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REVIEW ARTICLE

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Efficacy and safety assessment of lymphovenous anastomosis in patients with primary and secondary lymphoedema: A systematic review of prospective evidence

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Abstract

Introduction: Lymphoedema is a chronic, debilitating condition caused by an affected lymphatic system. Supermicrosurgical techniques like lymphovenous anastomosis (LVA) have gained popularity because of its minimal invasiveness, better aesthetic outcome, and lower costs in comparison to physical medicine. This systematic review aims to evaluate the clinical effectiveness and safety of LVA in comparison to conservative or other surgical treatments for primary or secondary lymphoedema patients.

Materials and Methods: A systematic literature search was performed in four databases in December 2017. We applied a methodological framework based on the HTA Core Model®. According to the grading of recommendations, assessment, development, and evaluation (GRADE) scheme, we synthesized the data on each selected outcome category. The studies were systematically assessed for risk of bias (RoB) using the Risk of Bias Assessment tool for Non-randomized controlled studies (RoBANS) and the Institute of Health Economics (IHE) Risk of Bias checklist for case series.

Results: A total of 629 citations were identified and five studies were assessed eligible for final inclusion (one non-randomized controlled trial and four prospective single-arm studies). Across the studies, 217 patients were enrolled. All studies showed a moderate to high RoB. The strength of evidence for the effectiveness and safety of LVA is "very low." Due to the methodological shortcomings of the available evidence, no conclusions can be made about the effectiveness of the procedure.

Conclusion: LVA might be a safe technique for patients with primary and secondary lymphoedema—particularly because no serious complications were reported. Furthermore, LVA may have a role in the prevention of lymphoedema.

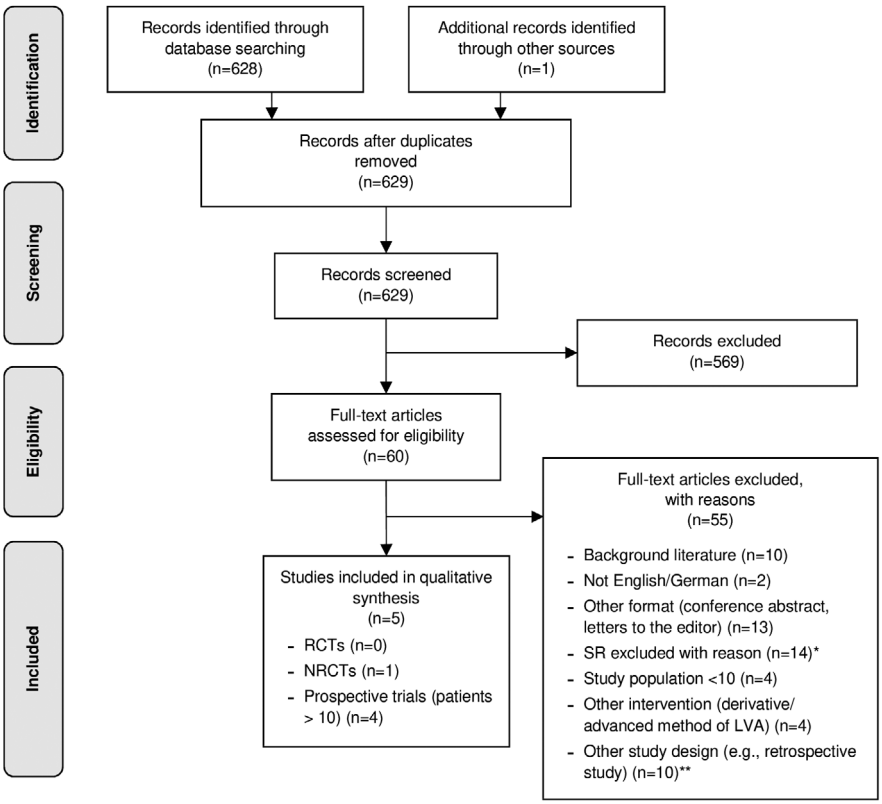
1 | INTRODUCTION

There is no cure for lymphoedema (Carl et al., 2017; Ingianni, 2003; Sharkey, King, Ramsden, & Furniss, 2017). Lymphoedema is a chronic, progressive, and debilitating condition caused by an affected lymphatic system. Without appropriate management, lymphoedema may worsen. It may cause pain, body image disturbances, infections, restrictions in range of motion (functional impairment), swelling, cellulitis, and a decrease in patients' quality of life (QoL) with functional, aesthetic, and psychic repercussions (e.g., ability to work, feeling of

tightness, narrowness of clothing, skin alterations). It may also lead to irreversible changes like fibrosis or the excess of adipose tissue. These patient-reported symptoms can occur individually or in combination (Gesellschaft Deutschsprachiger Lymphologen [GDL], 2017; Leung, Tirlapur, & Meads, 2015; Poumellec, Foissac, Cegarra-Escolano, Barranger, & Ihrai, 2017; Scaglioni, Fontein, Arvanitakis, & Giovanoli, 2017; Winters et al., 2017; Witty & Larouche, 2011).

Lymphoedema can occur at any age and can be congenital (so-called primary lymphoedema that is caused by a congenital abnormality or malfunction in the lymphatic system) or acquired (so-called secondary lymphoedema that is caused by defects to the lymphatic system, usually due to cancer treatment, infection, trauma, etc.) (Damstra, Voesten, van Schelven, & van der Lei, 2009; Oremus, Walker, Dayes, & Raina, 2010; Sharkey et al., 2017). The leading cause of lymphoedema in developed countries is mostly the consequence of malignancies and its treatments. Especially breast cancer therapies in the forms of radiotherapy and lymph node dissection are seen as the classic precursor of secondary lymphoedema (Allen Jr. & Cheng, 2016; Markkula Silja, Leung, Allen Victoria, & Furniss, 2019; Poumellec et al., 2017). Axillary lymph node dissection, radiation therapy to the axillary region, postoperative seroma in the axillary region, and obesity are seen as further major risk factors for developing lymphoedemas (Winters et al., 2017).

Supermicrosurgical techniques such as lymphovenous anastomosis (LVA) are used with satisfactory results since the first description of the technique for lymphoedema in the late '90s by Koshima (Cornelissen et al., 2017; Koshima, Inagawa, Urushibara, & Moriguchi, 2000). Since its development, the procedure has gained popularity because of its minimal invasiveness, better aesthetic outcome, and lower costs in comparison to physical medicine (e.g., lower [personnel] expenditures) (Hadamitzky, Pabst, Gordon, & Vogt, 2014; Sharkey et al., 2017). The aim of the LVA procedure is to redirect the lymphatic fluid into venous circulation and to restore lymphatic drainage. LVA is a minimally invasive method that aims to reconstruct the lymphatic pathway and to require less use of compression therapy postoperatively (Kung, Champaneria, Maki, & Neligan, 2017; Markkula Silja et al., 2019; Sharkey et al., 2017). Therefore, a connection of functioning lymphatic vessels (diameter of >0.1 and under 0.8 mm) and similarly sized subdermal venules is made to allow unidirectional flow of lymphatic fluid directly into the venous system, meaning that the lymph does not need to pass the damaged lymphatic area to return to the circulation (Carl et al., 2017; Executive Committee, 2016; Markkula Silja et al., 2019). In addition, with the intention to achieve a more permanent improvement of lymphoedema, subdermal venules should be used because the pressure is lower than that in the deep, larger, veins resulting in



** Systematic reviews were excluded if they had other aims, included retrospective studies, compared surgical methods without patient outcomes, or were written in another language.*

*** 1 publication presented sub-analytical results of another already included observational study. Therefore, only the overall data of the primary study are presented in the outcomes.*

FIGURE 1 PRISMA flow diagram outlining selection process of studies for analysis. PRISMA, preferred reporting items for systematic reviews and meta-analyses

less venous backflow (Ayestaray & Bekara, 2014; Chang, 2010). As most lymphatics range from 0.1 to 0.6 mm in diameter, supermicrosurgical techniques are required (Granzow, Soderberg, Kaji, & Dauphine, 2014).

The present systematic review aimed to evaluate the clinical effectiveness and safety of LVA concerning pain, functionality, QoL, recurrence, and complications in comparison to conservative or other surgical treatments (e.g., vascularized supraclavicular lymph node transfer [VSLNT]) for patients with primary or secondary lymphoedema stage I, II, and III.

2 | MATERIALS AND METHODS

We conducted this systematic review in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Figure 1) (Moher, Liberati, Tetzlaff, & Altman, 2009). The systematic review is based on four domains for rapid relative effectiveness assessments of the methodological framework of the Health Technology Assessment (HTA) Core Model® developed within EUnetHTA (European Network for Health Technology Assessment, www.eunethta.eu) (EUnetHTA, 2016).

A systematic literature search was performed in December 2017 in the following databases: Medline via Ovid, Embase, the Cochrane Library, and CRD (DARE, NHS-EED, HTA), and completed by a hand search for additional records. Our systematic search was not limited to a specific time period (from the earliest records to December 2017). To identify relevant articles, the following keywords were used: "lymphovenous," "anastomosis," "bypass," and "lymphoedema." The references were screened by two independent researchers and in case of disagreement, a third researcher was involved to solve the differences.

TABLE 1 GRADE categories to rank the strength of evidence (Guyatt et al., 2011)

High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	Evidence either is unavailable or does not permit a conclusion

Abbreviation: GRADE, grading of recommendations, assessment, development and evaluation.

Studies were eligible for inclusion if they included: (a) patients with primary or secondary lymphoedema stage I, II, and III in whom a conservative treatment is ineffective or does not lead to a substantial improvement of the lymphoedema; (b) lymphovenous/lymphaticovenous/lymphaticovenular anastomosis or bypass; (c) randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), prospective case series; (d) population ≥ 10 patients in prospective studies; (e) published in English or German. We did not include retrospective studies. Subanalytical results were excluded if already published by the same investigator in a previous article. Therefore, only the overall data of the primary studies are presented in the outcomes. Two reviewers extracted data retrieved from eligible studies in predefined tables independently (see Table 3).

2.1 | Methodological quality assessment

Based on the data-extraction-table, data on each selected outcome category were synthesized across studies according to grading of recommendations assessment, development and evaluation (GRADE) (Guyatt et al., 2011). Each study was rated by two independent researchers. A third researcher was called to resolve differences in case of disagreement. The GRADE scheme uses four categories to rank the strength of evidence of included studies (Table 1). A more detailed list of applied criteria can be found in the recommendations of the GRADE Working Group (Guyatt et al., 2011).

We applied no further data processing (e.g., indirect comparison). The studies were systematically assessed for quality and risk of bias (RoB) by two independent researchers using the risk of bias assessment tool for non-randomized controlled studies (RoBANS) (Kim et al., 2013) (Table 2) and the IHE Risk of Bias checklist for case series (Institute of Health Economics [IHE], 2014) (Figure 2). A third researcher was called to resolve differences in case of disagreement. We extended the checklist for an overall risk of bias rating, ranging from low to moderate to high, to compare the studies with each other (Table 3).

3 | RESULTS

3.1 | Study selection

Overall, 629 citations were identified through the literature searches and included after deduplication. After abstract screening, 60 full text articles were assessed for eligibility. Of those, five studies, one NRCT (Akita et al., 2015) was included for the analysis of effectiveness and safety and four prospective single-arm studies (Chang et al., 2013;

TABLE 2 Reporting and risk of bias according to RoBANS risk of bias assessment tool—study level (non-randomized controlled studies), (n = 1)

Study reference	Selection of participants	Confounding variables	Intervention (exposure) measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall risk of bias
Akita et al., 2015	High	Unclear	Low	High	High	High	Moderate to high

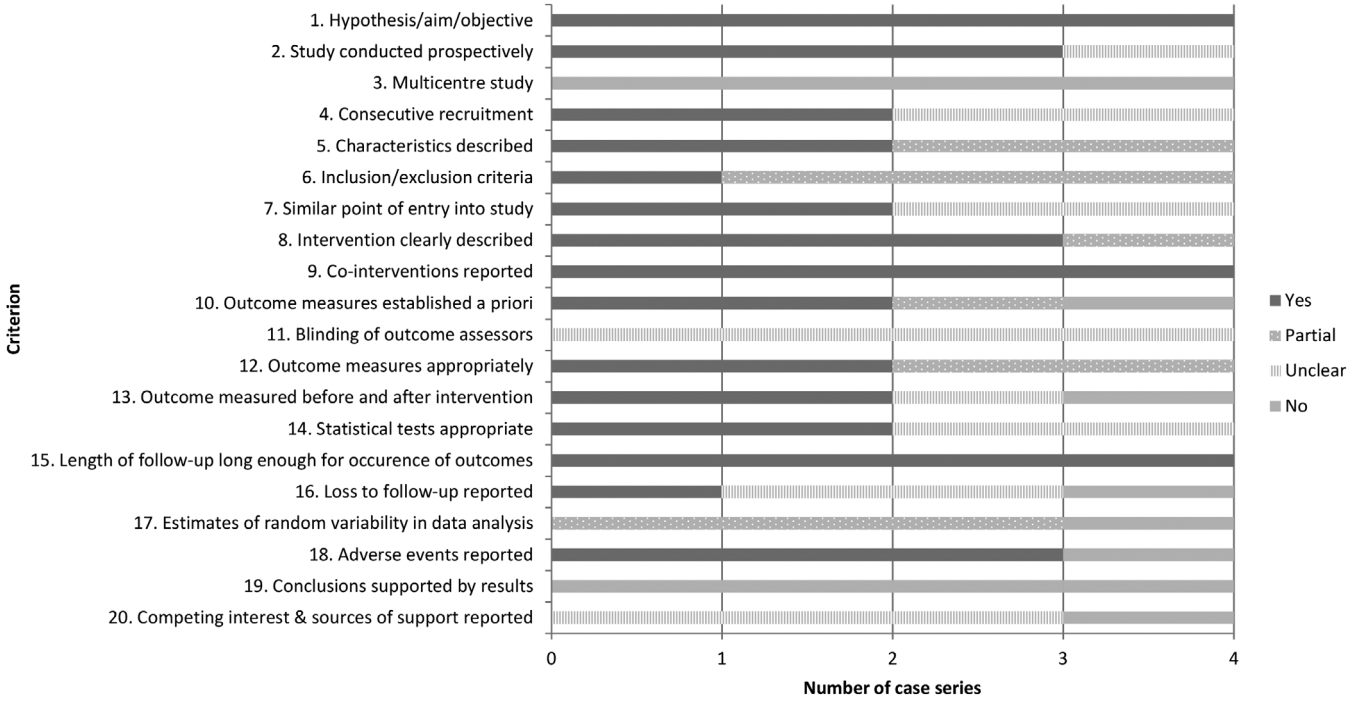


FIGURE 2 Reporting and risk of bias according to the IHE checklist—study level (case series), (n = 4)

Cornelissen et al., 2017; Damstra et al., 2009; Poumellec et al., 2017) were included for the final analysis of safety alone (Table 3). Further, a total of 14 systematic reviews and HTAs on LVA could be identified through the systematic literature search. However, due to methodological differences (e.g., other study purposes, inclusion of retrospective studies) of the reviews, we decided to exclude the systematic reviews and HTAs from our analysis. Nonetheless, we searched through the reviews to see if they identified studies that we did not find via our systematic literature search. Most of these provided relevant background information for this report, but no additional studies were identified.

3.2 | Study characteristics

A total of 217 patients (114 females, 3 males, 100 not specified) were enrolled in the included trials, of which 204 patients were treated with LVA and 13 with vascularized supraclavicular lymph node transfer (VSLNT). These patients suffered from primary or secondary lymphoedema, mostly due to breast cancer and its treatments (e.g., radiation or chemotherapy). In 1 study, 100 patients were included, but outcome data were only reported on 37 patients and the baseline data were reported on an unknown number of patients (Chang et al., 2013). This may distort the effect of LVA. Mean age of the patients ranged from 54.0 to 64.0 years across studies. The mean follow-up periods differed considerably between the studies with a range of 7.8 to 30.4 months.

LVA procedures were either performed side-to-end or end-to-end (Akita et al., 2015), end-to-end or end-to-side (Chang et al., 2013), end-to-side (Damstra et al., 2009), or end-to-end (Poumellec et al., 2017). One study did not report on the procedure modality of the performed LVA's (Cornelissen et al., 2017). LVA was performed only in lower extremities in (Akita et al., 2015), in upper and lower extremities in (Chang et al., 2013), and only for upper extremities in the three other studies (Cornelissen et al., 2017; Damstra et al., 2009; Poumellec et al., 2017).

Pre-interventional procedures comprised of indocyanine green (ICG) lymphography in two studies (Chang et al., 2013; Cornelissen et al., 2017), ICG lymphography, and supervised compression therapy for at least 3 months before surgery in one study (Akita et al., 2015), and standardized conservative treatment for 3 months and perioperative usage of antibiotics in another study (Damstra et al., 2009). The fifth study did not report on pre-interventional procedures (Poumellec et al., 2017). Compression bandages and elevation of affected limb were performed as post-interventional procedures in two studies (Chang et al., 2013; Damstra et al., 2009), and simple self-lymph drainage directly after discharge together with the occasional elastic garments until the final follow-up in one study (Akita et al., 2015). Further procedures were removal of the sleeve and lymphatic drainage physiotherapy beginning 2 weeks post-surgery (Poumellec et al., 2017), prophylactic intravenous antibiotics and compression garments 4 weeks post-surgery (Chang et al., 2013), and elastic stockings during follow-up (Damstra et al., 2009). One study did not report on post-interventional procedures (Cornelissen et al., 2017). Additional interventions were only reported in one study: VLNT was performed due to no improvement of lymphoedema after an LVA in one patient (Chang et al., 2013).

No losses to follow-up were reported in two studies (Akita et al., 2015; Damstra et al., 2009). The other three studies had unclear

TABLE 3 Study characteristics of individual studies included in the analysis, sorted alphabetically

Study reference	Title	Country	Performed LVA	Mean lymphoedema duration, yrs (range)	Study type	Number of patients	Mean age of patients, years (SD)	Follow-up (months)	Loss to follow-up, n (%)	Overall risk of bias[a]
Akita et al., 2015	Comparison of vascularized supraclavicular lymph node transfer and lymphaticovenular anastomosis for advanced stage lower extremity lymphedema.	Japan	Side-to-end or end-to-end (lower extremity)	NR	Two-centre NRCT	LVA: 43 VSLNT: 13	LVA: 54.1 (±14.8) VSLNT: 63.7 (±7.0)	LVA: 18.3 (±8.8) VSLNT: 15.1 (±1.9)	0 (0)	Moderate to high
Chang, Suami, & Skoracki, 2013	A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema.	United States	End-to-end or end-to-side (upper and lower extremities)	Upper extremity: 3.5 (range, 1–10) lower extremity: 6.6 (range, 1–25)	Single-Centre prospective interventional single-arm study	100	54.0 (NR)	Upper extremity: 30.4 (range, 3–84) lower extremity: 18.2 (range, 1–36)	NR	High
Cornelissen et al., 2017	Lymphatico-venous anastomosis as treatment for breast cancer-related lymphedema: a prospective study on quality of life.	Netherlands	NR (upper extremity)	6 (range, 2–30)	Single-Centre prospective interventional single-arm study	20	55.9 (range, 51.9–59.9)	7.8 (range, 6.3–9.3)	Unclear	Moderate
Damstra et al., 2009	Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature.	Netherlands	End-to-side (upper extremity)	5.3 (range, 3–14)	Single-Centre prospective interventional single-arm study	10	58.7 (range, 46–68)	12	0 (0)	Moderate

(Continues)

TABLE 3 (Continued)

Study reference	Title	Country	Performed LVA	Mean lymphoedema duration, yrs (range)	Study type	Number of patients	Mean age of patients, years (SD)	Follow-up (months)	Loss to follow-up, n (%)	Overall risk of bias[a]
Poumellec et al., 2017	Surgical treatment of secondary lymphedema of the upper limb by stepped microsurgical lymphaticovenous anastomoses.	France	End-to-end (upper extremity)	NR	Single-Centre prospective interventional single-arm study	31	64 (range, 38–65)	Mean 12.8	Unclear	High

Abbreviations: NR, not reported; SD, standard deviation.
[a]According to the IHE Risk of Bias checklist for case series (Institute of Health Economics [IHE], 2014) or the RoBANS risk of bias assessment tool (Kim et al., 2013).

reporting of loss to follow-up (Cornelissen et al., 2017; Poumellec et al., 2017) or did not report on loss to follow-up (Chang et al., 2013). Study characteristics reported by each paper are summarized in Table 3.

3.3 | Quality of evidence

None of the studies was categorized with a low risk of bias, the NRCT showed a moderate to high RoB, two studies showed a moderate RoB, and two studies a high RoB due to unclear blinding of outcome assessors, unclear or no reporting of losses to follow-up, no reporting of estimates of the random variability in the data analysis of relevant outcomes and no statement of competing interests and sources of support. The ratings for each individual criterion are plotted in Figure 2.

Overall, the strength of evidence according to GRADE for the effectiveness and safety of LVA is "very low" and was mainly downgraded due to the high risk of selection, detection and reporting biases, small sample sizes, no control groups in four studies, and insufficient outcome reporting (Table 4).

3.4 | Effectiveness of LVA

Only one NRCT could be identified that assessed only one important outcome on the clinical effectiveness of LVA compared to VSLNT (Akita et al., 2015). Changes in the postoperative volume were compared using the lower extremity lymphoedema index (LEL). This index was calculated from the circumferences of five points on the limb (the superior edge of the patella, 10 cm above and below the patella, the lateral malleolus, and the dorsum of the foot) and the body mass index, which aimed to yield an accurate quantitative assessment of the severity of lymphoedema. Akita et al. stated that the mean changes of volume compared with preoperative volumes were in the LVA group 21.2 (±2.0) and in the VSLNT group 26.5 (±4.4) with statistical significance in favor of the VSLNT group. Data on QoL, pain, and functionality were not assessed in this NRCT (Akita et al., 2015).

3.5 | Safety of LVA

In terms of safety, the NRCT as well as the four included prospective interventional single-arm studies reported procedure-related adverse events; however, no major complications were reported in any of the studies.

In the LVA group of the NRCT, no adverse events were reported compared to the VSLNT group, where adverse events were reported in three patients (23.1%) who completed the follow-up (of 13 patients), with statistical significance in favor of LVA. The most frequent adverse event reported was congestion to the skin paddle in three patients (23.1%) after the treatment with VSLNT (Akita et al., 2015).

In the prospective interventional single-arm studies, adverse events occurred in 2 patients who completed the follow-up, out of 161 included patients across these studies (1.2%). The most

TABLE 4 Evidence profile: Efficacy and safety LVA surgical treatment in lymphoedema (GRADE)

Certainty assessment							Number of patients		Effect			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LVA	VSLNT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mean changes of volume compared with preoperative volume measurements (follow up: Mean 15.1–18.3 months)												
1	Observational studies (before-after study)	Very serious[a]	NA (only 1 trial)	Not serious	Very serious[b]	None	Improvement value of LEL index: LVA: 21.2 (±2.0) vs. VSLNT: 26.5 (±4.4), s.s.				⊕◯◯◯ VERY LOW	Important
Quality of life—Not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Critical
Recurrence (worsening of lymphoedema)—Not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Important
Procedure-related adverse events (follow up: Mean 7.8–30.4)												
4	Observational studies (before-after studies)	Very serious[c]	Not serious	Not serious	Not serious	Publication bias strongly suspected[d]	2/194 (1.0%)	3/13 (23.1%)	Not estimable	Not estimable	⊕◯◯◯ VERY LOW	Critical
Procedure-unrelated adverse events—Not reported												
–	–	–	–	–	–	–	–	–	–	–	–	Important

Note: Nomenclature for GRADE table: Limitations: 0: no limitations or no serious limitations; −1: serious limitations. Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; −1: important inconsistency. Indirectness: 0: direct, no uncertainty, −1: some uncertainty, −2 major uncertainty. Other modifying factors: publication bias likely (−1), imprecise data (−1), strong or very strong association (+1 or + 2), dose–response gradient (+1), Plausible confounding (+1).

Abbreviations: GRADE, grading of recommendations, assessment, development, and evaluation; LVA, lymphovenous anastomosis; s.s., statistical significant; VSLNT, vascularized supraclavicular lymph node transfer.

[a]High risk of selection, detection, and reporting biases.

[b]Small sample size, small number of events.

[c]No control group.

[d]Chang reported on 100 patients, but outcome data are only reported for 37.

frequently described adverse event was skin irritation at the site of contrast injection in two patients (10%) after the treatment with LVA (Cornelissen et al., 2017). Two studies reported no procedure-related adverse events for the treatment with LVA (Chang et al., 2013; Poumellec et al., 2017). One study did not report on procedure-related adverse events for LVA (Damstra et al., 2009). None of the studies reported on procedure-unrelated adverse events.

4 | DISCUSSION

Lymphoedema has a decisive impact on the QoL of LVA patients and on their ability to work and participate in social activities. Consequently, the improvement of patients' QoL is the main goal of lymphoedema treatments (Cornelissen et al., 2017). With the advancement of microsurgical techniques, LVA is gaining popularity and is used as a surgical treatment for extremity lymphoedema regardless of the fact that its clinical profile is not supported by high-quality data (Akita et al., 2015; Lee, Laredo, & Neville, 2011; Winters et al., 2017).

The included studies in this report demonstrate mixed results following the LVA procedures and the quality of these studies varies. The included patient group in the NRCT was not representative of the range of LVA patients because only patients with advanced primary and secondary lymphoedema of the lower extremities were included (Akita et al., 2015). A major concern of most of the identified prospective interventional single-arm studies is the low number of included patients (see Table 3). For instance, one study included only 10 patients (Damstra et al., 2009). In order to identify rare procedure related adverse events, low patient numbers are insufficient. Moreover, only one study had a longer follow-up period of 12 months (Chang et al., 2013). Therefore, reliable data of long-term safety and efficacy outcomes are missing.

Consecutive patient recruitment and the prospective study design were unclear in one study (Poumellec et al., 2017), but the study was still included. Another study was included at first, but excluded after data extraction because of retrospective analysis of patient data (Winters et al., 2017).

Patient-relevant outcomes, such as QoL were only described in uncontrolled studies and inconsistently reported (e.g., different measurement scales). The utilized LVA procedures as well as pre-procedure interventions differed slightly between the individual studies, challenging a comparison. For instance, LVA was performed either side-to-end, end-to-end or end-to-side for primary, and/or secondary lymphoedema. Further, the number of performed anastomoses differed also across the studies. One important finding is that four of the included studies performed different post-interventional procedures, such as compression bandages in two studies (Chang et al., 2013; Damstra et al., 2009) or lymphatic drainage in two other studies (Akita et al., 2015; Poumellec et al., 2017). The fifth study did not report on this baseline characteristic, but stated the importance of discontinuation of compressive stockings after surgery (Cornelissen et al., 2017) (contrary to the two studies mentioned above [Damstra et al., 2009; Chang et al., 2013]). Hence, it is currently unknown, due to conflicting evidence, if peri-interventional procedures such as compression therapy directly post-surgery may either harm or benefit the effectiveness of LVA. Further, it might also be a confounder of the post-procedural lymphoedema evaluation. It is possible that all these factors had an impact on the recorded outcomes of the studies.

As reported in the included literature, LVA seems to be successful in controlling the progression of early stages of lymphoedema (Chang, 2010). Nonetheless, a difficulty is the understanding of the optimal patient selection for LVA procedures as well as the optimal number of LVAs performed on the patient (Chang et al., 2013; Oremus et al., 2010). Yet with imaging modalities such as ICG lymphography the identification of suitable (healthy and functioning) lymphatic vessels for LVA procedures may be improved and the patency of the anastomosis can be approved (Cornelissen et al., 2017; Markkula Silja et al., 2019; Scaglioni et al., 2017; Tourani, Taylor, & Ashton, 2016). According to the literature, there seem to be two factors that determine the effectiveness of LVA: the identification of viable lymphatic vessels and the extent of tissue fibrosis related to lymphoedema (Chang, 2010).

The present systematic review indicates that only limited evidence reporting the clinical effectiveness and safety of LVA procedures for patients with lymphoedema is presently available. Nevertheless, we identified three ongoing studies (two RCTs and one pilot study) that might show effects of LVA with a higher quality of evidence (NCT-02790021; JPRN-UMIN000025137; NTR6465).

Further, there are several studies that describe the use of LVA as preventive procedure after cancer therapies. As it was not in the scope of this systematic review, no conclusion can be made if LVA is effective and safe as a prevention treatment for secondary lymphoedema. Nevertheless, LVA may have a role in prevention of lymphoedema (Boccardo et al., 2016; Gomberawalla et al., 2017; Szolnoky, Dobozy, & Kemeny, 2014). Jorgensen et al. performed a systematic review on the effect of prophylactic LVA and concluded that due to the heterogeneity between studies, the treatment could not be concluded effective and pointed out that there is a need for high quality studies on this topic (Jorgensen, Toyserkani, & Sorensen, 2017).

Moreover, some relevant systematic reviews are in line with our conclusions despite the fact that these systematic reviews had a different aim (Sharkey et al., 2017) or included also retrospective studies (Scaglioni et al., 2017). Due to the methodological shortcomings of the available evidence, no conclusions can be made about the effectiveness of the procedure. Despite the heterogeneity of study characteristics, the included studies show that LVA might be a safe technique for patients with primary and secondary lymphoedema—particularly because no serious complications were reported.

5 | CONCLUSION

The included studies showed poor quality of evidence and high risk of bias, and therefore makes it difficult to draw a reliable conclusion on

the clinical effectiveness of LVA. Furthermore, there were various methods of LVA performed in the studies, data on upper extremity lymphoedema were reported more frequently, and the estimation of ongoing post-interventional treatments (e.g., compression treatment) is scarce and presented a large variety. Nevertheless, LVA seems to be safe for the treatment of primary and secondary lymphoedema.

There is a need for high-quality studies to confirm the consistent positive findings based on observational evidence with respect to limb volume reduction. Furthermore, there is a need to find the optimal lymphoedema management algorithm and to determine the exact patient group that would benefit most from the procedure. New study results based on a high-quality RCT will potentially influence the effect estimate considerably.

CONFLICT OF INTEREST

The authors have no financial conflicts or commercial associations to disclose.

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REFERENCES

Akita, S., Mitsukawa, N., Kuriyama, M., Kubota, Y., Hasegawa, M., Tokumoto, H., … Satoh, K. (2015). Comparison of vascularized supraclavicular lymph node transfer and lymphaticovenular anastomosis for advanced stage lower extremity lymphedema. *Annals of Plastic Surgery*, *74*(5), 573–579.

Allen, R. J., Jr., & Cheng, M.-H. (2016). Lymphedema surgery: Patient selection and an overview of surgical techniques. *Journal of Surgical Oncology*, *113*(8), 923–931.

Ayestaray, B., & Bekara, F. (2014). Pi-shaped lymphaticovenular anastomosis: The venous flow sparing technique for the treatment of peripheral lymphedema. *Journal of Reconstructive Microsurgery*, *30*(8), 551–560.

Boccardo, F., Valenzano, M., Costantini, S., Casabona, F., Morotti, M., Sala, P., … Campisi, C. (2016). LYMPHA technique to prevent secondary lower limb lymphedema. *Annals of Surgical Oncology*, *23*(11), 3558–3563.

Carl, H. M., Walia, G., Bello, R., Clarke-Pearson, E., Hassanein, A. H., Cho, B., … Sacks, J. M. (2017). Systematic review of the surgical treatment of extremity lymphedema. *Journal of Reconstructive Microsurgery*, *33*(6), 412–425.

Chang, D. W. (2010). Lymphaticovenular bypass for lymphedema management in breast cancer patients: A prospective study. *Plastic and Reconstructive Surgery*, *126*(3), 752–758.

Chang, D. W., Suami, H., & Skoracki, R. (2013). A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plastic and Reconstructive Surgery*, *132*(5), 1305–1314.

Cornelissen, A. J. M., Kool, M., Lopez Penha, T. R., Keuter, X. H. A., Piatkowski, A. A., Heuts, E., … Qiu, S. S. (2017). Lymphatico-venous anastomosis as treatment for breast cancer-related lymphedema: A prospective study on quality of life. *Breast Cancer Research and Treatment*, *163*(2), 281–286.

Damstra, R. J., Voesten, H. G. J., van Schelven, W. D., & van der Lei, B. (2009). Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. *Breast Cancer Research and Treatment*, *113*(2), 199–206.

EUnetHTA *Joint action 2 work package 8. HTA Core model® version 3.0*. 2016; EUnetHTA. Available from: www.htacoremodel.info/BrowseModel.aspx.

Executive Committee. (2016). The diagnosis and treatment of peripheral lymphedema: 2016 consensus document of the International Society of Lymphology. *Lymphology*, *49*(4), 170–184.

Gesellschaft Deutschsprachiger Lymphologen (GDL). S2k Leitlinie - Diagnostik und Therapie der Lymphödeme. AWMF Reg.-Nr. 058–001. 2017; Available from: http://www.awmf.org/uploads/tx_szleitlinien/058-001l_S2k_Diagnostik_und_Therapie_der_Lymphoedeme_2017-05.pdf.

Gomberawalla, A., Vandenberge, J., Borden, B., Rohde, C., Ascherman, J., Taback, B., … Feldman, S. (2017). Lymphatic microsurgical preventive healing approach (LYMPHA) for the primary prevention of lymphedema. *Cancer Research*, *77*(4), P2-01-14.

Granzow, J. W., Soderberg, J. M., Kaji, A. H., & Dauphine, C. (2014). Review of current surgical treatments for lymphedema. *Annals of Surgical Oncology*, *21*(4), 1195–1201.

Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., … deBeer, H. (2011). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, *64*, 383–394.

Hadamitzky, C., Pabst, R., Gordon, K., & Vogt, P. M. (2014). Surgical procedures in lymphedema management. *Journal of Vascular Surgery. Venous and Lymphatic Disorders*, *2*(4), 461–468.

Ingianni, G. (2003). Microsurgical lympho-venous anastomosis in the treatment of secondary lymphoedema of the upper extremity. *Handchirurgie, Mikrochirurgie, Plastische Chirurgie*, *35*(4), 216–220.

Institute of Health Economics (IHE). Quality appraisal of case series studies checklist. Edmonton (AB): Institute of Health Economics; 2014; Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.

Jorgensen, M. G., Toyserkani, N. M., & Sorensen, J. A. (2017). The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphedema: A systematic review and meta-analysis. *Microsurgery*, *38*(5), 576–585.

Kim, S. Y., Park, J. E., Lee, Y. J., Seo, H.-J., Sheen, S.-S., Hahn, S., … Son, H.-J. (2013). Testing a tool for assessing the risk of bias for non-randomized studies showed moderate reliability and promising validity. *Journal of Clinical Epidemiology*, *66*(4), 408–414.

Koshima, I., Inagawa, K., Urushibara, K., & Moriguchi, T. (2000). Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *Journal of Reconstructive Microsurgery*, *16*(6), 437–442.

Kung, T. A., Champaneria, M. C., Maki, J. H., & Neligan, P. C. (2017). Current concepts in the surgical management of lymphedema. *Plastic and Reconstructive Surgery*, *139*(4), 1003e–1013e.

Lee, B. B., Laredo, J., & Neville, R. (2011). Current status of lymphatic reconstructive surgery for chronic lymphedema: It is still an uphill battle! *International Journal of Angiology*, *20*(2), 73–79.

Leung, E. Y. L., Tirlapur, S. A., & Meads, C. (2015). The management of secondary lower limb lymphoedema in cancer patients: A systematic review. *Palliative Medicine*, *29*(2), 112–119.

Markkula Silja, P., Leung, N., Allen Victoria, B., & Furniss, D. (2019). Surgical interventions for the prevention or treatment of lymphoedema after breast cancer treatment. *Cochrane Database of Systematic Reviews* http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011433/abstract.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). The PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097.

Oremus M, Walker K, Dayes I, Raina P. Diagnosis and Treatment of Secondary Lymphedema - Technology Assessment Report. Agency for

Healthcare Research and Quality; 2010; Available from https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id66aTA.pdf.

Poumellec, M.-A., Foissac, R., Cegarra-Escolano, M., Barranger, E., & Ihrai, T. (2017). Surgical treatment of secondary lymphedema of the upper limb by stepped microsurgical lymphaticovenous anastomoses. *Breast Cancer Research and Treatment*, *162*(2), 219–224.

Scaglioni, M. F., Fontein, D. B. Y., Arvanitakis, M., & Giovanoli, P. (2017). Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery*, *37*(8), 947–953.

Sharkey, A. R., King, S. W., Ramsden, A. J., & Furniss, D. (2017). Do surgical interventions for limb lymphoedema reduce cellulitis attack frequency? *Microsurgery*, *37*(4), 348–353.

Szolnoky, G., Dobozy, A., & Kemeny, L. (2014). Towards an effective management of chronic lymphedema. *Clinics in Dermatology*, *32*(5), 685–691.

Tourani, S. S., Taylor, G. I., & Ashton, M. W. (2016). Long-term patency of lymphovenous anastomoses: A systematic review. *Plastic and Reconstructive Surgery*, *138*(2), 492–498.

Winters, H., Tielemans, H. J. P., Hameeteman, M., Paulus, V. A. A., Beurskens, C. H., Slater, N. J., & Ulrich, D. J. O. (2017). The efficacy of lymphaticovenular anastomosis in breast cancer-related lymphedema. *Breast Cancer Research and Treatment*, *165*(2), 321–327.

Witty MF, Larouche K. Treatment of cancer-related secondary lymphedema. Montreal: L'institut National d'excellence en Sante et en Services Sociaux; 2011.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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