

Evidence-based exercises intervention in adults diagnosed with Lymphoma

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ABSTRACT

الأهداف: تقييم فعالية العلاج الطبيعي/التمارين العلاجية على جودة الحياة، مستوى الاجهاد، النوم، الحالة النفسية والأداء البدني لدى البالغين المصابين بسرطان الغدد الليمفاوية.

المنهجية: أجري بحث منهجي في قواعد بيانات لكل من: PubMed، المنشورة خلال الفترة من مارس 2010م إلى ديسمبر 2020م. وتم تقييم مخاطر التحيز والجودة المنهجية ومستوى الأدلة باستخدام قائمة التحقق لقاعدة بيانات أدلة العلاج الطبيعي (بيدرو).

النتائج: من بين 577 مقالة تم تحديدها من البحث الأولي، تم اختيار 12 مقال لتجربة عشوائية منتظمة لهذه المراجعة المنهجية. من بين 12 مقالة، اشتملت 9 مقالات على مشاركين بالغين مصابين بسرطان الغدد الليمفاوية و كانوا في مراحل مختلفة من العلاج الكيميائي أو أكملوا العلاج. 3 مقالات شملت مشاركين يعانون من أورام خبيثة في الدم وزرع الخلايا الجذعية. تم تقييم جودة كل دراسة باستخدام مقياس بيدرو (PEDro) بمتوسط درجة 6.3 ± 0.89 . فيما يتعلق بجودة المقالات المشمولة تراوحت درجات PEDro من 5-8 (متوسط إلى جيد).

الخلاصة: هناك أدلة معتدلة القوة تشير إلى أن التمارين العلاجية للمرضى الذين تم تشخيصهم بسرطان الغدد الليمفاوية وتشمل: التمارين الهوائية، وتمارين القوة، وماشبهها لها آثار مفيدة على مستوى الاجهاد والأداء البدني و أيضاً على تحسين مستوى جودة الحياة في الأشخاص الذين تم تشخيصهم بمرض سرطان الغدد الليمفاوية.

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 a 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.

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Keywords: Lymphoma, physical therapy, exercise, systematic review

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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%).¹ 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 2018.² 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.^{3,4} 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.³⁻⁵

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.⁶⁻⁹ 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.¹⁰⁻¹²

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.¹³ 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.¹³ 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.

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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.¹⁴ 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**. In addition, the electronic search was supplemented by the manual inspection of the reference lists pertaining to papers included in the present review, to identify other eligible studies.

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.

Table 1 - Keywords and searching strategy of the electronic databases.

Database	No. of articles
<i>PubMed</i>	
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 Cardio-toxicity	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	996
33 32 filters: published in the last 10 years; humans; English; adult: 19+ years	344
<i>Cumulated Index to Nursing and Allied Health Literature</i>	
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
<i>Cumulated Index to Nursing and Allied Health Literature</i>	
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	52784
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
<i>Cochrane Library</i>	
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
<i>Physiotherapy Evidence Database</i>	
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,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

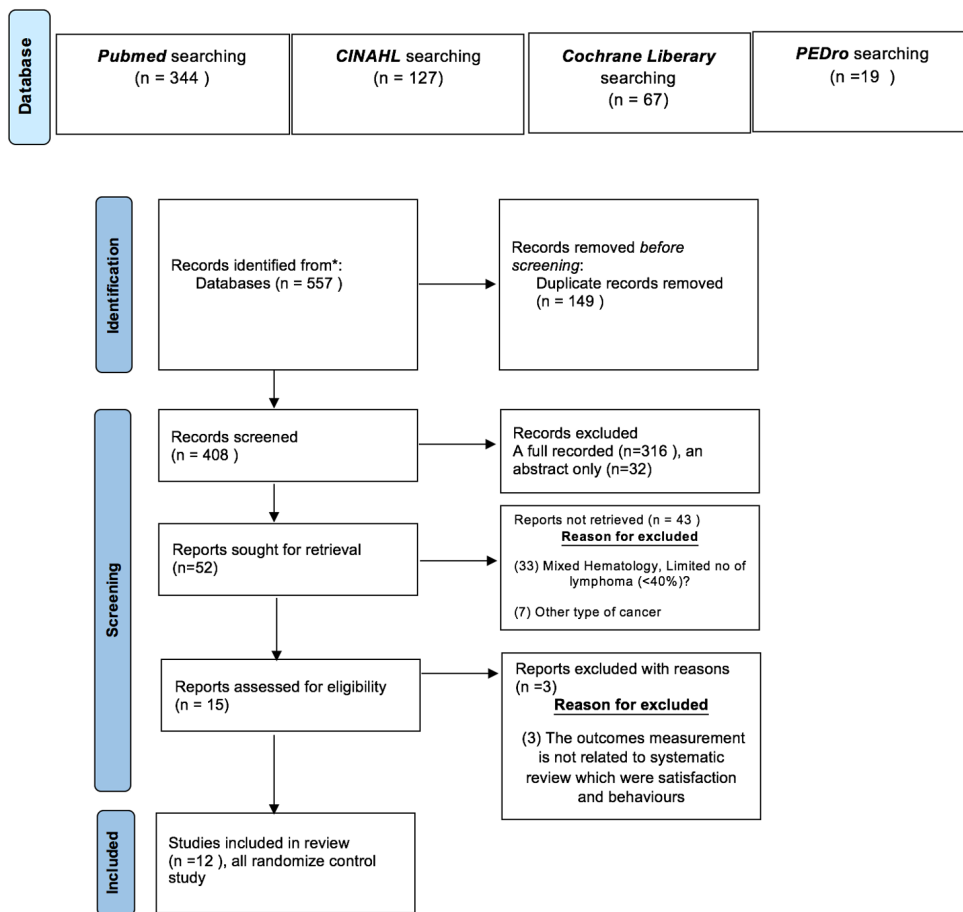


Figure 1 - The Preferred Reporting Items for Systematic Review and Meta-analysis flowchart of the entire search and selection procedure.

Table 2 - The data items extracted.

Authors	Patients characteristics			Intervention group	Control group/UC	Results
	Lymphoma percentage	Intervention group	Control group			
Hung et al ²⁷	37 patients undergoing autologous transplantation are recruited (lymphoma 17 [45.9], MM 20 [54.1])	n=16/18 Mean age: 57.5±9.8 Male= 10 (55.6)	n=17/18 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.
Zimmer et al ²⁰	26 patients participated and 10 healthy population (NHL) after 1st line chemotherapy	n=14 (5 healthy) Patients mean age: 62.23±13.09 Healthy mean age: 56.6±10.73 Patient's gender: F=6, M=20 Healthy's gender: F=3, M=7	n=12 (5 healthy)	Exercising on a bicycle ergometer 30 mins at moderate intensity	No intervention	Interleukin-6 was higher in the NHL patients compared with control subject, acetylation of the CD8+ T-cell histone H4K45 increased in response to the exercise.
Courneya et al ²¹	122/117 lymphoma patient were receiving chemotherapy or no treatments	n=57/60 Mean age: 18±31.6 (<50 years) 39±68.4(>50 years) Male= 35 (61.4) Female= 22 (38.6)	n=60/62 Mean age: 20±33.3 (<50 years) 40±66.7 (>50 years) Male= 34 (56.7) Female= 26 (43.3)	12-weeks supervised exercise program on a cycle ergometer.	Not increase their exercise from baseline.	It has a significant improvement of sleep pattern in specifically patient with indolent NHL.
Streckmann et al ¹⁸	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 M=20 (71)/ F=8 (29)	n=31/28 Mean age: 48 years M=22 (79)/ F=6(21)	Supervised exercise 2/36 weeks 1) Aerobic endurance training. 2) Sensorimotor training. 3) Strength training.	Standard clinical care including physiotherapy	IG showed a significant improvement in health-related QoL score and activity level with no change in UC. Slight improvement in PNP sensitivity in IG.
Vallerand et al ²⁵	51 survivors; leukemia: 19 (37), NHL: 10 (20), HL: 22 (43), and total lymphoma: 32 (63)	n=25 Mean age: 52.6±13.7 <60 years: 33 (65) ≥60 years:18 (35) F= 31 (61); M= 20 (39)	n=26	Participants in both groups received a copy of Canada's Physical Activity Guideline Telephone counselling sessions	Received no other intervention	Satisfaction of telephone counselling sessions was high (93%) and changes in exercise behavior by increasing weekly aerobic exercise.

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

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 determine 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**.

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

Table 2 - The data items extracted. (continuation)

Authors	Patients characteristics			Intervention group	Control group/UC	Results
	Lymphoma percentage	Intervention group	Control group			
Van Dongen et al ²⁶	109 participants recently treated with autologous stem cell transplantation (MM: 58 (53.2) or lymphoma: 51 (46.8))	n=54/48 Mean age: 53.5±20.67 M= 32 (59)	n=55/45 Mean age: 56±19.67 M= 37 (67)	18-weeks High-intensity resistance and interval training ex's.	No exercise intervention	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.
Furzer et al ²⁴	37 haematological cancer having completed treatment (NHL: 27 (73), HL: 6 (16), MM: 4 (11))	n=18 Mean age: 48.2±12.3 (range: 22-64)	n=19 Mean age: 49.6±14.1 (range: 25-68)	12 weeks tailored exercise intervention which includes progressed cardiovascular training and resistance program.	Did not complete any structured exercise. Provided diary & general healthy life-style advice	The physiological outcomes showed a significant improvement in: cancer related fatigue, cardiovascular fitness, QoL, and body composition.
Chuang et al ¹⁷	96 NHL patients who underwent their first course of chemotherapy	n=48 Mean age: 55.85±16.78 M= 26 (27.1) F= 22 (22.9)	n=48 Mean age: 64.54±15.51 M= 29 (30.2) F= 19 (19.8)	A Chan-Chuang Qigong program for 21 days. The nursing guidance booklet is modified and tailored to patients with NHL	No intervention	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.
Yeh et al ¹⁹	108 non-Hodgkin's lymphoma patients who were undergoing chemotherapy (1st cycle chemotherapy)	n=51 M= 28 (54.9) F= 23 (45.1) Mean age: 59.79±16.54 years (range 23-90 years)	n=51 M= 29 (56.9) F= 22 (43.1)	Chan-Chuang qigong for 21 days	Usual care	The qigong group showed a significant decreased over time in the average fatigue, worse fatigue, and overall sleep.
Courneya et al ²³	122 lymphoma receiving chemotherapy or no treatments.	n=57 Mean age: 53 years F=48 and M=69	n=60	Supervised aerobic exercise program (bike). Telephone follow-up of missed sessions.	Asked not to increase their exercise during the intervention.	Effects of aerobic exercise on sleep quality: improvement in global sleep quality compared with UC.
Courneya et al ²¹	122 lymphoma patients	n=60 Mean age: 52.8 (range: 18-77)	n=62 Mean age: 53.5 (range: 18-80)	12 weeks of supervised aerobic exercise program (gradual increase intensity)	Not to increase their exercise during the intervention	There was no any statistically significant associations between exercise levels and cancer-specific mortality.

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

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

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

Quality assessment	Corresponding & authors											
	Hung et al ²⁷	Zimmer et al ²⁰	Courneya et al ²²	Streckmann et al ¹⁸	Vallerand et al ²⁵	Persoon et al ²⁸	Furzer et al ²⁴	Chuang et al ¹⁷	Van Dongen et al ²⁶	Yeh et al ¹⁹	Courneya et al ²¹	Courneya et al ²³
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	Yes	No	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	No	Yes	No	Yes	No	No	No	No	No	No
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	No	Yes	No	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	No	Yes	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	7/10	8/10	5/10	6/10	6/10	6/10	7/10	7/10
Level of evidence (based on Sackett)	1b	2b	1b	1b	1b	1b	2b	1b	1b	1b	1b	1b

oxygen consumption or heart rate max.^{18,20,21,23,24,26,28} The range of resistive exercise intensity was 50±80% 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).^{17-19,23-28} Five trials assessed CV fitness whereas 3 other studies assessed the muscle strength of the upper and lower limbs.^{24,26,28} Streckmann et al¹⁸ 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 al²⁵ included leukemia and Lymphoma patients, 5 studies^{18,24,26-28} 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.²⁶ 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 al²⁸ 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.^{17,19,20,22-28} 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.^{17-19,22-25,28}

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.^{17,18,22,24-28} Furthermore, 4 trials assessed CV fitness.^{18,21,24,26} Two reported significant improvements in physical performance^{18,24} and 3 trials assessed the muscle strength in the upper and lower limbs.^{24,26,28}

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.

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