Systematic Review

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Vascularized lymph node transfer for the treatment of lymphedema: a systematic review and meta-analysis of clinical and patient-reported outcomes

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Abstract

Aim: The aim of this systematic review was to summarize clinical and patient-reported outcomes (PROs) for various vascularized lymph node transfer (VLNT) donor sites and identify gaps in the literature to guide future research.

Methods: A literature search of five databases was performed for articles related to VLNT that were published prior to November 2021. Studies that included clinical outcomes or PROs from at least five adult patients who received VLNTs to treat lymphedema were included.

Results: Sixty-six studies met the study criteria. Most studies reported improved limb circumference/volume, reduction or discontinuation of conservative therapy, infection rate reduction, improved PROs, or postoperative imaging findings reflecting functional lymph nodes. There were significantly lower infection rates ($P < 0.05$) and a trend towards improved PROs in patients who received intra-abdominal flaps, but overall few studies reported these outcomes. There were no significant differences in complication rates at the donor or recipient site based on VLNT donor sites, or between intra-abdominal *vs.* extra-abdominal VLNT donor sites, although these outcomes are

not uniformly reported.

Conclusion: This meta-analysis identified that intra-abdominal donor sites have the potential to reduce postoperative infectious episodes more than extra-abdominal donor sites. Though recent investigations address many understudied VLNT donor sites, larger comparative studies and a standardized methodology are needed to better characterize postoperative outcomes, which can offer more concrete evidence to guide surgical practice.

Keywords: Lymphedema, vascularized lymph node transfer, lymphedema surgery

INTRODUCTION

Lymphedema is a chronic condition characterized by the accumulation of protein-rich lymphatic fluid within the interstitium, leading to swelling of the affected limb and overlying skin and tissue changes[1]. Lymphedema can result in significant functional and psychological morbidity for patients, as it can be disfiguring, lead to infection, and limit the range of motion[2-5]. Regardless of disease severity, conservative treatment remains a cornerstone of management[6,7]. The main conservative treatments involve complete decongestive therapy (CDT), compression bandages, exercise, and meticulous skin care[7].

In some patients, surgical options may be of benefit. Amongst these options, lymphovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT) have become increasingly popularized in recent years[6,7]. LVA involves the creation of a shunt between a high-pressure lymphatic system and a lower-pressure venule system, allowing for increased lymph drainage[8]. Vascularized lymph node transfer is theorized to operate through a different mechanism: the lymph nodes act like a "pump", siphoning lymph from the surrounding tissues and draining through natural lymphovenous anastomoses within the flap[9,10].

Since its introduction, VLNTs have expanded to involve various novel donor sites[11]. Apart from the groin, where VLNT was initially described, supraclavicular, submental, lateral thoracic, omental, and jejunal mesenteric lymph node flaps have also been reported[11]. More research is needed to clarify the outcomes for upper and lower extremity lymphedema following the use of each of these donor sites. This systematic review thus presents the current evidence regarding clinical and patient-reported outcomes (PROs) based on these various VLNT donor sites and identifies gaps in the literature.

METHODS

A literature search was performed using a combination of keywords and controlled vocabulary in Embase.com 1947-, Ovid Medline 1946-, Scopus 1823-, The Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), and Clinicaltrials.gov 1997-. The search strategy encompassed variations of terminology, including synonyms and differences in spelling, and was agreed upon by the authors of this review. All search strategies were completed on November 12, 2021, with no added limits. Fully reproducible search strategies for each database can be found in the Appendix [Supplementary Table 1]. All search strategies and written methodology were created using the standards and guidelines for conducting and reporting systematic reviews set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the National Academies (IOM) Standards for Systematic Reviews, the Cochrane Handbook of Systematic Reviews, and Peer Review of Systematic Search Strategies (PRESS)[12-15].

The articles obtained from the search were uploaded to Covidence. Studies were included if they adhered to the following criteria: (1) included at least 5 patients aged 18 years or older; (2) addressed VLNT;

(3) published before November 12, 2021; (4) involved original research; and (5) included at least one of the following: (i) clinical outcomes (limb size differences, infection rate, or reduction in conservative treatment); (ii) patient-reported outcomes using validated questionnaires/scales; or (iii) imaging outcomes. Exclusion criteria were as follows: (1) any avascularized/non-vascular lymph node transfers; (2) published in a language other than English; (3) included study designs with patients receiving only combination procedures (i.e., LVA and VLNT); (4) did not include any original, extractable data (i.e., review articles, commentaries, letters to the editor); (5) no full-text available; and (6) studies involving non-human subjects or cadaveric models.

Three reviewers (Raman S, Sanka S, Ji J) independently screened investigations based on title/abstracts. Two research personnel reviewed each full-text article. A third reviewer was used in each instance where there was dissonance of opinion. Data from full-text articles were extracted and stored in Microsoft Excel (Version 16.52).

After full-text articles were identified, duplicate studies which included patients from the same institution from the same time period were removed to avoid confounding any meta-analysis. If multiple articles included the same group of patients and reported the same clinical outcome variables, the investigation reporting the most variety of clinical outcomes or greatest sample size was included in this systematic review.

Data extracted from each article included study-specific information (author, year of publication, country, study design, and inclusion/exclusion criteria of patients for the study); clinical outcomes (limb circumference or volume differences postoperatively, infection rate reduction, and reduction in need for conservative therapy); imaging outcomes; patient sample demographics [age, body mass index (BMI), gender, comorbidities, etiology of lymphedema, duration of lymphedema]; number of patients in each experimental arm; details of surgical intervention (procedure performed, donor and recipient site); staging criteria utilized; method in which clinical outcome variables were obtained including the location in the limb for circumference/volume measurements; clinical outcomes reported [limb circumference or volume difference, infection rate reduction (annual episodes of infection), and reductions in conservative treatment]; PROs for each investigation in which a validated questionnaire was utilized; complications related to donor or recipient site; and length of follow-up. An American Society of Plastic Surgeons Level of Evidence was assigned to each investigation[16]. PROs were recorded for each domain in which a value was reported.

Studies reporting infection rates were reviewed to identify those that presented this information in a standard fashion (episodes of infection/year preoperatively and postoperatively) to encourage comparability between studies. Due to significant variability in methodology and study design, outcomes related to improvement in limb size and reductions in conservative treatment were qualitatively summarized in table format. Patients were stratified based on donor and recipient site (upper or lower limb lymphedema) for meta-analysis of infection rate reduction and PROs. Continuous variables were summarized with mean and standard deviation. Categorical variables were summarized with frequencies or percentages.

Statistical analysis was performed using GraphPad Prism 9.2.0 (Dotmatics, Boston, MA, USA) with a statistical significance set to 0.05. Weighted means and fixed-effects pooled variances were tabulated for each variable, and these values were used to perform statistical analyses. To compare continuous variables, Kruskall-Wallis or Mann-Whitney tests were performed, as appropriate. Meta-analysis heterogeneity was calculated using the meta[17] and metafor packages[18] in R version 4.0.3[19] on the R Studio version 2022.02.3

platform. Missing variances were imputed using the prognostic method described by Ma *et al.*, substituting mean variances for the missing values[20].

RESULTS

Summary of articles

Using the standardized search strategy, 1,301 studies with relevant titles and abstracts were retrieved from all databases. A total of 751 duplicate records were deleted after applying a deduplication process[21], and 550 citations were then imported into the project library. One further duplicate article was removed using Covidence.org. A total of 77 full-text investigations initially met the inclusion criteria for this study. Upon further review, 11 studies reporting the same outcomes from the same population were identified and removed. Ultimately, 66 studies were included in the systematic review. The selection process is described in a flowchart [Figure 1].

The ASPS level of evidence[16] for these articles ranged from Level II to Level IV [Table 1]. The majority of the studies (42 out of 66, 63.6%) were retrospective [Table 1].

Several staging scales were used to assess the severity of lymphedema. The most commonly used was the International Society of Lymphology scale (30 articles, 45.5%). A large subset (22 out of 66, 33.3%) did not use any imaging for staging [Table 1].

Out of all studies, 8 unique donor sites were identified: groin, submental, omentum, supraclavicular, lateral thoracic, appendicular, ileocecal, and jejunal mesenteric. Of note, twenty studies evaluated numerous VLNT donor sites in their investigation. Over half of all included studies (38 out of 66, 57.6%) addressed groin VLNT, followed by 20 (30.3%) which addressed omental, 14 (21.2%) submental, 13 (19.7%) supraclavicular, 9 (13.6%) lateral thoracic, and 2 (3.0%) each for appendicular and ileocecal, and 1 (1.5%) jejunal mesenteric. One article (1.5%) had a donor site from the neck region but was unclear about the specific flap utilized. The earliest investigations from our systematic review identify the groin VLNT as the initial donor site that propelled forward the era of VLNT. From 2010-2020, outcome-based research related to submental, supraclavicular, lateral thoracic, and jejunal mesenteric donor sites was published. The latest additions to VLNT within the past 5 years included additional intra-abdominal donor sites, such as appendicular and ileocecal.

Patient-reported outcomes using validated questionnaires were addressed in 16 (24.2%) of the investigations. These outcomes were most frequently from studies addressing groin, submental, and omental VLNT, while jejunal mesenteric, appendicular, and ileocecal VLNT had no articles addressing PROs for patients. Most studies (71.2%) reported on recipient-site complications, while 68.1% reported on donor complications.

Patient demographics

There were a total of 2316 patients and 2376 VLNTs reported in the 66 articles [Table 2]. It should be noted that not all investigations reported every patient demographic characteristic. Out of the studies reporting the gender of the patients, the majority of patients were female (63.9%). Overall, the mean age of patients was 54.0 ± 5.4 years and the mean BMI was 27.2 ± 2.5. Most of the patients (79.4%) had a secondary cause of lymphedema [Table 2]. Patients experienced symptoms for 51.1 ± 34.1 months prior to their surgery.

Large subsets of the overall sample received groin (26.1%) or omental (20.2%) flaps. Fewer received jejunal mesenteric, appendicular, and ileocecal VLNTs. More patients were treated for upper extremity

Table 1. Article characteristics

Characteristic	Number of articles, *n* (%)
Retrospective	42 (63.6)
Prospective	24 (36.4)
Levels of evidence	
I	0 (0)
II	24 (36.4)
III	41 (62.1)
IV	1 (1.5)
V	0 (0)
Staging scale	
ISL	30 (45.5)
Cheng	8 (12.1)
Taiwan	1 (1.5)
MD anderson scale	2 (3.0)
Campisi	1 (1.5)
ICGN	1 (1.5)
Unspecified	2 (3.0)
None	22 (33.3)

ISL: International society of lymphology; ICGN: indocyanine green. † Unspecified donor site in the neck region.

lymphedema than lower extremity lymphedema. On average, patients followed up for 24.1 ± 16.4 months after surgery [Table 2].

Clinical outcomes

Overall, 47 out of 66 (71.2%) studies reported differences in limb circumference or volume postoperatively [Table 1 and Supplementary Table 2]. The vast majority (95.7%) of these investigations reported improved limb circumference/volume following VLNT, while two studies found no significant improvement. These 2 studies involved groin, supraclavicular, and lateral thoracic donor sites [Supplementary Table 3]. The remaining donor sites reported improvements in limb size differences within all studies evaluating this outcome [Supplementary Table 3].

Fourteen (21.2%) studies reported reduction or discontinuation of conservative therapy following the VLNT. In all studies assessing this outcome, a reduction or discontinuation of conservative therapy was observed postoperatively [Supplementary Table 3].

Twenty-four (36.4%) studies reported preoperative and postoperative episodes of cellulitis. The overall reduction of infection was 76.6% ± 1.4 % postoperatively [Table 3].

Intra-abdominal flaps had a more significant reduction in postoperative infectious episodes than extra-abdominal flaps, 88.2% ± 2.8 % *vs.* 79.9% ± 2.2%, respectively ($P = 0.009$). There was no significant difference in infection rate reduction for patients who underwent VLNT for treatment of upper limb lymphedema and lower limb lymphedema, 86.8% ± 1.6% *vs.* 73.3% ± 2.5 %, respectively ($P = 0.81$). Additionally, differences in infection rate reduction between the different donor sites were not significant ($P = 0.12$) [Figure 2]. While there was a 100% infection reduction rate for ileocecal and jejunal mesenteric flaps, there were only two investigations involving ileocecal VLNT and one involving jejunal mesenteric VLNT. Otherwise, the greatest infection rate reduction was found in omental VLNT (87.9% ± 2.9 %), while the smallest decrease in

Table 2. Patient demographics. Only data extractable from studies was reported

Variable	Outcome
Total number of patients	2316
Total number of flaps	2376
Gender (*n* patients, % of total)	
Male	175 (7.6)
Female	1479 (63.9)
Unspecified	662 (28.5)
Age (mean ± SD)	54.0 ± 5.4
BMI (mean ± SD)	27.2 ± 2.5
Etiology of lymphedema	
Primary	145 (6.3)
Secondary	1838 (79.4)
Unspecified	333 (14.4)
Medical comorbidities	
Radiation	636 (27.5)
Chemotherapy	314 (13.6)
Diabetes	31 (1.3)
HTN	59 (2.5)
Smoking	18 (0.8)
Duration of lymphedema (months)	51.1 ± 34.1
Donor site (*n* patients, % of total)	
Groin	604 (26.1)
Submental	304 (13.1)
Omentum	467 (20.2)
Supraclavicular	206 (8.9)
Lateral Thoracic	62 (2.7)
Appendicular	1 (0.04)
Ileocecal	2 (0.09)
Jejunal mesenteric	N.S.
Unspecified †	670 (28.9)
Extra- or intra-abdominal site	
Extra-abdominal site	1606 (69.3)
Intra-abdominal site	499 (21.5)
Unspecified †	211 (9.1)
Recipient site (*n* patients, % of total)	
Upper extremity	877 (37.9)
Lower extremity	624 (26.9)
Upper and lower extremity*	722 (31.2)
Unspecified	93 (4.0)
Mean length of follow-up (months)	24.1 ± 16.4

SD: standard deviation; BMI: body mass index; HTN: hypertension. †Unspecified donor site or intervention groups involving patients receiving vascularized lymph node transfer from numerous donor sites. It should be noted that some patients could be categorized into extra- and intra-abdominal site groups even if it was unclear how many patients received each specific flap. *Unspecified amount of patients receiving a vascularized lymph node transfer to the upper and lower limb within an intervention group.

infection rate was observed after supraclavicular VLNT (65.6% ± 9.5 %) [Table 3]. Follow-up periods for each investigation are reported in Supplementary Table 3.

Table 3. Infection rate reduction based on recipient and donor sites

Anatomical site	Infection rate reduction (%)
Total	76.6 ± 1.4
Donor site	
Groin	83.0 ± 3.2
Submental	79.5 ± 3.1
Omentum	87.9 ± 2.9
Supraclavicular	65.6 ± 9.5
Lateral thoracic	N/A*
Appendicular	N/A*
Ileocecal	100 ± 0
Jejunal mesenteric	100 ± 0
Unspecified †	N/A[#]
Intra-abdominal donor site	88.2 ± 2.8*
Extra-abdominal donor site	79.9 ± 2.2*
Recipient site	
Upper extremity	86.8 ± 1.6
Lower extremity	73.3 ± 2.5

†Unspecified donor site in the neck region. [#]Unclear infection rate reduction for this VLNT donor site. *$P < 0.05$.

Intra-abdominal *vs.* extra-abdominal
The donor sites were also grouped into intra-abdominal and extra-abdominal sites for further analysis. Omental, jejunal mesenteric, ileocecal, and appendicular flaps were recorded as intra-abdominal, while submental, groin, supraclavicular, lateral thoracic, and unspecified "neck" flaps were considered extra-abdominal. The majority of patients (69.3%) received an extra-abdominal VLNT, while 21.5% received an intra-abdominal flap [Table 2]. Investigations containing the remaining 9.1% of patients reported joint results from intra- and extra-abdominal flaps.

On average, the infection rate decreased by 81.3% ± 2.9% after surgery, with significantly more infection reduction for intra-abdominal flaps (88.2% ± 5.5 %) and extra-abdominal flaps (79.9% ± 4.3 %) ($P = 0.009$) [Table 3].

Complications
Fifty-seven (86.4%) of 66 articles reported donor, recipient, or medical complications. Only 42 of these articles were included in the meta-analysis since 15 investigations did not contain extractable data, either due to not reporting the number of patients who experienced a complication or not differentiating complications between various VLNT donor sites. There were no significant differences in donor site, recipient site, and medical complication rates between VLNT donor sites ($P = 0.50$; $P = 0.95$; $P = 0.29$) [Table 4]. There were also no statistically significant differences in donor site, recipient site, and medical complication rates when comparing intra-abdominal and extra-abdominal VLNT donor sites ($P = 0.43$; $P = 0.92$; $P = 0.09$).

Lateral thoracic donor sites had the highest donor site complication rate (12.2%), while the omental VLNT donor site had the highest recipient site complication rate (8.6%) [Table 4].

Patient-reported outcomes
Sixteen articles (24.2%) reported validated patient-reported scale outcomes for VLNT patients, but only 11

Table 4. Complication rates based on donor site

Complication type	Donor sites								P-value
	Omental	Jejunal mesenteric †	Groin	Lateral thoracic	Submental	Supraclavicular	Appendicular	Ileocecal	
Donor, %	10.4%	-	11.0%	12.2%	3.8%	6.1%	0.0%	0.0%	0.50
Recipient, %	8.6%	-	6.1%	4.9%	2.1%	7.1%	0.0%	0.0%	0.95
Medical, %	4.0%	-	1.4%	-	1.3%	-	-	-	0.29

†Investigations evaluating this donor site were unclear regarding the number of patients who experienced complications.
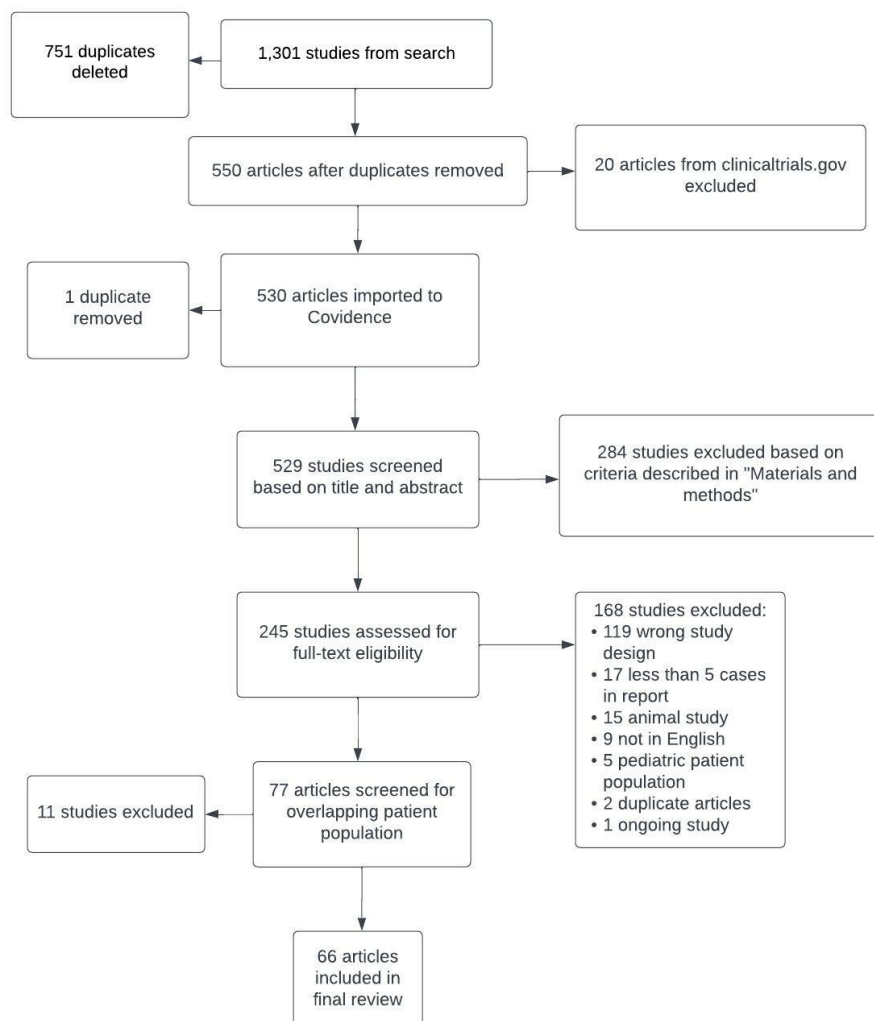

Figure 1. Flowchart depicting the screening process for inclusion of articles within our systematic review. Adhering to the inclusion/exclusion criteria of this study, 66 articles were included in the final review.

articles (16.7%) were used in statistical analysis due to inconsistent reporting within the remaining studies. The most commonly used instruments were LYMQOL (Lymphedema Quality Of Life) questionnaires, employed in 12 (75.0%) out of 16 studies. There are 2 versions of the LYMQOL scale, one for upper extremity and one for lower extremity[22,23]. Other validated measures utilized were the Upper Limb
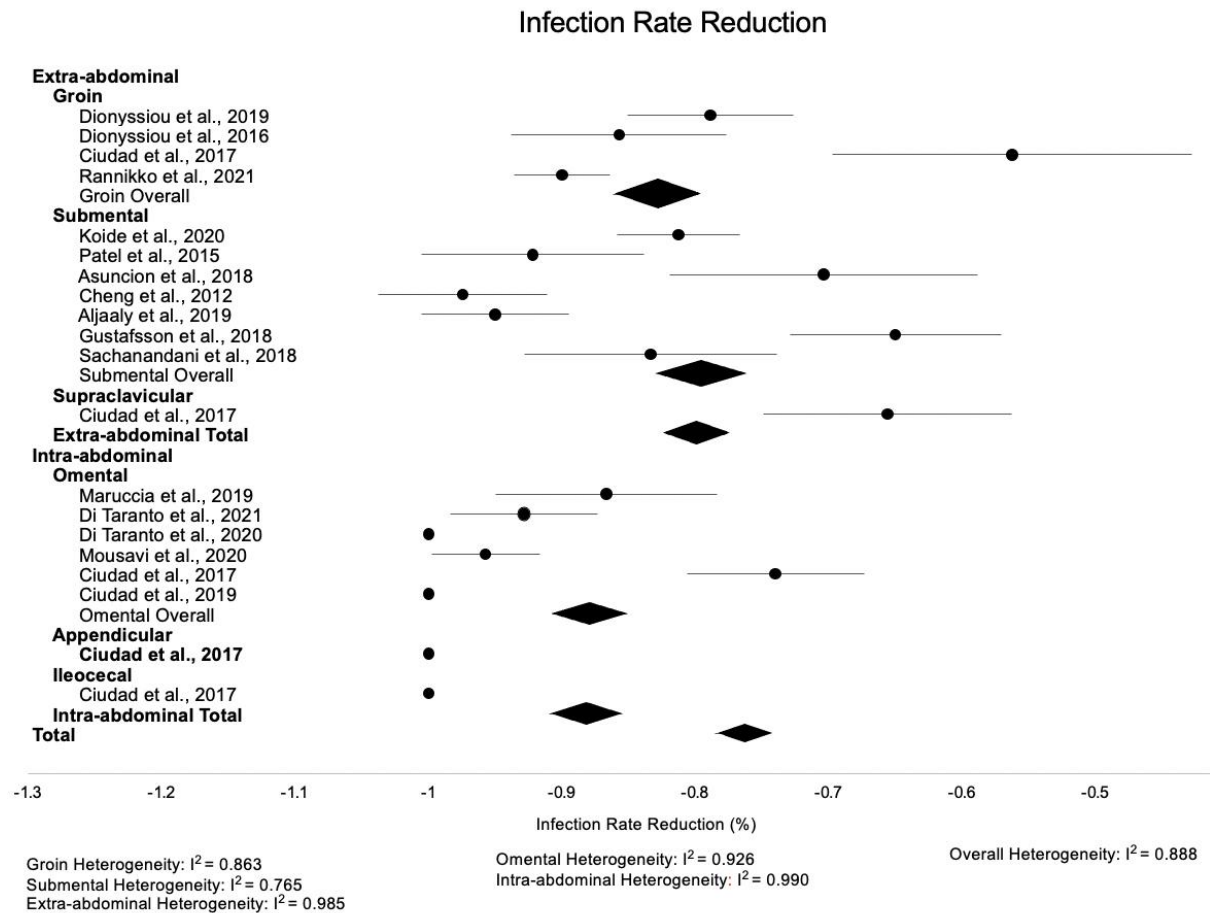
Figure 2. Forest plot depicting average infection rate reduction for each of these studies. Studies that did not report the number of preoperative and postoperative infections were excluded from this plot.

Lymphedema 27 (ULL-27) questionnaire, the Lymphedema Life Impact Scale version 2 (LLISv2), and the Patient Scar Assessment Questionnaire (PSAQ), which were all utilized by one investigation each. The pain and heaviness visual analog scale (VAS) was used in two studies.

Submental flaps had the largest number of articles that included patient-reported outcomes, with 6 articles. This is followed by 5 articles, each reporting on patient-reported outcomes for omental and groin flaps. There were no studies that addressed patient-reported outcomes in patients who received appendicular, ileocecal, and jejunal mesenteric flaps.

LYMQOL results were analyzed and compared. There are 2 versions of the LYMQOL scale, one for upper extremity and one for lower extremity[22,23]. Overall, there was an improvement in each of the 5 LYMQOL domains: symptoms, body image/appearance, function, mood, and overall quality of life, after VLNT [Table 5]. When conducting a meta-analysis, studies containing intervention groups involving multiple donor sites were excluded. Based on this consideration, only studies addressing submental and omental VLNT could be included for analysis [Figure 3]. No statistically significant difference was found when comparing each LYMQOL domain for omental and submental VLNT ($P = 0.06$).

Table 5. Patient-reported outcomes. A lower score in the functional, appearance, symptom, and mood domains of the LYMQOL reflect a more satisfactory patient response in those categories, while a higher score in the overall domain in the LYMQOL reflects a more satisfactory patient response.

	LYMQOL*					VAS*			Lymphedema life impact scale V2*		Patient scar Questionnaire*			Upper limb lymphedema Questionnaire*			
	F	A	S	M	O	PN	H	O	P	PS	F	A	S	P	PS	SO	O
Total	-14.7	-6.2	-8.1	-6.7	4.1	-4.0	-5.4	-4.3	-1.8	-1.0	-1.0	1.8	1.5	20	12	19	18
Donor																	
Groin	-13.8	-6.5	-7.8	-5.8	3.5	-4.8	-5.4	-4.3	-	-	-	-	-	20	12	19	18
Submental	-15.4	-4.6	-8.0	-6.2	4.4	-	-	-	-	-	-	-	-	-	-	-	-
Omentum	-18.1	-10.0	-10.2	-11.6	4.7	-3.2	-	-	-1.8	-1.0	-1.0	1.8	1.5	-	-	-	-
Supraclavicular†	-0.91	-1.0	-1.1	-0.8	2.1	-	-	-	-	-	-	-	-	-	-	-	-
Lateral thoracic†	-0.91	-1.0	-1.1	-0.8	2.1	-	-	-	-	-	-	-	-	-	-	-	-
Appendicular	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ileocecal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Jejunal Mesenteric	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intra-abdominal Donor site	-18.1	-10.0	-10.2	-11.6	4.7	-3.2	-	-	-1.8	-1.0	-1.0	1.8	1.5	-	-	-	-
Extra-abdominal Donor site	-14.1	-5.5	-7.7	-5.8	4.0	-4.8	-5.4	-4.3	-	-	-	-	-	20	12	19	18
Recipient site																	
Upper extremity	-15.9	-6.3	-8.6	-6.8	4.1	-4.8	-5.4	-4.3	-1.2	-0.55	-0.50	1.5	1.2	20	12	19	18
Lower extremity	-2.9	-2.3	-2.1	-2.4	4.8	-3.2	-	-	-2.6	-1.5	-1.7	2.3	2.0	-	-	-	-

F: Functional; A: appearance; S: symptom; M: mood; O: overall; PN: pain; H: heaviness; P: physical; PS: psychological; SO: social. †One study reported both donor site outcomes together. *Postoperative-Preoperative Scores for pain.

Eight articles reported LYMQOL measures for patients who had upper limb lymphedema and 7 articles reported LYMQOL measures for patients with lower limb lymphedema. Overall, no statistical significance was achieved when comparing upper and lower recipient sites for each LYMQOL domain ($P = 0.15$).

Imaging outcomes
Thirty of the 66 articles (45.5%) evaluated imaging outcomes. Of these 30 studies, most (22, 73.3%) used lymphoscintigraphy. Seven of these studies looked for the presence of nodes after VLNT, with two of these studies reporting that the majority of transplanted nodes were functioning postoperatively. Sixteen studies examined lymphatic drainage patterns, and the majority (14, 87.5%) indicated that flow improved after VLNT. The findings of these investigations are summarized in Supplementary Table 4.
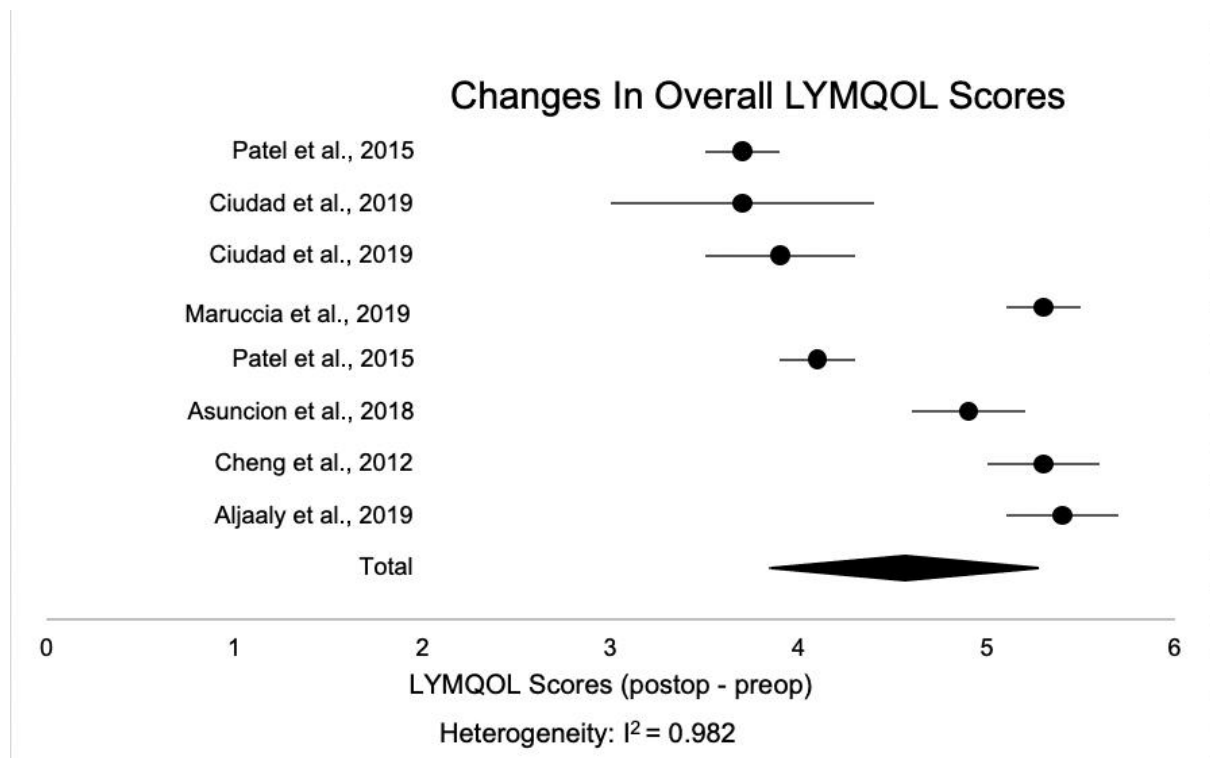
Figure 3. Forest plot depicting the average improvement in overall LYMQOL scores for each of these studies. Studies that did not report the standard deviations of the scores were excluded from this plot.

DISCUSSION

Lymphedema is a chronic, progressive condition that can significantly diminish the quality of life of patients[24]. Though conservative therapy is currently still the gold standard for management, evidence for physiologic procedures such as VLNT is increasing[25,26]. Given their recent development, this systematic review found that jejunal mesenteric, appendicular, and ileocecal donor sites have been relatively understudied and warrant more consideration in future research. Overall, standardization in protocols and outcome measures is lacking.

Clinical outcomes

There is limited data available to guide donor site selection in VLNT, leaving surgeon preference, considerations for patient preference, and prior surgery or anatomic concerns to determine current practice. Furthermore, the available studies implemented a variety of methodologies and study designs, which restricted direct comparisons between investigations and made it difficult to draw definitive conclusions regarding the optimal VLNT donor site [Supplementary Table 2].

Overall, some outcomes were reported in the literature more uniformly than others. For instance, the majority of investigations reported limb measurements as an outcome to characterize the efficacy of the procedure. From these studies, the vast majority reported reductions in limb size [Supplementary Table 3]. It cannot be understated, however, that contrasting methodologies could significantly affect the generalizability of these results. Limbs were measured in circumference[27-29] or volume[30,31], though variances were also present beyond these two categories, including circumference rate reduction[32-34], upper/lower extremity lymphedema index[35-37], and volume ratios[38] [Supplementary Table 2]. The specific method used to obtain circumference and volume measurements differed between investigations as well

[Supplementary Table 2]. Studies evaluating volume typically used the truncated cones method[30,31,38,39] - a method characterized by measuring the circumference at 4 cm intervals along the limb, and summating the volume segments calculated by the truncated cones formula to receive an estimated total volume of the limb[40]. Another tool to calculate volume in studies was perometry, which utilized a specialized device to emit infrared beams to quantify volume[41,42]. Given the substantial variability in reporting limb size outcomes, future studies should aim to standardize the approach to measurement. The current International Society of Lymphology (ISL) recommendation is 4 cm incremental measurements from the ulnar styloid of the wrist to the axilla for upper extremity lymphedema, and 4 cm incremental measurements from the medial malleolus until the popliteal fossa or gluteal crease, depending on the extent of the lower extremity lymphedema[43].

For the studies that reported reduction or discontinuation of conservative therapy following the procedure, it appeared that patients could rely less heavily on these treatments postoperatively. Variations in postoperative conservative treatment protocols and follow-up time points restricted direct comparisons between studies. There were also numerous investigations with unclear postoperative therapy protocols[30,31,44].

Infection rates were another more commonly reported outcome. It has been previously established in the literature that lymphedema increases the risk of developing cellulitis in the affected limb[45,46]. Specifically, the obstruction of lymphatic flow and accumulation of protein-rich colloid in the interstitium results in localized immunosuppression and a subsequent increase in infections[47]. Therefore, a procedure restoring lymphatic flow within the affected limb would be expected to mitigate the mechanism that propagates infection[47]. In this systematic review, only studies reporting the number of preoperative and postoperative episodes of cellulitis were included for meta-analysis purposes. All investigations reporting this outcome reported a successful reduction of postoperative infection following the VLNT. Particularly, patients who underwent intra-abdominal VLNT experienced a significant reduction in infectious episodes compared to those with an extra-abdominal donor site. Importantly, it should be noted that the majority of the intra-abdominal donor data regarding infection rate reduction was from omental VLNT. Therefore, more research is needed to clarify this advantage with intra-abdominal flaps, as ileocecal, appendiceal, and jejunal mesenteric VLNTs have especially limited evidence surrounding this outcome.

Another interesting finding related to the reduction of annual infectious episodes was observed when stratifying the data based on upper and lower limb recipient sites. Patients with upper limb lymphedema had a trend toward greater reduction (83.8 ± 3.4 %) in postoperative infectious episodes than those with lower extremity lymphedema (77.4 ± 4.8 %). Though lower extremity lymphedema patients are more likely to experience infection, the exact mechanism behind this predisposition is unclear in the literature[46]. Potentially, given that the lower extremities are in the dependent region of the body, disruptions in lymphatic flow could result in more significant accumulations of lymph, with markedly poorer responses to infection. This postulation could explain why, even after VLNT, the reduction in infectious episodes would be less substantial in comparison to upper limb recipient sites.

Intra-abdominal *vs.* extra-abdominal

In recent years, additional donor sites for lymphatic tissue have been found. There are several benefits to obtaining lymph nodes and tissue from the abdominal cavity, as it can mitigate the risk for donor-site lymphedema-a major concern when it comes to VLNTs from extra-abdominal sites[48]. Intra-abdominal sites also allow for the ability to harvest up to 3 vascularized flaps from 1 donor site[48]. With the possibility of laparoscopic harvest, the risk of donor-site morbidity may be reduced and minimal donor-site scars can

be well-hidden[48,49].

The most common intra-abdominal flap is derived from the omentum[49]. The omentum is highly vascularized and large in size, with large lymphatic channels, and lymphatic lakes, which make it a potentially ideal donor site candidate[48-50]. While VLNTs from other intra-abdominal donor sites like the ileocecum and appendix are being explored, currently, there is limited data on the efficacy and safety of these specific flaps.

The literature overall reveals the potential for improved outcomes with intra-abdominal flaps. On average, patients who received intra-abdominal flaps had significantly fewer episodes of infection postoperatively. This is likely due to the great angiogenic and immunomodulatory potential of the omentum[51]. However, despite the absence of iatrogenic lymphedema in patients who received intra-abdominal flaps, omental VLNT had the highest rate of recipient-site complications and one of the highest donor-site complication rates reported. Concerning donor-site complications, intra-abdominal sources of lymph nodes possess unique risks that are inherent with these procedures, such as ventral hernias and small bowel obstruction[35]. Overall, when interpreting these results, it should be noted that since few studies specifically reported complications, it is likely that the true frequency of many complications for both extra-abdominal and intra-abdominal flaps was not captured.

While the current research on intra-abdominal VLNT donor sites is promising, it is still unclear whether the benefits are significant enough to overcome the additional risks that come with intra-abdominal surgery. More research needs to be done on the efficacy of intra-abdominal flaps, especially the non-omental intra-abdominal sites, and techniques refined and standardized to minimize the risk of donor-site complications.

Patient-reported outcomes

The inclusion of patient-reported measures is crucial in analyzing outcomes of lymphedema treatment. Previous studies have shown that the severity of limb edema may not correlate with the amount of change in patient-reported outcomes, as patients can report significant impairments even when volume changes may not be evident[52-54]. Unfortunately, the vast majority of studies (50 articles out of 66, 75.8%) in this systematic review did not include any patient-reported outcomes using validated questionnaires/scales. For the studies that did address PROs, the lack of standardization in reporting the results made it difficult to compare these outcomes across studies. This was likely due to the fact that earlier studies often used non-validated tools or non-lymphedema-specific tools[52]. However, once the LYMQOL scale was validated in 2010, it became the most commonly used tool[52]. Using this scale, there is a trend toward patients who received omental flaps reporting the greatest improvement in LYMQOL scores, while those who received lateral thoracic flaps had the least improvement. Interestingly, patients with lateral thoracic flaps also had the highest rate of donor site complications, which could potentially explain the reduced postoperative PROs scores for lateral thoracic VLNT.

The LYMQOL showed greater improvement in scores in functional, appearance, symptom, and mood domains for patients who underwent VLNT for upper limb lymphedema, but the overall quality of life improved more after VLNT to the lower extremity.

Limitations

Limitations of the present study should be recognized. Inconsistent reporting of data, as well as significant heterogeneity of study design and methodology, prevented meta-analysis with many of the reported outcomes. Additionally, small sample sizes for some VLNT donor sites could have impacted statistical

outcomes and, in some instances, precluded any statistical analysis. Nevertheless, our study remains a comprehensive systematic review of the current outcome-based research on VLNT and should encourage future studies to standardize clinical staging, methodologies, and outcome measures.

CONCLUSION

VLNT is a promising treatment modality for many patients with lymphedema, which has previously been thought to be a progressive, chronic disease. New donor sites, such as the omental, appendiceal, ileocecal, and jejunal mesenteric, have offered possible advantages in mitigating the risk of donor-site lymphedema for patients while overall resulting in a greater reduction in infectious episodes in comparison to extra-abdominal donor sites. This warrants additional consideration in the literature. With more consistent methodology and reporting, patient-reported outcomes and clinical outcomes could be better compared between studies and offer more robust data to guide surgical practice in VLNT for lymphedema patients.

DECLARATIONS

Authors' contributions

Initial literature search: Yaeger L

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Christensen JM, Raman S, Sanka SA, Ji J, Skolnick GB

Performed data acquisition, as well as provided substantial contributions to the manuscript: Raman S, Sanka SA, Ji J

Provided significant guidance and feedback in manuscript editing process: Christensen JM, Skolnick GB

Availability of data and materials

Not applicable.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

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