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REVIEW

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Effectiveness of manual lymphatic drainage for breast cancer-related lymphoedema: an overview of systematic reviews and meta-analyses

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Abstract

There are several studies on the treatment of breast cancer-related lymphedema (BCRL) based on the manual lymphatic drainage (MLD) technique, making it a widely accepted conservative treatment for BCRL. In this study, PubMed, Embase and Cochrane Library databases were searched for systematic reviews (SRs) or meta-analyses (MAs) from inception till 28 March 2022. The methodological quality of the included SRs/MAs was evaluated using the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2), and the evidence quality of outcome measures using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). Grading of Recommendations, Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual) was used to describe the certainty of evidence from qualitative data. The study results identified 7 eligible SRs/MAs. Evaluation using AMSTAR-2 revealed only one moderate quality study, while the others were rated as low or critically low. The GRADE criteria identified 3 very-low-quality evidence studies, 1 low-quality evidence study, and 9 moderate-quality evidence studies. The GRADE-CERQual assessment showed the confidence for decision-making was either low or moderate. Overall, the results indicated that MLD could significantly reduce lymphedema in patients aged $<$60 years (standard mean difference (SMD): -1.77, 95% confidence interval (CI): (-2.23 to -1.31)), and the optimal intervention duration was 1 month. Although MLD for BCRL might reduce lymphoedema volume, their effects were not well established, and therefore, we could not recommend the addition of MLD to complete decongestive therapy (CDT) or compression therapy for patients with BCRL. Thus, MLD treatment appeared to be an ambiguous but potentially effective BCRL treatment. Rigorously designed high-quality randomized controlled trials with larger sample sizes are needed to further verify the effectiveness of MLD therapy in BCRL treatment.

Keywords

Manual lymphatic drainage; Breast cancer-related lymphoedema; Effectiveness; Overview

1. Introduction

Female breast cancer surpassed lung cancer as the most commonly diagnosed cancer globally in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases worldwide [1]. Identifying the most important breast cancer risk factors and further improvements in its prevention and treatment are key to reducing future global breast cancer burden [1]. Breast cancer-related lymphedema (BCRL) is a serious post-treatment complication that is associated with the extent of mastectomy, axillary lymph node dissection (ALND), regional nodal irradiation (RNI), and taxane-based chemotherapy [2–5]. Approximately 19% of breast cancer patients develop BCRL within 12 months and $<$24 months after treatment [4, 6]. Patients with chronic BCRL have reduced quality of life due to functional impairment or disability, anxiety, depression, social difficulty, and huge financial burden due to high medical costs [2, 4, 6–8]. Therefore, it is vital to modify the progress of this potentially disabling condition through effective early intervention to improve the patients' outcomes.

Manual lymphatic drainage (MLD) is a mild, rhythmic and superficial massage technique. MLD focuses on improving the activity of the lymphatic system, and reducing the consistency of the edema and its volume *via* manual massaging techniques on the skin [9, 10]. MLD techniques were described as effective in reducing edema volume and pain [11–13], preventing

the aggravation of lymphedema [14], and improving patients' well-being. However, some studies have reported that MLD has no volume reduction effects on complete decongestive therapy (CDT) for BCRL treatment [15].

Due to such controversy, it remains unclear whether MLD among certain groups of BCRL patients should be part of the treatment or whether MLD is effective without bandaging. SRs and MAs concerning the clinical efficacy of MLD for BCRL on the basis of randomized controlled trials (RCTs) have been published. Nevertheless, the overall outcomes have remained mixed or indefinite, and their quality is uneven. An overview of the systematic reviews (OoSRs) is designed to synthesize multiple evidence from existing literature on a specific topic to address the growing problem of information overload and provide a way to filter large bodies of complex evidence to inform healthcare decision-making [16–18]. Therefore, we used OoSRs to synthesize findings on the clinical effectiveness of MLD in treating BCRL by critically assessing the quality of existing literature and attempting to resolve discordant outcomes.

2. Methods

The study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19] and the guidance on recommendations from the Cochrane Collaboration [20].

2.1 Search Strategy

A thorough search was performed using PubMed, Embase and Cochrane library from inception to 28 March 2022. We combined the Medical Subject Headings or EMTREE with the following keywords: breast neoplasms, lymphedema, breast cancer lymphedema, breast cancer-related lymphedema, systematic review, and meta-analysis. Other search terms and strategies retrieved using the PubMed database are shown in Table 1. The original published studies cited references and relevant review articles were also manually searched to identify additional eligible studies to ensure a comprehensive data collection. The searches were limited to human subjects.

2.2 Eligibility Criteria

We included SRs or MAs on MLD treatment for BCRL. Participants were restricted to patients with BCRL.

The inclusion criteria were as follows:

(1) Participants: Participants involved were clinically diagnosed with BCRL [2].

(2) Intervention: MLD therapy alone or in combination with other physiotherapy (PT). The physiotherapy (PT) represented different combinations of treatments such as involved CDT, compression bandaging (CB), compression garments (CG), low-level laser therapy (LLLT), electrotherapy (ET), sequential pneumatic compression (SPC), intermittent pneumatic compression pump (IPC), simplified/self-MLD (SLD), skin care (SC), exercise guidance (EG) or any combination of above.

(3) Control: PT or combinations.

(4) Outcomes: Lymphedema volume, volume reduction and percent reduction were eligible as primary outcome indicators. Secondary outcomes included follow-up times, functional measures, subjective sensations, quality of life and cost of care.

(5) Study design: Only included SRs/MAs of RCTs on MLD therapy in BCRL patients published in English. If several SRs reported on the prevention simultaneously or comprehensive intervention measures on BCRL, we chose the one in which the data could be extracted. If SRs reported the same topic, we compared their differences and reviewed the most comprehensive one.

This study's exclusion criteria included: observational studies, protocols, conference abstracts, and studies in which the data could not be extracted or without full text.

2.3 Study Selection and Data Extraction

Two investigators independently reviewed all titles and abstracts for relevant systematic review/meta-analysis and independently extracted the data. An agreement was reached through mutual discussion when differences arose.

Initially, all titles and abstracts were screened to single out potentially relevant studies and excluded those unrelated to the effects of MLD therapy on BCRL patients or not described as SRs/MAs. Duplicated studies were removed from the study analysis.

The basic characteristics extracted from the eligible studies included: the information of first author, year of publication, country, number of included studies, sample size, interventions (experimental and control interventions), outcomes, quality evaluation tools and main findings. The corresponding author of the study was contacted *via* email to obtain the information present for studies with unclear or missing information.

2.4 Quality assessment

Two independent investigators performed methodology quality and evidence quality assessment. In case of discrepancies, an agreement was reached by mutual discussion.

The quality of methodology was rated using the AMSTAR-2 tool [21]. The tool assessed 16 items, among which 7 are critical domains (items 2, 4, 7, 9, 11, 13 & 15). The evaluation is reduced to three options ("Yes", "Partial Yes" and "No"). AMSTAR-2 rates the overall confidence in the review results as high, moderate, low, and critically low.

GRADE was used to evaluate the quality of quantitative evidence [22]. Eligible studies were initially rated as high quality because of RCTs, which may lead to their downgrading after evaluating five factors (inconsistency, imprecision, indirectness, quality and publication bias). They were eventually rated as high, moderate, low or very low-quality levels of evidence.

We used the GRADE-CERQual [23] to assess the confidence that could be placed in each review finding. GRADE-CERQual was used to assess the confidence in the retrieved literature based on four components: methodological limitations, coherence, adequacy of the data contributing, and relevance to the review question. Lastly, we judged the confidence as high, moderate, low, or critically low based on the evaluation.

TABLE 1. Search strategy: take the search process *via* Pubmed as an example.

Query	Search term
#1	Breast Neoplasms (MeSH Terms)
#2	(breast neoplasm* (Title/Abstract)) OR (breast tumor* (Title/Abstract)) OR (breast tumour* (Title/Abstract)) OR (breast cancer* (Title/Abstract)) OR (breast carcinoma* (Title/Abstract)) OR (breast malignant tumor* (Title/Abstract)) OR (breast malignant neoplasm* (Title/Abstract)) OR (mammary cancer* (Title/Abstract)) OR (mammary carcinoma* (Title/Abstract)) OR (mammary neoplasm* (Title/Abstract))
#3	#1 OR #2
#4	"lymphedema" (MeSH Terms)
#5	(lymphedem* (Title/Abstract)) OR (lymphoedem* (Title/Abstract)) OR (oedema* (Title/Abstract)) OR (edema* (Title/Abstract)) OR (swelling (Title/Abstract)) OR (dropsy (Title/Abstract)) OR (hydrops (Title/Abstract)) OR (elephantiasis (Title/Abstract))
#6	#4 OR #5
#7	#3 AND #6
#8	"breast cancer lymphedema" (MeSH Terms)
#9	(breast cancer lymphedema* (Title/Abstract)) OR (postmastectomy lymphedema* (Title/Abstract)) OR (post mastectomy lymphedema* (Title/Abstract)) OR (post mastectomy lymphedema (Title/Abstract)) OR (breast cancer treatment related lymphedema (Title/Abstract)) OR (breast cancer treatment related lymphedema (Title/Abstract)) OR (breast cancer related lymphedema (Title/Abstract)) OR (breast cancer related arm lymphedema (Title/Abstract)) OR (breast cancer related arm lymphedema (Title/Abstract))
#10	#8 OR #9
#11	#7 OR #10
#12	"Meta-Analysis as Topic" (Mesh) OR (Meta-Analysis (Publication Type))
#13	(meta analysis (Title/Abstract)) OR (meta analyses (Title/Abstract)) OR (metaanalysis (Title/Abstract)) OR (metaanalyses (Title/Abstract)) OR (metanalysis (Title/Abstract)) OR (metanalyses (Title/Abstract)) OR (met-analysis (Title/Abstract)) OR (met-analyses (Title/Abstract)) OR (meta-study (Title/Abstract)) OR (meta-studies (Title/Abstract)) OR (meta study (Title/Abstract)) OR (meta studies (Title/Abstract)) OR (data pooling (Title/Abstract)) OR (data poolings (Title/Abstract)) OR (clinical trial overview (Title/Abstract)) OR (clinical trial overviews (Title/Abstract))
#14	"Systematic Reviews as Topic" (Mesh) OR (Systematic Review (Publication Type))
#15	(systematic review (Title/Abstract)) OR (systematic reviews (Title/Abstract)) OR (systematic study (Title/Abstract)) OR (systematic studies (Title/Abstract))
#16	#12 OR #13 OR #14 OR #15
#17	#11 AND #16

2.5 Statistical Analysis

The methodology and evidence quality assessments were performed using descriptive analyses. The summary measures of the effectiveness of MLD for BCRL are described for different outcome indicators. The presentation form included standard mean difference (SMD), mean difference (MD) or relative risk (RR), both with 95% CI. The percentage bar chart of AMSTAR-2 evaluation results was made using the Microsoft Office Excel software (2017, 64 bits, Redmond, WA, USA). Based on the studies, the 16 items of AMSTAR-2 and the number of the evaluation answers (Y, N, PY, NMA) corresponded to the 16 items. The x-axis represented the 16 AMSTAR-2 items in the retrieved SRs/MAs studies. The y-axis represented the eligible studies. Different colors represented different evaluation results: green strips indicate Y, yellow strips indicate PY, red strips indicate N and gray strips indicate NMA. The length of the bar indicates the number of item evaluation results.

A bubble chat was created according to the number of studies, evidence quality for each clinical outcome indicator, and effectiveness estimate with a 95% confidence interval using Microsoft Office Excel 2017. The size of the bubbles reflected the variety in the clinical efficacy evaluation indication of each indicator. The x-axis showed the primary indicators in the included studies. The y-axis showed the number of studies for each clinical outcome. The varying strengths of GRADE evidence were represented by different colors: green bubbles denote moderate-quality evidence, yellow denote low-quality evidence, and red denote very low-quality evidence. As there was no high-quality level of evidence, it is not shown in the bubble chart. When the value of the clinical effectiveness estimate was negative, the color of the bubble was displayed in gray with a black ring.

3. Results

3.1 Search Results

824 articles were initially identified (PubMed: 251 articles, Embase: 524 articles, and Cochran Library: 49 articles). Of them, 192 were excluded due to duplications by computer. After screening abstracts and titles, we manually excluded 54 additional duplicated studies. After excluding 349 studies due to non-BCRL related, 199 due to non-MLD related, 9 due to non-SRs/Mas related and 21 considered ineligible after screening their full text, 7 articles were found eligible for this present study. A flow chart of study screening and selection process is presented in Fig. 1.

3.2 Study Characteristics

All studies in the final analysis were published between 2009 and 2020, including three literatures from China [24–26], and one each from Australia [27], America [28], Belgium [29] and Finland [30]. The RCTs numbers for each review ranged from 4 to 13. The number of participants included ranged from 153 to 552. The interventions in the experimental groups were MLD alone or MLD + PT, and PT alone in the controversial group. The outcome indicators were volume reduction, lymphedema volume, percent reduction, follow-up times, subjective sensations, functional measures, quality of life, cost of care and compliance. Among the included SRs/MAs, the methodological quality assessment scales differed: the five [24–26, 28, 30] used the Cochrane Collaboration's tool, and the two [27, 29] used the Physiotherapy Evidence Database (PEDro) scale. The efficacy of MLD in BCRL treatment was conflicted in both primary and secondary outcome indicators. Table 2 summarized the characteristics of included seven articles in our final analysis.

3.3 Methodological Quality of SRs/MAs

AMSTAR-2 score revealed the quality of one review (14.2%) [28] was moderate, two (28.6%) [25, 27] were low, and the remaining (57.1%) [24, 26, 29, 30] were of critically low quality. The key factors affecting the quality of the literature included item 2 (only one review article [28] was registered, and the protocol was published before performing the review), item 4 (one review article [28] used a comprehensive strategy of literature seeking to retrieve references of relevant reviews and retrieve relevant gray literature), item 7 (only one review article [28] provided a list of excluded studies and justified the exclusions), item 9 (four review articles [24, 27, 28, 30] reported risk of bias using a satisfactory technique), item 11 (four review articles [24–26, 28] combined the results statistically using appropriate methods), item 13 (six review articles [24–28, 30] considered the risk of bias when interpreting the results), and item 15 (two review articles [25, 28] performed a well-investigation of publication bias study). Details on the methodological quality are listed in Table 3. A percentage bar chart of the AMSTAR-2 assessment results is shown in Fig. 2.

3.4 Evidence Quality of Outcomes

Among these 13 outcome indicators, nine (69.2%) were of moderate-quality evidence, one (7.7%) of low-quality evidence, and three (23.0%) of very low-quality evidence. The Summary of GRADE assessment results is shown in Table 4. Fig. 3 shows a graphical representation of the evidence.

The GRADE-CERQual assessed the confidence in the evidence based on the methodological limitations, relevance, coherence and adequacy. The results showed only one moderate-quality evidence and nine low-quality evidence from the 10 comprehensive results included in 3 qualitative studies [27, 29, 30]. The reasons for downgrading evidence quality to moderate or low included mild methodological quality and medium consistency due to inconsistencies between the comprehensive and the original results. The results of the CERQual assessment are summarized in Table 5.

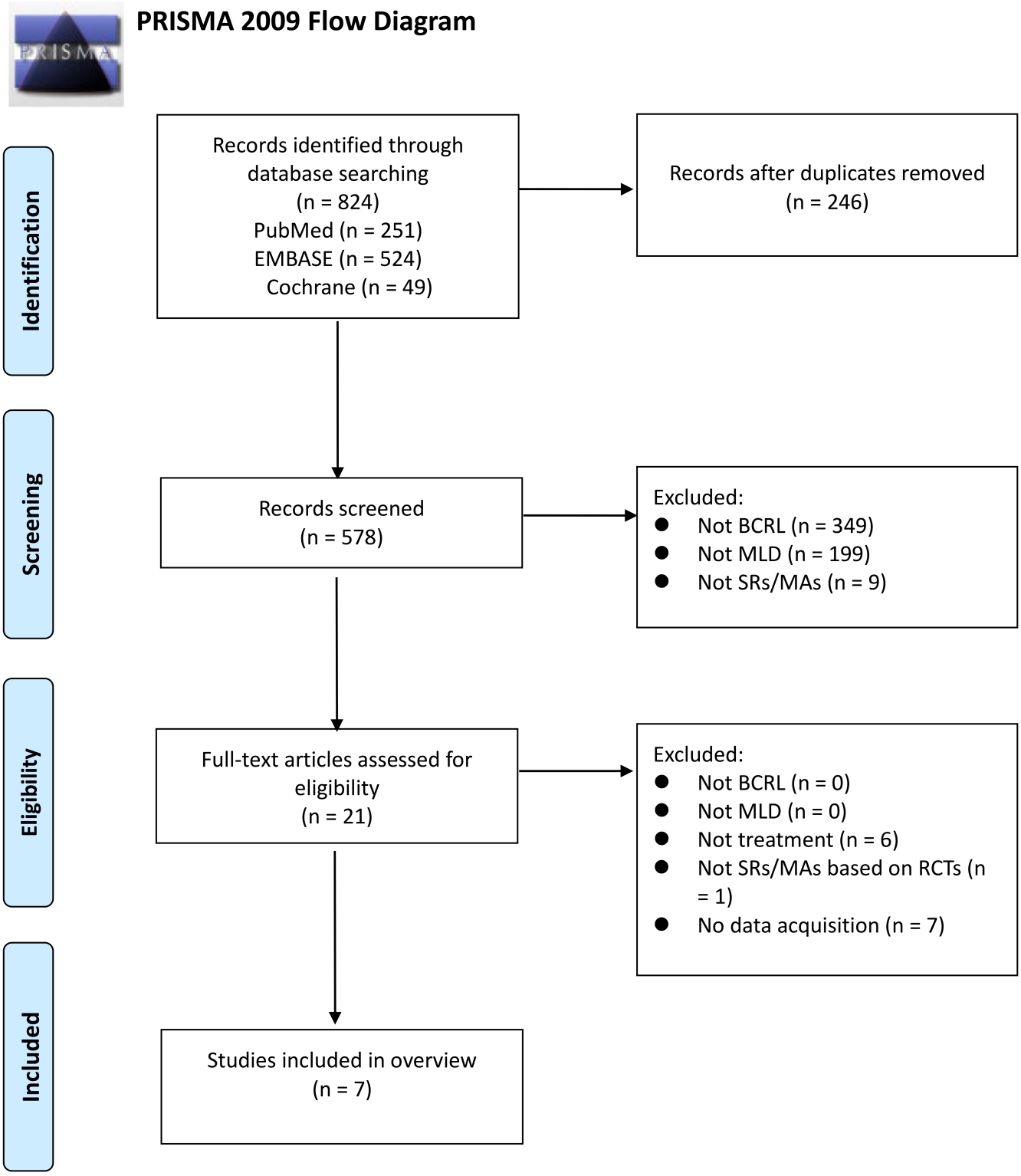

FIGURE 1. A flow diagram of study screening and selection procedures is illustrated. BCRL: breast cancer-related lymphedema; MLD: manual lymphatic drainage; SRs: systematic reviews; Mas: meta-analyses; RCTs: randomized controlled trials.

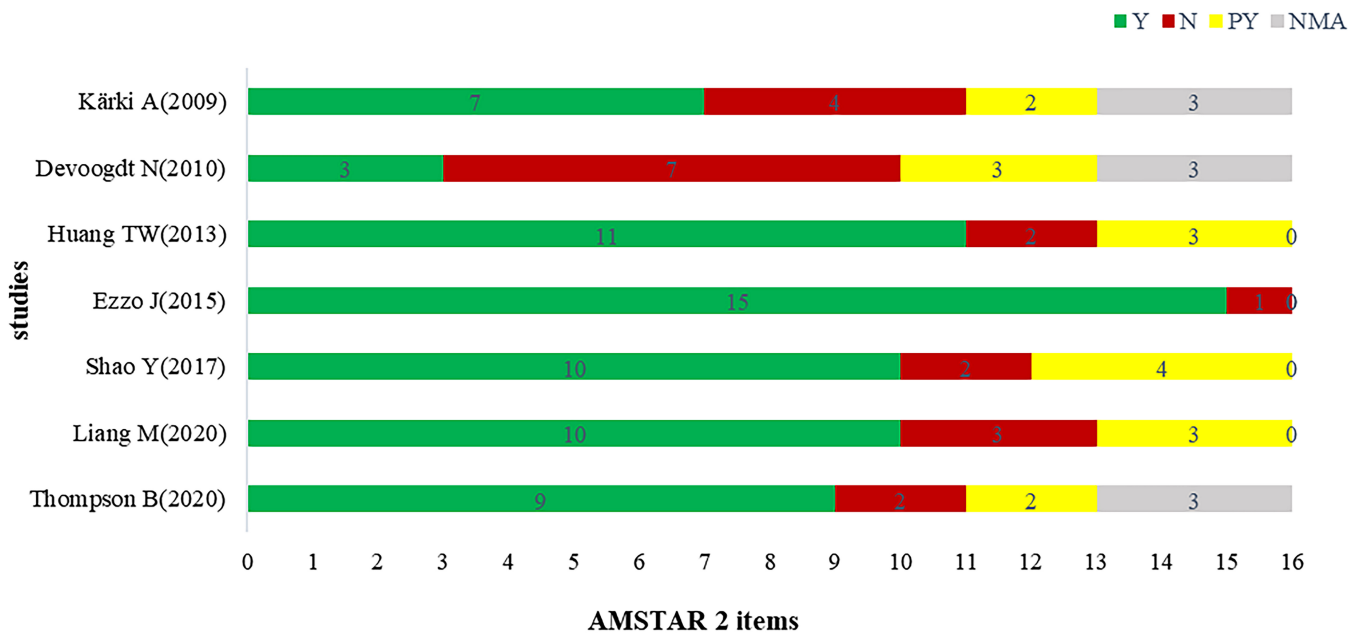

FIGURE 2. A percentage bar chart of AMSTAR-2 assessments results. Y: Yes; PY: partial Yes; N: No; NMA: No Meta-analysis.

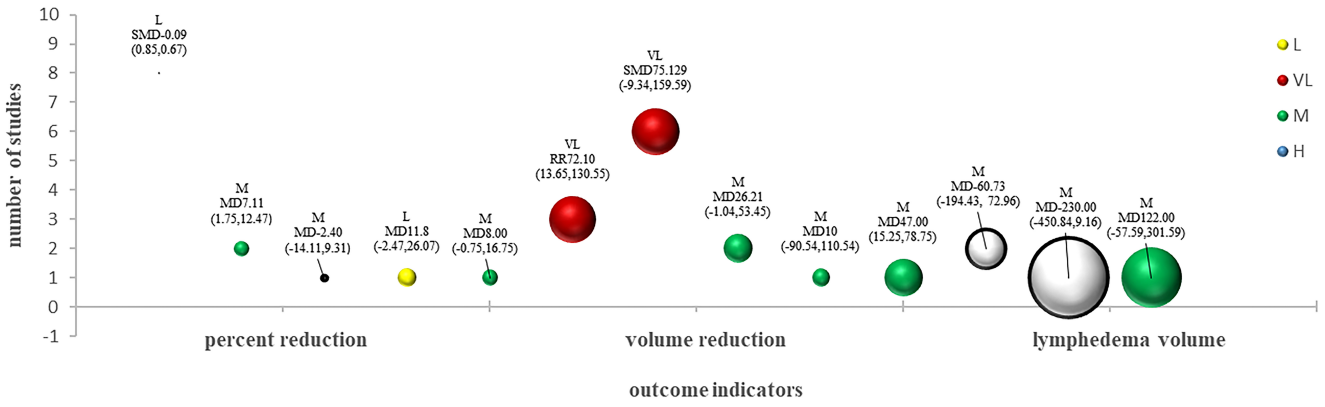

FIGURE 3. The bubble plot of GRADE evaluation results. VL, Very low; L, Low; M, Moderate; H, High. MD, standard mean difference.

TABLE 2. Characteristics of the included reviews.

Author (Year)	Country	Time limit of retrieval	Trials (Sample size) Participants	Intervention		Outcomes	Quality assessment tool	Main conclusions
				Experiment intervention	Control intervention			
Thompson B [27], (2020)	Australia	From inception to 28 Feb 2020	13 (1415) 552	MLD + PT; MLD	PT	Volume reduction, subjective symptoms, quality of life	PEDro scale	The effectiveness of MLD was well investigated but there was conflicting evidence.
Liang M [25], (2020)	China	From inception to May 2019	8 (413) 338	MLD + PT	PT	Percent reduction	Cochrane Collaboration's tool	MLD did not significantly reduce lymphedema, but MLD could significantly reduce lymphedema in patients under the age of 60 years and an intervention time of 1 month.
Shao Y [26], (2017)	China	From 1990 to Sep 2015	4 (728) 234	MLD + PT	PT	Volume reduction, subjective symptoms, functional measures	Cochrane Collaboration's tool	The addition of MLD to PT helped to reduce BCRL more effectively. there was no superiority of the adding of MLD on subjective symptoms or arm function.
Ezzo J [28], (2015)	America	From inception to 24 May 2013	6 (834) 208	MLD + PT	PT; SLD + PT	Lymphedema volume, Volume reduction, percent reduction, follow-up times, subjective sensations, functional measures, quality of life, cost of care	Cochrane Collaboration's tool	MLD with or without compression therapy showed no significant improvement from baseline and no significant between-group differences for percent reduction. MLD is safe and may offer additional benefit to compression bandaging for swelling reduction and an intensive course for Mild-to-moderate BCRL.
Huang TW [24], (2013)	China	From inception to Dec 2012	8 (170) 288	MLD + PT	PT	Volume reduction	Cochrane Collaboration's tool	The addition of MLD to a standard treatment procedure, producing a non-significant effect on reducing arm volume for BCRL
Devoogdt N [29], (2010)	Belgium	-	6 (317) 230	MLD; MLD + PT	PT	Lymphedema volume, subjective sensations, compliance	PEDro scale	There was no consensus on the effectiveness of MLD for BCRL.
Kärki A [30], (2009)	Finland	Jan 1998 to Feb 2006	6 (242) 219	MLD + PT	PT	Lymphedema volume	Cochrane Collaboration's tool	Based on one trial CB reduces lymphoedema, but adding MLD does not bring any additional effect.

MLD: Manual lymphatic drainage; PT: physiotherapy; SLD: simplified/self-MLD; BCRL: breast cancer-related lymphedema; CB: compression bandaging; PEDro: Physiotherapy Evidence Database.

TABLE 3. Result of the AMSTAR-2 assessments.

study	AMSTAR-2																Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	
Thompson B [27], (2020)	Y	N	Y	PY	Y	Y	PY	Y	Y	N	NMA	NMA	Y	Y	NMA	Y	L
Liang M [25], (2020)	Y	N	Y	PY	Y	Y	PY	Y	PY	N	Y	Y	Y	Y	Y	N	L
Shao Y [26], (2017)	Y	N	Y	PY	Y	Y	PY	PY	PY	Y	Y	Y	Y	Y	N	Y	CL
Ezzo J [28], (2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	M
Huang TW [24], (2013)	Y	N	Y	PY	Y	Y	PY	PY	Y	Y	Y	Y	Y	Y	N	Y	CL
Devoogdt N [29], (2010)	Y	N	Y	PY	N	N	N	PY	PY	N	NMA	NMA	N	Y	NMA	N	CL
Kärki A [30], (2009)	Y	N	Y	PY	Y	Y	N	PY	Y	N	NMA	NMA	Y	Y	NMA	N	CL

Y: Yes; PY: partial Yes; N: No; NMA: No Meta-analysis; CL: Critically low; L: Low; M: Moderate; H: High; AMSTAR-2: Assessing the Methodological Quality of Systematic Reviews 2.

Q1: Did the research questions and inclusion criteria for the review include the components of PICO?

Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

Q3: Did the review authors explain their selection of the study designs for inclusion in the review?

Q4: Did the review authors use a comprehensive literature search strategy?

Q5: Did the review authors perform study selection in duplicate?

Q6: Did the review authors perform data extraction in duplicate?

Q7: Did the review authors provide a list of excluded studies and justify the exclusions?

Q8: Did the review authors describe the included studies in adequate detail?

Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

Q10: Did the review authors report on the sources of funding for the studies included in the review?

Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

TABLE 4. Result of the GRADE assessments.

Study	Intervention	Control	Outcomes	Effect estimate 95% CI	Studies (partici-pants)	Limitatior	Inconsiste	Indirectne	Impreciisic	Publication bias	Quality	Related RCTs
Liang M [25], (2020)	MLD + PT	T	Percent reduction (%)	SMD −0.09 (0.85, 0.67)	8 (364)	−1①	−1②	0	0	0	L	Tambour [15], (2018), Bergmann [33], (2014), McNeely [37], (2004), Williams [42], (2002), Sitzia [41], (2002), Andersen [31], (2000), Johansson [42], (1999), Johansson [36], (1998)
Shao Y [26], (2017)	MLD + PT	T	Volume reduction (mL)	RR 72.10 (13.65, 130.55)	3 (144)	−1①	0	0	0	−1④	VL	Andersen [31], (2000), Dayes (2013), McNeely [37], (2004)
Huang TW [24], (2013)	MLD + PT	T	Volume reduction (mL)	SMD 75.129 (−9.34, 159.59)	6 (208)	−1①	−1②	0	0	−1④	VL	Johansson [36], (1998), Andersen [31], (2000), Johansson [42], (1999), McNeely [37], (2004), Sitzia [41], (2002), Williams [42], (2002)
Ezzo J [28], (2015)			Lymphedema volume (mL)	MD −60.73 (−194.43, 72.96)	2 (90)	0	0	0	0	−1④	M	Johansson [42], (1999), McNeely [37], (2004)
	MLD + PT	PT	Volume reduction (mL)	MD 26.21 (−1.04, 53.45)	2 (90)	0	0	0	0	−1④	M	Johansson [42], (1999), McNeely [37], (2004)
			Per cent reduction (%)	MD 7.11 (1.75, 12.47)	2 (90)	0	0	0	0	−1④	M	Johansson [42], (1999), McNeely [37], (2004)
			Lymphedema volume (mL)	MD −230.00 (−450.84, 9.16)	1 (31)	0	0	0	−1③	0	M	Williams [42], (2002)

TABLE 4. Continued.

Study	Intervention	Control	Outcomes	Effect estimate 95% CI	Studies (partici-pants)	Limitatior	Inconsiste	Indirectne	Impreciси	Publication bias	Quality	Related RCTs
		PT (SLD + CT)	Volume reduction (mL)	MD 10 (−90.54, 110.54)	1 (31)	0	0	0	−1③	0	M	Williams [42], (2002)
	MLD		Percent reduction (%)	MD −2.40 (−14.11, 9.31)	1 (31)	0	0	0	−1③	0	M	Williams [42], (2002)
				MD 11.8 (−2.47, 26.07)	1 (28)	−1①	0	0	−1③	0	L	Sitzia [41], (2002)
			Lymphedema volume (mL)	MD 122.00 (−57.59, 301.59)	1 (28)	0	0	0	−1③	0	M	Johansson [36], (1998)
		PT (ISP + CT)	Volume reduction (mL)	MD 47.00 (15.25, 78.75)	1 (28)	0	0	0	−1③	0	M	Johansson [36], (1998)
			Percent reduction (%)	MD 8.00 (−0.75, 16.75)	1 (28)	0	0	0	−1③	0	M	Johansson [36], (1998)

VL: Very low; L: Low; M: Moderate; H: High. ①*: The experimental design had a large bias in random, distributive findings or was blind.* ②*: The confidence intervals overlapped less, the p-value for the heterogeneity test was very small, and the I2 was larger.* ④*: The confidence interval was not narrow enough.* ③*: Fewer studies were included, and publication bias cannot be carried out.*

MLD: manual lymphatic drainage; PT: physiotherapy (representatives of different combinations); SLD: simplified/self-MLD; CT: compression therapy; ISP: intermittent sequential pneumatic pump; SMD: standard mean difference; MD: standard mean difference; RR: relative risk; RCTs: randomized controlled trials; CI: confidence interval.

TABLE 5. Result of the CERQual assessments.

Study	Comprehensive results		Methodological limitations	Relevance	Coherence	Adequacy of data	CERQual evidence rating	Rating explanations	Related RCTs
Thompson B [27], (2020)	volume reduction		0	0	−1①	0	M	13 studies have mild methodological limitations and medium consistency due to the inconsistency between the comprehensive results and the original results. High relevance and sufficient information.	Andersenet (2000), Belmonte [32], (2011), Bergmann [33], (2014), Gradalski [34], (2015), Ha [35], (2017), Johansson [36], (1998), McNeely [37], (2004), Odebiyi [38], (2014), Ridner [39], (2013), Sanal-Toprak [40], (2019), Sitzia [41], (2002), Tambour [15], (2018), Williams [42], (2002)
	volume reduction	arm circumfer-ences	0	0	−1①	−1②	L	2 studies have mild methodological limitations and high relevance. Inconsistency between the comprehensive results and the original results. Inadequacy due to limited studies.	Andersenet (2000), Williams [42], (2002)
		volumeter	0	0	−1①	−1②	L	2 studies have mild methodological limitations and high relevance. Inconsistency between the comprehensive results and the original results. Inadequacy due to limited studies.	Johansson [36], (1998), McNeely [37], (2004)
Devoogdt N [29], (2010)		shoulder mobility Symptoms	0	0	−1①	−1②	L	Only one study has mild methodological limitations and high relevance. Both inconsistency and inadequacy due to limited study.	Johansson [36], (1998)

TABLE 5. Continued.

Study	Comprehensive results		Methodological limitations	Relevance	Coherence	Adequacy of data	CERQual evidence rating	Rating explanations	Related RCTs
	symptoms	pain	0	0	−1①	−1②	L	Only one study has mild methodological limitations and high relevance. Both inconsistency and inadequacy due to limited study.	Johansson [36], (1998)
		heaviness	0	0	−1①	−1②	L	Only one study has mild methodological limitations and high relevance. Both inconsistency and inadequacy due to limited study.	Johansson [36], (1998)
		tension	0	0	−1①	−1②	L	Only one study has mild methodological limitations and high relevance. Both inconsistency and inadequacy due to limited study.	Johansson [36], (1998)
		arm circumfer-ences	0	0	−1①	−1②	L	Only one study has mild methodological limitations and high relevance. Both inconsistency and inadequacy due to limited study.	Andersenet (2000), Ridner [39], (2013), Williams [42], (2002)
Kärki A [30], (2009)	volume reduction	percentage change	0	0	−1①	−1②	L	Only one study has mild methodological limitations and high relevance. Both inconsistency and inadequacy due to limited study.	Sitzia [41], (2002)
		volumeter	0	0	−1①	−1②	L	Only one study has mild methodological limitations and high relevance. Both inconsistency and inadequacy due to limited study.	McNeely [37], (2004)

VL, Very low; L, Low; M, Moderate; H, High. ①*: Differences in the degree of conformity between the comprehensive results and the corresponding original research, and the differences in the original research are insufficiently explained;* ②*: No comprehensive evaluation has been made on the richness and quantity of relevant information. RCTs: randomized controlled trials; CERQual: Confidence in the Evidence from Reviews of Qualitative Research.*

3.5 Summary of Research Results

3.5.1 Thompson B (2020)

The study involved 13 RCTs [15, 31–42], consisting of a total of 552 patients, which assessed the effectiveness of MLD on BCRL, and reported conflicting results [27]. While several research studies documented positive outcomes of MLD compared with other treatments in terms of volume reduction, quality of life and symptom-related outcomes, others reported no additional advantage of MLD as a component of CDT. This might be linked to the varying MLD and the outcome measurement methods used [27].

3.5.2 Liang M (2020)

One [25] of the SR/Mas involved 8 RCTs [15, 31, 33, 36, 37, 41–43] which demonstrated that MLD did not have a significant reduction in lymphedema compared to PT. The results of subgroup analysis showed MLD could have a significant reduction in lymphedema on patients aged <60 years (SMD: −1.77, 95% CI: (−2.23 to −1.31)), with 1 month intervention duration (SMD: −1.77, 95% CI: (−2.23 to −1.30)) [25].

3.5.3 Shao Y (2017)

No superiority of adding MLD in improving subjective symptoms or arm functions [26]. The meta-analysis results showed a significant difference between two trials on volume reduction (RR: 72.10, 95% CI (13.65 to 130.55). Two trials reported subjective symptoms improvement, with no significant differences between the groups ($p > 0.1$) [2, 31]. Two trials reported on arm functions, with no significant differences detected by the DASH scale. No differences between groups in Mobility measured by standard goniometry ($p > 0.1$) [2, 44]. The lymphatic system was still functional in mild or moderate lymphoedema, but when developed to severe stages, available lymphatic vessels, which are necessary for MLD to be effective, were missing. Therefore, MLD could not target all etiologies [26].

3.5.4 Ezzo J (2015)

One [28] of the SR/Mas involved 6 RCTs [31, 36, 37, 41–43], including 208 patients, and showed that MLD was safe and might offer additional benefit to CB for reducing swelling. Compared with participants who had moderate-to-severe BCRL, those with mild-to-moderate BCRL benefited from adding MLD to an intensive course of treatment with CB.

The primary outcomes involved in this study were percent reduction, volume reduction and lymphedema volume (LE volume), while follow-up times, subjective sensations, functional measures, quality of life and cost of care were regarded as the secondary outcomes [28]. Based on similar study designs, the trials were divided into three categories. Category 1 (one trial): MLD + PT (standard physiotherapy) versus PT (standard physiotherapy). Category 2 (two trials): MLD + PT (CB) versus PT (CB). Category 3 (three trial): MLD + PT (compression therapy) versus PT (compression therapy) [28].

Percent reduction:

Category 1 showed significant improvements from baseline, but there was no significant difference for percent reduction. Category 2 showed a significant 30% to 38.6% reductions for CB alone, and MLD had an additional 7.11% reduction. Percent reduction was borderline significant ($p = 0.07$) in Category 3. A third trial on MLD + PT versus SLD + PT (CB) in Category 3 was not significant ($p = 0.10$) for percent reduction [28].

Volume reduction:

Category 2 reported that volume reduction was of marginal significance ($p = 0.06$). The volume reduction was reported in Category 3 was of statistical significance (MD: 47.00, 95% CI (15.2 to 78.75)) [28].

LE volume:

Category 2 reported the compression sleeve + MLD and compression sleeve + pneumatic pump in one of the trials. The other trial reported that compression sleeve + MLD compared with compression sleeve + SLD, and the result was significant for MLD for LE volume [28].

3.5.5 Huang TW (2013)

Seven studies [31, 36, 37, 41–43, 45] contained information on the reduction in lymphedema volume after MLD treatment. Water displacement volumetry was used to estimate the arm volume at the beginning of the treatment and 1, 3, and 12 months after treatment in these studies. Our results showed no significant difference and the significant heterogeneity was observed.

3.5.6 Devoogdt N (2010)

Six RCTs [31, 36, 37, 42–44] met the inclusion criteria, and the results indicated no agreement on the validity of MLD for BCRL. Two trials could not show a positive effect of MLD with bandaging and skin care [37] or with wearing a compression sleeve [31]. Nonetheless, the other trials indicated that the MLD group had a borderline significantly higher reduction in arm edema than the group with the simplified form. The study of secondary outcome indicators also showed different results in different trials. In all studies, MLD was performed by a specialist and each session lasted between 45 minutes and 1 hour. The number of sessions varied from 5 [31]to 8 [31], 15 [42] and 20 [37] in four articles.

3.5.7 Kärki A (2009)

One involved study identified 6 RCTs [31, 36, 37, 41, 42, 44]. They compared MLD to shorter therapy sessions and more simplified drainage [41, 42], CB or CS only [31, 37, 42] or compression pumps [36]. No studies were found on the effects of the combination therapies (MLD, CB, therapeutic exercises, guidance) that were most in use according to the survey of current practices in Finland. In one trial, it was reported that CB could reduce lymphoedema, and the addition of MLD showed no significant benefit.

4. Discussion

In 2020, two SR/MAs were published on the effectiveness of MLD therapy on BCRL. One [27] of them was a qualitative study reporting conflicting evidence of MLD therapy for BCRL, while the other [25] was a quantitative study which showed that MLD did not significantly reduce lymphedema in the overall cohort but was associated with a significant

reduction in lymphedema in patients aged <60 years and 1 month intervention duration. Shao *et al.* [26] reported that adding MLD to PT helped reducing BCRL more effectively. Huang *et al.* [24] reported that adding MLD to a standard treatment procedure produced no significant effects on arm volume reduction. Devoogdt *et al.* [29] reported that there was no consensus on the effectiveness of MLD for BCRL. Kärki *et al.* [30] indicated that based on one trial which showed that CB could reduce lymphoedema, the addition of MLD did not bring any additional benefit to the patients. In general, we could not derive the exact efficacy of MLD for treating BCRL based on existing studies. Due to the influence of variable factors, the results were biased. Most studies indicated that MLD was ineffective in treating BCRL, but some subgroup analyses showed certain advantages with MLD in terms of age, degree of edema and length of intervention. Based on these findings, we performed a comprehensive analysis of the inconsistencies and limitations of SR/Mas to determine the efficacy of MLD in the treatment of BCRL.

MLD is a treatment method in which the therapist manually determines the location of the lymphatic vessels, lymph nodes and the direction of fluid flow based on the lymph anatomical structure and then maintains a consistent massage rhythm to slowly push and operate [46]. MLD can not only re-enter the stasis of lymph fluid into the blood, promote the return of lymph fluid, make the lymph fluid bypass the blocked or damaged lymphatic vessels and reduce lymphedema, but also improve the function of the upper limbs and promote the peripheral blood circulation of the upper limbs, thereby improving issues such as upper limb stiffness, pain and patients' quality of life of patients. These benefits were not evaluated in the current study, which were shown to help reduce anxiety and improve sleep and treatment adherence.

Since MLD is a manual form of treatment, inter-individual differences between therapists during the treatment process might exist in regard to the intensity of the applied pressure, which makes it difficult to accurately quantify the persistence of the pressure applied. To a large extent, this might be an influencing factor for inconsistency between the results obtained among various studies. Only one reported on the pressure applied by the hands, but it was unclear how this pressure was measured [40]. Although difficult to quantify, higher-quality research is needed to quantify the pressure and speed exerted by this technique and to explore the influence of different pressures and speeds, for which the use of precise instruments by therapists could be pivotal as machines could be set certain pressure and speed instead of manipulating based on the underlying lymphatic anatomy.

Many different types of combined treatments could have significantly affected the quality and conclusions of the included studies, which makes it difficult to establish the effects of MLD on lymphedema outcomes. All four RCTs have shown that compared with CDT without MLD, MLD showed no benefits in reducing arm volume [15, 28, 31, 32, 34]. However, it should be noted that the MLD was applied only for 2 [31, 34] and 3 weeks [15, 33]. Comparing compression and aging with and without MLD was in one of the studies [37]. The results showed that patients with mild lymphedema who received MLD had greater relative volume reductions than all other subgroups, which could be related to the degree of functioning lymphatics [37].

It is important to determine whether the measurement of edema is accurate or does not directly affect the effectiveness of MLD on lymphedema outcomes. Although clinical correlation of various volumetric measurements should be established, there are currently no uniform volume measurement techniques and no set standards for measuring the changes in girth or volume. Despite the fact that water displacement volumetry is often considered as the gold standard for measuring limb volume [47, 48], the included studies did not use it as a measurement standard and instead used circumferential measurements. The water replacement method is not only inconvenient to operate due to difficulty in movement and requirement of a lot of water to change, but also unsuitable for patients suffering from skin ulcers, limited motion range of shoulder or just immediately after surgery [49]. Based on the measurement methods in current studies, we have noted inconsistent results for three volumetric outcomes, including lymphedema volume (mL), volume reduction (mL) and percent reduction (%). More studies on measurement instruments should be explored, with attention to early detection of lymphedema flow, convenient clinical application, and accurate measuring [28].

The evidence levels evaluated by GRADE and GRADE-CERQual for outcome indicators in the included studies varied from very low to low, which might be due to small sample size, high risk of bias, and/or inconsistencies across studies. We observed interstudy heterogeneity, which might result from variable clinical parameters [50]. First, it should also be noted that the duration and frequency of the MLDs included in the study were different [25], the method of MLD was poorly described, the combination of MLD with other treatments and the lack of a control group might also have increased the uncertainty surrounding the benefit of MLD on the outcome of lymphedema. Second, the characteristics (*i.e.*, sample size, age and degree of edema [25]) of the participants were different in each study. Third, the treatment between the control group differed, like compression treatment and exercise strategy. Fourth, the evaluations used to detect arm volume reduction in the included studies were also different and might have affected the comparison of the clinical results.

Overall, this overview is the first one which systematically reviewed MLD technique on BCRL. Our comprehensive search, the systematic and clear qualification criteria, consideration of study quality, and our rigorous analytical approach were contributed to our overview advantages. However, the present study was limited by the methodological quality and the original studies only included RCTs, not observational studies.

5. Conclusion

We do not recommend the addition of MLD to CDT or compression therapy for patients with BCRL based on the results of the present review. More well designed and large RCTs are needed to provide a higher level of evidence to confirm the role of MLD in CDT, especially for patients under 60 years of age or with 1 month intervention duration.

AUTHOR CONTRIBUTIONS

WTX, DD and WQC—Conceptualization, Resources, Supervision; WTX, DD, YGG, YYL, HJL and JKW—Data curation; WTX, DD and YGG—Formal analysis; WTX, CXY, CC and WQC—Funding acquisition; WTX, DD, YGG, YYL, HJL, JKW and WQC—Investigation; WTX and DD—Methodology, Software, Visualization; WTX, WQC—Project administration; YYL, HJL, JQW and WQC—Validation; WTX—Writing-original draft; DD, CXY, CC—Writing-review & editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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