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Review

Risk-of-bias assessment of the randomized clinical trials and systematic reviews on surgical treatments for breast cancer-related lymphedema: A mapping review

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KEYWORDS
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Risk-of-bias assessment;
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Abstract *Background:* Breast cancer treatment is the principal cause of lymphedema in the upper extremities. Breast cancer-related lymphedema (BCRL) treatments were previously based on conservative therapy; surgical treatments are alternative options that could be highly beneficial, especially for patients who are not responsive to conservative therapy. The main aim of this study was to describe and critically assess the risk of bias of randomized clinical trials (RCTs) and systematic reviews (SRs) on surgical treatment for BCRL.
Methods: We conducted an evidence mapping review according to the methodology proposed by Global Evidence Mapping (GEM). An update was done for our previous systematic search in MEDLINE, EMBASE, CENTRAL (Cochrane), and Epistemonikos from the year 2000 onward. We assessed the risk of bias for the RCTs and SRs using the RoB-2 and ROBIS tools, respectively.
Results: Two surgical RCTs and eight SRs were found among the 47 surgical studies that met the eligibility criteria. The overall risk-of-bias assessments of these studies were rated as some concerns (six outcomes) and high risk (three outcomes) for the measured outcomes among the RCTs and as a high risk of bias (five studies) and low risk (three studies) for the included SRs.

Abbreviations: BCRL, Breast cancer-related lymphedema; RCTs, Randomized control trials; SRs, Systematic reviews; GEM, Global Evidence Mapping; LVA, lymphaticovenular anastomosis; VLNT, vascularized lymph node transfers

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Conclusions: The overall evidence in the literature on surgical treatment for BCRL is low, as there are few published RCTs and SRs, and the risk-of-bias assessment for the majority was rated as high risk of bias or with some concerns. High-quality studies are needed to improve evidence-based decision-making by surgeons and patients.

Contents

Background

Lymphedema is defined as the abnormal collection of lymphatic fluid within subcutaneous structures. In advanced countries, damage to the lymphatic system due to cancer or its treatment is the most common cause of secondary lymphedema. In the upper extremities, breast cancer treatment is the principal cause of lymphedema.[1]

According to the literature, the incidence of breast cancer-related lymphedema (BCRL) depends on the type of axillary treatment; axillary lymph node dissection results in lymphedema in up to 53.5% of cases, and sentinel lymph node biopsy results in lymphedema in up to 15.8% of cases.[2,3] Other risk factors that aggravate the condition are adjuvant radiation, docetaxel chemotherapy, infection, iatrogenic injury, and obesity. Consequently, developing lymphedema leads to a chronic condition that is usually challenging to treat.[4-10]

BCRL treatment options have long been based on conservative therapy, such as compression garments/bandages and manual lymph drainage. These conservative measures are mainly aimed at alleviating lymphedema symptoms without curative intent. Surgical treatments are alternative options that could be highly beneficial, especially for patients who are not responsive to standard conservative therapy, which includes mostly excisional and reconstructive techniques.[11-13]

Both excisional and reconstructive surgical approaches have been described in the treatment of BCRL. Excisional or nonphysiological procedures include the Charles operation and liposuction. These strategies are most often performed in a later stage of disease when there are no remaining functional lymphatic vessels.[14,15] Reconstructive options, on the other hand, are physiological operations that aim to restore lymphatic flow to aid in lymphatic drainage from the affected extremity. These include lymphaticovenular anastomosis (LVA) and vascularized lymph node transfers (VLNT), which currently have promising results for treating the early stages of lymphedema.[16-20]

Our team previously conducted a mapping review on all treatments for BCRL, without assessing the risk of bias of the included studies, and did not focus on surgical treatment.[21] Therefore, based on our previous mapping findings and the limited knowledge of the quality of the available research, the main aim of this study was to describe and critically assess the risk of bias of randomized clinical trials (RCTs) and systematic

reviews (SRs) on surgical treatment for BCRL. Other objectives are to identify gaps in knowledge, enumerate the limitations and constraints that exist in this field, and provide recommendations for future research needs.

Methods

An evidence mapping review was conducted according to the methodology proposed by Global Evidence Mapping (GEM)[22] and adhered to the Preferred Reporting Items for Systematic Reviews and Metanalysis (PRISMA)—Extension for Scoping Reviews.[23] All methods were specified a priori in a protocol *(available on request)*.

Eligibility criteria

We updated our search strategy based on our previous mapping work.[21] It was built on the population, intervention, comparison, outcome, and type of study (PICOT) framework to formulate the eligibility criteria.[24] We considered eligible patients (older than 18 years) with BCRL. Those who had either surgical or nonsurgical treatments for BCRL were initially eligible. Due to the nature of this study, we included studies with any type of comparison and those without a comparison group. All outcomes were eligible for this mapping review. This mapping review included all published studies in full text from the year 2000 onward, including SRs with or without metanalysis, RCTs, quasi-experimental clinical trials, and observational studies (prospective and retrospective studies), to have a broader look at the available evidence in this field. When several studies published on the same topic and by the same team were identified, we considered the most recent publication. We excluded animal studies, in vitro studies, single case reports, case series, letters to the editor, narrative reviews, studies including different types of edemas or mixed edema, studies including less than 10 patients or reviews with fewer than three studies, and studies addressing other than treatment of BCRL or addressing both prevention and treatment together.

Search strategy

The search strategy was conducted in MEDLINE (via PubMed) and EMBASE (via Ovid), Epistemonikos, and the Cochrane Library from the year 2000 onward. A search algorithm was designed, including a combination of controlled vocabulary, the use of MeSH descriptors, free-text term, and thesaurus term when available, adapting it accordingly for each database, with no language restriction, and no gray literature was searched. The last update was done on 22nd of October 2021 *(the search strategy is attached as* Supplementary material*)*.

Study selection and data extraction

The studies were retrieved by titles and abstract and were uploaded to *Mendeley* and then managed with *Rayyan QCRI software*. After removing duplicates, three reviewers (AMA, AIS, and LVC) independently screened all titles and abstracts, with each article screened by at least two reviewers. Afterward, full-text screening was done independently by the same three reviewers who confirmed eligibility based on the inclusion and exclusion criteria. Disagreements between the two reviewers were resolved mainly by the third reviewer. At this step, the reasons for exclusion were recorded.

For each study, data extraction was conducted separately by the two reviewers in a predesigned spreadsheet (AMS and AIS). The results were then compared, and in case of disagreement, the third reviewer (LVC) acted as a referee to reach consensus. All extracted data were recorded in a data extraction sheet using *Microsoft Excel*.

Assessment of risk of bias

Methodological assessment of risk of bias was independently assessed by three reviewers (AMA, SAR, and JBK). Each article was assessed blindly by two reviewers (AMA and SAR), and any disagreement in the results was resolved by the third reviewer (JBK). The risk-of-bias assessment was done only for high evidence studies addressing the surgical intervention (SRs and RCTs); for that reason, we did not consider the necessity of assessing the risk of bias for the nonrandomized studies.

For RCTs, the Cochrane risk-of-bias tool for randomized trials—version 2 (RoB-2) was used for the assessment of each outcome in the RCTs.[25] The domains included in the RoB-2 are as follows: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The risk-of-bias judgment for the RCTs was then assigned to one of three levels to each domain: low risk of bias, some concerns, or high risk of bias.[25]

SRs were assessed by the ROBIS tool.[26] The tool is completed in three phases: phase 1 consists of assessing the relevance *(this was optional and not applied in this article)*; phase 2 consists of identifying concerns with the review process, covering four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings; and phase 3 consists of judging the risk of bias and assessing the overall risk of bias in the interpretation of review findings and whether this considered limitations identified in any of the phase 2 domains. The risk-of-bias judgment for SRs is then assigned as low risk, high risk, or unclear concern.[26]

Data synthesis and analysis

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*,[27] a flow chart for the whole process of study selection was elaborated based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P diagram).[28] The obtained results were presented in a narrative and visual format using tables, figures, and a bubble plot. The bubble plot was created to illustrate the study designs in relation to their risk-of-bias assessment; the color of the figures indicated the study design (RCTs or SRs); the size of the figure reflected the number of population or number of studies in the included RCTs and SRs, respectively; and their positions in the graph were based on their overall risk-of-bias assessment.

The analysis of the selected studies was divided into two parts: first, a general mapping presentation of the included

surgical studies included in this review, providing a more detailed description of the available SRs and RCTs and, second, an assessment of the risk of bias of the RCTs and SRs addressing the surgical intervention, using the RoB-2 and ROBIS tool, respectively. Due to the large amount of data collected from the eligible studies, we focused mainly on the important results that contributed to the objectives of this article.

Results

Search results

The flowchart of the study selection of the baseline research and update is shown in Figure 1. The search after the last update yielded a total of 5663 studies. After removing 1919 duplicates, we proceeded with 3744 studies to screen by title and abstract. In total, 3355 studies were excluded because they were unrelated to the review's main topic. Then, a full-text review of 389 studies was conducted. After the resolution of discrepancies by consensus between researchers, we excluded 110 studies. Similarly, seven studies in which the full text was missing were also excluded from the descriptive analysis. Finally, a total of 272 studies were included, of which 225 were nonsurgical studies and 47 studies addressed the surgical treatment for BCRL. Of these surgical studies, only two RCTs and eight SRs were critically assessed for the purpose of this mapping review.

The main reason for excluding studies was that the articles were published as conference abstracts (41). Other reasons included foreign languages (other than English and Spanish) (19), wrong population (18), wrong design (10), wrong objective (7), published protocol (3), case report (1), editorial reply (1), literature review (1), population < 10 patients (7), reviews including < 3 studies (2), and the aforementioned missing full text (7).

Surgical studies on treatment for BCRL

There were 47 studies addressing surgical intervention (39 primary studies and eight secondary studies), which included 15 experimental studies (13 quasi-experimental clinical trials and two RCTs), 24 observational studies (14

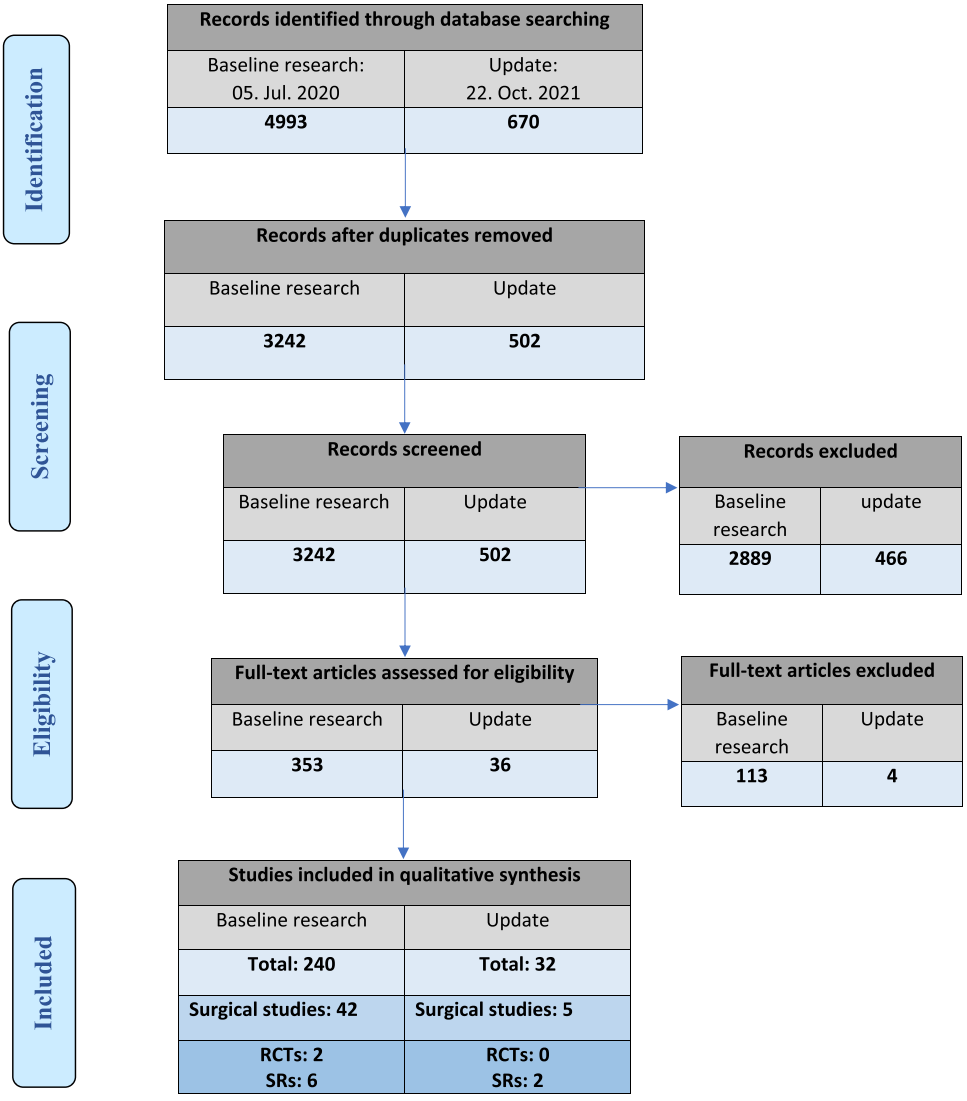

Figure 1 PRISMA flow diagram and selection process of studies on surgical treatments for BCRL (baseline research and update).

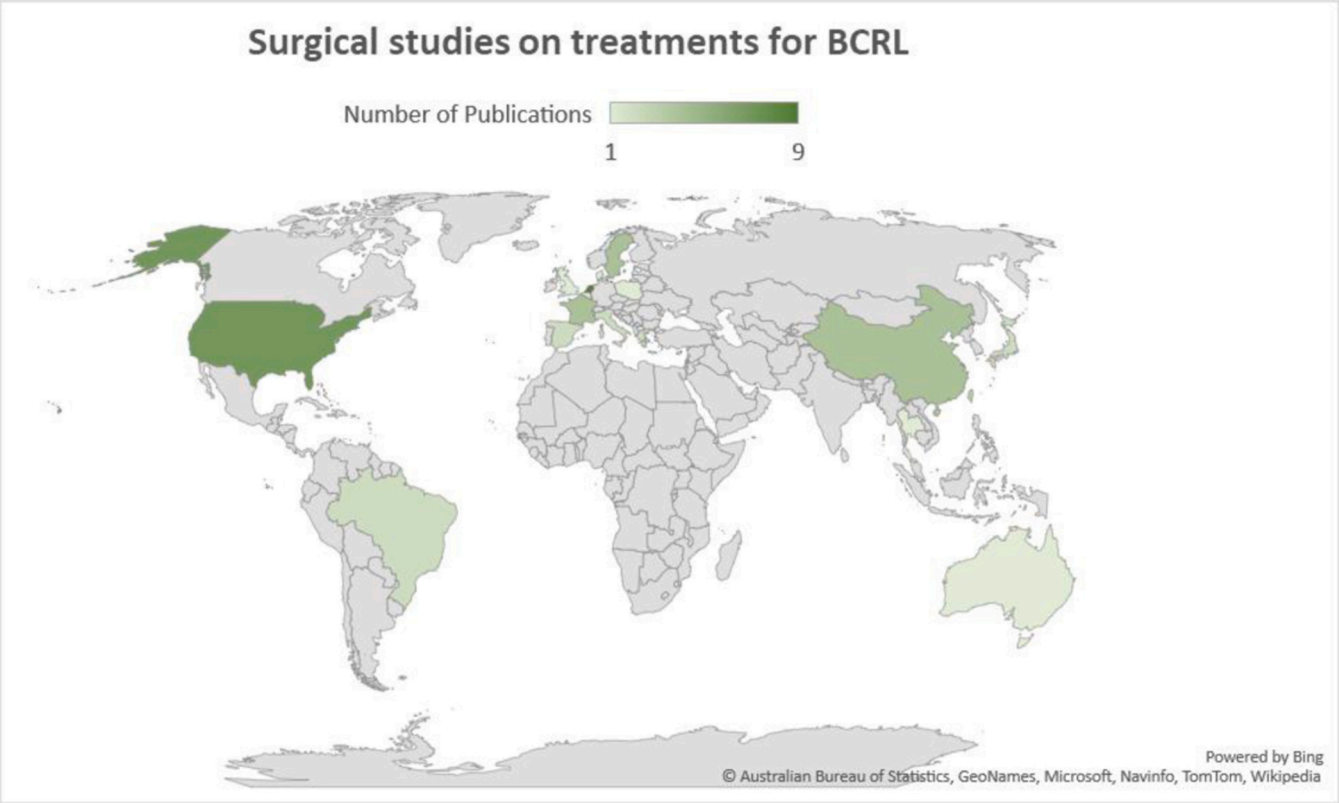

Figure 2 Geographic distribution of total published studies on surgical treatments for breast cancer-related lymphedema (BCRL).

prospective cohorts and 10 retrospective cohorts), and eight SRs with and without meta-analysis.

These published studies were geographically distributed among the following countries: the Netherlands had the highest number of publications (9), followed by the United States of America (7), France (4), Sweden (4), China (4), Taiwan (3), Japan (2), Brazil (2), Spain (2), Italy (2), Greece (2), the United Kingdom (1), Belgium (1), Denmark (1), Poland (1), Thailand (1), and Australia (1) (see Figure 2).

RCTs' characteristics

The first RCT, by *Dionyssiou* et al.,[29] was conducted in Greece and compared the VLNT to the conservative measurements, and the second RCT, by *Van Mulken* et al.,[30] conducted in the Netherlands, compared the robotic versus the manual LVA. Both RCTs assessed different outcomes. *Dionyssiou* et al. mainly assessed three patients' outcomes: upper limb volume, infection episode, and subjective symptoms using the subjective analog scaling system.[31] *Van Mulken* et al. assessed various outcomes, including four patients' outcomes: the daily use of compression garment, the need for manual lymphatic drainage, the arm circumference using the mean upper extremity lymphedema index (mean UEL index), and quality of life using a validated health questionnaire, the mean Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF).[32] Furthermore, this RCT assessed two surgeons' related outcomes: the duration of surgery and quality of anastomosis using the Structured Assessment of Microsurgery Skills (SAMS)[33] and the University of Western Ontario Microsurgical Skills Acquisition Instrument (UWOMSA) scoring[34] (see Table 1).

SRs' characteristics

Among the eight SRs on surgical treatments for BCRL,[35-42] three SRs performed quantitative assessment (metanalysis).[36,37,41] Three were conducted in the Netherlands,[35,36,41] three in the United States of America,[37,39,40] one in Greece[42], and one in Brazil.[38] There was heterogeneity in the included study designs, mainly among case series, case reports, prospective studies, retrospective studies, and nonrandomized trials. Two SRs did not mention the type of the included study design. The range of included studies was from five to 17 studies. One SR included a total of 67 studies, but only 13 were described in the qualitative synthesis, which were addressed in our results.[42] These SRs addressed different surgical interventions, such as VLNT,[38,41] LVA,[3] both VLNT and LVA,[35,42] or combined treatment such as autologous reconstruction with VLNT[37,40] or lipoaspiration with VLNT.[39] The only common outcome that was measured in all included SRs was limb volume, although different outcomes were also assessed, such as subjective symptoms, quality of life, infectious episodes, complications, and discontinuation of conservative treatments (see Table 1).

Matrix of evidence

We created a matrix of evidence to show the SRs linked to the included primary studies and the overlaps of the primary studies between these SRs. Because there was

Table 1 Characteristics of the included SRs and RCTs on surgical treatments for BCRL.

Randomized Clinical Trials

Number	Study ID	Country	Title	N. of population	Intervention	Comparison	Measured outcomes	Reported results
1	Dionyssiou et al.[29]	Greece	A randomized control study of treating secondary stage II breast cancer-related lymphoedema with free lymph node transfer	36 patients	Vascularized lymph node transfer (VLNT), physiotherapy and compression	Physiotherapy and compression alone	1. Upper limb volume 2. Infection episodes 3. Subjective symptoms	Results favor toward intervention
2	Mulken et al.,[30]	Netherlands	First-in-human robotic supermicrosurgery using a dedicated microsurgical robot for treating breast cancer-related lymphedema: a randomized pilot trial	20 patients	Robot-assisted supermicrosurgical lymphaticovenous anastomosis (LVA)	Manual supermicrosurgical lymphaticovenous anastomosis (LVA)	1. Daily use of compression garment 2. Manual lymphatic drainage 3. Mean lymph - ICF 4. Mean UEL Index 5. Duration of surgery 6. Quality of anastomosis	No difference between both comparative groups

Systematic Reviews

Number	Study ID	Country	Title	N. of studies	Intervention	Metanalysis	Measured outcomes	Reported results
1	Penha et al.[35]	Netherlands	Microsurgical techniques for the treatment of breast cancer-related lymphedema: a systematic review	10 studies (Case series)	Lymph node transplantation (VLNT), lymph vessels transplantation, or derivative lymphatic surgery (LVA).	No	1. Limb volume or circumference 2. Lymph flow by lymphoscintigraphy 3. Symptoms relief 4. Discontinuation of post operative conservative therapy 5. Complications	Consist positive finding with regards to limb volume reduction and limited complications
2	Cornelissen et al.[36]	Netherlands	The effect of lymphaticovenous anastomosis in breast cancer-related lymphedema: A review of literature	15 studies (10 prospective and 5 retrospective studies)	Lymphaticovenous anastomosis (LVA)	Yes	1. Limb volume or circumference 2. Quality pf life	Heterogeneous results in volume/ circumference reduction and improvement of quality of life in most of the studies

(*continued on next page*)

Table 1 (*continued*)

3	Siotos et al.[37]	USA	Delayed breast reconstruction on patients with upper extremity lymphedema a systematic review of the literature and pooled analysis	8 (7 case series and 1 case report)	Delayed autologous breast reconstruction with or without lymph node transfer (VLNT)	Yes	Any outcomes reported	The VLNT composite of the autologous breast reconstruction might be the largest contributing factor leading to lymphedema improvement
4	Ribeiro et al.[38]	Brazil	Lymph node transplantation in the management of post-mastectomy lymphedema: a systematic review with metanalysis	10 studies	Autologous lymph node transplantation (VLNT)	No	Limb volume	There is a considerable reduction in limb volume higher than 50%
5	Forte et al.[39]	USA	Lipoaspiration and lymph node transfer for treatment of breast cancer-related lymphedema: a systematic review	5 studies (3 prospective studies, 1 case series and 1 case report)	Lipoaspiration and venous lymph node transfer (VLNT)	No	Limb volume	Meaningful volume reduction was achieved in all cases, patients who underwent lymph node transfer first followed by lipoaspiration appear to have the best results
6	Forte et al.[40]	USA	Lymph node transfer combined with deep inferior epigastric perforators and transvers rectus abdominis myocutaneous procedures	6 studies	Autologous breast reconstruction with Lymph node transfer (VLNT)	No	1. Limb volume or circumference 2. Symptoms relief	Most of the studies demonstrated subjective symptoms improvement, also good results with limb circumference size and infectious episodes

(*continued on next page*)

Table 1 (*continued*)

7	Winter et al.[41]	Netherlands	A systematic review and metanalysis of vascularized lymph node transfer for breast cancer-related lymphedema	17 studies (non-randomized trials)	vascularized lymph node transfer (VLNT)	Yes	1. Limb volume 2. Quality of life 3. Infectious episodes 4. Complication 5. Discontinuation of compression garment	Evidence from all studies suggest that VLNT reduce volume up to 40%, although in few studies it has also some affect in improving quality of life, infectious episodes, the use of compression garment and complication rate
8	Gasteratos et al.[42]	Greece	Microsurgical techniques in the treatment of breast cancer-related lymphedema: a systematic review of efficacy and patient outcomes	67 studies, but only 13 studies addressed in the synthesis (6 Prospective studies, 3 retrospective studies, 2 RCTs, 1 SRs and 1 narrative review)	LVA, LYMPHA technique and VLNT	No	1. All patients' outcomes 2. Efficacy of microsurgical techniques 3. Complications	Microsurgical techniques can be beneficial to many patients with BCRL

*SRs: Systematic reviews, RCTs: Randomized clinical trials, BCRL: Breast cancer-related lymphedema, LVA: Lymphatic venous anastomosis, VLNT: Vascularized lymph node transfer, LYMPHA: Lymphatic microsurgical preventive healing approach.

heterogenicity in the objectives and in the assessed surgical interventions of the SRs, we found that a total of 55 primary studies were included in all SRs, but only 19 studies overlapped between two or more SRs. *Saaristo* et al.[43] overlapped in five SRs: *Chang* et al.[44] overlapped in four SRs; *Lin* et al.[18], *Becker* et al.[17], *Damstra* et al.[45], *De Brucker* et al.[46], and *Montag* et al.[47] overlapped in three SRs; and the rest overlapped in two SRs (see Table 2).

Risk-of-bias assessment for RCTs

Based on the RoB-2, nine outcomes were assessed in the two included RCTs.

Three outcomes were assessed in the RCT of *Dionyssiou* et al.[29] Two were rated as having a high risk of bias (limb volume and subjective symptoms) and one had some concerns (infection episodes). Three RoB-2 domains, 'the

Table 2 The overall SRs on surgical treatments for BCRL: the overlaps matrix of their included studies and their overall risk of bias assessment.

Systematic Reviews / Included Studies	Penha, et al. 2013	Cornelissen, et al. 2018	Siotos, et al. 2018	Ribeiro, et al. 2019	Forte, et al. 2019	Forte, et al. 2020	Winter, et al. 2021	Gasteratos, et al. 2021¶
Lin et al, 2009	■			■			■	
Becker et al, 2008	■			■				
Becker et al, 2006	■			■			■	
Saaristo et al, 2012	■		■	■		■	■	
Baumeister et al, 2002	■							
Weiss et al, 2002	■							
Furukawa et al, 2011	■							
Chang et al, 2010	■	■	■					■
Damstra et al, 2009	■	■						■
Yamamoto et al, 2003	■							
Koshima et al, 2000		■						■
Auba et al, 2010		■						
Mihara et al, 2012		■						
Ayestaray et al, 2013		■						
Chang et al, 2013		■						■
Chen et al, 2015		■						
Torrisi et al, 2015		■						
Gennaro et al, 2016		■						
Cornelissen et al, 2018		■						
Engel et al, 2017		■						
Lee et al, 2017		■						
Poumellec et al, 2017		■						■
Winter et al, 2017		■						■
De Brucker et al, 2016			■			■	■	
Chen et al, 2014			■			■		
Blanchard et al, 2012			■					
Lee et al, 2012			■					
Khan et al, 2011			■					
Fosnot et al, 2015			■					
Leppapuska et al, 2019					■			
Agok et al, 2018					■			
Cook et al, 2016					■			
Nicoli et al, 2015				■	■			
Granzow et al, 2014					■		■	
Dancey et al, 2013						■		
Nguyen et al, 2015						■	■	
Montag et al, 2019				■		■	■	
Cheng et al, 2013				■				
Dionyssiou et al, 2016				■			■	
Gratzon et al, 2017				■			■	
Liu et al, 2018				■			■	
Akita et al, 2017							■	
Aljaaly et al, 2018							■	
Engel et al, 2017							■	
Gharb et al, 2011							■	
Maruccia et al, 2019							■	
Patel et al, 2014							■	
Yang et al, 2017							■	
Jorgensen et al, 2018								■
Feldman et al, 2015								■
Boccardo et al, 2019								■
Hahamoff et al, 2019								■
Winter et al, 2019								■
Mulken et al, 2020								■
Becker et al, 2012								■

¶ Gasteratos et al.,[42]; 67 studies were included in the study, but only 13 studies were addressed in the study synthesis.
$ The colors of the systematic review reveal the risk of bias assessment, where: green is low risk of bias and red high risk of bias.
*SRs: Systematic reviews, BCRL: Breast cancer-related lymphedema.
The included SRs, the overlaps matrix and their risk of bias assessment.

Table 3 RoB-2 assessment (per outcome) of the randomized clinical trials on surgical treatments for BCRL.

RCTs	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Dionyssiou et al.[29]	LNT + Physiotherapy	Physiotherapy	Limb volume	1	!	-	+	!	+	-
Dionyssiou et al.[29]	LNT + Physiotherapy	Physiotherapy	Infection episodes	1	!	!	+	!	+	!
Dionyssiou et al.[29]	LNT + Physiotherapy	Physiotherapy	Subjective symptoms	1	!	!	+	-	+	-
Mulken et al.,[30]	Robot-assisted LVA	Manual LVA	Daily use of compression garment	1	!	!	+	+	+	!
Mulken et al.,[30]	Robot-assisted LVA	Manual LVA	Manual lymphatic drainage	1	!	!	+	+	!	!
Mulken et al.,[30]	Robot-assisted LVA	Manual LVA	Mean lymph - ICF	1	!	!	+	+	+	!
Mulken et al.,[30]	Robot-assisted LVA	Manual LVA	Mean UEL index	1	!	!	-	+	+	-
Mulken et al.,[30]	Robot-assisted LVA	Manual LVA	Duration of surgery	1	!	!	+	+	+	!
Mulken et al.,[30]	Robot-assisted LVA	Manual LVA	Quality of the anastomosis	1	!	!	+	+	+	!

¶ **Domains explanation** D1: Randomization process, D2: Deviation from intended intervention, D3: Missing outcome data, D4: Measurement of the outcome, and D5: Selection of the reported results.
$ **The colors indication** Green: Low risk, Yellow: Some concerns, Red: High risk of bias.
* BCRL: Breast cancer-related lymphedema, LVA: Lymph-venous anastomosis, LNT: Lymph node transfer, Lymph ICF: Lymphedema Functioning, Disability and Health Questionnaire, and UEL Index: Upper extremity lymphedema index.

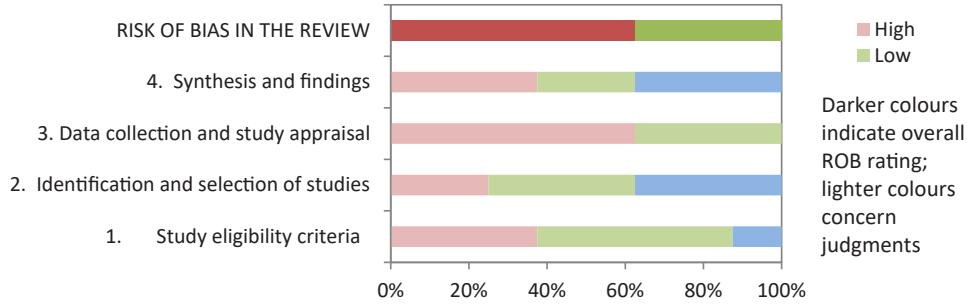

Figure 3 ROBIS risk-of-bias assessment of the systematic reviews (SRs) on surgical treatments for breast cancer-related lymphedema (BCRL); overall and per-domain percentages. * Total number of the included SRs = 8.

randomization process domain, deviation from intended intervention domain, and measurement of the outcome domain', had a probability of introduced bias in all RCT outcomes and downgraded the rating to some concerns or high risk of bias.

Six outcomes were assessed in the RCT of *Van Mulken* et al.[30] Five were rated as with some concerns (daily use of compressive garment, use of manual lymphatic drainage, the mean lymph - ICF, duration of surgery, and quality of the anastomosis) and one as high risk of bias (mean UEL index). Two RoB-2 domains, 'the randomization process domain and deviation from intended intervention domain', were rated as having some concerns regarding the probability of introduced bias in all RCT outcomes. In addition, "the missing outcome data" domain was rated as having a high risk of bias in the mean UEL index outcome, downgrading this outcome to a high risk of bias (see Table 3).

Risk-of-bias assessment for SRs

Based on the ROBIS tool, five SRs (5/8, 62.5%) were rated as high risk of bias[37-40,42] and three (3/8, 37.5%) were rated as low risk of bias.[35,36,41]

The five SRs rated as having a high risk of bias were downgraded because there was a probability of introducing bias in more than one domain. All rated as high risk of bias in the 'data collection and study appraisal' domain (5/8, 62.5%),[37-40,42] three in the 'study eligibility criteria' domain (3/3, 37.5%),[38,39,42] three in the 'synthesis of finding' domain (3/3, 37.5%),[38-40] and two in the 'identification and selection of studies' domain (2/8, 25%).[38,40] Finally, 50% of all included SRs had rated the domain of 'study eligibility criteria' as having a low risk of bias,[35-37,41] which was the best rated ROBIS domain (see Figure 3).

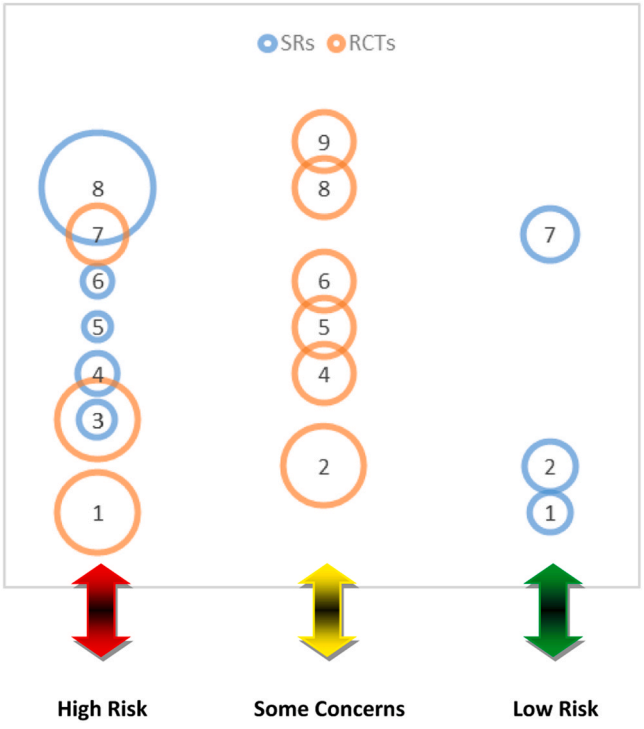

Figure 4 Bubble plot for the overall risk of bias of the systematic reviews and randomized clinical trials outcomes on surgical treatments for BCRL. Studies descriptions: Systematic reviews (Blue circles): 1: Penha et al.[35], 2: Cornelissen et al.[36], 3: Siotos et al.[37], 4: Ribeiro et al.[38], 5: Forte et al.[39], 6: Forte et al.[40], 7: Winter et al.[41], 8: Gasteratos et al.[42]. Randomized clinical trials (Orange circles): 1-3: Dionyssiou et al.[29] (Outcomes; Limb Volume, Infection Episodes & Subjective symptoms, respectively), 4-9: Van Mulken et al.[30] (Outcomes; Daily use of compressive garment, Manual lymphatic drainage, Mean lymph - ICF, Mean UEL Index, Duration of surgery & Quality of the anastomosis, respectively). * SRs: systematic reviews, RCTs: randomized clinical trials, BCRL: breast cancer-related lymphedema.

The overall risk-of-bias assessment for both RCTs and SRs in relation with the number of population or number of studies in the included RCTs and SRs, respectively, has been demonstrated in a bubble plot figure for an overall visual presentation of the results (see Figure 4).

Discussion

The main objective of this research was to describe and critically assess the risk of bias of RCTs and SRs on the surgical treatment for BCRL. To achieve this purpose, we conducted a systematic mapping review, which allowed a visual understanding of the evidence base of any treatment, apart from supporting the process of decision-making by facilitating information in a user-friendly format. Furthermore, it is the best study design to identify gaps of knowledge in any research topic.[48]

Our previous mapping review was conducted to provide an overview of the current situation in the treatment for BCRL but did not focus on the surgical treatment and did not include the risk-of-bias assessment.[21] Furthermore, after updating our previous search in all the databases, our findings result in only two RCTs and eight SRs were among the 47 surgical studies that met the eligibility criteria.

The overall risk-of-bias assessment of the two surgical RCTs[29,30] was rated as some concerns (six outcomes) and high risk (three outcomes) of bias for the measured outcomes among the included RCTs using the RoB-2 and high risk of bias (five studies) and low risk (three studies) for the eight included SRs[35-42] using the ROBIS tool. In addition to the low-quality SRs and RCTs published in the surgical treatment for BCRL, there was a significant heterogeneity in the assessed intervention, the measured outcomes, and the included studies in the case of SRs.

A study with a similar scope was an SR conducted by *Chang* et al.[49] that addressed surgical treatment and prevention for secondary lymphedema. In general, it showed that there was evidence to support some efficacy of LVA and VLNT, but their evidence was mainly based on observational studies and expert consensus. Other SRs that were involved in our results had positive findings on surgical interventions but were based mainly on case series,[35,37] observational studies,[36,39,42,] and nonrandomized trials,[41] and some did not mention which study design they included, probably not including high-quality studies as we assumed.[38,40] Generally, there is a lack of level 1 evidence to support the efficacy of the applied intervention.

Chang et al.[49] assessed the risk of bias for their two included RCTs: one on surgical prevention[50] and another on surgical treatment.[29] The latter RCT was also assessed in our study, but in contrast, they used a different risk-of-bias tool; nevertheless, they reached a conclusion similar to ours. They rated that RCT[29] with a high risk of bias regarding performance and detection biases, which is comparable to our rating as high risk of bias in the deviation from the intended intervention and measurement of the outcome in the RoB-2. Similar to our finding, *Gasteratos* et al.[42] included in their results one similar RCT on surgical treatment,[30] but they did not assess the risk of bias in their included studies.

There are more promising surgical treatments in the field of BCRL, and demonstrating the effectiveness of these interventions has become more challenging. However, both patients and surgeons need high-quality information about treatment outcomes to inform decision-making.[51] Surgeons now have to adopt more scientific methodologies and evidence-based strategies to improve the standards of care for patients undergoing surgery.[52] Based on our results, the overall evidence in the literature on surgical treatment for BCRL is low, and the limited number of well-designed RCTs in this field is an established barrier that needs to be addressed.

The constraints to conducting high-quality studies in surgery are attributed to the challenges related to the implementation of well-designed studies, the nature of the interventions, and the lack of methodological experience among surgeons. *Ergina* et al.[53] highlighted the difficulties in evaluating surgical innovations, especially in comparison to pharmacological research, which usually contributes to uncertainty about the risk of biases and has led to skepticism about the value of surgical research. Yet, this is applicable by understanding the processes of evaluation in

surgery and creating alternative designs to maximize validity and reduce the chance of bias.[53]

This study has some limitations. First, the search strategy years were from 2000 onward because we assumed that the evolution of the surgical treatments occurred in the previous two decades. Second, the mapping review usually requires additional expertize to create the visual output. Finally, in this kind of study, there is a probable risk of publication bias.

Among the strengths of this study, the systematic screening was performed by three independent reviewers to ensure the reliability of the reported results. The methodological quality assessment consideration was adequately done by defining the eligibility criteria and identifying the risk of bias of the studies. The graphic presentation of the results was made to be relatively easy to interpret and understand. Moreover, the findings of this research illustrate the gaps in the literature and provide a clear picture of future needs in research in the field of surgery.

The shortage of strong evidence in the surgical treatment for BCRL makes the implications of this work in research and practice significantly important and indicates the need to conduct higher quality studies in this field, which can guide health policy and clinical decision-making.

Conclusion

The overall evidence in the literature on surgical treatment for BCRL is low because there are only two RCTs and eight SRs among the 47 published studies. The risk-of-bias assessment for the RCTs outcomes and most SRs were rated either as high risk of bias or with some concerns, and only three SRs were rated as low risk of bias.

High-quality RCTs on different surgical interventions for BCRL should be conducted to measure their real effectiveness, risks, and complications and to compare their benefit with other nonsurgical treatments. Moreover, better quality SRs on BCRL surgical treatments are needed to improve evidence-based decision-making by surgeons and patients.

Conflicts of interest

All remaining authors have declared no conflicts of interest.

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Ethical approval

Not required.

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Disclosure

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bjps.2023.05.002.

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