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STUDY PROTOCOL

The effectiveness of non-pharmacological interventions on cancer related fatigue in breast cancer patients: A protocol for systematic review and network meta-analysis

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Abstract

Aim: To assess the effect of different non-pharmacological interventions on cancer-related fatigue (CRF) in breast cancer (BC) patients and identify the most effective method for improving CRF.

Design: A systematic review and network meta-analysis.

Methods: Literature will be searched in the ongoing trail in the Clinical Trials.gov, World Health Organization, the International Clinical Trials Registry Platform, Cochrane Library, PubMed, EMBASE, Web of Science and CINAHL, from the inception until December 31, 2020. Two independent researchers will rigorously screen the literature according to the inclusion and exclusion criteria and assess the risk of bias based on the Cochrane Collaboration's Tool of RCTs. Stata 13.0 and Aggregate Data Drug Information System will be used for data analysis.

Results: This protocol has been registered on the PROSPERO website (registration number is CRD42020222093). This study will provide the reliable evidence of the most effective non-pharmacological intervention to improving CRF.

KEYWORDS

breast cancer, cancer-related fatigue, effectiveness, network, non-pharmacological interventions, systematic review

1 | INTRODUCTION

According to the latest data from the International Agency for Research on Cancer, an estimation of 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 (Sung et al., 2021). What is shocking is that female breast cancer (BC) has surpassed lung cancer as the most commonly diagnosed malignant tumour (Sung et al., 2021). With the development of medical technology, the 5-year survival rate of BC patients has been continuously improved. Patients actually live with it in their daily lives. However, patients also struggle with the adverse symptoms associated with medical treatment, such as cancer-related fatigue (CRF), sleep disorder, anxiety and depression. Among these, CRF is one of the most prevalent symptoms of cancer patients. This may be as a result of the

Yu Liu is first author. Pengzhu Xu and Chunli Song are co-first author.

PROSPERO registration number: CRD42020222093

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interaction of multiple factors, throughout the cancer development, treatment and prognosis of the whole process (Hu & Liang, 2017). The National Comprehensive Cancer Network (NCCN) defines CRF as a persistent, subjective physical or cognitive fatigue related to cancer or its treatment (NCCN Guidelines, 2003). At present, the mechanism of CRF is still unclear. However, some studies believe that CRF is related to factors such as inflammatory cytokines, hypothalamic-pituitary-adrenal axis and the 5-hydroxytryptophan system, as well as changes in muscle metabolism and adenosine triphosphate (Barsevick et al., 2010; Karshikoff et al., 2017; LaVoy et al., 2016). Unlike ordinary types of fatigue, CRF cannot be alleviated by improving sleep quality (Morrow et al., 2005). More than 80% of BC patients have CRF before, during or after treatment (Janz et al., 2007). Unfortunately, while coexisting with many other cancer-related symptoms (e.g., anxiety, depression, pain, sleep disturbances), CRF can also exacerbate these symptoms, significantly worsening the survivors' daily functioning and quality of life (Janelsins et al., 2011). As data show, more than one-third of women with BC have reduced their workload due to CRF, and more than one-quarter of women stopped working (Curt et al., 2000). Therefore, more and more researchers regard CRF as one of the main points of the disease management in BC patients.

Until now, there has been no consistent treatment for CRF in women with BC. A series of CRF treatment methods can be summarized into two aspects: pharmacological interventions and non-pharmacological interventions. Considering the side effects and economic costs of pharmacological interventions, researchers are gradually exploring the effectiveness of non-pharmacological interventions on the improvement of CRF in BC patients. The Clinical Practice Guidelines in Oncology of NCCN indicate that non-pharmacological interventions are the best recommendations for managing CRF (Berger et al., 2015). These include exercise therapy (e.g. aerobic exercise, resistance exercise, relaxation exercise, yoga, Tai Chi, and Qigong), cognitive behavioural therapy, mindfulness therapy (e.g. mindfulness-based stress reduction, acceptance and commitment therapy), physical therapy (acupuncture and massage) and music therapy (Pearson et al., 2018). However, the NCCN guidelines do not clearly indicate which non-pharmacological interventions are most effective. With the newly published studies and more BC patients participating in the researches, the effectiveness of non-pharmacological interventions is gradually being demonstrated. A systematic review has conducted the pairwise meta-analysis about the efficacy of drug therapy, psychological intervention and exercise therapy (Mustian et al., 2017). In addition, a recent network meta-analysis (NMA) has explored the effectiveness of different non-pharmacological interventions on CRF (Wu et al., 2019). In this review, it focused on patients with all types of cancer and may cause some heterogeneity in clinical practice. As well, in BC patients, it is not clear which non-pharmacological interventions are most effective.

As far as we know, the NMA can exactly solve this problem. Unlike traditional pairwise comparisons, NMA aggregates direct and indirect evidence and allows simultaneous multi-pairwise comparisons of a range of different interventions (Jansen et al., 2008; Mills et al., 2013). Moreover, NMA can also rank interventions based on study results and provide valid evidence for future research to assist medical decision-making (Debray et al., 2018). This study, therefore, aims to assess the effect of different non-pharmacological interventions and identify the most effective method that improves CRF in BC patients using systematic review and NMA.

2 | METHODS

2.1 | Design

A NMA method will be conducted. The protocol has been registered on the PROSPERO website (registration number is CRD42020222093). We will conduct it in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines (Page et al., 2021). If there are any program adjustments during the whole study period, we will timely correct and update them in the final systematic review and NMA report.

2.2 | Inclusion and exclusion criteria

2.2.1 | Types of study

All the randomized controlled trials (RCTs) of non-pharmacological interventions for the management of CRF will be approved. The language will be limited to English.

2.2.2 | Types of participants

This review will include women BC patients who have been diagnosed by pathology (≥18 years old). The race, education status, types of treatment, clinical stage and pathological stage are not restricted. If the integrated results fail to explain the problem, the subgroup analysis will be described in the report.

2.2.3 | Types of interventions

The interventions included multiple non-pharmacological interventions (types are not restricted). The control group received routine nursing or treatments (e.g. placebo, usual care, no intervention, wait-list control or other non-pharmacological interventions).

2.2.4 | Type of outcomes

Our primary outcome was to evaluate changes of CRF in the included study. However, there is no limit to the types of CRF assessment instruments such as Piper Fatigue Scale, Functional Assessment of Cancer Therapy-fatigue (FACT/FACIT-fatigue) and Brief Fatigue Inventory.

2.2.5 | Exclusion criteria

Several literature which meet the following conditions were excluded: (1) The experimental group combined with two or more non-pharmacological interventions; (2) Non-RCTs studies such as case reports, series studies, review, qualitative studies or animal studies; (3) Duplicated publication by the same author; (4) Studies used a self-reported fatigue scale and (5) Non-English literature.

2.3 | Data sources and search strategies

According to the inclusion criteria of this NMA, all researchers work together to formulate a search strategy that can be translated between databases. After that, the two researchers (Liu and Xu) cross-searched the following databases: Cochrane Library, PubMed, EMBASE, Web of Science and CINAHL. Ongoing trials with unpublished data will be searched from the three following clinical trial registries: the Clinical Trials.gov, World Health Organization and the International Clinical Trials Registry Platform. At the same time, references and gray literature were searched to avoid omission.

The search terms were formulated according to the participants, interventions, outcomes and research types. In the searching process, subject terms and free words are combined to search from database inception until December 31, 2020. Taking PubMed database as an example, the specific retrieval strategies are shown in Table 1.

TABLE 1 Search strategy for PubMed

No.	Search items
#1	breast neoplasms[Mesh]
#2	breast neoplasm[Title/Abstract]
#3	breast neoplasms[Title/Abstract]
#4	breast carcinoma[Title/Abstract]
#5	breast carcinomas[Title/Abstract]
#6	breast malignan*[Title/Abstract]
#7	breast tumor[Title/Abstract]
#8	breast tumors[Title/Abstract]
#9	breast tumour[Title/Abstract]
#10	breast tumours[Title/Abstract]
#11	breast cancer[Title/Abstract]
#12	breast cancers[Title/Abstract]
#13	mammary cancer[Title/Abstract]
#14	mammary cancers[Title/Abstract]
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	Fatigue[Mesh]
#17	cancer related fatigue[Title/Abstract]
#18	fatigue*[Title/Abstract]
#19	weariness[Title/Abstract]
#20	exhaustion[Title/Abstract]
#21	asthenia[Title/Abstract]
#22	#16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	randomized controlled trial [Publication Type]
#24	controlled clinical trial [Publication Type]
#25	randomized [Title/Abstract]
#26	randomly [Title/Abstract]
#27	trial [Title/Abstract]
#28	groups [Title/Abstract]
#29	placebo[Title/Abstract]
#30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#31	#15 AND #22 AND #30

2.4 | Study selection

After literature retrieval, search results were imported into the Endnote X8 software. First, we deleted the duplicated studies. Then, the two researchers (Liu and Jiang) read the title and abstract of these studies independently to make a preliminary selection. After that, the two researchers read the full text to select the eligible studies. During the screening process, if the two researchers have different opinions, a third researcher (Song CL) will participate in the discussion and make the final decision.

2.5 | Data extraction

The data of the included studies were independently extracted by two main researchers (Liu and Jiang), who will make data comparisons. If there is a disagreement, the item will be resolved by discussion until 100%. All data will be recorded in an Excel form. The extracted data will include the following aspects:

- Study characteristic: first author, year of publication, country, sample size of different groups, etc.
- Participants characteristic: cancer type, treatment type, etc.
- Intervention and control detail: methods, time, frequency, intensity, duration, follow-up duration, etc.
- Outcome: assessment instrument of fatigue.

2.6 | Risk of bias assessment

Two researchers (Liu and Jiang) will independently evaluate and cross-check the included studies according to the Cochrane Collaboration's tool of RCTs (Higgins et al., 2011). It consists of the six items: random sequence generation, allocation concealment, blinding methods (participants, personnel and outcome assessment), incomplete outcome data, selective reporting and other biases. Each domain of bias is classified as “high risk”, “medium risk” and “unclear risk”. When the two people's opinions are not consistent, a third

researcher (Shi TY) will participate in the discussion and make a decision. We will use Review Manager 5.3 software to generate the risk of bias graph.

2.7 | Data synthesis and statistical analysis

2.7.1 | Dealing with missing data

If the data are incomplete in the included studies, we will contact the corresponding author by email to obtain the original information. If the author cannot be contacted or the missing data cannot be used, we will rely on the existing data for analysis. Sensitivity analysis will also be used to address potential impact. In the final report, we will use descriptive analysis to elaborate.

2.7.2 | Pairwise meta-analysis

The Stata 13.0 will be selected for pairwise meta-analysis. We will test the clinical heterogeneity of the included patients' baseline characteristic data. Heterogeneity will be determined by the calculation results of I^2 and p values. When $I^2 \geq 50\%$ and $p \leq .1$, indicating heterogeneity between studies. At this time, the random effects model will be used for analysis; otherwise, the fixed effect model will be used. A p value (two-tailed) less than .05 will be considered statistically significant. Standard mean differences with 95% confidence intervals (95% CI) will be calculated as the scores of fatigue are continuous data.

2.7.3 | Network meta-analysis

In order to compare the effects of different non-pharmacological interventions on CRF in BC patients, we will use the Bayesian Network Meta-analysis method. First, we will select Stata 13.0 to draw the network plot for NMA of the data. The network plot will be used to understand which interventions are directly compared in the included studies, how indirect interventions flow, and the contribution of different interventions (Mavridis et al., 2015). In the network plot, the lines between nodes represent direct comparisons between included studies. The bigger the node, the larger the sample size focused on the intervention; and the wider the line, the more studies focused on the comparison. Second, we will generate a contribution plot to calculate and summarize the contribution of each direct comparison to each network estimate (Krahn et al., 2013). Third, we will investigate for consistency between direct and indirect comparisons. The inconsistency factor (IF) is calculated and the IF value and p value are used to determine whether there is any inconsistency. If the *IF* is close to 0, the 95% CI contains 0 and $p > .05$, and there is no global inconsistency in the direct comparison and indirect comparison (Salanti et al., 2011), otherwise, calculating the local inconsistency between each node by the node-split model. The fourth step, the Bayesian NMA will be conducted by the code from Dias et al. (2013) in Aggregate Data Drug Information System 1.16.5. This software performs Bayesian framework and the Markov chain Monte Carlo method for the pooled estimation to rank the effectiveness of interventions. In this study, four Markov chains will be used to set the initial value. The number of iterations for the initial burn-in period of the model will be set as 20,000, and then the number of iterations for the further update will be set as 100,000. We will use the results of kernel density and auto-correlation plots to evaluate model convergence. The last step is to rank the different interventions. This will rank the effects of various interventions by calculating the surface under the cumulative ranking curve (SUCRA). The value ranges from 0 to 100. The larger the value, the greater the likelihood that the intervention method will be the best. When the number of included studies exceeds 10, it needs to estimate the publication bias (Sutton et al., 2000). We will draw a funnel plot. If all studies are uniformly distributed and symmetrically around the 0 line, it is proved that there is no publication bias.

3 | DISCUSSION

To the best of our knowledge, this is the first systematic review and NMA to compare the effectiveness of different non-pharmacological interventions on CRF in BC patients. The NMA can rank these interventions for improving CRF by comparing efficacy and safety. The results of this NMA will help doctors, nurses and patients choose the best CRF approach. In addition, we also hope that the results of this study can provide a basis for the recommendations of the guidelines and facilitate the decision-making sharing process.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

YL: Protocol design, Literature search, Literature assessment, Writing. PZX: Protocol design, Literature search, Literature assessment, Writing. CLS: Protocol design, Quality control. TTJ: Literature search, Literature assessment, Writing. JEL: Quality control. TYS: Protocol design, Quality control.

ETHICAL APPROVAL

Not applicable.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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