

Predictors of response to compression therapy in breast cancer-related lymphoedema: a systematic review and meta-analysis



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Summary

Background Breast cancer-related lymphoedema (BCRL) affects one in six breast cancer survivors and causes significant morbidity. Compression therapy is a cornerstone of BCRL treatment, yet response varies considerably and predictors of efficacy are not well-characterised, often conflicting across studies. Accordingly, this study aimed to identify and synthesise predictive factors for compression treatment response in BCRL.

Methods In this systematic review and meta-analysis, Medline ALL, Embase, Scopus, Web of Science, and Cochrane controlled trials and systematic review databases were systematically searched from inception to Dec 9, 2025. Eligible studies included all study designs, across any setting or timepoint, that evaluated compression treatment response predictors for BCRL. Studies comparing treatment modalities without evaluation of predictive factors on response were excluded. For each study, two independent reviewers conducted screening, data extraction, and bias/uncertainty assessments (QUIPS, GRADE). The primary outcome was percentage reduction in excess volume (PREV). Findings were integrated using narrative synthesis and random-effects meta-analysis, with subgroup analyses based on study characteristics. This review was registered with PROSPERO, CRD42025633750.

Findings Across 3247 studies, 67 met eligibility criteria (N = 6401). Mean PREV across 39 studies and 4529 patients was 45.13% (SD: 59.27; 95% CI: 43.41–46.86). Study quality was moderate, with 78.95% (45/57) articles having low bias in $\geq 3/6$ QUIPS domains. Moderate-certainty evidence supported high baseline excess volume (n = 12 studies), severe lymphoedema (n = 9), prior arm infection (n = 4), or prior lymphoedema therapy (n = 3) as predictors of lower PREV, and increased treatment compliance (n = 6) or lymphoscintigraphic uptake (n = 4) for higher PREV. Meta-analysis of nine studies revealed significant associations between lower PREV and older age (r = -0.135; 95% CI: -0.239, -0.028; p = 0.013; moderate certainty; $I^2 = 30.78$), higher baseline excess volume (r = -0.276; 95% CI: -0.453, -0.079; p = 0.0067; moderate certainty; $I^2 = 86.87$), and longer lymphoedema duration (r = -0.229; 95% CI: -0.361, -0.087; p = 0.0018; high certainty; $I^2 = 10.38$). Heterogeneity was low except for baseline volume, with minimal publication bias. Qualitative synthesis identified heterogeneity in age and lymphoedema duration categorisation, BCRL criteria, treatment protocols, and outcome measures.

Interpretation This synthesis of 71 distinct factors identified multiple predictors of compression response with moderate supportive evidence. Our findings support early intervention and adherence strategies in BCRL and provide an evidence base to enhance treatment decisions, patient counselling, and predictive model development. However, variability in study characteristics and analysis methodologies constrained comparability across predictors, limiting precision and consistency in low-certainty factors, like body-mass index or postoperative duration before lymphoedema onset, that may require further evidence before clinical application.

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Keywords: Breast cancer-related lymphoedema; Compression therapy; Treatment response; Breast cancer; Cancer survivorship

Research in context

Evidence before this study

We conducted a preliminary search of PubMed, MEDLINE, Embase, Google Scholar, and PROSPERO from database inception to December 11th, 2024, without language restrictions, to identify existing evidence on compression therapy response predictors in BCRL. Search terms included ("breast cancer" OR "breast neoplasm" OR "breast carcinoma") adj2 ("lymphoedema" OR "lymphoedema") AND ("response" OR "treatment effect" OR "reduction") AND ("factor*" OR "predictor*" OR "determinant*" OR "component*"). Multiple individual studies have reported associations between response outcomes and patient demographics, tumour or lymphoedema characteristics, prior treatments, and comorbid conditions. However, many were limited by small cohorts, incomplete reporting of datapoints, or inconsistent analytical approaches, contributing to variable study quality and inconsistent findings. Prior systematic reviews in BCRL described general trends for treatment efficacy predictors but were largely qualitative and based on few studies. One systematic review published in 2024 reported effect size estimates of 14 studies stratified by lymphoedema severity. To date, no systematic review or meta-analysis has comprehensively identified and synthesised predictive factors for compression therapy response in BCRL.

Added value of this study

This review of 67 studies, including more than 6000 patients, showed that older age and greater severity of lymphoedema presentation (higher baseline excess volume and longer lymphoedema chronicity) significantly predicted worse responses to compression therapy. Increased treatment compliance was associated with better outcomes. Patient BMI, number of positive or removed lymph nodes, and use of chemotherapy, radiotherapy, or hormone therapy were not found to be predictors of response. Patients with severe lymphoedema experience greater absolute volumetric improvements despite smaller relative changes.

Implications of all the available evidence

Clinical factors can assist in predicting treatment response to compression therapy. Evidence supports early intervention in mild, non-chronic lymphoedema when compression therapy is most effective. Emphasis on treatment adherence strategies and closer monitoring of older patients with severe or chronic lymphoedema may optimise treatment outcomes. However, the certainty of evidence for individual predictors remains moderate, with evaluations tempered by inadequate confounding adjustments by studies and heterogeneity in treatment protocols, outcome measures, and analytical methods. Further studies using larger cohorts, robust multivariable modelling, and standardised outcomes may strengthen the validity of identified predictors and enhance clinical applicability.

Introduction

Breast cancer-related lymphoedema (BCRL) represents one of the most debilitating challenges in breast cancer survivorship. It arises from lymphatic injury in surgery, radiation therapy, chemotherapy, or tumour-related changes. BCRL involves the accumulation of protein-rich interstitial fluid, which can cause symptoms of swelling, heaviness, tightness, and functional impairment that significantly impact quality of life (QoL), range of motion, and motor function. Patients may experience significant morbidity. Severe BCRL can be characterised by chronic inflammation, fibrosis, skin hardening, and increased risk of infections.¹ Among breast cancer survivors, BCRL has an overall incidence of 16.6% (95% CI: 13.6–20.2),² with a prevalence of 8–31% within five years post-cancer treatment.³

Complete decongestive therapy (CDT) remains the recommended treatment for lymphoedema management; it consists of education, skin care, manual

lymphatic drainage (MLD), exercises, and compression. Randomised controlled trials and multiple systematic reviews demonstrated that CDT is effective in reducing limb volume and improving clinical and patient-reported outcomes in BCRL.^{4–7} The utility of compression therapy has also expanded into prophylaxis prior to BCRL development.⁸ Percent Reduction of Excess Volume (PREV) is the preferred method for evaluating treatment response in BCRL, as it provides a proportional assessment of severity change.⁹

Despite the demonstrated efficacy of compression-based therapies, BCRL remains a chronic condition difficult to manage clinically. Treatment response varies considerably across patients. Demographic factors, lymphoedema characteristics, and surgical treatment history may predict treatment response, but evidence supporting these predictive factors shows considerable variability with conflicting findings across studies.

No systematic review has examined predictive factors for treatment response to compression therapy in BCRL. Understanding this landscape would assist in identifying patients who would benefit most from compression therapy and recognising those at risk of poor treatment responses.

This systematic review aims to identify predictive factors of treatment response (PREV) for compression therapy in patients with BCRL and determine their relative importance.

Methods

Study design

The systematic review and meta-analysis was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42025633750). Reporting was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA 2020).¹⁰ Given this study design and the exclusive use of published material, no formal ethics approval was sought. Ethical approval and written informed consent was gathered by individual studies included here, but not specifically for this work.

Search strategy and selection criteria

Eligible studies included any clinical trial, observational study, and systematic review evaluating patient-level factors associated with compression therapy response for patients who developed BCRL. All forms of compression therapy were included, such as garments, pneumatic wraps, or CDT. Studies comparing different forms of compression or treatment were eligible only if analyses examined patient-level characteristics associated with response. Outcome measures included any treatment response, like volume, circumference, lymphoscintigraphy, or QoL. Studies solely on primary lymphoedema, lower-limb, or head and neck lymphoedema were excluded. This search was limited to human studies, without language restrictions. Conference abstracts, dissertations, preprints, books, and other grey literature were excluded.

A comprehensive literature search was conducted across multiple databases, including MEDLINE ALL (Medline and Epub Ahead of Print and In-Process & Other Non-Indexed Citations), Embase Classic, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Scopus from Elsevier, and Web of Science Core Collection from Clarivate, from database inception until December 9th, 2025. Where available, each search strategy used a combination of controlled vocabulary terms and text words, adapting the database-specific search syntax. The search was iteratively revised (EY, RF, JYK) to ensure comprehensiveness (Medline ALL search

strategy: [Supplementary Table S1](#)). Additionally, reference lists of included studies after full-text and relevant systematic reviews^{4,5,11,12} were screened to identify further potentially relevant studies. References from database searches were imported to Covidence, a web-based collaboration software platform, for article screening.¹³ Following duplicate removal, 25 articles (four exemplars, seven similar but ineligible, 14 ineligible) underwent pilot screening independently for reviewer training, with a pair-wise 0.86–0.93 Cohen's kappa across the three reviewers. Each article's abstract and title were screened by two of three independent reviewers (EY, NL, SH). Articles meeting inclusion criteria or with conflicting decisions underwent full-text review. Full texts were screened independently by two of three reviewers and disagreements were resolved through discussion. Non-English articles were translated using Google Translate and DeepL, and compared for verification.

Data analysis

A standardised data extraction sheet was piloted on ten articles (selected alphabetically) for revision. The following study-level information was extracted independently by two of three reviewers (EY, NL, SH): title, authors, date of publication, country, study design, sample size and characteristics, statistical methods, treatment protocol, follow-up duration, volume measurement methods, lymphoedema definition, baseline and post-therapy volumes, outcome measures, predictive factors evaluated, and their degree of association. Conflicts were resolved through discussion. For non-English articles, translated data were used for data synthesis.

Two independent reviewers (EY, NL) used the Quality in Prognosis Studies (QUIPS) tool to evaluate methodological quality. QUIPS evaluated six domains on high, moderate, or low bias: participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis or reporting bias.¹⁴ QUIPS overall bias calculations were based on Grooten et al.¹⁵ Bias assessments used AMSTAR2 (A Measurement Tool to Assess Systematic Reviews 2) for systematic reviews¹⁶ and SANRA (Scale for the Assessment of Narrative Review Articles) for narrative reviews.¹⁷ Conflicts were resolved through discussion.

Outcomes

The primary outcome was PREV, defined as $PREV = 100\% \times ((\text{baseline EV} - \text{post-treatment EV}) / \text{baseline EV})$, where EV is the excess volume difference between normal and lymphoedematous arms.¹⁸ Secondary outcomes included absolute volume reduction in millilitres (baseline excess volume – post-treatment excess volume), and percentage reduction (baseline % excess volume – post-treatment % excess volume).¹⁸

Other response measures, like arm circumference reduction (CR), lymphoscintigraphy tracer assessments, or QoL score changes were also documented.

Statistical analysis

Pooled outcome means and variances were calculated using sample size-weighted averages. Individual studies were stratified by subgroups based on patient populations or study characteristics to identify overarching trends and concerns for heterogeneity. Two-tailed 95% confidence intervals (CIs) were derived using the t-distribution. If not reported, an estimated study-level PREV was imputed using available excess volume measurements, as volume reduction divided by baseline excess volume (both in either millilitres or percentage), with variance estimated using the propagation of error formula. If reported as medians, interquartile ranges, or ranges, data were converted to means and standard deviations using established methods.¹⁹ Studies lacking sufficient data for imputation, requiring both a measure of central tendency and variation, were excluded in pooled estimates for that section. For predictive factors, both significant and non-significant variables were extracted (e.g., Pearson correlation coefficients, t-tests). When study results were incomplete, such as p-values without corresponding effect sizes or measures of variance, study authors were contacted.

A meta-analysis was conducted to evaluate the association between predictive factors and PREV following compression therapy. Two types of effect sizes were assessed: correlation coefficients and standardised mean differences. Correlation coefficients were transformed using Fisher's Z-transformation, and a weighted average was calculated. If articles reported only univariate beta-regression, correlation coefficients were estimated by t-statistics of the beta coefficient ($t = \beta/SE$ of β ; $r = t/\sqrt{t^2 - df}$ where $SE =$ standard error, $df = n - 2$). For mean differences, a Hedges' g statistic was computed and analysed. Statistical heterogeneity was assessed using the inconsistency index I^2 , with heterogeneity defined as follows: very low if $\leq 25\%$, low if $\leq 50\%$, moderate if $< 75\%$, and high if $\geq 75\%$. Effect sizes and 95% CIs were calculated using the DerSimonian and Laird random-effects model to account for expected heterogeneity.²⁰

Publication bias was evaluated using Begg's and Egger's test in conjunction with funnel plots. Sensitivity analyses were performed to assess the robustness of pooled estimates, including the exclusion of studies at high and moderate risk of bias and studies that included patients without BCRL in measures of association. Additional analyses included leave-one-out sensitivity testing and trim-and-fill analysis for publication bias.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

assessed evidence certainty for predictive factors,²¹ by two independent reviewers (EY, NL). Starting certainty was set to high and adjusted by GRADE domains.²² All analyses were conducted using Excel, Python 3.10, MedCalc, and R (metafor).^{23–27}

Role of the funding source

There was no funding source for this study.

Results

From 3247 articles screened, 67 articles met inclusion criteria (63 primary studies, four reviews) (Fig. 1) with a median sample size of 72 patients and total cohort of 6401 patients (Supplementary Figure S1 and Supplementary Table S2).¹⁰ The predominant reason for screening exclusion involved the article focussing on BCRL, but without analysis that identified factors for differential treatment response.^{28,29} Seven articles were multicentre studies, and 16 employed some form of multivariable or adjusted analysis. Most studies utilised outpatient compression within all CDT modalities, calculating volume using arm circumference measurements with the truncated cone formulae. Follow-up ranged from five days to three years, with lymphoedema thresholds for study patient inclusion varying from 5% to 20% interlimb differences. Common patient exclusion criteria included bilateral BCRL, sub-threshold lymphoedema, or compression contraindications including active infections or concomitant venous occlusion. Each study was outlined in Supplementary Table S3, with bias assessments in Supplementary Table S4. QUIPS assessments of 57 primary studies identified overall bias being low, moderate, and high for 14 (25%), nine (16%), and 34 (60%) studies respectively. 45 studies had low bias in three or more of the six domains. Confounding bias was high in 15 studies. Three systematic reviews scored 7/16,³⁰ 15/16,⁵ and 14/16³¹ (AMSTAR2). One narrative review scored 7/12¹¹ (SANRA).

Volumetric change was the most frequently reported outcome, expressed as PREV (mean of 45.13% from 39 studies), absolute volume reduction (342.26 ml from 29 studies), or percentage reduction (10.65% from 22 studies). Other reported outcomes included classification of high/low responder status,^{32–36} arm circumference reduction,^{37–40} lymphoscintigraphic tracer testing,⁴¹ QoL,⁴² treatment failure,⁴³ and compression dependence.⁴⁴ Imputed datapoints were approximated using available study data where required. Volumetric changes calculated without imputation were presented in Supplementary Table S5, which exhibited similar values to post-imputation.

Retrospective cohort studies ($n = 28$) included more patients who underwent mastectomy or chemotherapy and had lower initial excess volume and shorter post-operative, lymphoedema, and follow-up durations than

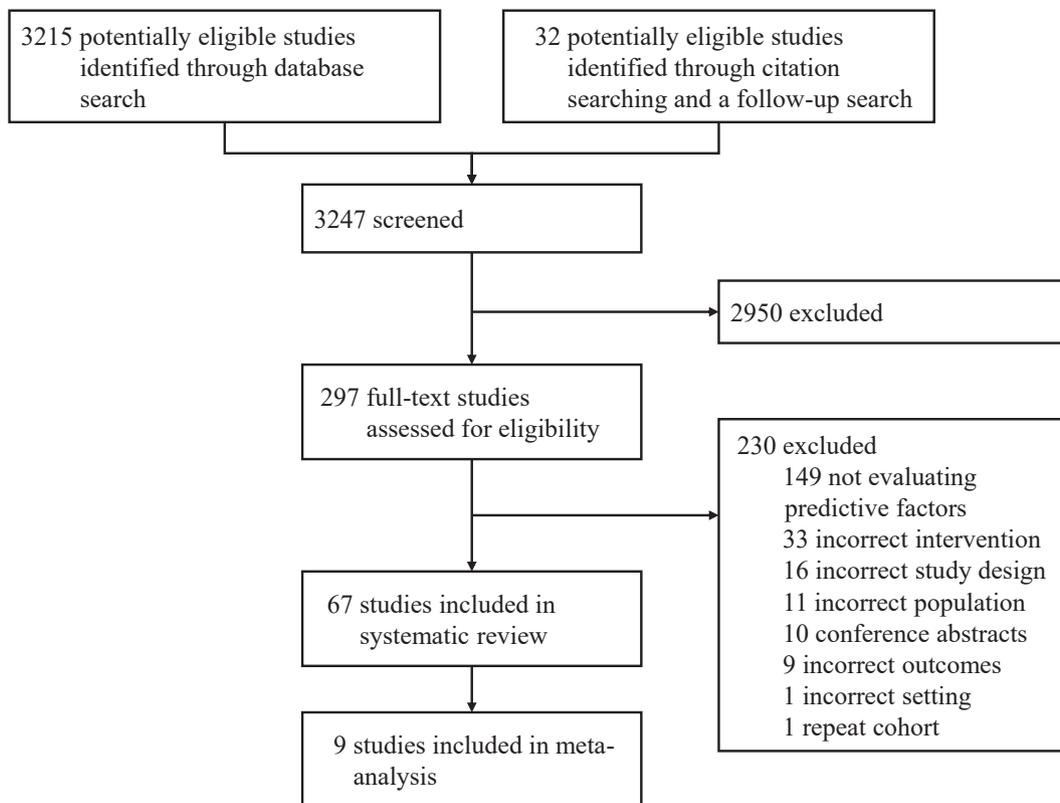


Fig. 1: Flowchart of study selection for inclusion in this review and meta-analysis*. *A total of 67 articles were included from a comprehensive search of databases and citations. PRISMA 2020 was followed.

prospective cohort studies ($n = 26$) (Supplementary Table S2). Randomised controlled trials (RCTs) ($n = 8$) included patients with more advanced tumour stages and longer postoperative and lymphoedema durations, but with the shortest follow-up and generally lower volume reduction than retrospective/prospective cohort studies.

Minimal PREV differences were found between single and multicentre studies, studies with and without eligibility restrictions (e.g., only including patients with unilateral BCRL or mastectomy), or across geographic regions and volume measurement methods (Table 1). Studies using outpatient treatment saw similar PREV ($n = 30$) to inpatient treatment ($n = 5$), both significantly higher than self-administered treatment ($n = 3$). PREV was lower in studies without full CDT modalities ($n = 6$) than with CDT ($n = 36$); RCT trial arms (CDT and CDT without MLD) were separately analysed for this comparison. However, these reflected study-level comparisons and should not be interpreted in place of trials explicitly designed to compare treatment methods. While absolute and percentage reductions generally increased with higher baseline percentage excess volume (PEV), no trend for PREV was qualitatively observed. No trend between

study follow-up duration and volumetric reduction was also identified.

71 distinct factors were reported, summarised in Table 2 by directionality and statistical significance. 21 factors were assessed by one article, while the remaining 50 were grouped: eight patient factors, 14 BCRL factors, four BCRL-treatment factors, 14 cancer or cancer-treatment factors, and ten baseline comorbidity and symptom factors. Each factor's directionality was classified as strong, moderate, weak, or inconclusive using modified criteria from Disipio et al.² Both strong and moderate levels required at least one high quality study of low bias, with consistent findings in 75% and 50% of studies involved, respectively. Factors were classified as weak when these criteria were not met, and inconclusiveness was assigned when few studies were available or when direction of findings was unclear.

Age was the most studied patient factor, with older age weakly linked to poorer response, supported by three studies^{18,45,46} with two low bias.^{45,46} However, 17 others (81%) reported insignificant associations and one saw older age associated with lower treatment failure.⁴³ Higher body-mass index (BMI) weakly associated with poorer response in four studies^{43,46–48} with one low bias.⁴⁶ However, 14 others (74%) reported

Variable	Included Studies (n)	n	Absolute Reduction (%)	Absolute Reduction (ml)	PREV
	All Studies	63	10.65 (14.38) n = 22 N = 2100 95% CI: 10.04-11.27	342.26 (384.91) n = 29 N = 3966 95% CI: 330.28-354.25	45.13 (59.27) n = 39 N = 4529 95% CI: 43.41-46.86
Centre	Single centre	56	10.30 (13.95) n = 19 N = 1716 95% CI: 9.64-10.97	341.81 (391.44) n = 26 N = 3582 95% CI: 328.98-354.63	44.84 (60.54) n = 35 N = 4018 95% CI: 42.96-46.71
	Multicentre	7	12.21 (16.07) n = 3 N = 384 95% CI: 10.60-13.82	346.54 (318.05) n = 3 N = 384 95% CI: 314.62-378.45	47.48 (48.12) n = 4 N = 511 95% CI: 43.30-51.66
Unilateral BCRL	Only Unilateral BCRL	46	9.48 (15.52) n = 20 N = 1691 95% CI: 8.74-10.22	319.61 (310.68) n = 23 N = 2837 95% CI: 308.17-331.04	45.82 (61.41) n = 30 N = 3266 95% CI: 43.71-47.92
	Unspecified Laterality	17	15.52 (5.99) n = 2 N = 409 95% CI: 14.94-16.10	399.20 (523.04) n = 6 N = 1129 95% CI: 368.66-429.74	43.38 (53.33) n = 9 N = 1263 95% CI: 40.43-46.32
Post-Mastectomy	Only Post-mastectomy	13	6.06 (8.67) n = 4 N = 366 95% CI: 5.17-6.96	243.54 (313.56) n = 5 N = 480 95% CI: 215.42-271.66	39.13 (106.95) n = 7 N = 531 95% CI: 30.01-48.24
	Mixed Surgery	50	11.62 (15.14) n = 18 N = 1734 95% CI: 10.91-12.33	355.86 (391.82) n = 24 N = 3486 95% CI: 342.85-368.87	45.93 (49.58) n = 32 N = 3998 95% CI: 44.40-47.47
Region	Asia	17	7.66 (13.51) n = 6 N = 562 95% CI: 6.54-8.78	172.36 (351.75) n = 7 N = 580 95% CI: 143.68-201.05	43.26 (111.72) n = 8 N = 607 95% CI: 34.36-52.17
	Australasia	2	24.66 (11.51) n = 2 N = 103 95% CI: 22.41-26.91	580.10 (53.46) n = 1	62.34 (36.70) n = 2 N = 103 95% CI: 55.17-69.51
	Europe	20	12.21 (15.76) n = 4 N = 475 95% CI: 10.79-13.63	424.43 (414.31) n = 7 N = 2058 95% CI: 406.52-442.34	49.80 (47.64) n = 10 N = 2340 95% CI: 47.87-51.73
	Middle East	10	11.17 (9.32) n = 6 N = 618 95% CI: 10.43-11.90	321.83 (315.50) n = 8 N = 845 95% CI: 300.53-343.14	40.08 (36.84) n = 8 N = 857 95% CI: 37.61-42.55
	North America	15	8.69 (20.90) n = 2 N = 213 95% CI: 5.86-11.51	174.92 (283.11) n = 4 N = 276 95% CI: 141.37-208.47	36.57 (47.68) n = 9 N = 493 95% CI: 32.35-40.79
	South America	3	7.57 (14.08) n = 2 N = 129 95% CI: 5.12-10.02	143.35 (253.39) n = 2 N = 129 95% CI: 99.21-187.50	21.91 (56.30) n = 2 N = 129 95% CI: 12.10-31.72
Volume Measurement Method	Measurement via Truncated Cone/Cylinder Formula	38	12.13 (14.76) n = 16 N = 1596 95% CI: 11.41-12.86	353.52 (394.28) n = 23 N = 3398 95% CI: 340.26-366.78	47.40 (59.30) n = 29 N = 3689 95% CI: 45.48-49.31
	Measurement via Water Displacement Volumetry	5	3.57 (5.36) n = 2 N = 219 95% CI: 2.86-4.29	361.55 (315.79) n = 3 N = 347 95% CI: 328.20-394.89	38.87 (67.06) n = 4 N = 458 95% CI: 32.71-45.03
	Measurement of Both Cone and Water	3	ND	253.00 (191.00) n = 1	42.60 (20.00) n = 1
	Perometer	3	8.94 (18.70) n = 2 N = 175 95% CI: 6.15-11.73	93.28 (321.30) n = 1	20.69 (57.10) n = 2 N = 175 95% CI: 12.17-29.21
Treatment Protocol	Complete CDT Protocol	59	11.11 (13.75) n = 20 N = 1842 95% CI: 10.48-11.73	359.41 (387.01) n = 27 N = 3687 95% CI: 346.92-371.91	46.56 (59.30) n = 36 N = 4194 95% CI: 44.77-48.36
	Incomplete CDT with Compression	8	7.42 (17.95) n = 4 N = 258 95% CI: 5.22-9.63	115.44 (268.98) n = 5 N = 279 95% CI: 83.74-147.14	21.37 (57.57) n = 6 N = 293 95% CI: 14.75-27.98
Treatment Level of Supervision	Inpatient	5	4.19 (2.30) n = 1	374.84 (445.89) n = 5 N = 1930 95% CI: 354.94-394.75	47.36 (71.74) n = 5 N = 1930 95% CI: 44.16-50.57
	Outpatient	48	12.13 (14.70) n = 18 N = 1626 95% CI: 11.42-12.85	342.46 (308.12) n = 21 N = 1787 95% CI: 328.16-356.76	46.43 (45.68) n = 30 N = 2336 95% CI: 44.58-48.28
	Self-Administered	6	6.69 (18.35) n = 2 N = 190 95% CI: 4.07-9.32	70.77 (284.85) n = 2 N = 190 95% CI: 30.00-111.53	16.82 (65.56) n = 3 N = 204 95% CI: 7.77-25.87
Follow-Up Duration to Outcome Assessment	0-2 weeks	13	9.20 (16.26) n = 4 N = 498 95% CI: 7.76-10.63	286.63 (290.09) n = 8 N = 1059 95% CI: 269.14-304.12	40.69 (85.78) n = 8 N = 1029 95% CI: 35.44-45.94
	2-4 weeks	24	13.82 (11.08) n = 9 N = 983 95% CI: 13.13-14.52	372.03 (290.97) n = 12 N = 1243 95% CI: 355.84-388.23	50.11 (37.98) n = 17 N = 1565 95% CI: 48.23-51.99
	4 weeks to 3 months	11	7.50 (18.95) n = 5 N = 367 95% CI: 5.55-9.44	163.60 (368.01) n = 6 N = 386 95% CI: 126.77-200.43	29.07 (54.05) n = 7 N = 455 95% CI: 24.09-34.05
	3 months-6 months	1	ND	^a	^a
	6 months to 1 year	9	5.34 (10.16) n = 3 N = 195 95% CI: 3.90-6.77	381.06 (692.26) n = 2 N = 596 95% CI: 325.37-436.75	34.34 (67.63) n = 5 N = 741 95% CI: 29.46-39.22
>1 year	3	7.26 (13.27) n = 1	441.60 (215.59) n = 1	61.51 (35.24) n = 2 N = 739 95% CI: 58.96-64.05	
Average Baseline PEV	0-10%	4	3.48 (3.48) n = 3 N = 387 95% CI: 3.13-3.83	91.80 (304.20) n = 1	39.34 (126.23) n = 3 N = 387 95% CI: 26.73-51.96
	10-20%	5	3.59 (12.26) n = 2 N = 112 95% CI: 1.29-5.88	33.87 (208.94) n = 1	26.16 (54.72) n = 3 N = 130 95% CI: 16.66-35.65
	20-30%	9	9.47 (18.83) n = 6 N = 476 95% CI: 7.78-11.17	203.75 (339.98) n = 5 N = 419 95% CI: 171.11-236.40	38.88 (46.23) n = 8 N = 672 95% CI: 35.38-42.38
	30-40%	6	13.27 (9.06) n = 6 N = 717 95% CI: 12.60-13.93	351.47 (334.04) n = 5 N = 692 95% CI: 326.54-376.40	45.30 (43.64) n = 6 N = 717 95% CI: 42.10-48.50
	>40%	8	19.99 (20.22) n = 4 N = 300 95% CI: 17.70-22.29	418.21 (115.07) n = 5 N = 657 95% CI: 409.39-427.02	45.03 (21.03) n = 6 N = 690 95% CI: 43.45-46.60

^aMean (SD) unless otherwise specified; n: number of studies; N: combined patient cohort; if missing, values were imputed from available data (e.g., median, Q1, Q3). ^bCDT: complete decongestive therapy; PEV: percent excess volume; ND: no data.

Table 1: Volumetric treatment response to compression therapy in breast cancer-related lymphoedema^{a,b}

Factors	Significant		References		Non-Significant		References
	n	(%)	+	-	n	(%)	All
Patient Factors (8 factors)							
Age	4	19	Less Tx Failure: Vignes 2011	PREV: Bojinović-Rodić 2021, Liao 2013 VR %: Silva 2024	17	81	PREV: Forner-Cordero 2021 Forner-Cordero 2010 Haghghat 2013 Keskin 2020 Liao 2016 Mestre 2017 Quere 2014 Vignes 2013; VR %: Kim 2024; VR ml: Mondry 2004; VR: Hwang 2007 Jung 2020 Kim 2019; Arm CR: Ferrandez 2005 Ferrandez 1992; Post-Tx PEV: Eyigor 2015; Tracer Visibility: Medina-Rodriguez 2020; Change in QoL Scores: Mondry 2004; Change in Pain Scores: Mondry 2004
BMI	5	26	VR ml: Vignes 2006	PREV: Duyur Cakit 2019 VR %: Silva 2024 More Tx Failure: Vignes 2011 QoL: Yaman 2025; Function Subscores: Yaman 2025	14	74	PREV: Forner-Cordero 2021 Forner-Cordero 2010 Haghghat 2013 Keskin 2020 Mestre 2017 Vignes 2013; VR %: Kang 2012 Kim 2024 Vignes 2006 Yaman 2025; VR ml: Bunce 1994; VR: Jung 2020 Yaman 2025; Arm CR: Ferrandez 2005; Tracer Visibility: Medina-Rodriguez 2020
Post-Operative Weight Gain	2	67	Low Post-Tx PEV: Eyigor 2015	PREV: Bertelli 1992	1	33	PREV: Eyigor 2015
Education Level	1	33	PREV: Keskin 2020	^a	2	67	PREV: Haghghat 2013; VR: Jung 2020
Employment status	1	33	PREV: Quere 2014	^a	2	67	PREV: Haghghat 2013 Keskin 2020
Body Weight	1	50	^a	More Tx Failure: Vignes 2011	1	50	VR ml: Mondry 2004; Change in QoL Scores: Mondry 2004; Change in Pain Scores: Mondry 2004
Activity Level	0	0	^a	^a	2	0	PREV: Eyigor 2015; Arm CR: Sapula 2017; Post-Tx PEV: Eyigor 2015
Marital Status	0	0	^a	^a	2	0	PREV: Haghghat 2013; VR: Jung 2020
Lymphoedema-Related Factors (14 factors)							
Lymphoedema Duration	12	52	VR ml: Vignes 2006	PREV: Haghghat 2013, Keskin 2020, Liao 2013, McNeely 2004, Michopoulos 2021; VR %: Borman 2022, Kim 2024; VR: Su 2025; Arm CR: Sapula 2017; Tracer Visibility: Medina-Rodriguez 2020; Qual: Dennis 1993	11	48	PREV: Bojinović-Rodić 2021 Forner-Cordero 2021 Mestre 2017 Vignes 2013; VR %: Silva 2024 Szuba 2002 Vignes 2006; VR ml: Dayes 2013; VR: Kim 2019 Silva 2024; Treatment Failure: Vignes 2011; QoL Subscale Improvement: Haghghinejad 2016
Baseline PEV	13	81	PREV: Haghghat 2013; VR %: Choi 2022, Hwang 2013, Kim 2024; VR ml: Vo 2024	PREV: Bojinović-Rodić 2021, Duyur Cakit 2019, Forner-Cordero 2021, Forner-Cordero 2010, Keskin 2020, Liao 2013, Quere 2014, Vo 2024 VR: Jung 2020	3	19	PREV: Eyigor 2015 Liao 2016; VR %: Johansson 2010
Postoperative Duration	5	36	PREV: Vignes 2013; VR ml: Mondry 2004; Arm CR: Mondry 2004; Low Post-Tx PEV: Eyigor 2015	PREV: Keskin 2020; VR: Jung 2020	9	64	PREV: Bojinović-Rodić 2021 Eyigor 2015 Haghghat 2013 Mestre 2017 Quere 2014; VR %: Johansson 2010; VR: Cariddi 1991; Arm CR: Sapula 2017; Treatment Failure: Vignes 2011
Lymphoedema Severity	8	73	VR %: Choi 2022, Kim 2024; Arm CR: Kim 2011	PREV: McNeely 2004; VR: Jung 2020; Tracer Visibility: Medina-Rodriguez 2020; Qual: Dennis 1993	3	27	VR %: McNeely 2022; VR ml: Dayes 2013; Arm CR: Li 2020
Lymphoedema Stage	6	55	VR %: Wozniowski 2001; VR: Gilchrist 2024; RoM improvement (shoulder flexion, abduction): Varshini R. 2025	PREV: Keskin 2020, Wozniowski 2001; VR %: Borman 2022; Qual: Smile 2018; RoM improvement (shoulder internal rotation): Varshini R. 2025	5	45	PREV: Forner-Cordero 2021 Forner-Cordero 2010 Haghghat 2013; VR: Kim 2019; Arm CR: Varshini R 2025; RoM improvement (external rotation): Varshini R 2025
Baseline Vol ml	5	71	VR ml: Karadibak 2009; VR %: Wilburn 2006	PREV: Forner-Cordero 2010, Karadibak 2009, Ramos 1999; High Post-Tx PEV: Eyigor 2015	2	29	VR %: Kang 2012; Arm CR: Ferrandez 1992
Lymphoedema Grade	4	80	VR ml: Mondry 2004, Morgan 1992; VR %: Morgan 1992; Arm CR: Mondry 2004; QoL Subcale Improvement: Haghghinejad 2016	PREV: Morgan 1992; VR %: Borman 2022	1	20	QoL Subscale Improvement: Haghghinejad 2016

(Table 2 continues on next page)

Factors	Significant		References		Non-Significant		References
	n	(%)	+	-	n	(%)	All
(Continued from previous page)							
Dominant/Non-Dominant Sided BCRL	1	20	^a	Arm CR: Ferrandez 1992	4	80	PREV: Forner-Cordero 2010 Haghighat 2013; VR %: Kim 2024; VR: Jung 2020
Left/Right Side of BCRL	0	0	^a		5	100	PREV: Keskin 2020; VR %: Bergmann 2014; VR ml: Randheer 2011; VR: Jung 2020
ECF Ratio from Bioimpedance				Arm CR: Kim 2011			VR: Jung 2020
SFBIA Ratio	2	67		VR %: Kim 2024; Arm CR (above elbow): Kim 2011	1	33	Arm CR (below elbow): Kim 2011
Lymphoscintigraphy LN Uptake	2	40		PREV: Kim 2020 (QAI for axillary LN uptake), Szuba 2002 (pre-therapeutic ARR)	3	60	VR %: Szuba 2002 (pre-therapeutic ARR); VR: Kim 2019 (axillary LN uptake ratio, upper extremity uptake ratio); Clinical Response: Hwang 2007 (axillary LN uptake)
Lymphoscintigraphy Structure Visibility	2	50		VR: Kim 2019 (visible axillary LNs); Clinical Response: Hwang 2007 (visible main lymphatic vessel)	2	50	PREV: Kim 2020 (visible axillary and/or supraclavicular LNs); VR: Kim 2019 (visible main lymphatic vessels, visible collateral vessels)
Lymphoscintigraphy for Dermal Backflow	1	33	^a		2	66	VR %: Szuba 2002 (DBR, rDBR); VR: Kim 2019 (dermal backflow)
Treatment-Related Factors (4 factors)							
Compliance	6	43		PREV: Forner-Cordero 2021, Forner-Cordero 2010, Boris 1997; VR: Kim 2019; Less Risk of Regaining BCRL: Vignes 2007, Gallagher 2021	8	57	PREV: Bojinović-Rodić 2021 Rockson 2023; VR %: Brown 2015; VR ml: Bunce 1994 Ergin 2018 Mondry 2004 Rockson 2023; VR: Jung 2020 Change in QoL Scores: Mondry 2004 Change in Pain Scores: Mondry 2004
Prior Lymphoedema Therapy	3	75	^a		1	25	VR ml: Vo 2024
Number or duration of compression sessions	2	66		VR: Su 2025	1	33	PREV: Liao 2016
Seasonality of Tx	1	25		PREV: Forner-Cordero 2010	3	75	PREV: Forner-Cordero 2010 Liao 2013 VR: Jung 2020
Tumour and Cancer-Treatment Related Factors (14 factors)							
Use of Radiotherapy	2	11		QoL Subscale Improvement: Haghighinejad 2016	16	89	PREV: Bojinović-Rodić 2021 Forner-Cordero 2021 Forner-Cordero 2010 Haghighat 2013 Keskin 2020 Liao 2013 Thomas 2007 Yamamoto 2007; VR %: Bergmann 2014 Kim 2024 McNeely 2022; VR ml: Mondry 2004; VR: Cariddi 1991 Jung 2020; Treatment Failure: Vignes 2011; Sessions to Plateau: Thomas 2007; QoL Subscale Improvement: Haghighinejad 2016; Change in QoL Scores: Mondry 2004; Change in Pain Scores: Mondry 2004
Type of Surgery (Mastectomy vs Other)	3	23	^a		10	77	PREV: Forner-Cordero 2010 Haghighat 2013 Keskin 2020 Liao 2013 Vignes 2013; VR %: Bergmann 2014; VR: Cariddi 1991; Arm CR: Ferrandez 2005; Treatment Failure: Vignes 2011; QoL Subscale Improvement: Haghighinejad 2016
Use of Chemotherapy	4	36	^a		7	64	PREV: Forner-Cordero 2010, Keskin 2020; VR: Jung 2020; Arm CR: Ferrandez 1992
Number of Removed LNs	1	11	^a		8	89	PREV: Bojinović-Rodić 2021 Keskin 2020 Liao 2016 Liao 2013 Thomas 2007; VR %: Bergmann 2014 Szuba 2002; Arm CR: Ferrandez 2005; Sessions to Plateau: Thomas 2007

(Table 2 continues on next page)

Factors	Significant		References		Non-Significant		References
	n	(%)	+	-	n	(%)	All
(Continued from previous page)							
Tumour Stage	2	25	VR %: Kim 2024	VR: Jung 2020	6	75	PREV: Mestre 2017 Vignes 2013; VR %: Bergmann 2014; VR ml: Mondry 2004 Jahan 2025; Arm CR: Ferrandez 1992; Change in QoL Scores: Mondry 2004; Change in Pain Scores: Mondry 2004
Use of Hormone Therapy	0	0 ^a		^a	7	100	PREV: Bojinović-Rodić 2021 Forner-Cordero 2021 Haghghat 2013 Keskin 2020 Vignes 2013; VR ml: Mondry 2004; Treatment Failure: Vignes 2011; Change in QoL Scores: Mondry 2004; Change in Pain Scores: Mondry 2004
Tumour Grade	1	33	QoL Subscale Improvement: Haghghinejad 2016	^a	2	67	PREV: Keskin 2020; QoL Subscale Improvement: Haghghinejad 2016
Presence of Positive LNs	1	33	^a	VR: Jung 2020	2	67	VR %: Bergmann 2014; VR ml: Randheer 2011
Tumour Type	1	50	^a	VR: Jung 2020	1	50	PREV: Keskin 2020
Axillary Radiation	1	50	^a	PREV: Forner-Cordero 2010	1	50	VR %: McNeely 2022
Number of Positive LNs	0	0 ^a		^a	2	100	PREV: Bojinović-Rodić 2021 Keskin 2020
Dosage of Radiotherapy	0	0 ^a		^a	2	100	PREV: Forner-Cordero 2021 Forner-Cordero 2010
Hormone Therapy Duration	0	0 ^a		^a	2	100	Post-Tx PEV: Eyigor 2015 Eyigor 2015
Use of ALND	0	0 ^a		^a	2	100	PREV: Yamamoto 2007; VR %: Kim 2024
Presence of Comorbid Conditions or Other Baseline Factors (10 factors)							
Prior Arm Infection	4	44	^a	PREV: Bojinović-Rodić 2021, Forner-Cordero 2021, Keskin 2020; VR: Jung 2020	5	56	PREV: Forner-Cordero 2010 Vignes 2013; VR %: Bergmann 2014; VR ml: Randheer 2011; Arm CR: Ferrandez 2005
Baseline Limited RoM	1	25	VR %: Bergmann 2014	^a	3	75	PREV: Forner-Cordero 2021 Forner-Cordero 2010 Keskin 2020
Baseline Pain	0	0 ^a		^a	4	100	PREV: Bojinović-Rodić 2021 Keskin 2020; VR %: Bergmann 2014; VR ml: Mondry 2004
Baseline Heaviness	1	33	^a	PREV: Forner-Cordero 2010	2	67	PREV: Keskin 2020; VR %: Bergmann 2014
Presence of Fibrosis	1	33	VR %: Bergmann 2014	^a	2	67	PREV: Forner-Cordero 2021 Forner-Cordero 2010
Baseline Numbness	0	0 ^a		^a	3	100	PREV: Forner-Cordero 2010 Keskin 2020
Venous Insufficiency	1	50	PREV: Forner-Cordero 2010	^a	1	50	PREV: Forner-Cordero 2021
Locoregional Disease	1	50	^a	Sessions to Plateau: Pinell 2008	1	50	PREV: Pinell 2008
Presence of Comorbidities	0	0 ^a		^a	2	100	PREV: Bojinović-Rodić 2021 Haghghat 2013
Metabolic Syndrome	1	100	^a	PREV: Pirincci 2024; VR %: Pirincci 2024	0	0	^a

Factors with only 1 assessment (21 factors): Significant (+): Mental Health (Haghghinejad 2016); Blood D-Dimer Levels (Kim 2024); Presence of Lymphorrhoea (Ferrandez 2005). **Significant (-):** Arm Paraesthesia (Bergmann 2014); Poorer Social/Financial Supports or Health (Dennis 1993); Taxane Chemotherapy Regimen (Jung 2020), Presence of Inflammatory Episodes (Cariddi 1991). **Insignificant (n = 14):** Breast Reconstruction, Supraclavicular Radiation, Number of Prior Arm Infections, Lymphoscintigraphic Infection Site Clearance, Winged Scapula, Number of Comorbidities, Hypertension, Proteinemia, Puckered Scarring, Presence of Breast Oedema, Presence of Hand Oedema, Nervous Impairment, Pre-Tx QoL, Pre-Tx EORTC QLQ Scores. ^aFactors were ordered by category and number of studies that assessed it. + factors were associated with better treatment response with the presence or increase of the factor. - factors were associated with poorer treatment response. Individual article citations are available in [Supplementary Table S3](#). ^bCDT: complete decongestive therapy; MLD: manual lymphatic drainage; PREV: percentage reduction of excess volume; VR: volume reduction; CR: circumference reduction; RoM: range of motion; Tx: treatment; PEV: percent excess volume; LN: lymph node; SFBIA: single frequency bioelectrical impedance analysis; QAI: quantitative asymmetry index; ARR: axillary radioactivity ratio; DBR: dermal backflow radioactivity ratio (affected to non-affected); rDBR: DBR (non-affected to affected).

Table 2: Studies reporting treatment response in BCRL and associated predictive factors^{a,b}

insignificant associations and one saw opposite associations.⁴⁹ Higher education and employment status were linked to higher PREV in two studies,^{50,51} but found insignificant by two others. Trends for body weight, activity level, and marital status were inconclusive.

Longer lymphoedema duration was moderately linked to poorer response, supported by eleven

studies with three having low bias.^{1,31,52} It was associated with better response in one study⁴⁹ and insignificant in 11. Postoperative duration before lymphoedema onset was found to be inconclusive, with longer duration linked to better response by three studies,^{33,53,54} poorer response by two studies,^{44,50} and insignificant in nine.

Baseline PEV was moderately predictive of response, with a disparity between modes of volumetric outcome. Higher PEV linked to lower PREV in eight studies,^{9,18,45,47,50,51,55,56} but higher absolute reduction in four studies,^{56–59} with another two studies in opposing directions^{44,52} and three studies insignificant.^{54,60,61} Similarly, millilitre baseline volume was moderately predictive, with higher volume linked to lower PREV in three studies^{9,62,63} and to greater volume reduction in two studies. Other measures like lymphoedema severity, stage, or grade generally corresponded to lower PREV^{50,64–66} and higher absolute volume or circumference reduction.^{5,40,53,57,59,65,66} Notably, this directionality difference between PREV and absolute measures was observed intra-study for three studies.^{56,62,66} Indirect severity measures like bioimpedance extracellular fluid (ECF) ratio,⁴⁰ single frequency bioimpedance analysis (SFBA) ratio,^{40,59} and axillary lymph node tracer uptake or visibility^{32,67,68} generally correlated with better response. One study identified greater lymphoedema severity as linked to greater improvements in range of motion for shoulder flexion and abduction, but less improvements in shoulder internal rotation.⁶⁹

Higher compliance was associated with better response in six studies, though insignificant in eight (57%). Having prior lymphoedema therapy or more treatment sessions was linked to poorer response^{37,50,51,56} except to better response in one³¹ and was insignificant in another.⁶⁰ One study found better responses in autumn,⁹ but seasonality was not significant in two others.^{18,44}

Most studies found tumour characteristics or cancer treatment modality not significant for BCRL treatment response. While studies found the use of radiotherapy,⁴⁴ axillary radiation,⁹ mastectomy (compared to breast-conserving surgeries or lumpectomies),^{37,44,55} chemotherapy,^{9,37,44,50} or more removed lymph nodes⁴⁴ as linked to poorer response, 42 studies found the association as not significant (17 studies on radiotherapy, ten on mastectomy, seven on chemotherapy, and eight on lymph node removal). Factors like hormone therapy use and duration, radiotherapy dosage, or receiving axillary lymph node dissection (ALND) (compared to sentinel lymph node biopsy SLNB) were not significantly related to treatment response. For tumour stage, two studies reported significant results in opposing directions^{44,59} while six studies were insignificant. Tumour grade, type, and presence of positive lymph nodes were insignificant. One study linked invasive carcinoma and metastatic lymph nodes to higher compression dependency.⁴⁴

Prior arm infections, like cellulitis, erysipelas, or lymphangitis, was associated with poorer response in four^{44,45,50,55} but insignificant in five.^{9,33,39,70,71} Better treatment response was found in patients with fibrosis,⁷⁰ venous insufficiency,⁹ limited range of motion,⁷⁰ lymphorrhea presence,³⁹ or higher blood D-dimer

levels,⁵⁹ and worse response in patients with baseline heaviness,⁹ metabolic syndrome,⁷² arm paraesthesia,⁷⁰ or inflammatory episodes.⁷³ Baseline QoL across different subscales was not significantly linked to volume reduction.⁷⁴

Meta-analysis of nine studies assessed the association of eleven factors with PREV with random-effects models (Fig. 2), using correlation coefficients for continuous variables or standardised mean differences for categorical variables. Study quality was moderate, with eight having low-to-moderate bias across at least five QUIPS domains. Older age was significantly associated with lower PREV in six studies ($r = -0.135$; 95% CI: $-0.239, -0.028$; $p = 0.013$; $I^2 = 30.78\%$),^{9,18,45,50,52,60} along with higher baseline excess volume (percentage or millilitres) ($r = -0.276$; 95% CI: $-0.453, -0.079$; $p = 0.0067$),^{9,18,45,47,50,52,55,60} and longer lymphoedema duration ($r = -0.229$; 95% CI: $-0.361, -0.087$; $p = 0.0018$; $I^2 = 10.38\%$).^{18,45,50} Significant heterogeneity was observed between studies assessing baseline excess volume ($Q = 53.32$; $p < 0.0001$; $I^2 = 86.87\%$ – high).

Non-significant relationships were reported for BMI ($r = 0.046$; 95% CI: $-0.058, 0.151$; $p = 0.38$; $I^2 = 0.00\%$),^{9,50,52} number of removed lymph nodes ($r = -0.0197$; 95% CI: $-0.289, 0.252$; $p = 0.89$; $I^2 = 80.19\%$),^{18,45,50,60,75} number of positive lymph nodes ($r = 0.0756$; 95% CI: $-0.118, 0.263$; $p = 0.44$; $I^2 = 0.00\%$),^{45,50} postoperative duration ($r = -0.0988$; 95% CI: $-0.353, 0.169$; $p = 0.47$; $I^2 = 74.24\%$),^{45,50,52} adjuvant radiotherapy ($d = -0.0166$; 95% CI: $-0.241, 0.208$; $p = 0.88$; $I^2 = 3.55\%$),^{9,18,45,50,52} adjuvant chemotherapy ($d = -0.517$; 95% CI: $-3.815, 2.781$; $p = 0.76$; $I^2 = 98.75\%$),^{9,50,52} hormone therapy ($d = -0.0486$; 95% CI: $-0.282, 0.185$; $p = 0.68$; $I^2 = 0.00\%$),^{9,45,50,52} and prior mastectomy ($d = -0.0912$; 95% CI: $-0.310, 0.127$; $p = 0.41$; $I^2 = 0.00\%$).^{9,18,50,52} Significant heterogeneity was observed between studies assessing removed lymph nodes ($Q = 20.19$; $p = 0.0005$; $I^2 = 80.19$ –high) and postoperative duration ($Q = 7.76$; $p = 0.021$; $I^2 = 74.24\%$ –moderate).

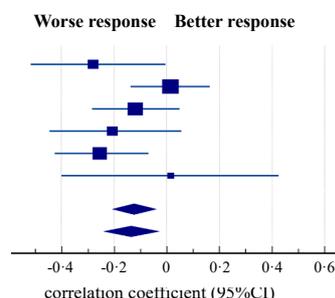
Across all factors, Begg's test detected no evidence of publication bias at 5% significance. Egger's test suggested potential bias for positive lymph nodes (intercept: -20.99 ; $p < 0.0001$). GRADE assessment for most factors reported moderate certainty, with 72.73% (8/11) factors having inconsistency concerns (Supplementary Table S6). Notably, lymphoedema duration had high certainty of evidence, while age and baseline excess volume had moderate certainty. Funnel plots and trim-and-fill plots for publication bias were presented in Supplementary Figure S2. Visual inspection of funnel plots did not demonstrate asymmetry for any factor. However, trim-and-fill analyses imputed two studies with higher effect sizes for postoperative duration and BMI, one study with a lower effect size for lymphoedema chronicity, and one study with a higher effect size for radiotherapy. Imputation did not alter the

Meta-Analysis for PREV

a Age

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.28 (-0.52 to -0.005)
Forner-Cordero et al., ⁹ 2010	171	0.014 (-0.14 to 0.16)
Haghighat et al., ⁵² 2013	137	-0.12 (-0.28 to 0.049)
Keskin et al., ⁵⁰ 2020	57	-0.21 (-0.44 to 0.057)
Liao et al., ¹⁸ 2013	107	-0.26 (-0.42 to -0.068)
Liao, ⁶⁰ 2016	23	0.016 (-0.40 to 0.43)
Total (fixed effects)	546	-0.124 (-0.21 to -0.039)
Total (random effects)	546	-0.135 (-0.24 to -0.028)

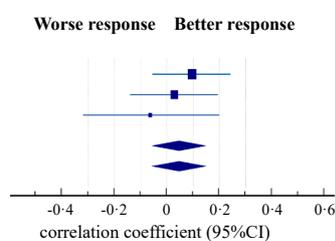
Heterogeneity: $Q=7.22, I^2=30.78\%$ Egger's Test: intercept=-1.16 (P=0.52)
 Test for overall effect: $z=-2.47$ (P=0.013) Begg's Test: tau=-0.20 (P=0.57)



b BMI

Source	Sample size	Correlation coefficient (95%CI)
Forner-Cordero et al., ⁹ 2010	171	0.096 (-0.050 to 0.24)
Haghighat et al., ⁵² 2013	137	0.028 (-0.14 to 0.20)
Keskin et al., ⁵⁰ 2020	57	-0.064 (-0.32 to 0.20)
Total (fixed effects)	365	0.046 (-0.058 to 0.15)
Total (random effects)	365	0.046 (-0.058 to 0.15)

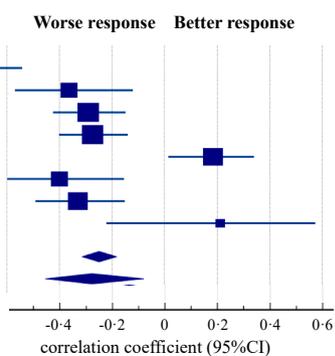
Heterogeneity: $Q=1.12, I^2=0\%$ Egger's Test: intercept=-2.59 (P=0.24)
 Test for overall effect: $z=0.873$ (P=0.38) Begg's Test: tau=-1.00 (P=0.12)



c Baseline Excess Volume (percentage/millilitres)

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.71 (-0.82 to -0.54)
Duyur Cakit et al., ⁴⁷ 2019	59	-0.36 (-0.57 to -0.12)
Forner-Cordero et al., ⁹ 2010	171	-0.29 (-0.42 to -0.15)
Forner-Cordero et al., ⁵⁵ 2021	194	-0.27 (-0.40 to -0.14)
Haghighat et al., ⁵² 2013	137	0.18 (0.017 to 0.34)
Keskin et al., ⁵⁰ 2020	57	-0.40 (-0.60 to -0.15)
Liao et al., ¹⁸ 2013	107	-0.33 (-0.49 to -0.15)
Liao et al., ⁶⁰ 2016	23	0.21 (-0.21 to 0.58)
Total (fixed effects)	799	-0.249 (-0.31 to -0.18)
Total (random effects)	799	-0.276 (-0.45 to -0.079)

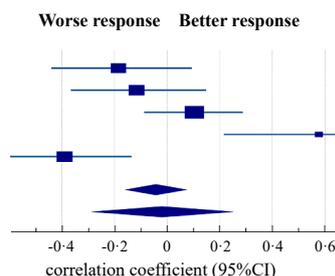
Heterogeneity: $Q=53.32^{***}, I^2=86.87\%$ Egger's Test: intercept=-1.55 (P=0.66)
 Test for overall effect: $z=-2.71$ (P=0.0067) Begg's Test: tau=-0.43 (P=0.14)



d Number of Removed Lymph Nodes

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.19 (-0.44 to -0.094)
Keskin et al., ⁵⁰ 2020	57	-0.12 (-0.37 to 0.15)
Liao et al., ¹⁸ 2013	107	0.10 (-0.088 to -0.29)
Liao, ⁶⁰ 2016	23	0.58 (-0.22 to 0.80)
Thomas et al., ⁷⁵ 2007	53	-0.39 (-0.60 to -0.13)
Total (fixed effects)	291	-0.043 (-0.16 to 0.075)
Total (random effects)	291	-0.020 (-0.30 to 0.25)

Heterogeneity: $Q=20.19^{**}, I^2=80.19\%$ Egger's Test: intercept=1.63 (P=0.74)
 Test for overall effect: $z=-0.139$ (P=0.89) Begg's Test: tau=0.00 (P=1.00)



e Number of Positive Lymph Nodes

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.016 (-0.29 to 0.26)
Keskin et al., ⁵⁰ 2020	57	0.16 (-0.109 to 0.40)
Total (fixed effects)	108	0.076 (-0.12 to 0.26)
Total (random effects)	108	0.076 (-0.12 to 0.26)

Heterogeneity: $Q=0.76, I^2=0\%$ Egger's Test: intercept=-20.99 (P<.0001)
 Test for overall effect: $z=0.76$ (P=0.44) Begg's Test: tau=-1.00 (P=0.31)

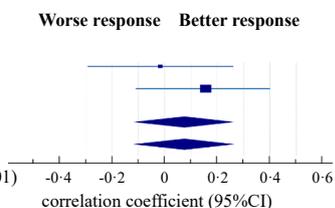
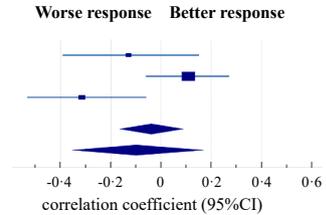


Fig. 2: Association of predictive factors with treatment response from random-effects meta-analysis*. *Random-effects meta-analysis analysed the association of a) age, b) BMI (body-mass index), c) baseline lymphoedema severity, d) number of removed lymph nodes

f Postoperative Duration

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.13 (-0.39 to 0.15)
Haghighat et al., ⁵² 2013	137	0.11 (-0.060 to 0.27)
Keskin et al., ⁵⁰ 2020	57	-0.31 (-0.53 to -0.058)
Total (fixed effects)	245	-0.039 (-0.17 to 0.089)
Total (random effects)	245	-0.099 (-0.35 to 0.17)

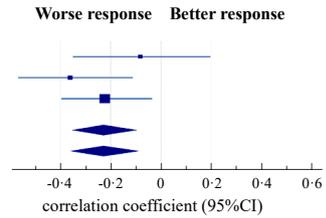
Heterogeneity: $Q=7.76^*$, $I^2=74.24\%$ Egger's Test: intercept=-6.08 (P=0.29)
 Test for overall effect: $z=-0.72$ (P=0.47) Begg's Test: tau=-0.33 (P=0.60)



g Lymphoedema Chronicity

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.082 (-0.35 to -0.096)
Keskin et al., ⁵⁰ 2020	57	-0.36 (-0.57 to -0.11)
Liao et al., ¹⁸ 2013	107	-0.22 (-0.396 to 0.035)
Total (fixed effects)	215	-0.23 (-0.35 to -0.096)
Total (random effects)	215	-0.23 (-0.36 to -0.087)

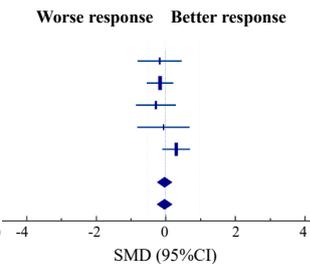
Heterogeneity: $Q=2.23$, $I^2=3.58\%$ Egger's Test: intercept=0.39 (P=0.95)
 Test for overall effect: $z=-3.13$ (P=0.0018) Begg's Test: tau=0.33 (P=0.60)



h Prior Adjuvant Radiotherapy

Source	Sample size	SMD (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.16 (-0.79 to 0.48)
Forner-Cordero et al., ⁹ 2010	171	-1.93 (-0.53 to 0.23)
Haghighat et al., ⁵² 2013	137	-0.27 (-0.84 to 0.31)
Keskin et al., ⁵⁰ 2020	57	-0.047 (-0.80 to 0.71)
Liao et al., ¹⁸ 2013	107	0.32 (-0.082 to 0.72)
Total (fixed effects)	523	-0.015 (-0.23 to 0.21)
Total (random effects)	523	-0.017 (-0.24 to 0.21)

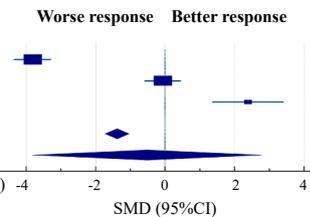
Heterogeneity: $Q=4.15$, $I^2=3.55\%$ Egger's Test: intercept=-1.39 (P=0.57)
 Test for overall effect: $t=-0.15$ (P=0.88) Begg's Test: tau=0.20 (P=0.82)



i Prior Adjuvant Chemotherapy

Source	Sample size	SMD (95%CI)
Forner-Cordero et al., ⁹ 2010	171	-3.81 (-4.35 to -3.28)
Haghighat et al., ⁵² 2013	137	-0.062 (-0.59 to -0.46)
Keskin et al., ⁵⁰ 2020	57	2.39 (1.36 to 3.42)
Total (fixed effects)	365	-1.38 (-1.73 to -1.03)
Total (random effects)	365	-0.52 (-3.82 to 2.78)

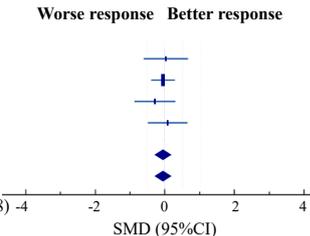
Heterogeneity: $Q=159.55$, $I^2=98.75\%$ Egger's Test: intercept=16.61 (P=0.60)
 Test for overall effect: $t=-0.31$ (P=0.76) Begg's Test: tau=0.33 (P=0.60)



j Prior Hormone Therapy

Source	Sample size	SMD (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	0.034 (-0.59 to 0.65)
Forner-Cordero et al., ⁹ 2010	171	-0.045 (-0.38 to 0.29)
Haghighat et al., ⁵² 2013	137	-0.27 (-0.85 to 0.30)
Keskin et al., ⁵⁰ 2020	57	0.083 (-0.47 to 0.64)
Total (fixed effects)	416	-0.049 (-0.28 to 0.19)
Total (random effects)	416	-0.049 (-0.28 to 0.19)

Heterogeneity: $Q=0.89$, $I^2=0\%$ Egger's Test: intercept=-0.068 (P=0.98)
 Test for overall effect: $t=-0.41$ (P=0.68) Begg's Test: tau=0.00 (P=1.00)



k Prior Mastectomy

Source	Sample size	SMD (95%CI)
Forner-Cordero et al., ⁹ 2010	171	-0.16 (-4.7 to 0.15)
Haghighat et al., ⁵² 2013	137	-0.089 (-0.52 to 0.34)
Keskin et al., ⁵⁰ 2020	57	-0.13 (0.78 to 0.51)
Liao et al., ¹⁸ 2013	107	0.27 (-0.39 to 0.92)
Total (fixed effects)	468	-0.091 (-0.31 to 0.13)
Total (random effects)	468	-0.091 (-0.31 to 0.13)

Heterogeneity: $Q=1.41$, $I^2=0\%$ Egger's Test: intercept=1.37 (P=0.50)
 Test for overall effect: $t=-0.82$ (P=0.41) Begg's Test: tau=0.67 (P=0.33)

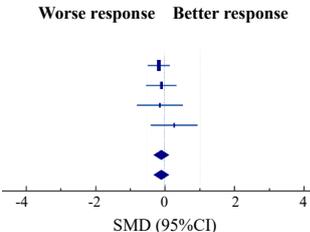


Fig. 2: Continued.

interpretation of insignificance for postoperative duration, BMI, or radiotherapy. In contrast, trim-and-fill adjustment for lymphoedema chronicity increased the pooled effect, suggesting publication bias may have underestimated the observed effect.

Given observed trends, we examined the co-occurrence of older age, longer lymphoedema duration, and greater baseline volume, a trend also seen in literature specifically between age and severity.⁷⁶ While inter-factor associations were not assessed within individual studies, an analysis of study-level means showed moderate correlation between age and lymphoedema duration ($r = 0.557$; 28 studies), with weak correlations between age and PEV ($r = 0.143$; 29 studies) and between lymphoedema duration and PEV ($r = 0.142$; 17 studies). These findings indicate population-level co-occurrence, though patient-level relationships cannot be inferred from aggregated data.

Sensitivity analysis was conducted to evaluate the robustness of results by excluding studies with potential heterogeneity or bias. Exclusion of two studies that examined cohorts mixed with non-BCRL lymphoedema^{55,60} did not significantly reduce heterogeneity for removed lymph nodes ($Q = 9.59$; $p = 0.022$) or baseline excess volume ($Q = 48.73$; $p < 0.0001$), nor alter the significance of effect sizes across all factors (Fig. 3). Mixed-effects correlation coefficients shifted from -0.135 without omission to -0.147 with omission for age, -0.276 to -0.332 for baseline excess volume, and -0.020 to -0.137 for removed lymph nodes. Separate sensitivity analysis with exclusion of high and moderate risk-of-bias studies was reported in Supplementary Figure S3, which resulted in only insignificant effect sizes. Subsequent leave-one-out sensitivity testing demonstrated that the directionality for PREV with age, baseline excess volume, and lymphoedema duration remained stable, with baseline excess volume remaining significant across all tests (Supplementary Table S7). However, the overall effect became statistically insignificant when omitting either of 2 out of 6 studies for age or 1 out of 3 studies for chronicity, indicating the moderate sensitivity of these estimates to individual studies.

Discussion

This systematic review of 67 studies extensively examined 71 unique predictive factors of compressive therapy response in BCRL. Factors were identified that can guide clinical decision-making and inform development of future predictive models. Meta-analysis of nine

studies showed that older age, greater baseline excess volume, and longer lymphoedema chronicity were associated with poorer treatment response. Other studies suggested prior lymphoedema therapy and prior arm infection were associated with poorer response. Increased treatment compliance, higher education or employment, and higher bioimpedance or lymphoscintigraphic axillary lymph node uptake or visibility were associated with better treatment response. While these studies were suggestive of association, the lack of appropriate statistics limited their inclusion for meta-analysis. Early identification of poor responders could enable treatment intensification, closer monitoring with timely adjustments, and/or alternative interventions. On the other hand, identifying good responders may help avoid overtreatment. Of note, while ALND and removed lymph nodes are established factors in developing BCRL,^{77–79} they were not found as predictors of response,^{59,80} highlighting the distinction between factors for development versus treatment. Regional lymph node radiotherapy is another risk factor for BCRL,^{78,81,82} though its association with treatment response is inconsistent, with axillary radiotherapy linked to poorer response in one study⁹ but not in another,⁸³ and insignificant differences were found for supraclavicular radiotherapy.³⁷

The pooled estimate of 45.13% PREV across 4529 patients aligns with prior systematic reviews and individual estimates of 28–56%.^{64,84,85} These findings, however, represent the first systematic review and meta-analysis to synthesise predictive factors. Prior reviews observed general trends, but without extensive synthesis or systematic examination of the literature, including Lasinski et al.⁴ and Gallagher et al.,¹¹ which observed similar comments to this review on age, BMI, baseline volume, locoregional disease, and lymphoscintigraphic findings with treatment response. Smile et al. noted higher BCRL stage as linked to poorer response,³⁰ with Dzupina et al.¹² attributing this to fibrosis or irreversible changes in severe BCRL. On the other hand, a review of systematic reviews by Gilchrist et al. found mild-moderate BCRL studies had smaller effect sizes (0.3–0.4) than moderate-severe BCRL studies (0.6–1.1) for CDT response.⁵

Heterogeneity in findings was also a documented concern in reviews, and our subgroup analysis suggested study-level contributors to heterogeneity like follow-up durations, compression methods, and baseline PEV. For example, Liao (2016) included patients with malignant lymphoedema and notably high baseline PEV, which may have contributed to increased

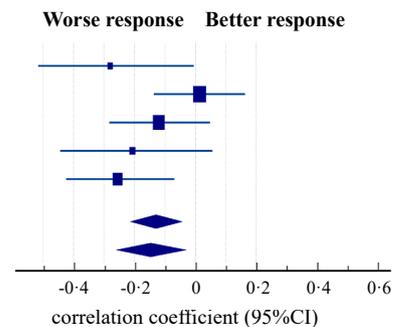
(LNs), e) positive LNs, f) postoperative duration, g) lymphoedema duration, h) prior radiotherapy, i) prior chemotherapy, j) prior hormone therapy, and k) prior mastectomy with treatment response as measured by percent reduction of excess volume. Significance levels of heterogeneity were reported as * ($p < 0.05$), ** ($p < 0.01$), and *** ($p < 0.001$). Blue squares represented point estimates of individual studies, sized by weighting with a 95% CI line. Diamonds represented pooled results with a 95% CI line.

Sensitivity Analysis for PREV

a Age

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.28 (-0.52 to -0.005)
Forner-Cordero et al., ⁹ 2010	171	0.014 (-0.14 to 0.16)
Haghighat et al., ⁵² 2013	137	-0.12 (-0.28 to 0.049)
Keskin et al., ⁵⁰ 2020	57	-0.21 (-0.44 to 0.057)
Liao et al., ¹⁸ 2013	107	-0.26 (-0.42 to -0.068)
Total (fixed effects)	523	-0.129 (-0.21 to -0.043)
Total (random effects)	523	-0.147 (-0.26 to -0.030)

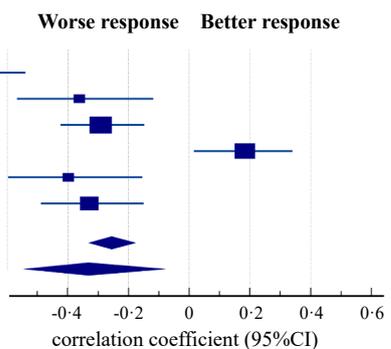
Heterogeneity: $Q=6.81, I^2=41.29\%$ Egger's Test: intercept=-3.82 ($P=0.060$)
 Test for overall effect: $z=-2.46$ ($P=0.014$) Begg's Test: tau=-0.60 ($P=0.23$)



b Baseline Excess Volume (percentage/millilitres)

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.71 (-0.82 to -0.54)
Duyur Cakit et al., ⁴⁷ 2019	59	-0.36 (-0.57 to -0.12)
Forner-Cordero et al., ⁹ 2010	171	-0.29 (-0.42 to -0.15)
Haghighat et al., ⁵² 2013	137	0.18 (0.017 to 0.34)
Keskin et al., ⁵⁰ 2020	57	-0.40 (-0.60 to -0.15)
Liao et al., ¹⁸ 2013	107	-0.33 (-0.49 to -0.15)
Total (fixed effects)	582	-0.256 (-0.33 to -0.18)
Total (random effects)	582	-0.332 (-0.55 to -0.079)

Heterogeneity: $Q=48.73, I^2=89.74\%$ Egger's Test: intercept=-7.39 ($P=0.23$)
 Test for overall effect: $z=-2.54$ ($P=0.01$) Begg's Test: tau=-0.87 ($P=0.011$)



c Number of Removed Lymph Nodes

Source	Sample size	Correlation coefficient (95%CI)
Bojinović-Rodić et al., ⁴⁵ 2021	51	-0.19 (-0.44 to -0.094)
Keskin et al., ⁵⁰ 2020	57	-0.12 (-0.37 to 0.15)
Liao et al., ¹⁸ 2013	107	0.11 (-0.088 to -0.29)
Thomas et al., ⁷⁶ 2007	53	-0.39 (-0.60 to -0.13)
Total (fixed effects)	268	-0.097 (-0.22 to 0.025)
Total (random effects)	268	-0.137 (-0.35 to 0.086)

Heterogeneity: $Q=9.59, I^2=68.72\%$ Egger's Test: intercept=-8.15 ($P=0.12$)
 Test for overall effect: $z=-1.209$ ($P=0.23$) Begg's Test: tau=-0.67 ($P=0.33$)

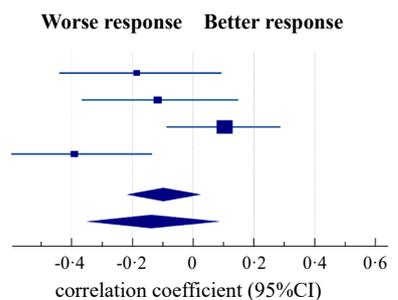


Fig. 3: Sensitivity analysis for random-effects meta-analysis, with exclusion of studies mixed with patients without breast cancer-related lymphoedema*. *Analysed factors included: a) age, b) baseline lymphoedema severity, and c) number of removed lymph nodes (LNs). Significance levels of heterogeneity were reported as * ($p<0.05$), ** ($p<0.01$), and *** ($p<0.001$). Blue squares represented point estimates of individual studies, sized by weighting with a 95% CI line. Diamonds represented pooled results with a 95% CI line.

variability in correlation measures for meta-analyses.⁶⁰ Inconsistent definitions of variables, like continuous versus categorical, was observed for factors like age (e.g., <60 vs ≥ 60) and lymphoedema duration (e.g., <2 years vs ≥ 2 years). This likely contributed to heterogeneity; while meta-analyses were unaffected since only continuous definitions were synthesised, this approach restricted the number of studies eligible for inclusion.

Unlike prior reviews that grouped outcome measures together, this review examined multiple volumetric outcomes separately, revealing important nuances in response patterns. Higher baseline PEV was associated with lower PREV but higher absolute reduction. This suggested a pattern where compression is relatively more effective for milder BCRL, while severe BCRL may experience greater absolute improvements despite smaller relative changes. The paradoxical

relationship may explain the previously mentioned discrepancies within literature on baseline excess volume.

Lymphoedema chronicity, prior lymphoedema therapy, older age,⁷⁶ and higher BMI¹² are associated with more severe lymphoedema and have also been linked with worse treatment response. One study found PREV associated with longer duration of lymphoedema, PEV, and number of prior CDT sessions, but multivariate analysis revealed PEV as the key independent factor.⁵⁰ One RCT suggested adherence as another potential rationale behind worse response in older patients,⁴⁶ but another study found older age to be significantly linked to increased CDT adherence.⁸⁶

This review provides novel synthesised insights to guide BCRL management and also supports future research into predictive model development for treatment response. These findings support the clinical utility of early lymphoedema detection and intervention of mild, non-chronic lymphoedema, as well as measures to promote treatment adherence, with moderate-to-high certainty of evidence. Key strengths include its comprehensive approach to capture nuances across different outcome measure modalities, and evaluation of predictors on both intra-study and inter-study levels. This analysis covered a large adult population drawn from geographically diverse cohorts, spread across six continents, offering a global perspective on BCRL management. This review further highlighted key limitations in available evidence and provided recommendations for future studies to inform predictive factor research (Supplementary Table S8). Core examples include the standardisation of outcome measures, adjusting models for established predictors in literature, and reporting measures of association comprehensively with measures of variation (e.g., standard deviation, confidence intervals) and regardless of significance.

Several limitations should be noted. Substantial heterogeneity across studies in lymphoedema definition, treatment protocols, follow-up, outcome measures, or baseline patient characteristics limited precision of estimates and assessing trends from subgroup analysis. PREV measures required imputation from provided study-level data in 25 studies, rather than calculated directly per patient, which may have reduced precision of estimates but maximised data inclusion. Only few studies provided appropriate statistics for inclusion in meta-analysis, which thwarted investigations for subgroup testing to explain causes of heterogeneity. Thirdly, most studies had small sample sizes, with only six studies having a patient cohort of greater than 200 patients. Fourthly, many studies did not adequately control for confounding variables. While 16 studies applied multivariate or statistical adjustments, heterogeneity in their methodologies limited comparability across studies within this review. As such, only results

from univariate analyses were presented and confounding adjustments were not conducted.

Studies also relied on chronological, rather than biological or functional age, and were conducted on predominantly female patients, which may limit generalisability to male patients with BCRL. In addition, cohorts typically included patients either receiving ALND or SLNB, not neither. This precluded the evaluation of SLNB omission as a factor that may impact BCRL treatment response, which may hold growing relevance given the new American Society of Clinical Oncology (ASCO) recommendations for SLNB omission over axillary surgery in select early-stage breast cancer patients, as supported by recent non-inferiority trials.^{87–89}

In conclusion, this is the first systematic review and meta-analysis examining predictive factors for treatment response to compression therapy in BCRL. Older age, baseline excess volume, and lymphoedema chronicity are predictive of poorer treatment response. These represent factors that future prediction response models should account for within their analysis. BMI, activity level, laterality of BCRL, number of removed or positive lymph nodes, and hormone therapy use were not found to be predictive of treatment response. These findings may inform more personalised counselling and management for patients undergoing compression-based therapies for BCRL. This review also highlights key heterogeneities in study design and outcome measures to improve upon in future research.

Contributors

EY and JYK generated the idea for this work. EY submitted the protocol and RH developed the literature search, in consultation with EY and JYK. EY, NL, and SH conducted the study screening and data extraction. EY and NL conducted quality appraisal. EY carried out data analyses, prepared the figures and tables, and drafted the manuscript, with guidance from JYK. ZAL contributed to the development and review of the statistical analysis plan. EY, NL, and SH had full access to all the data in the study. NL and SH accessed and verified the data. All authors provided input on the writing of the manuscript. All authors reviewed, revised, and approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

Data sharing statement

This systematic review does not include original data. Data are extracted from the literature and are publicly available. Data extracted are presented in the [Supplementary Material](#).

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2026.103832>.

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