Evidence-based exercises intervention in adults diagnosed with Lymphoma

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ABSTRACT

Objectives: To evaluate the efficacy of physical therapy or exercise intervention on quality of life (QOL), fatigue, sleep, and psychological and physical functioning in adults diagnosed with Lymphoma.

Methods: A systematic literature search of the PubMed, CINAHL, Cochrane Library, and PEDro databases was carried out to identify articles published from March 2010 until December 2020. The risk of bias, methodological quality, and level of evidence was evaluated using the Physiotherapy Evidence Database (PEDro) checklist.

Results: Out of the 577 articles identified from the initial search, a total of 12 randomised control trials were shortlisted for this systematic review. From the 12 articles, 9 studies included participants with Lymphoma who were at various stages of chemotherapy or had completed treatment and 3 studies included participants with various haematological malignancies and had stem cell transplantation. The quality of each study was assessed using the PEDro scale with the average mean score of 6.3±0.89. The PEDro scores regarding the quality of studies ranged from 5-8 (fair to good).

Conclusion: There is moderate evidence strength suggesting that exercises therapy for persons diagnosed with Lymphoma can include aerobic or cardiovascular exercise, strength training, and mind-body exercise has beneficial effects on fatigue, physical performance, and QOL in persons diagnosed with Lymphoma patients.

PROSPERO No.: CRD42021227418

Keywords: Lymphoma, physical therapy, exercise, systematic review

Lymphoma patients can suffer from poor quality of life (QOL) and reduced functional capacity because of the disease or treatment-related complications. Lymphoma, defined as malignant neoplasms of lymphoid origin, can be broadly classified.
into 2 main categories: Hodgkin Lymphoma (HL; prevalence-10%) and non-Hodgkin Lymphoma (NHL; prevalence-90%). Hodgkin Lymphoma is an uncommon B-cell Lymphoma, which accounted for 83,087 new registered cases and 23,376 deaths, whereas 544,352 new cases of NHL were registered with 259,793 deaths globally in the year 2018. The prevalence of HL has been reported to be higher in the age group of 20-39 years, whereas NHL is more prevalent in patients ≥60 years of age. Lymphoma is believed to be more common among males than in females. In addition, male patients display increased mortality rates and the risk is 3.1-fold and 1.7-fold higher among individuals with a family history of HL and NHL.

Depending on the type of Lymphoma, the treatment protocol can involve active surveillance of the condition, chemotherapy, radiation therapy, and autologous or allogeneic stem cell transplants. Patients diagnosed with Lymphoma who undergo therapeutic interventions for the management of HL and NHL are often imperilled to several systemic and non-systemic complications. Cardiac or pulmonary complications, and risk of infections are some of the common complications observed in patients diagnosed with Lymphoma. Lymphoma survivors usually suffer from diminished physical capacity, cardiopulmonary compromise, reduced muscle power, and limited physical function during and after treatment and the survivorship related complications can last for up to 10 years.

Physical therapy (PT) intervention has been advocated as a part of the multidisciplinary approach to help improve QOL and physical function. However, the PT intervention mostly depends on the treatment regime, associated complications, and its impact on patients’ function, thereby making it challenging for the rehabilitation specialists. A recent systematic review reported positive outcomes from aerobic endurance training, sensorimotor, and strength training on patients fatigue, psychological symptoms, and QOL. Mind-body exercises, such as yoga and Chan-Chuang qigong, have also been reported as having favorable effects on fatigue, general QOL, and sleep pattern. However, there are concerns regarding the study design and quality of trials; and hence the current systematic review aim is to evaluate the overall effectiveness of PT intervention on QOL, fatigue, sleep, and psychological and physical function in adults diagnosed and treated for Lymphoma.

Methods. The current systematic review was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. A literature search was carried out to cover the period between April to June 2020. Additionally, the literature search was regularly updated during the review and writing process (July to December 2020).

A comprehensive, electronic literature search was carried out using the following databases: PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), and Cochrane Library. The search strategy involved the use of several keywords and Medical Subject Headings (MeSH) terms. The Boolean operators “and” and “or” were used to combine the search terms. Moreover, thesaurus terms and relevant truncation or wildcard symbols were used to retrieve all possible suffix variations of a root word. Initially, the search was carried out using every single keyword. In the second step, the keywords were combined in pairs and trios, and finally, a conclusive search was carried out using a combination of all the keywords. All the electronic searches were limited to full-text, peer-reviewed publications in English involving human adults. The electronic search was carried out to identify articles published from March 2010 to March 2020. Duplicate studies from separate databases were eliminated. The detailed list of keywords and search strategies employed to perform the literature search of electronic databases are presented in Table 1.

Articles were included if they were full, peer-reviewed articles, written in English involving human adults, were randomized controlled trials, discussing any PT interventions, including participants >18 years of age, with a confirmed diagnosis of any type or stage of Lymphoma; and there were no demographic or other restrictions, studies published during the time period from March 2010 to December 2020 date, owing to significant changes in the medical management of Lymphoma that would affect the incidence of adverse effects.

The exclusion criteria employed by the present review were abstracts, conference reports, unpublished studies, articles published in non-peer-reviewed journals, case study, case series, single case reports, qualitative studies, trials published in languages other than English, and studies involving subjects/patients <18 years of age.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.
Table 1 - Keywords and searching strategy of the electronic databases.

| Database                                                                 | No. of articles |
|--------------------------------------------------------------------------|-----------------|
| **PubMed**                                                              |                 |
| 1  Haematological cancer                                                | 9603            |
| 2  Non-Hodgkin lymphoma                                                 | 109943          |
| 3  Hodgkin lymphoma                                                     | 75296           |
| 4  Haematological malignancies                                          | 43353           |
| 5  Lymphoma                                                              | 266086          |
| 6  Lymphoma or haematological malignancies or Hodgkin lymphoma or non-Hodgkin lymphoma or Haematological cancer | 307747          |
| 7  Cancer rehabilitation                                               | 33711           |
| 8  Rehabilitation                                                       | 621523          |
| 9  Physical therap                                                       | 86136           |
| 10  Physiotherap                                                        | 49154           |
| 11  Physical therapy modalities                                         | 154132          |
| 12  Home exercises                                                      | 12463           |
| 13  Physical exercises                                                  | 430431          |
| 14  Physical function                                                   | 1226213         |
| 15  Physical activity                                                   | 552715          |
| 16  Aerobic exercise                                                    | 426161          |
| 17  Exercise                                                            | 426161          |
| 18  Endurance                                                           | 38508           |
| 19  Strength                                                            | 320906          |
| 20  Strength or endurance or exercise or aerobic exercise or physical activity or physical function or physical exercises or home exercises or physical therapy modalities or physiotherap or physical therap or rehabilitation or cancer rehabilitation | 2276859         |
| 21  Quality of life                                                     | 395059          |
| 22  Chronic fatigue                                                     | 105793          |
| 23  Fatigue                                                             | 18650           |
| 24  Pain                                                                 | 824389          |
| 25  Impairments                                                         | 65601           |
| 26  Bone health                                                          | 123100          |
| 27  Spine metastasis                                                    | 4052            |
| 28  Chemotherapy induced neuropathy                                     | 6521            |
| 29  Cardiotoxicity                                                      | 117             |
| 30  Cardiotoxicity                                                      | 11778           |
| 31  Bone health or cardiotoxicity or cardio-toxicity or spine metastasis or impairments or fatigue or chronic fatigue or pain or quality of life or chemotherapy induced neuropathy | 1426700         |
| 32  6 and 20 and 31 filters: published in the last 10 years; humans; English; adult: 19+ years | 996              |
| 33  Cumulated Index to Nursing and Allied Health Literature              |                 |
| 1  Haematological cancer                                                | 2461            |
| 2  Non-Hodgkin lymphoma                                                 | 6255            |
| 3  Hodgkin lymphoma                                                     | 2920            |
| 4  Haematological malignancies                                          | 2276            |
| 5  Lymphoma                                                             | 28843           |
| 6  Lymphoma or haematological malignancies or Hodgkin lymphoma or non-Hodgkin lymphoma or haematological cancer | 32046           |
| 7  Cancer rehabilitation                                               | 4913            |
| 8  Rehabilitation                                                       | 183177          |
| 9  Physical therap                                                      | 131986          |
| 10  Physiotherap                                                        | 22376           |
| 11  Physical therapy modalities                                         | 4824            |
| 12  Home exercises                                                      | 312             |
| 13  Physical exercises                                                  | 324             |
| 14  Physical function                                                   | 7974            |
| 15  Physical activity                                                   | 79573           |
**Table 1** - Keywords and searching strategy of the electronic databases. (continuation)

| Database | No. of articles |
|----------|-----------------|
| **Cumulated Index to Nursing and Allied Health Literature** | |
| 16 Aerobic exercise | 21258 |
| 17 Exercise | 188792 |
| 18 Endurance | 15238 |
| 19 Strength | 49351 |
| 20 Strength or endurance or exercise or aerobic exercise or physical activity or physical function or physical exercises or home exercises or physical therapy modalities or physiotherap or physical therap or rehabilitation or cancer rehabilitation | 559761 |
| 21 Quality of life | 182158 |
| 22 Chronic fatigue | 3133 |
| 23 Fatigue | 522784 |
| 24 Pain | 314617 |
| 25 Impairments | 95347 |
| 26 Impairments or fatigue or chronic fatigue or pain or quality of life | 591160 |
| 27 6 and 20 and 31 | 299 |
| 28 32 filters: published in the last 10 years; humans; English; adult | 127 |
| **Cochrane Library** | |
| 1 Rehabilitation and lymphoma | 2 |
| 2 Rehabilitation and haematological cancer | 1 |
| 3 Rehabilitation and non-Hodgkin lymphoma | 0 |
| 4 Rehabilitation and Hodgkin lymphoma | 0 |
| 5 Rehabilitation and cancer | 24 |
| 6 Rehabilitation and haematological malignancies | 1 |
| 7 Physical therapy and lymphoma | 7 |
| 8 Physical therapy and haematological malignancies | 5 |
| 9 Physical therapy and haematological cancer | 7 |
| 10 Physical therapy and non-Hodgkin lymphoma | 1 |
| 11 Physical therapy and cancer | 87 |
| 12 Physical therapy and Hodgkin lymphoma | 1 |
| 13 Physiotherapy and Haematological cancer | 0 |
| 14 Physiotherapy and Hodgkin lymphoma | 0 |
| 15 Physiotherapy and haematological malignancies | 0 |
| 16 Physiotherapy and lymphoma | 0 |
| 17 Physiotherapy and non-Hodgkin lymphoma | 0 |
| 18 Physiotherapy and cancer | 6 |
| 19 Exercise and lymphoma | 4 |
| 20 Exercise and non-Hodgkin lymphoma | 1 |
| 21 Exercise and Hodgkin lymphoma | 1 |
| 22 Exercise and haematological cancer | 5 |
| 23 Exercise and haematological malignancies | 4 |
| 24 Exercise and cancer | 49 |
| 25 Quality of life and lymphoma | 28 |
| 26 Chronic fatigue and lymphoma | 0 |
| 27 Fatigue and lymphoma | 9 |
| 28 Pain and lymphoma | 4 |
| 29 Impairments and lymphoma | 4 |
| 30 Quality of life and haematological cancer | 57 |
| 31 Chronic fatigue and haematological cancer | 1 |
| 32 Fatigue and haematological cancer | 14 |
| 33 Pain and haematological cancer | 12 |
| 34 Impairments and haematological cancer | 0 |
| 35 Duplication removed | 67 |
| **Physiotherapy Evidence Database** | |
| 1 Haematological cancer | 6 |
| 2 Non-Hodgkin lymphoma | 5 |
| 3 Hodgkin lymphoma | 5 |
| 4 Haematological malignancies | 4 |
| 5 Lymphoma | 20 |
| 6 Duplication removed | 19 |
Five authors (AJ, GJ, SS, HX, and JX) independently screened the titles, abstracts, and full texts of the articles (as needed) identified through the literature search against the selection criteria. The authors then agreed on and excluded the studies that failed to meet the inclusion/exclusion criteria. Full-text articles were reviewed by 3 independent reviewers (AJ, GJ, and SS). Any disagreements with regard to the selection of studies were resolved through discussions and the involvement of a fourth reviewer (SM). The process of selection and reasons for exclusion are illustrated in a PRISMA flow diagram (Figure 1).

Three reviewers (AJ, GJ, and SS) independently completed the data extraction and tabulation of information including: authors, title, publication date, aims, participants, age, diagnoses, treatment, inclusion/exclusion criteria, study design, and level of evidence using the Sackett’s levels of evidence (type and duration of intervention, duration of follow-up, outcomes and quality assessment).

The extracted data are presented in Table 2. All the entered data were manually cross-checked for discrepancies through a zoom meeting and disagreements were referred to a fourth reviewer (SM).

Quality assessment/appraisal. The methodological quality of the trials included in the present review was evaluated using the PEDro scale,\textsuperscript{15} which is a 10-item scale designed to assess the internal validity (8 items) of a trial, including randomization, concealed allocation, blinding, baseline similarity, intention to treat, and 2 items, namely, measures of key outcomes from more than 85.0% of subjects and relevant reporting of the trial’s statistical comparisons. The score for each article ranged from 0 (lowest quality) to 8 (highest quality). Scores of 4-10 denote fair to high quality and 0-3 denote poor to low quality. The methodological quality of each study was independently assessed by 3 reviewers (AJ, GJ, and SS). Disagreements among the reviewers were resolved through consensus-based discussions and the assistance of a fourth reviewer (SM) was enlisted.

![Figure 1 - The Preferred Reporting Items for Systematic Review and Meta-analysis flowchart of the entire search and selection procedure.](image-url)
Participants in both groups received a copy intervention group

Patients characteristics

Control group
n=12 )5 healthy(

Intervention group
n=16/18
Mean age: 57.5±9.8
Male= 10 (55.6)

Mean age: 59.9±9.2
Male= 10(52.6)

All patients received best practice nutrition care. Nutrition care included: an initial nutrition assessment and counselling

- There is an increase in protein consumption in home-based nutrition and exercise program comparing to UC but not Significant
- IG improved in cognitive and social functioning in comparing to UC.

Results

Sackett’s levels of evidence.

3 reviewers )AJ, GJ, and SS(, in accordance with studies(. Each study was independently assessed by scale has 5 levels, ranging from 1a )well-designed meta-evidence regarding an intervention.

to determine the degree of confidence concerning the evidence regarding an intervention.16 The mentioned system developed by the Oxford Centre for Evidence-based Medicine to grade the levels of evidence, in order to the PRISMA flowchart of the search and selection procedure is shown in Figure 1. The current review included 12 randomized controlled trials that involved 1010 participants, among which, 824 were diagnosed with Lymphoma. The sample size ranged from 36-122 and age of the participants ranged from 19-90 years.

Out of the 577 articles identified from the initial search, a total of 12 randomised control trials were shortlisted for this systematic review. From the 12 articles, 9 studies included participants with Lymphoma who were at various stages of chemotherapy or had in case of persistent disagreements. The results of the quality assessment of studies are presented in Table 3.

Evidence assessment. The current review employed the system developed by the Oxford Centre for Evidence-based Medicine to grade the levels of evidence, in order to the degree of confidence concerning the evidence regarding an intervention.16 The mentioned scale has 5 levels, ranging from 1a (well-designed meta-analysis or high-quality RCTs) to 5 (no well-designed studies). Each study was independently assessed by 3 reviewers (AJ, GJ, and SS), in accordance with Sackett’s levels of evidence.

Results. The systematic literature search yielded 577 results (PubMed: 344; CINAHL: 27; Cochrane Library: 67; and PEDro: 19). Subsequently, duplicate publications were excluded and 408 articles were retained for review, among which, 12 articles met the inclusion criteria. The PRISMA flowchart of the search and selection procedure is shown in Figure 1.

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### Table 2 - The data items extracted.

| Authors          | Lymphoma percentage | Patients characteristics | Intervention group | Control group/UC | Results |
|------------------|---------------------|--------------------------|--------------------|------------------|---------|
| Hung et al17     | 37 patients         | n=16/18                  | Mean age: 57.5±9.8 | n=17/18          | All patients received best practice nutrition care. Nutrition care included: an initial nutrition assessment and counselling
|                  | undergoing autologous transplantation are recruited (lymphoma 17 [45.9], MM 20 [54.1]) | Male= 10 (55.6)   | Male= 10(52.6)   |                  |         |
| Zimmer et al10   | 26 patients         | n=14 (5 healthy)         | Mean age: 62.2±13.0 | n=12 (5 healthy) | Exercising on a bicycle ergometer 30 mins at moderate intensity No intervention |
|                  | participated and 10 healthy population (NHL) after 1st line chemotherapy | Patient's mean age: 56.6±10.73 | Healthy's gender: F=6, M=20 |                  |         |
|                  |                     |                          | Patient's gender: F=6, M=20 |                  |         |
| Courneya et al12 | 122/117 lymphoma    | n=57/60                  | Mean age: 20±33.3 (<50 years) | n=60/62          | 12-weeks supervised exercise program on a cycle ergometer. Not increase their exercise from baseline. |
|                  | patient were receiving chemotherapy or no treatments | 18±31.6 (<50 years) | 40±66.7 (>50 years) |                  |         |
|                  |                     | Female= 22 (38.6)        | Male= 34 (56.7)    |                  |         |
|                  |                     | Female= 26 (43.3)        |                  |                  |         |
| Streckmann et al8 | 61 lymphoma newly diagnosed prior to chemotherapy (MM: 14, NHL: 32, HL: 12), total lymphoma: 44 (75.9) | n=30/28 | Mean age: 44 years | n=31/28 | Supervised exercise 2/36 weeks: 1) Aerobic endurance training. 2) Sensorimotor training. 3) Strength training. |
|                  |                     | M=20 (71)/ F=8 (29)     | Mean age: 48 years | M=22 (79)/ F=6(21) |         |
| Vallerand et al15 | 51 survivors: leukemia: 19 (37), NHL: 10 (20), HL: 22 (43), and total lymphoma: 32 (63) | n=25 | Mean age: 52.6±13.7 years | n=26 | Participants in both groups received a copy of Canada's Physical Activity Guideline |
|                  |                     | 60 years: 33 (65)       | 260 years:18 (53) |                  |         |
|                  |                     | F= 31 (61); M= 20 (39)  |                  |                  |         |

Values are presented as a number and (%), mean±standard deviation (SD). AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, IG: intervention group, UC: usual care, M: male, F: female, QOL: quality of life
Evidence-based exercises ... AlJohi et al

Table 2 - The data items extracted. (continuation)

| Authors                        | Patients characteristics | Intervention group | Control group | Results                                                                 |
|--------------------------------|--------------------------|--------------------|---------------|-------------------------------------------------------------------------|
| Van Dongen et al               | 109 patients recently    | n=54/48            | n=55/45       | 86% patients showed up in average of 10 sessions of supervised exercise in IG. Result showed up to 25% improvement in physical fitness. Fatigue level was improved in both groups with no different. |
|                               | treated with autologous   | Mean age: 53.5±20.67 | Mean age: 56±19.67 |                                                          |
|                               | stem cell transplantation | M= 32 (59)         | M= 37 (67)    |                                                          |
| (MM: 58 (33.2) or lymphoma: 51 |                          |                    |               |                                                          |
|                               |                          |                    |               |                                                          |
| Furer et al                   | 37 haematological cancer | n=18               | n=21          | The physiological outcomes showed a significant improvement in: cancer related fatigue, cardiovascular fitness, QoL, and body composition. |
|                               | having completed          | Mean age: 48.2±12.3 | Mean age: 49.6±14.1 |                                                          |
|                               | treatment (NHL: 27        | (range: 22-64)     | (range: 25-68) |                                                          |
|                               | (73), HL: 6 (16), MM: 4  |                    |               |                                                          |
|                               |                          |                    |               |                                                          |
| Chuang et al                  | 96 NHL patients who      | n=48               | n=48          | It showed significant decreased in fatigue intensity and interference in the qigong group. Also, improvement in the IG in white blood cell counts, hemoglobin levels, sleep quality, and QoL. |
|                               | underwent their first    | Mean age: 55.85±16.78 | Mean age: 64.54±15.51 |                                                          |
|                               | course of chemotherapy   | M= 26 (27.1)       | M= 29 (30.2)  |                                                          |
|                               |                          | F= 22 (22.9)       | F= 19 (19.8)  |                                                          |
| Yeh et al                     | 108 non-Hodgkin's        | n=51               | n=51          | The qigong group showed a significant decreased over time in the average fatigue, worse fatigue, and overall sleep. |
|                               | lymphoma patients        | Mean age: 59.79±16.54 | Mean age: 64.54±15.51 |                                                          |
|                               | who were undergoing      | (range: 23-90)     | (range: 25-68) |                                                          |
|                               | chemotherapy (1st cycle  |                    |               |                                                          |
|                               | chemotherapy)            |                    |               |                                                          |
| Courneya et al                | 122 lymphoma receiving   | n=57               | n=60          | Effects of aerobic exercise on sleep quality: improvement in global sleep quality compared with UC. |
|                               | chemotherapy or no       | Mean age: 53 years |               |                                                          |
|                               | treatments.              | F=48 and M=69      |               |                                                          |
| Courneya et al                | 122 lymphoma patients    | n=60               | n=62          | There was no any statistically significant associations between exercise levels and cancer-specific mortality. |
|                               |                          | Mean age: 52.8 (range: 18-77) | Mean age: 53.5 (range: 18-80) |                                                          |

Values are presented as a number and (%), mean±standard deviatin (SD), AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, IG: intervention group, UC: usual care, M: male, F: female, QOL: quality of life

completed treatment and 3 studies included participants with various haematological malignancies and had stem cell transplantation. 17,28

Quality of the studies. Physiotherapy Evidence Database scale was used for assessing the quality of the studies and the mean PEDro score for the 12 RCTs was 6.3±0.89. Detailed information regarding the PEDro scores pertaining to the studies is presented in Table 3. The data presented in Table 3 shows that all the studies exhibited a baseline similarity, reported statistical comparisons, were randomly assigned, and provided both point measures and measures of variability. However, none of the trials complied with the items of blinding and was considered to have a high risk of bias with reference to blinding the subjects, therapists, and assessors, except for the study by Persoon et al, 28 which involved a low risk of bias associated with blinding the assessors alone. In addition, all the studies stated that the allocation was concealed, except 3 studies. 18,20,24 Additionally, 4 trials included in the present review did not comply with the item of intention to treat. 17,19,20,27

Furthermore, details regarding the grading of levels of evidence using the system developed by the Oxford Centre for Evidence-based Medicine16 are presented in Table 3. Most of the studies (10/12) were assigned with the grade of 1b (high-quality RCTs), whereas 2 studies were assigned with the grade of 2b (limited non-randomized trials). Overall, the studies displayed reliable methodological quality, indicating a low risk of bias.

Interventions. The primary PT intervention was exercise and included aerobic exercises, resistance exercises, balance exercises, education, and mind-body exercises. 17-24,26,28 Two studies used telephone consultations as the primary intervention. 25,27 The mean duration of the exercise interventions varied from 3-36 weeks, and majority of the studies used moderate-to-high-intensity aerobic exercises with 50-85% of peak
Evidence-based exercises ... AlJohi et al

**Table 3 - The results of the quality assessment of the included intervention studies.**

| Quality assessment                                                                 | Hung et al 22 | Zimmer et al 22 | Courneya et al 21 | Streckmann et al 18 | Vallerand et al 25 | Persoon et al 24 | Furzer et al 13 | Chuang et al 17 | Van Dongen et al 16 | Yeh et al 19 | Courneya et al 21 | Courneya et al 18 |
|-----------------------------------------------------------------------------------|--------------|-----------------|------------------|-------------------|-------------------|----------------|---------------|----------------|-------------------|-------------|----------------|-----------------|
| Eligibility criteria were specified                                                | Yes          | Yes             | Yes              | Yes               | Yes               | Yes            | Yes           | Yes            | Yes               | Yes         | Yes            | Yes              |
| Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received) | Yes          | Yes             | Yes              | Yes               | Yes               | Yes            | Yes           | Yes            | Yes               | Yes         | Yes            | Yes              |
| Allocation was concealed                                                          | Yes          | No              | Yes              | No                | Yes               | No             | Yes           | Yes            | Yes               | Yes         | Yes            | Yes              |
| The groups were similar at baseline regarding the most important prognostic indicators | Yes          | Yes             | Yes              | Yes               | Yes               | Yes            | Yes           | Yes            | Yes               | Yes         | Yes            | Yes              |
| There was blinding of all subjects                                                | No           | No              | No               | No                | No               | No             | No            | No             | No                | No         | No            | No               |
| There was blinding of all therapists who administered the therapy                | No           | No              | No               | No                | No               | No             | No            | No             | No                | No         | No            | No               |
| There was blinding of all assessors who measured at least one key outcome         | No           | No              | Yes              | No                | No               | Yes            | No            | No             | Yes               | No         | Yes            | Yes              |
| Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups | Yes          | Yes             | Yes              | Yes               | Yes               | Yes            | Yes           | No             | Yes               | Yes         | Yes            | Yes              |
| All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat” | No           | No              | Yes              | Yes               | Yes               | Yes            | Yes           | No             | Yes               | Yes         | No            | Yes              |
| The results of between-group statistical comparisons are reported for at least one key outcome | Yes          | Yes             | Yes              | Yes               | Yes               | Yes            | Yes           | Yes            | Yes               | Yes         | Yes            | Yes              |
| The study provides both point measures and measures of variability for at least one key outcome | Yes          | Yes             | Yes              | Yes               | Yes               | Yes            | Yes           | Yes            | Yes               | Yes         | Yes            | Yes              |
| Total score                                                                       | 6/10         | 5/10            | 7/10             | 7/10              | 8/10              | 5/10           | 6/10          | 6/10           | 6/10              | 7/10        | 7/10          | 7/10            |
| Level of evidence (based on Sackett)                                               | 1b           | 2b              | 1b               | 1b                | 1b                | 1b             | 1b            | 2b             | 1b                | 1b          | 1b            | 1b               |

The range of resistive exercise intensity was $50\pm80\%$ of the indirectly determined one-repetition maximum. The mean frequency of exercise interventions varied from once to daily per week for 15-60 minutes.

**Multiple outcomes measures.** The studies included in the current review, evaluated subjective and patient-reported outcomes concerning several variables, including the QOL, fatigue, psychological wellbeing, monitored side-effects, sleep pattern, and lifestyle (physical activity and nutritional status). Five trials assessed CV fitness whereas 3 other studies assessed the muscle strength of the upper and lower limbs. Streckmann et al 18 evaluated the balance and peripheral deep sensitivity.

**Discussion.** This systematic review, showed that PT treatment programs and individualized exercises
for different Lymphoma stages significantly improved physical function and endurance. Studies showed various exercise programs and PT interventions have been tested for those patients to assess the improvement of patients' outcomes.

The current review aimed to assess the available evidence regarding the effectiveness of PT or exercise intervention in adults diagnosed with Lymphoma with reference to the improvements in QOL, fatigue, sleep, and psychological and physical function. The literature review yielded 12 randomized controlled trials (RCTs) of varying methodological quality and sample sizes, which displayed considerable variation with regard to the inclusion criteria concerning diagnosis. Vallerand et al included leukemia and Lymphoma patients, 5 studies included Lymphoma and multiple myeloma patients and 6 studies included Lymphoma patients alone. Moreover, the baseline characteristics of the patients diagnosed with Lymphoma ranged from newly diagnosed cases to long-term survivors, which increased the likelihood of heterogeneity and made the interpretation and comparison of results difficult.

Furthermore, the studies displayed considerable variation with reference to the PT interventions, including aerobic training, strength training, sensorimotor training, strength training, home-based exercise, telephone counseling sessions, and other intervention with mind-body exercise. In addition, the current review observed variations in the frequency, intensity, and duration of interventions across the studies. Consequently, the determination of a standardized intervention protocol for clinical practice was challenging. An additional, significant constituent of the current objectives and practice of PT is the assessment of the carryover effect. The present review included only one longitudinal study that reported the results of a one-year follow-up. Consequently, the long-term effects and the ability of Lymphoma patients to maintain the beneficial effects of the interventions remain ambiguous.

A majority of the studies did not comply with the criteria of blinding the patients, therapists, or assessors. In the current review, only Persoon et al described the blinding methods employed. Although blinding the patients, therapists, or assessors is an effective method that can be employed to control the confounding variables in RCTs, the implementation may not always be possible. Although blinding may be initially possible in many studies, the maintenance of the same throughout a trial might become challenging.

A major cause of missing data in clinical trials is the dropout/withdrawal of subjects, which creates uncertainty in relation to the interpretation of results. Dropout of subjects is also an important outcome, as it may reflect the lack of tolerance to interventions, adverse effects, or lack of compliance. Among the 12 studies, 10 discussed the dropout/withdrawal status of their respective subjects. Moreover, it is important to take note of the occurrence of any adverse events during the intervention. In the current review, 8 studies addressed the incidence of adverse events.

Several standardized tools have been used to evaluate the outcomes of PT interventions in persons diagnosed with Lymphoma. Eight studies used QOL to assess the outcomes of interventions. Furthermore, 4 trials assessed CV fitness. Two reported significant improvements in physical performance and 3 trials assessed the muscle strength in the upper and lower limbs.

The current review used stringent inclusion criteria and a narrow population to reduce some of the inconsistencies that bulge the current body of literature. It provides high-quality evidence-based practice to determine whether the PT intervention is an effective and safe intervention for adult patients with Lymphoma.

Study limitations. First, the review may not offer a comprehensive picture of the available evidence, because of the fact that the review was limited to English articles. Consequently, there is a possibility that good-quality studies written in other languages, which might have supported the present recommendations, were excluded. The statistical heterogeneity among the studies included in the review was another limitation. Potential sources of heterogeneity include variations in the type, duration, and intensity of interventions. Moreover, the initiation of PT interventions varied across the studies. Hence, the results of the current review must be interpreted with caution, owing to the baseline differences and heterogeneity of the study population.

Future research warrants RCTs with larger samples and long-term follow-ups, in order to improve the understanding of the effects of PT interventions and exercise on Lymphoma patients.

In conclusion, there is moderate evidence strength suggesting that exercises therapy for persons diagnosed with Lymphoma can include aerobic or CV exercise, strength training, and mind-body exercise has beneficial effects on fatigue, physical performance, and QOL in persons diagnosed with Lymphoma patients. Future research should focus on more robust and well-defined exercises therapy intervention protocols, in order to establish the long-term benefit of exercises therapy intervention.
Acknowledgment. The authors gratefully acknowledge Dr. Deborah Doherty for her support in all process during the study period and the writing of this manuscript. The authors also would like to thank Wiley Editing Services for English language editing.

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