Research Square

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Psychological Well-Being and Quality of Life Improvements Following Strength-Based Resistance Training in Older Adults with Chronic Lymphocytic Leukemia: ADRENALINE Case Report

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Abstract

Background

Chronic lymphocytic leukemia (CLL) patients often experience decreased quality of life due to low daily living activities, increased infection risk, and treatment uncertainties, particularly during the "watch-and-wait" phase. Interventions are needed to mitigate these effects.

Aims

This study, as part of the ADENALINE trial, evaluates the impact of a 16-week individualized resistance training program on health-related quality of life (HRQOL) among treatment-naive CLL patients.

Methods

The trial included 11 patients aged 45–80 years with confirmed CLL, randomized into a resistance exercise (REx, n = 4) group or usual care control (CG, n = 7). Health-related Quality of Life outcomes were assessed using the FACIT-F and EORTC QLQ-30/CLL17 questionnaires to evaluate well-being and quality of life changes.

Results

Results indicated significant improvements in functional well-being and physical functioning for the REx group compared to controls, although emotional well-being improvements were not statistically significant. Notable trends in general quality of life also favored the resistance training group.

Conclusions

The study underscores the potential benefits of strength-based training for enhancing specific HRQOL aspects in CLL patients, providing insights for future exercise protocols. While results show promise for improving quality of life before treatment onset, larger trials are needed to validate findings and explore long-term effects to optimize exercise interventions for this population.

Trial Registration:

This study is registered at the ClinicalTrials.gov (NCT06396611).

Introduction

Described as the proliferation of monoclonal mature B lymphocytes [1], Chronic Lymphocytic Leukemia (CLL) is the most common chronic leukemia in western countries [2]. With leukemia arising as the eighth leading cause of cancer-related deaths in Europe since 2019, CLL shows a prevalence of 25–35% in older adults between 65–74 years old [3]. Typically, whereas patients with cancer have poor overall physical condition, associated with the progression of disease symptoms and negative outcomes during and after therapy [4], exercise engagement can serve as an adjunct in preventing the physiological decline, while promoting adequate daily physical activity and exercise [4, 5]. This line of evidence, elicited a novel field of investigation, due to the recognized importance of physical activity and structured exercise on immunomodulatory effects [6]. Treatment naïve CLL patients represent a unique oncological model to explore the effects of exercise training in cancer patients without the complications of therapy associated side-effects and to understand how exercise training interventions impacts hematologic malignancies [6].

Frequently, the low engagement in daily physical living activities appear as correlates to the increased risk of infections, loss of physical functioning, and along with CLL-specific side effects, negatively affecting well-being and quality of life

for CLL patients [7]. Thus, interventions that could minimize dysfunction (physical, functional, social, role, phycological, among others) will impact the stress imposed by patients' oncological expectations and improve quality of life and well-being.

Cardiovascular training is strongly associated to improvements in quality of life, with studies suggesting that moderate-to-vigorous aerobic activity can effectively reduce symptoms of depression and anxiety, mainly due to the release of endorphins, serotonin and other neurochemicals [8, 9]. Likewise, resistance training also showed an important impact on quality of life, reducing depressive symptoms and anxiety levels, slightly more beneficial for long-term improvement on self-esteem, while setting the focus on goal-setting and physical empowerment [8, 9]. The combination of Cardiovascular and Resistance Training also revealed a reduction in depressive symptoms, blood pressure, and enhanced health-related quality of life, compared to cardiovascular alone in other populations with different diseases [10]. In studies with CLL patients, the relationship between physical activity and health-related quality of life was observed with large effect sizes for improved functional well-being [11], physical fitness, fatigue and health-related quality of life [12], but without significant changes across the mental component score [13]. However, regarding CLL population, there is no literature that address the influence of a resistance training independently of cardiovascular. Knowing that a structured resistance training promotes behavioral changes linked to goal setting, self-monitoring, and promoting autonomy during interventions [8], that amplify these effects, our study adds to previous knowledge, through the assessment of the influence of this type of training in psychological traits, and how resistance training could be emphasized for long-term self-esteem improvements.

Our purpose is to assess the influence of an individualized resistance training with a strength-based approach program, in health-related quality of life and well-being in CLL patients. In addition, our sample population of treatment naïve CLL patients is unique due to the untreated phase of the disease. We hypothesize that the exercise program will improve health-related quality of life in domains specific to function, well-being, and CLL-related symptoms in comparison to a usual care control group.

Material and Methods

Study Participants

The ADENALINE (r**A**ndomise**D** cont**R**oll**E**d cli**N**ical tri**AL** of exerc**I**se as Intervention in chro**N**ic lymphocytic leuk**E**mia) is a blind randomized controlled trial (RCT) study, novel in CLL research. Here, we present data from a pilot that included patients with confirmed CLL according to the International Workshop on CLL Guidelines [14], within the age interval 45–80 years old, without history of previous treatment of CLL. Included participants were referred and consecutively recruited at São João University Hospital Centre under stringent inclusion and exclusion criteria.

Those able to walk on treadmill or cycle on an ergometer, able to carry weights or use weight machines, approved in initial evaluations [Cardiopulmonary Exercise Test (CPET) for cardiac health and dynamometer for muscular health], willing to adhere to the exercise program were included after signing the informed consent. Exclusion criteria comprised previous immunochemotherapy or targeted therapies for CLL, participation on ongoing exercise program, clinical criteria to start treatment, history of other malignancies, or inability for performing exercise due to clinical conditions as evaluated by the MD.

All participants received a screening assessment including medical history, blood chemistry and hemogram, and physical examination (for skin pallor, palpable cervical lymph nodes, and hepatomegaly) prior to the assessment of health-related quality of life using questionnaires. Fitness evaluations included anthropometric and body composition measures.

The study protocol has been approved by the Ethics Committees of São João University Hospital Centre and of the Faculty of Sport of the University of Porto. All patients provided written informed consent to participate. The trial is registered at ClinicalTrials.gov.

Study Design

Eligible patients who met the inclusion criteria were randomized into a controlled 16-week intervention program with a maximum of 2 sessions per week, ensuring at least 24h rest period between similar sessions for the same aims and muscular groups. All participants were evaluated before and after the intervention period. The intervention had two arms: a) Resistance Exercise Training with a Strength-based Training exercise program (REx) and b) a control group with usual care (CG). Patients were re-assessed during follow-up after exercise intervention period, in routine consultation at 6 months to acquire data to support long term effects. The scheme of the study can be consulted in Fig. 1.

Insert Fig. 1 *here*

Randomization

Randomization was performed using the Clinical Trial Randomization Tool from The National Cancer Institute's Division of Cancer Prevention [15], with 2 arms allocation and a maximum tolerated imbalance of three between arms, blinded for laboratory staff but not for physical intervention fellows.

Evaluations

Physical Fitness testing

At each time point, T0 and T1, patients were evaluated for anthropometric and body composition measures (DEXA).

Standard anthropometric methods (SECA 899 digital floor scale and SECA 217 stadiometer) were used for height and weight assessment. Body mass index was calculated as weight/height^2 (Kg/m^2). Body composition and bone mineral density were collected using dual-energy X-ray absorptiometry [DEXA scans (Horizon Wi, Hologic)], to quantify percent body fat, fat mass, trunk fat mass, skeletal muscle mass and bone mineral density (from whole body test) and non-dominant hip bone mineral density.

The American College of Sports Medicine (ACSM) 1-RM protocol was used to access whole body strength [16] for the exercises prescribed in protocol intervention (Leg Press, Leg Curl, Leg Extension, Chest Press, Latissimus Front Row, Shoulder Press, Triceps Extension, and Biceps Curl). The Epley prediction Eq. (1RM = (0.033 * number repetitions * weight lifted) + weight lifted)) was used to provide safe 1-RM [17].

Quality of Life testing

At each time point, T0, T1 and T2, two self-reported questionnaires were used to assess well-being and quality of life: the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30) and Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL17).

The FACIT-F [18] is a 27-item compilation of general questions divided into four primary Well-Being domains: Physical, Social/Family, Emotional, and Functional Well-Being, which is appropriate for use with cancer patients to assess fatigue. The FACT-General (FACT-G) score was determined by summing the totals from the four domains of physical, social/family, emotional, and functional well-being, and the FACIT-Fatigue (FACIT-F) score was determined by adding the

FACT-G total and the fatigue subscale score. The maximum score for the FACIT-F is 160, with higher scores indicating greater Well-Being for all domains.

The EORTC QLQ-C30 comprises 30 items evaluating Health-Related Quality of Life with five functional scales (physical, role, cognitive, emotional, social), seven symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation and diarrhea), one item assessing perceived financial impact of disease and treatment, and two items to rate overall health and quality of life [19]. All the scales and single-item measures range in score from 0 to 100 with a high scale score representing a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

The EORTC QLQ-CLL17 supplement consists of 17 items, incorporates three multi-item scales to assess Symptom burden, Physical condition / fatigue and Worries / fears about health and functioning with all multi-item scales range scoring from 0 to 100. A high score for all the multi-item scales represents a higher level of symptomatology or problems [19].

Outcomes

Well-being and Health-related Quality of Life in CLL patients were assessed using the FACIT-F, EORTC QLQ-30 and EORTC QLQ-CLL17 questionnaires. Domains and total scores were calculated based on instrument scoring guidelines to deliver information regarding fatigue, symptom burden, physical condition, worries/fears about health and functioning.

Body composition measures, anthropometric, were also obtained.

Intervention Protocol

The intervention program was composed of 16 weeks of exercise with 2 sessions per week ensuring at least 24h rest period between sessions. The structure of the exercise program is depicted in Table 1. Patients in the REx group were submitted to resistance machine exercises for the major muscle groups. A warmup of 10 minutes and cool down of 5 minutes are included in each session aiming workloads of 60%-85% of peak heart rate (HRpeak).

Table 1
Structure of the exercise REx program. W = Work phase. R = Rest phase. 1-RM = One Repetition Maximum.

Week	Program design	Number of intervals	Aims of the training
1–3	2x per week, 45 min W: 60–70% 1-RM R: 60 to 90 sec passive rest	3 sets of 12–15 repetitions.	Leg Press, Leg Curl, Leg Extension, Chest Press, Latissimus Front Row, Shoulder Press, Triceps Extension, Biceps Curl, Abdominal Crunch
3–16	2x per week, 45 min W: 80% 1RM R: 60 to 90 sec passive rest	3 sets of 8–12 repetitions.	Leg Press, Leg Curl, Leg Extension, Chest Press, Latissimus Front Row, Shoulder Press, Triceps Extension, Biceps Curl, Abdominal Crunch

Table 1: *Structure of the exercise REx program. W = Work phase. R = Rest phase. 1-RM = One Repetition Maximum.*

Enrolment throughout the REx program in machines was conducted from major muscle groups to minor muscle groups, from polyarticular to monoarticular exercises, and alternating between agonist and antagonist contraction according to the following laydown: Leg Press ->Leg Curl ->Leg Extension ->Chest Press ->Latissimus Front Row ->Shoulder Press ->Triceps Extension ->Biceps Curl ->Abdominal Crunch. During workout, session effort was monitored using heart rate monitors (Garmin Vivosmart 4) and rate of perceived exertion scale (RPE) to support the control of intensity throughout exercise training sessions. The loads used in each exercise were calculated according to 1-RM evaluation measured after a 3-week adaptation period, with subsequent evaluations every 5 weeks.

In the control group, patients undergone usual care, receiving advice to follow their habitual PA routines and contacted bimonthly to assure retention in the study.

Statistical Analysis

Sample size calculation (using G-Power software) was based on the means and standard deviations of prior studies [20]. A minimum of 16 subjects overall was required to detect differences, with power set at 95% and significance at 5% (two-tailed). To account for potential dropouts, a total of 20 subjects were planned for enrollment. However, due to exceptional external circumstances beyond our control, only 11 participants were recruited.

Risk of bias was assessed with Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), which determined an overall **low risk of bias**, as well as in each individual domain [21].

Missing data in this study appeared to be missing completely at random, rather than due to systematic bias. Including all available data increased statistical power and prevented unnecessary exclusion of valuable information. Even partial datasets contributed to a more comprehensive understanding of trends and associations within the CLL population. Transparent reporting of missing data and handling procedures was provided in all tables to ensure study reproducibility.

Normality was assessed using the Shapiro-Wilk test. Descriptive data are presented as means and standard deviations, with t-tests used for continuous variables and Chi-square tests with Cramer's V effect size for categorical variables in baseline comparisons. To assess changes in HRQOL between REx and CG over the sixteen-week intervention, we conducted a two-way mixed ANOVA. Group-by-time interactions were analyzed for questionnaire subdomains and composite scores, without adjustments for multiple comparisons between subdomains, following recommendations regarding their independence. For HRQOL and well-being outcomes, a repeated-measures General Linear Model (GLM) was performed to analyze changes across three time points (baseline, 16 weeks intervention, and 6-month follow-up), assessing the persistence of intervention effects.

Clinically meaningful changes were defined as a score change of 3–7 points for the FACT-G total score and 2–3 points for the Functional Well-Being and Physical Well-Being domains [22, 23]. For the EORTC QLQ-C30, changes of 5–10 points were considered small, 10–20 points moderate, and > 20 points large, based on patient assessments of change [24].

Effect sizes were assessed using Hedges' g, as Cohen’s tends to overestimate effect size on small samples. Effects sizes of 0.2, 0.5, and 0.8 were interpreted as small, medium, and large, respectively [25]. Percentage differences in variables changes, were calculated using the formula: (*Intervention Value - Baseline Value) / Baseline Value* x 100.

Statistical significance was set at $p < 0.05$. All analyses were conducted using IBM SPSS, Mac version 29 (Armonk, NY, United States).

Results

From the 23 patients accessed for eligibility, eleven consented to integrate the study with final groups assigned to either REx (n = 4) or Control (n = 7) groups. The complete diagram is depicted in Fig. 1. All patients completed the 16-week intervention and completed questionnaires FACIT-F, EORTC QLQ-30 and QLQ-CLL17 in all 3 time points, with 6-months follow-up retaining information about 8 patients (4 males and 4 females, two of each gender from each group). Table 2 reports participants characteristics at baseline.

Table 2

Baseline and Post-Intervention for demographic and disease characteristics of participants completing the intervention. [#]Chi-square test with Cramer's V effect size. Data are mean (SD) or mean difference (95% C.I.), unless otherwise indicated. Bolded effect sizes indicate large effect sizes for mean differences between groups. a = control group n = 6. b = control group n = 5.

	Controls (n = 7)		**Resistance Training (n = 4)**		**Baseline**		**Post-Intervention**	
Variable	**Baseline**	**16-week**	**Baseline**	**16-week**	**Mean Difference (95% C.I.)**	**Effect Size (g)**	**Mean Difference (95% C.I.)**	**Effect Size (g)**
Demographics and Body Composition								
Age (years)	66.4 (11.3)		64.0 (7.6)		2.4 (-11.9, 16.9)	0.22		
Sex (M/F)	5/2		2/2					
Height (cm)	163.0 (11.1)		163.5 (15.3)		-0.5 (-18.4, 17.4)	-0.04	-0.5 (-18.4, 17.4)	-0.04
Weight (kg)	70.8 (14.1)	71.8 (14.7)	73.9 (17.4)	74.1 (17.6)	-3.1 (-24.6, 18.5)	-0.19	-2.3 (-24.6, 19.9)	-0.14
BMI (kg/m^2)	26.4 (2.3)	26.7 (2.4)	27.3 (2.3)	27.3 (2.0)	-0.9 (-4.2, 2.3)	-0.36	-0.6 (-3.9, 2.7)	-0.23
Lean Mass (kg)	50.2 (11.8)	50.8 (12.1)	45.6 (11.7)	46.4 (12.7)	4.5 (-12.0, 21.1)	0.36	4.5 (-13.0, 21.9)	0.33
Body Fat (%)	25.0 (7.5)	25.3 (8.2)	35.5 (6.9)	33.9 (6.5)	**-10.5 (-20.9, -0.2)**	**-1.32**	**-8.4 (-19.2, 2.5)**	**-1.00**
Clinicopathological								
Time Since Diagnosis (yrs.)	4.0 (3.3)		3.0 (0.6)		1.0 (-2.9, 4.9)	0.34		
RAI Disease Stage[#]						0.63		
0 Low Risk	2 (28.6%)		0					
I Intermediate Risk	2 (28.6%)		4 (100%)					
II Intermediate Risk	1 (14.3%)		0					
Unknown	2 (28.6%)		0					
BINET Stage[#]						0.32		
A Low Risk	4 (57.1%)		4 (100%)					
B Intermediate	1 (14.3%)		0					
Unknown	2 (28.6%)		0					
ECOG Performance Status[#]						0.09		

	Controls (n = 7)		Resistance Training (n = 4)		Baseline		Post-Intervention	
Variable	**Baseline**	**16-week**	**Baseline**	**16-week**	**Mean Difference (95% C.I.)**	**Effect Size (g)**	**Mean Difference (95% C.I.)**	**Effect Size (g)**
Demographics and Body Composition								
0 Fully Active	4 (57.1%)		3 (75%)					
1 Restricted Physical Strenuous Activity	2 (28.6%)		1 (25%)					
Unknown	1 (14.3%)		0					

Table 2: *Baseline and Post-Intervention for demographic and disease characteristics of participants completing the intervention. #Chi-square test with Cramer's V effect size. Data are mean (SD) or mean difference (95% C.I.), unless otherwise indicated. Bolded effect sizes indicate large effect sizes for mean differences between groups. a = control group n = 6. b = control group n = 5.*

There were no adverse events recorded during any of the evaluation or exercise sessions. All participants completed 100% of prescribed sessions, and of tests at baseline and post-intervention.

Quality of life and fatigue were measured in both groups at baseline and post-intervention, using FACIT-F, EORTC QLQ-30 and CLL-17 questionnaires. Results on Individual Domains of FACIT-F revealed major improvements in the Functional Well-being with significant improvements observed in the resistance training group compared to controls (effect size = -1.47, p = 0.03). In the Individual Domains of EORTC QLQ-30, Physical Functioning showed a significant improvement over time (p = 0.01) and a significant Group × Time interaction (p = 0.03), favoring the resistance training group. The FACIT-F Total Score demonstrated that the resistance training group had notable improvement, with a borderline effect size (-1.26) and p-value (p = 0.06), whilst in the FACT-G Total Score the resistance training group showed a significant improvement (p = 0.02).

In Composite Scores of EORTC QLQ-30, the Average Symptom Scale revealed a significant improvement over time (p = 0.04), indicating reduced symptom severity, particularly in the resistance training group.

When extending the analysis to three time points (baseline, 16- weeks, and 6-month follow-up) using a repeated-measures General Linear Model (GLM), no significant group-by-time interactions were observed for any outcome, indicating that the initial improvements in the REx group were not maintained over time. Functional well-being and the FACT-G Total Score, which showed significant improvements at 16 weeks (p = 0.03 and p = 0.02, respectively), returned to baseline levels by the 6-month follow-up (p = 0.53 and p = 0.26, respectively). Similarly, while the time effect remained marginally significant for emotional well-being (p = 0.07) and cognitive functioning (p = 0.09), these did not reach conventional significance thresholds. Table 3 reports main results.

Table 3

Changes in well-being and quality of life in REx and Control groups. FACIT-F TOI = Functional Assessment of Cancer Therapy – Fatigue Trial Outcome Index. FACT-G = Functional Assessment of Cancer Therapy – General. FACIT-F = Functional Assessment of Cancer Therapy – Fatigue. Values are means (SD). * p ≦ 0.05; Significant difference between REx group and Control group. † p ≦ 0.05; Significant time effect. ‡ p ≦ 0.05; Significant group x time effect. Bolded effect sizes indicate large effect sizes for mean differences between groups. # GLM (3 time points) was conducted with Resistance Training n = 4 and Controls n = 4.

	Controls (n = 7)		Resistance Training (n = 4)		T-Test (16-week)		ANOVA (16-week)		GLM (3 time points) #	
Variable	**Baseline**	**16-week**	**Baseline**	**16-week**	**Effect Size (g)**	**p-value**	**Time (p-value)**	**Group x Time (p-value)**	**Time (p-value)**	**Group x Time (p-value)**
Individual Domains										
FACIT-F										
Physical Well-being (0–28)	25.3 (1.1)	26.0 (3.2)	22.5 (3.4)	25.8 (0.5)	0.10	0.88	0.07	0.23	0.34	0.42
Social Well-being (0–28)	19.3 (4.7)	20.0 (5.7)	26.5 (3.0)	25.8 (2.1)	**-1.09**	0.09	0.99	0.45	0.09	0.97
Emotional Well-being (0–24)	17.7 (5.6)	19.0 (4.5)	21.25 (4.2)	23.3 (1.0)	**-1.04**	0.10	0.12	0.72	0.07	0.46
Functional Well-being (0–28)	21.7 (2.5)	21.1 (3.1)	24.0 (1.8)	25.5 (1.7)	**-1.47**	**0.03***	0.62	0.28	0.53	0.74
Fatigue Subscale (0–52)	43.4 (2.4)	41.0 (5.7)	37.0 (5.1)	41.3 (3.8)	-0.05	0.94	0.65	0.12	0.68	0.17
EORTC QLQ-30										
Physical functioning (0-100)	87.6 (11.2)	89.5 (10.8)	76.7 (16.8)	91.7 (6.4)	-0.21	0.73	**0.01†**	**0.03‡**	0.09	0.24
Role functioning (0-100)	95.2 (12.6)	92.9 (13.1)	91.7 (16.7)	100.0 (0.0)	-0.61	0.20	0.63	0.40	0.65	0.45
Emotional functioning (0-100)	71.4 (19.2)	73.8 (16.3)	85.4 (14.2)	91.7 (6.8)	**-1.18**	0.07	0.34	0.66	0.20	0.16
Cognitive functioning (0-100)	85.7 (20.2)	85.7 (11.5)	54.2 (43.8)	91.7 (9.6)	-0.50	0.41	0.07	0.07	0.09	0.26

	Controls (n = 7)		Resistance Training (n = 4)		T-Test (16-week)		ANOVA (16-week)		GLM (3 time points) #	
Variable	Baseline	16-week	Baseline	16-week	Effect Size (g)	p-value	Time (p-value)	Group x Time (p-value)	Time (p-value)	Group x Time (p-value)
Individual Domains										
Social functioning (0-100)	90.5 (13.1)	90.5 (13.1)	79.2 (31.6)	100.0 (0.0)	**-0.81**	0.10	0.22	0.22	0.46	0.24
Fatigue (0-100)	26.2 (21.2)	14.3 (20.2)	8.4 (9.6)	0.0 (0.0)	**0.80**	0.11	0.08	0.73	0.46	0.46
Composite Scores										
FACIT-F										
FACIT-F TOI (0-108)	90.4 (2.6)	88.1 (9.3)	83.5 (9.6)	92.5 (5.1)	-0.49	0.42	0.30	0.10	0.42	0.25
FACT-G Total Score (0-108)	84.0 (6.9)	86.1 (9.6)	94.3 (8.1)	100.3 (2.2)	**-1.62**	**0.02***	0.06	0.34	0.26	0.48
FACIT-F Total Score (0-160)	127.4 (7.3)	127.1 (12.3)	131.3 (13.0)	141.5 (4.8)	**-1.26**	0.06	0.15	0.13	0.40	0.34
EORTC QLQ-30										
Global health status (0-100)	70.2 (18.6)	75.0 (16.0)	70.8 (15.9)	83.3 (13.6)	-0.50	0.41	0.23	0.58	0.24	0.23
Average symptom scale (0-100)	11.7 (8.1)	8.5 (6.5)	16.5 (9.6)	5.1 (3.5)	0.54	0.37	**0.04†**	0.20	0.09	0.17
EORTC QLQ-CLL17										
Symptom burden (0-100)	14.3 (10.1)	15.9 (13.8)	20.8 (20.0)	6.9 (8.3)	0.67	0.27	0.20	0.12	0.43	0.29
Physical condition/fatigue (0-100)	10.7 (9.3)	10.7 (12.5)	25.0 (20.4)	8.3 (6.8)	0.20	0.74	0.16	0.16	0.69	0.07

	Controls (n = 7)		Resistance Training (n = 4)		T-Test (16-week)		ANOVA (16-week)		GLM (3 time points) #	
Variable	Baseline	16-week	Baseline	16-week	Effect Size (g)	p-value	Time (p-value)	Group x Time (p-value)	Time (p-value)	Group x Time (p-value)
Individual Domains										
Worries/fears about health and functioning (0-100)	20.4 (23.0)	21.8 (17.8)	35.7 (14.3)	19.0 (3.9)	0.17	0.77	0.24	0.17	0.28	0.21

Table 3: *Changes in well-being and quality of life in REx and Control groups. FACIT-F TOI = Functional Assessment of Cancer Therapy – Fatigue Trial Outcome Index. FACT-G = Functional Assessment of Cancer Therapy – General. FACIT-F = Functional Assessment of Cancer Therapy – Fatigue. Values are means (SD). * p ≦ 0.05; Significant difference between REx group and Control group. † p ≦ 0.05; Significant time effect. ‡ p ≦ 0.05; Significant group x time effect. Bolded effect sizes indicate large effect sizes for mean differences between groups. # GLM (3 time points) was conducted with Resistance Training n = 4 and Controls n = 4.*

Discussion

To our knowledge, this is the first study to investigate the effects of a strength-based resistance training on HRQOL measures in CLL patients. Key findings of this study showed that, when compared to controls, the REx group significantly improved functional well-being (FACIT-F) and physical functioning (EORTC QLQ-30). General quality of life, as measured by FACT-G Total Score, also improved significantly in the resistance training group, while other domains showed trends of improvement without statistical significance. These findings suggest that a 16-week strength-based resistance training intervention may be beneficial, positively impacting specific domains of HRQOL, particularly physical and functional well-being, in treatment-naive CLL patients. Since older adults, as seen in CLL, are often in risk of functional limitations that hinder daily life activities [26], our results are promising to improve these outcomes.

Research on clinically meaningful changes (CMCs) for cancer-specific quality of life measures has provided valuable insights. Recent trends show a shift from broad "legacy" thresholds towards contemporary, subscale-specific, and population-specific thresholds for the EORTC QLQ-C30. However, this trend is less evident for FACT-G, with most clinical trials still using thresholds of 3–7 points for total score [22].

For the FACT-Lym, CMCs are associated with score changes of 6.5–11.2 for the total score and 2.9–5.4 for the lymphoma subscale [27]. The FACT-P study estimated CMCs of 6–10 for the total score and 2–3 for the prostate cancer subscale [28]. For the FACT-Hep, CMCs were estimated as 6–7 for FACT-G, 5–6 for the hepatobiliary subscale, and 8–9 for the total score [23]. Across various cancer types, CMCs for FACT-G total score ranges from 3–7 points [22]. For individual FACT-G domains, CMCs of 2–3 points are considered meaningful for the Functional Well-Being (FWB) and Physical Well-Being (PWB) subscales [22, 23]. In our data, mean changes for strength intervention group were consistently greater than 2 points change for subdomains (with the exception for Social Well-Being [-0.75 (2.5)] and Functional Well-Being [1.5 (1.0)]), and higher than 6 points for composite scores, while for control group, all subdomains and composite scores remained below the threshold for meaningful changes. This suggest that patients from our study experienced a reduction in Fatigue related domains, with a resistance training protocol demanding higher exertion during

intervention (+ 80% of 1-RM). Artese, Sitlinger [11] reported lower scores in comparison to reference, although the intervention focused more on muscular endurance than strength and have not included exercises for all major muscle groups. Our strength-based resistance training intervention highlights the positive effects of this type of exercise.

For the EORTC QLQ-C30, changes of 5–10 points are considered small, 10–20 points moderate, and > 20 points large, based on patients' subjective assessments of change [24]. A study in CLL with cardiovascular and endurance muscular training [12], where EORTC-QLQ-C30 questionnaire was used, found lack of significance on fatigue, global quality of life and physical, role and social functioning. When comparing to our data, although without statistical significance, the intervention improved Cognitive Function and Social Function with large changes, Quality of Life, Physical Function and Average Symptom Scale with moderate changes, and Role Function and Emotional Function with small changes. Expressive changes occurred in Cognitive Function where previous data depicted a value of -3.6 points while our intervention incremented 37.5 points, whereas in Average Symptom Scale the cardiovascular and endurance training achieved + 2.1 reported symptoms while in our study reported symptoms were reduced by -11.4. This may support the importance of strength-based resistance training affecting positively the overall quality of life in naïve CLL patients.

Whilst resistance training (RT) interventions have shown significant improvements in strength, body composition, function, and well-being in older adults, the long-term maintenance of these improvements remains challenging. Studies have found that HRQOL gains tend to diminish or revert to baseline levels after the supervised intervention period ends [29, 30]. In our data the decline in quality-of-life and well-being scores at the 6-month follow-up highlights the transient nature of the improvements observed with resistance training. The fact that functional well-being and overall quality of life returned to baseline levels suggests that continued participation in RT appears crucial for sustaining benefits, with those who voluntarily maintain training showing better HRQOL outcomes compared to those who stop (Inaba et al., 2008). Despite high levels of self-determined motivation during interventions, long-term adherence to RT remains low, with common barriers including lack of time, interest in other activities, and financial costs [31]. Future studies should explore strategies to promote exercise adherence beyond the initial supervised intervention period to ensure prolonged benefits.

The limitations of our study include the small sample size. However, social interactions remained consistent throughout the intervention, with personal supervision of the protocol implementation. We also acknowledge that the control group had higher baseline values for cognitive and social function than the intervention group. Therefore, the potential for improving scores may have been lower in the control group because their baseline HRQOL was better. For the generalizability of the data, multicenter recruitment should be implemented to encompass the differences in daily living between cities and rural areas that might bias the results. However, as this mode of intervention (strength-based resistance training) is novel in CLL patients, we highlight the feasibility and positive results of such interventions, which should be pursued with larger samples.

Findings suggest that a 16-week strength-based resistance training program may improve and sustain HRQOL components during early disease stages, prior to treatments that typically impair quality of life.

Conclusions

Our findings highlight the potential of a 16-week strength-based resistance training program to significantly improve key aspects of Well-being and HRQOL in naïve CLL patients. The intervention demonstrated notable benefits in physical, emotional, and social well-being, as well as overall quality of life and fatigue management. Additionally, the program upheld stability in all measured domains without negative impacts. Future studies should focus on confirming these findings, exploring long-term outcomes, and refining exercise protocols to better meet the needs of diverse patient populations, including older adults and those with greater impairments.

Declarations

Declaration of Interests

There is no competing interest of any authors of this manuscript.

Ethics Approval and Consent to Participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study had the approval by the Ethic Commission of São João University Hospital Center, and by the Ethic Commission of Faculty of Sport from the University of Porto, and all patients provided written informed consent upon recruitment and prior to participation.

Author Contribution

CRediT author statement:Pedro M P Cunha: Conceptualization, Methodology, Writing – Original Draft, Funding acquisitionRicardo J Ribeiro: Supervision, Writing – Review & EditingAndreia Pizarro: Writing – Review & Editing Jorge Mota: Resources, Writing – Review & Editing, Funding acquisitionJose C D Ribeiro: Resources, Validation, Writing – Review & Editing, Supervision, Funding acquisition

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Data Availability

The datasets generated during the present study will not be publicly available but can be obtained from the corresponding author on reasonable request.

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Figures

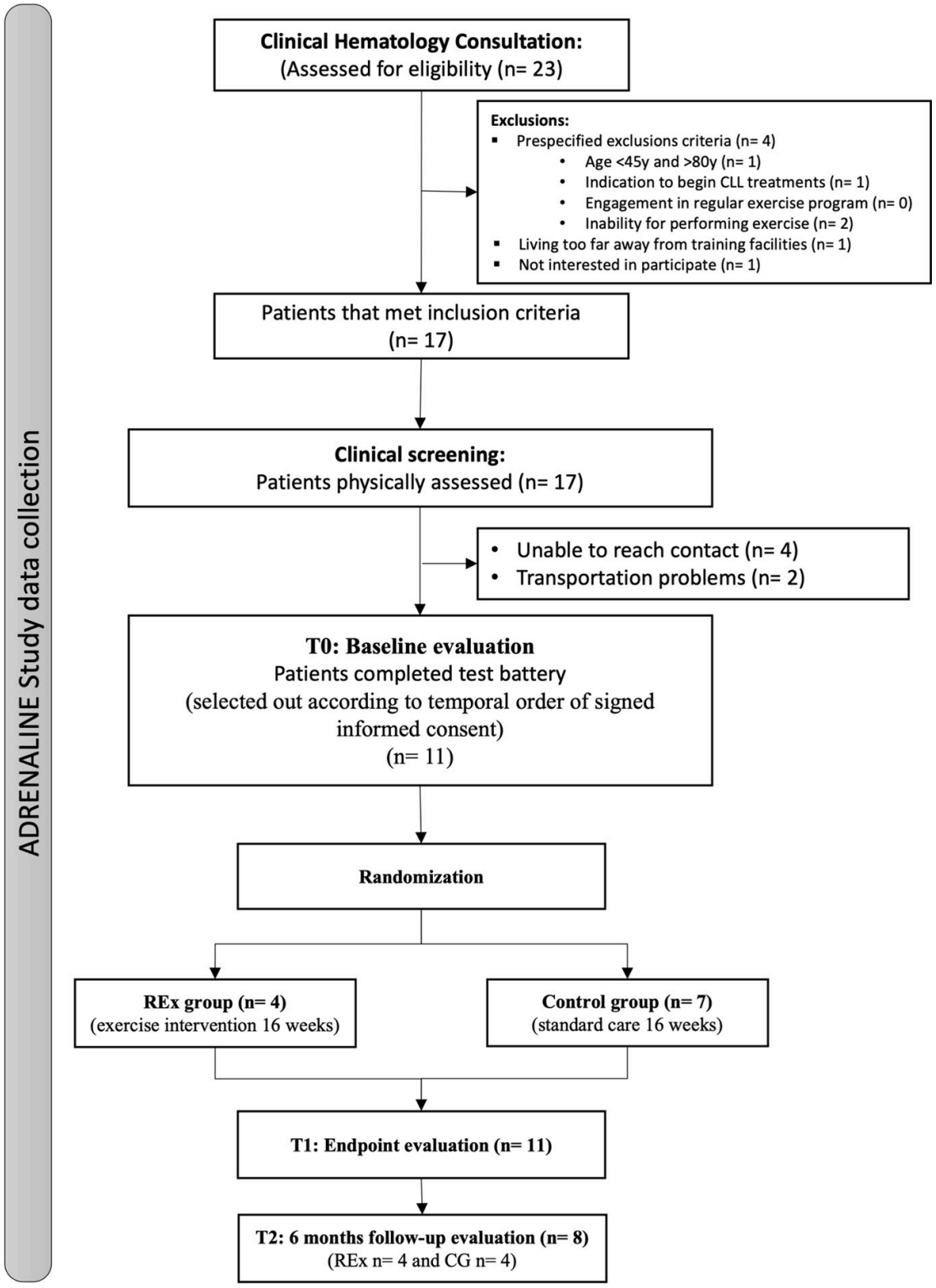


Figure 1

Consolidated standards of reporting trials (consort) diagram. REx=Resistance Exercise. CLL=Chronic Lymphocytic Leukemia.