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REVIEW ARTICLE

Exercise on quality of life and cancer-related fatigue for lymphoma survivors: a systematic review and meta-analysis

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Abstract

Background People treated for lymphoma can experience several significant long-term and late effects, including fatigue and decreased quality of life. This study aimed to systematically review the evidence from randomized controlled trials (RCTs) and to conduct a meta-analysis of the effect of exercise on quality of life and other health outcomes for adults suffering from lymphoma.

Methods We searched the following databases and sources: PubMed, Cochrane Library, Embase, Web of Science, and MEDLINE. Such studies would be included if they were RCT designs which focus on observing the evaluated health outcomes of exercise intervention for lymphoma patients or survivors, comparing with non-exercise or wait-list control groups. Two review authors independently screened search results, extracted data, and assessed the quality of trials. We used standardized mean differences for quality of life (QoL), fatigue, sleep quality, and depression.

Results Six publications have met the inclusion criteria and the exercise interventions are short term. Slight improvement can be seen on QoL, fatigue, sleep quality, and depression due to exercise for lymphoma patients. Subgroup analysis was carried out according to the classification of mind-body exercise and aerobic exercise, and significant progress can be seen after mind-body exercise intervention in the area of fatigue and sleep.

Conclusions Short-term exercises do not appear to convey benefits to quality of life and other psychosocial outcomes. Subgroup analysis showed that physical activity together with mental exercise may be more beneficial to lymphoma patients, but it needs more research to verify this finding. The interpretation of this result should be cautious due to the baseline difference, completion efficiency of intervention process, and high heterogeneity.

Keywords Exercise · Randomized controlled trial · Quality of life · Fatigue · Lymphoma

Background

There is a huge increase in the number of patients diagnosed with lymphomas worldwide, which is 451,691 in 2012 [1], while the number is growing up to about 79,990 new cases of HL (Hodgkin's lymphoma) and 509,590 new cases of NHL (non-Hodgkin's lymphoma) in 2018 [2]. Unlike children lymphoma, which has a 5-year survival of 80–95%, the 5-year survival of adult lymphoid malignancies usually ranges from 40 to 70% in most countries [1]. Fortunately, the trend of 5-year survival from the period of 2000–2004 to 2010–2014 was increased by 10% in most countries [1]. It is estimated that there were 219,570 HL survivors and 686,370 NHL survivors until January 1, 2016 [1]. Improvement in cancer detection and treatment has led to an increase in the number of cancer survivors. Lymphoma patients are generally treated with multi-drug chemotherapy, sometimes combined with radiotherapy, which can cause a variety of significant long-term

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and late effects, including fatigue, sleep disruption, neuropathy, physical loss, chronic pain, depression, anxiety, cognitive impairment, and decreased quality of life (QoL) [3–5]. Fatigue, affecting 60–100% of patients [6], is the most commonly diagnosed side effect of cancer and after cancer treatment, which could have a long-term existence in cancer patients and especially present in lymphoma survivors [7]. And it can be a vicious circle of life that significantly affects the quality of life of cancer patients. The loss of lean muscle mass, along with reduced muscle strength and endurance, severely affects the physical function of cancer survivors [8]. Thus, how to improve quality of life and relieve cancer-related fatigue (CRF) becomes a key issue. Strategies to reduce the side effects of lymphoma are needed.

Many studies have shown that physical activity is helpful in improving symptoms in some chronic diseases such as obesity, type II diabetes [9, 10], and even showing a preventive function in some kinds of cancers, like breast cancer, ovarian cancer, colon cancer, and lung cancer [11–14]. However, lymphoma patients have always been restricted of exercise due to suffering from severe anemia and thrombocytopenia. Multiple system reviews and meta-analysis about the effect of physical activity on cancer patients have been published. In 2010, Rebecca et al. [15] summarized 102 articles, 90% of which were randomized controlled trials and 6% were lymphomas. Forty percent of trial interventions have a period of more than 3 months. They found small to moderate positive effects of physical activity on the improvement of life quality, physical activity levels, anxiety, and self-esteem during and after cancer treatment. Mishra et al. [16] analyzed the effect of exercise on health-related QoL in adult cancer survivors after treatment in 2012. In 40 randomized controlled or controlled trials, 3694 participants diagnosed with various cancers were included, and the results suggest that exercise may be beneficial for health-related QoL, but attention is needed due to high heterogeneity. The authors also suggest that it is important to focus on one type of cancer to analyze the greatest impact on QoL. Bergenthal et al. [17] conducted a review that included 9 RCTs involving 818 participants with hematological malignancies in 2014. They found that between the exercise intervention and control groups, there was no significant difference in mortality. Exercise can improve physical functions, depression, and fatigue but it does not improve adverse events, physical performance, and anxiety. Buffart et al. [18] pooled 34 randomized exercise trials with 4519 cancer survivors in 2018. They found that targeting specific subgroups with high levels of fatigue and low levels of self-reported physical functions showed the greatest benefits on muscle strength and QoL. However, few studies focused on the lymphoma survivors. Some studies showed that CRF and its possible relations with biochemical/inflammatory changes, or it is characterized by its subjective property, cannot be relieved by rest [19]. They believe that exercise can regulate the expression of cytokines and has a positive effect on the immune system of patients with non-Hodgkin's lymphoma [20–22].

Thus, clinical evidences are important to prove whether and how much the lymphoma patients can get benefits from exercise. Here, we review the related RCT trials and try to get the evidence of exercise effectiveness on QoL and fatigue for lymphoma survivors.

Methods

Inclusion criteria

The definition of physical activity refers to any bodily movement produced by the contraction of skeletal muscles that increase energy expenditure to above a basal level [23]. Exercise is a form of physical activity that is planned, structured, repetitive, and designed to improve or maintain physical fitness, physical performance, or health [24]. In the present study, we include all kinds of physical activities which have been planned and designed to improve physical and mental health, such as moderate cycling, walking, running, swimming, yoga, Qigong, Tai Chi Chuan, and other related forms of exercises. Yoga, Tai Chi, and Qigong, which have some variations and are sometimes referred to as "mind-body" activities, are also included in our search, because these activities also combine muscle strengthening, balance training, low-intensity aerobic activities, and flexibility in one package [23]. We considered only randomized controlled trials (RCTs) for inclusion. Full-text publications written in English were included. The trials that involved adult lymphoma survivors were needed. There were no gender or ethnicity restrictions. All kinds of exercises as a means of intervention are compared with non-exercise or wait-list group alone.

Outcomes

We focused on analyzing the effects of exercise on the following outcomes: quality of life, fatigue, sleep function, and depression.

Literature search

The following databases and sources were searched: PubMed (for search strategy, see Table S1); Cochrane Library (CENTRAL) (for search strategy, see Table S2); Embase (for search strategy, see Table S3); and Web of Science (for search strategy, see Table S4). We adapted MeSH terms and free terms for "exercise" and also the extensive list of search terms were adapted to make sure the most related studies are included. There were no restrictions by date while we screened articles only in English. Manual reference retrieval:

other articles are identified by manually checking the list of references that contain papers and related review articles.

Data collection and analysis

Selection of studies

Firstly, articles that are not related to the topic of this study are removed by reading the titles and abstracts. Two people did the first screening work independently (LxL and XrH). If there are inconsistent articles, we need to check the full text and discuss them before deciding whether to include them. Then the articles included by the first screening were read through the full text to determine whether they met the inclusion criteria of this study, which were also done by two people independently. If there were any disagreements in this part, the third author (LF) would be required to join and discuss together to reach a consensus.

Data extraction and management

Two people have finished the data extraction independently (LxL and XrH). If there were any disagreements, the third author (LF) would be required to join and discuss together to reach a consensus. We extracted the following information of each included study.

1. Basic information of studies: authors, title, publication date, country, language, research date, aims, participants, age, diagnoses, treatment, and inclusion criteria;
2. Methods of studies: trial design, comparability of groups, randomization, sequence generation method, allocation concealment method, masking and blinding, numbers of loss to follow-up, and compliance with the assigned treatment.
3. Intervention characteristics of studies: type of interventions, duration and intensity of exercise, and length of follow-up.
4. Outcomes: extract the mean and SD of the two compared groups on QoL, fatigue, sleep quality, and depression.

We try our best to make the data comprehensive and accurate by contacting the author when necessary or consulting relevant literature to avoid data missing. After extracting data from the articles, we entered the data into the Review Manager software (RevMan 5.1). This part of the work was completed by one person (LxL), and another person was responsible for checking whether the data input is accurate (XrH).

Quality assessment

We used a questionnaire (validity assessment form) to assess the quality of the included studies and risk of bias according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions [25]: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, (detection bias) incomplete outcome data, selective reporting, and other potential sources of bias.

We gave the grade as high risk, low risk, or unclear risk for each study according to the recommendations for judging risk of bias suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* [25].

Measurement of treatment effect

In the calculation of continuous data, mean differences, or standardized mean differences (SMDs) of 95% confidence intervals (CIs) were used for each trial. Since different studies used different rating scales, we used standardized mean difference (SMD) analysis and random effect models to combine data from different rating scales in the same field.

Assessment of heterogeneity and sensitivity analysis

Chi-squared test was used to evaluate the heterogeneity of therapeutic efficacy in the trial when $P < 0.1$ was significant. We also assessed possible levels of heterogeneity using I^2 ($I^2 > 75\%$ considerable heterogeneity, $I^2 > 30\%$ moderate heterogeneity).

If it is permitted, the subgroup analysis or sensitive analysis will be performed when there is a significant clinical or statistical heterogeneity. We analyzed quality of trials and excluded studies at high risk of bias.

Results

Results of the search

We identified 765 potentially relevant references through databases and searches and discarded 222 duplicate publications. Four hundred twenty-four publications were excluded at the initial stage of screening due to unfulfillment of our predefined inclusion criteria. For 121 potentially relevant reports, we retrieved the full text for detailed evaluation and 2 articles by hand searching. Of these 121 publications, we excluded 115 because of being not RCT or not related with the effect of exercise on QoL of lymphoma patients (see Table 1 for exclusion reasons). There were 3 ongoing trials registrated in the Cochrane Clinical Trials without final data were also excluded (Table S5). At the end of the screening procedure, six articles met the inclusion criteria. The PRISMA flow diagram showed the whole process of reference screening (Fig. 1).

Table 1 The characteristics and reasons of excluded studies

Study	Reason for exclusion
Vallerand 2018	This study was excluded as the two arms were both exercise intervention groups.
Repka 2018	This study was excluded as it was pseudorandomization.
Lopez 2018	This study was excluded as it did not focus on exercise effect.
Kimball 2018	This study was excluded as it was not a RCT.
Pophali 2017	This study was excluded as it was retrospective survey other than RCT.
Knobf 2017	This study was excluded as the two arms were both exercise intervention groups.
Chaou 2017	This study was excluded as it was a conference abstract and also it was a single arm test.
Courneya, K.S. 2015	The outcomes in this study were not related with this meta-analysis.
Terry Boyle, 2015	This study was excluded as it was not a RCT.
Zimmer, P. 2014	The outcomes in this study were to observe the effect of exercise on pro inflammatory cytokine levels.
Oechsle, K. 2014	The patients in this study had all kinds of cancers, not only lymphoma.
Leal, B. 2014	Abstracts from the 2014 Annual Scientific Meeting of the American Psychosomatic Society.
Kauhanen, L. 2014	It was a trial design without data.
Jose, S. 2014	The patients in this study had all kinds of cancers, not only lymphoma.
Cormie, P. 2014	Conference abstract
Soares-Miranda, L. 2013	It was a trial design without data.
Prinsen, H. 2013	The patients in this study had all kinds of cancers, not only lymphoma.
Susan Lakoski 2013	The outcome of this study was not related with our meta-analysis.
Streckmann, F. 2012	Conference abstract
Courneya, K.S. 2012	This article was not about the effect of exercise.
Courneya, K.S. 2012	The outcomes in this study were not related with this meta-analysis.
Streckmann, F. 2011	Conference abstract
LaStayo, P.C. 2011	The patients in this study had all kinds of cancers, not only lymphoma.
Elter, T. 2009	The patients in this study had all kinds of cancers, not only lymphoma.
Courneya, K.S. 2009	This study was excluded as it did not focus on exercise effect.
Adamsen, L. 2009	The patients in this study had all kinds of cancers, not only lymphoma.
Oh, B. 2008	The patients in this study had all kinds of cancers, not only lymphoma.
Thorsen, L. 2005	The patients in this study had all kinds of cancers, not only lymphoma.
Persoon 2017	The patients in this study had other cancers, not only lymphoma.
Yildiz 2016	The patients in this study had other cancers, not only lymphoma.
Knols, R.H. 2011	The patients in this study had other cancers, not only lymphoma.
Persoon, S. 2010	The patients in this study had other cancers, not only lymphoma.
Shelton, M.L. 2009	The patients in this study had other cancers, not only lymphoma.
Hayes, S. 2004	The patients in this study had other cancers, not only lymphoma.
Zelasko, K. 1984	Article in Polish
Sandler, E.D. 1992	Case report
Sacco, C. 1995	Review
Dimeo, F.C. 1997	This study was excluded as it was not a RCT.
Wright, M.J. 1998	The patients in this study had other cancers, not only lymphoma.
Jereczek-Fossa, B.A. 2002	Review
Adamsen, L. 2003	This study was excluded as it was not a RCT.
Flechtner, H. 2003	Review
Lee, J.Q. 2003	The study focused on describing and comparing physical performance profiles between men and women with lymphoma.
Oldervoll, L.M. 2003	This study was excluded as it was not a RCT.
Ankermann, T. 2004	Case report
Merli, F. 2004	This article was not about the effect of exercise.
Demark-Wahnefried, W. 2005	This article was not about the effect of exercise.

Table 1 (continued)

Study	Reason for exclusion
Nct, 2005	This article was not about the effect of exercise.
Vallance, J.K. 2005	This study was excluded as it was not a RCT.
Wilson, R.W. 2005	This study was excluded as it was not a RCT.
Carlson, L.E. 2006	This study was excluded as it was not a RCT.
Keegan, T.H.M. 2006	This study was excluded as it was not a RCT.
Kelemen, L.E. 2006	This article was not about the effect of exercise.
Thompson, C. 2006	Conference abstract
Calaminus, G. 2007	The patients in this study had other cancers, not only lymphoma.
De Backer, I.C. 2007	This study was excluded as it was not a RCT.
Ganz, P.A. 2007	This study was about some of the potential biological mechanisms for fatigue problem in cancer survivors.
Lim, U. 2007	This study was about serum high-density lipoprotein cholesterol and risk of non-Hodgkin's lymphoma.
Oldervoll, L.M.	This study was a cross-sectional study, not RCT.
Wu, H.S. 2007	This study was semi-structured individual interviews, not RCT.
Morgan, N.P. 2008	This article was not about the effect of exercise.
Velensek, V. 2008	This study was about the cardiac damage after treatment of childhood cancer.
Jarden, M. 2009	The interventions in this study were multimodal program of exercise, relaxation, and psychoeducation.
Kav, S. 2009	This article was not about the effect of exercise.
Litterini, A. 2009	Oncology platform and poster presentation
Ater, J. 2010	This study was a mailed survey of dietary intake and physical activity.
Bauer, K. 2010	Eleventh biannual report of the Cochrane
Courneya, K.S. 2010	The study was about exercise adherence research.
McTiernan, A. 2010	Conference abstract
Robsahm, T.E. 2010	This study was excluded as it was not a RCT.
Kvillemo, P. 2011	The study was a semi-structured interviews, not RCT.
Baumann, F.T. 2012	The study was a non-randomized controlled pilot study.
Chadban, S. 2012	Conference abstract
Janíková, A. 2012	Review
Nct, 2012	Estimated study completion date: May 2019
Rabin, C. 2012	This study was excluded as it was not a RCT.
Rebholz, C.E. 2012	The study focused on clustering of health behaviors in adult survivors of childhood cancer and the general population.
Swinburn, P. 2012	Conference abstract
Swinburn, P. 2012	Conference abstract
Winter, C. 2012	Conference abstract
Yokoyama, T. 2012	This study was the Japanese version of the M. D. Anderson Symptom Inventory.
Arving, C. 2013	The intervention of this study was an individual stress management intervention.
Badr, H. 2013	The study had cross-sectional questionnaires.
Fuemmeler, B.F. 2013	This study was about diet, physical activity, and body composition changes during the first year of treatment for childhood acute leukemia and lymphoma.
Gates, P.R. 2013	Conference abstract
Gates, P.R. 2013	Conference abstract
Van Uden-Kraan, C.F. 2013	This study was focus group interviews, not RCT.
Hung, Yc 2014	This study was to evaluate the impact of nutrition and exercise counseling.
Janikova A. 2014	Conference abstract
Ruth Pettengell 2014	Actual study completion date: March 2017 but not applicable
Lillian Sung 2014	Estimated study completion date: October 2019
Vermaete, N. 2014	This study was excluded as it was not a RCT.
Diorio, C. 2015	This study was a pilot study to evaluate the feasibility of individualized yoga for inpatient children receiving intensive chemotherapy.

Table 1 (continued)

Study	Reason for exclusion
Hsu, Ch 2015	Conference abstract
Lauria Silva, 2015	This study was to observe the effect of low-level laser therapy.
Lukas Trachsel, L.D.T. 2015	This study was excluded as it was not a RCT.
Nct 2017	Estimated study completion date: March 15, 2019. Not applicable
Cocco, P. 2016	Conference abstract
De Cock, Erwin 2016	The outcomes in this study were not related with this meta-analysis.
Goswami, P. 2016	This study was a semi-structured face-to-face interviews, not RCT; conference abstract
Kuehl, Rea 2016	This study was to observe exercise adherence.
Mackenzie, M.J. 2016	This study was excluded as it was not a RCT.
Pituskin, E. 2016	This study was about rationale and design of the multidisciplinary Team Intervention in cArdio-oNcology (TITAN) study.
Stenehjem, J.S. 2016	The study was a retrospective study, not RCT.
Streckmann, F. 2016	Conference abstract
Turner, J.D. 2016	The study was about the evaluation of a weight management program for overweight and obese cancer survivors.
Boyle 2017	This study was excluded as it was not a RCT.
Kimball 2017	This study was excluded as it was not a RCT and also focused on investigating the most appropriate intervention for cancer patients.
Nct 2017	This study was to determine whether a theory-based telephone counseling intervention focused on closing the exercise intention-behavior gap is feasible and can improve exercise levels, motivation, quality of life, and fatigue in hematologic cancer survivors.
O′ Regan 2017	This study was to measure cancer-related fatigue (CRF) and explore fatigue self-care strategies used to ameliorate CRF among patients undergoing chemotherapy for primary cancer. A mixed methods design was utilized.
Persoon 2017	The study was a cross-sectional study and also the patients had myeloma or lymphoma.
Salchow 2017	Conference abstract
De Lima 2018	This article was not about the effect of exercise.
Saskia Persoon 2017	The patients in this study had other cancers, not only lymphoma.
Kerry S. Courneya 2013	The outcomes in this study were not related with this meta-analysis.

Included studies

The six articles included a total of 429 participants, fulfilled the inclusion criteria (Chuang et al. [26]; Yeh et al. [27]; Courneya et al. [28]; Courneya et al. [29]; Streckmann et al. [30], Cohen et al. [31]). The included articles were published in full text and we summarized the basic information of these six articles in the table of characteristics of the included studies (Table 2). The 6 included articles involved 5 studies. In general, there were 214 people in the exercise intervention group and 216 people in the control group. The average age in the exercise intervention group was 52.7 years old and that of the control group was 55.4 years old. Only non-Hodgkin's lymphoma patients were included in the studies of Chuang et al. [26] and Yeh et al. [27], and all types of lymphoma survivors were included in the remaining three studies. Patients with different stages of lymphoma were evenly distributed between the groups (Table 2). The patients in the studies of Chuang et al. and Yeh et al. are those who are undergoing the first chemotherapy [26, 27]; Cohen et al.'s research included patients who were undergoing treatment or have completed chemotherapy within 12 months [31]. Patients in Streckmann et al.'s study were undergoing chemotherapy without indicating the period [30], while there was no requirement for whether receiving treatment or not in Courneya et al.'s trial [28] (Table 2).

Quality assessment

We showed the assessment results for methodological quality in Figs. 2 and 3 and Table S6. In all six articles, they all mentioned random sequence generation method and allocation concealment. Therefore, we judged the potential risk of bias as "low." The authors used computer-generated programs to independently generate assignment sequences, which were hidden from the research coordinator. Due to the nature of the exercise intervention, it was impossible to blind the participants to the group assignment. Therefore, in all six articles, we believed that the potential risk of blinding participants and physicians was "high." It is difficult to be

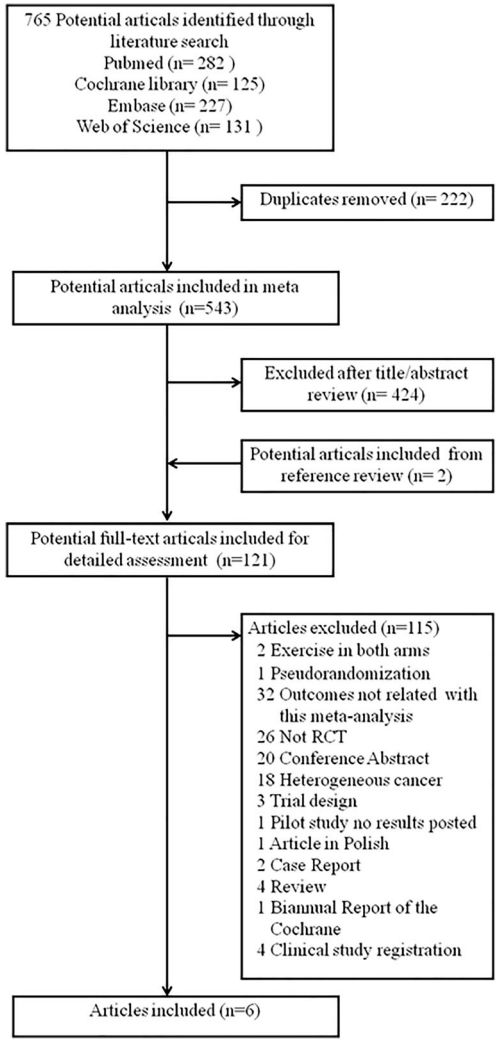

Fig. 1 Flow diagram

blind in the evaluation process of exercise intervention results, but the authors used some means to make the evaluators as fair as possible. In all six articles, four of them mentioned about the way they have tried to prevent the possible bias. Researchers at Chuang et al.'s study blindly performed a statistical analysis [26]; researchers involved in the recruitment were unable to access the randomized list in the Yeh et al.'s study [27]. Outcome assessors were trained in standardizing testing procedures in Courneya et al.'s studies [28, 29]. While in the studies of Streckmann et al. and Cohen et al., they did not mention the way to prevent detection bias, therefore we rated the risk as "unclear" [30, 31]. In all six studies, the number of participants in the trial design, the actual number of participants, and the number of shedding cases were listed in detail. The data from included participants in each study have been fully analyzed. So we rated "low" for the risk of attrition bias of these studies. We rated the potential risk of reporting bias as "unclear" since we were not able to judge the potential risk of reporting bias due to the lack of available protocol in all included studies. We have not found any more bias through the description of the articles in four articles [26–29]. However, one study has stopped early, due to the low recruitment, which may influence the evaluation of exercise effectiveness [30]. In addition, QoL resulted in a severe baseline imbalance that favored the control group. Therefore, we excluded the QoL of this trial in the sensitivity analysis.

Effect of interventions

Quality of life

In the domain of quality of life, three studies were analyzed. In Streckmann et al.'s trial, exercise intervention contained aerobic endurance training, sensorimotor training, and strength training. Streckmann et al. chose the scale of EORTC-QLQ-C-30 to assess the QoL and a Chinese version of the EORTC-QLQ-C30 was employed in Chuang et al.'s study whose exercise intervention was Qigong. Courneya et al. used the Functional Assessment of Cancer Therapy-Anemia (FACT-An) Trial Outcome Index-Anemia (TOI-An) to evaluate the effect of supervised aerobic exercise on the QoL. However, although it showed the positive effects of exercise on quality of life in these studies, the effect was insignificant (Fig. 4a). And Streckmann et al. reported a favorable outcome of the control group that may be due to the imbalanced baseline [30], and we therefore conducted a sensitivity analysis but still found insignificant advantages in the exercise arm (Figure S1). We also made a sensitivity analysis based on the similar assessment scales in the studies of Streckmann et al. and Chuang et al. However, there was still a large heterogeneity with no significant difference (Figure S2). A significant baseline difference was also seen in Chuang et al.'s study. It is hard to give any conclusion since there were two out of three studies with the significant baseline difference.

Fatigue

Fatigue was measured in five studies and unfortunately no statistically significant advantage was found, with a large heterogeneity ($I^2 = 97\%$) (Fig. 4b). The large heterogeneity may be caused by the use of different evaluation scales, small sample size, or the uneven baseline. Cohen et al. used the Brief Fatigue Inventory (BFI) and Chuang et al. used its Taiwan form (BFI-TF). FACT-An and the fatigue subscale was applied in Courneya et al.'s study while Streckmann et al. took the EORTC-QLQ-C-30 as the assessment. Yeh et al. chose an 11-point rating scale to make the evaluation. The sensitive test found that there was a statistically significant positive effect (Figure S3).

Table 2 The basic information of included studies

Characteristic of included studies

	Participants	Stage/type of disease	Mean age	Intervention	Recruitment period	Median follow-up time	Study region	Reported and relevant for this review
Chuang et al. 2017 [26]	• Intervention group ($N = 50$) • Control group ($N = 50$)	• Non-Hodgkin's lymphoma who underwent their first course of chemotherapy • Intervention group: stage II: 10, stage III: 17, stage IV: 21 • Control group: stage II: 17, stage III: 17, stage IV: 20	• Intervention group: 55.85 years • Control group: 64.54 years	• 2 arms: Qigong group ($n = 50$) that received a 21-day Chan-Chuang Qigong program or the control group ($n = 50$)	November 2010–October 2011	No follow-up analysis	Taiwan	• Fatigue • Blood cell counts • Sleep quality • Quality of life
Yeh et al. 2016 [27]	• Intervention group ($N = 54$) • Control group ($N = 54$)	• Non-Hodgkin's lymphoma who prepared the first course of chemotherapy with cyclophosphamide, vincristine, and prednisolone combined with rituximab • Intervention group: stage I: 1, stage II: 12, stage III: 17, stage IV: 21 • Control group: stage I: 1, stage II: 11, stage III: 18, stage IV: 21	• The average age was 59.79 ± 16.54 years (range 23–90 years).	• 2 arms: Qigong group ($n = 54$) that received a 21-day Chan-Chuang Qigong program or the control group ($n = 54$)	Not mentioned	No follow-up analysis	Taiwan	• Fatigue• Sleep quality
Courneya et al. 2012 [29]	• Intervention group ($N = 60$) • Control group ($N = 62$)	• NHL or HL receiving chemotherapy or no treatments • Intervention group: NHL indolent 25, NHL aggressive 24, Hodgkin's lymphoma 11 • Control group: NHL indolent 27, NHL aggressive 24, Hodgkin's lymphoma 11 • Intervention group: stage I: 11, stage II: 8, stage III: 9, stage IV: 15, no evidence: 16, unclear: 1 • Control group: stage I: 7, stage II: 15, stage III: 8, stage IV: 13, no evidence: 18, unclear: 1	• Intervention group:< 50 years: 31.6 years; > 50 years: 68.4 years • Control group: < 50 years: 32.5 years; > 50 years: 67.5 years	• 2 arms: supervised aerobic exercise ($n = 60$) or the control group ($n = 62$).	Between 2005 and 2008	A median follow-up of 61 months	Canada	• Sleep quality
Courneya et al. 2009 [28]	• Intervention group ($N = 60$) • Control group ($N = 62$)	• NHL or HL receiving chemotherapy or no treatments • Intervention group: NHL indolent 25, NHL aggressive 24, Hodgkin's lymphoma 11 • Control group: NHL indolent 27, NHL aggressive 24, Hodgkin's lymphoma 11 • Intervention group: stage I: 11, stage II: 8, stage III: 9, stage IV: 15, no evidence: 16, unclear: 1 • Control group: stage I: 7, stage II: 15, stage III: 8, stage IV: 13, no evidence: 18, unclear: 1	• Intervention group: 52.8 years • Control group: 53.5 years	• 2 arms: supervised aerobic exercise ($n = 60$) or the control group ($n = 62$).	Between 2005 and 2008	A median follow-up of 61 months	Canada	• Physical functioning • Quality of life • Psychosocial functioning
Streckmann et al. 2014 [30]	• Intervention group ($N = 30$) • Control group ($N = 31$)	• Intervention group: Hodgkin's disease 7, B-NHL 13, T-NHL 3; multiple myeloma 5 • Control group: Hodgkin's disease 5, B-NHL 13, T-NHL 3; multiple myeloma 8 • Intervention group: stage I: 3, stage II: 5, stage III: 4, stage IV: 10, International Staging System for Multiple Myeloma 4, not available 2	• Intervention group: 44 years• Control group: 48 years	Exercise group • Trained twice a week, over 36 weeks, supervised by certified sport-orphysiotherapists • Each 1-h session consisted of: aerobic endurance training; sensorimotor training; strength trainingControl group • No training intervention	May 2008 and July 2011	No follow-up analysis	Germany	• QoL • Peripheral deep sensitivity • Activity level

Table 2 (continued)

Characteristic of included studies

	Participants	Stage/type of disease	Mean age	Intervention	Recruitment period	Median follow-up time	Study region	Reported and relevant for this review
		• Control group: stage I: 2, stage II: 5, stage III: 3, stage IV: 7, International Staging System for Multiple Myeloma 8, not available 3						
Cohen et al. 2004 [31]	• Intervention group (*N* = 20) • Control group (*N* = 19)	• 32 Non-Hodgkin's lymphoma; 7 Hodgkin's lymphoma • Patients who were either receiving chemotherapy or had received it within the past 12 months • TY group: stage I, 22%; stage II, 39%; stage III, 17%; stage IV, 22%; • Control group: stage I, 22%; stage II, 33%; stage III, 12%; stage IV, 33% Ann Arbor Criteria	• In both groups, the average patient age was 51 years	• 2 arms: Tibetan yoga (TY) group (*n* = 20) that received a 21-day Chan-Chuang Qigong program or the wait-list control group (*n* = 19).	• Not reported	• 3 month follow-up analysis	• M. D. Anderson Cancer Center, USA	• Psychological adjustment • Fatigue • Sleep disturbances

Sleep quality

The 100-mm VAS scores, Verran and Snyder-Halpern Sleep Scale, Pittsburgh Sleep Quality Index, and PSQI total scale were employed in the studies of Chuang et al., Yeh et al., Courneya et al., and Cohen et al. The analysis result about sleep quality was still slightly superior in the exercise group without statistical signification (Fig. 4c). We made a sensitivity analysis based on the similar assessment scales in the studies of Courneya et al. and Cohen et al. However, there was still a large heterogeneity with no difference (Figure S4). However, in Courneya et al.'s study, the subjective sleep quality assessed by patients showed obvious improvement.

Depression

In the depression domain, it showed a good heterogeneity ($I^2 = 0\%$) that may be as the same assessment scale as the authors took in the two involved studies (Centers for Epidemiologic Studies-Depression [CES-D]). Though without significant statistical meaning in the exercise intervention group, there was a slight improvement in depression (Fig. 4d).

Subgroup analysis

We classify the six studies according to different types of exercises. Among them, the exercise interventions in the studies of Chuang et al., Yeh et al., and Cohen et al. are Qigong and yoga, which can be generalized as mind-body exercises. The remaining three researches employed aerobic exercise. Subgroup analysis was carried out according to the classification of mind-body exercise and aerobic exercise. The results showed that aerobic exercise still had little improvement in aspects of QoL and fatigue (Fig. 5a, b), while significant progress can be seen after mind-body exercise intervention in the area of fatigue and sleep (Fig. 5c, d). We can conclude from subgroup analysis that different types of exercises may bring different benefits for lymphoma survivors. Mind-body exercise is more helpful to improve the quality of life, fatigue, and sleep (depression cannot be analyzed in subgroup due to few studies). Subgroup analysis showed that physical and mental exercise may be more beneficial to lymphoma patients, but it needs more research to verify this finding.

Discussion

Summary of the main results

In the included 6 studies, 430 participants were randomly divided into the exercise intervention group ($n = 214$) and the control group ($n = 216$). Mainly diagnosed with non-Hodgkin's lymphoma in the study were 372 participants,

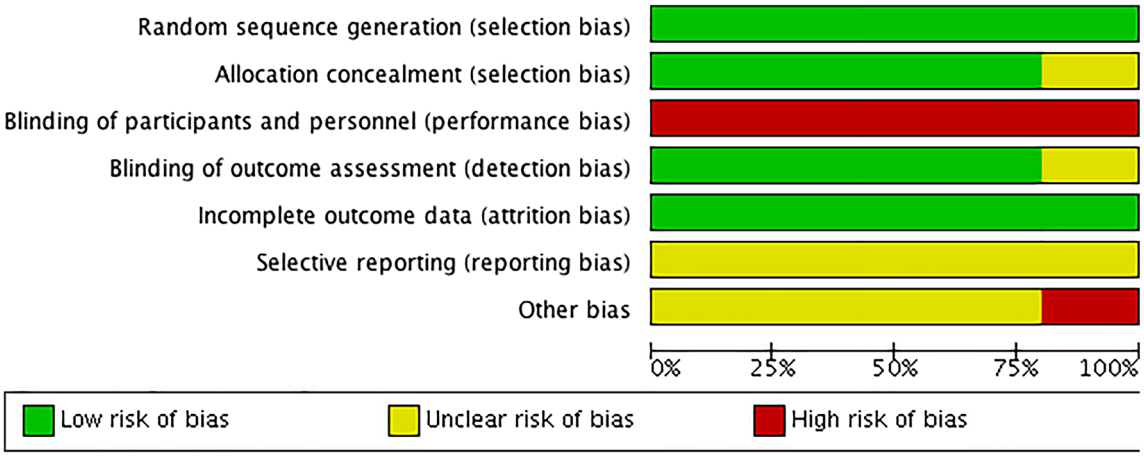

Fig. 2 Risk of bias graph: review of authors' judgements about each risk of bias item presented as percentage across all included studies

accounting for 86.51%. Exercise interventions varied in different trials, including aerobic training, strength training, yoga, and Qigong. In this meta-analysis, we made highly strict inclusion criteria of RCT trials and rigorous procedures.

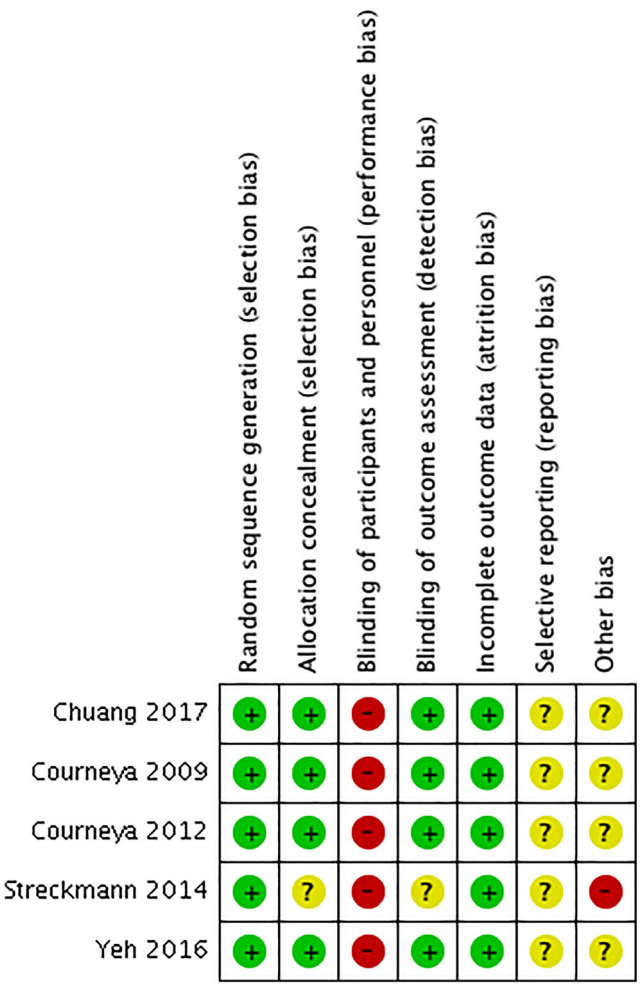

Fig. 3 Risk of bias summary: review of authors' judgements about each risk of bias item for each included study

Through the result, we can see the positive effects and slight improvement for QoL, fatigue, sleep quality, and emotional status of exercise on lymphoma patients. No significant beneficial effects produced by exercise on lymphoma patients compared with the group with no exercise. In the subgroup analysis, mind-body exercise intervention showed significant benefit for lymphoma patients. Based on the results shown above, we may conclude that a short-term intervention cannot make a significant change in the quality of life and cancer-related fatigue. Therefore, clinical trials with a long-term exercise intervention for lymphoma patients are worthy to conduct even though there is a great consumption of human and financial resources. Interestingly, mind-body exercise seemed promising for lymphoma patients. More attention should be paid on Tai Chi, Qigong, and yoga because of their significant benefits. The interpretation of this result should be cautious, because there were many confounding factors, such as baseline difference, quality control of intervention process, and completion efficiency of subjects as well as different evaluation scales and high heterogeneity, which all have an impact on the analysis of the results. On the other hand, it may be possible that there are few related trials and few participants in the study, which made it difficult to interpret the results. Although the studies we included were RCTs, we should be clear that it was hard to control each step to make sure quality of trials due to the character of exercise, such as the exercise intensity of each participant, and inevitable bias of participants and researchers due to the inapplicability of blind methods. We also calculated the ratio of patients undergoing treatment in the included studies. Cohen et al.'s study was conducted on the condition that patients were undergoing chemotherapy or had received it in the past 12 months. No specific data of ongoing treatment were given, but it was noted that more than 20% of patients included were receiving chemotherapy. Statistics from the remaining five studies showed that 73.8% of patients were experiencing treatment, including 18 cases of immunotherapy, 1 case of radiotherapy, and the rest of them

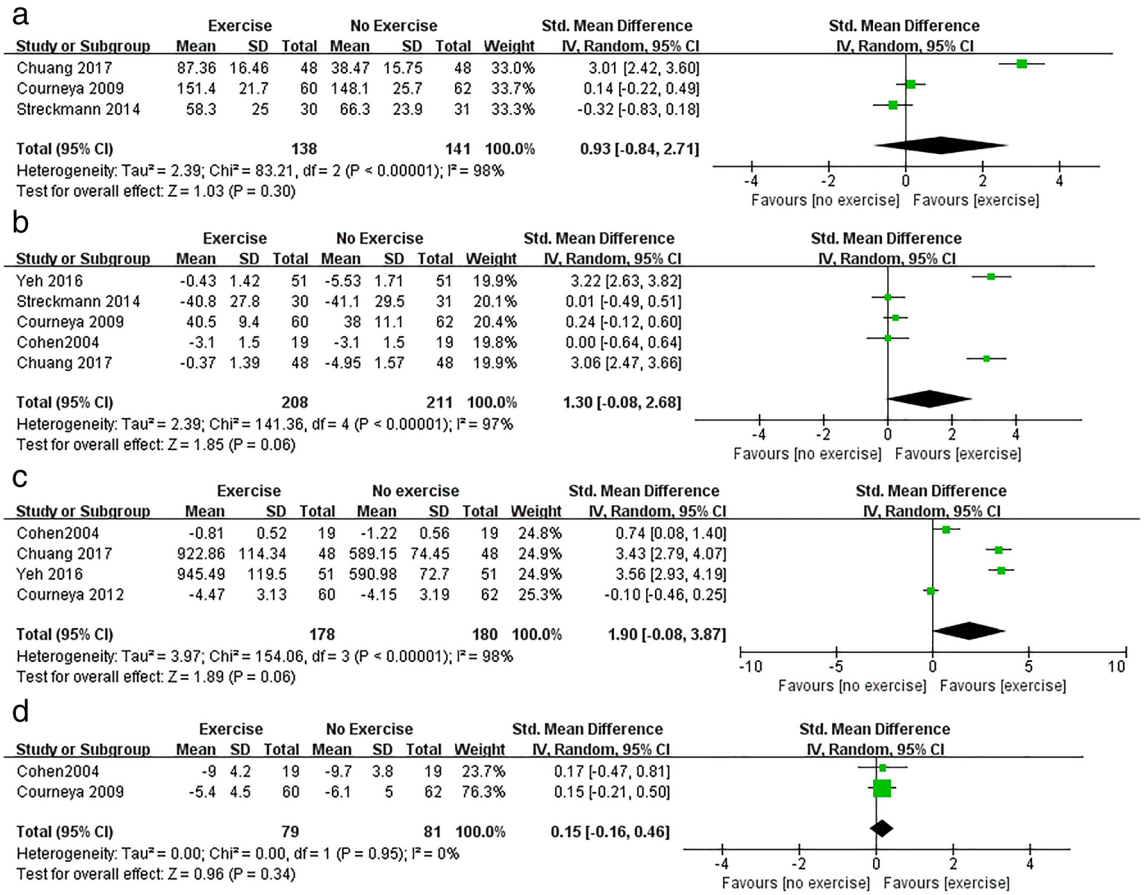

Fig. 4 Forest plot of comparison: exercise versus no exercise, outcomes of QoL (**a**), fatigue (**b**), sleep (**c**), and depression (**d**)

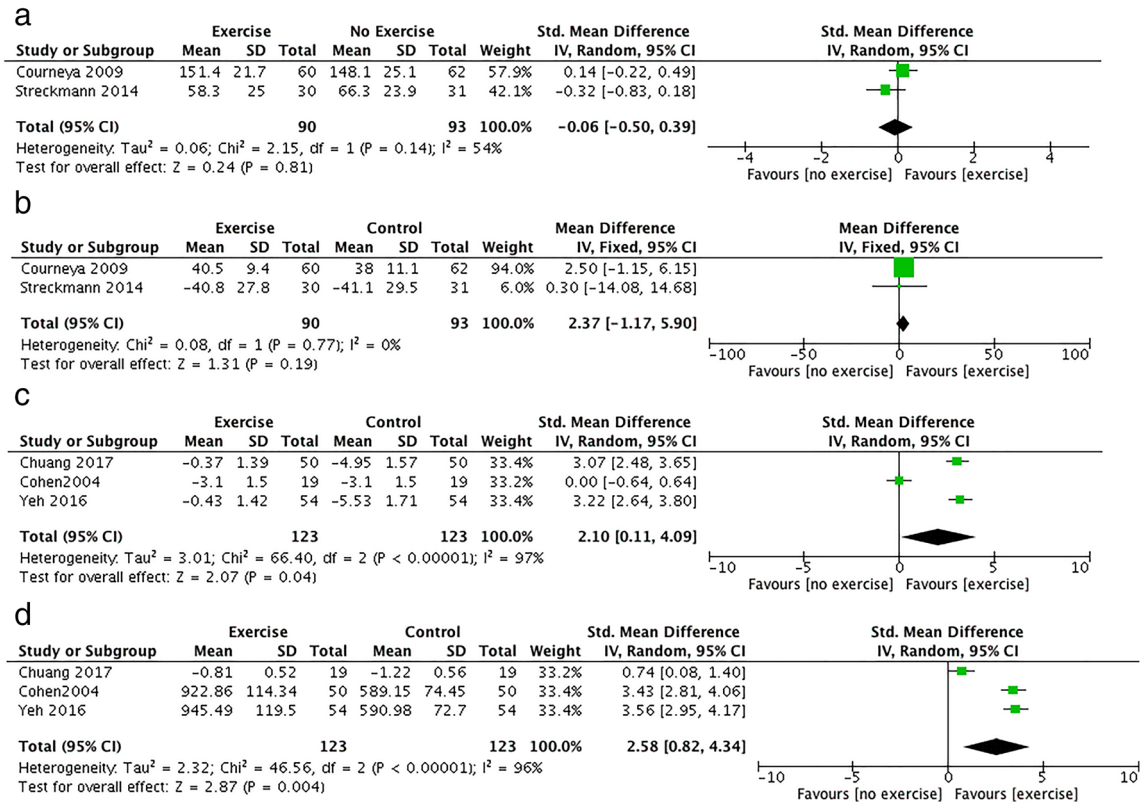

Fig. 5 Forest plot of comparison: subgroup analysis: outcomes of QoL (**a**), fatigue (**b**), sleep (**c**), and depression (**d**)

were given chemotherapy. As we all know, body experiences a very weak period when undergoing chemotherapy. While patients have different reactions to chemotherapy and exercise, which may be another factor influencing the outcomes of exercise. In addition, low sensitivity of the assessment instruments maybe also a contributor.

There are a lot of studies and comments that show the agreements and disagreements on the effect of exercise for lymphoma patients. Here, we review the following articles that are not RCT designs but we can still get some ideas from the results. Terry et al.'s study, which analyzed 1567 included cases, found that lifetime high physical activity was associated with a significantly reduced risk of non-Hodgkin's lymphoma [32]. The similar result can also be seen in a meta-analysis about the intensity and duration of physical activity on risk of NHL, which indicates that people with the highest level of physical activity may have a slightly lower risk of developing into NHL than those with the lowest level of physical activity [33]. Filipe et al.'s study [34] found that the fatigue degree of HL group was higher than that of the control group, while in the area of strength, muscle thickness, and muscle mass, no difference was found between the two groups, which showed that the CRF is self-perceived fatigue seemingly not to be strongly affected by muscle strength. In Vallance et al.'s study, 438 NHL survivors were asked with a questionnaire using a retrospective survey design, which showed that NHL patients would have a higher quality of life scores when they finished more than 150 min of moderate-to-vigorous exercise per week compared with NHL survivors who were not reaching the exercise levels [35]. In Oldervoll et al.'s study, exercise capacity (VO2max) did not seem to play an important role in the mechanism of chronic fatigue in Hodgkin's disease survivors (HDS), and there was no difference between the HDS ($n = 12$) and non-chronic fatigue HDS ($n = 15$). However, in the fatigue symptom assessment, the fatigue of the exercise intervention group was reduced by 43.7% ($P = 0.001$) [36]. Similar findings by Oldervoll et al. are also shown in an enlarged sample (HLSs with chronic fatigue ($N = 143$) and without chronic fatigue ($N = 333$)) that level of physical activity showed no significant difference between HLSs with and without chronic fatigue. This may indicate that the exercise plays a little role in fatigue improvement [37]. Keegan et al. surveyed 312 cases of Hodgkin's lymphoma (HL), and the results showed that during the entire adulthood, strong physical activity was associated with an insignificant reduction in the risk of HL, whereas strenuous physical activity at least twice a week for ≥ 1 month before the reference period leads to a 40% reduction in the risk of HL [38].

There are also inconsistent researches regarding the association of physical activity with reduction of cancer risk and improvement of life quality. Elizabeth et al.'s multi-center randomized controlled trial found that physical and psychosocial interventions for 12 weeks in children with cancer had no effect on health-related quality of life (HrQoL) or psychosocial function, except for parental reported pain and procedural anxiety [39]. Dodd et al.'s study of 119 cancer patients found that no effect was observed in home-based exercise intervention group on fatigue or symptoms associated with cancer treatment [40]. Sprod et al.'s study of breast cancer and prostate cancer patients ($n = 38$) showed no significant improvement in the sleep quality before and after exercise intervention in the exercise group [41]. The well-known EXIST study also showed that supervised high-intensity exercise programs have no significant beneficial effects on physical health and fatigue compared to conventional care [42].

More researches need to be done

The analysis did not include many studies due to the highly restriction of RCT researches which made the population to research not large. Some researches indicate that the intensity and duration of physical activity are also important for their effect on cancer patients [43–45]. Pophali et al. followed up the exercise effect on lymphoma patients for 3 years, and the results showed that, compared with the inactivity patients, the higher the level of daily physical activity in adults, the higher the overall survival rate (OS), while the lower the level of physical activity, the worse the prognosis [46]. Therefore, more researches are needed with a comparable and randomized design to determine which type of exercise, duration, and intensity are best for improving the quality of life of patients and to select the most appropriate type of exercise based on cancer type and treatment. Furthermore, longer follow-up time is needed to observe any possible long-term effects. In addition, the range of heterogeneity of measurement methods used to evaluate the same field makes it extremely hard to compare the results of different tests, so it is recommended to conduct more studies to unify the indicators of outcome evaluation in the same field.

Conclusion

The meta-analysis results showed few significant beneficial effects produced by short-term exercises on lymphoma patients compared with the group with no exercise. Subgroup analysis showed that physical activity together with mental exercise may be more beneficial to lymphoma patients, but it needs more research to verify this finding. The interpretation of this result should be cautious due to the baseline difference, completion efficiency of intervention process, and high heterogeneity. A long-term exercise intervention and follow-up should be considered in the future studies as well.

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Availability of data and materials Sufficient data and material are provided in the manuscript and the supplement information part.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Abbreviations *OS*, Overall survival; *RCTs*, Randomized controlled trials; *QoL*, Quality of life; *HL*, Hodgkin's lymphoma; *NHL*, Non-Hodgkin's lymphoma; *CRF*, Cancer-related fatigue

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