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Physical function, nutritional status, and quality of life before and after chemotherapy in patients with malignant lymphoma

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Abstract

This study investigates the efficacy of and gender differences in exercise therapy in patients with malignant lymphoma undergoing chemotherapy. Twenty-six patients (13 men, 13 women) received physical therapy (based on the Borg Scale 13) during hospitalization. Physical function was measured using grip and knee extension strength, 6-minute walking distance, and body composition; nutritional status assessed via Mini Nutritional Assessment (MNA®); and serum albumin levels analyzed. Fatigue was evaluated using the Brief Fatigue Inventory, and health-related quality of life was assessed with the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36v2). The analysis of all patients indicated that the right grip strength, skeletal muscle mass, skeletal muscle index, and leg muscle mass significantly decreased, whereas the serum albumin level, MNA® score, and scores of many items of the SF-36v2 significantly increased after chemotherapy. In a gender-specific analysis, only men showed significant declines in the skeletal muscle mass and skeletal muscle index, and improvement in the MNA® score after chemotherapy. In the SF-36v2, there were significant improvements in general health and physical component summary scores among men, and general health and mental component summary scores among women. Exercise therapy at a Borg Scale intensity of 13 may not prevent muscle mass decline in patients with malignant lymphoma, especially male patients. In addition, this study revealed that there is a gender difference in the effect of exercise therapy on quality of life. Thus, gender should be considered in exercise therapy for patients with malignant lymphoma.

Abbreviations: 6MWT = 6-minute walk test, BFI = the Brief Fatigue Inventory, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, GH = general health, MCS = mental component summary, MH = mental health, MNA® = the Mini Nutritional Assessment, PCS = physical component summary, QOL = quality of life, SF-36v2 = the Medical Outcome Study 36-Item Short-Form Health Survey, SMI = skeletal muscle mass index, SMM = skeletal muscle mass.

Keywords: chemotherapy, malignant lymphoma, nutritional status, physical function, quality of life

1. Introduction

Malignant lymphoma is the most common type of hematopoietic malignancies[1] and presents with lymphadenopathy or extralymphatic masses. B symptoms such as fever, night sweats, and weight loss are present in up to one-third of patients. Chemotherapy is the most common treatment for patients with malignant lymphoma, and with the introduction of rituximab since 1997, the overall survival rate has increased and estimated to be 72%.[2–4] However, chemotherapy is prone to side effects such as severe blood cell loss, fever, malaise, and anorexia, limiting physical activity, and decreasing physical and mental function. In a previous study, many patients with malignant lymphoma who received chemotherapy reported the appearance of fatigue and decreased

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Informed consent was obtained from all individual participants included in the study.

Written informed consent was obtained from the patients regarding publishing their data.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Kita-Fukushima Medical Center (Approval No. 74).

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physical activity and muscle strength.[5,6] It has been pointed out that maintaining physical activity during chemotherapy is important for these patients' subsequent quality of life (QOL),[7] thus it is important to provide them with appropriate rehabilitation to prevent deterioration of physical function.

The main approach for rehabilitating patients with malignant lymphoma undergoing chemotherapy is exercise therapy, which has been reported to improve physical function, QOL, fatigue, self-efficacy, depressive symptoms, cardiovascular function, and slow fat body weight.[8–10] On the one hand, exercise therapy is considered an effective means of preventing disuse syndrome; on the other hand, in studies on the efficacy of exercise therapy in rehabilitating patients with malignant lymphoma undergoing chemotherapy, it is unclear whether the outcomes have been measured before or after chemotherapy, or whether the preintervention measurement was performed after the start of chemotherapy. In most previous studies, the outcome of physical therapy was measured after the established intervention period (e.g., after 12 weeks of exercise therapy) and not at the end of chemotherapy. In other words, to rigorously demonstrate the efficacy of exercise therapy in patients with malignant lymphoma undergoing chemotherapy, it is important to measure outcomes before and after chemotherapy. However, to the best of our knowledge, previous studies have not performed such measurements. Therefore, there is a need to examine the effects of exercise therapy in patients with malignant lymphoma undergoing chemotherapy using measurements taken before and after chemotherapy.

We previously reported that in hematopoietic stem cell transplant recipients, the efficacy of exercise therapy on health-related QOL depends on gender.[11] Therefore, there may also be a sex difference in the efficacy of exercise therapy in patients with malignant lymphoma undergoing chemotherapy. However, the effect of exercise therapy on patients with malignant lymphoma undergoing chemotherapy has not been analyzed previously.

Therefore, the purpose of this study was to rigorously investigate the efficacy of exercise therapy in patients with malignant lymphoma undergoing chemotherapy by measuring outcomes before and after chemotherapy, and to clarify gender differences in the efficacy of exercise therapy.

2. Method

2.1. Study design and participants

This prospective observational study was designed to investigate physical function, nutritional status, and QOL before and after chemotherapy in patients with malignant lymphoma.

From October 2017 to December 2020, 97 patients with malignant lymphoma received inpatient chemotherapy and physical therapy at Hospital A. Of these, 26 patients who met the following criteria were included in our study: patients in the first-episode of the disease and scored ≤ 2 in the Eastern Cooperative Oncology Group Performance Status (ECOG-PS). Exclusion criteria were as follows: patients with an ECOG-PS of ≥ 3 at admission, had a history of cerebrovascular disease, had failed to complete chemotherapy at discharge, had a recurrence of malignant lymphoma, had transferred to another hospital, had died, had disagreed to participate in the study, for whom some of the planned assessment items could not be measured, and had difficulty in rehabilitation during hospitalization (Fig. 1). This study was conducted with the approval of the Ethical Review Committee of the Kita-Fukushima Medical Center (Approval No. 74), and written informed consent was obtained from all participants.

2.2. Chemotherapy

Most patients received regimens of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).[12–14] Patients treated with R-CHOP received rituximab at 375 mg/m^2 of the body on day 1, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2 of the body on day 2, vincristine at 1.4 mg/m^2 of the body up to a maximum dose of 2 mg/m^2 of the body on day 2, and prednisone at 40 mg/m^2 of the body per day for 5 days. They were treated every 3 weeks for 6 or 8 cycles of CHOP.

2.3. Physical therapy intervention

All subjects underwent physical therapy with a focus on muscle-strengthening and aerobic exercises. Muscle-strengthening exercises for the lower limbs consisted of closed kinetic chains such as squats and calf raises, dead weights, and manual resistance by a physical therapist, while those for the upper limbs consisted of exercises with dead weights and body weight. Aerobic exercises included riding a bicycle ergometer and walking. Exercises were performed 6 days per week for 20 minutes per day. The intensity of exercise was "somewhat hard," that is, equivalent to a Borg Scale intensity of 13, which has been widely used in previous studies[15–18] on exercise therapy for cancer patients after surgery or during chemotherapy. The decision whether or not to provide physical therapy during chemotherapy-induced bone marrow suppression was made according to the "Cancer Rehabilitation Discontinuation Criteria".[19] Additionally, if the physician judged that it was feasible to continue physical therapy even if the patient's blood cell count was below the standard value, we acted in consideration of the patients' physical condition. Specifically, when the white blood cell count was less than 2000/μL, the physical therapy was performed not in the rehabilitation room, but in the ward or hospital room, to prevent infection. When the platelet count was less than 30,000/μL, the exercise program was performed according to the platelet count.[20] When the hemoglobin level was less than 8 g/dl and the physician judged that a blood transfusion was necessary, physical therapy was performed after the transfusion was completed.

2.4. Measurements and measurement schedule

Pre-chemotherapy evaluations were performed one day before the first inpatient chemotherapy session, and the post-chemotherapy evaluations were performed after completing the scheduled inpatient chemotherapy session and just before discharge.

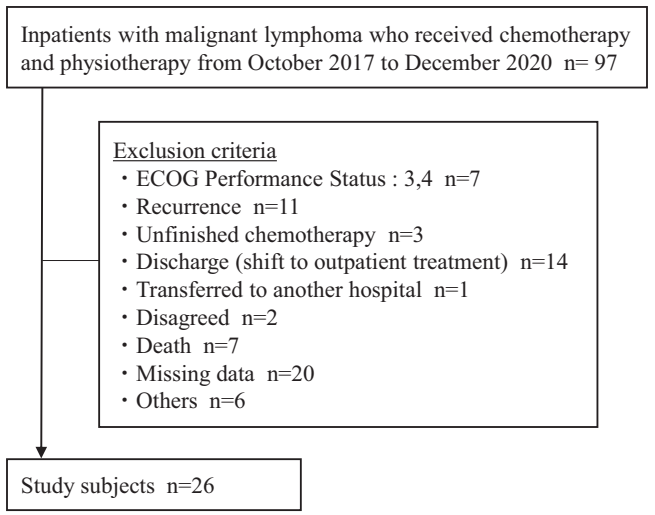

Figure 1. Study subject flow chart. ECOG = Eastern Cooperative Oncology Group.

2.4.1. Attributes of the participants. Data on the following participant attributes were collected: age, gender, weight, body mass index, ECOG-PS at admission, type of malignant lymphoma, type of chemotherapy, number of chemotherapy cycles, and total hospitalization days. Additionally, the numbers of days that physical therapy was scheduled, performed, and discontinued (for various reasons) were also collected. The percentage of physical therapy performed was calculated by dividing the number of days that physical therapy was performed by the scheduled days of physical therapy and multiplying this by 100.

2.4.2. Physical function measurements. To measure physical functions, we measured muscle strength (grip and knee extensor strength) and performed 6-minute walk tests (6MWT) according to the standards of the American Thoracic Society.[21] Measurements for 6MWT included the distance traveled, heart rate, dyspnea, fatigue, and transcutaneous arterial oxygenation. If patients experienced symptoms such as dyspnea or lower extremity pain, they were allowed to rest as needed, resume if they could, or terminate the session if they were unable to continue. We also measured skeletal muscle mass (SMM), skeletal muscle mass index (SMI), and limb/trunk region-specific skeletal muscle mass, all of which are associated with physical function, nutritional status, physical activity, self-efficacy, and life expectancy in patients with hematologic tumors for which they are undergoing chemotherapy[22] and hematopoietic stem cell transplantation.[23] SMM, SMI, and limb/trunk region-specific skeletal muscle mass were measured using a body composition analyzer (InBody S10, InBody Japan, Tokyo, Japan).

2.4.3. Nutritional measurements. Nutritional status was assessed by the Mini Nutritional Assessment (MNA®) test and serum albumin level measurements. MNA® is a nutritional assessment tool for the elderly that consists of 18 questions addressing dietary intake, weight change, physical function, body mass index, anthropometric data, stress due to diseases, and views on health. The MNA® has been used to assess various types of cancer patients and has been reported to be predictive of survival rate, cancer progression, and health-related QOL.[24] Each item of the MNA® is scored from 0 to 3 points, and a total score of <17 points indicates "low nutritional status"; 17 to 23.5 points indicates "possible low nutritional status"; and 24 to 30 points indicates "good nutritional status." Serum albumin levels were measured at the first chemotherapy session and at the end of the last chemotherapy session.

2.4.4. Fatigue measurement. The Brief Fatigue Inventory (BFI) is a simple questionnaire for assessing fatigue in patients with cancer and hematopoietic tumors.[25] It consists of nine questions that seek to gage the intensity of fatigue in the "past 24 hours" and its interference with daily life. The BFI classifies patient fatigue into three categories: mild (1–3), moderate (4–6), and severe (7–10). The higher the average score, the higher the severity of the disease.

2.4.5. Health-related QOL. Health-related QOL was assessed using the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36v2),[26–28] a questionnaire that has been used to examine patients undergoing chemotherapy for various types of cancer and those who have undergone hematopoietic stem cell transplantation.[29–33] The SF-36v2 consists of multiple questions designed to measure eight health concepts: physical functioning, daily role functioning (physical), body pain, general health (GH), vitality, social functioning, daily role functioning (mental), and mental health (MH). A higher score indicated a better the QOL. We also calculated three QOL factor summary scores from the scores of the aforementioned eight subscales: physical component summary (PCS), mental component summary (MCS), and roll/social component summary, as per Suzukamo et al.[28]

2.5. Statistical analysis

The subjects' demographics and physical therapy status were compared by gender using the unpaired *t* test and Fisher's exact test. The changes in physical function, nutritional status, fatigue, and health-related QOL before and after chemotherapy were compared using the correspondence *t* test, Wilcoxon's signed rank sum test, and Fisher's exact probability test. Additionally, gender-based comparisons and two-way analysis of variance were performed to examine differences by gender. Statistical software used was IBM SPSS Statistics (Version 27.0; IBM Corporation, Armonk, NY) at a significance level of <5%.

3. Results

Table 1 shows the attributes of the subjects in this study. The average age of all subjects was 71.1 ± 7.8 years, and 13 (50.0%) subjects were male. Moreover, 20 (76.9%), 5 (19.2%), and 1 (3.8%) of the subjects had ECOG-PS scores of 0, 1, and 2, respectively. The most common type of malignant lymphoma was diffuse large B-cell lymphoma, which afflicted 18 patients (69.2%). The average number of chemotherapy cycles was 6.7 ± 1.3, and the average number of total hospitalization days was 115.3 ± 26.9. The average number of days for which physical therapy was scheduled and performed was 74.8 ± 20.8 and 72.0 ± 21.3, respectively. The average percentage of physical therapy performed was 95.5 ± 4.6%. When comparing background attributes by gender, men were significantly heavier than women ($P < .01$), but there were no significant differences between the two groups in any other attribute.

Physical function, serum albumin levels, and MNA® scores before and after chemotherapy are shown in Table 2. In all subjects, the right grip strength, SMM, SMI, and right and left leg muscle masses after chemotherapy were significantly lower than values before chemotherapy ($P < .05$); other physical functions did not differ significantly before and after chemotherapy. Comparisons of male and female physical functions showed that SMM, SMI, and right leg muscle mass were significantly lower in males after chemotherapy ($P < .05$). Female subjects showed no significant difference in physical functions before and after chemotherapy. A comparison of nutritional status before and after chemotherapy in all subjects showed no significant difference in severity classification, but serum albumin levels and MNA® scores increased significantly after chemotherapy ($P < .05$). Nutritional status comparisons of males and females before and after chemotherapy show that the MNA® scores of only the males increased significantly ($P < .05$) after chemotherapy.

A comparison of BFI and SF-36v2 scores before and after chemotherapy (Table 3) show that the BFI score of all subjects, as well as male and female, did not differ significantly before and after chemotherapy. In the SF-36v2 questionnaire, GH, MH, PCS, and MCS significantly increased after chemotherapy compared to before chemotherapy ($P < .05$). By gender, GH and PCS increased significantly after chemotherapy in men, and GH and MCS increased significantly in women compared to before chemotherapy ($P < .05$).

4. Discussion

A comparison of all subjects undergoing physical therapy before and after chemotherapy show that right hand grip strength, SMM, and SMI significantly decreased, while nutritional status significantly increased after chemotherapy. By gender, only men showed similar results. Additionally, the QOL, GH, MH, PCS, and MCS of all subjects increased significantly after chemotherapy, and PCS and MCS increased significantly among male and female subjects, respectively.

Previous studies have reported that physical functions such as grip strength and knee extension muscle strength decrease

Table 1

Demographic and clinical characteristics data of patients with Malignant lymphoma.

Characteristics	Total (n = 26)	Men (n = 13)	Women (n = 13)	*P*
Age, yr	71.1 ± 7.8	73.0 ± 9.0	69.2 ± 6.2	.23
Sex, n (%)				
Male	13 (50.0)			
Female	13 (50.0)			
Body weight, kg	56.5 ± 9.8	61.9 ± 6.7	51.1 ± 9.6	<.01
BMI, kg/m^2	22.8 ± 3.3	23.2 ± 2.7	22.4 ± 4.0	.57
ECOG-PS at admission, n (%)				
ECOG-PS 0	20 (76.9)	9 (69.2)	11 (84.6)	.65
ECOG-PS 1	5 (19.2)	3 (23.1)	2 (15.4)	
ECOG-PS 2	1 (3.8)	1 (7.7)	0 (0.0)	
Malignant lymphoma type, n (%)				
DLBCL	19(73.1)	8(61.5)	11 (84.6)	.21
FL	3 (11.5)	3 (23.1)	0 (0.0)	
MCL	1 (3.8)	1 (7.7)	0 (0.0)	
NMZBCL	1 (3.8)	0 (0.0)	1 (7.7)	
PTCL	2 (8.0)	1 (7.7)	1 (7.7)	
Chemotherapy type, n (%)				
R-CHOP	19 (73.1)	7 (53.8)	12 (92.3)	.09
R-CHOP + other	2 (7.7)	2 (15.4)	0 (0.0)	
Other than R-CHOP	5 (19.2)	4 (30.8)	1 (7.7)	
Chemotherapy cycles, counts	6.7 ± 1.3	6.6 ± 1.3	6.8 ± 1.3	.65
Total hospitalization days, d	115.3 ± 26.9	116.2 ± 33.0	114.5 ± 20.4	.88
Physical therapy				
Scheduled days, d	74.8 ± 20.8	73.7 ± 25.4	76.0 ± 15.8	.78
Performed days, d	72.0 ± 21.3	71.5 ± 26.1	72.5 ± 16.2	.91
Discontinued days, d	3.2 ± 3.2	2.8 ± 3.3	3.5 ± 3.2	.59
The percentage of performed, %	95.5 ± 4.6	95.8 ± 5.1	95.2 ± 4.3	.73

Mean ± SD.

BMI = body mass index, DLBCL = diffuse large B-cell lymphoma, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, FL = follicular lymphoma, MCL = mantle cell lymphoma, NMZBCL = nodal marginal zone B-cell lymphoma, PCL-NOS = peripheral T-cell lymphoma, not otherwise specified, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, SD = standard deviation.

Table 2

Physical function, muscle mass, serum albumin, and MNA® before and after chemotherapy.

	Total (n = 26)			Men (n = 13)			Women (n = 13)			Gender Interaction
Variables	Before	After	*P*	Before	After	*P*	Before	After	*P*	*P*
Rt Handgrip (%)	41.9 ± 10.5	39.4 ± 8.6	<.05	47.6 ± 9.4	44.4 ± 5.3	.17	36.3 ± 8.5	34.4 ± 8.4	.08	.58
Lt Handgrip (%)	37.2 ± 11.0	36.2 ± 8.0	.51	44.0 ± 7.4	40.7 ± 4.5	.20	30.3 ± 9.8	31.8 ± 8.3	.26	.10
Rt Knee ext (%)	41.2 ± 10.8	41.8 ± 8.8	.74	42.0 ± 13.0	41.1 ± 10.0	.78	40.3 ± 8.5	42.5 ± 7.7	.34	.43
Lt Knee ext (%)	40.7 ± 9.4	41.6 ± 8.5	.60	40.9 ± 7.9	41.5 ± 7.6	.84	40.4 ± 11.0	41.8 ± 9.6	.62	.82
6MWT (m)	438.6 ± 86.9	462.5 ± 77.3	.18	428.5 ± 87.3	468.6 ± 81.6	.21	448.6 ± 88.9	456.3 ± 75.4	.22	.37
SMM (kg)	21.5 ± 4.3	20.5 ± 4.3	<.01	25.0 ± 2.9	23.6 ± 3.6	<.05	18.0 ± 1.9	17.4 ± 1.8	.19	.27
SMI (kg/m^2)	6.5 ± 1.1	6.1 ± 1.0	<.05	7.3 ± 0.9	6.8 ± 0.9	<.05	5.8 ± 0.6	5.5 ± 0.7	.18	.30
Rt Arm muscle mass (kg)	2.0 ± 0.6	1.9 ± 0.6	.34	2.4 ± 0.4	2.4 ± 0.4	.92	1.6 ± 0.4	1.5 ± 0.3	.20	.28
Lt Arm muscle mass (kg)	1.9 ± 0.6	1.9 ± 0.6	.41	2.3 ± 0.4	2.3 ± 0.4	.65	1.5 ± 0.4	1.4 ± 0.3	.48	.91
Trunk muscle mass (kg)	17.3 ± 3.5	17.1 ± 3.6	.33	19.9 ± 2.4	19.9 ± 2.5	.91	14.7 ± 2.3	14.3 ± 1.9	.23	.42
Rt Leg muscle mass (kg)	6.3 ± 1.6	5.8 ± 1.4	<.05	7.5 ± 1.2	6.7 ± 1.2	<.05	5.1 ± 0.7	4.8 ± 0.7	.14	.25
Lt Leg muscle mass (kg)	6.2 ± 1.6	5.8 ± 1.4	<.05	7.5 ± 1.1	6.8 ± 1.1	.05	4.9 ± 0.8	4.7 ± 0.7	.33	.21
Serum albumin (g/dL)	3.9 ± 0.4	4.1 ± 0.2	<.01	3.9 ± 0.5	4.1 ± 0.2	.12	4.0 ± 0.4	4.2 ± 0.2	.08	.84
MNA®										
Total Assessment score (points)	21.1 ± 4.5	23.1 ± 2.8		21.2 ± 5.5	24.3 ± 2.7	<.05	21.1 ± 3.4	21.8 ± 2.4	.50	.18
Severity (n, %)										
Normal (>24 point)	8 (30.8)	11 (42.3)	<.05	5 (38.5)	8 (61.5)	.08	3 (23.1)	3 (23.1)	.53	
At risk (17–23.5 points)	16 (61.5)	15 (57.7)	.40	6 (46.2)	5 (38.5)		10 (76.9)	10 (76.9)		
Malnourished (<17 points)	2 (7.7)	0 (0.0)		2 (15.4)	0 (0.0)		0 (0.0)	0 (0.0)		

Mean ± SD or Median (25%–75% tile).

6MWT = 6-minute walk test, Knee ext = knee extension, Lt = left, MNA® = Mini Nutritional Assessment, Rt = right, SD = standard deviation, SMI = Skeletal Muscle Mass Index, SMM = Skeletal Muscle Mass.

after chemotherapy in patients with malignant lymphoma.[5] In this study, we examined the effectiveness of exercise therapy in rehabilitating patients with malignant lymphoma undergoing chemotherapy by comparing the results of various tests performed before and after chemotherapy. Tests for physical functions showed that although right grip strength decreased after chemotherapy, other physical functions (left grip strength, bilateral knee extension strength, and 6MWT) were maintained, suggesting that exercise therapy is effective in preventing a decrease in physical functions during chemotherapy.

Table 3

BFI and Quality of life measures before and after chemotherapy.

Variables	Total (n = 26)			Men (n = 13)			Women (n = 13)			Gender Interaction
	Before	After	P	Before	After	P	Before	After	P	P
BFI										
Global fatigue score (points)	2.7 ± 2.4	2.1 ± 2.4	.78	2.1 ± 2.0	1.7 ± 2.3	.56	3.4 ± 2.6	2.4 ± 2.6	.37	.60
Severity (n, %)			.65			.42			1.00	
Mild (1–3 points)	18 (69.2)	20 (76.9)		10 (76.9)	11 (84.6)		8 (61.5)	9 (69.2)		
Moderate (4–6 points)	6 (23.1)	6 (23.1)		3 (23.1)	2 (15.4)		3 (23.1)	4 (30.8)		
Severe (>7 points)	2 (7.7)	0 (0.0)		0 (0.0)	0 (0.0)		2 (15.4)	0 (0.0)		
SF-36v2										
Physical functioning	75.0 (53.8–85.0)	80.0 (70.0–91.3)	.06	80.0 (60.0–85.0)	90.0 (73.9–95.0)	.06	70.0 (47.5–87.5)	80.0 (62.5–87.5)	.48	.34
Role physical	65.6 (42.2–100.0)	75.0 (43.8–100.0)	.94	68.8 (34.4–100.0)	75.0 (62.5–100.0)	.34	62.5 (50.0–100.0)	62.5 (6.25–93.8)	.48	.19
Bodily pain	62.0 (42.0–100.0)	74.0 (62.0–100)	.13	100.0 (46.5–100.0)	84.0 (62.0–100)	.58	52.0 (41.5–73.0)	74.0 (63.0–100)	.10	.38
General health	43.5 (27.5–52.0)	52.0 (40.0–67.0)	<.01	42.0 (20.0–48.5)	52.0 (42.5–67.0)	<.01	45.0 (30.0–52.0)	52.0 (38.5–67.0)	<.05	.44
Vitality	50.0 (31.3–62.5)	65.6 (42.2–68.8)	.16	50.0 (28.1–71.9)	62.5 (31.3–68.8)	.58	50.0 (37.5–62.5)	68.8 (43.8–71.9)	.23	.63
Social functioning	87.5 (50.0–100.0)	68.8 (46.9–87.5)	.19	87.5 (43.8–100.0)	75.0 (43.8–93.8)	.51	87.5 (56.3–100.0)	50.0 (43.8–87.5)	.19	.67
Role emotional	66.7 (45.8–100.0)	95.8 (50.0–100.0)	.11	75.0 (37.5–100.0)	100.0 (70.8–100.0)	.10	58.3 (41.7–91.7)	75.0 (29.2–100.0)	.48	.57
Mental health	57.5 (48.8–75.0)	77.5 (55.0–86.3)	<.05	60.0 (52.5–82.5)	80.0 (55.0–92.5)	.13	50.0 (40.0–70.0)	75.0 (55.0–85.0)	.09	.54
Physical component summary	39.8 (28.9–48.0)	45.8 (40.9–52.5)	<.01	40.2 (33.5–49.1)	49.8 (44.1–53.4)	<.05	33.8 (26.8–48.1)	43.1 (36.8–51.6)	.20	.24
Mental component summary	45.9 (41.6–50.1)	53.6 (44.8–58.6)	<.05	47.7 (44.0–51.8)	48.8 (43.3–56.9)	.51	44.7 (38.2–50.0)	55.8 (48.5–63.2)	<.05	.02
Role/social component summary	42.2 (30.6–60.0)	39.6 (29.5–53.5)	.29	48.9 (27.3–64.7)	48.9 (36.3–55.5)	.60	39.5 (31.2–55.0)	35.1 (17.0–53.0)	.28	.37

Mean ± SD or Median (25%–75% tile).
BFI = Brief Fatigue Inventory, SF-36 = MOS 36-Item Short-Form Health Survey.

Previous studies[8,10,34] with similar aims as this study reported that for patients with malignant lymphoma, exercise therapy not only "maintained" but actually "improved" muscle strength and endurance. This difference in results may be related to differences in the timing of the initial measurement, that is, in previous studies, the first measurement was taken during treatment (i.e., not before chemotherapy), at which point the subject's physical function may have already declined. In contrast, in the present study, the baseline was the subject's functional status before the start of chemotherapy, that is, before any decline in the subject's functional status due to chemotherapy. By performing measurements before and after chemotherapy this study demonstrated for the first time that exercise therapy during chemotherapy is effective in maintaining the physical function of patients with malignant lymphoma relative to their pre-chemotherapy physical function.

We also examined the effect of exercise therapy on skeletal muscle mass in patients with malignant lymphoma, because a decrease in SMM and SMI may lead to sarcopenia, a condition that should be avoided as much as possible. Recent findings have shown that a combination of exercise and nutrition therapy is effective in preventing SMM loss and the development of sarcopenia in cancer patients.[35,36] Interestingly, our comparisons of nutritional status before and after chemotherapy showed improvements in serum albumin levels and MNA scores after chemotherapy. The reason for improved nutritional indices despite the lack of any special nutritional therapy may be that the appetite, which had been reduced by B symptoms, improved after chemotherapy; moreover, all the subjects received well-controlled hospital food. In the future, it will be necessary to investigate whether the combination of exercise and nutrition therapies, which has been shown to be effective in other diseases, can prevent the loss of SMM in patients with malignant lymphoma.

We observed a significant improvement in QOL after chemotherapy, with improvements occurring mainly in the subjects' mental aspects, such as GH, MH, PCS, and MCS. It has been reported that exercise therapy improves QOL in patients with malignant lymphoma undergoing chemotherapy,[8,34,37] and the results of this study support this. Nevertheless, we did observe a decline in SF, which may be due to the practical difficulty in fulfilling social roles during inpatient chemotherapy.

Gender differences in the effects of exercise therapy in patients with malignant lymphoma have not been investigated before. Here we found that women generally maintained muscle strength and mass, while men experienced significant decreases in SMM and SMI, as well as a non-significant decrease in muscle strength. This result may be due to the fact that men had more SMM than women prior to the start of chemotherapy, making them more susceptible to the effects of the reduced activity caused by inpatient chemotherapy. In the present study, the exercise regimen lasted for 20 minutes per day, and was set at a Borg Scale of 13. It is possible that this exercise load may not prevent the decline in muscle strength and SMM in men, suggesting the need to set different exercise intensities for men and women.

Gender differences were also observed in the subjects' nutritional status, with only males showing a significant increase in MNA after chemotherapy, while females showed no significant change. We observed gender difference in the changes in QOL before and after chemotherapy, with the physical QOL summary score in men and the mental QOL summary score in women improving significantly after chemotherapy. In particular, the study identified a gender interaction in the mental QOL summary score. This result indicates that the mental and physical aspects of QOL in men and women, respectively, did not improve after chemotherapy. Morishita et al[11]reported that among hematopoietic stem cell transplant patients, physical QOL summary scores were lower in women than in men, and depression and anxiety were closely related to QOL in men,

suggesting the need for a psychological intervention through physical therapy during chemotherapy. These results are consistent with our findings in patients with malignant lymphoma, suggesting that exercise therapy during chemotherapy needs to address the psychological and physical well-being of male and female patients, respectively.

Our study has two major limitations. First, the sample size was small because many patients did not meet the eligibility criteria. In particular, many subjects dropped out due to missing data, and the main reason for this was difficulty in conducting the assessments related to this study in a timely manner due to medical treatment and testing, and the response to COVID-19. In addition, there were many dropouts because of discharge due to return to work (shift to outpatient treatment). Second, we were unable to observe physical activity outside of exercise therapy in detail; therefore, the causal relationship between physical activity and physical function was not accurately captured.

The highlight of the current study is that we demonstrated that 20 minutes of daily exercise at a Borg Scale intensity of 13 may not prevent muscle mass decline in male patients with malignant lymphoma. In addition, this study revealed that there is a gender difference in the QOL improvement effect of exercise therapy, and that physical QOL tends to improve in male patients and mental QOL tends to improve in female patients. This study provides a new perspective for rehabilitation on gender differences in response to exercise therapy, a subject that has never been systematically examined before. In the future, it will be necessary to determine the specific intensity of exercise that can result in improved muscular strength and endurance in patients with malignant lymphoma. Moreover, our results indicate the need for comprehensive intervention that includes psychological approach for men and appropriate exercises to enhance the physical well-being of women.

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