Accepted Manuscript

Submission Date: 2023-09-14
Accepted Date: 2023-11-30
Accepted Manuscript online: 2024-01-25

Archives of Plastic Surgery

Surgical Treatment for Primary Lymphedema: A Systematic Review of the Literature.

Miguel Angel Gaxiola-García, Joseph Escandón, Oscar J Manrique, Kristin A Skinner, Beatriz Hatsue Kushida Contreras.

Affiliations below.

DOI: 10.1055/a-2253-9859

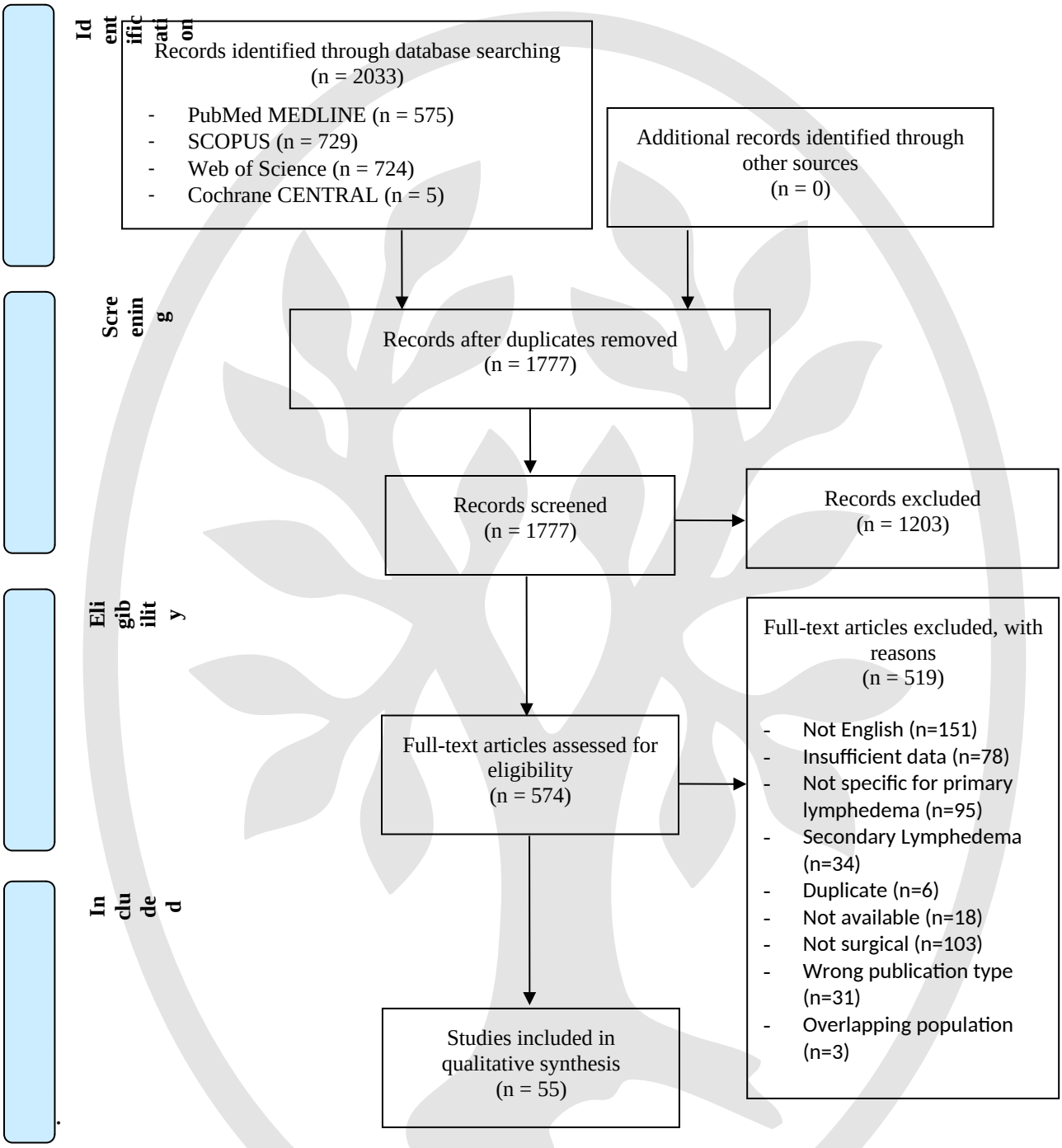
Please cite this article as: Gaxiola-García M, Escandón J, Manrique O J et al. Surgical Treatment for Primary Lymphedema: A Systematic Review of the Literature. Archives of Plastic Surgery 2023. doi: 10.1055/a-2253-9859

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Objective: Retrospective review of surgical management for primary lymphedema.
Methods: Data were extracted from 55 articles from PubMed MEDLINE, Web of Science, SCOPUS, and Cochrane CENTRAL between the data base inception and December 2022 to evaluate the outcomes of lympho-venous anastomosis (LVA) and vascularized lymph node transfer (VLNT), and outcomes of soft tissue extirpative procedures such as suction-assisted lipectomy (SAL) and extensive soft tissue excision.
Results:
Data from 485 patients were compiled; these were treated with LVA (n=177), VLNT (n=82), SAL (102), and excisional procedures (n=124). Improvement of the lower extremity lymphedema (LEL) index, the quality of life, and lymphedema symptoms were reported in most studies. LVA and VLNT led to symptomatic relief and improved quality of life, reaching up to 90% and 61% average circumference reduction, respectively. Cellulitis reduction was reported in 25% and 40% of LVA and VLNT papers, respectively. The extirpative procedures, used mainly in patients with advanced disease, also led to clinical improvement from the volume reduction, as well as reduced incidence of cellulitis, although with poor cosmetic results; 87.5% of these reports recommended postoperative compression garments. The overall complication rates were: 1% for LVA, 13% for VLNT, 11% for SAL, and 46% for extirpative procedures. Altogether, only one paper lacked some kind of improvement.
Conclusions:
Primary lymphedema is amenable to surgical treatment; the currently performed procedures have effectively improved symptoms and quality of life in this population. Complication rates are related to the invasiveness of the chosen procedure.

Corresponding Author:
Dr. Beatriz Hatsue Kushida Contreras, Hospital General de Mexico Dr Eduardo Liceaga, General Surgery, Ciudad de Mexico, Mexico, mdkushida@gmail.com

Affiliations:
Miguel Angel Gaxiola-García, Hospital Infantil de Mexico Federico Gomez, Plastic and reconstructive surgery, Mexico City, Mexico
Joseph Escandón, Strong Memorial Hospital, Plastic and reconstructive surgery, Rochester, United States
Oscar J Manrique, Strong Memorial Hospital, Plastic and reconstructive surgery, Rochester, United States
Kristin A Skinner, Strong Memorial Hospital, Plastic and reconstructive surgery, Rochester, United States
Beatriz Hatsue Kushida Contreras, Hospital General de Mexico Dr Eduardo Liceaga, General Surgery, Ciudad de Mexico, Mexico



PRISMA 2020 Checklist

TITLE			
Title	1	Identify the report as a systematic review.	Title, Methods
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods Fig. 1 Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods Fig. 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods Fig. 1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods
	13c	Describe any methods used to tabulate or visually display results	Methods

		of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Appendix 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Appendix 2, 3, 4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1, 2, 3, 4, 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1, 2, 3, 4, 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Appendix 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Appendix 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not	-

protocol		registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Disclosures
Competing interests	26	Declare any competing interests of review authors.	Disclosures
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

APPENDIX , SUPPLEMENTAL TABLE 1

PubMed - MEDLINE (Inception through December 2022)
((Lymphedema) OR (Lymphoedema)) AND ((Primary) OR (Hereditary) OR (Congenital) OR (Praecox) OR (Tarda) OR (Meige's syndrome) OR (Milroy's disease)) AND ((Lymph node transfer) OR (lymphaticovenular anastomosis) OR (Lymphovenous anastomosis) OR (Liposuction) OR (Lipectomy) OR (lymph node transplant) OR (Excision) OR (radical reduction preservation perforators)) NOT ((Conservative) OR (Compression) OR (Cancer-related) OR (Mastectomy) OR (Postmastectomy) OR (treatment-related) OR (Oncologic) OR (Breast cancer) OR (Post-breast) OR (Filarial) OR (Filariasis) OR (Animal) OR (Animals) OR (Congress) OR (Cadaver) OR (Cadavers) OR (Reply) OR (Leiomyosarcoma) OR (Vulvar Cancer) OR (nonsurgical) OR (gynecologic malignancy) OR (gynecologic malignancies) OR (melanoma) OR (Lymphadenectomy))
Web of Science (Search Limit: Title, Abstract and Keywords) [January 2001 through December 2022]
((primary) OR (congenital) OR (hereditary)) AND (Lymphedema) NOT ((Secondary Lymphedema) OR (cancer-related) OR (breast cancer) OR (Filariasis) OR (filarial) OR (Carcinoma) OR (Melanoma) OR (Mastectomy))
SCOPUS (Search Limit: Title, Abstract and Keywords) [Inception through December 2022]
(Primary AND Lymphedema) OR (Hereditary AND Lymphedema) OR (Congenital AND Lymphedema) NOT (Secondary Lymphedema)
The Cochrane Central Register of Controlled Trials (CENTRAL) (Inception through December 2022)
Primary Lymphedema

Supplemental Table 2: Oxford Centre for Evidence-Based Medicine: Levels of Evidence.

Grade of Recommendation	Therapy, Prevention, Etiology, Harm:†
1a	Systematic Review (with homogeneity) of Randomized Controlled Trials
1b	Individual Randomized Controlled Trial (with narrow Confidence Interval)
1c	All or none. Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
2a	Systematic Review (with homogeneity*) of cohort studies
2b	Individual cohort study (including low quality Randomized Controlled Trials)
2c	“Outcomes” Research; Ecological studies
3a	Systematic Review (with homogeneity*) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies

† Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009)

Supplemental Table 3: Newcastle - Ottawa Quality Assessment Scale Cohort Studies

SELECTION †

1) Representativeness of the exposed cohort
- Truly representative of the average (described) in the community
- Somewhat representative of the average in the community

2) Selection of the non-exposed cohort
- Drawn from the same community as the exposed cohort

3) Ascertainment of exposure
- Secure record (e. g. surgical records)
- Structured interview

4) Demonstration that outcome of interest was not present at start of study
- Yes

COMPARABILITY Ω

1) Comparability of cohorts on the basis of the design or analysis
- Study controls for _____ (select the most important factor)
- Study controls for any additional factor (These criteria could be modified to indicate specific control for a second important factor.)

OUTCOME †

1) Assessment of outcome
- Independent blind assessment
- Record linkage

2) Was follow-up long enough for outcomes to occur
- Yes (select an adequate follow up period for outcome of interest)

3) Adequacy of follow up of cohorts
- Complete follow up - all subjects accounted for
- Subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost)

† A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories.

Ω A study can be awarded A maximum of two stars can be given for Comparability category

Supplemental Table 4: Tool for evaluating the methodological quality of case reports and case series

Tool for evaluating the methodological quality of case reports and case series §	
Domains	Leading exploratory questions
Selection	1. Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
Ascertainment	2. Was the exposure adequately ascertained?
	3. Was the outcome adequately ascertained?
Causality	4. Were other alternative causes that may explain the observation ruled out?
	5. Was there a challenge/rechallenge phenomenon?
	6. Was there a dose–response effect?
	7. Was follow-up long enough for outcomes to occur?
Reporting	8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

§ Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *Evid Based Med*.

Surgical Treatment for Primary Lymphedema: A Systematic Review of the Literature

Miguel Angel **Gaxiola-García**, MD, MSc † ORCID 0000-0003-3431-5150

Joseph M. **Escandón**, MD § ORCID 0000-0002-8982-1950

Oscar J. **Manrique**, MD, FACS Δ ORCID 0000-0002-6177-0709

Kristin A. **Skinner**, MD ¥

Beatriz Hatsue **Kushida-Contreras**, MD Ω ORCID 0000-0003-3027-3707

† MA Gaxiola-García. Plastic and Reconstructive Surgery Department, Mexico's Children's Hospital (Hospital Infantil de México "Federico Gómez"). Mexico City, Mexico.

§ Escandón JM. Division of Plastic and Reconstructive Surgery, Strong Memorial Hospital, University of Rochester Medical Center, Rochester, NY, USA

Δ OJ Manrique. Division of Plastic and Reconstructive Surgery, Strong Memorial Hospital, University of Rochester Medical Center, Rochester, NY, USA

¥ KA Skinner. Department of Surgical Oncology, Strong Memorial Hospital, University of Rochester Medical Center, Rochester, NY, USA

Ω BH Kushida-Contreras. Plastic and Reconstructive Surgery Department, Mexico's General Hospital (Hospital General de México). Mexico City, Mexico.

Corresponding author:

Dr. Beatriz Hatsue Kushida-Contreras

Servicio de Cirugía General, Hospital General de México

Calle Doctor Balmis Número 148

Colonia Doctores, C.P. 06720, Ciudad de México, México

Email: mdkushida@gmail.com

Post- publication corresponding author:

Dr. Beatriz Hatsue Kushida-Contreras

Structured Abstract

Objective: Retrospective review of surgical management for primary lymphedema.

Methods: Data were extracted from 55 articles from PubMed MEDLINE, Web of Science, SCOPUS, and Cochrane CENTRAL between the data base inception and December 2022 to evaluate the outcomes of lympho-venous anastomosis (LVA) and vascularized lymph node transfer (VLNT), and outcomes of soft tissue extirpative procedures such as suction-assisted lipectomy (SAL) and extensive soft tissue excision.

Results:

Data from 485 patients were compiled; these were treated with LVA (n=177), VLNT (n=82), SAL (102), and excisional procedures (n=124). Improvement of the lower extremity lymphedema (LEL) index, the quality of life, and lymphedema symptoms were reported in most studies. LVA and VLNT led to symptomatic relief and improved quality of life, reaching up to 90% and 61% average circumference reduction, respectively. Cellulitis reduction was reported in 25% and 40% of LVA and VLNT papers, respectively. The extirpative procedures, used mainly in patients with advanced disease, also led to clinical improvement from the volume reduction, as well as reduced incidence of cellulitis, although with poor cosmetic results; 87.5% of these reports recommended postoperative compression garments. The overall complication rates were: 1% for LVA, 13% for VLNT, 11% for SAL, and 46% for extirpative procedures. Altogether, only one paper lacked some kind of improvement.

Conclusions:

Primary lymphedema is amenable to surgical treatment; the currently performed procedures have effectively improved symptoms and quality of life in this population. Complication rates are related to the invasiveness of the chosen procedure.

Keywords: *Lymphedema, Primary lymphedema, Congenital lymphedema, Lymphovenous anastomosis, Lymph node transplant.*

INTRODUCTION

Lymphedema is a pathological entity characterized by volume enlargement of a body part caused by the accumulation of lymphatic fluid due to an affected lymphatic system; its causes are varied. When the blockage of lymphatic flow is due to surgery, trauma, radiation, or infection, the condition is termed secondary lymphedema; 1 in 1000 people is affected.[1] Conversely, primary lymphedema entails a preexisting anomaly of the lymphatic system in patients with a family history or a genetic background for the disease.[2] The prevalence of primary lymphedema is 1.15 in 100,000 individuals[3] and involves either the lower extremity (91%) or upper extremity (9%).[2,4,5]

Primary lymphedema has been classified into praecox to designate an early development of the disease, affecting mainly female patients aged from 10 to 24 years old, and congenital, present at birth, and subdivided into simple and familial (Milroy's disease).[4] The term lymphedema *tarda* was subsequently introduced to designate the late presentation of the disease, which usually occurs after 35 years of age.[6]

In the wide spectrum of congenital vascular malformations, primary lymphedema can appear as an isolated entity or be accompanied by other anomalies such as venous malformations or lymphangioma.[7] Also, primary lymphedema is an accompanying clinical feature of several syndromes with identified genetic associations: Hennekam syndrome (CCBE1), Noonan syndrome 1 (PTPN11), Emberger syndrome (GATA2), hypotrichosis-lymphedema-telangiectasia syndrome (SOX18), oculodentodigital dysplasia (GJA1), among others.[8] The usual clinical presentation in isolated primary lymphedema frequently shows an extremity with a woody, brawny texture, prominent veins, deep toe creases, "sky-jump" toenails, and papillomatosis (most severe over the second toe), and episodes of cellulitis and/or lymphangitis.[9]

Various underlying pathological features have been identified in primary lymphedema, including hypoplasia, dilatation, and aplasia of the lymphatic trunks in 55%, 24%, and 14% of patients, respectively,[6] as well as diseased lymph nodes.[10] Magnetic resonance lymphangiography has confirmed defects of inguinal lymph nodes with mild or moderate dilatation of afferent lymph vessels in 17% of cases, lymphatic vascular

anomalies (aplasia, hypoplasia, or hyperplasia) with no obvious defect of the draining lymph nodes in 32% of cases, and involvement of both lymph vessels and lymph nodes in 51% of cases.[11] These findings can potentially correlate to clinical features, considering the affected levels of the limb and the involvement of lymphatic hypoplasia.[11,12] It's been recognized that the defective development occurs in the later stage of lymphangiogenesis.[13] All these severe structural abnormalities have traditionally led primary lymphedema to be considered an incurable disease, unlike secondary lymphedema where originally the lymphatic structure and anatomy are normal, and continue to be until advanced stages, and the basic principle of surgical treatment is the restoration of flow in the severed lymphatic channels.[3]

Hence, for the past twenty years, lymphaticovenular anastomosis (LVA) and its derivative mechanism through supermicrosurgery have become a popular physiological treatment modality for lymphedema;[14] nevertheless, few studies have focused on the treatment of primary cases.[15,16] In consequence, non-surgical treatment, compression therapy being the cornerstone, is critical in treating lymphedema, providing symptom relief, and halting the progression of the disease.[17,18] The results of these conservative therapies have been moderately successful: decreases in absolute limb volume (around 30%), decreases in body mass index, and improvement in quality of life assessed through patient-reported outcome measures have been published.[19]

Despite the above, several surgical treatment modalities are available nowadays. The vascularized lymph node transfer (VLNT) for primary lymphedema with hypoplastic lymph vessels has proven to be a beneficial physiological procedure;[16,20–22] this modality works mainly in two ways: as a source for vascular endothelial growth factor (VEGF-c), stimulating lymphangiogenesis in the affected limb, and drawing lymph forth into the venous circulation through a pressure gradient.[23] These fluid dynamics are further complicated by the role of the endothelial glycocalyx layer functioning as a monitor of fluid filtration from blood capillaries, causing most interstitial fluid to be reabsorbed by lymphatic rather than venous capillaries, as is now dictated by the revised Starling's principle.[24,25]

Conversely, excisional and debulking procedures have been used as palliative surgeries for lymphedema. These include the Charles procedure, which is performed predominantly for advanced stages of lymphedema, resulting in evident scarring with tissue breakdown and poor cosmetic results, as well as

lymphorrhea, recurrence, and residual distal edema;[26,27] and suction-assisted lipectomy (SAL), which started as a conjunct procedure for compression-resistant lymphedema.[28,29]

Although lymphedema has been an object of special attention in recent years, the special considerations of primary lymphedema etiopathology, concurrently with the unavoidable long-standing progression of the disease before an accurate diagnosis is made, have altogether contributed to the current lack of well-established protocols in the surgical treatment for this condition. Indeed, primary lymphedema is considered a rare or orphan disease.[30] Therefore, in this study, we aimed to perform a systematic review of the literature focusing on the reported outcomes of surgical treatment in the context of primary lymphedema of the extremities.

METHODS

Protocol and Search Strategy

This review was performed commensurate with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[31,32] A comprehensive search design by J.M.E across PubMed MEDLINE, Web of Science, SCOPUS, and Cochrane Central Register of Controlled Trials (CENTRAL) was performed from database inception through December 2022. The terms “Lymphedema”, “Primary”, “Hereditary”, “Congenital”, “Praecox”, “Tarda”, “Meige’s syndrome”, “Milroy’s disease”, “Lymph node transfer”, “Lymphovenous anastomosis”, “Liposuction”, “Lipectomy”, “lymph node transplant”, “Excision”, and “radical reduction preservation perforators” were used as keywords with Boolean operators in several combinations (See **Supplemental Table 1**, which exhibits the specific search terms used for the different databases).

Inclusion and Exclusion Criteria

We included original articles written in English, reporting outcomes and surgical techniques for the management of primary lymphedema of extremities in human patients. Preclinical studies and survey studies were excluded. Studies reporting outcomes in which multiple patients with primary and secondary lymphedema were included when the outcomes of primary lymphedema were explicitly distinguished from the analysis. Otherwise, studies dealing with primary and secondary lymphedema where data was aggregated

without distinction were excluded. Studies reporting outcomes of the surgical management of exclusively lymphatic malformations, malignancies secondary to lymphedema, or genital lymphedema, were excluded.

Study Selection and Data Extraction

Once duplicated citations were excepted, two independent authors (B.H.K.C. and J.M.E) evaluated the included references based on the title and abstract. Subsequently, a full-text assessment was accomplished in the remaining studies. Disagreements through this 2-step process were solved by a third author (M.A.G.G.). Two authors performed data extraction independently. Extracted data included as follows: author and year, location, number of patients, age, lymphedema stage, duration of lymphedema, associated syndromes or comorbidities, surgical technique, adjuvant procedures, postoperative protocol, outcomes, complications, and follow-up. Cumulative estimates were calculated as weighted means.

Quality Assessment and Risk of Bias

Appraisal of the levels of evidence was performed independently by two reviewers (J.M.E. and M.A.G.G.) using the Oxford Centre for Evidence-Based Medicine (OCEBM) (Supplemental Table 2).[33] The risk of bias was evaluated by operating the Newcastle-Ottawa Scale (NOS) (Supplemental Table 3) for observational cohort studies, and the Methodological Quality Assessment Tool (MQAT) for case reports and case series (Supplemental Table 4).[34,35]

RESULTS

Literature Search

Overall, 2033 citations were identified during the electronic bibliographic search. After duplicated references were eliminated, 1777 records were screened, and 1203 were excluded based on the title and abstract review. Following a full-text review, 55 articles met the inclusion criteria and were selected for data extraction. The PRISMA flow chart can be seen in figure 1.[5,21,22,26,36–84]

An overview of the studies' characteristics is displayed in table 1.

Quality Assessment

All studies had a level of evidence of 4 using the OCEBM instrument (Table 1), indicating that most studies included were case series and poor-quality cohort and case-control studies. Most case series and case reports had a moderate risk of bias when using the MQAT as twelve studies scored 5, nineteen scored 4, and three scored 3. The evaluation of the methodological quality of cohort studies was as follows: twelve studies had a NOS score of 6, and nine scored 5, which showed a low-to-moderate risk of bias.

Demographic and Clinical Characteristics

This review included 485 patients with primary lymphedema. The average age was 36.44 years and ranged from 1 to 94 years, reported in fifty-two studies. Seven (12%) and fifty-three (96%) articles reported the surgical management for upper extremity lymphedema (UEL) and lower extremity lymphedema (LEL), respectively. The average follow-up was 24.74 months (range, 1 - 324 months), reported in forty-seven studies. The average duration of lymphedema before the surgical intervention reported in the articles was 14.2 years (range, one month to 52 years), reported in 365 patients. Different lymphedema staging systems were reported in the included studies; the most common was the international society of lymphology (ISL) scale (n=17), followed by the Cheng's lymphedema grading scale (n=7) and the Campisi staging system (n=5). See Table I.

Several congenital malformations and syndromes were associated with primary lymphedema including Milroy's Disease (n = 16), Klippel-Trenaunay syndrome (n=7), Meige's disease (n = 3), turner syndrome (n=1), spina bifida with hydrocephalus (n=1), absence of the thoracic duct (n=1), congenital vascular lesions (n=3), and complex lymphatic malformations (n=1).

Lymphaticovenous Anastomosis (LVA)

This procedure has been reported since 2003. Twenty-four studies adequately reported the surgical outcomes of 177 patients with primary lymphedema treated with LVAs. Most studies reported LE (91%) surgical outcomes, and only two reported outcomes of the UE (8%). Staging of lymphedema was heterogeneously reported among studies. The most common stage treated with LVAs were ISL II (n=130) and ISL I (n=13). Only seven patients with lymphedema stage III were treated using this modality. When using Cheng's classification, most patients were in stage II-III (n=58). When using the Campisi staging system, most patients were in stage two (n=4), followed by stage three (n=3) and four (n=1).

The average number of LVAs per patient was 3.44 (range, 1-9), reported in 174 patients. The most common LVA techniques were the end-to-side, end-to-end, or side-to-end technique; nonetheless, several studies reported the use of π-shaped LVAs, octopus LVAs, and side-to-end anastomosis through temporary lymphatic expansion (SEATTLE). An overview of the results is displayed in table II. Surgical outcomes were not homogeneously reported. In most studies, an improvement of the LE lymphedema index, the QoL, and lymphedema symptoms, as well as a reduction of the cross-sectional area, episodes of cellulitis, the need for compression garments, and circumferential measures were reported. Some papers reported marginal improvements, for example, Mihara et al reported an average reduction rate of 2.7% in limb circumference,[69] while the same author had previously reported average size reductions of around 90%.[51] In contrast, Auba et al. reported an increment in the limb perimeter in comparison to preoperative measures.[53] Hara et al. also reported that the LE circumference increased following LVA treatment in patients with an onset age of <11 years; but significantly decreased in patients with an onset age >11 years.[15] Quality of life improvements were represented by diminution or absence of cellulitis episodes with less need for compression garments; [77] reported explicitly in at least 25% of papers. Systematic assessment of the quality of life was seldom reported using the Lymphoedema Quality of Life Questionnaire (LYMQoL).[16] The overall complication rate was 1%. The most common complications reported were several episodes of a lymphatic fluid leak in one patient and failure of the anastomosis.[52,55]

Vascularized Lymph Node Transfer

We found twelve articles reporting outcomes of VLNT for primary lymphedema, accounting for 82 treated patients. An overview of the results is displayed in table III. This technique was used mainly for the treatment of LE lymphedema. Pedicled VLNTs were described in two series. Fonkalsrud et al. reported an omentum transposition as described by Goldsmith, while Borz et al. reported modified enteromesenteric bridging.[72] The remaining eight studies reported the use of free VLNT, including the submental-VLNT (SM-VLNT) (33.33%), groin-VLNT (G-VLNT) (8.3%), vascularized omental lymph node transfer (VOLN)

(8.3%), gastroepiploic-VLNT (GE-VLNT) (16.6%), lateral thoracic-VLNT (LT-VLNT) (16.6%), and the first web space-VLNT (FWS-VLNT) (8.3%).

The outcomes were not reported uniformly; however, some reports stated that the average circumference reduction rate ranged from 17.2% to 61%, tonicity was reduced by 6.8 ± 0.8%, and the episodes of cellulitis decreased by 2.67-3 times/year during a follow up ranging from 16 to 63 months. As a whole, a reduction in cellulitis episodes was reported explicitly in at least 40% of papers. Qualitatively, most studies reported improved symptoms and QoL.[21,22,57,58,73,74,76] Unsatisfactory results were reported in the patient managed with omentum transposition: the leg swelling initially subsided during the first 6 months postoperatively, but the edema gradually returned as the patient became overweight. The overall complication rate was 13%; these included hematoma formation (n=1), venous congestion or thrombosis (n=4), and microsurgical revisions (n=4).[22,73]

Suction-Assisted Lipectomy (SAL)

One hundred and two patients were treated in 8 studies reporting the use of SAL; among them, one specifically used a 2-staged SAL technique. An overview of the results is shown in table IV. Most of the patients had stage II-III ISL lymphedema or had “end-stage” lymphedema. The mean reduction of original excess volume ranged from 71.9% to 94%.[64,71] Qualitatively, several articles reported a reduction in cellulitis episodes and an improvement of the QoL.[40,46,64] Remarkably, 87.5% of studies highlighted the importance of postoperative compression bandages. The overall complication rate was 11%; these included limited liposuction in certain areas (n=1), skin necrosis (n=5), significant blood loss (n=4), cellulitis (n=1), the requirement of further procedures (n=1), decubitus ulcers (n=1), and temporary peroneal nerve palsy (n=2).[64,65,71]

Excisional Procedures

We found fifteen studies reporting outcomes of excisional procedures for primary lymphedema of the extremities in 124 patients. An overview of the results is displayed in table IV. Studies reporting the stage of lymphedema included patients with stage III ISL or were referred to as “advanced” disease. Several excisional procedures were reported including a 2-stage modified Kondoleon-Sistrunk procedure (n=2); skin-sparing subcutaneous tissue excision (n=11); the Charles' procedure (n=16), the modified Charles (n=6), and

delayed modified Charles (n=8); the standard Homan's procedure (n = 7); a single-stage (n = 26), double-stage (n = 10), and triple-stage modified Homan's Procedure (n = 2); limb disarticulation (n=1); and tissue resection or shaving procedures (n=28). Most studies reported a remarkable reduction in the size of the LE, improvement of symptoms, and a reduction in the episodes of lymphangitis and cellulitis over a follow-up period ranging from 1 to 60 months. Remarkably, van der Walt et al. used a modified Charles' procedure delaying skin grafting by 5 to 7 days using negative pressure dressings. An average resection of 8.5 kg of lymphedematous tissue was reported without any major complication.[48] Karonidis et al. reported a modified Charles procedure with excision of the soft tissue at the dorsum of the toes while preserving the extensor tendon and its paratenon and the skin flaps at the web spaces.[49] Additionally, wedge resection was performed over the lateral and medial aspect thigh as a Homan's procedure, providing a smooth transition between the leg and the thigh.[49] In that series, eighteen of twenty patients achieved satisfactory aesthetic and functional results and no recurrent infections had been reported during a 3-year follow-up.[49] Poor cosmetic results were commonly reported (n=16). The overall complication rate was 46%; these included injury of the internal saphenous nerve (n=1), blood loss requiring transfusion (n=13), delayed wound healing (n=11), dermatosis (n=1), skin graft loss (n=6), presence of crevices and pits (n=1), chronic ulceration (n=1), the need of scar revision and release (n=2), reintervention (n=1), seroma (n=1), amputation (n=2), skin necrosis (n=3), hypertrophic scarring (n=2), focal wound tenderness (n=1).

DISCUSSION

The present study aimed to report on surgical treatments in the context of primary lymphedema.

Age of onset is undoubtedly relevant to the description and presentation of symptoms as well as the overall prognosis for every patient. The average age in our review was 36 years, seemingly old for most patients with primary lymphedema; this is due to the adulthood onset of the disease, as well as delays in the diagnosis. Ergo, primary lymphedema is not a synonym for childhood lymphedema.

Traditionally, primary lymphedema has been divided into categories based on the age of onset: congenital, *praecox*, or *tarda*, which failed to separate patients according to developmental age. To avoid miscommunication, a clearer classification has been proposed: infancy (between birth and one year of age), childhood (female patients between 1 to 8 years old, male patients 1 to 9 years old), adolescence (female

patients 9 to 12 years old, male patients 10 to 21 years old), and adulthood lymphedema (from 21 years old on).[85] The availability of a precise nomenclature may be helpful to successfully detect new and existing cases, with a classification based on a developmental approach.

Some considerations can be highlighted: despite the presence of diseased lymphatic structures, most patients remain at clinical stages I and II due to a probable intrinsic compensatory mechanism that stabilizes the lymphatic anomaly when conservative measures have been implemented.[86] Consequently, patients with an early diagnosis despite an abnormal lymphatic, yet balanced, function may have a better prognosis than those with long-standing untreated lymphedema.[87]

On this matter, treatment for lymphedema seeks to improve symptoms, cellulitis episodes, and quality of life. It is known that the mainstay treatment for lymphedema is compression therapy, which promotes mobilization of lymph to proximal areas, reduces capillary filtration, avoids tissue inflammation, and consequently reduces fat deposits and secondary fibrosis.[17] Surgical interventions in this review were synthesized into physiological procedures (LVA and VLNT) and volume reduction or excisional surgeries (SAL and excisional procedures).

Although a clear-cut for determining the required treatment based on the severity stage could be desired, this is not that straightforward. Hence, physiological procedures should be contemplated even if a patient responds well to compression alone: a next-to-normal extremity after a physiological surgery can enable a patient to discontinue the use of a compressive garment, with the accompanying improvement in quality of life.[22] Many patients may require more active compression with pneumatic devices, but these were not mentioned explicitly in the reviewed reports.

Despite an absence of uniformity in the reported surgical outcomes, circumferential measurements for volume reduction, episodes of cellulitis, improvement of symptoms, and quality of life assessments were somewhat commonly evaluated. Hopefully, lymphedema guidelines should develop a standard method for expressing outcome measures.

Lymphaticovenous anastomosis was overall the most performed procedure in this review. The size reduction of the affected limbs observed after this procedure in the studies of primary lymphedema patients is remarkable. Of note, isolated reports showed that LVA conditioned an increase in circumference in some patients,[15,53] especially those with an earlier onset of the disease.[15] Higher circumference reduction rates were

observed for LVA procedures compared to VLNT, although this should be considered with caution since the sample sizes were heterogeneous. Nevertheless, from our perspective, LVA and VLNT may be considered equivalent in this respect. Finally, both LVA and VLNT improved symptoms and decreased cellulitis episodes. The complication rates appear to be higher in VLNT compared to LVA, owing to the higher complexity of the former. However, for both groups, only some complications were reported.

Since an intrinsic subnormal lymphatic anatomy is present, an essential aspect when selecting the optimal microsurgical treatment for primary lymphedema is the preoperative morphology determination in concordance with the severity of the disease. Cheng et al. suggest performing LVA in patients with Cheng's Lymphedema Grade 0 to early Grade 2, limb circumferential difference less than 20%, short duration of symptoms, patent lymphatic ducts on ICG (indocyanine green) lymphography, and partial obstruction on Tc-99 lymphoscintigraphy.[22] For patients with a greater circumferential difference, symptoms of over five years, and absence of patent ducts or total obstruction by imaging, VLNT should be considered. This rationale indicates that performing LVA on incompetent lymphatic vessels may not only be futile but might aggravate the clinical stage of lymphedema. Similarly, in the presence of competent lymphatic vessels, performing VLNT as a first surgical instance precludes taking advantage of the existing function through the less invasive LVA.

Suction-assisted lipectomy is currently the debulking procedure of choice for lymphedema and is indicated mainly for the advanced stages of the disease. In our review, patients showed a considerable decrease in circumference and improvement in cellulitis episodes and quality of life with an approximate complication rate of 14.7%. The role of postoperative compression therapy was emphasized. Additionally, SAL has shown satisfactory results when combined with physiologic procedures, as liposuction addresses the deposits of fibroadipose tissue, while LVA or VLNT corrects the lymphatic flow.[88,89] Recently, a treatment algorithm for the sequence of liposuction with LVA or VLNT for lymphedema stages II-III has been proposed.[90] Nonetheless, the outcomes of this combined treatment have not been exclusively evaluated for primary lymphedema.

Excisional procedures were usually performed in the advanced stages of lymphedema; several complications and poor cosmetic results were described. The earlier the report, the more encouraging perspective was noted, even if results were considered less than ideal.

The challenge that the treatment of primary lymphedema poses is considerable. For instance, the underdeveloped lymphatic system with either abnormal lymph vessels or lymph nodes, or even both, demands an accurate and integral delineation of the lymphatic anatomy and function before considering a physiological procedure; the altered structure and lymphangiogenesis in primary lymphedema may cause inferior surgical outcomes when compared to those obtained in secondary lymphedema. Another defiance is the scenario of bilateral primary lymphedema, where improvements in circumferential measures cannot be assessed concerning a non-affected contralateral limb. Moreover, as some authors have considered primary lymphedema as an orphan disease, late diagnosis and delayed referral are not uncommon in these patients, which notably influence the course of the disease and treatment indications.[91] This late referral may be because most reconstructive plastic surgeons were traditionally taught that primary lymphedema was not a candidate for physiologic procedures. The reflection of this situation can be seen in the continued use of excisional procedures from its first report in 1950 to the present. Importantly, it was not possible to discern the indications for LVA, neither the preoperative planning, nor the methods of preoperative lymphatic mapping that led to such indications in each study. In this context, detailed information on imaging would be greatly useful.

Similarly, postoperative objective assessments of lymphatic function are uncommon. Furthermore, although follow-up appears to be appropriate, more than two years on average, we still ignore the required time of monitoring; for example, some patients may develop LVA failure due to venous reflux after two or three years.[92]

To our knowledge, there are no previous systematic reviews about the whole treatment spectrum for primary lymphedema. There are two recent systematic reviews partially dealing with our subject. Tang et al focused mainly on quality of life and included patients with secondary lymphedema. According to the authors, both ablative and physiologic interventions appear to provide an improvement in both generic and disease-specific quality-of-life domains, these improvements are sustained for at least 6–12 months post-operatively, and the choice of treatment for a particular patient is not clear, ideally determined by an experienced team on a case-by-case basis.[93] The review by Fallahian included ten studies in total dealing only with lymphovenous bypass and vascularized lymph node transplant. The number of patients included was considerable (n=254); the authors claimed a statistically significant improvement in the included reports but

did not support this conclusion.[94] Half of their included papers (5/10) coincide with those in our review; from our standpoint, and according to the papers we gathered, statistical significance is far from conclusive. A recent meta-analysis dealt with outcomes after microsurgical treatments for lymphedema; the results are very optimistic: patients who underwent microsurgery achieved better outcomes (limb circumference diameter reduction, reduced rates of "skin infections", and enhanced lymphatic transport capacity). It is impossible to discern which patients and which results apply to primary lymphedema.[95]

The main limitation of our study is its dependence on previous and heterogeneous studies which impacts a qualitative synthesis; for example, the scantness of studies focusing only on this pathology reflects the absence of reliable data regarding the prevalence of the disease, which to our knowledge has not been updated after 36 years.[5] Despite this, we made an effort to disaggregate the information from the included articles and analyze only and exclusively cases with primary lymphedema. About the data reviewed, the predominance of case reports, small sample case series, and lack of extensive studies dealing specifically with the surgical treatment of primary lymphedema, obstacle the categorical and unequivocal selection of treatment. In this regard, granular details that would be useful to draw conclusions are missing: number of lymphovenous anastomoses performed in each limb, objective assessment of the long-term outcomes, and number of patients with combined procedures and their outcomes, among others. Unfortunately, most of the papers deal with patient groups, outcomes, and preoperative protocols that are vastly different. Also, because different lymphedema staging methods were used in the studies reviewed, comparisons were difficult to make.

However, although only low-quality data could be drawn from existing reports, an effort was made to further clarify the current management of this condition; in addition, we must consider the ethical and methodological difficulty of designing prospective and comparative studies. Also, it is possible that a selection bias had occurred, considering that those papers with positive findings are more likely to be published, and ineffective results, especially physiologic treatment, might have not been reported and therefore not included in the analysis.

More studies focusing solely on the surgical treatment for primary lymphedema are necessary; these should include detailed preexisting lymphatic morphology through imaging, clinical and surgical specifications, homogenization, and systematization in the reporting of outcomes. In this way, the endeavor of

the present work may draw attention to these issues aiding in consensus and adequate communication among different working groups. Consequently, we would recommend the use of the International Society of Lymphology staging system for future reports.

Notwithstanding, our review shows that some treatment can be offered: more complex and sophisticated physiological procedures for earlier presentations with more conserved microstructural anatomy. On the contrary, when the lymphatic vessels' anatomy is severely altered, fibrosis is dire, and the patient is facing the inexorable progression of the disease, excisional treatment provides some relief.

CONCLUSION

Staging, clinical measurements, symptoms duration, and an accurate objective preoperative description of the lymphatic anatomy and function through imaging techniques, are central in selecting proper surgical treatment, regardless of the age of onset.

Establishing the competence of lymphatic vessels is cardinal to the selection of the ideal supermicrosurgical or microsurgical treatment or a combination of these with an excisional procedure such as suction-assisted lipectomy. To better understand surgical treatment outcomes in the future, comparative studies, hopefully randomized controlled trials, with larger samples and longer follow-ups are required.

Primary lymphedema is amenable to surgical treatment; the currently performed procedures have effectively improved symptoms and quality of life in this population.

Author contributions.

MA Gaxiola-García: conception and design of the work, theoretical framework, analysis and interpretation of data, drafting, and revisions.

JM Escandón: acquisition and interpretation of data, statistical analysis, drafting and substantial revisions.

OJ Manrique: conception of the work, acquisition and interpretation of data, drafting and substantial revisions.

KA Skinner: analysis and interpretation of data, drafting and substantial revisions.

BH Kushida Contreras: corresponding author, conception and design of the work, analysis and interpretation of data, drafting, and substantial revisions.

Acknowledgments: None

Conflicts of interests: None

Ethics: Anonymity and confidentiality were preserved.

Disclaimers: None

Previous presentations: None

Disclosures: The authors declare no potential conflicts of interest concerning the research, authorship, and publication of this article.

Funding: None of the authors received any funds or has any financial interests to disclose for the research, authorship, and publication of this article.

Statement of institutional review board approval or statement of conforming to the Declaration of Helsinki: The present manuscript did not require IRB approval.

REFERENCES

1. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. *J Am Acad Dermatol*. 2017;77(6):1009-1020. doi:10.1016/j.jaad.2017.03.022
2. Schook CC, Mulliken JB, Fishman SJ, Grant FD, Zurakowski D, Greene AK. Primary lymphedema: Clinical features and management in 138 pediatric patients. *Plast Reconstr Surg*. 2011;127(6):2419-2431. doi:10.1097/PRS.0b013e318213a218

3. Greene AK, Goss JA. Diagnosis and Staging of Lymphedema. *Semin Plast Surg*. 2018;32(1):12-16. doi:10.1055/s-0038-1635117

4. Allen E. Lymphedema of the Extremities. Classification, Etiology and Differential Diagnosis:A Study of Three Hundred Cases. *Arch Intern Med*. 1934;54(4):606-624.

5. Smeltzer DM, Stickler GB, Schirger A. Primary lymphedema in children and adolescents: A follow-up study and review. *Pediatrics*. 1985;76(2):206-218.

6. Kinmonth J, Taylor G, Tracy G, Marsh J. Primary lymphoedema; clinical and lymphangiographic studies of a series of 107 patients in which the lower limbs were affected. *Br J Surg*. 1957;45(189):1-9. doi:10.1002/bjs.18004518902

7. Van Damme A, Seront E, Dekeuleneer V, Boon LM, Vikkula M. New and Emerging Targeted Therapies for Vascular Malformations. *Am J Clin Dermatol*. 2020;21(5):657-668. doi:10.1007/s40257-020-00528-w

8. Brouillard P, Boon L, Vikkula M. Genetics of lymphatic anomalies. *Journal of Clinical Investigation*. 2014;124(3):898-904. doi:10.1172/JCI71614

9. Connell F, Brice G, Mortimer P. Phenotypic characterization of primary lymphedema. *Ann N Y Acad Sci*. 2008;1131:140-146. doi:10.1196/annals.1413.013

10. Kinmonth J, Eustace P. Lymph nodes and vessels in primary lymphoedema their relative importance in aetiology. *Ann R Coll Surg Engl*. 1976;58:278-284.

11. Liu NF, Yan ZX, Wu XF. Classification of lymphatic-system malformations in primary lymphoedema based on MR lymphangiography. *European Journal of Vascular and Endovascular Surgery*. 2012;44(3):345-349. doi:10.1016/j.ejvs.2012.06.019

12. Wolfe JHN, Kinmonth JB. The Prognosis of Primary Lymphedema of the Lower Limbs. *Archives of Surgery*. 1981;116(9):1157-1160. doi:10.1001/archsurg.1981.01380210037007

13. Murdaca G, Cagnati P, Gulli R, et al. Current views on diagnostic approach and treatment of lymphedema. *American Journal of Medicine*. 2012;125(2):134-140. doi:10.1016/j.amjmed.2011.06.032

14. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J Reconstr Microsurg*. 2000;16(6):437-442. doi:10.1055/s-2006-947150

15. Hara H, Mihara M, Ohtsu H, Narushima M, Iida T, Koshima I. Indication of lymphaticovenous Anastomosis for lower limb primary Lymphedema. *Plast Reconstr Surg*. 2015;136(4):883-893. doi:10.1097/PRS.0000000000001631

16. Cheng MH, Yung Loh CY, Lin CY. Outcomes of vascularized lymph node transfer and lymphovenous anastomosis for treatment of primary lymphedema. *Plast Reconstr Surg Glob Open*. 2018;6(12):1-7. doi:10.1097/GOX.0000000000002056

17. Mosti G, Cavezzi A. Compression therapy in lymphedema: Between past and recent scientific data. *Phlebology*. 2019;34(8):515-522. doi:10.1177/0268355518824524

18. Chang DW, Masia J, Garza R, Skoracki R, Neligan PC. Lymphedema: Surgical and medical therapy. *Plast Reconstr Surg*. 2016;138(3):209S-218S. doi:10.1097/PRS.0000000000002683

19. Desai SS, Shao M. Superior Clinical, Quality of Life, Functional, and Health Economic Outcomes with Pneumatic Compression Therapy for Lymphedema. *Ann Vasc Surg*. 2020;63:298-306. doi:10.1016/j.avsg.2019.08.091

20. Becker C, Arrive L, Saaristo A, et al. Surgical Treatment of Congenital Lymphedema. *Clin Plast Surg*. 2012;39(4):377-384. doi:10.1016/j.cps.2012.08.001

21. Ciudad P, Manrique OJ, Bustos SS, et al. Comparisons in long-term clinical outcomes among patients with upper or lower extremity lymphedema treated with diverse vascularized lymph node transfer. *Microsurgery*. 2020;40(2):130-136. doi:10.1002/micr.30508

22. Cheng MH, Liu TTF. Lymphedema Microsurgery Improved Outcomes of Pediatric Primary Extremity Lymphedema. *Microsurgery*. 2020;40(7):766-775. doi:10.1002/micr.30622

23. Cheng MH, Chen SC, Henry SL, Tan BK, Chia-Yu Lin M, Huang JJ. Vascularized groin lymph node flap transfer for postmastectomy upper limb lymphedema: Flap anatomy, recipient sites, and outcomes. *Plast Reconstr Surg*. 2013;131(6):1286-1298. doi:10.1097/PRS.0b013e31828bd3b3

24. Wilting J, Becker J. The lymphatic vascular system: much more than just a sewer. *Cell Biosci*. 2022;12(1). doi:10.1186/s13578-022-00898-0

25. Gianesini S, Rimondi E, Raffetto JD, et al. Human collecting lymphatic glycocalyx identification by electron microscopy and immunohistochemistry. *Sci Rep*. 2023;13(1). doi:10.1038/s41598-023-30043-x

26. Dellon A, Hoopes J. The charles procedure for primary lymphedema: Long-term clinical results. *Plast Reconstr Surg*. 1977;60(4):589-595. doi:10.1097/00006534-197710000-00015

27. McKee DM EM. The Surgical Treatment of Lymphedema of the Lower Extremities. *Plast Reconstr Surg*. 1959;23(5):480-492. https://pubmed.ncbi.nlm.nih.gov/13657722/

28. Brorson H, Ohlin K, Olsson G, Svensson B, Svensson H. Controlled compression and liposuction treatment for lower extremity lymphedema. *Lymphology*. 2008;41(2):52-63.

29. Boyages J, Kastanias K, Koelmeyer LA, et al. Liposuction for Advanced Lymphedema: A Multidisciplinary Approach for Complete Reduction of Arm and Leg Swelling. *Ann Surg Oncol*. 2015;22:1263-1270. doi:10.1245/s10434-015-4700-3

30. Vignes S, Albuisson J, Champion L, et al. Primary lymphedema French National Diagnosis and Care Protocol (PNDS; Protocole National de Diagnostic et de Soins). *Orphanet J Rare Dis*. 2021;16(1). doi:10.1186/s13023-020-01652-w

31. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ (Online)*. Published online 2015:g7647. doi:10.1136/bmj.g7647

32. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2016;4(1):1. doi:10.1186/2046-4053-4-1

33. OCEBM Levels of Evidence Working Group. *The Oxford Levels of Evidence 1*.; 2009.

34. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *Evid Based Med*. Published online 2018. doi:10.1136/bmjebm-2017-110853

35. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. *(Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)*. Published online 2012. doi:10.2307/632432

36. MacKmull G, Weeder SD. Congenital lymphedema; case report with results of surgical correction. *Plast Reconstr Surg*. 1950;5(2):157-162.

37. Fonkalsrud EW. Congenital lymphedema of the extremities in infants and children. *J Pediatr Surg*. 1969;4(2):231-236. doi:10.1016/0022-3468(69)90397-2

38. Tilley AR, Douglas LG. Staged treatment of lymphedema praecox. *Can Med Assoc J*. 1974;110(3):309-312.

39. Feins NR, Rubin R, Crais T, O'Connor JF. Surgical management of thirty-nine children with lymphedema. *J Pediatr Surg*. 1977;12(3):471-476. doi:10.1016/0022-3468(77)90026-4

40. Louton RB, Terranova WA. The Use of Suction Curettage as Adjunct to the Management of Lymphedema. *Ann Plast Surg*. 1989;22(4):354-357.

41. Dumanian GA, Futrell JW. Radical excision and delayed reconstruction of a lymphedematous leg with a 15 year follow-up. *Lymphology*. 1996;29(1):20-24.

42. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S. Long-term follow-up after lymphaticovenular anastomosis for lymphedema in the leg. *J Reconstr Microsurg*. 2003;19(4):209-215. doi:10.1055/s-2003-40575

43. Fraga MFP, Júnior AH, Neto HJG. Disarticulation of the left upper extremity for treatment of giant primary lymphedema - Case report. *Lymphology*. 2004;37(4):199-201.

44. Hosnuter M, Buyukates M, Babuccu B. An unusual case of lymphedema tarda. *Medical Science Monitor*. 2006;12(10):99-102.

45. Greene AK, Slavin SA, Borud L. Treatment of lower extremity lymphedema with suction-assisted lipectomy. *Plast Reconstr Surg*. 2006;118(5):118-121. doi:10.1097/01.prs.0000237020.29209.22

46. Espinosa-de-los-Monteros A, Hinojosa CA, Abarca L, Iglesias M. Compression therapy and liposuction of lower legs for bilateral hereditary primary lymphedema praecox. *J Vasc Surg*. 2009;49(1):222-224. doi:10.1016/j.jvs.2008.07.073

47. Eryilmaz T, Kaya B, Ozmen S, Kandal S. Suction-assisted lipectomy for treatment of lower-extremity lymphedema. *Aesthetic Plast Surg*. 2009;33(4):671-673. doi:10.1007/s00266-009-9351-y

48. Van Der Walt JC, Perks TJ, Zeeman BJV, Bruce-Chwatt AJ, Graewe FR. Modified charles procedure using negative pressure dressings for primary lymphedema: A functional assessment. *Ann Plast Surg*. 2009;62(6):669-675. doi:10.1097/SAP.0b013e318180cd24

49. Karonidis A, Chen HC. Preservation of toes in advanced lymphedema an important step in the control of infection. *Ann Plast Surg*. 2010;64(4):446-450. doi:10.1097/SAP.0b013e3181b30416

50. de Godoy JMP, Azoubel LMO, Godoy M de FG. Surgical treatment of elephantiasis of the feet in congenital lymphedema to facilitate the use of a compression mechanism. *Int J Gen Med*. 2010;3:115-118. doi:10.2147/ijgm.s8962

51. Mihara M, Hayashi Y, Murai N, et al. Regional diagnosis of lymphoedema and selection of sites for lymphaticovenular anastomosis using elastography. *Clin Radiol*. 2011;66(8):715-719. doi:10.1016/j.crad.2011.03.004

52. Yamamoto T, Koshima I, Yoshimatsu H, Narushima M, Miahara M, Iida T. Simultaneous multi-site lymphaticovenular anastomoses for primary lower extremity and genital lymphoedema complicated with severe lymphorrhea. *Journal of Plastic, Reconstructive and Aesthetic Surgery*. 2011;64(6):812-815. doi:10.1016/j.bjps.2010.10.011

53. Auba C, Marre D, Rodríguez-Losada G, Hontanilla B. Lymphaticovenular anastomoses for lymphedema treatment: 18 months postoperative outcomes. *Microsurgery*. 2012;32(4):261-268. doi:10.1002/micr.20980

54. Suehiro K, Morikage N, Murakami M, Yamashita O, Hamano K. Primary lymphedema complicated by weeping chylous vesicles in the leg and scrotum: Report of a case. *Surg Today*. 2012;42(11):1100-1103. doi:10.1007/s00595-012-0193-x

55. Yamamoto T, Yoshimatsu H, Yamamoto N, Narushima M, Iida T, Koshima I. Side-to-End Lymphaticovenular Anastomosis through Temporary Lymphatic Expansion. *PLoS One*. 2013;8(3):1-6. doi:10.1371/journal.pone.0059523

56. Ayestaray B, Bekara F. π-shaped lymphaticovenular anastomosis: The venous flow sparing technique for the treatment of peripheral lymphedema. *J Reconstr Microsurg*. 2014;30(8):551-560. doi:10.1055/s-0034-1370356

57. Gómez Martín C, Murillo C, Maldonado AA, Cristóbal L, Fernández-Cañamaque JL. Double autologous lymph node transplantation (ALNT) at the level of the knee and inguinal region for advanced lymphoedema of the lower limb (elephantiasis). *Journal of Plastic, Reconstructive and Aesthetic Surgery*. 2014;67(2):267-270. doi:10.1016/j.bjps.2013.09.016

58. Qiu SS, Chen HY, Cheng MH. Vascularized lymph node flap transfer and lymphovenous anastomosis for Klippel-Trenaunay syndrome with congenital lymphedema. *Plast Reconstr Surg*. 2014;134(1):1-5. doi:10.1097/GOX.0000000000000099

59. Akita S, Mitsukawa N, Kuriyama M, et al. Comparison of Vascularized Supraclavicular Lymph Node Transfer and Lymphaticovenular Anastomosis for Advanced Stage Lower Extremity Lymphedema. *Ann Plast Surg*. Published online 2015. doi:10.1097/SAP.0000000000000513

60. Ito R, Wu CT, Lin MCY, Cheng MH. Successful treatment of early-stage lower extremity lymphedema with side-to-end lymphovenous anastomosis with indocyanine green lymphography assisted. *Microsurgery*. Published online 2016. doi:10.1002/micr.30010

61. Koshima I, Narushima M, Mihara M, et al. Lymphadiposal Flaps and Lymphaticovenular Anastomoses for Severe Leg Edema: Functional Reconstruction for Lymph Drainage System. *J Reconstr Microsurg*. 2016;32(1):50-55. doi:10.1055/s-0035-1554935

62. Chen WF, Yamamoto T, Fisher M, Liao J, Carr J. The "octopus" Lymphaticovenular Anastomosis: Evolving beyond the Standard Supermicrosurgical Technique. *J Reconstr Microsurg*. 2015;31(6):450-457. doi:10.1055/s-0035-1548746

63. Gennaro P, Gabriele G, Mihara M, et al. Supramicrosurgical lymphatico-venular anastomosis (LVA) in treating lymphoedema: 36-months preliminary report. *Eur Rev Med Pharmacol Sci*. 2016;20(22):4642-4653.

64. Greene AK, Maclellan RA. Operative treatment of lymphedema using suction-assisted lipectomy. *Ann Plast Surg*. 2016;77(3):337-340. doi:10.1097/SAP.0000000000000597

65. Lamprou DAA, Voesten HGJ, Damstra RJ, Wikkeling ORM. Circumferential suction-assisted lipectomy in the treatment of primary and secondary end-stage lymphoedema of the leg. *British Journal of Surgery*. 2017;104(1):84-89. doi:10.1002/bjs.10325

66. Lee M, Perry L, Granzow J. Suction assisted protein lipectomy (SAPL) even for the treatment of chronic fibrotic and scarified lower Extremity Lymphedema. *Lymphology*. 2016;49(1):36-41.

67. Yamamoto T, Yoshimatsu H, Yamamoto N. Complete lymph flow reconstruction: A free vascularized lymph node true perforator flap transfer with efferent lymphaticolymphatic anastomosis. *Journal of Plastic, Reconstructive and Aesthetic Surgery*. 2016;69(9):1227-1233. doi:10.1016/j.bjps.2016.06.028

68. Chen WF, Zhao H, Yamamoto T, Hara H, Ding J. Indocyanine Green Lymphographic Evidence of Surgical Efficacy Following Microsurgical and Supermicrosurgical Lymphedema Reconstructions. *J Reconstr Microsurg*. 2016;32(9):688-698. doi:10.1055/s-0036-1586254

69. Mihara M, Hara H, Tange S, et al. Multisite lymphaticovenular bypass using supermicrosurgery technique for lymphedema management in lower lymphedema cases. *Plast Reconstr Surg*. 2016;138(1):262-272. doi:10.1097/PRS.0000000000002254

70. Lee KT, Park JW, Mun GH. Serial two-year follow-up after lymphaticovenular anastomosis for the treatment of lymphedema. *Microsurgery*. 2017;37(7):763-770. doi:10.1002/micr.30200

71. Stewart CJ, Munnoch DA. Liposuction as an effective treatment for lower extremity lymphoedema: A single surgeon's experience over nine years. *Journal of Plastic, Reconstructive and Aesthetic Surgery*. Published online 2018. doi:10.1016/j.bjps.2017.11.003

72. Borz C, Muresan M, Jimborean O, et al. Modified enteromesenteric bridging operation for primary lymphedema. *Ann Ital Chir*. 2018;89(0):350-356.

73. Sachanandani NS, Chu SY, Ho OA, Cheong CF, Lin MCY, Cheng MH. Lymphedema and concomitant venous comorbidity in the extremity: Comprehensive evaluation, management strategy, and outcomes. *J Surg Oncol*. 2018;118(6):941-952. doi:10.1002/jso.25237

74. Bolletta A, Di Taranto G, Chen SH, et al. Surgical treatment of Milroy disease. *J Surg Oncol*. 2020;121(1):175-181. doi:10.1002/jso.25583

75. Giacalone G, Yamamoto T, Belva F, et al. The Application of Virtual Reality for Preoperative Planning of Lymphovenous Anastomosis in a Patient with a Complex Lymphatic Malformation. *J Clin Med*. 2019;8(3):371. doi:10.3390/jcm8030371

76. Maruccia M, Pezzolla A, Nacchiero E, et al. Efficacy and early results after combining laparoscopic harvest of double gastroepiploic lymph node flap and active physiotherapy for lower extremity lymphedema. *Microsurgery*. 2019;39(8):679-687. doi:10.1002/micr.30511

77. AlJindan FK, Lin CY, Cheng MH. Comparison of Outcomes between Side-to-End and End-to-End Lymphovenous Anastomoses for Early-Grade Extremity Lymphedema. *Plast Reconstr Surg*. 2019;144(2):486-496. doi:10.1097/PRS.0000000000005870

78. Drobot A, Bez M, Abu Shakra I, et al. Microsurgery for management of primary and secondary lymphedema. *J Vasc Surg Venous Lymphat Disord*. 2021;9(1):226-233.e1. doi:10.1016/j.jvsv.2020.04.025

79. Onoda S, Nishimon K. The utility of surgical and conservative combination therapy for advanced stage lymphedema. *J Vasc Surg Venous Lymphat Disord*. 2021;9(1):234-241. doi:10.1016/j.jvsv.2020.05.007

80. Scaglioni MF, Meroni M, Fritsche E. Combining superficial and deep lymphovenous anastomosis for lymphedema treatment: Preliminary results. *Microsurgery*. Published online 2021. doi:10.1002/micr.30701

81. Robertson B, Neville E, Broering M, Tobler W, Recht M, Muck P. Multidisciplinary approach to management of severe lymphedema with one-stage radical excision and split-thickness skin grafting: Report of two cases. *J Vasc Surg Venous Lymphat Disord*. 2020;8(4):658-661. doi:10.1016/j.jvsv.2020.01.004

82. Damstra RJ, Dickinson-Blok JL, Voesten HGJM. Shaving Technique and Compression Therapy for Elephantiasis Nostras Verrucosa (Lymphostatic Verrucosis) of Forefeet and Toes in End-Stage Primary Lymphedema: A 5 Year Follow-Up Study in 28 Patients and a Review of the Literature. *J Clin Med*. 2020;9(10):3139. doi:10.3390/jcm9103139

83. Hayashi A, Visconti G, Yang CSJ, Hayashi N, Yoshimatsu H. Additional Lymphaticovenular Anastomosis on the Posterior Side for Treatment of Primary Lower Extremity Lymphedema. *J Clin Med*. 2022;11(3). doi:10.3390/jcm11030867

84. Mavili M, Naldoken S, Safak T. Modified Charles operation for primary fibrosclerotic lymphedema. *Lymphology*. 1994;27(1):14-20.

85. Greene AK, Schook CC. Primary lymphedema: Definition of onset based on developmental age. *Plast Reconstr Surg*. 2012;129(1):221-222. doi:10.1097/PRS.0b013e3182365c91

86. Barone V, Borghini A, Tedone Clemente E, et al. New Insights into the Pathophysiology of Primary and Secondary Lymphedema: Histopathological Studies on Human Lymphatic Collecting Vessels. *Lymphat Res Biol*. 2020;18(6):502-509. doi:10.1089/lrb.2020.0037

87. Goss JA, Maclellan RA, Greene AK. Adult-onset primary lymphedema: A clinical-lymphoscintigraphic study of 26 patients. *Lymphat Res Biol*. 2019;17(6):620-623. doi:10.1089/lrb.2018.0032

88. Ciudad P, Manrique OJ, Bustos SS, et al. Single-stage VASER-assisted liposuction and lymphatico-venous anastomoses for the treatment of extremity lymphedema: A case series and systematic review of the literature. *Gland Surg*. 2020;9(2):545-557. doi:10.21037/gs.2020.01.13

89. Forte AJ, Huayllani MT, Boczar D, Ciudad P, Manrique O. Lipoaspiration and Lymph Node Transfer for Treatment of Breast Cancer-related Lymphedema: A Systematic Review. *Cureus*. 2019;11(11). doi:10.7759/cureus.6096

90. Brazio PS, Nguyen DH. Combined Liposuction and Physiologic Treatment Achieves Durable Limb Volume Normalization in Class II-III Lymphedema: A Treatment Algorithm to Optimize Outcomes. *Ann Plast Surg*. 2021;86(5S Suppl 3):S384-S389. doi:10.1097/SAP.0000000000002695

91. Vignes S, Albuisson J, Champion L, et al. Primary lymphedema French National Diagnosis and Care Protocol (PNDS; Protocole National de Diagnostic et de Soins). *Orphanet J Rare Dis*. 2021;16(1):1-12. doi:10.1186/s13023-020-01652-w

92. Scaglioni MF, Fontein DBY, Arvanitakis M, Giovanoli P. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery*. 2017;37(8):947-953. doi:10.1002/micr.30246

93. Tang NSJ, Ramakrishnan A, Shayan R. Quality-of-life outcomes after operative management of primary and secondary lymphoedema: a systematic review. *ANZ J Surg*. 2021;91(12):2624-2636. doi:10.1111/ans.16764

94. Fallahian F, Tadisina KK, Xu KY. Efficacy of Microsurgical Treatment of Primary Lymphedema: A Systematic Review. *Ann Plast Surg*. 2022;88(2):195-199. doi:10.1097/SAP.0000000000002862

95. Kong X, Du J, Du X, Cong X, Zhao Q. A Meta-analysis of 37 Studies on the Effectiveness of Microsurgical Techniques for Lymphedema. *Ann Vasc Surg*. 2022;86:440-451.e6. doi:10.1016/j.avsg.2022.04.038

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

Table 1: Overview and quality assessment of included studies reporting surgical outcomes of primary lymphedema.

Author, year	Journal	Location	OCEBM	NOS	Patients (n)	Age (years)	Site	Grading	Lymphedema Duration (years)	Syndrome or Comorbidities	Follow-up (months)
MacKmull et al. 1950	Plastic and Reconstructive Surgery	Philadelphia, Pennsylvania	4	5 §	1	25	LE	NR	25	NR	8
Fonkalsrud et al. 1969	Journal of Pediatric Surgery	Los Angeles, California	4	3 §	4	(Range, 3-15)	LE	NR	NR	NR	> 6
Tilley et al. 1974	The Canadian Medical Association Journal	Toronto, Canada	4	4 §	1	40	LE	III ISL	26	NR	10
Dellon et al. 1977	Plastic and Reconstructive Surgery	Baltimore, Maryland	4	4 §	9	31 (Range, 22-40)	LE	NR	Range, 12-18	NR	127 (Range, 14-277)
					1	1.5	UE	NR	1.45	NR	216
Feins et al. 1977	Journal of Pediatric Surgery	Boston, Massachusetts	4	5	38	Range, 1-19	LE (n = 36) UE (n = 2)	NR	NR	NR	Range, 1-60
Smeltzer et al. 1985	Pediatrics	Rochester, Minnesota	4	5	16	NR	NR	NR	NR	Milroy's Disease (n = 1) Meige's Disease (n = 3)	Range, 0-324
Louton et al. 1989	Annals of Plastic Surgery,	Charleston, South Carolina	4	3 §	1	26	LE	NR	13	NR	NR
Mavili et al. 1994	Lymphology	Ankara, Turkey	4	4 §	4	NR	LE	NR	NR	NR	Range, 12-36
Dumanian et al. 1996	Lymphology	Pittsburgh, Pennsylvania	4	4 §	1	35	LE	NR	15	NR	180
Koshima et al. 2003	Journal of Reconstructive Microsurgery	Okayama, Japan	4	4 §	4	33 (Range, 12-53)	LE	NR	9.25 (Range, 2-24)	NR	93 (Range, 60-108)
Fraga et al. 2004	Lymphology	São Paulo, Brazil	4	4 §	1	21	UE	NR	15	NR	0.5
Hosnuter et al. 2006	Medical Science Monitor	Zonguldak, Turkey	4	4 §	1	47	LE	III ISL	16	NR	12
Greene et al. 2006	Plastic and Reconstructive Surgery	Boston, Massachusetts	4	4 §	1	34	LE	NR	10	Spina bifida Paraplegia Hydrocephalus Ventriculoperitoneal shunt	18
Espinosa et al. 2009	Journal of Vascular Surgery	Mexico City, Mexico	4	4 §	1	26	LE	III ISL	10	NR	14
Eryilmaz et al. 2009	Aesthetic Plastic Surgery	Ankara, Turkey	4	5 §	1	29	LE	NR	20	NR	22

van der Walt et al. 2009	Annals of Plastic Surgery	Cape Town, South Africa	4	5	8	34.8 (Range, 13-57)	LE	NR	17.6 (Range, 12-31)	NR	27.3 (Range, 12-90)
Karonidis et al. 2010	Annals of Plastic Surgery	Kaohsiung, Taiwan	4	6	8	21.6 (Range, 16-51)	LE	Advanced	6.37 (Range, 3-10)	NR	36
Pereira et al. 2010	International Journal of General Medicine	São José do Rio Preto, Brazil	4	3 §	2	59 (Range, 65-64)	LE	III ISL	NR	NR	3
Mihara et al. 2011	Clinical Radiology	Tokyo, Japan	4	4 §	2	52	LE	II ISL	NR	NR	23.6
Yamamoto et al. 2011	Journal of Plastic, Reconstructive & Aesthetic Surgery	Tokyo, Japan	4	4 §	2	20 (Range, 15-25)	LE & Scrotum	NR	20 (Range, 15-25)	NR	34 (Range, 15-53)
Auba et al. 2012	Microsurgery	Pamplona, Spain	4	4 §	1	52	LE	III Campisi	24	NR	18
Suehiro et al. 2012	Surgery Today	Yamaguchi, Japan	4	4 §	1	25	LE & Scrotum	NR	12	Absence of the thoracic duct and dilated iliac lymph trunks	12
Yamamoto et al. 2013	PLOS ONE	Tokyo, Japan	4	6	6	Range, 25-71	LE	I II III ISL	Range, 0.75-18	NR	6
Ayestaray et al. 2014	Journal of Reconstructive Microsurgery	Evry, France	4	5 §	1	34	LE	NR	23	Turner Syndrome	12
Gómez Martín et al. 2014	Journal of Plastic, Reconstructive & Aesthetic Surgery	Madrid, Spain	4	4 §	1	57	LE	NR	5	NR	5
Qiu et al. 2014	Plastic and Reconstructive Surgery - Global Open	Taoyuan, Taiwan	4	4 §	1	13	LE	NR	NR	Klippel - Trenaunay	3
Akita et al. 2015	Annals of Plastic Surgery	Chiba, Japan	4	6	1	34	LE	NR	13	NR	12
Hara et al. 2015	Plastic and Reconstructive Surgery	Tokyo, Japan	4	6	62	42 (Range, 10-90)	LE	1 (n = 8) 2a (n = 23) 2b (n = 46) 3 (n = 2) ISL	10.6 (Range, 0.1-52)	NR	19.5 (Range, 5.6-54.3)
Koshima et al. 2015	Journal of Reconstructive Microsurgery	Tokyo, Japan	4	5 §	2	17.5 (Range, 15-20)	LE	NR	2.25 (Range, 2-2.5)	NR	3.5 (Range, 3-4)
Chen et al. 2015	Journal of Reconstructive	Iowa City, Iowa	4	5 §	1	50	LE	IV Campisi	NR	NR	Range, 6–9

	Microsurgery										
Ito et al. 2016	Microsurgery	Taoyuan, Taiwan	4	5 §	2	32.5 (Range, 29-36)	LE	1.5 Cheng's	8 (Range, 2-14)	NR	10.5 (Range, 3-19)
Gennaro et al. 2016	European Review for Medical and Pharmacological Sciences	Siena, Italy	4	6	8	42 (Range, 16-56)	LE	I (n = 1) II (n = 6) III (n = 1) ISL	7.85 (Range, 2-15)	NR	36
					1	48	UE	III ISL	4	NR	36
Greene et al. 2016	Annals of Plastic Surgery	Boston, Massachusetts	4	4 §	8	41.87 (Range, 17-66)	LE	NR	NR	NR	36
Lee et al. 2016	Lymphology	Los Angeles, California	4	5 §	1	65	LE	NR	35	NR	15
Yamamoto et al. 2016	Journal of Plastic Reconstructive & Aesthetic Surgery	Tokyo, Japan	4	5 §	1	49	LE	NR	5	NR	18
Chen et al. 2016	Journal of Reconstructive Microsurgery	Iowa City, Iowa	4	6	4	54.5 (Range, 50-62)	LE	III (n = 1) IV (n = 3) Campisi	NR	NR	12
Mihara et al. 2016	Plastic and Reconstructive Surgery	Saitama, Tokyo	4	5	15	Range, 24–94	LE	I-III ISL	NR	NR	Range, 6–51
Lamprou et al. 2017	British Journal of Surgery	Drachten, The Netherlands	4	6	47	43.6 (Range, 12-4)	LE	"End-stage"	20 (Range, 10–33)	NR	12
Lee et al. 2017	Microsurgery	Seoul, South Korea	4	5 §	7	37 (Range, 11-58)	LE	II (n = 4) III (n = 3) Campisi	6.78 (Range, 1-15)	NR	24
Stewart et al. 2018	Journal of Plastic Reconstructive & Aesthetic Surgery	Dundee, UK	4	6	42	41 (Range, 20-68)	LE	2-3 ISL	20 (Range, 4–45)	NR	16 (Range, 6-48)
Borz et al. 2018	Annali italiani di chirurgia	Munes, Romania	4	4 §	18	18	LE & Scrotum	NR	14	Praecox	3
Cheng et al. 2018	Plastic and Reconstructive Surgery - Global Open	Taoyuan, Taiwan	4	6	17	31.5 (Range, 2-57)	LE	I (n = 2) II (n = 10) III (n = 2) IV (n = 5) Cheng's	4.51 (Range, 0.25-9.6)	Klippel - Trenaunay (n = 4)	18.2 ± 8.9
Sachanandani et al. 2018	Journal of Surgical Oncology	Taoyuan, Taiwan	4	5 §	3	25 (Range, 13-	LE	I (n = 1) IV (n = 4)	13 (Range, 8-18)	Klippel - Trenaunay (n = 2)	23 (Range, 19-

						43)		Cheng's		Concomitant vascular lesions (n = 3)	30)
Giacalone et al. 2019	Journal of Clinical Medicine	Mechelen, Belgium	4	4 §	1	27	LE	NR	27	Complex Lymphatic Malformation	4
Maruccia et al. 2019	Microsurgery	Bari, Italy	4	5 §	1	32	LE	III ISL	3	NR	3
Al Jindan et al. 2019	Plastic and Reconstructive Surgery	Taoyuan, Taiwan	4	6	15	NR	LE (n=14) UE (n=1)	1.2 Cheng's	NR	NR	14.2 (Range, 12.3–16.1)
Bolleta et al. 2020	Journal of Surgical Oncology	Taichung, Taiwan	4	5	15	16 ± 0.8	LE	II-III Cheng's	16 ± 0.8	Milroy disease	20.2 ± 2.8
Robertson et al. 2020	Journal of Vascular Surgery	Cincinnati, Ohio	4	4 §	2	42.5 (Range, 35-50)	LE	NR	4.5 (Range, 3-6)	NR	12
Damstra et al. 2020	Journal of Clinical Medicine	Drachten, The Netherlands	4	6	28	44.7 (Range, 32–66)	LE	III ISL	27.5 (Range, 6–36)	NR	54 (Range, 36-60)
Ciudad et al. 2020	Microsurgery	Taichung, Taiwan	4	6	11	(Range, 26-53)	LE & UE	II and III ISL	3.5 (Range, 0.6-6.3)	NR	32.8 (Range, 24-49)
Cheng et al. 2020	Microsurgery	Taoyuan, Taiwan	4	5 §	9	9.2 (Range, 2-19)	LE	2.6 ± 1.6 Cheng's	9.3 (Range, 2-19)	NR	38.4 (Range, 16-63)
Drobot et al. 2021	Journal of Vascular Surgery	Hiroshima, Japan	4	5	22	34	LE	II ISL	7.3	NR	9 (Range, 3-24)
Onoda et al. 2021	Journal of Vascular Surgery	Kagawa, Japan	4	5	2	46 (Range, 30-62)	LE	II ISL	NR	NR	31 (Range, 6-48)
Scaglioni et al. 2021	Microsurgery	Lucerne, Switzerland	4	5	1	46	LE	III Campisi	NR	NR	9
					2	4.5 (Range, 2-7)	UE	2.5 Cheng's	4 (Range, 3-5)	NR	37 (Range, 31-43)
Hayashi et. al. 2022	Journal of Clinical Medicine	Chiba, Japan	4	5	26	44.2 (Range, 16-82)	LE	1 (n = 3) 2a (n = 15) 2b (n = 14) 3 (n = 1) ISL	8.6 (0.8-29)	NR	17.5 (Range, 6-36)

ISL, international society of lymphology; LE, lower extremity; OCEBM, Oxford Centre for Evidence-Based Medicine: Levels of Evidence; NOS, Newcastle-Ottawa Scale; NR, not reported; UE, upper extremity; UK, United Kingdom.

§ Case reports and case series in which the methodological quality assessment tool (MQAT) proposed by Murad et al. was used.

Table 2: Studies reporting surgical outcomes of primary lymphedema using lymphaticovenous anastomosis.

Author, year	Patients (n)	Site	Surgical Technique	Other procedures	Postoperative Treatment	Outcomes	Complications
Koshima et al. 2003	4	LE	LVA No. of Anastomoses (mean): 4.25 (Range, 2-5)	Fat flap	Compression garments	Remarkable reduction in the circumference (8cm each in the B/L lower legs) Patients achieved a 55.6% reduction of the excess circumference.	NR
Mihara et al. 2011	2	LE	LVA No. of Anastomoses (mean): 3.5 (Range, 3-4)	NR	NR	The average size reduction was 90.15% Degree of limb hardness decreased from 2 to 1.	NR
Yamamoto et al. 2011	2	LE & Scrotum	Multi-site LVA No. of Anastomoses (mean): 6 (Range, 3-9)	NR	NR	No recurrence (n = 2)	Several episodes of Lymphorrhea (n = 1)
Auba et al. 2012	1	LE	LVA	NR	Limb elevation	The average preoperative limb perimeter increased from 32.1 to 32.9cm	
Suehiro et al. 2012	1	LE & Scrotum	LVA (n = 2)	NR	Medium-chain triglycerides supplement Compression therapy	2,000 ml reduction from the initial presentation Episodes of cellulitis decreased from every month to none	NR
Yamamoto et al. 2013	6	LE	SEATTLE (n = 2) Standard LVA (n = 4)	NR	NR	The LEL index decreased 18.2 ± 15.9 in patients with primary lymphedema. LEL index reduction in SEATTLE group was significantly greater that in non-SEATTLE group	11% of LVAs resulted in anastomosis failure
Bekara et al. 2014	1	LE	LVA π-shaped No. of Anastomoses: 4	NR	NR	The circumferential reduction rate was 17%, Cross-sectional area reduction rate was 32.2% Average volume reduction rate was 36.5%	No complications
Akita et al. 2015	1	LE	Multiple LVA	NR	NR	LEL index improved from 258.8 to 245.2 for the right leg and from 292.5 to 265.5 for the left leg	NR
Hara et al. 2015	62	LE	LVA (n = 79) No. of Anastomoses (mean): 4.5 (Range, 0-9)	NR	NR	LE circumference increased after LVA in patients with an onset age of 1 year or later and before age 11 years, but significantly decreased in patients with an onset age older	NR

						than 11 years	
Ito et al. 2015	2	LE	LVA No. of Anastomoses (mean): 2	NR	Compression therapy	The mean circumference reduction rate was 70.4%	NR
Yamamoto et al. 2015	1	LE	No. drainage pathways/ octopus LVA: 14 in 4	NR	NR	Postoperative Campisi stage: II Reduction of the LEL index from 378 to 352	NR
Gennaro et al. 2016	8	LE	LVA No. of Anastomoses (mean): 5.75 (Range, 5-7)	NR	Lymphatic drainage and compression stocking	Average size reduction was 61% (Range 41-87%)	No complications
	1	UE	LVA No. of Anastomoses: 5	NR	Lymphatic drainage and compression stocking	41% Size reduction	No complications
Yamamoto et al. 2016	1	LE	LT-VLNT + ELLA LVA No. of Anastomoses: 2	NR	Compression garment	No episode of cellulitis with reduced degree of compression treatment Lymphedematous volume decreased from 306 to 264 in terms of LEL index.	No complications
Chen et al. 2016	4	LE	LVA No. of Anastomoses (mean):not specified	NR	NR	12-month postoperatively Campisi stage II (n = 2) and III (n = 2) Significant improvement in QoL scores: decreased 10.5 Overall Reduction of 17 point in the LEL index	NR
Mihara et al. 2016	15	LE	Multi-site LVA	NR	NR	The average reduction rate was 2.7%	NR
Lee et al. 2017	7	LE	LVA No. of Anastomoses (mean): 2.42 (Range, 1-3)	NR	Physical Therapy	Reduction rate of volume: 39.2 ± 43.9 at 6 months, 20.2 ± 44.2 at 12 months, 38.7 ± 57.4 at 24 months	NR
Cheng et al. 2018	17	LE	LVA (n = 4) No. of Anastomoses: 1	SM-VLNT (n = 15)	NR	Following LVA: Limbs had a mean 1.9±2.9cm circumference reduction Reduction in body weight 6.6±5.9kg in VLNT and of 1.7±0.6kg in LVA LYMQoL improvement for LVA	NR
Giacalone et al. 2019	1	LE	LVA	NR	NR	The difference in volume between the left and right leg was reduced from 1222mL to 224mL	No complications
Al Jindan et al. 2019	15	LE (n=14) UE (n=1)	LVA No. of Anastomoses (mean): 1	NR	NR	Episodes of cellulitis were significantly reduced from 1.7 times/year to 0.7 times/year Circumferential Difference improvement was 3% Patients did not need compression	No complications

						garments postoperatively	
Drobot et al. 2020	22	LE	LVA No. of Anastomoses (mean): 3.1 (Range, 1-4)	NR	Compression therapy protocol (3 months)	Absolute Volume Change (in milliliters) at 6-months postoperatively: 372 ± 52 (55%)	No complications
Cheng et al. 2020	2	UE & LE	LVA	NR	None of the patients used compression garments postoperatively	The mean limb circumferential difference was improved by 5.5% (preoperative, 7.7; postoperative 5.5) Episodes of cellulitis decreased by 2.2 times/year	No complications
Onoda et al. 2020	2	LE	LVA No. of Anastomoses (mean): 4.5 (Range, 4-5)	NR	Inpatient Complex decongestive physiotherapy	Percentage reduction from admission to follow up: 19.4% (Range, 8.1-30.7%)	No complications
Scaglioni et al. 2020	1	LE	LVA No. of Anastomoses (mean): 1 Deep LVA and 5 Superficial LVAs	NR	NR	Initial Campisi stage III to Final Campisi stage Ib Overall improvement of symptoms	NR
Hayashi et al. 2022	26	LE	LVA No. of Anastomoses (mean): 8.7 total; Posterior side 3.5 LVAs and Medial-anterior side 4.6 LVAs	Previous LVAs	NR	Mean reduction of the LEL index 5.3–32.9 (18.1) After second procedure: 10.5 ± 4.5 in Posterior side LVAs, 5.5 ± 3.6 in Medial-anterior side LVAs	NR

B/L, bilateral; ELLA, efferent lymphaticolymphatic anastomosis; LVA, lymphaticovenous anastomosis; LE, Lower extremity; LEL, lower extremity lymphedema; LYMQoL, Lymphoedema Quality of Life Study; NR, not reported; SEATTLE, Side-to-end anastomosis through temporary lymphatic expansion; UE, upper extremity; VLNT, vascularized lymph node transfer.

Table 3: Studies reporting surgical outcomes of primary lymphedema using Vascularized Lymph Node Transfer.

Author, year	Patients (n)	Site	Surgical Technique	Other procedures	Postoperative Treatment	Outcomes	Complications
Fonkalsrud et al. 1969	1	LE	Omentum transposition as described by Goldsmith	NR	NR	Leg swelling subsided during the first 6 months after operation, but gradually returned as the patient became overweight	NR
Gómez Martín et al. 2014	1	LE	G-VLNT (1st Stage) LT-VLNT (2nd Stage)	NR	Manual drainage, compressive bandages	Average circumference reduction rate of 59.4% No episodes of cellulitis	No complications
Qiu et al. 2014	1	LE	SM-VLNT	NR	NR	Symptomatic improvement Circumferential reduction rates in the right LE at 15cm AK, 15cm BK, and 10cm AA were 50%, 53.3%, and 33%, respectively	No complications
Koshima et al. 2015	2	LE	FWS-VLNT (n = 2)	NR	Compression therapy (n = 1)	Dramatic improvement without any postoperative complications	NR
Yamamoto et al. 2016	1	LE	LT-VLNT + ELLA	LVA	Compression garment	No episode of cellulitis with reduced degree of compression treatment, and lymphedematous volume decreased from 306 to 264 in terms of Lower extremity lymphedema index were reported	No complications
Borz et al. 2018	18	LE & Scrotum	Modified enteromesenteric bridging	NR	NR	Decrease of the mid-calf diameters with 5.2cm on the right and 4.8cm on the left.	No complications
Cheng et al. 2018	17	LE	SM-VLNT (n = 15)	LVA (n = 4)	NR	Limbs that underwent VLNT had a mean 3.7 ± 2.9cm circumference reduction Reduction in body weight 6.6 ± 5.9 kg in VLNT and of 1.7 ± 0.6 kg in LVA LYMQoL in overall score improvement for VLNT and LVA	NR
Sachanandani et al. 2018	3	LE	SM-VLNT (n = 3)	LVA (n = 1)	NR	Final circumferential reduction rate of 39.16% above the knee and 34.5% below the knee	Hematoma (n = 1) Venous Thrombosis (n = 2) Revision Surgery (n = 2)
Bolleta et al. 2019	15	LE	GE-VLNT* (n=15)	Brorson's Secondary SAL	NR	The average circumference reduction was of 5.9 ± 1.2cm at mid-thigh, 4.9 ± 2.2cm at mid-calf, 3.7 ± 0.8cm at the ankle, and 1.7 ± 0.9cm at mid-foot. Tonicity overall was reduced by 6.8 ± 0.8%. No episodes of cellulitis	No complications
Maruccia et al. 2019	1	LE	GE-VLNT - Laparoscopic	CDP - 1 week preoperatively	Compression garments	The limb circumference reduction was 62.5% below the knee, and 41.4% above the knee	No complications
Ciudad et al. 2020	11	LE & UE	G-VLNT SC-VLNT GE-VLNT – Open and Laparoscopic A-VLNT IC-VLNT	NR	NR	Circumference reduction rate, % (mean ± SD): 18.9 ± 14.0 The positive circumference reduction was not significantly associated with VLNT	NR
Cheng et al. 2020	9	LE	SM-VLNT (n = 9) VOLNT* (n = 1)	NR	NR	The mean limb circumferential difference was improved by 17.2% (preoperative, 26.98; postoperative 22.34) Episodes of cellulitis decreased by 2.67 times/year No use of compression garments postoperatively	Venous congestion with successful salvage (n = 3) Partial skin paddle necrosis (n = 2)
	2	UE	SM-LNT (n = 1)	NR	NR	The mean limb circumferential difference was improved by 61% (preoperative, 22.7; postoperative, 8.3) Episodes of cellulitis decreased by 3 times/year	No complications

AA, Above the ankle; AK, above the knee; BK, below the knee; A-VLNT, appendicular VLNT; CDP, Complex decongestive physiotherapy; ELLA, efferent lymphaticolymphatic anastomosis; FWS-VLNT, first web space VLNT; G-VLNT, groin VLNT; GE-VLNT, gastroepiploic VLNT; LE, lower extremity; IC-VLNT, ileocecal VLNT; LT-VLNT, lateral thoracic; NR, not reported; VLNT; LVA, lymphaticovenous anastomosis; SAL, Suction-Assisted Lipectomy; SC -VLNT, supraclavicular VLNT; SM-VLNT, submental VLNT; UE, upper extremity; VLNT, vascularized lymph node transfer; VOLNT, vascularized omental lymph node transfer.

*Although labeled differently, these flaps correspond to the same procedure.

Table 4: Studies reporting surgical outcomes of primary lymphedema using suction-assisted lipectomy and excisional procedures.

Author, year	Patients (n)	Site	Surgical Technique	Other procedures	Postoperative Treatment	Outcomes	Complications
MAINLY SUCTION-ASSISTED LIPECTOMY							
Louton et al. 1989	1	LE	SAL	NR	Excision of redundant tissue, 4 days postoperatively	Large amount of redundant skin and subcutaneous tissue draped over an otherwise normal leg	The fibrotic areas over the dorsum of the feet were difficult to debulk
Greene et al. 2006	1	LE	SAL	NR	Pressure bandaging	Lower extremity circumferential measurements corresponded to a 75% reduction from her preoperative volume	NR
Espinosa et al. 2009	1	LE	SAL	NR	40 mmHg compression bandages	Volume of the legs decreased from 10.7L and 8.9L to 6.4L and 6.1L, postoperatively Cellulitis has not occurred, and antibiotics have not been required so far	No complications
Eryilmaz et al. 2009	1	LE	2-stage SAL	NR	NR	20% reduction from his first preoperative measurements	No complications
Greene et al. 2016	8	LE	SAL	NR	Compression bandages	The mean reduction in excess extremity volume was 73% (range, 48% to 94%) Better quality of life; none exhibited recurrence	Skin necrosis (n = 2) Significant blood loss (n = 2) Cellulitis (n = 1) Surgical debridement (n = 1)
Lamprou et al. 2016	47	LE	SAL	NR	Compression bandages	Average size reduction was 79% and absolute volume reduction of 3670ml compared with preoperative affected leg volume A reduction from 8 attacks of cellulitis to 0.2 attacks per year	Decubitus ulcer (n = 1)
Lee et al. 2016	1	LE	SAL	NR	Continuous compression garment	A stable overall excess volume reduction of 4227 cc (86%) was achieved at 15 months postoperatively which remained stable thereafter	NR
Stewart et al. 2017	42	LE	SAL	NR	Wrap garments	71.9 % Reduction of original excess volume at 3 months postoperative 84.3 % Reduction of original excess volume at 1 year postoperative	Skin necrosis (n = 3) Temporary peroneal nerve palsy (n =2) Significant blood loss (n = 2)
MAINLY EXCISIONAL PROCEDURES							
MacKmull et al. 1950	1	LE	2-stage Modified Kondoleon-Sistrunk Procedure	NR	Elevation 75º	Remarkable reduction in size of the leg No recurrence of lymphangitis	Internal saphenous nerve injury (n = 1)
Fonkalsrud et al. 1969	3	LE	Skin-sparing subcutaneous tissue excision	NR	Elastic bandages	Adequate cosmesis during postoperative assessment	Transfusion of Blood Units (n = Multiple) Delayed wound healing (n = 2)
Tilley et al. 1974	1	LE	Charles' Procedure - STSG Staged-tissue excision	NR	NR	Marked improvement in function; the appearance is less than ideal but is vastly improved	Transfusion of Blood Units (n = 2) Dermatosis (n = 1) Skin graft loss (n = 1)
Dellon et al. 1977	9	LE	Charles Procedure	NR	Wrap garments	Excellent functional and cosmetic outcomes Lymphedema in the dorsum of the foot (n =2)	Crevices and pits (n = 1) Chronic ulceration (n =

							1) Scar revision and release (n = 1)
	1	UE	Charles Procedure - FTSG	NR	NR	Excellent functional and cosmetic outcomes	Scar revision and release (n = 1)
Feins et al. 1977	38	LE (n = 36) UE (n = 2)	Single-stage Modified Homan's Procedure (n = 26) Double-stage (n = 10) Triple-stage (n = 2)	NR	Compression therapy 3 months	Improvement of symptoms (n=38) No episodes of lymphangitis and cellulitis	Wound dehiscence (n = 2) Revision surgery (n = 1) Seroma (n = 1)
Smeltzer et al. 1985	16	NR	Homan's Procedure (n = 7) Charles Procedure (n = 3) Genital Procedure (n = 4)	Thompson buried flap (n = 7)	NR	Scores: (Excellent-good, fair, or poor): - Homan's Procedure (Fair: 3; Poor: 4) - Charles Procedure (Good: 1; Fair: 2)	Recurrent infections in 33% of patients Below-the-knee amputation (n = 1) Ischemic necrosis (n = 3) Delayed wound healing (n = 4) Poor cosmetic results (n = 16)
Mavili et al. 1994	4	LE	Modified Charles Procedure	NR	Wrapped with elastic bandages	No progression of disease	Hypertrophic scarring (n = 2)
Dumanian et al. 1996	1	LE	Charles Procedure	NR	Gauze dressing	Near normal contour and appearance No spontaneous cellulitis	Skin graft loss (n = 1)
Fraga et al. 2004	1	UE	Disarticulation	NR	NR	Limb disarticulation	NR
Hosnuter et al. 2006	1	LE	Limited Charles Procedure - FTSG Sistrunk procedure 1 year later	NR	Physical Therapy	After the second operation, the left calf measurement decreased from 106 to 57cm	No major complications
van der Walt et al. 2009	8	LE	Delayed Modified Charles Procedure. (Negative Pressure 90 mmHg - 7 Days)	NR	NR	The mean weight of lymphedematous tissue removed was 8.5kg (range, 5–14.6kg). A 45% improvement of the LE Functional Scale.	Minor additional grafting (n = 3) Transfusion of Blood Units (n = 8) Wound breakdown (n = 2)
Karonidis et al. 2010	8	LE	Charles' procedure with preservation of toes	Homan's Procedure - Thigh	Non-adherent dressings and leg elevation	The average size reduction was of 28.75% (Range, 22-37%)	NR
Pereira et al. 2010	2	LE	Tissue resection	NR	Manual lymph drainage and mechanical lymph drainage	The size of the limbs can be maintained within the normal range by following the treatment guidelines	NR
Robertson et al. 2020	2	LE	Modified Charles Procedure	Preoperative Decongestive Therapy	Physical Therapy	Improved QoL	Focal wound tenderness (n = 1) Minor skin graft loss (n = 1)
Damstra et al. 2020	28	LE	Shaving Procedure	Preoperative short-stretch compression bandaging Circumferential SAL	Analgesic, silicone wound dressings and compression bandages	Decreased episodes of erysipelas: preoperative 17.6, postoperative 0.6	NR

LE, lower extremity; mmHg, millimeters of mercury; NR, not reported; SAL, suction-assisted lipectomy. FTSG, full-thickness skin graft; QoL, quality of life; STSG, split-thickness skin graft; UE, upper extremity.