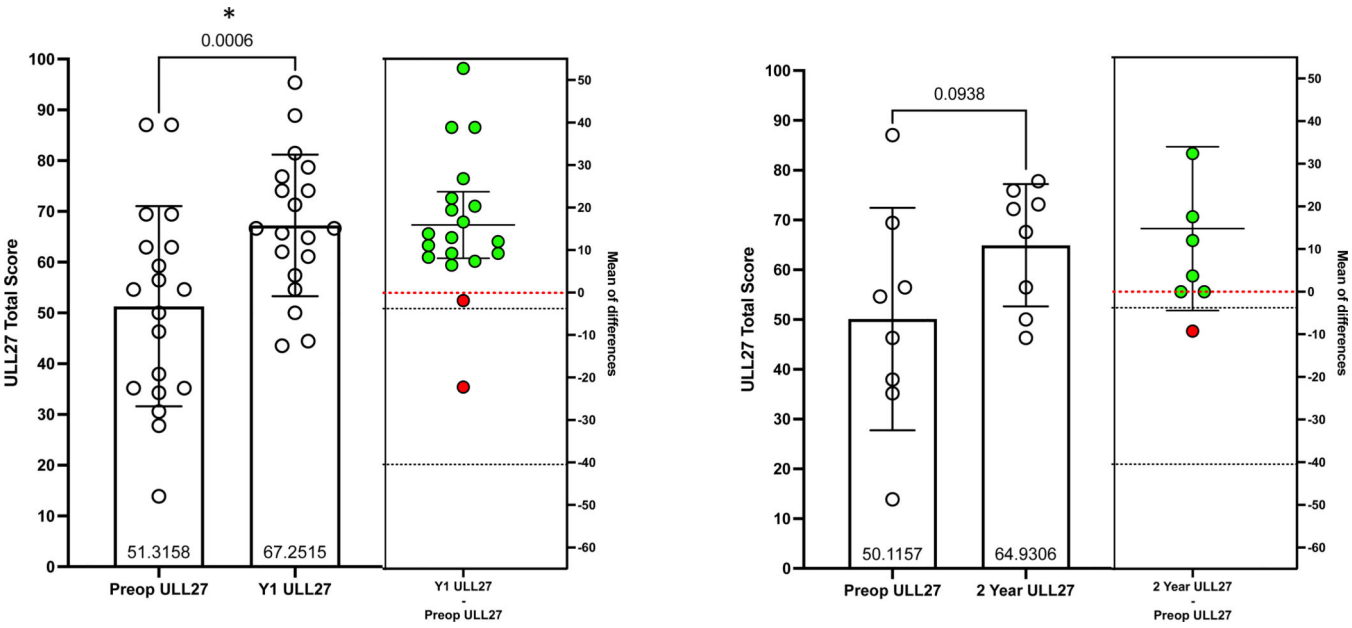

Figure 12 -

ULL27 Total scores at 1 year and 2 years post-VLNT in upper extremity lymphedema patients

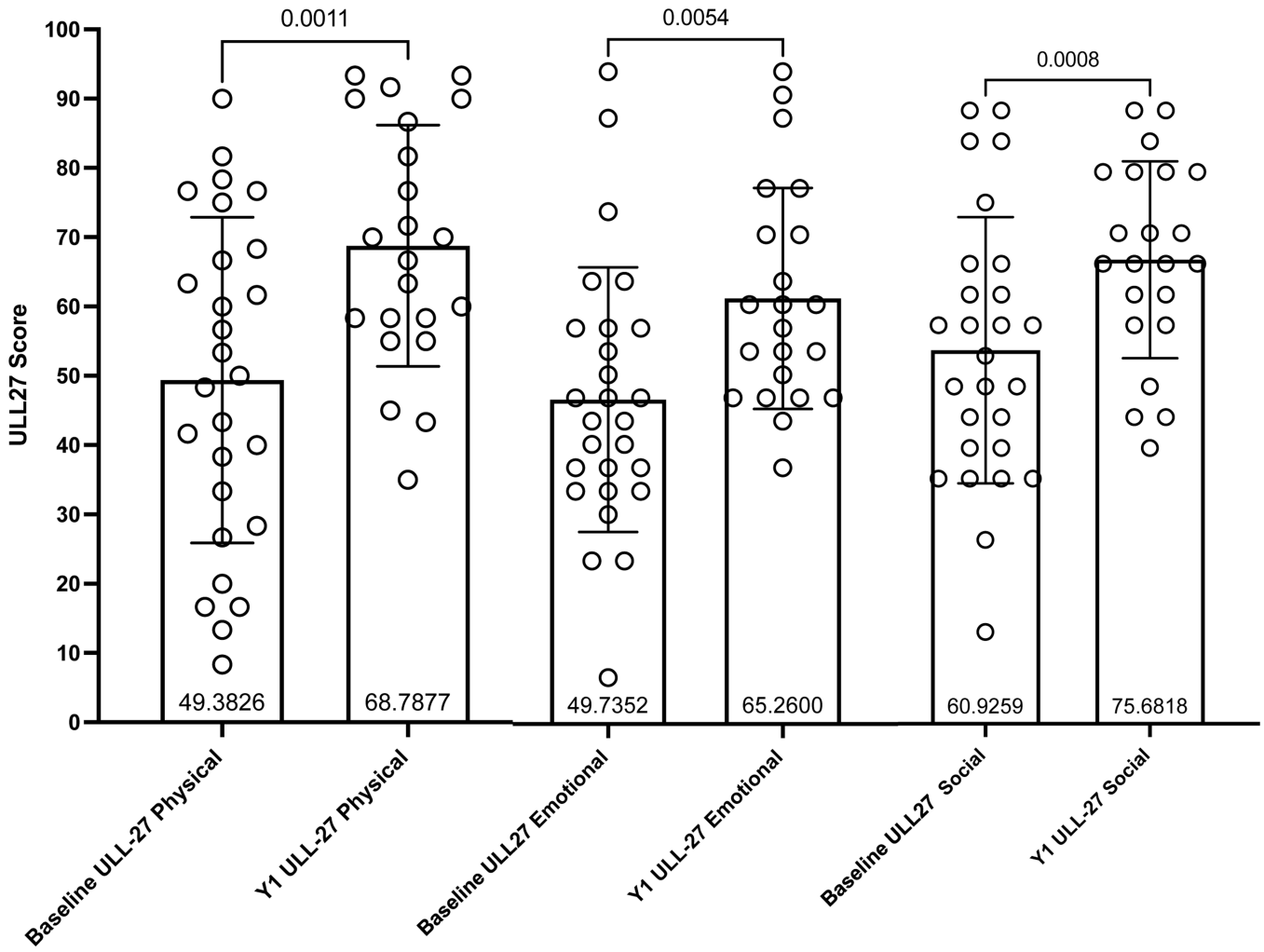

Figure 13 -
ULL27 Physical, Emotional and Social Scores 1 year post-VLNT

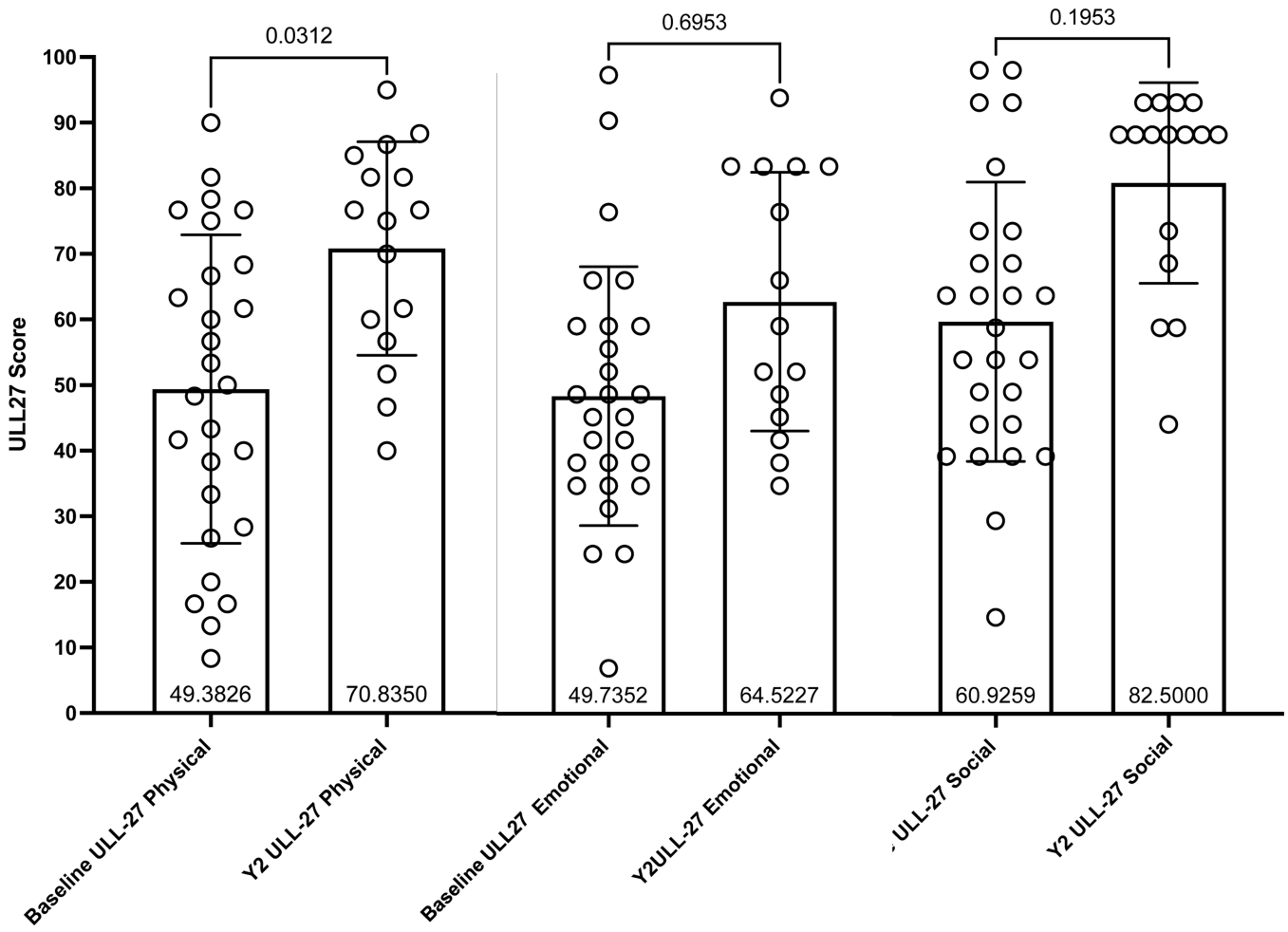

Figure 14 -
ULL27 Physical, Emotional and Social Scores 2 years post-VLNT

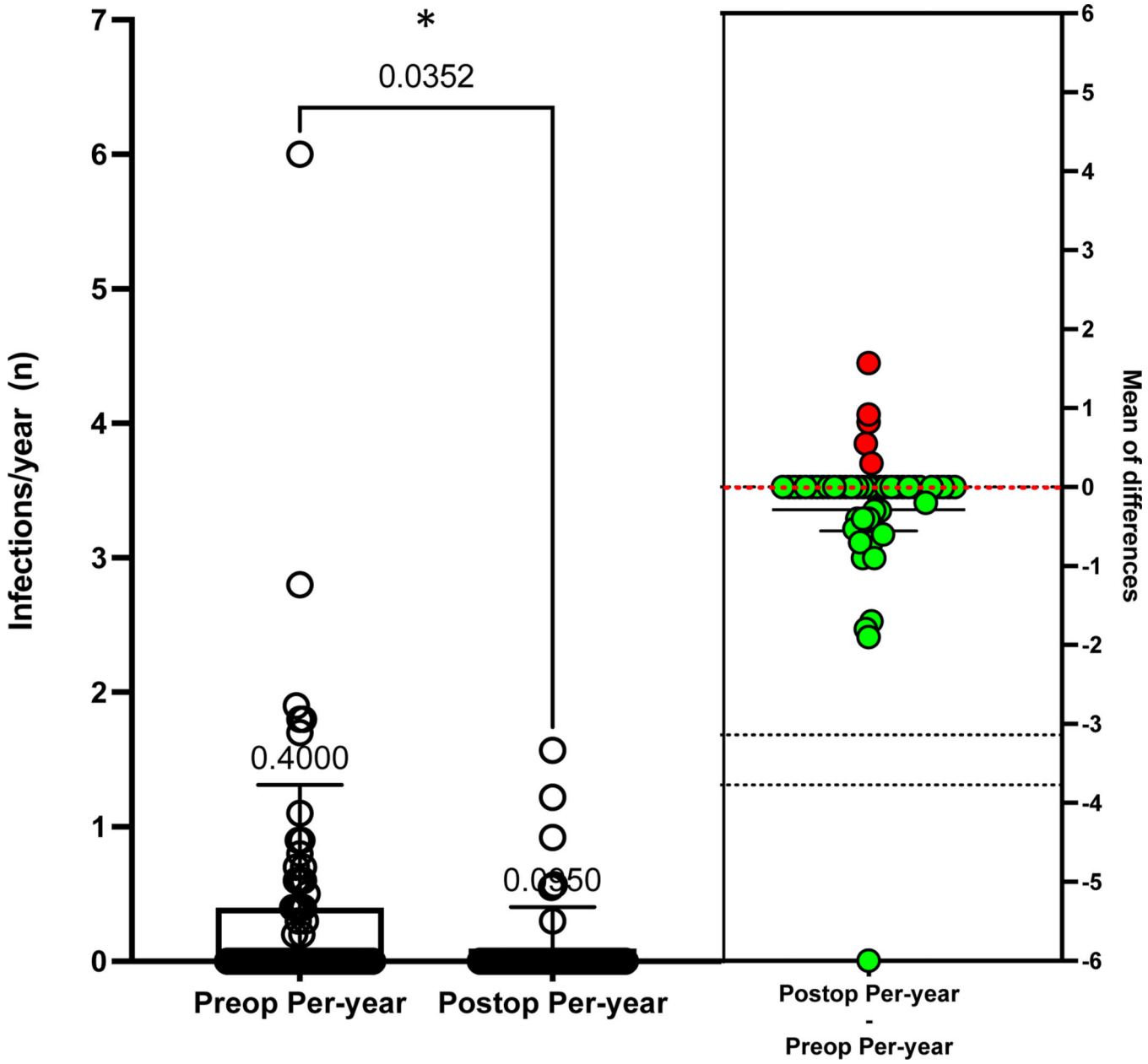

Figure 15 -
Cellulitis episodes post-VLNT

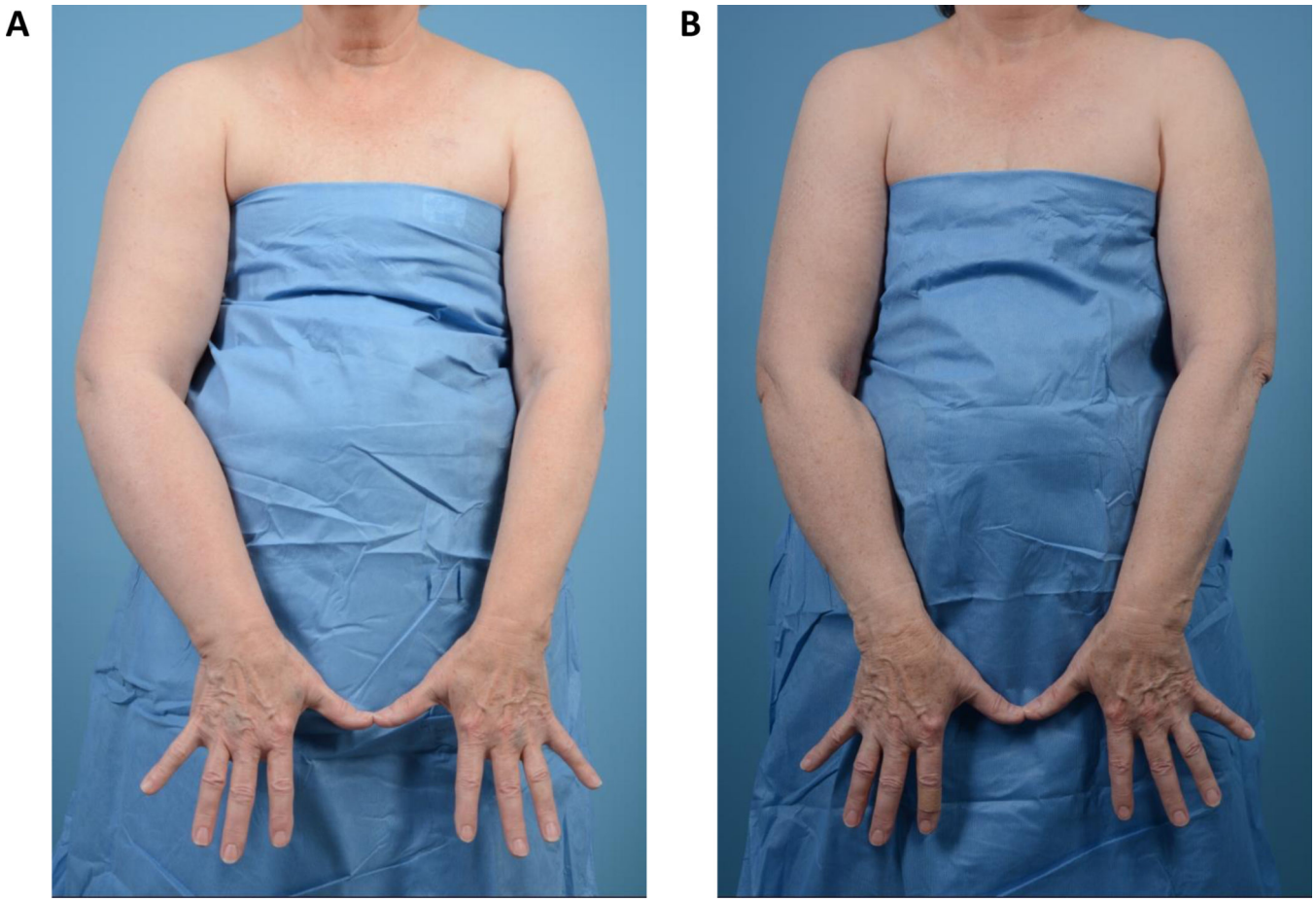

Figure 16 -

Case 1: A. Preoperative photographs of a 68-year-old vascularized omentum lymphatic transplant (VOLT) patient**. B.** 2-year postoperative photographs of the same patient

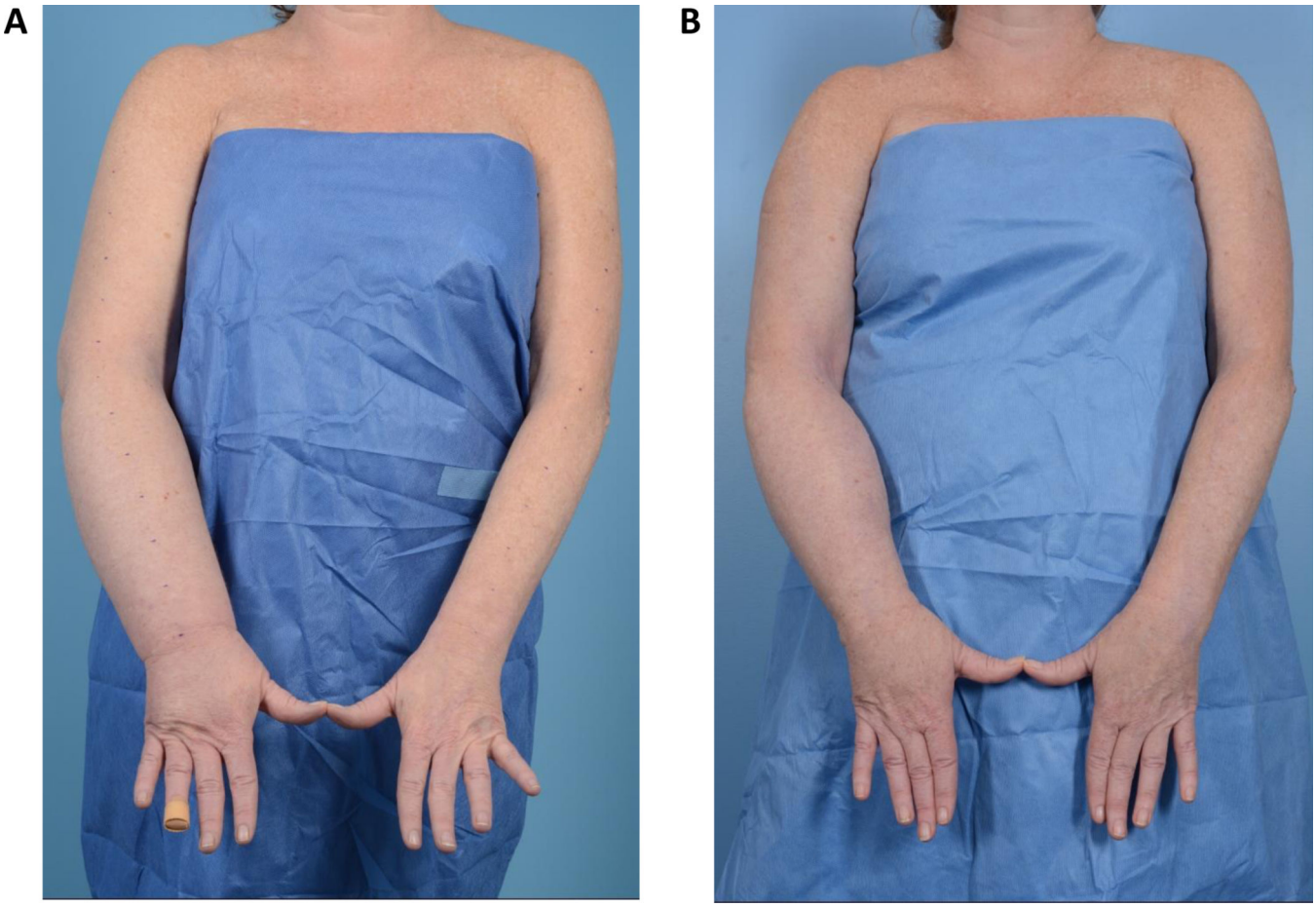

Figure 17 -

Case 2: A. Preoperative photographs of a 49-year-old vascularized omentum lymphatic transplant (VOLT) patient**. B.** 2-year postoperative photographs of the same patient

Table 1:

Potential advantages and disadvantages of different donor sites used for vascularized lymph node transplant

	Groin	Lateral Thoracic	Supraclavicular	Omentum	Submental
Potential Advantages	• Familiar anatomy • Hidden scar • Simple harvest	• Abundance of lymph nodes for transplant • Skin abundance	• Low risk of donor site lymphedema • Acceptable scar	• Ease of harvest • No donor-site lymphedema • Double-flap • Large amount of soft tissue	• Low risk of donor-site lymphedema • Acceptable scar • Large lymph nodes for transplant
Potential Disadvantages	• Higher risk of donor-site lymphedema • Higher risk of seroma • More significant pain	• More difficult harvest • Nerve injury • Higher risk of donor-site lymphedema • Future breast carcinoma?	• Small skin island • Neuropathic pain • Thoracis duct injury • Chyle leak	• Risk of hernia • Risk of intraabdominal complications • Difficult with prior abdominal surgery	• Possible submental nerve injury • Short pedicle • Relatively difficult dissection • Small skin paddle

Table 2:

Demographic and clinical information of patients with lymphedema who underwent VLNT

Parameter		**Mean ± SD/n (%)**
Age (years)		58.8±10.6
Gender	Female	88 (98.9%)
	Male	1 (1.1%)
Body mass index (kg/m2)		25.8±3.4
Duration of lymphedema (months)		55.1±67.4
Follow-up (months)		23.7±12
Etiology of lymphedema	Breast cancer	65 (73%)
	Gynecologic cancer	18 (20.2%)
	Melanoma	2 (2.2%)
	Other	4 (4.5%)
Location of lymphedema	Upper extremity	65 (73%)
	Lower extremity	24 (27%)
ISL Stage	0	1 (1.1%)
	I	8 (8.9%)
	II	79 (8.8%)
	III	1 (1.1%)
History of cellulitis preoperatively		35 (39.3%)
Total free flaps	Single flap	68 (61.8%)
	Double flap	21 (19%)
Donor site	Omentum	65 (73%)
	Axilla	3 (3.3%)
	Supraclavicular	6 (6.7%)
	Groin	3 (3.3%)
	Other	3 (3.3%)

Table 3:

Main outcomes in all patients who underwent VLNT

	Pre-VLNT (mean±SD)	1-year post-VLNT (mean±SD)	Change (%)	Pts improved (%)	P value	2 years post-VLNT (mean±SD)	Change (%)	Pts improved (%)	P value
Volume differential	31.4±14.7	28.7±14.9	8.6%	60.8%	0.0954	26.8±14.1	20.0%	51.6%	0.0239*
LDEX Score	34.0±29.5	31.1±25.9	8.5%	58.8%	0.1516	29.2±23.7	27.2%	58.6%	0.0398*
LLIS Total Impairment Score	45.8±17.6	32.4±16.3	29.3%	84.0%	0.0003*	32.8±13.0	28.5%	72.7%	0.0322*
LLIS Physical Score	12.6±4.6	8.8±5.2	30.5%	92.0%	<0.0001*	9.1±2.9	27.8%	91.0%	0.0117*
LLIS Psychological Score	10.2±5.4	7.4±4.3	27.8%	76%	0.0830	7.0±2.9	31.4%	72.7%	0.1230
LLIS Functional Score	8.4±4.3	5.9±3.2	29.1%	80.0%	0.0104*	6.2±4.2	26.1%	63.6%	0.5763
Total Cellulitis Episodes	3.0±3.4	0.5±1.2	85.0%	93.5%	0.0002*		-		
Cellulitis Episodes per-year	1.1±1.3	0.2±0.4	81.8%	90.0%	0.0008*		-		

Table 4:

Main outcomes in upper extremity patients who underwent VLNT

	Pre-VLNT (mean±SD)	1-year post-VLNT (mean±SD)	Change (%)	Pts improved (%)	P value	2 years post-VLNT (mean±SD)	Change (%)	Pts improved (%)	P value
Volume differential	30.2±15.4	25.6±15.4	14.9%	60.6%	0.0704	25.5±11.9	15.6%	55.6%	0.0524
LDEX Score	34.7±31.2	26.4±25.2	24.0%	62.2%	0.0400*	23.9±23.2	31.1%	57.9%	0.0696
LLIS Total Impairment Score	47.5±18.1	31.5±16.1	33.7%	89.4%	0.0002*	31.5±12.2	33.7%	75.0%	0.0781
LLIS Physical Score	12.3±4.7	8.0±5.2	34.4%	89.5%	0.0005*	8.6±4.3	29.6%	85.7%	0.0625
LLIS Psychological Score	10.9±5.3	7.5±4.5	31.2%	78.9%	0.0060*	6.2±3.1	43.1%	75%	0.8438
LLIS Functional Score	9.2±4.5	5.9±2.9	35.9%	83.3%	0.0081*	6.6±3.5	28.3%	62.5%	0.8438
ULL27 Total Score	51.5±19.7	69.1±14.7	34.2%	89.4%	0.0006*	72.6±16.6	40.9%	85.7%	0.0938
ULL27 Physical Score	49.4±23.5	68.8±17.4	39.3%	88.9%	0.0011*	70.8±16.3	43.3%	85.7%	0.00312*
ULL27 Emotional Score	49.7±20.3	65.3±16.9	31.4%	84.2%	0.0054*	64.5±20.3	50%	29.8%	0.6953
ULL27 Social Score	60.9±20.7	75.7±16.1	24.3%	88.9%	0.0008*	82.5±15.6	35.4%	71.4%	1.1953
Cellulitis Episodes per-year	0.4±0.9	0.09±0.3	77.5%	90.74%	0.00352*		-		

Table 5:

Complications in patients who underwent VLNT

	Complication	No. of cases (%)
Donor site	Hernia	1 (1.1%)
	Pancreatitis	1 (1.1%)
	Ileus	0 (0.0%)
	Small bowel obstruction	0 (0.0%)
Recipient site	Total flap loss *	2 (1.8%)
	Partial flap loss *	1 (0.9%)
Other	Hematoma	3 (3.3%)
	Seroma	3 (3.3%)
	Infection	2 (2.2%)

* Total flaps = 110