

Research Article

The Effects of Supervised Exercises Program on upper limb dysfunction and Quality of Life in breast cancer survivors following different treatment strategies: Meta-Analysis

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Citation: Milambo JPM, Ndayisaba L, Kabego L, Tshilombo KV, Tamuzi JL (2018) The Effects of Supervised Exercises Program on upper limb dysfunction and Quality of Life in breast cancer survivors following different treatment strategies: Meta-Analysis. J Oncol Res Ther: JONT-146. DOI: 10.29011/2574-710X. 000046

Received Date: 12 February, 2018; **Accepted Date:** 20 August, 2018; **Published Date:** 28 August, 2018

Abstract

Purpose: The review was conducted to assess the efficacy of supervised exercises program in reducing upper limb dysfunction and improving health related quality of life among breast cancer patients following different treatment strategies.

Methods: PRISMA was used to conduct the present review of literature in PubMed/Medline, Embase and Cochrane Breast cancer registry. The study included only randomised controlled trials investigating the efficacy of medically supervised exercises program versus no supervised exercises programs. The details of exercises mode, frequency, length of follow up and BCRL mean reduction and HRQOL scores were computed for meta-analysis. The guideline for exercises regimen published by ISL and American College of Sports Medicine exercise guidelines for cancer survivors were included in the present study just limited to English language. Two authors performed data extraction, eligibility criteria and risk of bias assessment independently and the third reviewer was consulted for disagreement.

Results: Meta-analysis was performed using a random-effects model for potential nine RCTs. The results have illustrated the MD of BCRL volume reduction (%) between supervised versus no supervised exercises was 1.35 (95%CI 0.63 to 2.07, 6 studies, 371 females, P=0.002). Heterogeneity: $\tau^2 = 0.71$; $\chi^2 = 112.14$, $df = 5$ ($P < 0.00001$); $I^2 = 96\%$. These results have shown that the MD was 35% reduced in supervised exercises compared to no supervised exercises (Statistically significant with $P=0.0002$) Forest plot Figure 2. However, the statistical heterogeneity between RCTs was high. The pooled summary of supervised exercises versus no supervised exercises in improving HRQOL has shown that supervised exercises enhanced the MD HRQOL compared to no supervised exercises 3.02 (95%CI 2.59 to 3.45, 4 studies, 201 females, $P < 0.00001$). The results were statistically significant.

Conclusion: The findings from our meta-analysis revealed that supervised medically exercises combined with CDT are more effective in reducing LE volume and potentially improve HRQOL among BCRL survivors. The studies on the effect of the supervised exercises on LE survivor's adherence and the exercises mode and frequency are recommended to extend the level of evidence. The healthcare providers should consider ISL guideline for supervised exercise prescription in clinical settings.

Abbreviations

ACS	:	American Cancer Society
ACSM	:	American College of Sports Medicine
BIS	:	Bioimpedance Spectrometry
BCRL	:	Breast Cancer-Related Lymphoedema
BMI	:	Body Mass Index
BC	:	Breast Cancer
CDT	:	Complex Decongestive Therapy
HRQOL	:	Health Related Quality of Life
ISL	:	International Society of Lymphedema
LE	:	Lymphedema
LCM	:	Limb Circumference Measurement
MLD	:	Manual Lymphatic Drainage
MSEP	:	Medically Supervised Exercise Program
QOL	:	Quality of Life
ROM	:	Range of Motility
RCT	:	Randomized Controlled Trial
SF	:	Short -Form
SLE	:	Secondary Lymphedema
ULL27	:	Upper Limb Lymphedema 27
USA	:	United States of America
VAS	:	Visual Analogue Score

Introduction

Breast Cancer-Related Lymphedema (BCRL) is known long-life complication related to breast cancer management [1-5]. It is resulted to lymphatic system dysfunction which affects the function, psychosocial and economic implications of BCRL survivors [1-3,5-11]. The incidence of BCRL varies from 7% up to 83%; depending to various methods used to diagnose BCRL [5,12-14]. These include limbs circumference measurements, water displacement, patients self-reporting, laser scanning, Bio Impedance Spectroscopy (BIS) and optoelectricperometry [5,15-19]. These diversities methods used to define LE; have led to both over/under estimations of LE burden in literature [5]. The BCRL is a chronic inflammatory disease mainly associated with clinical management of breast cancer [11,20,21]. Its risk factors including surgery, radiation therapy, chemotherapy, Body Mass Index (BMI) > 25/kg², ethnicity, age, cellulitis, and genetic susceptibility are the additional predictors for LE development [13-22]. The current

standard of care recommended by International Society for Lymphology (ISL) for BCRL management is Complex Congestive Therapy (CDT) and exercises [23]. CDT improves Health Related Quality of Life (HRQOL), reduces BCRL volume, and increases the intention to exercise. It is a safe treatment for patients with ongoing local/regional tumours [23]. CDT includes Manual Lymphatic Drainage (MLD), compression sleeves, congestive exercises, skin care, and patient oriented education [23-26]. The exercises for patients with upper limbs LE have been discussed to be both risk reduction and risk factors in literature [27-37]. These exercises aim to restore the affected limbs, chest, cervical and thoracic trunk range of motion (ROM) and improve strength among BC following surgery [38-40]. The recommended medically supervised exercises programs aim to restore ROM, increase muscles strength, to maximize limbs function and management of LE related inflammation [37]. In addition, exercises improve arterial blood flow from heart to peripheral tissues and it increases the lymphoangogenesis [37]. The current position statement for cancer rehabilitation including SLE and associated post-surgery disabilities risk reduction were recommended by American Cancer Society (ACS) [30]; American College of Sports Medicine (ACSM) [38], and lymphedema related studies that the aerobic exercises of 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity activity, or an equivalent combination should be initiated for each patient [39-50]. Resistance exercises should be performed for muscle-strengthening activities of at least moderate intensity at least 2 days/week for each major muscle group. The flexibility of stretch major muscle groups and tendons on days other activities should be performed. The 1-repetition maximum (1-RM) is a standard practice for muscle strength measurement, method to assess patient comorbidities and maximizes benefits of the patients during the resistance exercises. Evidence suggests that 59-69% of 1-RM should be lifted to improve muscle strength. The range of exercises repetition varies 8-12 repetitions for initiation [51]. Moreover, a review on the effect of exercises among BC patients related postoperative impairments revealed that mean Assessing the Methodological Quality of Systematic Reviews (AMSTAR) score = 7.66/11 (± 2.04) suggested moderate quality of evidence for the benefits of slight, moderate and rigorous exercises in improving HRQOL among cancer survivors following radiation therapy and surgery. The addition results of the review revealed that medically patient oriented exercises programs were more effective comparing to non-supervised exercises programs and serious side effects were minimized [50]. The meta-analysis comparing supervised exercises and non-supervised exercises among BCRL have not yet conducted to evaluate the effects of these types of exercises for both the patients at both intense and maintenance phase of CDT. Further, the review conducted on the efficacy of exercises for LE risk reduction revealed that all different types of exercises are effective for LE management, but the exercises should be performed under medical supervision to

prevent additional complications [48]. The review also identified that the recommended physical activity by ISL which include resistance and aerobic, aquatic, yoga could be prescribed under medical supervised, but the level of evidence was low to moderate for the most randomized clinical trials included. Personalized exercises program was recommended for BCRL survivors with the purpose to restore range of motility, increase muscle strength, increase upper limbs strength and to mitigate inflammation [46]. Lifestyle strategies which include eating healthy combined with exercises for weight lost was also proved effective among BCRL survivors in improving HRQOL [30,32]. Although exercises were recommended as adjunct to CDT; Therefore, the adherence on the patients at maintenance of therapy without medical supervision is associated with decreased HRQOL due to poor adherence of LE survivors [52-53]. Data on the safety, intensity and duration of the exercises toward different stage of ISL stages are scanty internationally. No review has not yet conducted to evaluate the efficacy of supervised exercises program versus no exercise program for evidence based clinical practice recommendation for BCRL survivors. Therefore, this systematic review and meta-analysis was conducted to compare the efficacy of personalized oriented exercises programs versus no supervised exercises programs on BCRL risk reduction and in improving HRQL. Data from this meta-analysis can be used to guide clinical decisions, and support the development of evidence-based guidelines for recommendation of specific exercise protocol among BCRL patients at both intensive and maintenance phase of CDT.

Review Question

Are supervised medical exercises programs effective in reducing lymphedema volume and improves quality of life among women with breast cancer related lymphedema at intensive or maintenance phase of CDT comparing to no supervised medical exercises program combined with CDT”?

Methodology

Search Strategy and Selection Criteria

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [54]. We conducted the search strategy and the clinical trials conducted in all countries that have been published in peer-reviewed medical journals. We conducted a review of literature in PubMed/Medline, Embase and Cochrane Breast cancer registry. The study included only Randomised Controlled Trials (RCTs) investigating the efficacy of medically supervised exercises programs describing mode of exercises, frequency, length of follow up and BCRL mean reduction and HRQOL scores were computed for meta-analysis. The guideline for exercises regimen published by ISL and American College of Sports Medicine exercise guidelines for cancer survivors were

included in the present study just limited to English language. We used the search term: (Breast cancer related lymphedema [MESH] OR BCRL [MESH]) AND (supervised exercise program OR mentored exercise program) AND (quality of life [tw] OR QOL [tw] OR reduction in volume [tw]). The protocol of the review was registered with PROSPERO 2017 CRD42017079864 Available from:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017079864

Eligibility criteria were established using the PICO (participants, interventions, comparator and outcomes) framework for this review.

- **Participants:** RCT studies involving patients diagnosed with BCRL; with well detailed supervised exercises programmes (frequency, duration, ROM, types of exercises) of the patients treated with BCRL following their BC cancer management comparing to no supervised exercises. Mean differences, tools used to diagnose LE, p-values and 95% confidence interval were compared between intervention and control groups of the included studies without years and settings restriction. The review was limited with the articles published in English, and randomised controlled trials comparing two groups of participants using exercises as adjunctive to CDT.
- **Interventions:** Medical supervised exercises programs with a specified and described exercise mode, intensity, duration, ROM, length of follow-up and records of adverse events if available. CDT combined with other forms of the exercises recommended by ISL were also included. These comprised stretching exercises, aerobic exercises, weight lifting, resistance exercises, aqua exercises, swimming or walking. Other type’s patients-oriented exercises prescribed by healthcare providers were included if supervised by a sport physician or physiotherapist. In addition, trials reporting the female’s patients > 18 years old with BCRL (all clinical stages of LE were included). The types of the treatment used such as: surgical procedures performed for breast cancer with axillary lymph node dissection, sentinel lymph node biopsy or axillary sampling, with or without radiotherapy to the axilla or the supraclavicular fossa or both; or radiotherapy therapy combined with surgery or alone, chemotherapy combined with surgery or radiotherapy.
- **Comparators:** Studies involving standard exercises for BCRL such as CDT related decongestive exercises, recommended resistance, aerobic exercises without medical supervision. Specified exercise regimen (frequency, duration, follow-up) and tools used to measure LE.
- **Outcomes:** Studies involving lymphedema assessment using the recommended tools by ISL (limbs circumference measurements, BIS, water displacing, laboratory tests, lymphoscintigraphy, and self- reports). The validated QOL tools for upper limbs recommended by ISL were reported by

the primary study’s authors. Additionally, level for physical function, symptoms related to comorbidity, psychosocial level, physical appearance, emotional status were assessed using the international classification of disability questionnaire.

Exclusion Criteria

Children and adolescents, studies included men, BCRL women with metastatic cancer, pharmacological interventions, traditional medicines, Individual studies (non-randomized studies, case controls, duplicated studies, narrative reviews, no exercises defined interventions, studies included both primary and secondary LE, study without control groups, case studies, case reports, cross-sectionals, qualitative, systematic reviews and other languages than English.

Screening and Data Abstraction

Two medical investigators (JPM, L) independently select the study abstracts, full articles and the risk of bias was performed using the tools. The senior researchers were consulted in case of risen disagreement (J.M, M.J.); and disagreements was resolved by commitment. The clinical heterogeneity was assessed by comparing the study designs, settings, sample sizes, countries of publication, methods used for diagnosis, identified risk factors and the outcomes measures at each study endpoint. Random effects meta-analysis was conducted for pooling of the effect size. Further, the statistical heterogeneity was evaluated by using chi-square test of homogeneity and I² statistic test was conducted for quantitative data. The subgroup analysis was conducted for different tools used to measure the primary outcomes which is LE volume

reduction and secondary outcomes included HRQOL standardized questionnaire for the identified a substantial heterogeneity. Articles were classified as potentially eligible if the titles indicated a Randomised Controlled Trial (RCT) on the prevention or management of BCRL. If no judgment could be made about the eligibility of a study based on the title, the judgment was based on title and abstract. Any disagreements about eligibility was resolved in consensus meetings. The same procedure was applied for references included in this systematic review. Review articles identified in the search were screened for relevance and reference lists were checked to identify additional potentially eligible studies. Final decisions about inclusion for all articles judged potentially eligible was based on the full text of the published articles.

Quality Assessment and Personal Study Quality

Two authors (JPM, JL) independently assessed the quality of eligible nine RCTs (Table 1). Risk of bias was conducted using the Cochrane risk of bias tool for the appraisal of RCTs, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [55]. The tool contains six domains and each domain was assigned a judgement related to the risk of bias (Table 2 and Figure 5). The judgement could be ‘low risk’, ‘high risk’, or ‘unclear risk’. The latter judgement was assigned if the risk of bias of a characteristic in an included study was judged to be unclear, or if there was insufficient information on which to base the judgement. We compared excel datasets between two data extractors and the third author was consulted to resolve discrepancies. We reported the summary of the risk of bias in Table 2. All analyses were performed using Review Manager Software [55].

Authors/ years Country	Design/ outcomes	Exercises program/types	Sample inter vention	Sample control	Mean (SD) Age,	Mean reduction intervention	Mean (SD) Control	P value	Conclusion
Hayes, et al. 2009, Australia	RCT/LCM, QOL, BIS, perometry	Supervised versus no, resistance, mixed, aero, 30-5/3 times daily. 12 weeks	16 F	16 F	I: 59(7) C:60(11)	0.2(0.7)	0.01(0.09)	0.75 0.88	Exercise is beneficial for physical and psychosocial/ no difference
McClure, et al. 2010	QOL, AROM, SF36	Supervised, biweekly, 1h, 17 weeks	16 F	16 F	I:57.7(2.9) C:59(2.1)	22.86(7.51)	12.57(7.30)	0.19	Adherence was in TG, improved physical and emotional of TG.
Bushan, et al. 2016, Australia	RCT, aero and resistance on AROM, QOL, BIS, self-report	Supervised versus no; Resistance and aero, 150 weekly, 3-5times,12 weeks,	20 F	21 F	56	6.5(...) DASH 15.3	5.1 DASH 14.8	0.48 0.5	No difference between 2 groups

Kim, et al. 2010, Korea	RCT, supervised exercise +CDT versus No supervised. LCM tool. SF-36, LVR.	Resistance, 15min/d, 5 days, 8 weeks.	20 F	20 F	I: 50.5(10.58) C: 50.9(9.15)	16.74(1.01) SF-36: 66.75(13.40)	12.76(-1.4) SF-36: 60.24 (12.73).	0.5	Supervised exercises reduce LE and improve QOL.
Irdelsel, et al. 2007	RCT, supervised s no; CG. VAS, LVR/ AROM	3 to 6 months, 3 times daily, resistance and aerobic,	10 F	9 F	51.6(8.8)	3(1.3)	2.7(2.0)	-	Supervised exercises plus compression is effective than CDT and non-Supervised exercises.
Buragadda, et al. India. 2015	RCT/ LVR, QOL. LCM. DASH.	Remedial, glenohumeral, deep breathing, 5 times weekly, 6 weeks. Versus standard of care without supervision	30 F	30 F	I: 56.3(3.3) C: 56(3.5)	24.6(1.9) DASH 5(1.1)	23(2.6) DASH 2(0.5).		CDT and home supervised program reduce LV and improve QOL.
Melan, 2016, India	RCT/ HRQOL EORTC QLQ C 30 function VAS	IDEM /VAS	30	30	I: 56.3(3.3). C: 56(3.5)	81.83(1.42) VAS: 2.93(0.87)	85.27(1.98) VAS: 1.40(0.50)		Supervised remedial exercises program adjunct to CDT improve HRQOL.
Schmitz et al. 2009, SA	RCT/ LVR, water displacing	Supervised weight lifting exercises, 90 mints twice weekly, 12 weeks.	70	69	I:56(9) C: 58(10)	-0.51(0.80)	-0.22(0.71)	0.03	Progressing weight lifting moderate to rigorous reduce LV.
Sener et al. 2017, Turkey	RCT/LVR, LCM. DASH-30	Supervised pilates exercises versus No, 5-8 persons 3 times a week/8 weeks.	30	30	I: 53.2(7.7) C: 54.03 (12.57)	1.24(0.43). DASH 37.99(15.02)	0.12(-0.2) DASH 32.15(12.11)	0,01	Supervised clinical pilate exercises are safe and could be considered for the programs.

Table 1: List of Included Studies.

Patient or population: patients with						
Settings: Australia, USA, Turkey, South Africa						
Intervention: Lymphoma volume reduction						
Outcomes	Illustrative (95% CI)	Comparative risks*	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Control Lymphoma reduction volume						
Lymphedema volume reduction		The mean lymphedema volume reduction in the intervention groups was 1.35 higher (0.63 to 2.07 higher)		371 (6 studies)	⊕⊕⊖⊖ low1,2	
Improved HRQOL		The mean improved hrqol in the intervention groups was 3.02 higher (2.59 to 3.45 higher)		201 (4 studies)	⊕⊕⊕⊖ moderate3	
Mean age of developing Lymphedema		The mean age of developing lymphedema in the intervention groups was 0.34 lower (1.23 lower to 0.56 higher)		483 (9 studies)	⊕⊕⊕⊖ moderate3	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						
¹ Other bias were more than 75% ² Heterogeneity was more than 75%						

Table 2: Risk of Bias Assessment.

Results

Search strategy identified 4 408 reports. 4370 did not meet the eligibility criteria. A total of 38 articles were assessed. From these, 8 were wrong publications, 12 did not describe the exercises programs; 5 did not include well reported outcomes and 4 were duplicates. Nine eligible original RCTs with 483 patients met the

inclusion criteria. No adverse events were reported in the included studies evaluating the efficacy of supervised exercises versus standard exercises among the patients treated for secondary LE. In addition, the resistance and aerobic exercises were common among the selected studies. The authors described the mode, frequency of each component of exercises regimen as recommend by ACS and ISL.

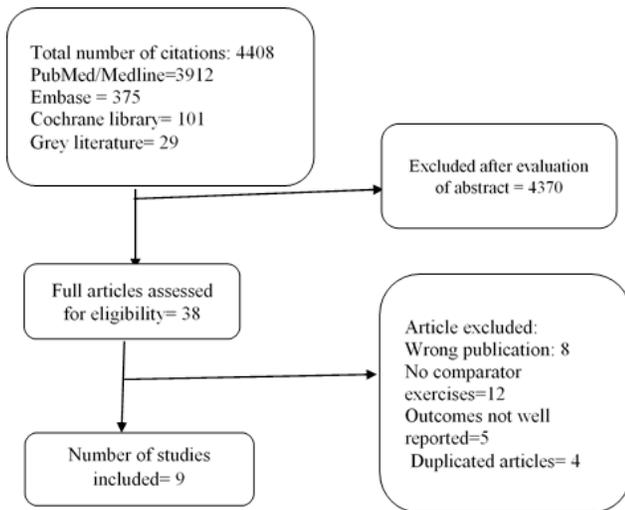


Figure 1: PRISMA flow chart.

Exercises Mode, Frequency, Duration among Included Studies

Buragadda, et al. [56] evaluated the efficacy of CDT and supervised community-based exercises on LE risk reduction and Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire was used to quantify HRQOL [57]. The exercises programs included glenohumeral mobilization, deep breathing exercises, and decongestive resistance exercises (5 days a week/ 6 weeks) and both groups used CDT as a standard of care. The tools used to measure the outcomes were respectively Limbs Circumference Measurement (LCM) and DASH questionnaire for HRQOL scores. The result of this study showed that supervised exercises programs at maintenance phase of CDT improved HRQOL and potentially decreased LE volume [56]. In addition, Milan, et al. [58] evaluated the supervised exercises combined with CDT on HRQOL using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [59], and the authors found that supervised exercised coupled with CDT at maintenance phase improved QRQOL among BCRL survivors [58]. Hayes, et al. [60] assessed the effect of aerobic, resistance exercises and mixed (30- 5/ 3 times daily/12 weeks) coupled with CDT on LE reduction and QOL. The final result showed that Supervised exercises group improved in physical and psychosocial dimensions of HRQOL comparing to no supervised exercises group [60]. McClure, et al. [61] assessed the efficacy of supervised decongestive exercises on HRQOL, AROM; the maximum follow-up time was 17 weeks. The final report revealed that the supervised exercises increased adherence of BCRL patients on CDT and improved HRQOL comparing to no supervised exercises group [61]. Bushan, et al. [62] evaluated the efficacy of aerobic and resistance exercises (150 weekly, 3-5 times /12 weeks) on LE risk reduction, HRQOL and AROM, the

tools used were BIS, self-report questionnaire for LE and DASH questionnaire. The result showed that there was no statistically significant difference between supervised exercises group comparing with no supervised exercises programs [62]. Kim, et al. [63] evaluated the effectiveness of resistance exercises (15 min/ daily, 5 days/ 8 weeks) on LE volume reduction and QOL; the tooled used were LCM and SF-36 scores. The results showed that supervised exercises group improved in HRQOL and LE reduction were significantly reduced comparing to no supervised group [63]. Schmitz, et al. [64] used water displacement to measure LE volume among two groups randomly allocated to supervised weight lifting exercises (90 min twice weekly/12 weeks fp). The results showed that progressive supervised weight lifting moderate to rigorous exercises reduced LE volume comparing to control group [64]. Irdelsel, et al. [65] evaluated the efficacy of aerobic and resistance exercises (3 to 6 months, 3 times daily) on LE risk reduction and AROM; the results showed that supervised exercises coupled with compression sleeves are effective than CDT coupled with non-supervised exercises. Sener, et al. [66] evaluated the efficacy of supervised pilates exercises (5- 8 persons 3 times weekly /8 weeks fp) on LE reduction and HRQOL; the tools used to measure outcomes were respectively LCM and DASH-30. The authors found that supervised clinical Pilate exercises are safe and could be considered for LE programs [66].

Meta-Analysis and Heterogeneity Assessment

Our screening revealed the studies of rigorous methods of RCTs. The six domains of risk bias assessed revealed that the biases were reduced in the most of included studies.

This meta-analysis included nine RCTs, comparing the Mean Difference (MD) of age between Supervised and no supervised exercises in breast lymphedema cancer. The age range of the mothers varies from 50 to 60 years old. The MD of between supervised exercises and no supervised exercises was -0.34 (95%CI -1.23 to 0.56, 9 studies, 483 females) forest plot Figure 2. The results were not statistically significant with p-value of 0.46. The pooled effect size of supervised exercises versus no supervised exercises in reducing LE volume has shown low evidence that supervised exercises programs reduce LE volume compared to no supervised exercises 1.35 (95%CI 0.63 to 2.07, 6 studies, 371 females, P=0002). Heterogeneity: Tau² = 0.71; Chi² = 112.14, df = 5 (P < 0.00001); I² = 96%.

These results have shown that the MD was 35% reduced in supervised exercises compared to no supervised exercises (Statistically significant with P=0.0002) forest plot Figure 3. However, the statistical heterogeneity between RCTs was high. The pooled summary of supervised exercises versus no supervised exercises in improving HRQOL has shown moderate evidence that supervised exercises enhanced the MD HRQOL compared to no supervised exercises 3.02 (95%CI 2.59 to 3.45, 4 studies, 201

females, $P < 0.00001$). The results were statistically significant. Forest plot Figure 4 shows the pooled effect size and grading is included in forest plot interpretation Figure 5. Heterogeneities were assessed in three forest plots. The overall clinical heterogeneity was high in all meta-analysis. Bias assessment revealed that the random allocation was adequate in all RCTs. Confounding was minimized and then the Cochran tool of bias assessment does not mention it. Other risk of bias was likely; the final report was graded as moderate. Therefore, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Meta-analysis

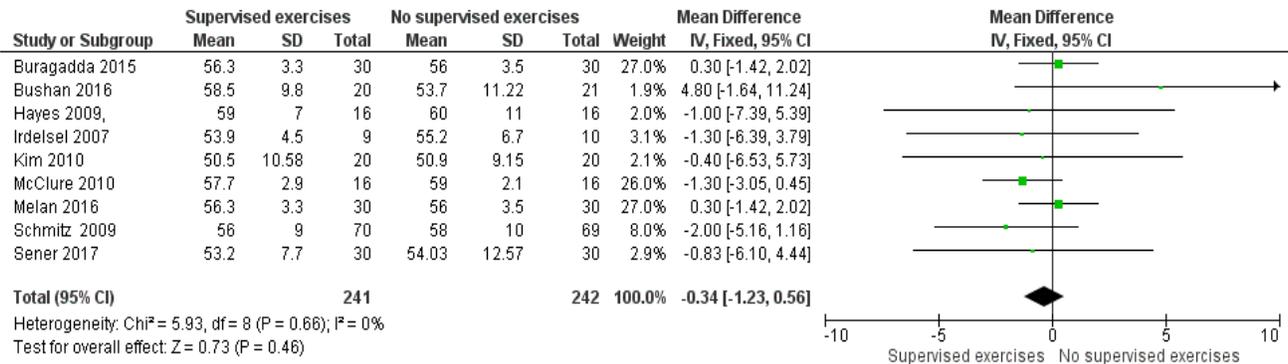


Figure 2: Forest plot of comparison: NSE vs SE: NSE vs SE. Outcome: Age.

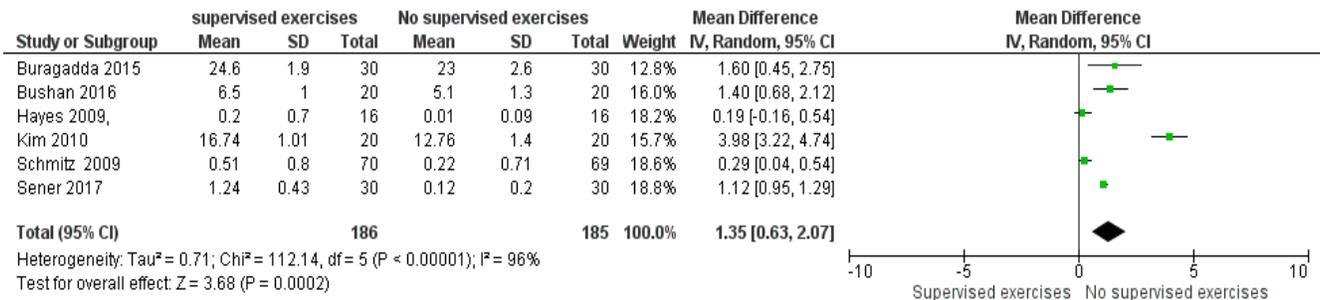


Figure 3: Forest plot of comparison: NSE vs SE. Outcome: lymphedema volume reduction.

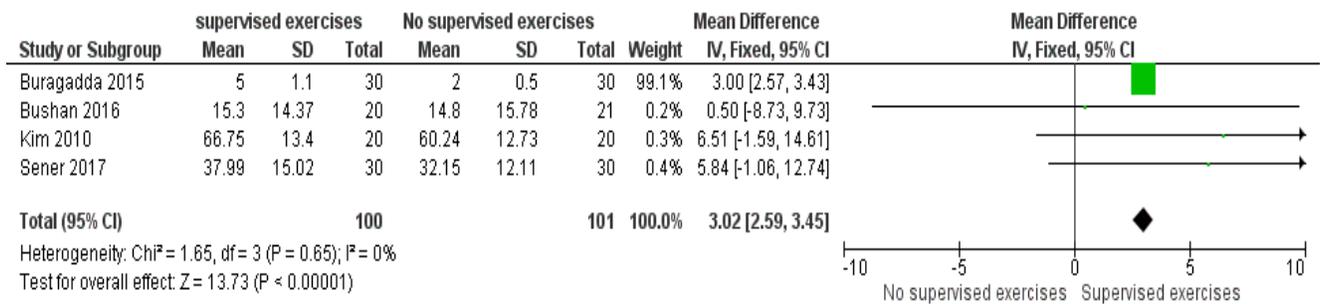


Figure 4: Forest plot of comparison: NSE vs SE. Outcome: improved HRQOL.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Buragadda 2015	+	-	-	+	+	+	-
Bushan 2016	+	+	-	-	+	+	+
Hayes 2009,	+	?	-	+	+	+	-
Irdelsel 2007	+	-	+	+	?	+	-
Kim 2010	+	-	-	-	+	+	-
McClure 2010	+	+	?	+	+	+	-
Melan 2016	+	-	-	+	+	+	-
Schmitz 2009	+	+	+	+	+	-	-
Sener 2017	+	+	?	?	+	+	+

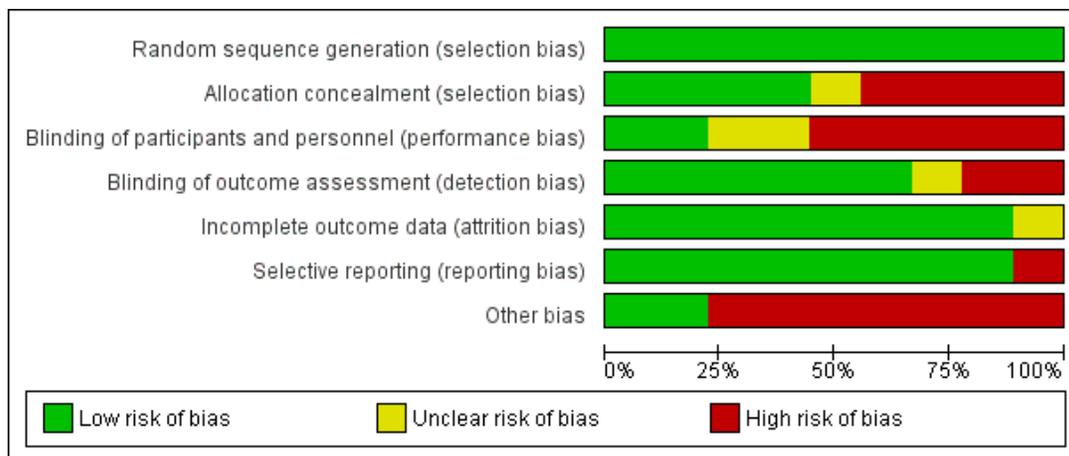


Figure 5: Risk of bias assessment. Legends: NSE= No supervised exercises, SE= supervised exercises, P= p value, DASH= Disabilities of the Arm, Shoulder, and Hand; EORTC QLQ= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; LCM= limb circumference measurement.

Discussion

This is the first meta-analysis conducted to assess the effect of personalized -patients oriented exercises programs in management of LE related breast cancer management as recommended by ISL. The findings from our meta-analysis revealed that supervised medically exercises combined with CDT are more effective in reducing LE volume (MD: 1.35 (95%CI 0.63 to 2.07, 6 studies, 371 females, P=0002). Heterogeneity: Tau² = 0.71; Chi² = 112.14, df= 5 (P < 0.00001); I² = 96%). The MD LE volume reduction was 35% in supervised exercises compared to no supervised exercises (P=0.0002). In addition, the pooled MD of HRQOL score of BCRL survivors in intervention group compared to control group was 3.02 (95%CI 2.59 to 3.45, 4 studies, 201 females, P <0.00001). The summary of findings has shown that supervised exercises programs are the best strategies to recommend in clinical practice for BCRL management as adjunct to CDT at both intensive and maintenance phase of CDT. Subgroups analysis for exercises mode (aerobic, stretching, weight lifting, mixed, yoga, swimming) were not conducted for heterogeneity of the regimen throughout the studies; the mean intervention duration was > 3 months < 6 months. The studies evaluating the effect of supervised exercises versus no supervised exercises on LE status were scarce in the included studies. Additionally, the studies evaluating the effect of medically supervised exercises on patient's adherence on standard of care should give more evidence-based data to extend the body of the knowledge. Moreover, the mode of exercises and frequencies of exercises were not evaluated as prescribed by different protocols for exercises prescriptions as well as the exercises for each stage of LE based on ISL guideline still a challenge to be investigated in further studies.

Considering the impact of LE for BCRL survivors with associated functional limitations, psychosocial distress, and economical implications of patients; the efforts need to be made to reduce his incidence which is globally health system challenge. Due to global high burden of breast cancer and the techniques used to manage this condition [67-75].

Currently, the evidence supports the use of CDT to improve HRQOL, reduce LE volume and increase patients' ability to exercise [23]. CDT is considered the standard care for LE management, but the level of evidence is not yet established for each component of this intervention. Two reviews conducted on the conservative therapies of BCRL demonstrated that all types' exercises and self-management may be effective to reduce LE and to improve HRQOL [10,23]. The evidence available on efficacy of CDT and the results of clinical trials are controversial and inconclusive for its recommendation at maintenance phase of therapy without adjunctive therapy. In addition, CDT alone were proved ineffective at maintenance phase of therapy and many countries faced the economic challenges to implement CDT as

standard of care although it international accreditation [52,53]. Lifestyle strategies which include both eating balanced diet and physical activity were recommended based on evidenced based clinical trials [32,36]. For the above limitations related to CDT implementation and lack of high level of evidence for its efficacy at maintenance phase of BCRL survivors; the authors identified that patient's non-adherence on self-care and impact of LE on HRQOL should be addressed [53]. Various studies were conducted to assess the safety of exercises regarding the BCRL risk reduction or the risk of developing BCRL; showing the advantages and disadvantages based on intensity and duration of the exercises [41,42,45]. Many studies demonstrated that all types of exercises are safe, effective and can improve the quality of life among BCRL survivors [33,37, 41,45,]. In addition, the recent review on the efficacy of exercises for BCRL revealed that there was not effect of exercises mode (aerobic, resistance, or mixed) and duration of intervention on BCRL status or HRQOL (MD ranging between -0.2 and 0.1 (P values \geq .22). The authors recommended more studies to support or refute the current standard care which including wearing compression sleeves during decongestive exercises [50]. Moreover, the review assessing the efficacy of exercises mode and frequency revealed that moderate- or vigorous-intensity versus mild-intensity exercise programs should slightly improve HRQOL of patients which include physical, psychosocial and fatigue. The authors recommended a study that investigating long-term outcomes of exercises focused on mode, frequency, ISL stage and duration [49]. The quality of this review was graded low because of the heterogeneity of exercises regimens, variation of tools used to assess patient's quality of life scores, and the included studies RCTs had high risk of biases [49,50]. Moreover, medically supervised exercises programs were recommended to be implemented for BCRL to increase adherence and potentially prolong survivorship. ACSM guideline for supervised exercises include four main types of exercises, resistance or stretching exercises, aerobic exercises, mixed exercises and decongestive exercises [38]. The exercises prescription starts with slow progressive gentle exercises; increased exercises frequency from moderate to rigorous about 3 to 5 times/week; each session comprises approximately 30-60 minutes depending to exercises physician appreciation. In addition, 1-RM is performed first, moderate aerobic exercises include 8-15 repetitions, 65 -75% of Heart Rate Reserve (HRR) and stretching or resistance include 2 series of 5- 12 repetitions with high intensity of 75 -90% of HHR and mixed aerobic depend on 1-RM calculation [38,43].

Among nine studies included in the review; we accounted different interventions among which complied with ACS, ISL and ACSM guidelines for the supervised exercises prescriptions for LE. These recommendations were based on evaluation of 1-RM, mode, frequency and duration [23,30,38]. But the heterogeneity related to the variations of exercises types could not help us for quantifying

the level of evidence based on ISL stages. The studies comparing exercises mode, frequency and 1-RM were published in recent reviews showing that high frequency exercises were associated with LE volume reduction and improved HRQOL [49,50]. In addition, serious side effects of exercises were not reported in many studies included in our review; this may be explained by the fact that the studies considered only those with stable ISL, and who were screened to be eligible for physical activities. Moreover, the review conducted by Romerberg, et al; with 30 studies on effects of exercises whereby exercises prescriptions were divided into high-medium and low frequency groups [76]. The authors concluded that resistance exercises combined with standard care maybe beneficial for BCRL patients in improving HRQOL and upper limbs strength [76]. Our review confirmed the same findings; however, measuring of dimensions of quality of life was limited given the variability used to quantify the HRQOL score. Further study should be conducted to correlate exercises mode, intensity and duration with ISL stages and functional, psychosocial and emotional dimensions of QOL scores for evidence-based recommendation in clinical practice.

Limitations

ROM based physical activities outcomes, the correlation of the effects of the exercises based on ISL stages, and subgroup-based analysis focused on tools used to measure the efficacy of exercises across the intervention and control arms were not reported. The meta-analysis of the above limitations was not conducted because of significant heterogeneity within the studies and these results were reported narratively. Additionally, the results did not consider exercises in patients on pneumatic pumps and other types of unestablished conservative therapies for BCRL such as yoga, acupuncture, Chinese medicine, and African traditional medicine, chemotherapy for LE or paediatrics-based exercises. In addition, finding from these meta-analyses should be considered in light of small sample sizes and few studies evaluating supervised exercises versus no supervised in management of BCR. About half of the studies included in this review were graded low quality of evidence for primary outcomes and moderate for secondary outcome measured. The exercises mode and frequency and duration varied according to setting and author's flexibility. Suggesting threat to internal validity. Study samples included with the females initially with a stable upper limb LE. Since many subjects were used to routine standardized exercises, the adherence should be maximized by the fact that safety and feasibility were generally compromised before participating into the trials. As such, the effectiveness, relevance, adherence, side effects, and safety of exercises among those patients with severe LE could not be assessed in this study and the work of this nature could be considered for further assessment. Other bias should be introduced by the lack blinding of patient's outcomes assessors in many studies. While blinding is not always possible in exercises interventional studies or in using

of compression sleeves. Moreover, potential bias may be likely by objectives assessment of LE for primary outcomes and publication bias was not addressed with funnel plot because of number of studies less than 10; and the review included only peer-reviewed articles. It is likely that the omission of unpublished studies and other well conducted observational studies resulted in publication bias. This because the studies with negative results are less likely to be published and the inclusion of these types of studies may reduce the threats to internal validity. The generalizability of these findings to other population with severe stage of LE should be established with enough high level of evidence.

Conclusion

The findings from our meta-analysis revealed that supervised medically exercises combined with CDT are more effective in reducing LE volume and potentially improve HRQOL among BCRL survivors. The studies on the effect of the supervised exercises on LE survivor's adherence and the exercises mode and frequency are recommended to extend the level of evidence. The healthcare providers should consider ISL guideline for supervised exercise prescription in clinical settings. These including screening for safety and comorbidities. The trials to strengthen uniformity of clinical guidelines and integration of supervised exercises in community based-clubs should be enforced to improve adherence.

Author's Contributions

- Designing, search strategy, registering of review, protocol writing, data extraction, risk of bias assessment, critical appraisal, data analysis, interpretation of final report and writing of manuscript
- Data collection, edition, critical appraisal, data extraction, risk of bias assessment, quality improvement.
- Data collection, edition, critical appraisal, data extraction, risk of bias assessment, quality improvement.
- Designing, search strategy, registering of review, protocol writing, data extraction, risk of bias assessment, critical appraisal, data analysis, interpretation of final report and writing of manuscript;

Potential Conflicts of Interest: The author indicated no potential conflicts of interest.

Acknowledgments

The authors acknowledge Prof. Vikash Sewram of African Cancer Institute for supporting the initial phase of the project. Prof. Delva Shamly and Colleen Marco for supporting in sharing their expertise in cancer rehabilitation and management in Africa. Dr. Andre Bulabula for search strategy and methodology guidance; Dr. Landry Kabego for statistical analysis.

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