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LYMPHOVENOUS ANASTOMOSIS FOR THE TREATMENT OF LYMPHEDEMA: A SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS

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ABSTRACT

Lymphovenous anastomosis (LVA) has been described as an effective treatment for early stages of lymphedema (LE). The aim of this study was to deepen the evaluation of the effectiveness of LVA by performing a meta-analysis to provide information about its utility in specific anatomical sites, clinical stages, duration of lymphedema, and surgical technique. A systematic literature search using PubMed/Medline, Google Scholar, and Cochrane Database was performed in November 2019. Only original studies in which exclusively LVA was performed for primary and/or secondary lymphedema in humans were eligible for data extraction. A meta-analysis was performed on articles with a well-defined endpoint and a subgroup analysis was conducted in relation to surgical technique, duration of lymphedema, stage of pathology. Forty-eight studies, including 6 clinical trials and 42 low-risk bias observational studies were included in our meta-analysis. 1,281 subjects were included and the majority of articles reported a pre-post analysis. Lymphaticovenular anastomosis appears to result effectively in treatment of lymphedema with an odds ratio of 0.07 (CI: 0.04, 0.13, p<0.001). All subgroup meta-analyses were statistically significant for LVAs specifically with regard to anatomical site, clinical stage, duration of LE, or type of microsurgical procedure (p<0.05).

Our meta-analysis confirmed the efficacy of LVAs for the treatment of lymphedema, even when subgroup analysis was performed for clinical stage, duration of pathology, anatomical site of lymphedema, or type of microsurgical procedure. Further prospective trials with a common clearly defined outcome measure are warranted for an unbiased evaluation.

Keywords: LVA, lympho-venous anastomosis, lymphedema, treatment, lymphatics, meta-analysis

Lymphedema (LE) is a condition characterized by accumulation of lymphatic fluid in the interstitial tissue of the arms, legs, and occasionally other parts of the body (1). It is the result of an impairment to the outflow of lymphatic fluid from the affected area and accumulating lymphatic fluid is responsible for the consequent inflammation, lipogenesis, fibrosis, infections, and elephantiasis (2). LE may be primary – due to dysplasia of lymphatic vessels or valvular dysfunction – or secondary to infection, surgical lymphadenectomy, and/or radiotherapy (3). Although worldwide the most common cause of LE is filariasis, the

most frequent etiology in developed countries is related to cancer and its treatment (4-6). The International Society of Lymphology established a staging system for lymphedema into 4 clinical classes (7); Chang et al developed a classification based on ICG lymphangiography findings (8), while Campisi et al introduced a classification that combines clinical presentation and lymphoscintigraphic patterns (9). Correct lymphedema staging is an important tool for the management of LE and a guide to better therapeutic options. Although surgical procedures for prevention or treatment of LE have been already widely described, the majority of patients are still managed non-operatively, reserving surgery to those who are dissatisfied (10). Non-surgical procedures include manual lymphatic drainage, compression therapy with low-stretch bandages, skin care, and exercises (11). While the effectiveness of these approaches have been documented, the success of these procedures requires an intense training of therapists and patients as well as continued maintenance for the rest of a patient's life (12). Surgery could overcome these limits by improving the physiological circulation of lymphatic fluid in progressive and resistant lymphedema. A variety of procedures have been proposed in the past decades, but modern accepted surgical techniques for treating lymphedema include liposuction, vascularized lymph node transfer, and lymphovenous anastomosis (LVA) (13-18). The effectiveness of these procedures has been reported in previous studies, but the literature demonstrates a great heterogeneity in presented outcomes. Specifically, while measurement of limb circumference is the most commonly used method to evaluate LE, other tests are available such as volume assessment based on computer tomography (CT), lymphography, ICG-lymphoscintigraphy, US evaluation, magnetic resonance imaging (MRI), measurement of water displacement, or condition-specific quality of life assessment tools (19,20).

LVA has been well described as an effective treatment for early stage lymphedema of the extremities demonstrating a very low risk of complications and the possibility to be performed under local anesthesia (21-24). Nevertheless, there is no consensus on the best surgical technique or how to measure surgical outcome and effectiveness of the procedure. There are meta-analyses available in literature addressed to the advantages and disadvantages of LVAs in treatment of lymphedema, but they include only few available clinical trials and enrolled patients only with a specific site or etiology of the lymphedema and with-out appropriate subgroup analysis (25,26).

The aim of this study was to evaluate the effectiveness of LVA for the treatment of lymphedema by performing a meta-analysis with subgroup evaluations to provide information about its utility in specific anatomical sites, stages of lymphedema, duration of pathology, and also examining the different surgical techniques.

MATERIALS AND METHODS

Selection of Studies

A literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. In November 2019, an electronic search was conducted through PubMed/Medline, Google Scholar, and Cochrane Database restricted to the English language. The databases were searched using the following set of search Medical Subject Headings (MeSH) terms including 'lymphedema', 'lymphatic venous', 'lympho-venous', 'lymphaticovenular', 'anastomosis', 'bypass', 'shunt', 'lymphoplasty', in combination with the Boolean logical operators (AND or OR). Only original studies in which exclusively LVA was performed for the treatment of primary and/or secondary lymphedema in humans were eligible for data extraction. Studies on filariasis-related lymphedema, on preventive techniques, or on lymph nodes transfers were excluded from the review. No limitation was placed on the number of patients included in the studies. Data extraction was performed by two independent reviewers (EN and FR) identifying relevant

articles for retrieval. Relevant data was determined prior to reading selected articles. For all included studies, we documented the type of study, year of publication, authors, number of patients, number of anastomosis, primary endpoints, type of microsurgical technique, duration of lymphedema prior to surgery, stage of lymphedema, follow-up period, complications, and presence of a control group. A meta-analysis was performed on articles with a well-defined end-point. Papers published by the same research group and reporting duplicate data were excluded. Both retrospective comparative studies and retrospective case series and prospective studies were included in this review and meta-analyses. Two independent reviewers (EN and FR) reported extracted data in a spreadsheet that included relevant information. In case of divergent opinions, another independent investigator (MM) was requested to help reach a consensus. The methodological index for non-randomized studies (MINORS) was used to assess the methodological quality or risk of bias for nonrandomized studies (27). Analysis on effectiveness of LVA on LE treatment was performed both in the few published controlled clinical trials and in high quality non-randomized studies. Moreover, additional analysis of subgroups was performed to com-pare whether LVA was more effective accord-ing to the surgical technique, duration of lymphedema prior to surgery, and stage of pathology. Given that included studies used different types of classification systems, the methodology used in the current study to uniform the different classification systems can be found in *Table 1* (28).

TABLE 1
Uniform Stage Classifications of Lymphedema developed for the Meta-Analysis and the Associated Notations by the Campisi, ISL and Cheng Scales

Stage	Campisi	ISL	Cheng
Early	I	0 – 1	0 – 1
Moderate	II – III	2	2
Severe	IV - V	3 - 4	3 - 4

In the following sections, we focus our attention on the difference between two groups with respect to a binary outcome. Specifically, we employ odd ratios to make the results uniform. The odds for a group is defined as the ratio of the number of patients in the group who achieve the stated endpoint and the number of patients who don't. We treat an increase in the reference index – for example, volumetry – as the main event. This means that if the majority of patients experience a reduction in the volumetry, the odd ratio will be smaller than 1. A ratio of 1 indicates no difference – that is, the outcome is just as likely to occur in the control group as it is in the treatment group.

Statistical Analysis

When pooling study results, two main approaches can be used depending on the effect size heterogeneity: the Fixed-Effect Model or the Random Effect Model. Under the first model, the main assumption is that all results originate from a single homogeneous population. By contrast, with the latter, we assume that the true effect distribution varies from study to study. I-square was used to calculate heterogeneity among the studies. A probability value of I-square ≥50% indicated the presence of significant heterogeneity. The fixed effects model was used in the presence of no significant inter-study heterogeneity; otherwise, the random effects model was used. Dichotomous variables were pooled by the Mantel-Haenszel method and compared using Odds Ratio with 95 percent confidence intervals. Continuous variables were analyzed with the inverse variance method, using weighted mean differences with 95 percent confidence intervals. A p-value <0.05 was considered statistically significant. Subgroups analysis dwell in two main parts: (1) pooling the effect within each subgroup, and (2) analyzing the effects between the subgroups. This latter aggregation is performed using a fixed or random effect according to heterogeneity measures. The Begg and Mazumdar test (using Kendall's method) was used in analysis involving a small number of studies; otherwise, the Egger test was used to

detect publication biases. Values of $p<0.05$ indicated presence of significant biases among studies. All statistical analyses were performed using SAS Software Release 9.4 (SAS Institute, Cary, NC).

RESULTS

Studies Included in Meta-Analysis

A total of 1221 records were retrieved (*Fig. 1*). After removal of duplicates, the literature search identified 916 studies. Case reports, studies on animals, non-original articles, and studies on preventive LVAs were excluded, identifying 99 eligible full-text articles. After full-text screening, additional 37 articles were excluded by further analysis because of inadequate report of cases or results, simultaneous use of LVAs and lymph node transfers or grafts, or presence of duplicated data in different papers. Of the remaining 62 studies, 6 clinical trials (29-34) were included in meta-analysis, while 58 observational studies were subjected to a further qualitative analysis using MINOR index to quantify the risk of bias (*Table 2*). The global ideal MINOR index score was 16 for non-comparative studies and 24 for comparative studies. We considered comparative studies with a MINOR index score >20 and non-comparative studies with a MINOR index score >12 as low risk of bias (35). Using these criteria, 14 observational studies (36-49) were excluded for high risk of bias, while 42 low-risk of bias studies were included in current meta-analysis.

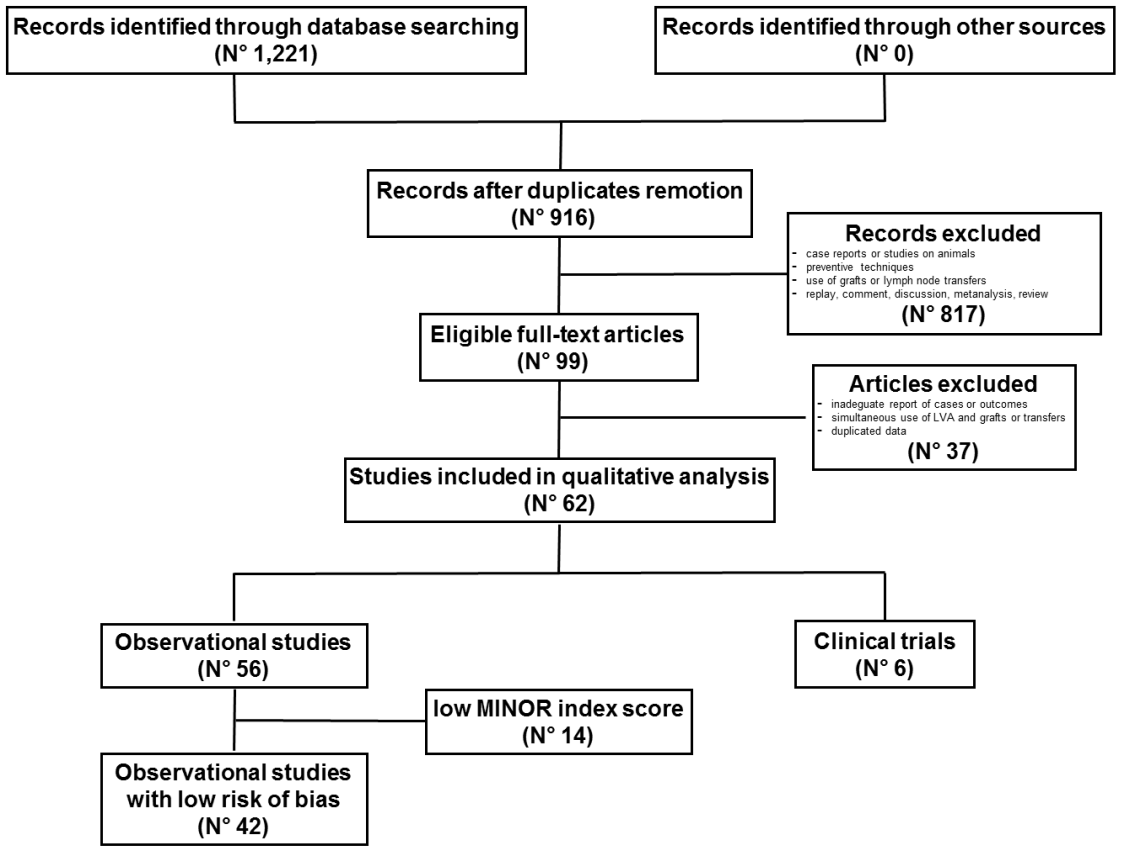

Fig. 1. PRISMA algorithm detailing the selection of studies for analysis.

TABLE 2
Characteristics of the Included Studies for Assessment of Bias

Year	Author	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study aim	<5% lost to follow-up	Prospective calculation of study size	Adequate control group	Contem-porary groups	Baseline equival-ence of groups	Adequate statistical analyses	Score	Risk of bias
2019	Suzuki Y[34]	1	1	2	1	0	2	2	2	/	/	/	/	11/16	high
2019	Seki Y[75]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2019	Yasunaga Y[70]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2019	Gentileschi S[35]	2	1	2	1	0	0	2	2	/	/	/	/	10/16	high
2019	Khan AA[76]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2019	Philips GSA[69]	2	2	2	1	1	2	2	2	/	/	/	/	14/16	low
2018	Seki Y[79]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2018	Salgarello M[36]	2	1	1	1	1	1	2	2	/	/	/	/	11/16	high
2018	Hara H[37]	1	1	1	1	1	2	2	2	/	/	/	/	11/16	high
2018	Chung J-H[77]	2	2	2	1	1	2	2	2	/	/	/	/	14/16	low
2018	Mihara M[88]	2	2	2	2	2	2	2	2	/	/	/	/	15/16	low
2017	Akita S[64]	2	1	2	1	1	2	2	2	/	/	/	/	13/16	low
2017	Gentileschi S[71]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2017	Campisi CC[62]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2017	Onoda S[65]	1	1	2	2	1	1	2	1	/	/	/	/	16/16	low
2017	Engel H[38]	2	1	1	1	2	1	2	2	1	2	1	2	18/24	high
2017	Lee KT[78]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2017	Paumellec MA[53]	2	2	2	1	1	2	2	2	/	/	/	/	14/16	low
2016	Gennaro P[54]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2016	Mihara M[39]	2	2	2	2	2	2	2	2	/	/	/	/	11/16	high
2016	Chen WF[55]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2016	Ito R[72]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2016	Yamamoto T[86]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2015	Seki Y[79]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2015	Mihara M[80]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2015	Torrisi JS[40]	1	1	2	0	0	1	2	2	/	/	/	/	9/16	high
2015	Chen WF[55]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2015	Yamamoto T[57]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low

Year	Author	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study aim	<5% lost to follow-up	Prospective calculation of study size	Adequate control group	Contem-porary groups	Baseline equival-ence of groups	Adequate statistical analyses	Score	Risk of bias
2014	Yamamoto T[58]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2014	Ayestaray B[60]	2	2	2	2	2	2	2	2	/	/	/	/	15/16	low
2014	Yoshimatsu H[87]	2	1	2	2	2	2	1	2	/	/	/	/	14/16	low
2014	Yamamoto T[52]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2014	Yamamoto T[86]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2013	Boccardo F[63]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2013	Mukenge S[50]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2013	Ayestaray B[48]	2	1	2	2	2	1	2	2	/	/	/	/	14/16	low
2013	Yamamoto T[88]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2012	Todokoro T[49]	2	2	2	1	1	2	2	2	/	/	/	/	14/16	low
2012	Auba C[81]	2	2	2	2	1	2	1	2	/	/	/	/	14/16	low
2011	Lee BB[73]	2	2	2	2	2	2	1	2	/	/	/	/	15/16	low
2011	Furukawa H[66]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2011	Mihara M[67]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2011	Chang DW[68]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2010	Demirtas Y[82]	2	2	2	2	1	2	2	2	/	/	/	/	15/16	low
2008	Damstra RJ[41]	2	1	1	1	0	2	2	2	/	/	/	/	11/16	high
2006	Matsubara S[61]	2	2	1	1	1	2	2	2	/	/	/	/	13/16	low
2004	Koshima I[83]	2	2	2	2	2	2	2	2	/	/	/	/	16/16	low
2003	Koshima I[51]	2	2	1	2	2	1	2	2	2	2	2	2	22/24	low
2001	Campisi C[42]	1	1	1	2	0	2	2	2	/	/	/	/	11/16	high
2000	Koshima I[51]	2	2	2	2	2	2	2	2	2	2	1	2	23/24	low
1990	O'Brien B[74]	2	2	2	2	1	2	0	2	/	/	/	/	13/16	low
1990	Ipsen T[43]	2	2	1	0	1	0	2	2	/	/	/	/	10/16	high
1988	Gloviczki P[44]	2	1	1	2	1	1	2	2	/	/	/	/	12/16	high
1988	Struick van Bemmelen SP[45]	1	1	1	1	1	1	2	2	/	/	/	/	10/16	high
1985	Gong-Kang H[46]	1	1	1	1	1	1	2	2	/	/	/	/	10/16	high
1978	Degni M[47]	1	1	1	1	1	1	2	2	/	/	/	/	10/16	high

Characteristics of Studies Included in Meta-Analysis

Overall, 48 studies reporting the use of LVAs for the treatment of lymphatic disorders were analyzed: 6 clinical trials and 42 low-risk of bias observational studies (*Table 3*). The majority investigated the treatment of upper and lower limbs LE, while only 3 studies reported the effect of LVAs on lymphedema of other fields: head and neck (50), pelvis (51), and scrotum (52). In total 1,281 subjects were included in the current analysis and the mean follow-up period ranged from 3 months to 12 years. A control group was present only in 2 studies (53,54), while the majority of articles reported a pre-post analysis. The classification scales used in the staging of lymphedema were Campisi staging, the International Society of Lymphology (ISL) classification system, and Cheng's lymphedema scale. Using the methodology detailed in *Table 1* to uniform the different classification systems, we classified the stage of LE into early, moderate, and severe. Almost all the patients showed an early or moderate stage of LE at diagnosis, while only 8 studies included patients with severe stage of LE (51,55-61). Regarding the technical procedure, end-to-end and side-to-end anastomosis were the most utilized, while other procedures like end-to-side anastomosis (50,62,63) and multiple-lymphatic-venous anastomosis (64,65) (MLVA) were reported in a low number of studies. In some studies the type of anastomosis was not specified (42,61, 66-71); while in others, authors performed varied types of anastomoses but they didn't specify the technique applied in each patient (29-31,72-76). The primary outcome measure used in the majority of studies was volumetry (41,77-86), specifically volume or circumference reduction, while standardized and validated indices (like LEL and UEL) were used as primary outcome in others (87-91). Only few studies included in the current meta-analysis reported subjective indices such as improvement in quality of life (57,71) or US/CT or lymphoscintigraphic images (51,66) as primary outcomes.

Results of Meta-Analysis

Only 6 clinical trials were included in the current meta-analysis and none had a control group. These studies investigated the effectiveness of end-to-end and/or side-to-end anastomosis for the treatment of upper and lower limb LE and the primary outcome was volumetry or LEL or UEL indices. The positive outcome was reported as means or difference of means between pre and post measurements, while Shih et al (33) reported the frequency of patients with a significant volumetric improvement. Akita et al (34) showed the improvement in LEL index in patients with lymphoscintigraphy, venous reflux, and without venous reflux after LVAs separately. The pooled analyses presented a high heterogeneity (I-square=68%), thus a random effect model for analysis was used. The results revealed a significant positive effect of LVAs in treatment of LE (OR=0.34, 95%CI=0.14-0.81, p<0.01) (*Fig. 2*). No publication bias was observed in these analyses by the Egger test (t=0.33; p=0.75). Because of the low number of errors, which measure the uncertainty of each study, the grey squares indicate the odds ratio of each study while the area reflects the relative weight contribution of the studies when pooling the results. The horizontal line indicates their 95% confidence interval, i.e., how many times the interval would contain the true underlying effect if the experiment is repeated multiple times. The solid vertical line (OR = 1) indicates that there is no difference in terms of outcome with or without the treatment. If the confidence interval is containing 1, then this difference is not statistically significant at a 95% level. The overall effect for each study is calculated as a weighted average of the individual studies and displayed as a diamond. Both the fixed effect and random effect model are displayed. In the specific case, data exhibit a high level of heterogeneity as indicated by I-square, thus a random effect model would be more appropriate. Furthermore, subgroups are also pooled according to a random effect model given the high level of I-square=74%). The center of the diamond

TABLE 3
Characteristics of Studies Included in the Meta-Analysis

Year	Author	Type of study	Subjects	Pathology	Field	Stage of lymph-edema	Tech-nique	mean N° anasto-mosis	end-point	Positive outcome	Comp-lica-tion	Control group	Follow-up (months)	Duration of pathology		
														<5 y	5-9 y	>=10 y
2019	Winters H[27]	Trial	12	SL	UL	early moderate	ETE ETS	1.8±0.7	volumetry	-32,3% (p=0.002)	none	no	12	2 (1)	6 (6)	4 (4)
2019	Wolfs JAGN[28]	Trial	25	SL	UL	early moderate	ETE STE	1.9	UEL index	15.8 post vs 16.2 pre (p=0.82)	N/R	no	12	6.2±5.1		
2017	Winters H[29]	Trial	29	SL	UL	early moderate	ETE STE	1.8±0.8	volumetry	-33,0% (p<0.001)	N/R	no	12	9+7.3		
2017	Cornelissen AJM[30]	Trial	20	SL	UL	early moderate	ETE	N/R	UEL index	12.99±7.47 post vs 14.92±8.01 pre (p=0.582)	2/20	no	7.8±1.5	6 (range 2-30)		
2016	Shih HB, 2016[31]	Trial	5	4 SL 1 PL	3 UL 2 LL	moderate	ETE	2.2±0.7	volumetry	4/5 3/3 UL 1/2 L	1/5 1/3 UL 0/2 LL	no	9	N/R		
2013	Akita S[32]	Trial	53	Lymph-edema	LL	N/R	25 STE and 28 STE + vein valvulopl asty	6.0	LEL index	-0.09±0.06 in 38 pts without venous reflux and -0.07±0.07 in 15 pts with venous reflux	N/R	no	3	N/R		
2019	Seki Y[75]	Retro-spective	30	SL	UL	moderate	ETE	3	volumetry	26/30	N/R	no	6	2.33 (range 0.25-10.33)		
2019	Yasunaga Y[70]	Retro-spective	30	2 PL 28 SL	LL	early moderate	ETE STE	1.6	LEL index	264.2±30.7 post vs 276.8±37.2 pre (p<0.05)	N/R	no	6	N/R		
2019	Khan AA[76]	Prospec-tive	27	SL	UL	N/R	ETE	3 (2-5)	volumetry	16/24	2 celluli-tis	no	12	3.5 (range 5-18)		
2019	Philips GSA[69]	Prospec-tive	29	SL	LL	early moderate	N/R	N/R	LyMQoL questionn aire	90 (43-108) post vs 72 (31-98) pre (p<0.005)	N/R	no	6	11 (7)	8 (8)	10 (9)
2018	Seki Y[85]	Retro-spective	10	SL	LL	moderate	ETE using SEK	1	LEL index	-20.16±9.89	N/R	no	7.7±3.3	5.76 (range 1.17-14)		
2018	Chung J-H[77]	Retro-spective	18	SL	8 UL 10 LL	moderate severe	ETE (sleeve_ in)	2.7 (2-5)	volumetry	18/18 8/8 UL 10/10 LL	N/R	no	6	4 (range 2-10)		
2018	Mihara M[84]	Prospec-tive	38	10 PL 28 SL	LL	early moderate	ETE	N/R	volumetry	17/38	N/R	no	6	N/R		

Year	Author	Type of study	Subjects	Pathology	Field	Stage of lymph-edema	Tech-nique	mean N° anasto-mosis	end-point	Positive outcome	Comp-lica-tion	Control group	Follow-up (months)	Duration of pathology		
														<5 y	5-9 y	>=10 y
2017	Akita S[64]	Retro-spective	41	SL	5 UL 36 LL	N/R	N/R	N/R	Lymphosc intigraphy	18/41 3/5 UL 15/36 LL	N/R	no	6	N/R		
2017	Gentileschi S[71]	Retro-spective	16	SL	UL	moderate	ETE STE STS	3.4	Volumetr y	25.6±2.6 post vs 27.4±2.6 pre (p<0.01)	N/R	no	6	8 (6)	5 (5)	3 (3)
2017	Campisi CC[62]	Retro-spective	146	69 PL 77 SL	63 UL 83 LL	moderate severe	MLVA + Lipoaspi ration	N/R	Volumetr y	UL 1510.4 post vs 1771.7 pre (p<0.001) LL 7167.2 post vs 8492.2 pre (p<0.01)	none	no	12	19.3 (range 7-36) UL 18.9 (range 6-45) LL		
2017	Onoda S[65]	Retro-spective	19	PL	4 UL 15 LL	early moderate	N/R	N/R	Volumetr y	6/19 2/4 UL 4/15 LL	N/R	no	3	7 (3)	6 (2)	6 (1)
2017	Lee KT[78]	Prospec-tive	17	7 PL 10 SL	3 UL 14 LL	moderate	ETE	2.5 (1-3)	Volumetr y	9/17 1/3 UL 8/14 LL	N/R	no	24	7 (5)	8 (4)	2 (0)
2017	Poumellec MA[53]	Prospec-tive	31	SL	UL	moderate severe	ETE	N/R	volumetry	29/31 stage 1-3 28/28 stage 4-5 1/3	none	no	12	N/R		
2016	Gennaro P[54]	Retro-spective	69	9 PL 60 SL	42 UL 27 LL	moderate severe	ETE STE	5.3	volumetry	69/69 stage 1-3 43/43; stage 4-5 26/26 UL 42/42 LL 27/27	N/R	no	12	39 (39)	18 (18)	12 (12)
2016	Chen WF[55]	Retro-spective	18	4 PL 14 SL	11 UL 7 LL	early moderate severe	ETE STE	10	QOL questionn aire	204.1±101.2 post vs 193±101.2 pre (p<0.01)	N/R	no	12	N/R		
2016	Ito R[72]	Prospec-tive	5	2 PL 3 SL	LL	early moderate	STE ETE	10	volumetry	5/5	none	no	3.0±1.7	2 (2)	1 (1)	2 (2)
2016	Yamamoto T[86]	Prospec-tive	14	SL	LL	early	ETE	N/R	LEL index	216.4±12.5 post vs 217.6±15,1 pre (p=0.239)	none	no	12	N/R		
2015	Seki Y[79]	Retro-spective	30	SL	LL	moderate	ETE using SEK	2.1	volumetry	23/30	N/R	no	12	4.37 (0.33-20)		
2015	Mihara M[80]	Retro-spective	5	lymphatic displasia	UL LL	N/R	ETE	1	volumetry	2/5	no	no	N/R	N/R		
2015	Chen WF[56]	Retro-spective	9	1 PL 8 SL	6 UL 3 LL	early moderate severe	ETE STE	14.4	LEL e UEL index	178.7±84.8 post vs 195.1±90.4 pre (p=0.003)	none	no	6	N/R		

Year	Author	Type of study	Subjects	Pathology	Field	Stage of lymph-edema	Tech-nique	mean N° anasto-mosis	end-point	Positive outcome	Comp-lica-tion	Control group	Follow-up (months)	Duration of pathology		
														<5 y	5-9 y	>=10 y
2015	Yamamoto T[57]	Prospec-tive	5	SL	LL	early moderate severe	STE	7	volumetry	251±33 post vs 271±38.5 pre (p<0.001)	N/R	no	6		N/R	
2014	Yamamoto T[58]	Retro-spective	8	SL	3 UL 5 LL	moderate severe	STE	2.6	LEL index	203.2±60.5 post vs 215.9±60.7 pre (p=0.681)	0/8	no	N/R		N/R	
2014	Ayestaray B[60]	Retro-spective	20	PL SL	8 UL 12 LL	moderate severe	ETS	5.4 (4-8)	volumetry	16/20	1/20 Hyper-trophic scar	no	12		N/R	
2014	Yoshimatsu H[87]	Retro-spective	6	SL	LL	early moderate severe	STE	7	LEL index	6/6	no	no	6		N/R	
2014	Yamamoto T[59]	Prospec-tive	12	SL	LL	moderate severe	N/R	3.3	LEL index	238.0±32.5 post vs 254.9±35.8 pre (p<0.001)	N/R	no	N/R		N/R	
2014	Yamamoto T[86]	Prospec-tive	6	SL	LL	moderate	STE	N/R	LEL index	244.0±14.6 post vs 263.5±19.4 pre (p=0.002)	N/R	no	6		N/R	
2013	Boccardo F[63]	Retro-spective	41	SL	LL	N/R	MLVA	N/R	volumetry	41/41	none	no	6		N/R	
2013	Mukenge S[50]	Retro-spective	39	PL SL	7 scrotal 32 LL	N/R	ETE ETS	N/R	volumetry	5/7 scrotal 28/32 LL	N/R	no	6		N/R	
2013	Ayestaray B [48]	Retro-spective	4	SL	head and neck	N/R	ETS	2 ± 0.82	volumetry	3/4	1/4	no	12	4 (3)	/	/
2013	Yamamoto T[89]	Prospec-tive	14	SL	LL	early moderate	25 STE with LE 23 STE	1.7	LEL index	255.9±14.1 post vs 274.9±22.2 pre (p<0.001)	N/R	no	6		5.52 (0.67-18)	
2012	Todokoro T[49]	Retro-spective	11	lymphocele	pelvis	early moderate severe	ETE STE	8.2	CT or US	11/11 stage 1-3 10/10 stage 4-5 1/1	none	no	N/R		N/R	
2012	Auba C[81]	Retro-spective	12	1 PL 11 SL	7 UL 5 LL	moderate	ETE	N/R	volumetry	8/10 5/6 UL 3/4 LL	none	no	18	2 (1)	3 (3)	5 (4)
2011	Lee BB[73]	Retro-spective	19	4 PL 15 SL	LL	early moderate severe	STE ETE	3.4	volumetry	16/19	N/R	no	12		N/R	
2011	Furukawa H[66]	Retro-spective	9	SL	UL	N/R	N/R	3.7±0.5	volumetry	7/9	N/R	no	5	4 (2)	2 (2)	3 (3)
2011	Mihara M[67]	Retro-spective	11	2 PL 9 SL	LL	early moderate	N/R	4.4 (3-7)	volumetry	9/11	none	no	23.6 (1-60)		N/R	
2011	Chang DW[68]	Retro-spective	20	SL	UL	moderate	N/R	3.5 (2-5)	volumetry	13/20	none	no	12		4.8	

Year	Author	Type of study	Subjects	Pathology	Field	Stage of lymph-edema	Tech-nique	mean N° anasto-mosis	end-point	Positive outcome	Comp-lica-tion	Control group	Follow-up (months)	Duration of pathology		
														<5 y	5-9 y	>=10 y
2010	Demirtas Y[82]	Retro-spective	78	60 PL 18 SL	LL	moderate severe	ETE	2.4±0.5	volumetry	55/78	N/R	no	13.2		7.2± 6.2	
2006	Matsubara S[61]	Retro-spective	9	SL	LL	early moderate	ETS	3.9±0.6	volumetry	6/9	none	no	6	1 (1)	4 (2)	4 (3)
2004	Koshima I[48]	Retro-spective	52	Lymphede ma	LL	moderate severe	ETE	2.1±1.2	volumetry	-41.8±31.2	N/R	no	14.5±10.2		5.3±5.0	
2003	Koshima I[51]	Retro-spective	13	PL SL	LL	N/R	ETE	N/R	volumetry	8/13	N/R	1/12	47.2±10.9	6 (3)	5 (3)	2 (2)
2000	Koshima I[52]	Retro-spective	12	PL SL	UL	N/R	ETE	4.1 (1-7)	volumetry	11/12	N/R	0/12	26.4±8.7	3 (2)	5 (5)	4 (4)
1990	O'Brien B[74]	Retro-spective	134	PL SL	102 UL 32 LL	N/R	ETE ETS	N/R	volumetry	45/90	N/R	no	6		8 (range 6-29)	

represents the combined OR of 0.07 (CI: 0.04, 0.13), at the left of the line of no-effect, meaning that fewer episodes of the outcome of interest are observed in the treatment group. Given that no part of the diamond touches the 1-line, this result is statistically significant (*Fig. 2*). Egger test (t=9.31, p<0.01) testified an important publication bias, probably due to the great heterogeneity of population, LE etiology and outcomes reported in the included papers. To overcome this limit, subgroups analysis were then performed in more homogeneous cohorts, according to anatomical district, stage, duration of pathology, and microsurgical technique adopted.

The anatomic site of lymphedema was reported in all the included studies: one article reported LE in the pelvis (51), another one scrotal LE (52), one head and neck lymphedema (50), while the others show the treatment of lymphedema of the limbs. The efficacy of LVAs was testified in patients affected by lymphedema in pelvis, in which authors reported a positive outcome in all 11 patients included in the study; similar results were shown in scrotal (5/7) and head and neck (3/4) lymphedema, although a meta-analysis wasn't possible because of the lack of articles. On the other hand, results of meta-analysis in upper limbs LE in a random model effect (I-square=70%) testified a well-defined effect of LVAs in treatment of LE (OR=0.11, 95%CI=0.05-0.26, p<0.01) (*Fig. 3*, panel a). The efficacy of LVAs was evident also in meta-analysis with a random model effect (I-square=70%) of lower limbs LE (OR=0.08, 95%CI=0.04-0.17, p<0.01) (*Fig. 3*, panel b).

The efficacy of different microsurgical techniques was evaluated in 27 papers in which the technique itself was specified. The subgroup analysis reported an efficacy for all the tested procedures: specifically, analysis using a random effect model (I-square=80%) demonstrated statistical significant improvement using both end-to-end anastomosis (OR=0.03, 95%CI=0.01-0.10, p<0.01), or side-to-end anastomosis (I-square=70%, OR=0.07, 95%CI=0.01-0.45, p=0.01); similarly, analysis using a fixed model for MLVA (I-square=0%, OR=0.53, 95%CI=0.39-0.72, p=0.04) or end-to-

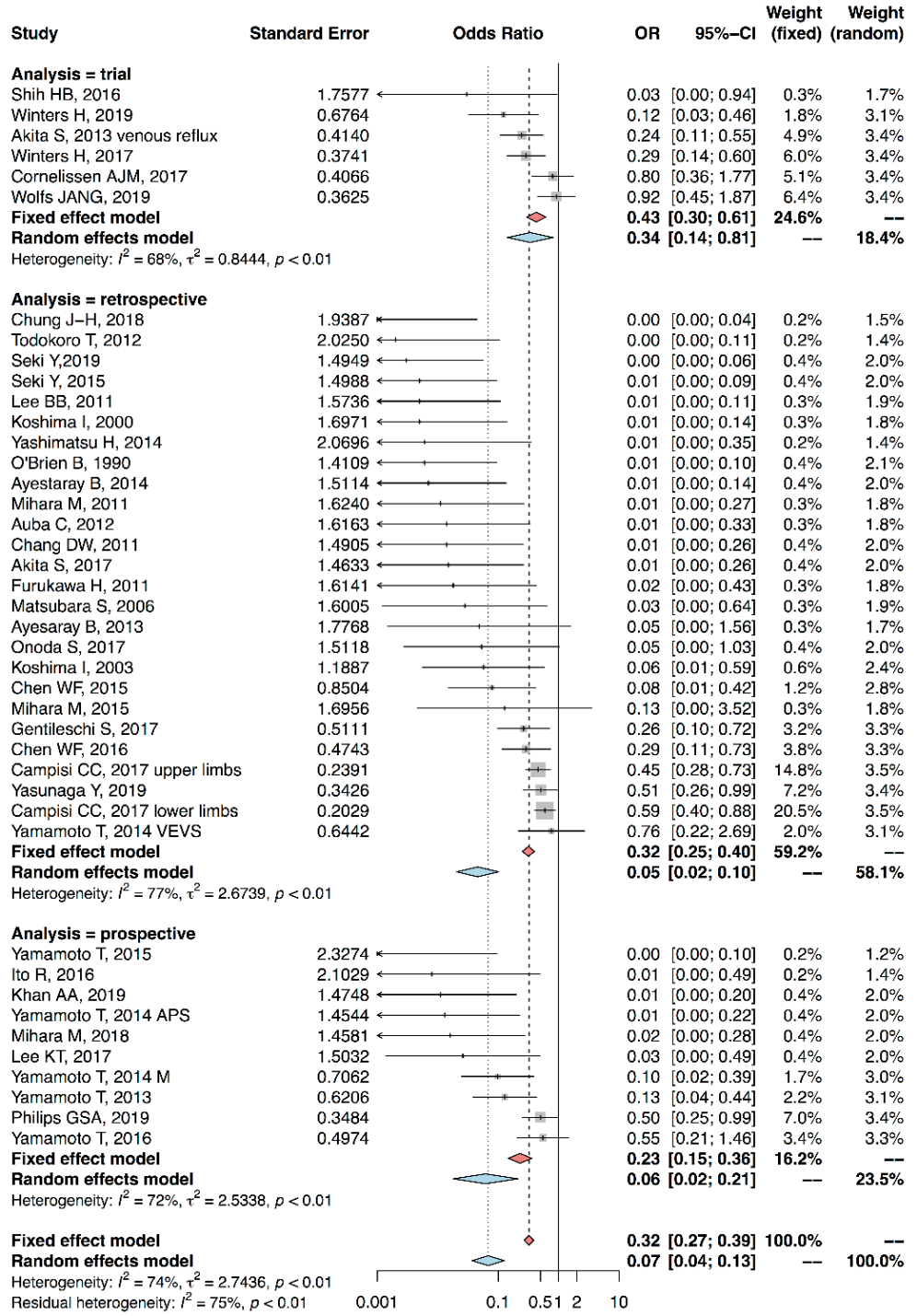

Fig. 2. Forest Plot of clinical trials and observational studies included in the meta-analysis examining the outcome efficacy of LVAs.

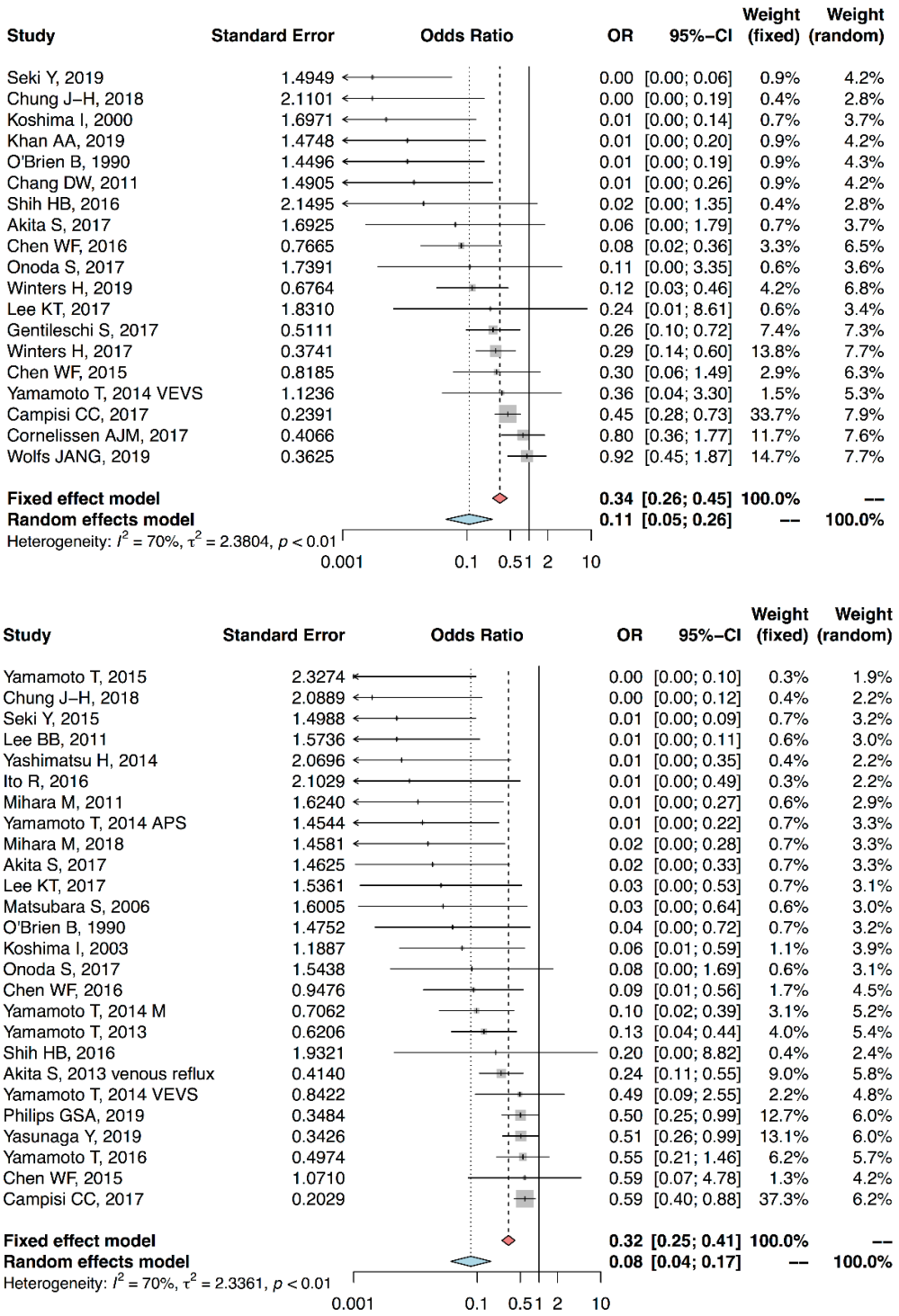

Fig. 3. Forest Plot of subgroup analysis for studies of both upper (a) and lower (b) limb lymphedema examining the outcome efficacy of LVA.

side anastomosis (I-square=0%, OR=0.02, 95%CI=0.00-0.12, p<0.01) testified the same efficacy (Fig. 4).

Information on the stage of pathology before surgery was available in 38 papers with 30 papers presenting patients affected by an early-moderate stage of pathology and the remaining 8 reporting cases of severe LE. The subgroup analysis resulted in similar efficacy for both groups with analysis using a random effect model (I-square=69%) in patients with an early-moderate stage demonstrating an OR=0.11 (95%CI=0.06-0.23, p<0.01), while the fixed model (I-square=32%) in patients with a severe stage showed an OR=0.21 (95%CI=0.07-0.61, p<0.01) (*Fig. 5*).

Similarly, the subgroup analysis on duration of pathology demonstrated the efficacy of LVAs in the treatment of LE independently from this variable. The fixed effect model (I-square=0%) showed an OR=0.06 (95%CI= 0.02-0.17, p<0.01) in patients with a surgical treat-ment within 5 years from diagnosis, while the fixed effect model (I-square=0%) in patients treated from 5 to 10 year from diagnosis showed an OR=0.02 (95%CI=0.01-0.07, p<0.01). In addition, subjects who had received microsurgical treatment after 10 years from diagnosis showed a fixed effect model (I-square=0%) of OR=0.02 (95%CI= 0.01-0.07, p<0.001) (*Fig. 6*).

DISCUSSION

We presented an updated overview and meta-analysis of the available literature about the efficacy of LVAs for the treatment of lymphedema. Although previous systematic reviews have been produced on this topic, the majority of them focused attention on specific site (12,92) or specific etiology of lymphedema (28,93). More consistent data are available for upper limb lymphedema secondary to breast cancer operation, and meta-analysis regarding effectiveness of LVAs in this pathology have been already performed. Results of these studies demonstrated a great heterogeneity of outcomes in volume/circumference reduction, while an improvement on quality of life, in particular in early-stage lymphedema, was confirmed (28). Less data are available for microsurgical treatment of lymphedema in other anatomical sites and studies on this topic highlighted the need for additional prospective studies (92,94,95).

The only comprehensive systematic review and meta-analysis concerning efficacy of micro-surgical techniques for the treatment of LE was performed by Basta et al (26). This study addressed the advantages and disadvantages of the various surgical techniques for the treatment of peripheral lymphedema, comparing results of 22 studies in which LVAs were used with 5 studies regarding lymph node transfers. This meta-analysis presented limitations related to the heterogeneity of the populations included into the subgroups as well as bias related to the comparison of lymphovenous shunt procedures with vascularized lymph node transfer and related to the inclusion into the lymphaticovenous anastomosis group, articles where lymph vessel transplantations were reported (96). Our meta-analysis included only studies reporting anastomosis between lymphatic and venous systems as a treatment for lymphedema. Subgroup analysis was performed to analyze more homogeneous populations, avoiding head-to-head comparison of different surgical procedures, different anatomical sites, and duration of pathology or stage of lymphedema.

Among the articles included in our meta-analysis, only 6 clinical trials were available, including a total of 144 patients. Four studies analyzed the efficacy of LVAs in secondary lymphedema in early or moderate stage of upper limbs using volumetry or UEL index as outcomes (29-32). Shih et al included 5 subjects with primary or secondary LE in moderate stage of upper or lower limbs (33), while Akita et al (34) compared the efficacy of side-to-end anastomosis alone and with vein valvuloplasty in lower limb lymphedema, showing results separately in patients with and without venous reflux at lymphography. Although meta-analysis results showed a statistically significant improvement of outcomes after performing LVAs, the low number of subjects included and the difference among studies related to follow-up, anatomical site, stage and duration of pathology, kind and

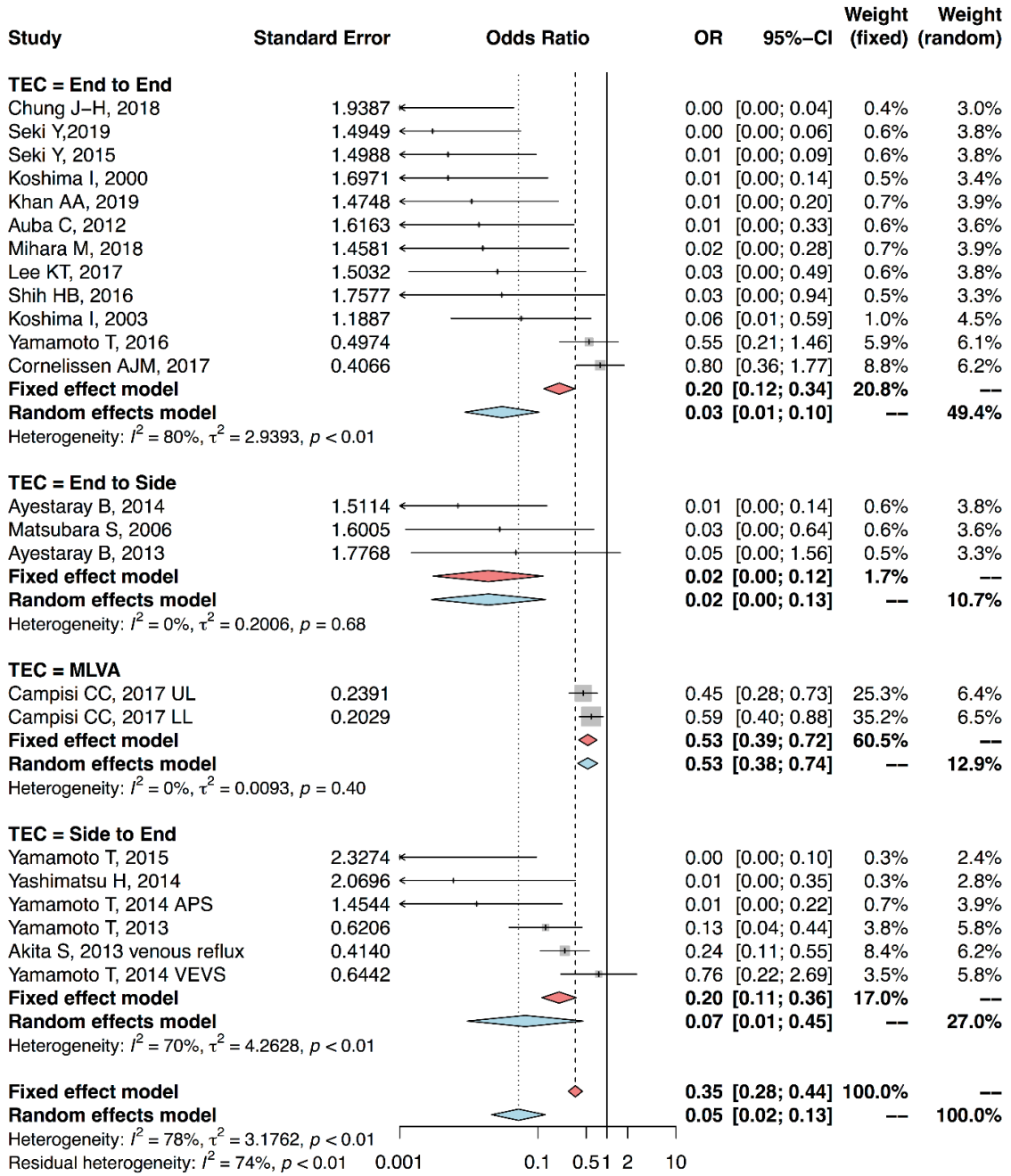

Fig. 4. Forest Plot of pooled results of all studies classified according to the surgical technique. The subgroup analysis reported an efficacy for all the tested procedures, either when using the fixed (end-to-end, side-to-end subgroups) or the random (MLVA, end-to-side) models.

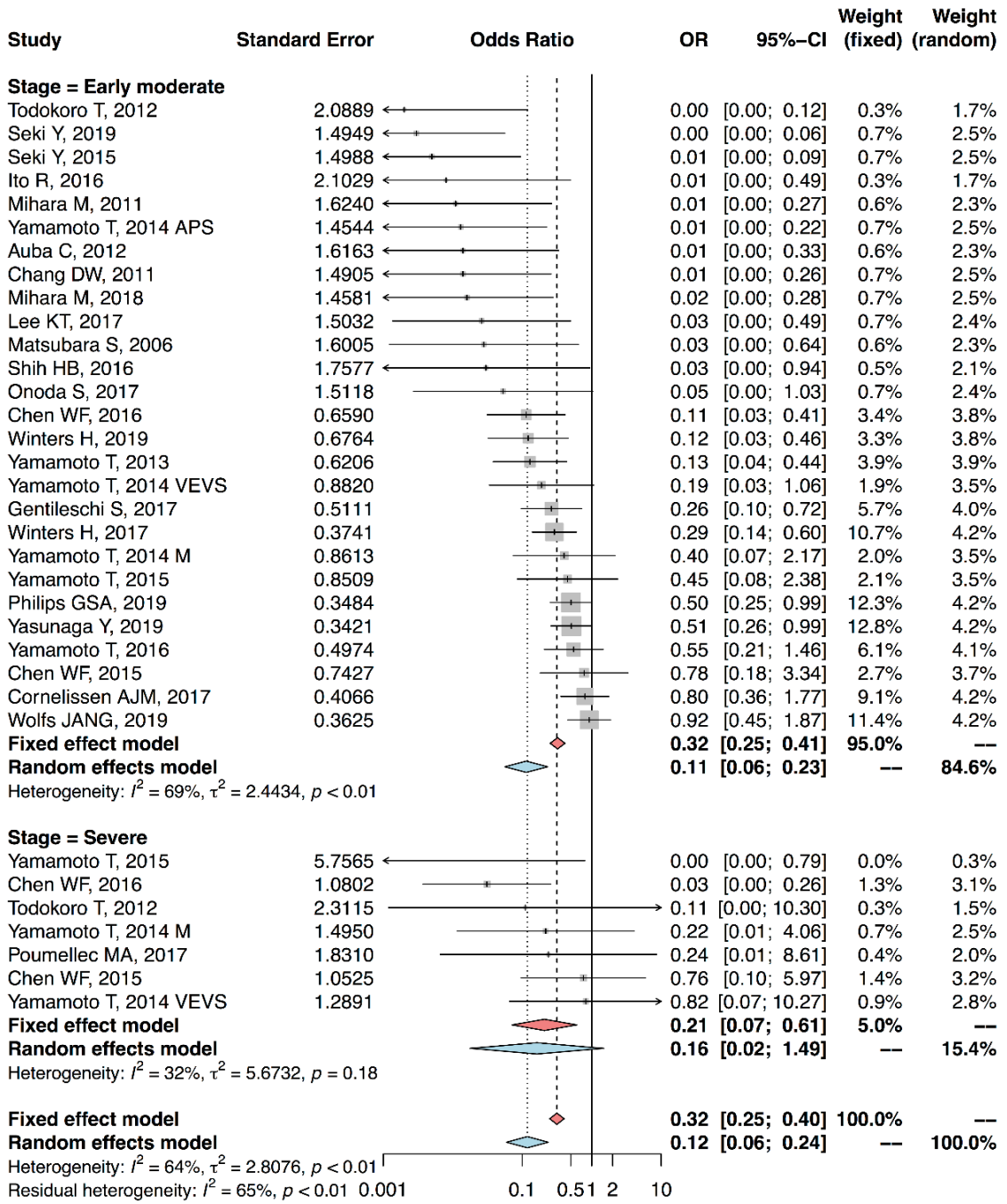

Fig. 5. Forest Plot of the pooled results of all studies classified according to the stage of pathology as early, moderate, or severe. Analysis using a random effect model (I-square=69%) in patients with an early-moderate stage showed an OR=0.11 (95%CI=0.06-0.23, p<0.01), while the fixed model (I-square=32%) in patients with a severe stage showed a OR=0.21 (95%CI=0.07-0.61, p<0.01). This demonstrates efficacy of LVAs in the treatment of LE is independent from the clinical stage of the lymphedema.

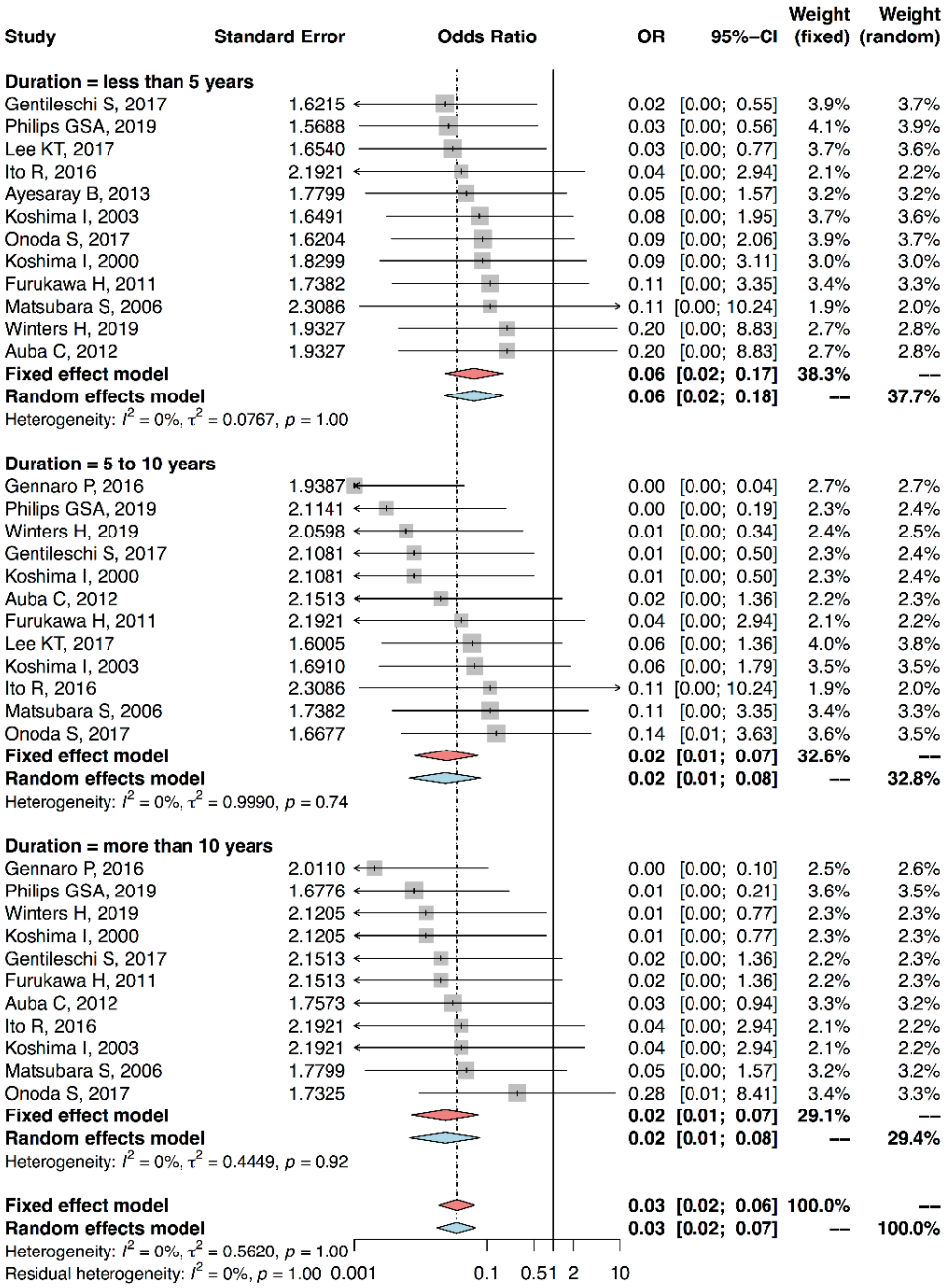

Fig. 6. Forest Plot of the pooled results of all studies classified according to the duration of the pathology for less than 5 years, from 5 to 10 years, and more than 10 years. Odds ratios are all smaller than one, with only some of the studies being not statistically significant at a 5% level. Data exhibit small to no heterogeneity between each trial, making the fixed-effect model the best fit. Values of I-squared around 0 and p-values higher than 0.05 for each subgroup demonstrate that there is strong evidence for a uniform result. Subgroups are also pooled according to a fixed-effect model with the red diamond indicating a combined OR = 0.03 with CI: 0.02 - 0.06. This result is statistically significant, as 1 is not included in the CI.

presentation (mean, difference of means, and percentage of subjects with positive outcomes) of endpoints did not allow an unbiased interpretation of results.

The inclusion of low risk of bias observational studies was performed to enlarge the cohort of study. MINOR index was used to select 42 high quality studies among 56 observational articles. The majority of studies confirmed a clear improvement in objective measurements, score of questionnaires or subjective symptoms after LVA, regardless of etiology, anatomical sites, surgical technique, stage or duration of LE. Results of the comprehensive meta-analysis performed in the overall cohort testified a strong efficacy of LVAs in treatment of LE, even if analysis was characterized by an important publication bias.

In relation to the anatomical field affected by LE, efficacy of LVAs was investigated in head and neck, pelvis, and scrotal lymphedema, but the presence of single studies on these topics did not allow the performance of a meta-analysis. On the contrary, a subgroup analysis for upper and lower limbs revealed a similar effectiveness of LVAs in treatment of lymphedema in both these fields, confirming the findings of several previous studies (76,84,85).

Our investigation revealed great heterogeneity in the surgical procedure itself. The mean number of performed anastomosis ranged between 1 and 14.4, but there is no reported consensus on the optimal number of anastomoses required to yield a significant reduction in lymphedema. However, the importance of the number of anastomosis was debated: some authors emphasized its importance in lymphedema treatment (8,41), while others did not specify the number of anastomoses, giving more importance to the adopted microsurgical technique (53,76,97). For this reason, we preferred to perform a subgroup analysis according to the reported technique (end-to-end, end-to-side, side-to-end anastomosis or multiple-lymphatic-venous-anastomosis). Results of this analysis demonstrated efficacy of these surgical procedure in reduction of lymphedema.

Some authors reported a better effect of LVAs in patients with low-moderate lymphedema (28), while our subgroup analysis on stage of lymphedema at diagnosis showed a statistically significant reduction of LE both in low-moderate and in severe lymphedema cases. Moreover, the efficacy of LVAs was demonstrated in a subgroup analysis independently from the duration of lymphedema.

The principal limitation of the current study is the risk of bias within studies. In fact, the level of evidence of the majority of studies was low, because of the lack of control groups in most studies (including trials) and the presence of a small sample size. True operative control groups are not possible or ethical for studies of LVA. Furthermore, information about inclusion of consecutive patients and experience of surgeons were often omitted, and some studies showed an insufficient follow-up period to evaluate long-term effect of LVAs. Thus, although we applied the MINOR index score to exclude the high risk of bias studies, the chance of selection bias could not be dismissed. Studies such as this meta-analysis on the LVA procedure in its current form is not something that is easily conducive to meta-analysis. There are many uncontrolled variables: primary vs secondary lymphedema, different severity of disease, varying surgeons' technical maturity/proficiency, varying quality of lymph vessels used to create LVA, varying number of LVA created per surgery, varying anastomotic configuration used in LVA, varying postoperative care, varying use of compression following surgery, and varying modalities used to track outcomes (volume, ICG lymphography, circumference measurement, bioimpedance), etc. Despite these limitations, improvement in subjective and/or objective outcomes was presented in the majority of the evaluated studies and a statistically significant effect of LVAs for the treatment of LE was demonstrated both in overall and in subgroup analysis. Specifically, effectiveness of LVAs was proven even when subgroup analysis was performed for stage, duration of pathology, anatomical site of lymphedema, or type of microsurgical procedure. Gaps among primary outcomes and heterogeneity in patients' characteristics

reported into the studies could be a critical source of bias for a definitive confirmation of effectiveness of LVAs for the treatment of LE. Considering the potential for bias and limitations in study design, retrospective studies such as those reviewed represent the best information we currently have to investigate and show effectiveness for operations such as LVA.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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