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Risk factors of breast cancer-related lymphoedema: protocol of an umbrella review

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ABSTRACT

Introduction Breast cancer-related lymphoedema (BCRL) is a progressive and debilitating complication post-breast cancer treatment. Identifying potential risk factors facilitates the prevention and management of BCRL. Multiple systematic reviews have been conducted to address the variables correlated with the occurrence of BCRL. This study aims to identify and examine factors predicting the development of BCRL, to clarify the predicting mechanism of these factors, as well to determine the credibility of risk factors for BCRL.

Methods and analysis This umbrella review will be conducted with the methodological guidance of the Joanna Briggs Institute and the Cochrane handbook. A comprehensive systematic search will be performed in ten databases: PubMed, Embase, CINAHL, Web of Science, Scopus, CNKI, SinoMed, Wangfang database, the JBI Database of Systematic Reviews, Cochrane Database of Systematic Reviews. The search for unpublished studies will include ProQuest and the PROSPERO register. Reference lists will also be hand searched. Two reviewers will independently screen the studies, extract data and assess the methodological quality using the Methodological Quality of Systematic Reviews-2 and the Risk of Bias in Systematic Reviews. The degree of overlap between included reviews will be assessed by calculating the Corrected Covered Area. The credibility of the associations between risk factors and lymphoedema will be graded into four classes: convincing, highly suggestive, suggestive and weak, referring to the classification system of recent umbrella reviews. A descriptive, narrative synthesis and suggestions for clinical practice and future research will be made based on included systematic reviews, considering the quality of the evidence.

Ethics and dissemination Ethical approval is not required for this umbrella review. We will seek to submit the results for publication in a peer-reviewed journal or present it at conferences.

PROSPERO registration number CRD42022375710.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This umbrella review will be conducted under the guidance of the Joanna Briggs Institute Manual for Evidence Synthesis of Umbrella Reviews and the Cochrane handbook for the conduct of systematic reviews.
⇒ Study screening, quality appraisal and data extraction will be conducted by at least two independent reviewers.
⇒ No language restrictions will be applied during study selection.
⇒ The methodological quality of the eligible reviews will be evaluated using both Assessing the Methodological Quality of Systematic Reviews-2 and Risk of Bias in Systematic Reviews.
⇒ The degree of overlap between included reviews will be assessed by calculating the Corrected Covered Area.

INTRODUCTION

Breast cancer-related lymphoedema (BCRL) has been characterised as a chronic, progressive and uncurable sequela following breast cancer-related treatment. BCRL has been defined as an abnormal accumulation of protein-rich lymph fluid in the interstitial spaces caused by the disruption of the lymphatic system, which manifests as the swelling of limb, hand, breast or chest wall.[1] As reported by two previously published meta-analyses, BCRL affected approximately one in five women treated for breast cancer.[2 3] Survivors suffering from BCRL reported lower quality of life, accompanying with discomfort symptoms (eg, swelling, numbness, pain, etc), functional limitation, body image disturbance, sexuality problems, economic burden and others related psycho-social problems.[4–6]

It has been commonly recognised that axillary surgery and regional lymph nodes radiation, which could both result in lymphatic disruption, are major contributors to the development of BCRL.[7] For the past few years, a growing body of research evidence showed that the development of BCRL is multifactorial, influenced by unmodifiable factors such as treatment regimens, and recovery capability of lymphatic system, also by some potentially modifiable factors such as body mass index (BMI) and subclinical oedema.[4 8] Risk factors refer to characteristics, traits or

exposures that increase an individual's possibility of developing a condition.[9] Identifying modifiable risk factors provides new insights into the prevention of BCRL.

Over the past 20 years, a great deal of studies focused on exploring possible risk factors contributing to the occurrence of BCRL, mainly focused on sociodemographic, disease and treatment, and lifestyle behaviour-related factors. However, these traditionally studied risk factors can only partially explain the development of BCRL. Currently, the hypothesis of lymphatic failure, haemodynamic hypothesis and interstitial hypothesis are main hypothesis about the pathogenesis of BCRL.[10] However, the pathogenesis of BCRL is still not fully understood. Recent studies have suggested that pathophysiological factors (eg, VEGF-C, MCP-1, CD4+ cell) and genetic predispositions (eg, genetic variations in interleukin 4 (IL-4), IL-6) might play a part in the pathogenesis of secondary lymphoedema.[11 12] Some researchers appraised and synthesised the available evidence on a single risk factor or some categories of risk factors for BCRL.[13 14] Whereas, readers including healthcare providers, researchers, informed patients, etc, might have difficulties in understanding information from these systematic reviews that possibly present inconsistent findings. For example, regarding whether old age increases the risk of BCRL, one systematic review indicated that age alone was not a significant risk factor,[15] while another one concluded that older age was associated with the development of BCRL.[16] Furthermore, despite of many publications on systematic reviews of risk factors for BCRL, there is no complete and concise research summary that can be applied to clinical practice. An umbrella review, which aims to synthesise the results of systematic reviews on a certain topic, and help inform evidence-based clinical practice, will be most appropriate in achieving this. We have performed a preliminary search and found no existing umbrella reviews on this topic. Herein, this review aims to identify, appraise and synthesise the results of published systematic reviews that assess risk factors contributing to BCRL, to provide an understandable and comprehensive review in one article.

OBJECTIVES

This study aims to identify and examine factors predicting the development of BCRL, to clarify the predicting mechanism of these factors, as well to determine the credibility of risk factors for BCRL.

METHODS AND ANALYSIS

Design and registration

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols[17] (see online supplemental file 1). The umbrella review will be conducted under the methodological guidance of the Joanna Briggs Institute Manual for Evidence Synthesis of Umbrella Reviews[18] and the Cochrane handbook for the conduct of systematic reviews,[19] as well as other methodological articles.[20 21]

Table 1 PECOS statement

Population	Breast cancer survivors
Exposure	Any factors which might have influence on the development of BCRL, for example, patients with higher body mass index (BMI) before surgery
Comparator	Breast cancer survivors who have not been exposed to the risk factors under investigation, for example, the comparator to those who present with higher presurgery BMI would be those who have lower BMI
Outcome	Diagnosis of breast cancer-related limb lymphoedema, which could be identified by objective measurements, survivors' self-report or by clinician diagnosis
Study designs	All systematic reviews (with or without meta-analyses) address on factors predicting BCRL
Setting	People who have been treated for breast cancer in hospital or community

BCRL, breast cancer-related lymphoedema.

Patient and public involvement

The patients or the public have not been involved in developing the present protocol. And they will not be involved in conducting the umbrella review.

Eligibility criteria

The eligibility criteria is established using a PECOS (Population, Exposure, Comparator, Outcome, Study designs) statement[22] (see table 1).

Population

This umbrella review targets on systematic reviews and/or meta-analyses that synthesise risk factors of BCRL. Primary studies within the systematic reviews and/or meta-analyses should focus on adult breast cancer survivors (aged over 18 years) with a history of breast cancer-related surgery. Primary studies of patients with recurrent breast cancer, metastatic disease, primary lymphoedema or lymphoedema secondary to other diseases will be excluded.

Exposure

We will identify systematic reviews reporting at least one clearly defined risk factors of BCRL, including demographic, disease-related, treatment-related and psychosocial factors. Risk factors could be reported with or without adjusted effect sizes across categories, such as ORs, relative risks, HRs with 95% CIs.

Outcomes

Systematic reviews take breast cancer-related limb lymphoedema as an outcome will be considered. We accept

definite diagnostic criteria for BCRL specified by potential systematic reviews, for example, relative volume change (RVC) or relative arm volume increase (RAVI) ≥200 mL or 10%, weight-adjusted RVC>10% from preoperative baseline, inter-limb circumference increase ≥2 cm or 10%, self-reported symptoms, clinical diagnosis, etc.[4] Primary studies recruiting participants with acute lymphoedema occurred within 3 months post-breast cancer diagnosis or surgery, latent or subclinical lymphoedema with RAVI<3%, breast or trunk lymphoedema will be excluded.

Study designs

Only systematic reviews will be included, all other study designs will be excluded. To be included, systematic reviews (with or without meta-analyses) need to focus on the question about risk factors of BCRL, and clearly describe an explicit and reproducible methodology, including a systematic search string, a systematic selection of included studies, predefined eligibility criteria, critical quality appraisal of included studies, and quantitative or qualitative synthesis of results. Systematic reviews can include studies with prospective/retrospective cohort design, analytical cross-sectional design, case–control design and randomised controlled trials. No language restrictions will be applied during study selection. Articles in other language will be translated by google translator for assessing and extraction. Publications without available full-text, conference abstracts and protocols will not be considered.

Information sources

A systematic search of electronic databases and grey literature will be conducted. All peer-reviewed, non-peer-reviewed and unpublished systematic reviews will be considered. The electronic databases will include: PubMed, Embase, CINAHL, Web of Science, Scopus, CNKI, SinoMed, Wangfang database. Other sources to search include the major repositories of systematic reviews including the JBI Database of Systematic Reviews and Implementation Reports, Cochrane Database of Systematic Reviews, and the PROSPERO register. The search for unpublished studies will include ProQuest Dissertations and Theses Database. Besides, the reference lists of all identified articles will also be examined for additional studies.

Search strategy

Search strategy will be developed following the guidance of the PECOS model.[19] A comprehensive search strategy using Medical Subject Headings terms and keywords will be used. The following key words will be considered: (1) P (Population): “breast cancer”, “breast carcinoma”, “breast tumor”, “breast neoplasm”; (2) E (Exposure): “epidemiologic factor*”, “epidemiologic variable*”, “risk factor*”, “risk variable*”, “prediction”, “predictor”, “predict factor*”, “contributing factor*”, “prognostic variable*”, “prognostic factor*”, “relevant variable*”, “related factors*”, “influencing factor*”, “relevant factor*”; (3) C (Comparator) will not be considered; (4) O (Outcome): “edema”, “oedema”, “lymphoedema”, “lymphedema”, “lymphatic”, “swelling”; (5) S (Study type): “systematic review*”, “comprehensive review*”, “systematic overview*”, “comprehensive overview*”, “meta-analys*”, “met aanalys*”. Search terms within each domain are combined with the operator “OR”, and the different domains are combined with the operator “AND”. The final search strategy will be developed by an iterative process and peer reviewed by the research team, and then adapted for each database. The search strategy will not be extending prior to 1990 since very few systematic reviews was published prior to that time.[21 23] A sample search strategy is included as online supplemental file 2.

Study selection

All identified records will be stored and managed using reference management software Endnote X9. After removing duplicates, screening of titles and abstracts for inclusion and exclusion criteria will be carried out by two independent reviewers to identity potential eligible articles. Articles obviously not meeting the eligibility criteria or not being a systematic review will be discarded. All records identified as potentially eligible by at least one reviewer will be retrieved for full text and further assessed for eligibility by two independent reviewers. If eligibility is unsure, the article will be identified as potentially relevant and will be enrolled in the next selection step. The authors of the article will be emailed for additional information to determine eligibility where necessary. Finally, reference lists of included articles will be manually scanned and searched to identify potential articles. If the original and updated versions of a system review are identified, both articles will be included and discussed. Any disagreements will be discussed until consensus is reached, if necessary, a third reviewer will be consulted. The study selection process and results will be summarised in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Assessment of methodological quality

A critical methodological quality appraisal of the included systematic reviews will be performed by two independent reviewers using the Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2) guidelines and checklist.[24] AMSTAR-2 (www.amstar.ca) is presently the most widely used methodological quality assessment tool of systematic reviews. It includes assessments of study eligibility criteria, identification and selection of studies, data collection methods, study appraisal methods and findings, and synthesis methods, consisting of 16 items, which can be rated as ‘yes’, ‘no’ or ‘partially yes’. Seven items (items 2, 4, 7, 9, 11, 13 and 15) are considered as critical and its conclusions are generally recommended as critical items. Overall confidence in the results of each systematic review will be rated as high, moderate, low or critically low. The criteria are as follows: (1) high quality: no

or only one non-critical weakness; (2) moderate quality: more than one non-critical weakness, but no critical item weakness; (3) low quality: one critical item weakness, with or without a non-critical item weakness; and (4) critically low quality: more than one critical item weakness, with or without a non-critical item weakness.

The Risk of Bias in Systematic Reviews (ROBIS)[25] tool is a new tool which can be used to assess the risk of bias in systematic reviews. ROBIS is divided into three phases and consists of 24 entries that assist in determining the risk of bias in the review process, results and conclusions. Responses to landmark questions are indicated by 'yes', 'probably yes', 'could be', 'no' and 'no information'. The final determination of the risk of bias is classified as 'low', 'high' or 'uncertain'. The risk of bias is considered 'low' if all the landmark questions are answered by 'maybe' or 'could be'. The risk of bias is considered 'high' if the answer to any of the landmark questions is 'may or may not' or 'no', and 'uncertain' if the information provided is insufficient to make a judgement.

Results of quality assessments will be compared between the two reviewers to ensure consistency. Any disagreements will be resolved through discussion to reach a consensus. If a consensus is not reached, we will consult a third reviewer for further opinion to make a final decision. The presentation of methodological quality assessment results will include a narrative summary of the overall quality and a tabular summary of details in the section of results. Besides, the assessment of methodological quality will be included in the discussion of the findings.

Data extraction

All included systematic reviews will be independently reviewed and extracted using a predesigned data extraction (see online supplemental file 3) form by two reviewers. There will be two levels of data extraction: systematic reviews and primary studies. The data extraction on the first level will consist of specific details about the systematic reviews (author, year, country, participants characteristics, participants' total number, number of lymphoedema cases, setting/context, risk factors), research question, search strategy (sources searched, range of years, number of studies included, types of studies included), inclusion/exclusion criteria (including types of studies included, diagnosis criteria of BCRL), quality appraisal (instruments used and results), method of analysis, outcomes of significance and results/findings. For meta-analyses, we will extract summary effect sizes (random effect size and/or fixed effect size, 95% CI) and significance levels. When available, information of between-study heterogeneity (Cochrane Q statistic or I^2), publication bias and small-study effects will also be extracted. The second level of data extraction regarding primary studies will include author, year of publication, country, participants characteristics, study design, sample size, diagnostic criteria of BCRL, number of lymphoedema cases, statistical methods, evaluated risk factors, etc.

For inconsistency between data reported in systematic reviews for the same primary study, we will refer to the full-text of the primary study to verify, for example, inconsistent results, sample size or other information. For inconsistencies in ratings of methodology quality or risk of bias, we will re-evaluate the methodology quality of the primary study using the same quality assessment tool, then compare and discuss the results to research a consensus within the review group. In the case of unclear or missing data, we will contact the authors via emails for further information. A second and last email will be sent if no response has been received in the following 2 weeks. If no reply is received from the author after the third attempt, the data will be reported as unavailable. Given the large number of primary studies that might be included, we plan to randomly select 10% of the primary studies for full-text reading to check for incorrect or inconsistent data between the systematic reviews report and primary studies. Incorrect or inconsistent data will be corrected according to the primary study articles. Additionally, for SRs rated with low methodology quality or high risk of bias, we will retrieve all primary studies included in these SRs to check and revise the results. The extracted information will also be compared between reviewers to ensure consistency. Any discrepancies will be solved through discussion. If consensus is not achieved, a third reviewer will be involved.

Data summary

A descriptive, narrative synthesis will be used to summarise the information from different included systematic reviews, framed with reference to the strength and quality of the evidence. Unpublished and non-peer-reviewed systematic reviews will be included and reported separately. Extracted information will be tabulated to help determine the commonalities and variations in important factors in the included studies. The tabulation will also help identify subgroups within the data. We will present groups of similar systematic reviews and/or outcome measures together, in order to group similar populations or outcome measures. Risk factors will be classified into the following five domains in accordance with the health ecological model[26 27]: innate personal trait (pathophysiological factors, genetic predisposition, age, BMI, family history, disease history, surgery type, treatment received, etc), behavioural lifestyles (physical exercise, diet, sleep quality, smoking and drinking history, self-management behaviours, etc), interpersonal network (marital status, family structure, social support, etc), socioeconomic status (education, occupation, family's financial situation), macro-environments (resident type, type of basic medical insurance, etc). Characteristics of the included studies will be tabulated alongside the factors they identify that affect the development of BCRL. This will facilitate discussion of variations. Narrative description will be given to the findings of the included systematic reviews, including explanation of study characteristics with reference to the study population targeted on, the number

and type of included studies, and conclusions drawn in terms of factors identified as influencing BCRL. Discussion will be orientated around similarities and differences between the findings of included studies.

For observational studies, the credibility of the associations between each risk factor and BCRL will be classified into the following categories[28 29]: *Convincing (Class I)*: a statistically significant association ($p<10^{-6}$), more than 1000 cases included, the largest component study reporting a significant result p<0.05, a statistically significant 95% prediction interval, I^2<50%, no evidence of small-study effects and excess significance bias. *Highly suggestive (Class II):* a statistically significant association ($p<10^{-6}$), more than 1000 cases included, the largest component study reporting a significant result p<0.05, and class I criteria not met. *Suggestive (Class III)*: a statistically significant association (p<0.001), more than 1000 cases included, and class I–II criteria not met. *Weak (Class IV):* a statistically significant association (p<0.05) and class I–III criteria not met; not significant associations with p>0.05.

The degree of overlap between included systematic reviews will be assessed through making citation matrices and calculating the 'Corrected Covered Area' (CCA).[30] The formula is calculated as CCA=(n−r)/(rc−r), where 'n' refers to all original studies included, 'r' is all original studies included after deduplication and 'c' is the number of studies included in the umbrella review. The overlap can be classified into four levels based on results of CCA: slight overlap (0–5), moderate overlap (6–10), high overlap (11–15) and very high overlap (>15). The overlap will be reported and recognised as a limitation, if necessary.

ETHICS AND DISSEMINATION

Ethical approval is not required for this umbrella review. We will seek to submit the results for publication in a peer-reviewed journal or present it at conferences.

DISCUSSION

With the increase of incidence and survival rate of breast cancer, the number of breast cancer survivors are growing faster. BCRL, which is a lifelong, distressing complication negatively influencing survivors' quality of life, are arousing more and more attention among healthcare providers, patients and caregivers.[5] Comprehensively identifying and illustrating the potential risk factors predicting the occurrence of BCRL are essential for the effective prevention and management of BCRL, through targeting high-risk populations, developing intervention strategies, etc.[4]

Researchers all over the world had continuously contributed a lot in publishing multiple primary studies and systematic reviews on this topic. By clarifying the strengths and weaknesses of the existing evidence on risk factors for BCRL, this umbrella review may contribute to a more thorough understanding of the associations between potential risk factors (from the pathophysiological factors to lifestyle-related behaviour factors) and the development of BCRL, enhance the needs and provide directions for future research. To the best of our knowledge, this will be the first umbrella review focusing on this topic. In order to present a synthesised and lucid results, we will organise all risk factors into categories according to the categories based on Health Ecological Model. Deviations from the reported methods in this protocol will be illustrated along with the presentation of the results.

Limitations

Some potential limitations should be considered. First, limited by language ability, we only intend to search databases in English and Chinese. Though language will not be restricted during study selection, bias is still possibly existed during study search and identification. Second, overlap of included primary studies among systematic reviews might exist, making the results biased by inflating the associations. Though we will calculate CCA to estimate the degree of overlap, the impact cannot be removed. Third, umbrella reviews only consider evidence that have already been synthesised in systematic reviews, which would lead to leaving out potential relevant primary studies.

Contributors QL is the guarantor of this umbrella review. AS and QL put forward the original idea and designed the umbrella review. All authors (AS, QL, LZ, JB, FZ, ZZ and WQ) contributed to the development of the selection criteria, the risk of bias assessment strategy, data extraction criteria and contributed to the manuscript and approved the final revised version of the manuscript. AS and QL developed the search strategy, and AS and LZ performed the preliminary search. AS wrote the first draft of the protocol and submitted the registration to PROSPERO.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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