

**Effects of Strength Training on Body Composition, Physical
Fitness, and Quality of Life in Older Adults with Treatment
Naïve Chronic Lymphocytic Leukemia**

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KEYWORDS: *PHYSICAL ACTIVITY*, EXERCISE, RESISTANCE TRAINING, QUALITY OF LIFE, CHRONIC LYMPHOCYTIC LEUKEMIA, ONCOLOGY.

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LIST OF FORMULAS AND EQUATIONS

Body Mass Index	$BMI = \frac{weight\ (kg)}{(height\ (m))^2}$
FOX's Maximal Heart Rate	$HR_{max} = 220 - age$
Epley 1-RM prediction equation	$1RM = (0.033 * number\ repetitions * weight\ lifted) + weight\ lifted$
Percentage Change in Variables	$\Delta\% = \frac{Intervention\ Value - Baseline\ Value}{Baseline\ Value} * 100$

ABSTRACT

Chronic Lymphocytic Leukemia (CLL) is the most prevalent leukemia among adults in Western countries, with patients often experiencing compromised physical fitness, immune dysfunction, and reduced health-related quality of life (HRQOL). Despite growing interest in exercise as an adjunct therapy, research on structured physical activity interventions in CLL remains limited. This dissertation aggregates findings from five studies exploring the effects of physical exercise on CLL patients, focusing on physical fitness, immune markers, and HRQOL outcomes.

A systematic review (study 1) assessed the impact of exercise on CLL patients, identifying six studies (n=323) that primarily investigated cardiovascular and resistance training interventions. The findings underscored significant improvements in physical fitness and immune parameters, though variability in study designs limited conclusive recommendations, and identified the strength-based resistance training understudied gap among literature. The ADRENALINE pilot study (study 2) further explored baseline activity levels, functional capacity, and immune markers in treatment-naïve CLL patients, revealing suboptimal cardiovascular fitness and a high prevalence of sedentary behavior despite self-reported functional competence. Notably, moderate-to-vigorous physical activity correlated positively with muscle strength and lean mass, suggesting a potential role for targeted exercise interventions in mitigating disease-related deterioration.

To address the need for structured interventions, study 3 evaluated the effects of a 16-week individualized strength-based resistance training program on HRQOL in CLL patients. Results demonstrated significant improvements in functional well-being and physical functioning, with promising trends in overall quality of life. Similarly, study 4 and 5 examined the feasibility and efficacy of a strength-based resistance training protocol, reporting large effect sizes for muscle strength gains and reductions in body fat percentage and neutrophil count, indicating potential immunomodulatory benefits.

Together, these studies highlight the feasibility and potential benefits of structured exercise interventions in CLL patients, particularly with a strength-

based resistance training approach. Findings emphasize the need for larger, long-term trials to establish evidence-based exercise guidelines, optimize patient outcomes, and explore mechanistic links between physical activity and disease progression. This research contributes to the growing body of evidence supporting exercise as an integral component of supportive care in CLL management.

KEYWORDS: PHYSICAL ACTIVITY, EXERCISE, RESISTANCE TRAINING, QUALITY OF LIFE, CHRONIC LYMPHOCYTIC LEUKEMIA, ONCOLOGY.

RESUMO

A Leucemia Linfocítica Crônica (LLC) é a forma mais prevalente de leucemia em adultos nos países ocidentais, com os doentes frequentemente apresentarem comprometimento da aptidão física, disfunção imunológica e redução da qualidade de vida relacionada com a saúde (HRQOL). Apesar do crescente interesse no exercício como terapia adjuvante, a investigação sobre intervenções estruturadas de atividade física na LLC continua limitada. Esta dissertação agrega os resultados de cinco estudos que exploram os efeitos do exercício físico em doentes com LLC, com foco na aptidão física, nos marcadores imunológicos e nos desfechos de HRQOL.

Uma revisão sistemática (artigo 1) avaliou o impacto do exercício em doentes com LLC, identificando seis estudos (n=323) que investigaram principalmente intervenções baseadas em treino cardiovascular e treino de resistência muscular. Os resultados evidenciaram melhorias significativas na aptidão física e nos parâmetros imunológicos, embora a variabilidade nos desenhos dos estudos tenha limitado recomendações conclusivas, e identificaram uma lacuna na literatura quanto ao estudo do treino de força. O estudo piloto ADRENALINE (artigo 2) explorou os níveis de atividade basal, a capacidade funcional e os marcadores imunológicos em doentes com LLC não submetidos a tratamento, revelando uma aptidão cardiovascular sub-ótima e uma elevada prevalência de comportamento sedentário, apesar de uma percepção positiva da função física. Notavelmente, a atividade física moderada a vigorosa correlacionou-se positivamente com a força muscular e a massa magra, sugerindo um papel potencial para intervenções de exercício direcionadas na mitigação da deterioração associada à doença.

Para responder à necessidade de intervenções estruturadas, o artigo 3 avaliou os efeitos de um programa individualizado de 16 semanas de treino de resistência muscular baseado na força sobre a HRQOL em doentes com LLC. Os resultados demonstraram melhorias significativas no bem-estar funcional e na capacidade física, com tendências promissoras na qualidade de vida geral. De forma semelhante, o artigo 4 e 5 examinou a viabilidade e a eficácia de um

protocolo de treino de resistência muscular baseado na força, reportando elevados tamanhos de efeito para os ganhos de força muscular e reduções na percentagem de gordura corporal e na contagem de neutrófilos, indicando potenciais benefícios imunomodeladores.

Em conjunto, estes estudos destacam a viabilidade e os potenciais benefícios das intervenções estruturadas de exercício em doentes com LLC, particularmente com uma abordagem de treino de resistência muscular baseado na força. Os resultados reforçam a necessidade de ensaios de maior dimensão e longa duração para estabelecer diretrizes baseadas em evidência, otimizar os desfechos dos doentes e explorar as ligações mecanísticas entre a atividade física e a progressão da doença. Esta investigação contribui para o crescente corpo de evidência que apoia o exercício como um componente integral dos cuidados de suporte na gestão da LLC.

PALAVRAS-CHAVE: ATIVIDADE FÍSICA, EXERCÍCIO, TREINO RESISTÊNCIA, QUALIDADE DE VIDA, LEUCEMIA LINFOCÍTICA CRÓNICA, ONCOLOGIA.

LIST OF ABBREVIATIONS

1-RM	One Repetition Maximum
ACSM	American College of Sports Medicine
ADRENALINE	Randomised controlled clinical trial of exercise as Intervention in chronic lymphocytic leukemia
AE	Adverse Events
CG	Control Group
CLL	Chronic Lymphocytic Leukemia
CLL-IPI	Chronic Lymphocytic Leukemia International Prognostic Index
CPET	Cardiopulmonary Exercise Test
CRF	Cardiorespiratory Fitness
DEXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Scale
EORTC-QLQ	European Organization for Research and Treatment of Cancer - Quality of Life Questionnaires
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-G	Functional Assessment in Chronic Therapy - General
FACT-An	Functional Assessment in Chronic Therapy - Anemia
FITT	Frequency, Intensity, Time and Type
FITT-VP	Frequency, Intensity, Time, Type - Volume and Progression
HIIT	High-Intensity Interval Training
HR	Heart Rate
HRQoL	Health-Related Quality of Life
MVPA	Moderate-to-Vigorous Physical Activity
NK	Natural Killer Cells
PA	Physical Activity
PetCO₂	Partial pressure of end-tidal carbon dioxide

QoL	Quality of Life
RCT	Randomized Controlled Trial
REx	Resistance Training Exercise Group
RPM	Revolutions per Minute
RT	Resistance Training
T0	1 st Evaluation Moment – Baseline Evaluation
T1	2 nd Evaluation Moment – 16-week Evaluation
VE/VCO₂	Ventilatory equivalent for carbon dioxide
VO₂	Absolut Oxygen Volume
VO₂/kg	Relative Maximum Oxygen Volume
VO_{2peak}	Peak oxygen uptake
WBC	White Blood Cells

LIST OF SYMBOLS

deg/s	Degrees per Second (velocity)
min	Minutes
s	Seconds

INTRODUCTION

Insufficient physical activity (PA) is a major risk factor for noncommunicable diseases, including cancer, and is among the leading causes of death worldwide. While active living has been extensively studied, gaps remain in understanding the optimal application of the Frequency, Intensity, Time and Type (FITT) principle for exercise prescription in specific diseases [1]. Chronic lymphocytic leukemia (CLL) is one such area where research is still evolving.

CLL is the most common form of leukemia in Europe and United States [2]. It primarily affects elderly individuals, with a median age at diagnosis of approximately 70 years and a slight male predominance. However, due to increased routine blood testing in younger populations, the proportion of patients diagnosed at earlier disease stages is rising [2, 3].

CLL is characterized by the clonal proliferation and accumulation of mature B-cells in the blood, bone marrow, lymph nodes and spleen. Prognosis is typically determined using two widely accepted clinical staging systems - Rai and Binet – which rely on physical examination findings (such as lymphadenopathy and hepatosplenomegaly) and standard laboratory tests (including hemoglobin levels and platelet counts) [2, 3]. Similar to other B-cell malignancies, CLL cell survival is heavily dependent on a supportive microenvironment [4, 5]. This microenvironment fosters disease progression through interactions between leukemic cells and various proteins (chemokines, cytokines and angiogenic factors) which signal via surface receptors or adhesion molecules. Additionally, immune responses against CLL cells are impaired due to T-cell “exhaustion” and a defective immunological synapse formation with antigen-presenting cells [6]. Natural Killer (NK) cells also exhibit functional deficiencies, including reduced cytotoxic activity associated with the absence of cytoplasmic granules and impaired immunological synapse formation [4].

Higher levels of self-reported exercise, PA, and cardiorespiratory fitness (CRF) have been inversely associated with the incidence of several cancer types. Exercise is widely regarded as a well-tolerated adjunct therapy that improves cancer-related and treatment-associated symptoms [1, 7]. Although associations between PA and hematological cancer risk have been explored in the literature,

findings remain inconsistent [7-11]. One study reported that higher exercise levels were associated with a reduced risk of myeloid neoplasm, CLL, and mature B-cell lymphomas, but not plasma cell disorders [8]. Several studies have assessed the feasibility, safety, and clinical impact of exercise programs, even in the presence of severe anemia and thrombocytopenia [12-15]. Among patients with mature B-cell neoplasm, including CLL, aerobic exercise has demonstrated beneficial effects on CRF, fatigue, self-reported physical function, and quality of life [12, 13, 15]. Resistance training has also shown to mitigate bone loss, musculoskeletal function, and enhance maximal strength [16, 17]. Additionally, high-intensity interval training (HIIT) has been found to produce lasting improvements in muscle strength, cardiopulmonary function, quality of life, and fatigue among cancer survivors [18]. Notably, HIIT has demonstrated similar benefits to moderate-intensity exercise while offering superior outcomes compared to standard care [19].

This thesis comprises five papers exploiting a shared dataset to investigate the role of exercise in CLL patients:

Paper I: A systematic review of physical activity interventions in CLL patients;

Paper II: A characterization of baseline variables in CLL patients, exploring the role of daily activity in disease risk and survival outcomes;

Paper III: An experimental study analyzing well-being changes following a strength-based resistance training program in older adults with CLL;

Paper IV and V: An experimental study investigating the physical and immunological benefits of strength-based training in treatment-naïve older adults with CLL.

CHAPTER 1 – THEORETICAL BACKGROUND

RATIONALE FOR EXERCISE

Chronic lymphocytic leukemia (CLL) is characterized by immune system dysfunction, chronic inflammation, and metabolic alterations, leading to progressive muscle loss, reduced physical function, and increased fatigue [20]. These physiological impairments may be mitigated through structured exercise, which has been shown to counteract inflammation, improve metabolic function, and enhance immune responses.

Exercise may play a crucial role in facilitating the return to an active lifestyle for CLL patients after treatment [18]. Regular physical activity is known to improve physical function, enhance mood and self-esteem, and contribute to overall well-being in CLL patients [1]. However, studies investigating the effects of physical activity in treatment-naïve patients (i.e., before disease progression demands treatment) remain scarce. Furthermore, existing studies often lack methodological rigor, limiting their reliability and generalizability [8, 11, 21, 22]. The absence of standardized exercise protocols, control groups, and long-term follow-up further complicates the ability to draw definitive conclusions regarding the efficacy of exercise interventions [16, 18].

Notably, exercise does not cause side effects commonly associated with pharmacologic treatments. Regarding safety and feasibility, a systematic review of 25 studies involving 1088 patients with various advanced cancer diagnoses reported only six minor adverse events reporting minor injuries to the hip, back and knee, musculoskeletal events related to exercise, and some cases of dizziness, fatigue, pain, fever and/or bodily discomfort [23]. Physical activity interventions included aerobic exercise (five studies), resistance training (two studies) and combined aerobic and resistance training (14 studies) [23]. These findings support the feasibility and safety of exercise interventions in cancer patients, reinforcing the rationale for investigation the potential benefits of a strength-based training protocol in CLL patients. Given the positive effects observed in other cancer populations, similar or even greater improvements might be expected in CLL patients.

EXERCISE GUIDELINES AND PRESCRIPTION IN CLL

Current public health guidelines recommend at least 150 minutes per week of moderate-intensity aerobic physical activity [24, 25]. While many studies emphasize low-to-moderate intensity exercise or endurance-based resistance training (typically 65-70% of 1-RM), emerging evidence suggests that exercise-induced myokines production plays a critical role in enhancing cytotoxicity and promoting immune cell infiltration into tumors [26].

When comparing different exercise modalities – aerobic-only, strength-only and combined training - strength training appears to confer greater benefits for reducing cardiovascular disease mortality and cancer-related mortality, with isolated strength training emerging as the superior modality [27].

CLL patients tend to exhibit reduced muscle mass compared to healthy adults [28] yet current research lacks studies specifically evaluating the effects of isolated strength training in this population. Given that unintentional weight loss is a major symptom of CLL, the inclusion of strength training in disease management could be particularly beneficial in preventing muscle mass and physical function. Moreover, exercise intensity may influence long-term adherence, as CLL patients commonly experience fatigue and shortness of breath as the disease progresses. In this context, strength training may be better tolerated than aerobic training, making it a more feasible and effective intervention for maintaining physical function in CLL patients.

EMPIRICAL SUPPORT OF EXERCISE IN CLL

Research on the role of exercise as an adjunctive therapy in cancer treatment has been encouraging, though studies specifically focusing on CLL patients remain limited. There is general consensus that exercise does not have adverse effects on immunological, endocrinological, and hematopoietic variables, nor does it exacerbate lymphedema. Notably, even high-intensity training appears to be well-tolerated in cancer survivors [16].

Among the available intervention studies, findings suggest that a structured training program lasting more than 12 weeks, incorporating at least 30 minutes of HIIT combined with muscle endurance-based resistance training, is both feasible and beneficial for treatment naïve CLL patients. Such programs have been associated with significant improvements in muscle strength and normal immune cell functions [29-31]. However, it is crucial to distinguish between cardiovascular and muscular exercise modalities and to recognize the limitations of analyzing combined training programs [32].

While cardiovascular exercise has been well-documented to enhance cardiovascular fitness and endurance [15, 33], combining training programs (incorporating both cardiovascular and resistance exercises) have demonstrated additional benefits [29-31, 34]. However, to fully understand the individual contributions of different exercise modalities, muscular training targeting strength, power, and muscle mass should be assessed separately.

Beyond physical health, exercise – especially cardiovascular training – is strongly linked to mental health benefits. Studies indicate that moderate-to-vigorous aerobic activity can significantly reduce symptoms of depression and anxiety, likely due to the release of endorphins, serotonin, and other neurochemicals [35, 36]. Strength training has also demonstrated positive effects on mental health well-being, with evidence suggesting greater long-term benefits for self-esteem due to its focus on goal-setting and physical empowerment [35, 36]. Furthermore, structured resistance training is associated with behavioral changes that promote self-monitoring, autonomy, and adherence to long-term physical activity [35]. However, in the context of CLL patients, the specific impact of resistance training on these behavioral outcomes remains largely unexplored.

EXERCISE EFFECTS ON IMMUNOLOGIC PARAMETERS IN CLL

Current evidence suggests that intensive endurance exercise can induce lymphocyte apoptosis, potentially compromising immune function [37]. Conversely, regular resistance training reduces oxidative stress by enhancing antioxidant enzyme activity, which may, in turn, attenuate apoptosis-related

proteins expression [38]. Notably, studies indicate that high-intensity interval training selectively eliminates differentiated T-cells, which are implicated in immunity control of latent infections. In contrast, continuous exercise appears to affect the survival of undifferentiated T-cells, potentially impairing immunosurveillance and cytotoxic capacity [39].

Beyond its role in locomotion, skeletal muscle is increasingly recognized as a key regulator of metabolic and immune processes, influencing glucose and lipid metabolism, immunomodulation, anti-inflammatory responses, and the inhibition of migratory mononuclear cells [40-42]. Exercise-induced myokines production has been linked to enhanced immune-mediated cytotoxicity, improved tumor infiltration by immune cells, and the promotion of muscle growth, differentiation, and bone mineral density [26, 43]. Key myokines such as IL-6, irisin, and SPARC have been shown to enhance immune-mediated cytotoxicity, inhibit tumor cell proliferation, and improve metabolic regulation [44]. Additionally, physical exercise has been shown to activate NK cells, with maximal exercise involving large muscle groups leading to sustained immune responses, not only during but also after repeated exercise bouts [45-47].

Recent studies have explored the impact of physical activity on CLL patients, revealing that many treatment-naïve individuals are physically inactive and exhibit elevated inflammatory markers [48]. Given that regular physical activity is associated with reduced infection risk in the general population [49] and acts as a countermeasure against chronic systemic inflammation [50], it may hold therapeutic potential for mitigating the immunological dysfunction characteristics of CLL.

QUALITY OF LIFE AND WELL-BEING IN CLL

While current treatment approaches aim to address the complex needs of CLL patients, significant challenges remain – particularly regarding their quality of life (QoL) and physical functioning. The progressive decline in QoL highlights the need for interventions that promote physical activity and independence.

Fatigue is one of the most debilitating symptoms for CLL patients, affecting daily activities, motivation, and overall well-being [51]. While traditional cancer care often overlooks exercise as a fatigue management strategy, evidence suggests that both resistance and aerobic exercise can significantly reduce cancer-related fatigue [52, 53]. Importantly, structured exercise interventions that incorporate progressive resistance training may be more sustainable for CLL patients, given that aerobic training alone can sometimes exacerbate fatigue symptoms in hematological cancers [15].

Interestingly, research suggest that CLL patient may not accurately perceive declines in their physical function, as they tend to be more responsive to improvements than deterioration when completing QoL questionnaires [54]. Several longitudinal studies indicate that CLL patients rate their physical functioning similarly to healthy individuals, despite having significantly lower objective fitness levels [55, 56].

For instance, Artese et al. [30] found that CLL patients with an average body fat percentage of 31% and a VO_{2max} of 26.7 ml/kg/min reported high self-rated scores for Physical Well-Being (27/28) and Functional Well-Being (25.7/28). Similarly, in a study by Furzer et al. [33], patients with 34.6% body fat and a VO_{2max} of 16.10 ml/kg/min reported a Functional Assessment in Chronic Therapy – General (FACT-G) score of 82/108. Additionally, a larger study including CLL patients by Courneya et al. [15] reported a Functional Assessment in Chronic Therapy - Anemia (FACT-An) score of 147.1(188) in a group with an average body fat of 32.6% and a VO_{2max} of 25.4 ml/kg/min.

EVALUATION CONSIDERATIONS IN CLL

The lack of standardized protocols for physical fitness evaluation in CLL research has led to inconclusive findings and weak evidence strength. While studies support intensive endurance exercise [37], resistance training [38] and High-Intensity Interval Training [39], methodological variability across studies limits the reliability and comparability of results.

Cardiovascular assessment protocols vary widely, including differences in:

- Equipment (Treadmill or Recumbent Cycle ergometer)
- Intensity markers (e.g., 90% Oxygen Volume (VO₂) reserve, 90% Heart Rate (HR) reserve, 65% maximal short exercise capacity, HR maximal, VO₂ peak)
- Duration (ranging from 8-minute intervals to 45-minute continuous sessions)
- Recovery periods (30-90 seconds active recovery vs. no recovery)

Muscular assessment protocols also lack uniformity, differing in:

- Resistance mode (machines, dumbbells, or bodyweight exercises)
- Intensity (e.g., 70% 1-RM for maximal reps, 80% 1-RM for 6-8 reps, 65-80% 1-RM)
- Volume (ranging from 2 sets of 10 reps to 2-3 sets of 6-8 reps or 2 sets of 20 reps)
- Recovery time (either described as ≥ 90 seconds or unspecified)

To improve reproducibility and accuracy, gold-standard assessment tools should be prioritized, including:

- Isokinetic Dynamometers for muscular strength evaluation
- Cardiopulmonary Exercise Test (CPET) with Electrocardiogram (ECG) for cardiac and pulmonary response
- Dual-energy X-ray Absorptiometry (DEXA) for body composition analysis

For strength-based training evaluation, continuous monitoring of volume and progression is crucial, with One-Repetition Maximum (1-RM) testing commonly used. However, some concerns have been raised. Wood et al. [57] cautioned that American College of Sports Medicine (ACSM) guidelines for older adults recommend moderate intensities, questioning the safety of 1-RM testing in untrained populations. Additionally, they suggest that lifting above 80% of 1-RM may increase the risk of adverse events (AE) in older individuals. However,

these claims rely on outdated ACSM recommendations and lack strong empirical backing, yet they continue to influence research negatively.

To establish consistent and safe exercise guidelines for CLL patients, the implementation of the American College of Sports Medicine [24] Frequency, Intensity, Time, Type, Volume, Progression (FITT-VP) principle is essential, with further clarification required for its application in this population.

OBJECTIVES AND HYPOTHESES

Our aims in this thesis are to:

1- Characterize the physical aptitude (cardiac and respiratory tests, strength tests, body composition) and physical activity patterns of CLL patients (using accelerometry).

2- Identify the benefits of a strength-based resistance training on CLL patients:

H1 – Strength training contributes to gains in muscular mass;

H2 – Overall quality of life is increased, in comparison to control group;

H3 – Physical activity patterns are increased during and after protocol intervention, with CLL patients becoming more active (before exercise protocol, using accelerometry, test 1 week of physical activity to compare at the end of study).

3- Consolidate knowledge about exercise prescription in CLL patients, verifying feasibility of the strength-based protocol, and patients' subjective effort perception.

CHAPTER 2 – EXPERIMENTAL WORK

EXPERIMENTAL WORK

The ADRENALINE (rAndomiseD contRollEd cliNical triAL of exercise as Intervention in chroNic lymphocytic leukEmia) is a blind randomized controlled trial (RCT).

Patients who were recruited for the study had a confirmed diagnosis of chronic lymphocytic leukemia according to the International Workshop on CLL Guidelines [20]. Eligible participants were aged 45-80 years, had no history of prior CLL treatment, and were physically capable of walking on a treadmill, cycling on an ergometer, and using weight machines. Eligibility was further confirmed through initial assessments, including Cardiopulmonary Exercise Test for cardiac health and a dynamometer test for muscular function. Patients also provided written informed consent and committed to adhering to the exercise program.

Exclusion criteria included prior immunochemotherapy or targeted therapies for CLL, ongoing participation in structured exercise program, disease progression warranting treatment initiation (per the International Workshop on CLL Guidelines), the presence of other primary malignancies, and significant comorbidities preventing exercise (e.g., severe cardiovascular, respiratory, renal, hepatic, neurological, or osteoarticular conditions). Individuals unable to adhere to the training protocol were also excluded.

All patients underwent clinical assessment before completing health-related quality-of-life questionnaires, fitness evaluations (including anthropometry and body composition), maximal strength testing using a dynamometer, and maximal exercise stress electrocardiogram with spirometry on a cycle ergometer. Daily physical activity was monitored using accelerometers for seven consecutive days, requiring a minimum of 10 hours of data collection per day.

The study protocol was approved by the Ethics Committees of São João University Hospital Center and the Faculty of Sport at the University of Porto (references CE 431-19 and CEFAD 14_2024, respectively). The trial was registered at ClinicalTrials.gov (NCT06396611).

Figure 1 presents an overview of participants characteristic, variables and instruments used in each paper of this thesis. Detailed methodological procedures are available in the materials and methods section of each respective paper.

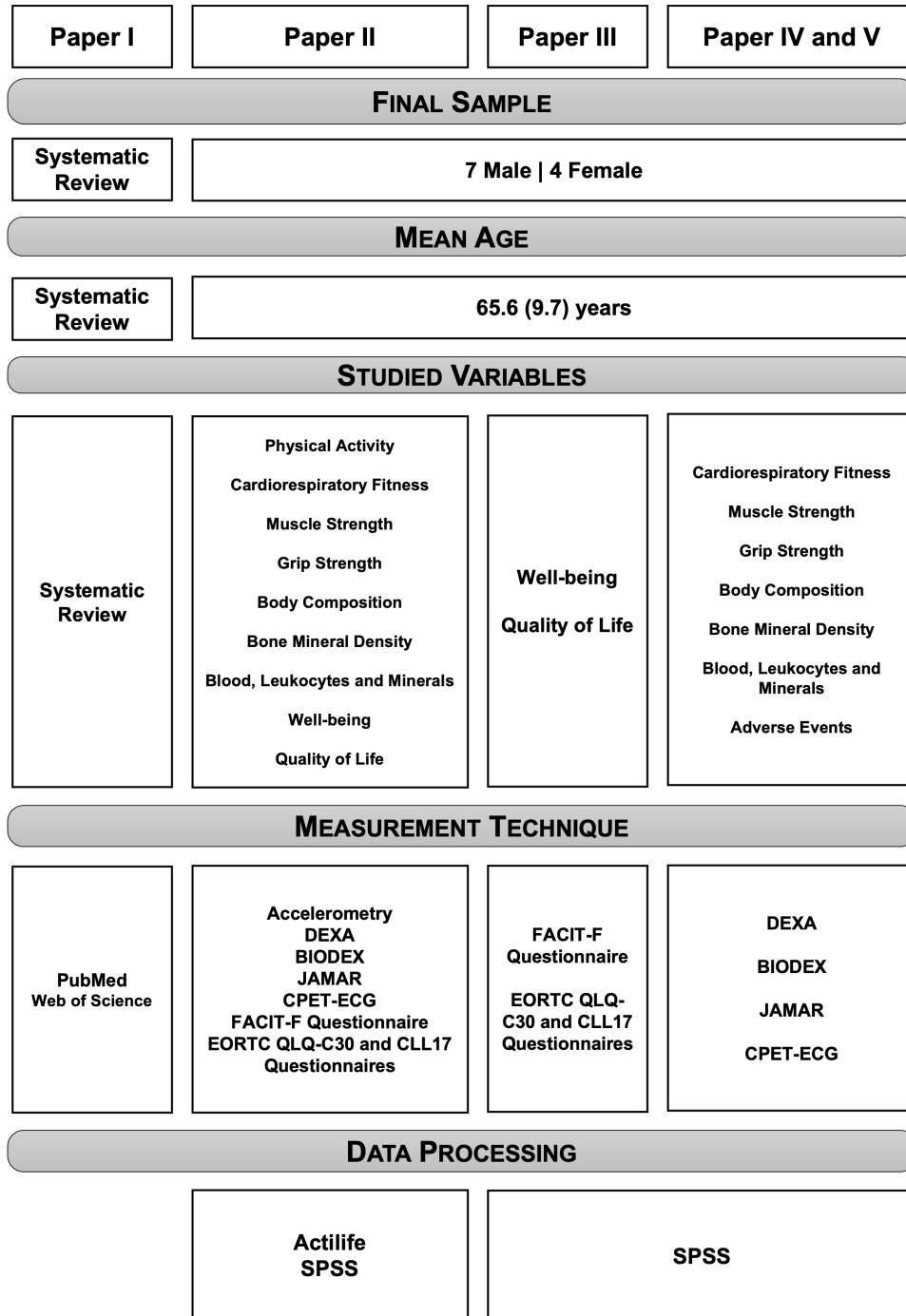


Figure 1: Experimental work diagram.

EVALUATION PROTOCOLS

At each time point, baseline evaluation (T0) and 16-week evaluation (T1), patients were evaluated: i) anthropometric, body composition measures and bone mineral density; ii) strength evaluation (dynamometry for lower limbs, handgrip for upper limbs for both patients groups, and one-repetition maximum for the whole body strength only in intervention group); iii) cardiac and respiratory evaluation CPET on a cycle ergometer with a stress electrocardiogram with spirometry; iv) objective assessment of physical activity with accelerometer.

The CPET performed to assess cardiorespiratory fitness and potential cardiovascular and cardiorespiratory limitations follows international guidelines concerning standardization and interpretation strategies [58]. The CPET is performed on a cycle ergometer Lode Corival CPET (Lode, The Netherlands) under supervision of a sports physician. Throughout the test, the ECG, saturation and blood pressure are monitored, and heart rate and gas exchange variables are recorded continuously and averaged at 30 seconds intervals (COSMED Quark CPET, Rome, Italy). The protocol comprehends 2 minutes rest without movement for respiratory adaptation, followed by a 3-minute warmup unloaded phase with 60 revolutions per minute (RPM) and zero watts to adapt to the cycling movement and warm-up. After the warm-up, begins the incremental exercise phase, with each step incrementing 15 watts per minute until 85% heart rate is achieved or other standardized criteria for stopping [58]. After the incremental phase ends, the recovery phase initiates with 2 minutes of active cool down with unloaded pedaling followed by 3 minutes of passive cool down without movement [59]. The highest recorded oxygen uptake (VO_{2peak}) was used as an indicator of cardiorespiratory fitness. VO_{2peak} represents the highest oxygen consumption achieved during the test rather than a true maximal effort. This approach is commonly used when maximal exertion is not feasible, particularly in clinical populations.

Upper extremity muscle strength was assessed using a grip strength dynamometer JAMAR PLUS (Sammons Preston, Chicago IL), calibrated according to standard protocols, and using 3 trials for each hand, with a contraction of 2-4 seconds, and with 30 seconds interval between attempts [60,

61]. For lower muscle strength it was used an Isokinetic Dynamometer BIODEX 850-000 System 4 Pro (Biodex Medical Systems, USA) following the standard procedures recommended by standard protocols, measuring Extension/Flexion of the dominant knee, and using the protocol Concentric/Concentric with 60 deg/s speed to evaluate strength, with 5 repetitions warmup and 3 repetitions for maximal effort after 1-2 min rest between warmup and test [62]. To assess whole body strength it was used the ACSM 1-RM protocol [24] using the baseline exercises prescribed for the protocol intervention (Leg Press, Leg Curl, Leg Extension, Chest Press, Latissimus Front Row, Shoulder Press, Triceps Extension, and Biceps Curl). Due to inexperienced patients in physical activity, the indirect measurement of 1-RM was implemented after 3 weeks of adaptation to the intervention protocol permitting familiarization with exercise machines/equipment. From a clinical perspective, if prediction aims to provide safe 1-RM values for patients starting a resistance training program, the Epley prediction equation [$1RM = (0.033 * \text{number repetitions} * \text{weight lifted}) + \text{weight lifted}$] is one of the equations that evidenced the lowest average error and highest relative accuracy while expecting a higher percent of mean 1-RM for all exercises compared to direct protocol [57]. The load used in each exercise was calculated according to indirect 1-RM evaluation, measured after an adaptation period of 3 weeks, and with subsequent evaluations every 5 weeks, while controlling for individual responses to exercise such as technique, breathing, rate of perceived effort, and volume of repetitions during progression.

Data collection of height and body mass was determined by standard anthropometric methods (SECA 899 digital floor scale and SECA 217 stadiometer). Body mass index was calculated from the ratio weight/height² (Kg/m²). Body composition and bone mineral density was 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 hip bone mineral density (from non-dominant hip side).

Objectively assessed levels of PA were acquired using the GT9XLink accelerometer (Actigraph, USA), to collect data on the PA patterns of

participants, over a period of seven consecutive days, with a minimum of 4 weekdays and 1 weekend day and 10 hours of daily assessment. Accelerometers were worn on the dominant side over the hip and aligned with the kneecap, and patients were instructed to use them all day long except during baths, water sports, potential hazard activities, or during sleep. A report sheet for the description of daily accelerometer usage was also provided [63].

Clinical parameters were collected by clinicians during routine hematology consultation at the time of evaluations in T0 and T1. These evaluations comprised standardized clinical assessments, including exercise- and disease-related symptoms/complications, physical exams (for skin pallor, palpable cervical lymph nodes, and hepatomegaly), and clinical exams. Routine clinical analytical parameters included hemogram and blood chemistry (hepatic, renal, mineral and metabolic markers). The CLL staging index (RAI and BINET) [30, 31], and the Eastern Cooperative Oncology Group Performance Scale (ECOG) [32] were used, because in clinical practice of participating hospital, the genetic characterization of the disease (needed for the CLL International Prognostic Index (CLL-IPI)) is only asked when the disease criteria evolve to the treatment phase.

At each time point, two self-reported questionnaires were implemented to assess clinical status, 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) with the Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL17).

The FACIT-F [64] is a 27-item compilation of general questions divided into four primary Well-Being domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being, which is appropriate for use with cancer patients to assess fatigue. The FACT-General (FACT-G) score is 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 is determined by adding the FACT-G total to 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 [65]. 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, incorporating 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 high level of symptomatology or problems [65].

PAPER I

RESEARCH

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High-intensity interval training and strength conditioning in patients with chronic lymphocytic leukemia: a systematic review



Pedro M P Cunha^{1*}, Ricardo J Ribeiro^{2,3,4,5}, Andreia Pizarro¹, Jorge Mota¹ and Jose C D Ribeiro¹

Abstract

Background This systematic review explores the impact of physical exercise on chronic lymphocytic leukemia (CLL) patients' physical fitness, immunologic, and quality of life outcomes.

Methods Eligible studies were searched in PubMed and Web of Science up to February 2024 and were included if they involved participants in adult age, with confirmed CLL diagnose, using physical activity protocols with study design holding intervention protocols, clinical trials, or quantitative data reporting. Bias was assessed with ROBINS-I and RoB2 tools from Cochrane. The results are presented in tables and figures. A qualitative synthesis describes the main outcomes of the included studies. Meta-analysis was not performed due to significant heterogeneity.

Results This review identifies 92 studies, with 6 meeting the inclusion criteria, with a sample size of 323 patients. These studies focus on cardiovascular training combined with resistance training (four studies with total sample of 177 patients), continuous cardiovascular training (one study with 122 patients), and endurance resistance training (one study with 24 patients), highlighting the importance of physical exercise in CLL patients before treatment, with significant improvements in physical fitness and immunologic parameters on intervention groups.

Discussion The paucity regarding exercise influence on CLL, with small samples of patients in pilot study experiments, noted that exercise plays a vital role in improving physical fitness and immunologic parameters. However, none addressed strength training, which is known as one of the best options to increase muscular mass in physical activity interventions. The inconsistency of intervention and/or evaluation protocols ravel the advice of exercise and medical professionals on prescribing different modes of exercise, improving compliance with the prescribed exercise program, and determining which intervention in the context of exercise prescription should be used. More studies are needed to evaluate the impact of physical activity on the health-related quality of life and life span of the CLL patient.

Trial registration PROSPERO CRD42023464877.

Keywords Physical activity, Exercise, Resistance training, Quality of life, Chronic lymphocytic leukemia, Oncology

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Introduction

Chronic lymphocytic leukemia (CLL) is a type of blood cancer described as a neoplasm composed of monomorphic small mature B cells that co-express CD5 and CD23 surface marker antigens [1], which leads to a progressive accumulation of monoclonal B lymphocytes [2]. In the diagnosis of CLL, CD5, CD19, CD20, CD23, surface or cytoplasmic kappa, and lambda light chains are regarded as essential markers, and CD10, CD43, CD79b, CD81, CD200, and ROR1 as additional targets useful in the differential diagnosis from other small B-cell lymphomas/leukemias [3].

CLL is the most common chronic leukemia among adults in Western countries, making up 25 to 35% of all leukemia cases in the USA [2, 4]. In Europe, leukemia has risen to become the eighth leading cause of cancer-related deaths since 2019, with an increasing tendency [2, 5]. With a male preponderance CLL represent 7% of non-Hodgkin lymphomas [1, 2], most frequently diagnosed between 65 and 74 years old, but individuals 45–64 already represent more than 30% of newly diagnosed cases [4]. Incidence rates are lower in the Asian and Black ethnic groups, compared with Caucasian due to genetic predisposition, environmental factors, healthcare disparities, or age distribution [5].

There are CLL-related mortality attributable risk factors that include elevated body mass index, occupational exposure to benzene, formaldehyde and to cigarette smoke [5]. However, when analysing data from low Social-Demographic Index areas, high body mass index showed a significant upward trend [5]. As the disease progresses, symptoms arise and include fatigue, shortness of breath during regular physical activity, lymph node enlargement, low-grade fever, unexplained weight loss, night sweats, feeling of fullness (related to enlarged spleen or liver) or infection of the skin, lungs, or sinuses [5, 6]. These symptoms impair physical fitness performance and daily activities, reducing the health-related quality of life. The diagnostic workup includes microscopic examination, immunophenotyping, fluorescence in situ hybridization (FISH), determination of CD38 and ZAP-70 expression, and the mutational status of IgHV genes in blood and/or bone marrow [6].

The most promising targeted therapies, including BCL-2 inhibitors and Bruton tyrosine kinase (BTK) inhibitors, are unable to offer a cure for CLL, while representing an economic burdensome with severe adverse events [5]. It is during the phase of active surveillance that physical activity may have an important role, putatively delaying symptoms and disease progression.

In chronic lymphocytic leukemia, prognostication has been supported by the Rai and Binet clinical staging systems, which rely on physical examination and standard

laboratory tests [7, 8]. However, they lack genetic and molecular testing, giving rise to the CLL International Prognostic Index (CLL-IPI) which emerged as a more comprehensive prognostic framework [9–12] that combines genetic, biochemical, and clinical parameters into a five-categories prognostic model [13].

A less favourable prognostic outcome is associated with blood lymphocyte doubling time, complex karyotypes (Del 17q and Del 11q), expression of CD38, CD49d, and ZAP-70, and mutations on *TP53*, *NOTCH1*, and *SF3B1* genes [14, 15].

The survival of CLL cells strictly depends on a permissive and nurturing microenvironment [16, 17], which produces various proteins (chemokines, cytokines, and angiogenic factors) that interact with leukemic cells via surface receptors or adhesion molecules to support their survival and aggressiveness. On the other hand, the immune response against leukemic cells is compromised due to “exhaustion” of the cytotoxic T cells, and a suppressive immunological synapse formation with antigen-presenting cells [18]. Furthermore, natural killer (NK) cells acquire a phenotype that yields reduced ability to lyse CLL cells due to lack of cytoplasmic granules and impaired establishment of immunological synapse [16].

Intensive endurance exercise is known to induce lymphocyte apoptosis, which may affect immune function [19]. Regular resistance exercise decreases oxidative stress by enhancing antioxidant enzyme activity, which may lead to attenuated apoptosis-related proteins, such as caspase-3, BAX and BCL-2 expression [20]. Noteworthy, high-intensity interval training (HIIT) studies suggest that it is able to delete mainly differentiated T cells known to affect immunity to control latent infections, in contrast with continuous exercise that impacts survival of undifferentiated T cells, which might affect immunosurveillance and cytotoxic ability [21]. In recent years, scientific evidence revealed that skeletal muscle role in human physiology goes beyond the locomotor unit responsible for movement and posture, to include a major part on regulation in energetic and metabolic processes involved in the regulation of glucose and lipid metabolism, immunomodulation, anti-inflammatory, and inhibition of migratory mononuclear cells (such as macrophages and T-cells) towards the inflamed microenvironment (such as adipose tissue of obese persons) [22–24]. Other studies associated exercise-induced myokines production with the ability to increase immune-mediated cytotoxicity and the tumour infiltration by immune cells [25], growth and differentiation of muscle tissue promoting hypertrophy, providing energy substrate for contracting muscle fibres, activating mechanisms of energy production during fasting and improving tissue sensitivity to insulin, stimulating thermogenesis, glucose uptake by myocytes,

and also contributing to an increase in bone mineral density [26]. Literature also demonstrated activation of NK cells after physical exercise [27, 28], with strenuous exercise increasing NK cytotoxicity during exercise, followed by a profound effect with 40% depression of the NK cell count even after cessation of exercise for as long as 7 days [29], with maximal exercise of large muscle groups leading to higher immune responses during repetitive bouts and elevated concentrations of leukocytes, neutrophilic granulocytes, and lymphocytes, resulting in leukocyte concentrations and the NK cell activity enhanced not only during exercise bouts, but also on the day after exercise [30]. A recent meta-analysis disclosed NK cell activity is largely elevated by acute physical exercise, with more significant effects in endurance versus resistance exercise and increasing with exercise intensity, providing solid evidence that elevated NK cell activity associated with exercise returns to baseline during the first 1–2 h of recovery, but not below the pre-exercise values, a proof that the functional change in NK cell activity exists independently from the quantitative change in NK cell count [31].

To address this complex landscape, many authors advocate for clarification of the effects of exercise on CLL, through the exploration of various exercise paradigms, including type, duration, and intensity, using state-of-the-art methods to detect immunological changes [32, 33]. In this review, we endeavour to review and comprehensively describe existing physical activity protocols for CLL patients and analyse their effects. Additionally, we aim to identify potential gaps in best practices related to the evaluation of physical activity, lifestyle patterns, and immunologic outcomes. Our findings will not only guide future research but also pave the way for innovative interventions in this crucial area.

Methods

This systematic review was elaborated based on the methods outlined in the Cochrane handbook [34], and we also adhere to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [35] reporting standards. The purpose of this systematic review was to identify the relationship between physical activity (particularly HIIT and resistance training) and chronic lymphocytic leukemia, regarding fitness, health-related quality of life and feasibility, and immunologic parameters.

Literature search strategy

This study was registered at PROSPERO database (CRD42023464877). Afterwards, automated searches were made in the PubMed and Web of Science databases up to February 2024, with no restriction on the

initial date period. Free text terms were searched using the Boolean operators AND/OR applied to the title or abstract:

PubMed search key: ((physical exercise) OR (aerobic training) OR (strength training) OR (exercise) OR (motor activity) OR (physical fitness) OR (physical activity) OR (intensive strength training) OR (resistance training) OR (plyometric exercise) OR (exhaustive exercise) OR (physical endurance) OR (exercise tolerance) OR (aerobic fitness) OR (strength endurance training) OR (strengthening exercise) OR (HIIT) OR (high intensity exercise) OR (high intensity interval training)) AND ((CLL) OR (Chronic lymphocytic leukemia) OR (leukemia)).

Web-of-Science search key: TS=((physical exercise) OR (aerobic training) OR (strength training) OR (exercise) OR (motor activity) OR (physical fitness) OR (physical activity) OR (intensive strength training) OR (resistance training) OR (plyometric exercise) OR (exhaustive exercise) OR (physical endurance) OR (exercise tolerance) OR (aerobic fitness) OR (strength endurance training) OR (strengthening exercise) OR (HIIT) OR (high intensity exercise) OR (high intensity interval training)) AND TS=((CLL) OR (Chronic lymphocytic leukemia) OR (leukemia)).

In the case of Web-of-Science, we opted for field tag topic (TS) because it searches for topic terms in the title, abstract, and author keywords, making the search broader.

Articles were systematically screened (from September 2023 to February 2024), resulting in 92 hits after duplicates removal.

The eligibility criteria for this review included any study investigating exercise-based interventions in adult patients with chronic lymphocytic leukemia, following criteria according to population, intervention, comparison, outcomes and study design (PICOS) guidelines: Participants must be in adult age, with confirmed CLL diagnose; intervention must be with physical activity protocols; comparison between control group, or between different physical activity approaches; outcomes are the attributable risk in cancer or molecules numbers progression, overall quality of life and feasibility, or changes in morphologic, biologic, immunologic or physiologic characteristics; study design must held intervention protocols, clinical trials, or quantitative data reporting.

There were no restrictions regarding study design, with both clinical trials (randomized or non-randomized) and cohort studies being included. The focus was on studies evaluating the effects of exercise on clinical or functional outcomes in this population.

Articles must be written in English and available in full text. Gray literature was not included, but a systematic screening of selected papers bibliography was conducted to search for other articles that could be absent on our search. For this review we focused only on chronic lymphocytic leukemia. Variants, such as acute lymphocytic leukemia, myeloid leukemias, and lymphomas, were not considered due to differences in affected cells. No other inclusion or exclusion criteria were applied.

Selection process

Two authors independently screened the retrieved records. Due to scarce literature retrieved, and the agreement in the manuscripts to include, there was no need for 3rd investigator for arbitrage. Automated removal of duplicates was performed using EndNote™ 20.3 for Mac (Clarivate™) but further manual removal was also used.

Data extraction and methodological study quality assessment

The main characteristics of participants (age, gender, CLL staging described as Rai or CLL-IPI staging) and main study outcomes (quality of life, feasibility, exercise and biologic/physiologic outcomes variables), as well as their interaction, were identified and appraised.

Differences between baseline and post-protocol evaluation are described as mean $\pm$ standard deviation, in some cases mean (range), or as % of change compared to baseline (with mean $\pm$ SD also). On our tables, we opted to highlight the non-statistical differences between control and interventions groups, to enlighten the path for future investigations to fulfil the gaps of current knowledge.

The scientific quality of the included randomized clinical trials and observational studies was assessed independently by two reviewers using respectively CONSORT [36] and STROBE [37] checklist, as they are designed to ensure comprehensive reporting of observational research. Although CONSORT and STROBE are reporting guidelines, we used it as a proxy for assessing the completeness and transparency of reporting studies. In cases of discrepancies, a consensus-based final score was attributed after discussion. It was attributed a score of 0 (if do not meet the criterion) or 1 (if meets the criterion) for every item of the CONSORT and STROBE checklist. The global score was then converted into a percentage qualifying into 3 categories: A, study meets more than 80% of the criteria; B, study meets 50–80% of the criteria; and C, study meets less than 50% of the criteria [38].

Additionally, the risk of BIAS was assessed based on study type. For non-randomized cohort studies, the risk of bias in non-randomized studies of interventions (ROBINS-I) tool was applied [39], which evaluates bias across seven domains, including confounding, selection

bias, and outcome measurement. For randomized trials, the Risk of Bias 2 (RoB 2) tool was used [40], which focuses on potential biases related to the randomization process, deviations from intended interventions, missing data, outcome measurement, and selection of reported results.

Results

For this systematic review, a total of 1853 studies were identified within the search criteria. However, after screening titles and abstracts and applying inclusion/exclusion criteria (adult age patients, CLL malignancy, physical activity intervention protocols, after duplicates removal and excluding review articles) only 6 relevant articles were retrieved for full-text appraisal. Literature also shows associations of exercise in paediatric ages, but as the response to exercise is different in adults, those studies were disregarded while screening titles. One other study [41] was not included because it addressed a study-case with an unstructured exercise intervention protocol, without the assessment of initial and end physical fitness outcomes. Among the selected studies, 3 studies were randomised clinical trials (RCT's) with physical activity (PA) intervention and without any prior treatment to CLL disease; 2 studies were pilot studies with CLL patients, and 1 interventional study with physical activity intervention but with previous or ongoing CLL treatment.

In the studies included, physical activity with different types and intensities (aerobic, strength, resistance and HIIT) were objectively assessed. Because CLL exercise intervention remains an unclear field of expertise, literature addressing PA influence in CLL patients (exclusively) disease parameters is rare (only one interventional study and two small Pilot Studies with 24 patients [32], 16 patients [33], and 15 patients [42]), reason that led us to select for inclusion any exercise intervention study that included CLL adult patients in the sample [43–45]. Figure 1 schematize the search flow diagram.

Table 1 summarizes the quality assessment of each study, according to CONSORT [36] and STROBE [37] guidelines (as they are designed to ensure comprehensive reporting of observational research, they were used as a proxy for assessing the completeness and transparency of reporting studies); the risk of BIAS was accessed with ROBINS-I tool for non-randomized interventions [39], and the RoB 2 tool for randomized controlled trials [40]. Although study quality of the selected studies were graded A or B, the authors did not include an estimation of BIAS direction and magnitude, for example, regarding differences in the medical surveillance of participants, physical activity surveillance, follow up of daily activities, and only focused on details about additional data

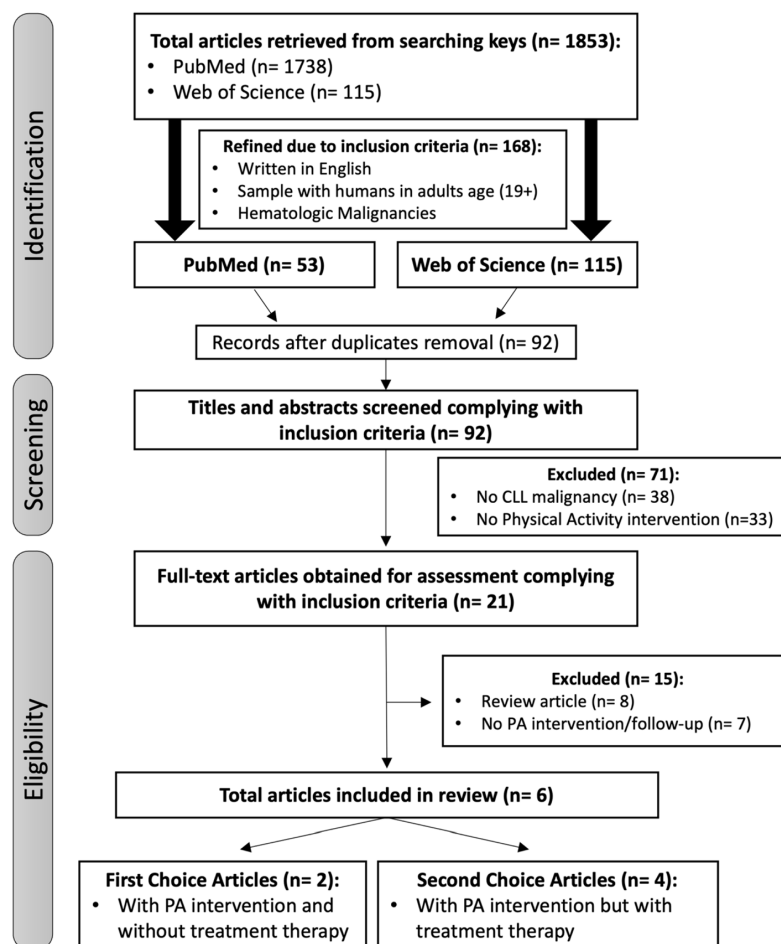


Fig. 1 PRISMA flow diagram

they collected to tackle this problem. The most impactful domains in non-randomized studies for overall risk of BIAS were BIAS due to confounding, while in randomized studies were BIAS due to randomization process and in measurement of outcomes. One study from Crane et al. [32] revealed not only Serious risk of BIAS on controlling confounding, but also in classification of intervention, deviation from intended interventions, missing data, and selection of reported result. Knowing the limitations of a home-based approach, it is not clear how the research team controlled the implementation of exercise protocol between groups, and even the BIAS of the selected outcomes (6 min walk test, timed up-and-go, chair stand test, and FACT questionnaires) could be critically contaminated upon measuring; and without a

control group to compare to. For primary outcome VO₂ assessment, most of the studies have used standardized protocols or gold standard physical evaluation equipment's to reduce BIAS, but regarding muscular evaluation, only Person et al. [45] have attempted that BIAS reduction. In all remaining studies were used evaluation tests subjected to major risk of BIAS, mainly due to missing measurement of outcome BIAS control. By using non gold standard physical evaluation while applying questionnaires (inherently subjective) to evaluate secondary outcomes like leisure time activity, physical and functional well-being, the risk of BIAS is greatly augmented.

From the 326 participants included in the selected studies, only 22.1% of the sample corresponds to CLL patients, 54.6% refers to non-Hodgkin's lymphoma, 19.0%

Table 1 Study quality according to CONSORT [36] and STROBE [37] guidelines; and risk of bias according to ROBINS-I tool [39] for non-randomized interventions and RoB 2 [40] for randomized clinical trials. HL Hodgkin's lymphoma, NHL non-Hodgkin's lymphoma

Study	Pathology	STROBE Study quality	ROBINS-I BIAS due to confounding	BIAS in selection of participants	BIAS in clas- sification of interventions	BIAS due to deviations from intended inter- ventions	BIAS due to missing data	BIAS in meas- urement of outcomes	BIAS in selection of reported result	Overall risk BIAS
Crane et al. (2023)	CLL	B	Serious	Low	Moderate	Serious	Moderate	Low	Serious	Serious
Artese et al. (2022)	CLL	B	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Macdonald et al. CLL (2021)	CLL	A	Low	Low	Low	Low	Low	Low	Low	Low
		CONSORT	RoB 2							
		Study quality	BIAS due to randomization process	BIAS due to deviations from intended inter- ventions	BIAS due to missing out- come data	BIAS in meas- urement of outcomes	BIAS in selection of reported result			
Persoon et al. (2017)	Multiple myelomaA and lymphoma		Low	Low	Low	Some concerns	Low	Some concerns		
Furzer et al. (2016)	HL, NHL and mye-B loma		Some concerns	Low	Low	Low	Low	Some concerns		
Courneya et al. (2009)	HL and NHL	A	Low	Low	Low	Low	Low	Low		

refers to multiple myeloma, and 4.3% refers to Hodgkin's lymphoma. Most of the studies include patients with median age around 50 years old, with body fat above the limits for age [46], and BMI in overweight range. Time for inclusion after diagnosis ranged between 2.1 ± 2.6 and 7.9 ± 9.1 years. In the two studies that engaged CLL patients without previous treatment [33, 42], patients recruited were in Rai stage 0 or I (83.3% of patients in intervention group and 80.0% in control group, remaining percentage are described as unknown) or CLL-IPI stage 0–1 and 2–3 (50.0% of patients in intervention group and 30.0% in control group, remaining percentage are described as unknown). In the remaining studies, this information is not addressed by the authors. Table 2 summarizes the baseline overview of the population.

The duration of intervention was predominantly 12 weeks with 2–3 training days per week, except for the Persoon et al. [45] intervention which lasted 18 weeks, and Crane et al. [32] that lasted 16 weeks. The main outcomes were associated with health-related quality of life questionnaires (reported in 4 studies), objective measured physical activity (reported in 4 studies), and immune characteristics (reported in 2 studies). On physical activity outcomes, the most analysed parameter was the cardiovascular outcomes, but with different characterizations. Crane et al. [32] used a home-based exercise program using 16 combinations of exercises but do not clearly describe the frequency, intensity, time and type (FITT) principles of exercise prescription. Artese et al. [42] did not present data about this parameter but concatenated to another study [33] where data was collected from. Equipment's used were treadmill and upright or recumbent cycle ergometer. Regarding muscular parameters, Courneya et al. [43] did not present any outcome, while others presented data regarding muscle strength, muscle endurance, or maximal torque. It was also assessed the physical activity with accelerometry technology in Persoon et al. [45], and leisure time activity (by questionnaire) as well as bone mineral density in the study by Furzer et al. [44]. Table 3 presented the characteristics of the included studies with physical intervention.

Although meta-analysis was not feasible due to the heterogeneity of interventions, populations, and outcome measures across the included studies, the following tables summarize key findings and trends observed in the data. The results are presented focusing on physical parameters and health-related quality of life (HRQoL) outcomes, with particular attention to the effects of the interventions.

Regarding physical parameters, the included studies report a variety of physical outcomes, including VO₂peak, muscle strength, body composition, and functional tests (e.g., 6-min walk test, timed up and go).

Across studies, most results show improvements in the intervention groups compared to control, though not all reach statistical significance. Macdonald et al. [33] and Persoon et al. [45] observed significant improvements in VO₂ peak in the intervention groups compared to controls (from 21 ± 04 to 22 ± 07 L/min and from 24 ± 7 to 28 ± 7 mL/kg/min, respectively), indicating enhanced aerobic capacity after HIIT and resistance training. Several studies noted increases in muscle strength, particularly in leg and chest press exercises. Even Crane et al. [32] home-based exercise intervention reported an increase from 112 ± 37 to 153 ± 46 kg in leg strength. These improvements suggest positive adaptations to both aerobic and resistance exercise protocols. Regarding body composition, there were no significant changes in body fat percentage or lean mass in most studies. This indicates that while functional and aerobic capacity improved, body composition remained relatively stable across interventions. Table 4 summarizes the objectively assessed physical parameters for each study.

Regarding health-related quality of life (HRQoL), a wide range of outcomes was reported using multiple instruments [47–52] such as the EORTC QLQ-C30 [53], symptom assessment scale [54], and functional assessment of cancer therapy [55]. Across studies, improvements were noted, particularly in physical functioning, role functioning, and fatigue, though again, not all differences were statistically significant. Crane et al. [32] reported significant improvements in fatigue scale (from 37 (IQR, 27.75; 45.75) to 45 (IQR, 39.50; 47.75)). These findings highlight the potential of structured exercise interventions to enhance both physical functioning and overall QoL in cancer survivors. Furzer et al. [44] noted positive trends in the FACT-Lym total score (from 81.2 ± 12.8 to 90.2 ± 10.1), suggesting improvements in both physical and emotional well-being following aerobic and resistance exercise training. Courneya et al. [43] also found significant statistical differences in FACT-An total score, and in happiness scale and depression scale, reflecting the importance of physical activity in mental health and HRQoL well-being. Table 5 summarizes the HRQoL outcomes.

While statistical significance was not reached in all studies, particularly due to small sample sizes, the effect sizes (Hedges' *G*) suggest that moderate improvements were achieved in most physical and QoL outcomes. The results in bold within the tables indicate non-significant findings, yet effect sizes suggest potential clinical relevance, especially in aerobic capacity and muscle strength.

Although meta-analysis was not performed, the overall trends observed in these studies support the effectiveness of combined aerobic and resistance exercise interventions in improving aerobic capacity, muscle strength, and

Table 2 Baseline overview of the population. Data are presented as mean $\pm$ standard deviation or as median (range). HIIT high-intensity interval training, BMI body mass index

	Crane et al. (2023)		Artese et al. (2022)		Macdonald et al. (2021)		Persoon et al. (2017)		Furzer et al. (2016)		Courmeya et al. (2009)	
	Intervention protocol	Baseline	Intervention protocol	Control	Intervention protocol	Control	Intervention protocol	Control	Intervention protocol	Control	Intervention protocol	Control
Intervention characteristics	Home-based aerobic only or aerobic with resistance exercises		HIIT	Usual care	HIIT	Usual care	HIIT + resistance Ex	Usual care	Aerobic + resistance Ex	Usual care	Aerobic exercise training	Usual care
Demographics												
Age (yrs)	63.04 $\pm$ 8.67		62.2 $\pm$ 9.4	66.5 $\pm$ 7.1	63.9 $\pm$ 10.8	66.5 $\pm$ 7.1	53.5 (20–67)	56 (19–67)	48.2 $\pm$ 12.3	49.6 $\pm$ 14.1	51.2 (18–77)	53.5 (18–80)
Sex (m/f)	16/8		3/6	4/2	4/6	4/2	32/22	37/18	18 (unknown m/f ratio)	19 (unknown m/f ratio)	37/23	35/27
BMI (kg/m ²)	27.4 $\pm$ 5.07	27.8 $\pm$ 4.83	27.3 $\pm$ 7	25.4 $\pm$ 3.1	27.3 $\pm$ 6.6	25.4 $\pm$ 3.1	25.6 $\pm$ 4.6	25.1 $\pm$ 3.6	24.2 $\pm$ 3.3	25.8 $\pm$ 4.7	27.4 $\pm$ 4.5	26.7 $\pm$ 5.4
Lean mass (kg)					48.2 $\pm$ 12.4	53.7 $\pm$ 10.5			48.34 $\pm$ 10.33	46.85 $\pm$ 10.21	52.4 $\pm$ 10.9	49.9 $\pm$ 10.0
Body fat (%)					37.7 $\pm$ 10.3	31.0 $\pm$ 10.3			29.79 $\pm$ 9.20	34.56 $\pm$ 11.16	32.6 $\pm$ 9.9	32.6 $\pm$ 10.9
Disease characteristics												
Chronic lymphocytic leukemia (N/total sample)	24/24		9/9	6/6	10/10	6/6	Unknown/54	Unknown/55	Unknown/18	Unknown/19	4/60	10/62
Time since diagnosis (yrs)			7.9 $\pm$ 9.1	4.6 $\pm$ 4.3	7.3 $\pm$ 8.7	4.6 $\pm$ 4.3					2.1 $\pm$ 2.6	2.8 $\pm$ 3.3
Prior treatment (N/total sample)	9/24											
Ongoing treatment (N/total sample)	12/24											
Rai stage (N)												
0	7		6	4	7	4					16	18
I+	17		1	1	1	1					43	43
Unknown			2	1	2	1					1	1
CLL-IPI (N)												
0–1					2	2						
2–3					1	1						
Unknown					7	3						

Table 3 Characteristics of the included studies with intervention. ND not described, MSEC maximal short exercise capacity (using steep ramp test), 1RM 1 repetition maximum, HRR heart rate reserve, CV cardiovascular training, HIIT high-intensity interval training, REX resistance exercise

Study	Sample size	Exercise duration and frequency	Aerobic mode	Aerobic intensity	Aerobic interval	Aerobic recovery	Resistance mode	Resistance intensity	Resistance interval	Resistance recovery	Supervised OR unsupervised
Crane et al. (2023)	24	16 weeks; combination of home-exercise routines	ND	ND	ND	ND	ND	ND	ND	ND	Unsupervised and self-reported
Artese et al. (2022)	15	12 weeks, 3 x /week (2 x HIIT + REX and 1 x only HIIT)	Treadmill	Warm-up: 5 min Work phase: 80–90% HRR Cool down: 5 min	60–90 s work followed by 60–90 s active recovery until complete max 20 min	50–60% HRR	Major muscle groups using machines (leg press, chest press, seated row)	Warm-up: 10 rep at 40–60% of 1RM Work phase: Many reps possible at 70% of 1RM for 2 sets	ND	ND	Supervised by exercise physiologist
Macdonald et al. (2021)	16	12 weeks, 3 x /week (2 x HIIT + REX and 1 x only HIIT)	Treadmill	Warm-up: 5 min Work phase: 80–90% VO2 reserve Cool down: 5 min	60–90 s work followed by 60–90 s active recovery until complete max 20 min	50–60% VO2 reserve	Major muscle groups using machines (leg press, chest press, seated row)	Warm-up: 10 rep at 40–60% of 1RM Work phase: Many reps possible at 70% of 1RM for 2 sets	ND	ND	Supervised by exercise physiologist
Persoon et al. (2017)	109	18 weeks, from 1–12 weeks 2 x /week From 13–18 weeks 1 x /week	Cycle ergometer	65% MSEC	2 x blocks of 8 min (MSEC) Week 1–8: 30 s work 60 s active rest Week 9–18: 30 s work 30 s active rest	30% MSEC	4 standardized exercises (vertical row, leg press, bench/ chest press, pullover/ flies) and 2 exercises for abdominal muscles and upper legs	Week 1–12: 65–80% 1RM Week 13–18: 35–40% 1RM	Week 1–12: 2 sets of 10 rep Week 13–18: 2 sets of 20 rep	ND	Supervised by instructed physiotherapists
Furzer et al. (2016)	37	12 weeks, 3 x /week	ND	Initial phase: 50% of HRmax Progression phase: 5% weekly increment until reach 85% HRmax	Max 30 min continuous CV training		6 machines and 2 dumbbells targeting major muscle groups	Initial load: 50% 1RM Aimed load: 80% 1RM	Initial load: 3 sets of 10–15 rep Aimed load: 2 to 3 sets of 6–8 rep	Minimum of 90 s recovery between sets	Supervised by exercise physiologist

Table 3 (continued)

Study	Sample size	Exercise duration and frequency	Aerobic mode	Aerobic intensity	Aerobic interval	Aerobic recovery	Resistance mode	Resistance intensity	Resistance interval	Resistance recovery	Supervised OR unsupervised
Courneya et al. (2009)	122	12 weeks, 3 x/ week	Upright or recumbent cycle ergometer	60–75% V02 peak	15–45 min continuous CV training						Supervised by exercise physiologist

Table 4 Objectively assessed physical parameters described as mean $\pm$ standard deviation. Bold text indicates non-statistical differences between groups. Because of the risk of recruitment bias, MacDonald et al. (2021) study did not report *p*-values throughout, so bold text represents small-medium effects size < 0.5 Hedges'G

	Crane et al. (2023)		Macdonald et al. (2021) (and Artese et al. (2022))		Persoon et al. (2017)		Furzer et al. (2016)		Courneya et al. (2009)	
	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1
Leisure time activity (questionnaires)										
Accelerometry (cpm)							816 $\pm$ 537	1964 $\pm$ 1236		
PASE-score					189.0 $\pm$ 79.2	241.4 $\pm$ 92.3				
VO2 peak (ml/kg/min)			26.7 $\pm$ 6.1	28.5 $\pm$ 5.5	96.9 $\pm$ 99.5	131.3 $\pm$ 82.4			24.7 $\pm$ 7.2	29.4 $\pm$ 8.6
VO2 peak (L/min)			2.1 $\pm$ 0.4	2.2 $\pm$ 0.7	21.7 $\pm$ 4.8	26.0 $\pm$ 6.3			2.02 $\pm$ 0.66	2.38 $\pm$ 0.81
W peak (Watt/kg)					2.0 $\pm$ 0.5	2.4 $\pm$ 0.7	1.45 $\pm$ 0.44	1.84 $\pm$ 0.48		
6 min walk test (m)	500.15	525.08								
Timed up and go (s)	5.58	5.67								
Muscle strength										
Leg			133.5 $\pm$ 30	137.9 $\pm$ 53.5			112 $\pm$ 37	153 $\pm$ 46		
Chest			48.8 $\pm$ 20.2	43.2 $\pm$ 26.9			32 $\pm$ 18	47 $\pm$ 25		
Back			65.7 $\pm$ 27.8	51.2 $\pm$ 24.9			52 $\pm$ 18	67 $\pm$ 24		
Arms							9 $\pm$ 4	12 $\pm$ 6		
Muscle endurance (max rep with 70% 1RM)										
Leg			20.6 $\pm$ 4.9	20.3 $\pm$ 5.7						
Chest			14.8 $\pm$ 1.7	14.4 $\pm$ 3.5						
Back			15.8 $\pm$ 1.3	15.7 $\pm$ 3.8						
Chair stand test (number rep)	13.5	13.5			15.5 $\pm$ 4.6	18.7 $\pm$ 6.0				
Grip strength (kg)	9.67	14.00			35.5 $\pm$ 10.7	40.9 $\pm$ 12				
Maximal torque m. quadriceps (Nm)					145.6 $\pm$ 51.4	173.9 $\pm$ 55.9				
Bone mineral density										
AP spine (after 24 wk)							1.226 $\pm$ 0.185	1.232 $\pm$ 0.180		
Femur (after 24 wk)							1.061 $\pm$ 0.170	1.063 $\pm$ 0.170		
Lean mass (kg)			48.2 $\pm$ 12.4	3.1 $\pm$ 5.2 (% change)			48.34 $\pm$ 10.33	50.07 $\pm$ 11.35	52.4 $\pm$ 10.9	52.3 $\pm$ 11.5
Fat mass (kg)									25.8 $\pm$ 9.5	26.0 $\pm$ 10.1
Body fat (%)			37.7 $\pm$ 10.3	-4.9 $\pm$ 12.5 (% change)	SUM SKF $\uparrow$	SUM SKF $\uparrow$	29.79 $\pm$ 9.20	28.68 $\pm$ 10.56	32.6 $\pm$ 9.9	32.8 $\pm$ 10.1

Table 5 Health-related quality of life outcomes. Data are shown as sum ± std dev or as median (interquartile range). *IQR* interquartile range. Bold text indicates non-statistical differences between groups

	Crane et al. (2023)		Artese et al. (2022)		Macdonald et al. (2021)		Persoon et al. (2017)		Furzer et al. (2016)		Courneya et al. (2009)	
	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1
HADS-anxiety [47]												
HADS-depression [47]												
SCFS-fatigue [48]												
PCS (SF-36)-physical component [49]												
Anxiety [50]												
Depression [51]												
Happiness scale [52]												
EORTC-QLQ30 [53]												
Global quality of life							62.2 ± 18	75.0 ± 18.7			18.4 ± 6.6	16.5 ± 5.2
Physical functioning							74.5 ± 18.3	83.1 ± 19.1			7.7 ± 5.7	5.4 ± 4.5
Role functioning							60 ± 31.6	81.0 ± 23.8			59 ± 22.4	70.9 ± 16.4
Emotional functioning							83.2 ± 14.9	86.2 ± 16.3				
Cognitive functioning							87.3 ± 15.6	83.7 ± 18.0				
Social functioning							71.7 ± 27.2	86.0 ± 20.3				
Disease symptoms							16.6 ± 13.1	18.7 ± 12.8				
Fatigue (MFI) [54]												
Physical fatigue							13.2 ± 4.2	9.8 ± 4.4				
General fatigue							12.7 ± 3.8	10.0 ± 4.5				
Mental fatigue							10.0 ± 4.3	9.7 ± 4.5				
Reduced activity							12.2 ± 4.1	9.6 ± 3.9				
Reduced motivation							8.8 ± 3.8	8.0 ± 3.2				
FACT [55]												
Physical well-being	24.9 ± 3.2		25.6 ± 2.1									
Social well-being	23.0 ± 3.2		24.6 ± 2.9									
Emotional well-being	19.6 ± 2.7		20.6 ± 2.2									
Functional well-being	21.7 ± 3.4		23.9 ± 3.2									
Lymphoma subscale	49.3 ± 3.9		53.3 ± 4.2									
FACT-G total	89.2 ± 6.6		94.6 ± 5.5						81.2 ± 12.8	90.2 ± 10.1	47.4 ± 8.7	50.3 ± 7.2
FACT-lym total	138.6 ± 9.4		147.9 ± 6.7									
FACT-An total											140.7 ± 26.8	151.4 ± 21.7

Table 5 (continued)

	Crane et al. (2023)		Artese et al. (2022)		Macdonald et al. (2021)		Persoon et al. (2017)		Furzer et al. (2016)		Courneya et al. (2009)	
	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1	T0	T1
FACT fatigue	Median 37.00 IQR (27.75; 45.75)	Median 45.00 IQR (39.50; 47.75)										

quality of life in cancer patients and survivors. However, the small sample sizes and the variability in outcomes measured across studies limited the ability to conduct a formal meta-analysis. The results nonetheless indicate positive trends that warrant further investigation in larger, more homogeneous samples.

Discussion

This systematic review sought to critically assess the available evidence on the relationship between physical activity (particularly HIIT and resistance training) and chronic lymphocytic leukemia, regarding fitness, health-related quality of life and feasibility, and immunologic parameters. Only 6 papers met our search criterion, with 2 addressing the HIIT type of physical activity intervention. Meta-analysis was not feasible due to the heterogeneity of interventions, populations, and outcome measures across the included studies but key findings and trends are reported.

Most of CLL studies were conducted throughout the last two decades, and before 2009, no intervention studies were reported, only observational using questionnaires and involving anthropometric parameters such as height, weight, waist and hip circumference, or the body mass index [56–58]. And because we are still in an early bird phase, many methodological problems are biasing results. Early meta-analysis in 2009 addressed resistance training in cancer survivors and displayed post training improvements in cardiopulmonary function from 6 to 39%, and increases in muscle strength between 11 and 110% [59]. We hypothesize that this disparity may be explained by factors such as the contribution of learning effect, variability in strength exercises, intensities and duration of exercise programs, genetic differences, type and stage of cancer, diverse cancer treatments, and the time elapsed since cancer diagnosis. This shows the importance of knowing the progress path between sedentary behaviour and physical active behaviour, and the interconnection with patient's physical active before and after diagnosis.

There is general agreement in the absence of adverse training effects on immunological, endocrinological, and hematopoietic variables, or lymphedema. Moreover, it seems that even high training intensities have been well-tolerated in cancer survivors [59].

A recent systematic review and meta-analysis confirmed that, in addition to clinical stage evaluation [60], the best practice to initial prognosis in CLL patients should include the chronic lymphocytic leukemia international prognostic index (CLL-IPI), which combines 5 parameters (age, clinical stage, *TP53* status, IGHV mutational status, and serum B2-microglobulin) [61]. In the studies of our review, only Macdonald et al. (2021)

implemented CLL-IPI, while Artese et al. (2022) and Courneya et al. (2009) used Rai staging.

The consistency of “best practice on evaluation” in the physical fitness evaluation is not met, leading to inconclusive data and poor strength evidence. Investigations until this date support intensive endurance exercise, known to induce lymphocyte apoptosis affecting the immune system [19]; regular resistance exercise, who can decrease oxidative stress which may lead to attenuate apoptosis related protein [20]; high-intensity interval training suggesting that it may be able to delete mainly highly differentiated T cells, known to affect immunity to control latent infections [21]. However, for the same physical fitness outcomes, cardiovascular protocols differ in equipment (treadmill or recumbent cycle ergometer); in intensity (90% VO₂ reserve, or 90% HR reserve, or 65% maximal short exercise capacity, or HR maximal, or VO₂ peak); on duration (20 min interval training, 15–45 min continuous, 30 min continuous, 8 min intervals); and on recovery (60–90 s active recovery, 30–60 s active recovery, no recovery). Muscular protocols differ in resistance mode (major muscle groups using machines, or dumbbells, or calisthenic exercises); resistance intensity (70% of 1-RM for maximal repetitions, 80% of 1-RM for 6–8 repetitions, 65–80% 1-RM); duration of effort (2 sets of 10 repetitions, 2–3 sets of 6–8 repetitions, 2 sets of 20 repetitions); and recovery (minimum of 90 s between sets, or not described at all). For the goodness of proof, it is mandatory that gold-standard equipment's are used, such as isokinetic dynamometers to evaluate muscular effort, cardiopulmonary exercise test (CPET) with electrocardiogram to assess cardiac and pulmonary response, dual-energy X-ray absorptiometry (DEXA) to evaluate corporal composition.

In the studies with intervention protocols available, one was based only on recumbent cycle ergometer training, regarding heart rate reserve as modulator of intensity [43], three studies with HIIT exclusively during 30 min, or with 1 h combining 30 min HIIT plus 30 min resistance training [33, 42, 45], and another study using continuous cardiovascular training concomitant with resistance training [44]. However, because there is a combination of continuous cardiovascular (or HIIT) plus RT, we cannot fully establish a relation between resistance/strength training only, and cardiovascular only, or the combined effect of training in CLL patients, neither infer about the difference between endurance and strength training in resistance training protocols. Nevertheless, findings showed that more than 12-weeks of training, with more than 30 min. of HIIT combined with muscle endurance-based resistance training for treatment naïve CLL patients, is feasible and is associated with significant

effects on muscle strength and normal immune cell functions [33, 42, 45].

Corroborated from current knowledge, urges the need to clarify the exercise characteristics and outcomes regarding HIIT, resistance training (also between strength and endurance approaches) and combined training in CLL patients. The difference between muscular endurance training (more repetitions, and fatigue resistance to exercise) and maximum strength training (increment in muscle strength and/or muscle hypertrophy) must also be assessed. Most studies use DEXA and BIA for body composition analysis, which are indirect measures, insensitive to changes in muscle size, that consequently would keep very small changes from muscle hypertrophy adaptations undetected [62]. As described elsewhere [63, 64], when volume is equated, resistance training frequency does not significantly or meaningfully impact muscle hypertrophy. However, higher training frequencies can help to accumulate more significant volumes of training, which may enhance hypertrophic response.

The studies obtained in this review shows a preference for low-moderate intensities, or endurance effort on resistance training (65–70% of 1-RM), but as literature suggest, exercise-induced myokines production have a critical role in increasing cytotoxicity and the infiltration of immune cells into the tumour [25]. When comparing aerobic only, strength only and both guidelines, the hazard ratio for all-cause mortality was lower when combining both guidelines, but when alone, strength training was better than aerobic; in the case of cardiovascular disease mortality, both guidelines combined are still the better choice to a lower hazard ratio; but in cancer mortality, strength only training shows to be the better option compared to combined guidelines [65]. There are no studies addressing the use of strength training on CLL patients but given the fact that one of the most evident symptoms as the disease progresses are fatigue and shortness of breath during regular physical activity, it seems reasonable that a strength training is better tolerated than a cardiovascular training. Confirming the feasibility and success of this type/mode of training should be engaged in future studies.

It is also important to objectively assess the daily lifestyle of patients to establish a possible etiology of CLL, implementing the accelerometry technology, to ensure correct lifestyle patterns recommendations, and make a connection point with anatomic/morphologic data (muscular mass, body fat percentage, weight, blood, and cardiovascular parameters), and physical condition (VO₂, strength, flexibility, mobility, and more).

Despite the medical conservative approach in leukemic patients regarding exercise prescription, leading exercise

oncologists suggest that all cancer patients should avoid inactivity and engage in safe exercise training [66]. It was reported in a small cohort with 12 patients with hematologic disease (7 patients with acute myeloid leukemia, 1 acute lymphoblastic leukemia and 4 non-Hodgkin's lymphoma) receiving high-dose chemotherapy, that none of the patients with thrombocyte counts below 10.000/ μ l suffered bleeding and no patient with haemoglobin counts below 8 g/dl suffered critical tachycardias, showing that physical exercise in patients with severe cytopenia is safe and results in increased physical performance and unchanged quality of life [67]. Also in the studies we collected, the feasibility of the intervention protocols were always highly rated, with $99 \pm 3.6\%$ attendance and 148.5 ± 5.4 min/week of exercise and with 100% safety [33, 42, 45]; with 91% attendance with 88 ± 17 min/week (Furzer et al., 2016); with small adverse events related with intervention protocol such as back, hip and knee pain (Courneya et al., 2009) but without impairment of patients maintenance on the protocol.

Considering immunologic outcomes, only two small pilot studies compared disease parameters. One revealed a significant effect on NK-cells, including increased absolute counts, cytotoxic function, as well as increased perforin and granzyme B expression, mimicking the response to exercise in subjects without cancer [33] while the other enlightened an increased ratio CD4:CD8 T-cell, and reduced proportion of T-cells subsets [32]. Although these results should be treated with care since a control group is missing, and patients received treatment before or during intervention with medication known to alter T-cell phenotype and function, this relationship between exercise and immune outcomes should be further explored in future studies. As reported elsewhere [68], exercise is an effective modulator in sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, exercise and tumour-promoting inflammation and reprogramming energy metabolism, evading immune destruction, with myokines playing a significant role in the prevention of cancer proliferation. The effect of exercise in these hallmarks of cancer should be evaluated in CLL cells.

Conclusion

This systematic review exposed the gap of few implemented studies and conflicting results in some physical activity approaches in CLL patients. To our knowledge, only three studies specifically addressed CLL patients, but with small samples of patients in pilot study experiments. Nevertheless, it is noted the vital role of exercise before treatment, with significant improvements in physical fitness, and immunologic parameters.

Aerobic exercise training significantly improved objective physical function when worked at 60–75% of VO₂ peak; aerobic and resistance exercises combined resulted in significant clinical improvements in cardiorespiratory fitness when worked at 85% HR_{max} and 80% of 1-RM; HIIT combined with muscle endurance-based resistance training is feasible and associated with large effects on muscle strength and immune function when worked at 90% VO₂ reserve and 70% of 1-RM; even a home-based physical activity program increased leisure-time PA and decreased fatigue. However, no significant beneficial effects of supervised high-intensity exercise programs on physical fitness and fatigue with intensities of 65% HR and 40% of 1-RM. This suggests that this population do not differ from healthy populations, and it seems to be more beneficial to adjust the intensity of workout to higher limits rather than low limits. Studies addressing strength-based resistance training are inexistent, since all the studies analysed just used endurance-based resistance training programs, or combined programs.

The present literature also shows a gap regarding evaluation process, advising that future studies should include most accurate instruments to address disease parameters: physical exam and health history, complete blood count, blood chemistry studies, lactate dehydrogenase testing, beta-2-microglobulin testing, flow cytometry to quantify tumour markers at cell surface, FISH analyses, gene mutation testing, serum immunoglobulin testing, chest x-ray for organs and bones, CT scan and/or PET-CT scan. Additionally, include reference instruments to evaluate physical fitness components objectively: DEXA scan for body composition, dynamometers for muscular strength or endurance, VO₂max protocol with ergospirometry and ECG, O₂ saturation, lactate, ultrasound for muscle density, blood pressure, heart rate and accelerometry. The physical activity must be precisely quantified to define the treatment dose of exercise.

The conclusions mentioned here are supported by a short number of studies. Therefore, care should be taken to interpret these findings. To be able to advise Exercise Professionals to prescribe different modes/types of exercise, improving compliance with the prescribed exercise program and determine which intervention in the context of exercise prescription should be used to maximize the benefits resulting from the regular practice of physical activity, more studies are needed to evaluate the impact of PA in the health-related quality of life and life span of the CLL patient.

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Authors' contributions

PC was responsible for Conceptualization, Methodology, Writing – Original Draft and Funding acquisition; RR was responsible for Writing – Review &

Editing; AP was responsible for Writing – Review & Editing; JM was responsible for Resources, Writing – Review & Editing and Funding acquisition; JR was responsible for Resources, Validation, Writing – Review & Editing, Supervision and Funding acquisition.

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Data availability

All data is available online and described in references.

Declarations

Ethics approval and consent to participate

Ethic Commission Approval Centro Hospitalar de São João: CE 431-19. Ethic Commission Approval Faculty of Sport - University of Porto: CEFAD 14_2024

Consent for publication

Not applicable.

Competing Interests

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

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References

1. Swerdlow, S.H., et al., WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. 2017, Lyon: International Agency for Research on Cancer.
2. Ou Y, et al. Trends in disease burden of chronic lymphocytic leukemia at the global, regional, and national levels from 1990 to 2019, and projections until 2030: a population-based epidemiologic study. *Front Oncol.* 2022;12: 840616.
3. Alaggio, R., et al., The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*, 2022; 36(7): p. 1720–1748.
4. NIH. SEER cancer stat facts: chronic lymphocytic leukemia. 2022 2023/01/12; Available from: <https://seer.cancer.gov/statfacts/html/clly.html>. [cited 2023 2023/01/12].
5. Yao Y, et al. The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. *Biomed Eng Online.* 2022;21(1):4.
6. LLS, The CLL guide: information for patients and caregivers. 2021, National Office: NY.
7. Swerdlow, S.H., et al., WHO classification of tumours of hematopoietic and lymphoid tissues. Revised 4th edition ed. 2017, Lyon: IARC Press.
8. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *Am J Hematol.* 2019;94(11):1266–87.

9. International, C.L.L.I.P.I.w.g., An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016; 17(6): p. 779–790.
10. Molica S, et al. The chronic lymphocytic leukemia international prognostic index predicts time to first treatment in early CLL: independent validation in a prospective cohort of early stage patients. *Am J Hematol*. 2016;91(11):1090–5.
11. da Cunha-Bang C, Christiansen I, Niemann CU. The CLL-IPI applied in a population-based cohort. *Blood*. 2016;128(17):2181–3.
12. Gentile M, et al. Validation of the CLL-IPI and comparison with the MDACC prognostic index in newly diagnosed patients. *Blood*. 2016;128(16):2093–5.
13. Kikushige Y, et al. Self-renewing hematopoietic stem cell is the primary target in pathogenesis of human chronic lymphocytic leukemia. *Cancer Cell*. 2011;20(2):246–59.
14. Kikushige Y. Pathogenesis of chronic lymphocytic leukemia and the development of novel therapeutic strategies. *J Clin Exp Hematop*. 2020;60(4):146–58.
15. Lee J, Wang YL. Prognostic and predictive molecular biomarkers in chronic lymphocytic leukemia. *J Mol Diagn*. 2020;22(9):1114–25.
16. Burger JA, Gribben JG. The microenvironment in chronic lymphocytic leukemia (CLL) and other B cell malignancies: insight into disease biology and new targeted therapies. *Semin Cancer Biol*. 2014;24:71–81.
17. Scott, D.W. and R.D. Gascoyne, The tumour microenvironment in B cell lymphomas. *Nature Reviews Cancer*, 2014.
18. Ramsay AG, et al. Multiple inhibitory ligands induce impaired T-cell immunologic synapse function in chronic lymphocytic leukemia that can be blocked with lenalidomide: establishing a reversible immune evasion mechanism in human cancer. *Blood*. 2012;120(7):1412–21.
19. Kruger, K, et al., Intensive resistance exercise induces lymphocyte apoptosis via cortisol and glucocorticoid receptor-dependent pathways. *J Appl Physiol* (1985), 2011. 110(5): p. 1226–32.
20. Lee MK, et al. Effects of resistance exercise on antioxidant enzyme activities and apoptosis-related protein expression of hippocampus in OLETF rats. *Technol Health Care*. 2018;26(3):457–67.
21. Kruger K, et al. Apoptosis of T-cell subsets after acute high-intensity interval exercise. *Med Sci Sports Exerc*. 2016;48(10):2021–9.
22. Goh J, Niksirat N, Campbell KL. Exercise training and immune crosstalk in breast cancer microenvironment: exploring the paradigms of exercise-induced immune modulation and exercise-induced myokines. *Am J Transl Res*. 2014;6(5):422–38.
23. Roy P, Chowdhury S, Roy HK. Exercise-induced myokines as emerging therapeutic agents in colorectal cancer prevention and treatment. *Future Oncol*. 2018;14(4):309–12.
24. Barbalho SM, et al. Myokines: a descriptive review. *J Sports Med Phys Fitness*. 2020;60(12):1583–90.
25. Kim JS, et al. Exercise-induced myokines and their effect on prostate cancer. *Nat Rev Urol*. 2021;18(9):519–42.
26. Vasyukova OV, et al. Myokines and adipomyokines: inflammatory mediators or unique molecules of targeted therapy for obesity? *Probl Endokrinol (Mosk)*. 2021;67(4):36–45.
27. Kotani T, et al. Influence of physical exercise on large granular lymphocytes, Leu-7 bearing mononuclear cells and natural killer activity in peripheral blood–NK-cell and NK-activity after physical exercise. *Nihon Ketsueki Gakkai Zasshi*. 1987;50(6):1210–6.
28. Radom-Aizik, S, et al., Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol* (1985), 2013. 114(5): p. 628–36.
29. Shek PN, et al. Strenuous exercise and immunological changes: a multiple-time-point analysis of leukocyte subsets, CD4/CD8 ratio, immunoglobulin production and NK cell response. *Int J Sports Med*. 1995;16(7):466–74.
30. Nielsen HB, et al. Lymphocytes and NK cell activity during repeated bouts of maximal exercise. *Am J Physiol*. 1996;271(1 Pt 2):R222–7.
31. Rumpf C, et al. The effect of acute physical exercise on NK-cell cytolytic activity: a systematic review and meta-analysis. *Sports Med*. 2021;51(3):519–30.
32. Crane JC, et al. Relationships between T-lymphocytes and physical function in adults with chronic lymphocytic leukemia: results from the HEALTH4CLL pilot study. *Eur J Haematol*. 2023;110(6):732–42.
33. MacDonald G, et al. A pilot study of high-intensity interval training in older adults with treatment naive chronic lymphocytic leukemia. *Sci Rep*. 2021;11(1):23137.
34. Higgins, J. and J. Thomas, *Cochrane handbook for systematic reviews of interventions* version 6, ed. J. Higgins and J. Thomas. 2019, Hoboken, NJ: Wiley Blackwell.
35. Page MJ, The PRISMA, et al. statement: an updated guideline for reporting systematic reviews. *Bmj-British Medical Journal*. 2020;2021:372.
36. Schulz KF, CONSORT, et al. statement: updated guidelines for reporting parallel group randomised trials. *Bmj-British Medical Journal*. 2010;2010:340.
37. Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg*. 2014;12(12):1500–24.
38. Mataratzis, P.S.R., E. Accioly, and P.d.C. Padilha, Micronutrients deficiency in children and adolescents with sickle cell anemia: a systematic review. *Rev. Bras. Hematol. Hemoter*, 2010. 32(3): p. 247–256.
39. Sterne JA, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355: i4919.
40. Flemming E, et al. Using risk of bias 2 to assess results from randomised controlled trials: guidance from Cochrane. *Bmj Evidence-Based Medicine*. 2023;28(4):260–6.
41. Sica, A, et al., An anecdotal case report of chronic lymphatic leukemia with del(11q) Treated with ibrutinib: artificial nourishment and physical activity program. *International Journal of Environmental Research and Public Health*, 2020. 17(6).
42. Artese, A.L., et al., Effects of high-intensity interval training on health-related quality of life in chronic lymphocytic leukemia: a pilot study. *J Geriatr Oncol*, 2022.
43. Courneya KS, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J Clin Oncol*. 2009;27(27):4605–12.
44. Furzer BJ, et al. A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients. *Support Care Cancer*. 2016;24(4):1697–707.
45. Persoon, S, et al., Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: Results from the EXIST study. *Plos One*, 2017. 12(7).
46. ACSM, ACSM's guidelines for exercise testing and prescription. Tenth ed. 2018, Philadelphia, PA: Wolters Kluwer Health.
47. Zigmund AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–70.
48. Schwartz AL. The Schwartz Cancer Fatigue Scale: testing reliability and validity. *Oncol Nurs Forum*. 1998;25(4):711–7.
49. McHorney, C.A., et al., The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*, 1994. 32(1): p. 40–66.
50. Smith TW, Ingram RE, Brehm SS. Social anxiety, anxious self-preoccupation, and recall of self-relevant information. *J Pers Soc Psychol*. 1983;44(6):1276–83.
51. Kohout FJ, et al. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J Aging Health*. 1993;5(2):179–93.
52. Fordyce, M.W., A review of research on the happiness measures: a sixty second index of happiness and mental health, in *Citation classics from social indicators research*, A.C. Michalos, Editor. 2005, Springer: Dordrecht.
53. Aaronson NK, et al. The European-organization-for-research-and-treatment-of-cancer QoL-C30-a quality-of-life instrument for use in international clinical-trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–76.
54. Aoun SM, et al. Measuring symptom distress in palliative care: psychometric properties of the Symptom Assessment Scale (SAS). *J Palliat Med*. 2011;14(3):315–21.
55. Finkelstein, F.O., et al., Measurement properties of the short form-36 (SF-36) and the functional assessment of cancer therapy-anemia (FACT-An) in patients with anemia associated with chronic kidney disease. *Health and Quality of Life Outcomes*, 2018. 16.
56. Cerhan JR, et al. Anthropometric characteristics, physical activity, and risk of non-Hodgkin's lymphoma subtypes and B-cell chronic lymphocytic leukemia: a prospective study. *Am J Epidemiol*. 2002;156(6):527–35.

57. Lu Y, et al. Body size, recreational physical activity, and B-cell non-Hodgkin lymphoma risk among women in the California teachers study. *Am J Epidemiol.* 2009;170(10):1231–40.
58. Walter RB, Buckley SA, White E. Regular recreational physical activity and risk of hematologic malignancies: results from the prospective VITamins And lifestyle (VITAL) study. *Ann Oncol.* 2013;24(5):1370–7.
59. Backer ICD, et al. Resistance training in cancer survivors: a systematic review. *Int J Sports Med.* 2009;30:703–12.
60. Parikh SA, et al. Should IGHV status and FISH testing be performed in all CLL patients at diagnosis? A systematic review and meta-analysis *Blood.* 2016;127(14):1752–60.
61. Molica S, et al. Chronic lymphocytic leukemia international prognostic index: a systematic review and meta-analysis. *Blood.* 2018;131(3):365–8.
62. Grgic J, Schoenfeld BJ, Latella C. Resistance training frequency and skeletal muscle hypertrophy: a review of available evidence. *J Sci Med Sport.* 2019;22(3):361–70.
63. Schoenfeld BJ, Grgic J, Krieger J. How many times per week should a muscle be trained to maximize muscle hypertrophy? A systematic review and meta-analysis of studies examining the effects of resistance training frequency. *J Sports Sci.* 2019;37(11):1286–95.
64. Schoenfeld BJ, Ogborn D, Krieger JW. Effects of resistance training frequency on measures of muscle hypertrophy: a systematic review and meta-analysis. *Sports Med.* 2016;46(11):1689–97.
65. Stamatakis E, et al. Does strength-promoting exercise confer unique health benefits? A pooled analysis of data on 11 population cohorts with all-cause, cancer, and cardiovascular mortality endpoints. *Am J Epidemiol.* 2018;187(5):1102–12.
66. Campbell KL, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc.* 2019;51(11):2375–90.
67. Elter T, et al. Is physical exercise possible in patients with critical cytopenia undergoing intensive chemotherapy for acute leukaemia or aggressive lymphoma? *Int J Hematol.* 2009;90(2):199–204.
68. Ruiz-Casado A, et al. Exercise and the hallmarks of cancer. *Trends Cancer.* 2017;3(6):423–41.

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PAPER II

Clinical Lymphoma, Myeloma and Leukemia

The Role of Daily Activity in Risk and Survival Outcomes for Chronic Lymphocytic Leukemia Patients: Baseline Insights from the ADRENALINE Pilot Study.

--Manuscript Draft--

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Abstract:	Objective: The ADRENALINE pilot study examines the impact of physical activity on health outcomes in Chronic Lymphocytic Leukemia (CLL) patients, focusing on disease markers, functional capacity, immune parameters, and quality of life. Given limited research on exercise in CLL, the present study evaluates baseline characteristics related to body composition, cardiovascular fitness, daily activity patterns, and immune profiles—an observational baseline assessment of treatment-naïve CLL patients enrolled in the ADRENALINE study, with assessments conducted from September 2023 to August 2024, before randomization. Methods: Eleven patients (47–78 years) completed baseline evaluations, including body composition, cardiovascular fitness, muscular strength testing, and immune profiling. Quality of life was assessed using validated questionnaires (FACIT-F, EORTC QLQ-30/CLL17), and daily activity levels were measured using accelerometry. Correlation analyses explored relationships between physical activity, muscle strength, lean mass, and physical aptitude. Results: Participants exhibited suboptimal body composition and cardiovascular fitness despite high self-reported physical function. Accelerometry revealed significant sedentary behavior, particularly among females. Although overall activity levels were below recommendations, moderate-to-vigorous physical activity correlated positively with muscular strength and lean mass. Immune profiling identified variations in key markers, warranting further investigation into their relationship with physical activity. Conclusions: These findings highlight the need for tailored strategies to promote physical activity and reduce sedentary time in CLL patients. The disconnect between subjective and objective assessments supports integrating routine functional and immune monitoring in survivorship care. Trial Registration: ClinicalTrials.gov (NCT06396611).
Opposed Reviewers:	

Title: *The Role of Daily Activity in Risk and Survival Outcomes for Chronic Lymphocytic Leukemia Patients: Baseline Insights from the ADRENALINE Pilot Study.*

Trial Registration: Registered at ClinicalTrials.gov (NCT06396611).

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Abstract

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Results: Participants exhibited suboptimal body composition and cardiovascular fitness despite high self-reported physical function. Accelerometry revealed significant sedentary behavior, particularly among females. Although overall activity levels were below recommendations, moderate-to-vigorous physical activity correlated positively with muscular strength and lean mass. Immune profiling identified variations in key markers, warranting further investigation into their relationship with physical activity.

Conclusions: These findings highlight the need for tailored strategies to promote physical activity and reduce sedentary time in CLL patients. The disconnect between subjective and objective assessments supports integrating routine functional and immune monitoring in survivorship care.

Trial Registration: ClinicalTrials.gov (NCT06396611).

KEYWORDS: Physical Activity; Exercise; Resistance Training; Quality of Life; Chronic Lymphocytic Leukemia; Oncology.

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Introduction

Chronic Lymphocytic Leukemia (CLL) is a hematological disease caused by the proliferation of monoclonal mature B lymphocytes [1] with a prevalence of 25% to 35% of all leukemias and one of the most common forms in adults in Western countries [1]. Patients with CLL tend to adopt sedentary behaviors due to disease symptoms as it progresses, including fatigue, shortness of breath during regular physical activity, lymph node enlargement, low-grade fever, unexplained weight loss, night sweats, feeling of fullness (related to enlarged spleen or liver) and multiple infections [2]. As a result of these changes, there is often a notable decrease in physical fitness with the consequent decrease of overall quality of life [3]. Additionally, the psychological impact of the disease, including anxiety and depression, further exacerbates this condition, underscoring the critical need for interventions that promote physical activity and support the maintenance of independence to perform daily activities.

Individuals with cancer are not any more likely to be physical inactive than those who never had cancer, however, in a Canadian Community Health Survey with patients with current cancer or cancer history it was found that activity levels in all studied groups were much lower than recommended [4]. While current treatment for patients with Chronic Lymphocytic Leukemia focuses on a multifaceted approach, aiming to address both physical and psychological challenges [5], many patients still experience significant discomfort that hinder daily functioning and reduce their quality of life [6].

Recent studies have explored the impact of physical activity on CLL patients with research suggesting that many treatment naïve CLL patients are physically inactive and have high levels on inflammation [7]. Regular physical activity has been shown to have significant positive effects in general population, with moderate to vigorous exercise being associated with reduced risk of infections [8], and improving immune competence acting as a countermeasure against chronic systemic inflammation [9], characteristics of CLL disease symptoms.

Physical activity may play a crucial role in maintaining an active lifestyle before, during and after treatment [10, 11] and regular physical activity may improve physical function enhancing mood, self-esteem, and overall well-being [12]. With the need for more robust research to determine the most effective exercise intervention for cancer population, many studies have already provided strong evidence supporting the prescription of exercise therapy for managing metabolic syndrome-related disorders (insulin resistance, type 2 diabetes, dyslipidemia, hypertension, obesity), heart and pulmonary diseases (chronic obstructive pulmonary

disease, coronary heart disease, chronic heart failure, intermittent claudication), muscle, bone and joint diseases (osteoarthritis, rheumatoid arthritis, osteoporosis, fibromyalgia, chronic fatigue syndrome) as well as cancer, depression, asthma and type 1 diabetes [13]. Several controlled trials indicate significant improvements on cardiovascular fitness with aerobic exercise [14-16], on muscle fitness with resistance exercise [17], with impact on immunologic response [17-19] and cancer related fatigue [14, 15]. Yet, in a study with a population from Canada, with 606 survivors of hematologic cancer, only 22% met combined exercise guidelines, and just 10% met strength-only guidelines [20].

Objectively assessed physical activity with accelerometry provide accurate and objective data [21, 22] regarding prognostic and quality of life measures such as objectively quantification of time in sedentary behavior, light and moderate to vigorous physical activity, and body position [23, 24]. This objective data on patients' activity levels, have been linked to better survival outcomes and lower disease symptoms [25, 26] and by integrating this technology and data, clinicians can tailor interventions to enhance physical activity levels, potentially improving patients overall health and treatment response [27]. This approach offers a non-invasive, continuous monitoring tool that aligns with personalized medicine initiatives in oncology [28] facilitating the accomplishment of clinical interventions.

Regarding CLL patients, a common symptom reported by patients is fatigue. From current studies interpretation, the circadian clock has been shown to influence numerous immune cells at both the molecular and cellular levels [29]. The maturation of neutrophils, the most common leukocytes found in human blood, is rhythmic, and their antimicrobial activity behaves in a time-of-day dependent manner [29]. The objectively assessed physical activity may enlighten if daily physical activity in CLL patients follows this circadian clock pattern.

The aim of the current study is to explore the interaction between daily physical activity levels with disease markers (blood counts and diagnose markers of the disease) and physical and functional capacity (aerobic and muscular), to analyze how CLL patients perceive their physical and functional capacity, and to investigate if different times of the day infers on physical activity patterns in diagnosed CLL patients in treatment naïve phase.

Materials & Methods

Study Design

The rAndomised contRolled cliNical triAL of exercise as Intervention in chroNic lymphocytic leukEmia (ADRENALINE), is a single-blind randomized controlled trial (RCT) study. The present manuscript reports baseline data from the undergoing research project, before randomization.

Patients with confirmed CLL, with stringent inclusion and exclusion criteria, were consecutively recruited at the Hematology Department in the participating Hospital (São João University Hospital Center), which represents the largest hospital in the Porto region (Portugal). The data on the present study, regarding initial evaluations (T0) of the ADRENALINE study and data collection, refers from September 2023 until August 2024. At this moment (T0 evaluation), no exposure to the ADRENALINE concept was done, neither follow-up.

The study protocol has been approved by the Ethics Committees of São João University Hospital Center and the Faculty of Sport from the University of Porto (references CE 431-19 and CEFAD 14_2024, respectively). All patients provided written informed consent upon recruitment to participate in the study. The ADRENALINE trial is registered at ClinicalTrials.gov (NCT06396611).

Participants

All patients received a screening assessment including medical history, blood chemistry and hemogram, and physical examination (for skin pallor, palpable cervical lymph nodes, and hepatomegaly) during Hematology routine workup, before the assessment of health-related quality of life using questionnaires and fitness assessments. Objectively assessed levels of daily physical activity were acquired after baseline assessments using accelerometry technology to collect data on the Physical Activity (PA) patterns of participants over a period of seven consecutive days, with a minimum of 10 hours of daily assessment.

Inclusion criteria comprise a confirmed CLL diagnostic as per the International Workshop on CLL Guidelines [30], age between 45-80 years old, no history of previous treatment of CLL, ability to walk on a treadmill or cycle on an ergometer, ability to carry weights or use weight machines, that have passed initial evaluations (Cardiopulmonary Exercise Test + Electrocardiogram (CPET+ECG) for cardiac health and

dynamometer for muscular health), and with a signed informed consent. Exclusion criteria included previous immunochemotherapy CLL treatments, ongoing engagement in a regular exercise program, an indication of disease progression or for starting treatment within 6 months (according to recommendations of the International Workshop on CLL Guidelines), other primary tumors, inability to perform exercise (heart, advanced stage respiratory, renal, hepatic, neurological or osteoarticular disease), and unable to travel to facilities or to comply with other study requirements. Figure 1 demonstrates the patient recruitment and data collection of the present study within the development of the ADRENALINE study.

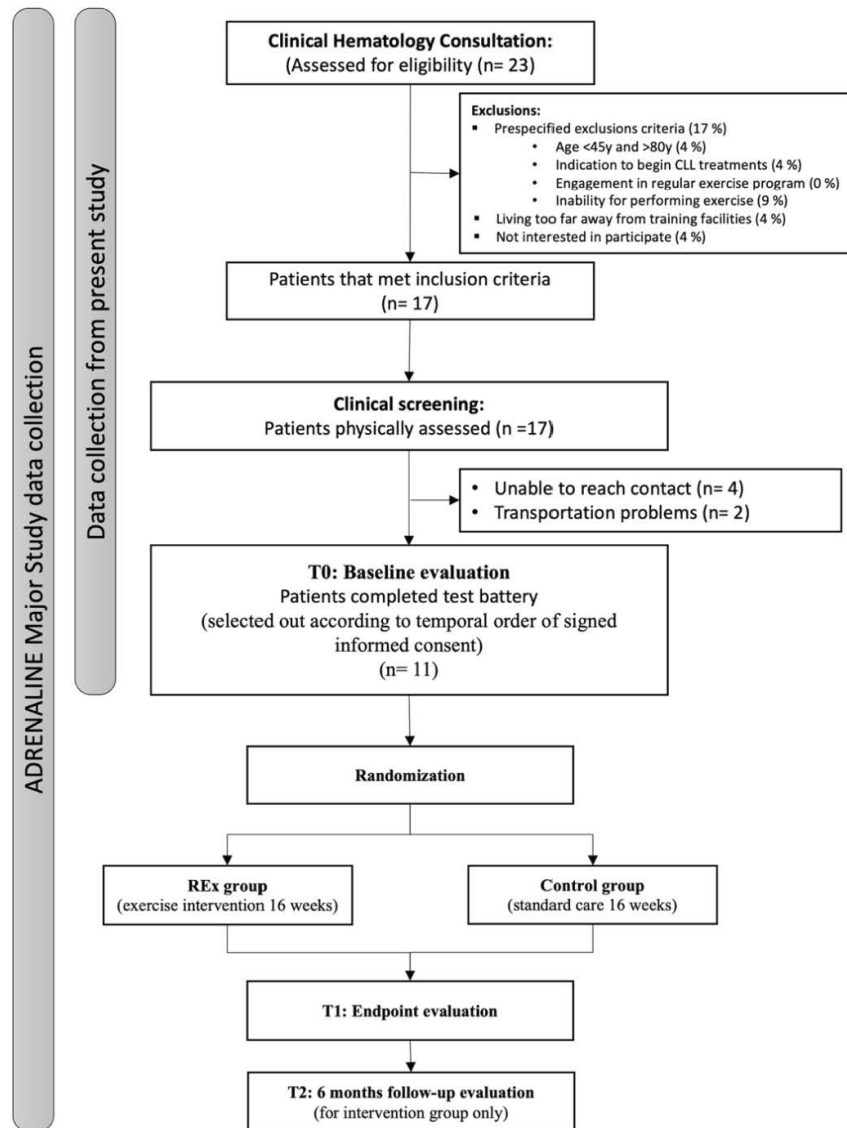


Figure 1: Scheme of patient's recruitment and data collection. REx=Resistance Exercise. CLL=Chronic Lymphocytic Leukemia.

Primary and Secondary Outcomes

Primary outcomes encompass the characterization of objective levels of physical activity, using accelerometry and quality of life and well-being, using questionnaires, body composition measures, anthropometric, strength evaluation, cardiac and respiratory capacity.

Secondary outcomes includes medical assessments performed by clinicians during the routine Hematology consultation before the baseline evaluations, including disease-related symptoms/complications, physical exam (for skin pallor, palpable cervical lymph nodes, and hepatomegaly) and clinical exams.

Evaluation

Exercise testing

At baseline, patients were evaluated on: i) anthropometric, body composition measures and bone mineral density; ii) strength; iii) cardiac and respiratory CPET on a cycle ergometer with a stress electrocardiogram with spirometry.

The CPET performed to assess cardiorespiratory fitness and potential cardiovascular and cardiorespiratory limitations followed international guidelines concerning standardization and interpretation strategies [31]. The CPET was performed on a cycle ergometer Lode Corival CPET (Lode, The Netherlands) under the supervision of a sports physician. Throughout the test, the Electrocardiogram (ECG) and blood pressure were monitored, and heart rate (HR) and gas exchange variables were recorded continuously, averaged at 30-second intervals (COSMED Quark CPET, Rome, Italy). The protocol comprehends 2 minutes rest without movement, for respiratory adaptation, followed by a 3-minute warmup unloaded phase at 60 revolutions per minute (RPM) and zero watts. After warmup, the incremental exercise phase is initiated, with each step incrementing 15 watts per minute until 85% heart rate is achieved or other standardized criteria for stopping occurs [31]. After the incremental phase, the recovery phase took place with 2 minutes of active cool down with unloaded pedaling followed by 3 minutes of passive cool down without movement [32]. The highest recorded oxygen uptake ($\text{VO}_{2\text{peak}}$) was used as an indicator of cardiorespiratory fitness. $\text{VO}_{2\text{peak}}$ represents the highest oxygen consumption achieved during the test rather than a true maximal effort. This approach is commonly used when maximal exertion is not feasible, particularly in clinical populations.

Upper extremity muscle strength was assessed using a handgrip dynamometer JAMAR PLUS (Sammons Preston, Chicago IL), calibrated according to standard protocols, and using 3 trials for each hand, with a contraction of 2-4 seconds, and with 30 seconds interval between attempts [33, 34]. For lower muscle strength it was used an Isokinetic Dynamometer BIODEX 850-000 System 4 Pro (Biodex Medical Systems, USA) following the standard procedures recommended by standard protocols, measuring Extension/Flexion of the dominant knee, and using the protocol Concentric/Concentric with 60 deg/s speed to evaluate strength, with 5 repetitions warmup and 3 repetitions for maximal effort after 1-2 min rest between warmup and maximal effort [35].

Data collection of height and body mass were determined by standard anthropometric methods (SECA 217 stadiometer and SECA 899 digital floor scale). Body mass index was calculated from the ratio weight/height² (kg/m²). 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, fat-free mass and bone mineral density (from whole body test) and hip bone mineral density (from non-dominant hip side).

Objectively assessed levels of physical activity (PA) were acquired using the GT9XLink accelerometer (Actigraph, USA) to collect data on the PA patterns of participants over a period of seven consecutive days, with a minimum 4 weekdays and 1 weekend day and of 10 hours of daily assessment [36]. Accelerometers were worn on the dominant side over the hip and aligned with the kneecap, and patients were instructed to use them all day long except during baths, water sports, potential hazard activities, or during sleep. A report sheet for the description of daily accelerometer usage was also provided.

All the referred tests were conducted at lab facilities, with medical surveillance during physical fitness protocols.

Clinical, Immunologic and Inflammatory testing

Clinicians performed clinical assessments during routine hematology consultations comprising standardized clinical assessments, including exercise- and disease-related symptoms/complications, hemogram and blood chemistry (hepatic, renal, mineral and metabolic markers), and physical exams (for skin pallor, palpable cervical lymph nodes, and hepatomegaly). Pre-intervention disease markers for characterization of CLL were also available (LDH, beta2-microglobulin, immunoglobulins, immunophenotyping and B cells characterization

measurements). The CLL staging index (RAI and BINET) [37, 38], and the Eastern Cooperative Oncology Group Performance Scale (ECOG) [39] were used due to typical clinical practice of participating hospital. The genetic characterization of the disease (needed for the CLL International Prognostic Index (CLL-IPi)) is not available since genetic markers are only asked when the disease criteria evolve to treatment phase.

Quality of Life

At baseline, two self-reported questionnaires were used to assess clinical status, well-being and quality of life: the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [40] to evaluate Well-Being, and where the maximum score is 160, with higher scores indicating greater Well-Being for all domains; and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30) [41] with the Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL17) evaluating Health-Related Quality of Life (QoL) and where 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.

BIAS

Risk of BIAS was assessed with the JBI Critical Appraisal Checklist for Cross-Sectional Studies [42], part of the Joanna Briggs Institute's critical appraisal tools. This checklist is specifically designed for cross-sectional studies, such as the present research, which assesses baseline differences between male and female participants. It evaluates potential biases in sample selection, measurement reliability, and statistical analysis. Additionally, it helps ensure the comparability of groups and the validity of data collection methods, thereby strengthening the study's methodological rigor.

Statistical Methods

Sample size calculation for the major ADRENALIN study (GPower software) was based on the means and standard deviations of prior studies [43]. An initial estimation indicated that a minimum of 16 subjects was required to detect differences with a power of 95% and a significance level of 5% (two-tailed). However, due to external constraints beyond our control—such as the distance between participants' residences and training facilities, as well as the challenge of recruiting treatment-naïve patients without pharmacological intervention—only 11 participants were included in the study. A post-hoc power analysis revealed a statistical power of 66.7% for detecting an effect size of 0.8. While this is below the conventional threshold of 80%, the significance of observed effects remains valid, as meaningful differences were detected despite the reduced sample size.

Descriptive statistics are presented as means and standard deviations (SD), or median and inter-quartile range. Normality analysis was conducted using the Shapiro-Wilk test. T-Test was employed to analyze differences between genders. To analyze the relationship between variables, Pearson correlation coefficients were calculated, and all assumptions for Pearson correlation were checked and met. To evaluate the influence of Moderate-to-Vigorous Physical Activity (MVPA), the participants were divided into tertiles based on their MVPA levels, creating three groups to compare the most active and the least active individuals. Parametric (ANOVA) and non-Parametric (Kruskal-Wallis) tests were deployed to verify differences across these groups for continuous variables and goodness-of-fit chi-square for categorical. Effect size was assessed using Hedges' g scores (due to tendency of hyper estimation with Cohen's d effect size on small samples), where values of 0.2, 0.5 and 0.8 were considered small, medium, and large effects, respectively [44]. Significance was maintained at $p < 0.05$.

For the questionnaire subdomains and composite scores, we followed recommendations from the authors (EORTC [41] and FACIT [40]) and similar exercise studies in cancer [45-47]. Therefore, in line with recommendations and the independence of each subdomain, no adjustments for multiple comparisons between subdomains were performed.

Accelerometry analysis was conducted using the algorithm Troiano (2007) defining non-wear period with minimum length of 60 minutes, with spike level to stop at 100 counts per minutes, over seven consecutive days, with a minimum four weekdays and one weekend day and of 10 hours of daily assessment [36]. For scoring algorithms, it was used Freedson VM3 2011 for energy expenditure, Freedson Adult 1998 for METs, and Troiano Adult 2008 for Cut Points and MVPA.

Statistical analyses were conducted using IBM SPSS mac version 29 (Armonk, NY, United States), and accelerometry analysis were conducted using Actigraph Actilife version 6.13.6 (Pensacola, FL, United States).

Results

During the recruitment phase, from September 2023 until August 2024, twenty-three patients were assessed for eligibility in clinical hematology consultation, with 6 patients excluded due to not meeting inclusion criteria. After clinical screening we were unable to reach contact with 4 patients, while another 2 referred transportation issues to comply with physical fitness screening. Eleven participants were consented into the study. The complete flowchart can be consulted in figure 1.

Total sample comprised eleven participants, 7 men and 4 women with mean age of 65.55 (± 9.73) (range: 47-78) years. Regarding baseline characteristics for body composition, this group of patients presents above weight recommendations with overall average BMI = 26.72 (2.22), and slightly overfat with body fat percentage for male and female patients of 36.7 (5.7) and 24.3 (6.8) percent, respectively. Regarding bone health, measured by DEXA, female group is in osteopenia stage (T-score less than -1 SD from normal values), while in male group only 3 patients reveal this condition. None of the patients reveal osteoporosis, however only 4 (36.4%) patients revealed healthy bone measures. Differences between genders show relevant statistical significances in height, body fat percentage, lean mass and femur neck bone mineral density, favoring male participants.

Overall mean time since diagnosis was 3.65 (range: 1.12-10.31) years. Participants were mostly on RAI stage I (54.5%), BINET stage A (72.7%) and ECOG status 0 (63.6%). Due to inclusion and exclusion criteria, this was expected, since patients were in surveillance phase, without treatment.

When analyzing the measured hematologic parameters, patients show percentages of lymphocytes counts above normal values (expected in CLL disease), while neutrophils appear particularly low [40.0% (11.7)]. Regarding immunologic parameters, only 1 patient revealed unfavorable prognostic with B2-microglobulin above 2.5 $\mu\text{g/l}$, an indicator of high tumoral charge and disease activity, while immunoglobulins appear controlled, with favorable values indicating low risk for infections. The complete description, at baseline, of Demographic, Body Composition, Hematologic and Immunologic data can be consulted in table 1.

Variable	Male (n=7)		Female (n=4)		Full Sample (n=11)	
	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)
Demographic and Body Composition Data						
Age (years)	47 - 73	61.7 (9.5)	63 - 78	72.3 (6.5)	47 - 78	65.6 (9.7)
Height (cm)	155 - 177	169.1 (8.6)	143 - 162	152.8 (10.1)	143 - 177	163.2 (12.0)
Weight (kg)	58.5 - 93.8	77.2 (14.0)	52.0 - 73.4	60.8 (9.7)	52 - 93.8	71.2 (14.6)
BMI (kg/m ²)	23.8 - 30.6	27.0 (2.6) †	24.6 - 28.4	26.3 (1.6) †	23.8 - 30.6	26.7 (2.2) †
Body Fat (%)	14.8 - 36.6	24.3 (6.8) †	29.7 - 43.4	36.7 (5.7) †	14.8 - 43.4	28.8 (8.7) †
Lean Mass (kg)	45.9 - 67.6	55.2 (7.3)	32.0 - 43.1	36.8 (5.6)	32 - 67.6	48.5 (11.3)
Femur Neck BMD (g/cm ³)	0.64 - 0.95	0.81 (0.13)	0.60 - 0.67	0.64 (0.03)	0.60 - 0.95	0.75 (0.13)
Femur Neck BMD (T-score)	-2.2 - 0.1	-0.91 (0.92)	-2.2 - -1.6	-1.83 (0.29) †	-2.2 - 0.1	-1.24 (0.86) †
Hematologic/Immunologic Data						
Hematocrit (%)	39.9 - 48.8	44.4 (2.9)	36.0 - 43.2	40.3 (3.5)	36 - 48.8	42.3 (3.3)
RBC (x10 ¹² /L)	4.2 - 5.2	4.7 (0.4)	3.9 - 5.1	4.7 (0.6)	3.9 - 5.2	4.7 (0.5)
Hemoglobin (g/dL)	12.8 - 16.2	14.5 (1.1)	11.6 - 14.2	13.1 (1.2)	11.6 - 16.2	14.0 (1.3)
Platelets (x10 ⁹ /L)	115 - 302	176.3 (75.9)	190 - 299	238.5 (49.3)	115 - 302	198.9 (71.9)
WBC (x10 ⁹ /L)	7.2 - 33.7	18.1 (9.2)	10.1 - 17.6	13.7 (3.1)	7.2 - 33.7	16.5 (7.6)
Lymphocytes (%)	37.1 - 72.2	52.6 (13.3) †	54.2 - 77.0	62.3 (10.2) †	37.1 - 77	56.1 (12.7) †
Monocytes (%)	0.5 - 5.3	3.2 (1.9)	2.6 - 4.9	3.6 (1.0)	0.5 - 5.3	3.4 (1.6)
Neutrophils (%)	12.5 - 47.6	27.4 (10.6) †	19.8 - 42.3	32.8 (9.4) †	12.5 - 47.6	29.4 (10.1) †
Albumin (g/L)	41.8 - 53.2	45.6 (4.1)	43.4 - 45.7	44.9 (1.1)	41.8 - 53.2	45.3 (3.1)
LDH (units/L)	132 - 186	160.4 (21.4) †	132 - 226	188.0 (40.6) †	132 - 226	170.5 (31.0) †
B2-microglobulin (μg/L)	1430 - 1690	1552.8 (108.3)	1369 - 2590	1854.8 (521.2)	1369 - 2590	1687 (364.8)
IgG (mg/dL)	706 - 1860	1169.2 (421.2)	896 - 1070	991.8 (75.7)	706 - 1860	1090.3 (315.6)
IgA (mg/dL)	53 - 328	175.2 (114.1)	106 - 180	140 (34.9)	53 - 328	159.6 (85.5)
IgM (mg/dL)	20 - 114	62.4 (34.3)	40 - 167	92.3 (53.6)	20 - 167	75.7 (43.7)

Table 1: Baseline of demographic, body composition, hematologic and immunologic data (n = 11). Values are means (standard deviations). BMI=Body Mass Index. WBC=White Blood Cells. RBC=Red Blood Cells. LDH=Lactate Dehydrogenase. †=Bold values are out of the normative reference intervals.

Regarding Physical Fitness parameters, this group of patients revealed a very low cardiovascular capacity with mean values of 16.1 (5.1) ml/kg/min ranging between 9.0 and 24.3 ml/kg/min VO_{2peak} . None of the patients exceeded 135 watts of peak power in the cycle ergometer maximal test, reaching 85% maximal heart rate criteria, with a mean value of 84 (45.4) watts. Regarding strength characteristics, a peak torque knee extension of 113.1 (54.3) N.m and flexion of 55.4 (21.3) N.m reveal a ratio of 52.6% between agonist/antagonist. Differences between genders show relevant statistical significances in all physical fitness parameters, favoring male participants.

Concerning accelerometry, participants have coped with a minimum of 4 weekdays and 1 weekend day established as inclusion criteria for analysis. So, for this group of patients, the usability and feasibility of the wearable device wear were accomplished, exceeding it. When analyzing sedentary behavior, the patients spent 58% of their time in this behavior, while light, moderate and vigorous physical activity counts for 39%, 2.4% and approximately 0%, respectively. When exploring daily physical activity and sedentary time, male patients revealed less sedentary time and more physical activity when compared to female patients, with male groups showing 53.5% of the time in sedentary behavior while the female group showed 67.5%. When comparing light and moderate-to-vigorous PA, both genders reveal more light PA between 12h00 and 18h00, but patterns of moderate-to-vigorous PA are different between genders, with female group revealing more MVPA between 7h00 and 12h00, while in male group appears to be around 12h00 until 18h00, as depicted in figure 2.

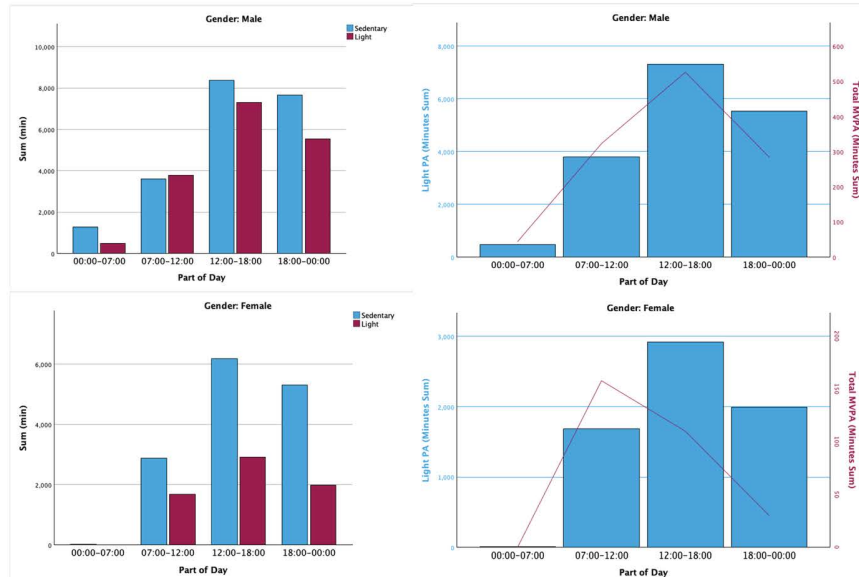


Figure 2: Representative accelerometry analysis to illustrate the differences between parts of the day and Physical Activity patterns grouped by gender. MVPA=Moderate-to-Vigorous Physical Activity. PA= Physical Activity.

When analyzing quality of life questionnaires our data reveal that in the EORTC, patients have a perception of high physical functioning 83.63 (13.79), also in line with FACIT-F with the perception of high physical well-being of 24.27 (2.49) of a maximal 28 points. The complete description of baseline of Physical and Functional capacity, Accelerometry and Quality of Life data can be consulted in table 2.

Variable	Male (n=7)		Female (n=4)		Full Sample (n=11)	
	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)
Physical and Functional Capacity						
Peak Power Output (watts)	75 - 135	112.5 (24.6)	15 - 90	41.3 (33.3)	15 - 135	84.0 (45.4)
VO2 (ml/kg/min)	12.5 - 24.3	19.3 (3.9)	9 - 14.1	11.5 (2.1)	9 - 24.2	16.1 (5.1)
Peak Torque Knee Extension (N.m)	92.2 - 238.1	140.5 (52.1)	42.8 - 102.1	72.1 (24.5)	42.8 - 238.1	113.1 (54.3)
Peak Torque Knee Flexion (N.m)	47.3 - 92.7	67.5 (19.5)	35.7 - 40.1	37.3 (2.1)	35.7 - 92.7	55.4 (21.3)
Peak Grip force Left (kg)	42.6 - 55.5	49.4 (5.0)	16.5 - 29.3	23.2 (7.0)	16.5 - 55.5	38.9 (14.6)
Peak Grip force Right (kg)	32.5 - 60.9	48.4 (10.6)	18.2 - 30.8	24.6 (7.1)	18.2 - 60.9	38.9 (15.2)
Accelerometry Data						
Average Wear Time (min)	739 - 937	832 (71)	685 - 821	761 (65)	685 - 937	805.9 (75.0)
Sedentary Time (min/day)	296 - 610	445.5 (107.1)	404 - 653	513.9 (104.2)	296 - 653	470.4 (106.5)
Light Physical Activity (min/day)	271 - 541	361.6 (92.5)	167 - 302	235.9 (59.5)	167 - 541	315.9 (101.1)
Moderate Physical Activity (min/day)	9.7 - 46.3	24.7 (14.0)	0.7 - 24.1	10.6 (11.5)	0.7 - 46.3	19.6 (14.4)
Vigorous Physical Activity (min/day)	0 - 0.6	0.08 (0.22)	0 - 0	0.00 (0.0)	0 - 0.6	0.05 (0.17)
Quality of Life Questionnaires						
FACIT-F						
Physical Well-being (0 - 28)	24 - 27	25 (1.2)	18 - 26	23 (3.8)	18 - 27	24.3 (2.5)
Functional Well-being (0 - 28)	20 - 26	23.1 (2.3)	19 - 25	21.5 (2.6)	19 - 26	22.6 (2.5)
Fatigue Subscale (0 - 52)	39 - 46	42.1 (2.5)	30 - 45	39.3 (7.2)	30 - 46	41.1 (4.7)
FACIT-G Total Score (0 - 108)	73 - 102	88.6 (10.8)	82 - 90	86.3 (3.5)	73 - 102	87.7 (8.6)
FACIT-F Total (0 - 160)	118 - 144	130.7 (10.2)	115 - 133	125.5 (7.5)	115 - 144	128.8 (9.3)
EORTC-QLQ30 (0 - 100)						
Physical functioning	73.3 - 100	89.5 (12.1)	60 - 86.7	73.3 (10.9)	60 - 100	83.6 (13.8)
Average Symptom Scale	2.5 - 23.5	11.5 (7.8)	2.5 - 23.5	17.0 (9.8)	2.5 - 23.5	13.5 (8.5)
EORTC-QLQ-CLL17 (0 - 100)						
Symptom burden	5.6 - 27.8	15.1 (8.9)	0 - 50	19.4 (21.5)	0 - 50	16.7 (13.8)

17

18

Physical condition / fatigue	0 – 25	11.9 (8.1)	0 – 50	22.9 (22.9)	0 – 50	15.9 (15.1)
Worries / fears about health and functioning	4.8 – 66.7	26.5 (19.4)	0 – 52.4	25 (26.5)	0 – 66.7	26.0 (20.9)

Table 2; Baseline of Physical and Functional capacity, Accelerometry Data and Quality of Life Questionnaires (n = 11). Values are means (standard deviations). FACIT-G=Functional Assessment of Cancer Therapy – General. FACIT-F=Functional Assessment of Cancer Therapy – Fatigue.

When analyzing the influence of MVPA on the outcomes of CLL patients, higher MVPA levels were associated, albeit without statistical significance, with a tendency toward lower B2-microglobulin levels and resting systolic blood pressure, as well as higher lean mass, BMI, and strength-related parameters, including left- and right-hand grip strength and isokinetic extension and flexion strength.

High positive correlations with statistical significance were found between total MVPA and peak torque knee extension ($r = 0.78$, $p = 0.008$), peak torque knee flexion ($r = 0.77$, $p = 0.010$), grip strength of right hand ($r = 0.74$, $p = 0.015$); and between Lean Mass and Femur Neck Bone Mass Density ($r = 0.66$, $p = 0.029$), VO_{2peak} ($r = 0.86$, $p = 0.002$), Peak Torque Knee (Extension ($r = 0.82$, $p = 0.004$) and Flexion ($r = 0.86$, $p = 0.001$)), Peak Grip Force [Left ($r = 0.88$, $p = 0.001$) and Right ($r = 0.82$, $p = 0.003$)]. The association between Lean Mass and MVPA ($r = -0.45$ and $r = -0.54$ respectively) with B2-microglobulin disease marker revealed a negative medium correlation, but without statistical significance. The complete description of correlations can be found in table 3.

	Total MVPA (min)		Lean Mass (g)		VO ₂ (ml/min)		VO ₂ (ml/kg/min)	
	r	p-value	r	p-value	r	p-value	r	p-value
Total MVPA (min)	-	-	0.57	0.068	0.28	0.438	0.005	0.988
Body Fat (%)	-0.31	0.359	-0.50	0.115	-0.55	0.103	-0.74**	0.014
Lean Mass (g)	0.57	0.068	-	-	0.86**	0.002	0.61	0.062
Femur Neck BMD (g/cm³)	0.21	0.530	0.66*	0.029	0.86**	0.002	0.84**	0.002
VO₂ (ml/min)	0.28	0.438	0.86**	0.002			0.87**	0.001
VO₂ (ml/kg/min)	0.01	0.988	0.61	0.062	0.87**	0.001		
Peak Torque Knee Extension (N.m)	0.78**	0.008	0.82**	0.004	0.69**	0.027	0.43	0.211
Peak Torque Knee Flexion (N.m)	0.77**	0.010	0.86**	0.001	0.62	0.057	0.41	0.240
Peak Grip force Left (kg)	0.58	0.078	0.88**	0.001	0.77**	0.009	0.59	0.074
Peak Grip force Right (kg)	0.74*	0.015	0.82**	0.003	0.57	0.086	0.41	0.235

Table 3: Correlations between total Moderate-to-Vigorous Physical Activity (MVPA) and Lean Mass against physical variables. (*) Correlation is significant at the 0.05 level (2-tailed). (**) Correlation is significant at the 0.01 level (2-tailed).

Discussion

The early dissemination of study baseline data offers important contributions to the understanding of CLL in treatment naive stage characteristics. The data collected to date offers valuable insights into the initial profile of patients, allowing sample characterization and identification of initial trends, that may diverge from common knowledge from available literature and clinical practice. The present study addresses the characteristics of diagnosed Chronic Lymphocytic Leukemia patients in “watch and wait” phase and the relation between PA levels with significant health outcomes, without implemented immunochemotherapy treatment or indication for treatment initiation.

Participants revealed values above baseline normative data in healthy populations regarding the percentage of body fat parameter. Considering that there are no universally accepted norms for body fat percentage, according to ACSM an optimal range of 10%-22% and 20%-32% for men and women, respectively, has long been viewed as satisfactory for health [48]. This group of patients, slightly above with 24.3% and 36.7% of body fat for men and women, respectively, reveal a factor that may impact symptom burden, since correlations of present data suggest a statistically significant association between body fat percentage and VO_{2peak} , Fatigue, Physical Functioning and Average Symptom Burden (last one with median correlation without statistical significance), also in line with available studies with CLL population [14, 15, 17].

The unfavorable body composition profile may be partially explained by the Physical Condition parameter, where this group of patients revealed a low cardiovascular fitness, with the best test value in our overall sample of 24.3 ml/kg/min VO_{2peak} , taken by a male patient nevertheless still below the minimal expected for a healthy female adult which is of 27 ml/kg/min according to literature [48]. Current knowledge advises that the increment in VO_2 is associated with lower levels of fatigue [14, 15], higher levels of muscular resistance and bone mineral density [14-16], improving physical functioning and well-being [12], which may directly impact daily tasks, maintaining daily physical activity, and reducing disease-related fatigue.

One factor that remains underexplored, is the influence of strength and muscle mass on CLL patients. Several studies show a preference for low-moderate intensities or endurance effort on resistance training (65-70% of 1-RM), but as the literature suggests, exercise-induced myokines production may have a critical role in increasing cytotoxicity and the infiltration of immune cells into the tumor [49]. When comparing aerobic-only,

Strength and Combined Guidelines in the Hazard Ratio for All-Cause Mortality, strength training was considered better than Aerobic in the case of cardiovascular disease mortality and in cancer mortality, where isolated strength training was shown to be the better option compared to other modes of training [50]. The presence of low muscle mass when compared to healthy adults [51] is similar between our study and other interventions with exercise training in CLL patients; however, there are still few studies addressing the use of strength training on CLL patients. In our data, correlation analysis suggests that greater muscle mass is strongly associated with higher strength levels in patients with CLL, similar to what is observed in the general population. Given that one of the major symptoms of the disease is the loss of weight, this underscores the potential importance of incorporating strength training into the management of CLL to keep muscle mass and physical function. Given that training intensity can influence long-term adherence, strength training—using weights at approximately 75–85% of one-repetition maximum—may be better tolerated than continuous aerobic endurance training. This is particularly relevant as fatigue and dyspnea during routine physical activity are among the most prominent symptoms of disease progression. The structure of strength training, which typically involves short sets with extended rest intervals (60–90 seconds), may facilitate greater respiratory comfort and improve exercise adherence.

One of the factors that may influence the auto-conscience for this problem is that when analyzing the quality-of-life questionnaires, the individuals do not report significant symptoms impairing their daily life quality. However, their perception of high physical functioning does not align with their fitness levels. Several longitudinal studies show that a higher perception of physical functioning by the CLL patient is very close to healthy control values [52, 53]. When crossing this data with interventions with exercise with CLL patients, we can confirm this tendency. In a study from Artese et al. [54] data show that CLL patients with 31% of body fat, VO_2 of 26.7 ml/kg/min., considered their Physical Well-Being and Functional Well-Being with a value of 27 and 25.7 (in a scale from 0-28), respectively; in another study from Furzer et al. [15], patients with 34.6% body fat and 16.10 in 75% VO_2 /kg reported a FACT-G score of 82 (in a scale from 0-108); another study with a wider sample of patients, but that also included CLL patients, Courneya et al. [14] found a value in FACT-An of 147.1 (in a scale from 0-188) in a group with 32.6% body fat and a VO_2 of 25.4 ml/kg/min.

One piece of evidence that arises from our data is that MVPA is not significant with any parameter besides lymphocyte percentage. Even after exploring data with median and tertile ranking, MVPA appears to have no impact on disease parameters. Nevertheless, in our sample, the hours of peak MVPA and light PA lays between 7:00 and 18:00, in line with the latest studies, that speculate a lower risk of incidence of cardiovascular diseases and cancer risk for those who are active between this timeline [55, 56]. The protective effect of chronoactivity

may be one variable, but we cannot disregard that, besides the low number of patients in our sample, the lack of minutes in MVPA recommended from major organizations [48, 57], defining at least 150min of moderate to vigorous activity per week, is critically low in our study barely reaching 19.61 minutes per day in this intensity, not according to available literature that explores the association of CLL and physical activity patterns [17, 58] who got higher values of objectively measured daily physical activity.

Regarding immunologic parameters, when comparing our sample values with normative values for Portugal healthy population [59], our CLL sample only presents above normal in Lymphocytes and Neutrophils percentage, with patients showing percentages of Lymphocytes high and above normal values (expected in CLL disease), and Neutrophils appearing particularly low revealing increased risk for infections. Literature concerning immunologic parameters of CLL patients in exercise interventions are scarce. As far as our knowledge, when comparing with the two available studies that implement immunologic analysis from Crane et al. [18] and Macdonald et al. [17], our sample present similar values for main serologic data, differing only with lower white blood cells counts, lower lymphocytes and monocytes percentages, higher neutrophils percentages, lower B2-microglobulin, lower LDH and Albumin. This may impact in future study analysis, because our sample of patients reveal a more favorable diagnostic of disease.

We recognize that limitations arising from ongoing recruitment may impact the generalizability of findings and the statistical power of the analysis. However, data presented in present study establishes a baseline analysis for CLL treatment naïve patients.

Conclusions

In conclusion, we demonstrate that our sample of patients with CLL in treatment naïve phase present values above baseline normative data for healthy populations in the body composition parameter, fact that may be explained by the Physical Condition parameter, where this group of patients revealed a low cardiovascular fitness. We also show that, for this sample of patients, they do not report significant symptoms impairing their daily life quality due to their perception of high physical functioning unaligned with their fitness levels. Our data, reflects that greater muscle mass appears to be strongly associated with higher strength levels in patients with CLL, similar to what is observed in the general population. Although there is an increasing body of literature that

links exercise training, muscle function and immune functions in older adults, the effects of strength training on CLL patients remains underexplored. Given that one of the major symptoms of the disease is the loss of weight, this underscores the potential importance of incorporating strength training into the management of CLL to keep muscle mass and physical function, and further studies who can measure the outcomes in physical fitness, quality of life and well-being.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

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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.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Centro Hospitalar de São João (CE 431-19), and by the Faculty of Sport - University of Porto (CEFADE 14_2024), and informed consent was obtained from all individual participants included in the study.

References

1. Ou, Y., et al., *Trends in Disease Burden of Chronic Lymphocytic Leukemia at the Global, Regional, and National Levels From 1990 to 2019, and Projections Until 2030: A Population-Based Epidemiologic Study*. Front Oncol, 2022. **12**: p. 840616.
2. Yao, Y., et al., *The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019*. Biomed Eng Online, 2022. **21**(1): p. 4.
3. Artese, A.L., et al., *Quality Of Life Changes Following High-intensity Interval Training In Older Adults With Chronic Lymphocytic Leukemia*. Medicine & Science in Sports & Exercise, 2022. **54**(9): p. 157-158.
4. Neil, S.E., C.C. Gotay, and K.L. Campbell, *Physical activity levels of cancer survivors in Canada: findings from the Canadian Community Health Survey*. Journal of Cancer Survivorship, 2014. **8**(1): p. 143-149.
5. Veliz, M. and J. Pinilla-Ibarz, *Treatment of relapsed or refractory chronic lymphocytic leukemia*. Cancer Control, 2012. **19**(1): p. 37-53.
6. Shanafelt, T.D., et al., *Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients*. British Journal of Haematology, 2007. **139**(2): p. 255-264.
7. Sitlinger, A., et al., *Exercise and Chronic Lymphocytic Leukemia (CLL) - Relationships Among Physical Activity, Fitness, & Inflammation, and Their Impacts on CLL Patients*. Blood, 2018. **132**: p. 3.
8. Chastin, S.F.M., et al., *Effects of Regular Physical Activity on the Immune System, Vaccination and Risk of Community-Acquired Infectious Disease in the General Population: Systematic Review and Meta-Analysis*. Sports Medicine, 2021. **51**(8): p. 1673-1686.
9. Krüger, K., F.C. Mooren, and C. Pilat, *The Immunomodulatory Effects of Physical Activity*. Current Pharmaceutical Design, 2016. **22**(24): p. 3730-3748.
10. De Backer, I.C., et al., *Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life*. Br J Cancer, 2008. **99**(1): p. 30-6.
11. Chen, L.J., et al., *The effects of exercise on the quality of life of patients with breast cancer: a systematic review and meta-analysis based on the QLQ-C30 quality of life scale*. Gland Surgery, 2023. **12**(5): p. 633-650.
12. Campbell, K.L., et al., *Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable*. Med Sci Sports Exerc, 2019. **51**(11): p. 2375-2390.
13. Pedersen, B.K. and B. Saltin, *Evidence for prescribing exercise as therapy in chronic disease*. Scandinavian Journal of Medicine & Science in Sports, 2006. **16**: p. 3-63.
14. Courneya, K.S., et al., *Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients*. Journal of Clinical Oncology, 2009. **27**(27): p. 4605-4612.
15. Furzer, B.J., et al., *A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients*. Supportive Care in Cancer, 2016. **24**(4): p. 1697-1707.
16. Nadler, M.B., et al., *The Effect of Exercise on Quality of Life, Fatigue, Physical Function, and Safety in Advanced Solid Tumor Cancers: A Meta-analysis of Randomized Control Trials*. Journal of Pain and Symptom Management, 2019. **58**(5): p. 899-+.
17. MacDonald, G., et al., *A pilot study of high-intensity interval training in older adults with treatment naive chronic lymphocytic leukemia*. Sci Rep, 2021. **11**(1): p. 23137.
18. Crane, J.C., et al., *Relationships between T-lymphocytes and physical function in adults with chronic lymphocytic leukemia: Results from the HEALTH4CLL pilot study*. European Journal of Haematology, 2023. **110**(6): p. 732-742.
19. Sitlinger, A., D.M. Brander, and D.B. Bartlett, *Impact of exercise on the immune system and outcomes in hematologic malignancies*. Blood Advances, 2020. **4**(8): p. 1801-1811.
20. Vallerand, J.R., et al., *Correlates of meeting the combined and independent aerobic and strength exercise guidelines in hematologic cancer survivors*. International Journal of Behavioral Nutrition and Physical Activity, 2017. **14**.
21. Troiano, R.P., et al., *Physical activity in the United States measured by accelerometer*. Medicine and Science in Sports and Exercise, 2008. **40**(1): p. 181-188.

22. Tudor-Locke, C., et al., *Accelerometer profiles of physical activity and inactivity in normal weight, overweight, and obese US men and women*. International Journal of Behavioral Nutrition and Physical Activity, 2010. **7**.
23. Stevens, W.R., A.M. Anderson, and K. Tulchin-Francis, *Validation of Accelerometry Data to Identify Movement Patterns During Agility Testing*. Frontiers in Sports and Active Living, 2020. **2**.
24. Khakurel, J., et al., *A Comprehensive Framework of Usability Issues Related to the Wearable Devices, in Convergence of ICT and Smart Devices for Emerging Applications*, S. Paiva and S. Paul, Editors. 2020, Springer International Publishing: Cham. p. 21-66.
25. Bade, B.C., et al., *Assessing the Correlation Between Physical Activity and Quality of Life in Advanced Lung Cancer*. Integrative Cancer Therapies, 2018. **17**(1): p. 73-79.
26. Chan, C., et al., *Wearable Activity Monitors in Home Based Exercise Therapy for Patients with Intermittent Claudication: A Systematic Review*. European Journal of Vascular and Endovascular Surgery, 2021. **61**(4): p. 676-687.
27. Ormel, H.L., et al., *Self-monitoring physical activity with a smartphone application in cancer patients: a randomized feasibility study (SMART-trial)*. Supportive Care in Cancer, 2018. **26**(11): p. 3915-3923.
28. Ferriolli, E., et al., *Physical Activity Monitoring: A Responsive and Meaningful Patient-Centered Outcome for Surgery, Chemotherapy, or Radiotherapy?* Journal of Pain and Symptom Management, 2012. **43**(6): p. 1025-1035.
29. Ella, K., R. Csepányi-Kömi, and K. Káldi, *Circadian regulation of human peripheral neutrophils*. Brain Behavior and Immunity, 2016. **57**: p. 209-221.
30. Hallek, M., et al., *iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL*. Blood, 2018. **131**(25): p. 2745-2760.
31. Pritchard, A., et al., *ARTP statement on cardiopulmonary exercise testing 2021*. Bmj Open Respiratory Research, 2021. **8**(1).
32. Radtke, T., et al., *Standardisation of cardiopulmonary exercise testing in chronic lung diseases: summary of key findings from the ERS task force*. European Respiratory Journal, 2019. **54**(6).
33. Harkonen, R., R. Harju, and H. Alaranta, *Accuracy of the Jamar dynamometer*. J Hand Ther, 1993. **6**(4): p. 259-62.
34. Research, N.I.f.H., *Procedure for Measuring Hand Grip Strength Using The JAMAR Dynamometer*. 2014, NIHR Southampton Biomedical Research Centre: Southampton. p. 6.
35. Kannus, P., *Isokinetic evaluation of muscular performance: implications for muscle testing and rehabilitation*. Int J Sports Med, 1994. **15 Suppl 1**: p. S11-8.
36. Broderick, J.M., et al., *A guide to assessing physical activity using accelerometry in cancer patients*. Supportive Care in Cancer, 2014. **22**(4): p. 1121-1130.
37. Binet, J.L., et al., *A New Prognostic Classification of Chronic Lymphocytic-Leukemia Derived from a Multivariate Survival Analysis*. Cancer, 1981. **48**(1): p. 198-206.
38. Rai, K.R., et al., *Clinical Staging of Chronic Lymphocytic Leukemia*. Blood, 1975. **46**(2): p. 219-234.
39. Sorensen, J.B., et al., *Performance status assessment in cancer patients. An inter-observer variability study*. Br J Cancer, 1993. **67**(4): p. 773-5.
40. Webster, K., D. Cella, and K. Yost, *The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation*. Health Qual Life Outcomes, 2003. **1**: p. 79.
41. Oerlemans, S., et al., *International validation of the EORTC QLQ-CLL17 questionnaire for assessment of health-related quality of life for patients with chronic lymphocytic leukaemia*. Br J Haematol, 2022. **197**(4): p. 431-441.
42. Institute, J.B., *Checklist for analytical cross-sectional studies*. 2020, Joanna Briggs Institute: Adelaide, Australia.
43. Kang, H., *Sample size determination and power analysis using the G*Power software*. Journal of Educational Evaluation for Health Professions, 2021. **18**.
44. Cohen, J., *Statistical Power Analysis for the Behavioral Sciences*. 2nd Edition ed. 1988, New York: Routledge.
45. Yamada, P.M., C. Teranishi-Hashimoto, and E.O. Bantum, *Paired exercise has superior effects on psychosocial health compared to individual exercise in female cancer patients*. Supportive Care in Cancer, 2021. **29**(11): p. 6305-6314.
46. Segal, R.J., et al., *Randomized Controlled Trial of Resistance or Aerobic Exercise in Men Receiving Radiation Therapy for Prostate Cancer*. Journal of Clinical Oncology, 2009. **27**(3): p. 344-351.
47. Milne, H.M., et al., *Effects of a combined aerobic and resistance exercise program in breast cancer survivors: a randomized controlled trial*. Breast Cancer Research and Treatment, 2008. **108**(2): p. 279-288.

48. ACSM, *ACSM's Guidelines for Exercise Testing and Prescription*. Tenth ed. 2018, Philadelphia, PA: Wolters Kluwer Health.
49. Kim, J.S., et al., *Exercise-induced myokines and their effect on prostate cancer*. *Nat Rev Urol*, 2021. **18**(9): p. 519-542.
50. Stamatakis, E., et al., *Does Strength-Promoting Exercise Confer Unique Health Benefits? A Pooled Analysis of Data on 11 Population Cohorts With All-Cause, Cancer, and Cardiovascular Mortality Endpoints*. *Am J Epidemiol*, 2018. **187**(5): p. 1102-1112.
51. Imboden, M.T., et al., *Reference standards for lean mass measures using GE dual energy x-ray absorptiometry in Caucasian adults*. *Plos One*, 2017. **12**(4).
52. Holzner, B., et al., *Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr*. *European Journal of Haematology*, 2004. **72**(6): p. 381-389.
53. Youron, P., et al., *Quality of life in patients of chronic lymphocytic leukemia using the EORTC QLQ-C30 and QLQ-CLL17 questionnaire*. *European Journal of Haematology*, 2020. **105**(6): p. 755-762.
54. Artese, A.L., et al., *Effects of high-intensity interval training on health-related quality of life in chronic lymphocytic leukemia: A pilot study*. *J Geriatr Oncol*, 2022.
55. Stein, M.J., et al., *Diurnal timing of physical activity and risk of colorectal cancer in the UK Biobank*. *Bmc Medicine*, 2024. **22**(1).
56. Albalak, G., et al., *Setting your clock: associations between timing of objective physical activity and cardiovascular disease risk in the general population*. *European Journal of Preventive Cardiology*, 2023. **30**(3): p. 232-240.
57. Okely, A.D., et al., *2020 WHO guidelines on physical activity and sedentary behavior*. *Sports Medicine and Health Science*, 2021. **3**(2): p. 115-118.
58. Persoon, S., et al., *Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: Results from the EXIST study*. *Plos One*, 2017. **12**(7).
59. Portugal, A.M.S. *VALORES LABORATORIAIS DE REFERÊNCIA (ADULTOS)*. 2018 [cited 2025 5 of March]; Available from: https://www.acss.min-saude.pt/wp-content/uploads/2018/09/Tabela_Final.pdf.

PAPER III

Psychological Well-Being and Quality of Life Improvements Following Strength-Based Resistance

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Title: *Psychological Well-Being and Quality of Life Improvements Following Strength-Based Resistance Training in Older Adults with Chronic Lymphocytic Leukemia: ADRENALINE Pilot Study*

Trial Registration: Registered at ClinicalTrials.gov (NCT06396611).

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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. 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-naïve CLL patients.

Methods: The trial included patients aged 45-80 years with confirmed CLL, randomized into a resistance exercise (REx) group or usual care control (CG). Primary and secondary 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).

KEYWORDS: Physical Activity; Exercise; Resistance Training; Quality of Life; Chronic Lymphocytic Leukemia; Oncology.

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Introduction

Described as the proliferation of monoclonal mature B lymphocytes (Ou et al., 2022), Chronic Lymphocytic Leukemia (CLL) is the most common chronic leukemia in western countries (NIH, 2022). With leukemia arising as the eighth leading cause of cancer-related deaths in Europe since 2019, CLL shows a prevalence of 25% to 35% in older adults between 65-74 years old (Yao et al., 2022). Typically, whereas patients with cancer have poor overall physical condition, associated with the progression of disease symptoms and negative outcomes during and after therapy (Schmitz, 2020), exercise engagement can serve as an adjunct in preventing the physiological decline, while promoting adequate daily physical activity and exercise (Campbell et al., 2019; Schmitz, 2020). This line of evidence, elicited a novel field of investigation, due to the recognized importance of physical activity and structured exercise on immunomodulatory effects (Sitlinger et al., 2020). 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 (Sitlinger et al., 2020).

Frequently, low daily 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 (Holzner et al., 2004). Thus, interventions that could minimize dysfunction (physical, functional, social, role, psychological, 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 mental health, 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 (Andersen et al., 2022; Noetel et al., 2024). Likewise, resistance training also showed an important impact on mental health, 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 (Andersen et al., 2022; Noetel et al., 2024). The combination of Cardio and Resistance Training also revealed a reduction in depressive symptoms, blood pressure, and enhanced health-related quality of

life, compared to cardio alone in other populations with different diseases (Parker et al., 2024). In studies with CLL patients, this relationship was observed with large effect sizes for improved functional well-being (Artese et al., 2022), physical fitness, fatigue and health-related quality of life (Persoon et al., 2017), but without significant changes across the mental component score (Furzer et al., 2016). However, regarding CLL population, there is no literature that address the influence of a resistance training independently of cardio. Knowing that a structured resistance training promotes behavioral changes linked to goal setting, self-monitoring, and promoting autonomy during interventions (Noetel et al., 2024), 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. 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 (rAndomiseD contRollEd cliNical triAL of exercIse as Intervention in chroNic lymphocytic leukEmia) 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 (Hallek et al., 2018), 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, maximal strength on dynamometer and maximal exercise stress electrocardiogram with spirometry on a cycle ergometer. The levels of physical daily activity were objectively evaluated using accelerometers, to collect data on the Physical Activity (PA) patterns of participants, over a period of seven consecutive days, with a minimum of 10 hours daily assessment.

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 in primary and secondary outcomes measures 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 figure 1.

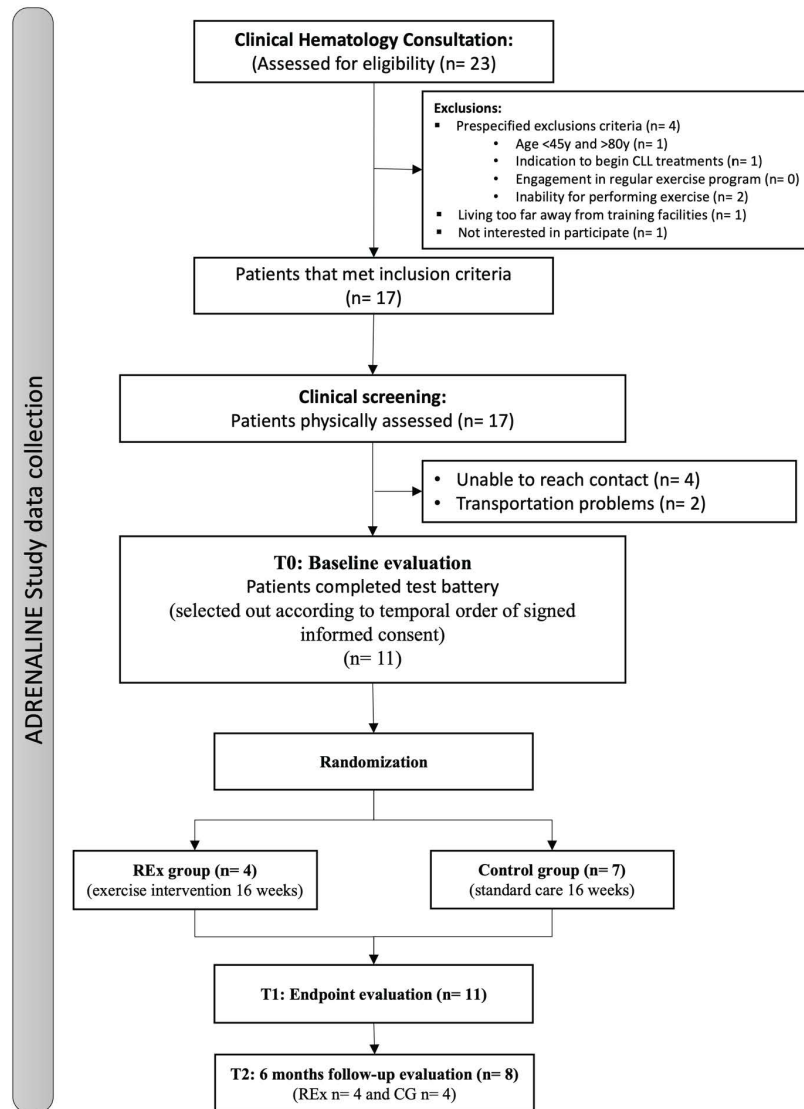


Figure 1: Consolidated standards of reporting trials (consort) diagram. REx=Resistance Exercise. CLL=Chronic Lymphocytic Leukemia.

Randomization

Randomization was performed using the Clinical Trial Randomization Tool from The National Cancer Institute's Division of Cancer Prevention (Institute, 2023), 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: i) anthropometric, body composition measures and bone mineral density; ii) strength evaluation (dynamometry and one-repetition maximum (1-RM) for the whole-body strength assessment); iii) cardiac and respiratory evaluation CPET on a cycle ergometer with 12-derivation electrocardiogram and spirometry.

The CPET was performed on a cycle ergometer Lode Corival CPET (Lode, The Netherlands) under supervision of a sports medicine physician. Throughout the test the Electrocardiogram (ECG), saturation and blood pressure were monitored, and heart rate (HR) and gas exchange variables were recorded continuously and averaged at 30 seconds intervals (COSMED Quark CPET, Rome, Italy). After warmup, the incremental exercise started, with increments of 15 watts per minute in each step, until 85% heart rate, or other standardized criteria for stopping (Pritchard et al., 2021; Radtke et al., 2019).

The American College of Sports Medicine (ACSM) 1-RM protocol was used to assess whole body strength (ACSM, 2018) 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 equation ($1RM = (0.033 * \text{number repetitions} * \text{weight lifted}) + \text{weight lifted}$) was used to provide safe 1-RM (Wood et al., 2002).

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 $\text{weight}/\text{height}^2$

(Kg/m²). 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.

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 (Webster et al., 2003) 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 (Oerlemans et al., 2022). 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 (Oerlemans et al., 2022).

Primary and Secondary 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, strength evaluation, cardiac and respiratory capacity 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).

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 (Kang, 2021). 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 (Flemyng et al., 2023).

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 (Clarke et al., 2024; Steel et al., 2006). 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 (Osoba et al., 2023).

Effect sizes was 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 (Cohen, 1988). Percentage differences in variables changes, were calculated using the formula: $(Intervention\ Value - Baseline\ Value) / Baseline\ Value \times 100$.

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. Prior to group allocation one patient did not complete the physical fitness tests due to uncertainty of a pre-existent cardiac condition under medical surveying. Final groups were assigned to either REx (n=4) or Control (n=7) groups. The complete diagram is depicted in figure 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). Therefore, eleven patients were included in the analysis, including a patient without physical fitness tests. Sensitivity statistical procedures were conducted to verify if there was an influence of this case in results. Table 2 reports participants characteristics at baseline.

Variable	Controls (n=7)		Resistance Training (n=4)		Baseline		Post-Intervention	
	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 ^a						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 ^a						0.32		
A Low Risk	4 (57.1%)		4 (100%)					
B Intermediate	1 (14.3%)		0					
Unknown	2 (28.6%)		0					
ECOG Performance Status ^a						0.09		
0 Fully Active	4 (57.1%)		3 (75%)					
I 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. ^aChi-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, except for minor muscle soreness after exercise training. 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 $\times$ 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. These findings suggest that the benefits observed immediately after the intervention were not sustained in the long term.

Variable	Controls (n=7)		Resistance Training (n=4)		T-Test (16-week)		ANOVA (16-week)		GLM (3 time points) *	
	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
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)										
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
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). * $p \leq 0.05$; Significant difference between REx group and Control group. † $p \leq 0.05$; Significant time effect. ‡ $p \leq 0.05$; 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-naïve CLL patients. Since older adults, as seen in CLL, are often in risk of functional limitations that hinder daily life activities (Goede et al., 2016), 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 (Clarke et al., 2024).

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 (Carter et al., 2008). The FACT-P study estimated CMCs of 6-10 for the total score and 2-3 for the prostate cancer subscale (Cella et al., 2009). 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 (Steel et al., 2006). Across various cancer types, CMCs for FACT-G total score range from 3-7 points (Clarke et al., 2024). 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 (Clarke et al., 2024; Steel et al., 2006). 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 et al. (Artese et al., 2022) 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 highlight 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 (Osoba et al., 2023). A study in CLL with cardiovascular and endurance muscular training (Persoon et al., 2017), 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 (Inaba et al., 2008; Steele et al., 2017). 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 (Van Roie et al., 2015). Future studies should explore strategies to promote exercise adherence beyond the initial supervised intervention period to ensure prolonged benefits.

Limitations to our study include a small sample size, however social interaction was the same across intervention, with an individualized personal supervision of protocol implementation. We also acknowledge that control group had higher baseline values for Cognitive and Social Function when compared to intervention group. Therefore, the potential for improving scores may have been lower in the control group because they had better baseline HRQOL. We also acknowledge that for the generalizability of data, a multicenter recruitment should be implemented, to encompass the differences between city and country daily living, that might bias results.

We demonstrated that 16-weeks of strength-based resistance training program produced significant improvements in several well-being and health-related quality of life (HRQOL) measures highlighting the clinically meaningful enhancements in general well-being, overall quality of life and physical fitness outcomes among treatment-naïve CLL patients. 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. However, further randomized trials with larger sample sizes are needed to strengthen these results, exploring long-term effects, and optimizing exercise protocols for CLL patients, particularly for older adults and those with more severe HRQOL impairments.

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.

Declaration of Interests

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

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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.

Availability of Data and Materials

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

References

- ACSM. (2018). *ACSM's Guidelines for Exercise Testing and Prescription* (Tenth ed.). Wolters Kluwer Health.
- Andersen, V., Fimland, M. S., Iversen, V. M., Pedersen, H., Balberg, K., Gasvaer, M., Rise, K., Solstad, T. E. J., Stien, N., & Saeterbakken, A. H. (2022). A Comparison of Affective Responses Between Time Efficient and Traditional Resistance Training. *Front Psychol*, *13*, 912368. <https://doi.org/10.3389/fpsyg.2022.912368>
- Artese, A. L., Sitlinger, A., MacDonald, G., Deal, M. A., Hanson, E. D., Pieper, C. F., Weinberg, J. B., Brander, D. M., & Bartlett, D. B. (2022). Effects of high-intensity interval training on health-related quality of life in chronic lymphocytic leukemia: A pilot study. *J Geriatr Oncol*. <https://doi.org/10.1016/j.jgo.2022.09.002>
- Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., Zucker, D. S., Matthews, C. E., Ligibel, J. A., Gerber, L. H., Morris, G. S., Patel, A. V., Hue, T. F., Perna, F. M., & Schmitz, K. H. (2019). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Medicine & Science in Sports & Exercise*, *51*(11), 2375-2390. <https://doi.org/10.1249/Mss.0000000000002116>
- Carter, G. C., Liepa, A. M., Zimmermann, A. H., & Morschhauser, F. (2008). Validation of the Functional Assessment of Cancer Therapy - Lymphoma (FACT-LYM) in Patients with Relapsed/Refractory Mantle Cell Lymphoma. *Blood*, *112*(11), 828-828. <Go to ISI>://WOS:000262104702709
- Cella, D., Nichol, M. B., Eton, D., Nelson, J. B., & Mulani, P. (2009). Estimating Clinically Meaningful Changes for the Functional Assessment of Cancer Therapy-Prostate: Results from a Clinical Trial of Patients with Metastatic Hormone-Refractory Prostate Cancer. *Value in Health*, *12*(1), 124-129. <https://doi.org/10.1111/j.1524-4733.2008.00409.x>
- Clarke, N. A., Braverman, J., Worthy, G., Shaw, J. W., Bennett, B., Dhanda, D., & Cocks, K. (2024). A Review of Meaningful Change Thresholds for EORTC QLQ-C30 and FACT-G Within Oncology. *Value in Health*, *27*(4), 458-468. <https://doi.org/10.1016/j.ival.2023.12.012>
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd Edition ed.). Routledge. <https://doi.org/https://doi.org/10.4324/9780203771587>
- Flemyng, E., Moore, T. H., Boutron, I., Higgins, J. P. T., Hrobjartsson, A., Nejstgaard, C. H., & Dwan, K. (2023). Using Risk of Bias 2 to assess results from randomised controlled trials: guidance from Cochrane. *Bmj Evidence-Based Medicine*, *28*(4), 260-266. <https://doi.org/10.1136/bmjebm-2022-112102>
- Furzer, B. J., Ackland, T. R., Wallman, K. E., Petterson, A. S., Gordon, S. M., Wright, K. E., & Joske, D. J. L. (2016). A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients. *Supportive Care in Cancer*, *24*(4), 1697-1707. <https://doi.org/10.1007/s00520-015-2955-7>
- Goede, V., Bahlo, J., Chataline, V., Eichhorst, B., Dürig, J., Stilgenbauer, S., Kolb, G., Honecker, F., Wedding, U., & Hallek, M. (2016). Evaluation of geriatric assessment in patients with chronic lymphocytic leukemia: Results of the CLL9 trial of the German CLL study group. *Leukemia & Lymphoma*, *57*(4), 789-796. <https://doi.org/10.3109/10428194.2015.1091933>
- Hallek, M., Cheson, B. D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Dohner, H., Hillmen, P., Keating, M., Montserrat, E., Chiorazzi, N., Stilgenbauer, S., Rai, K. R., Byrd, J. C., Eichhorst, B., O'Brien, S., Robak, T., Seymour, J. F., & Kipps, T. J. (2018). iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*, *131*(25), 2745-2760. <https://doi.org/10.1182/blood-2017-09-806398>
- Holzner, B., Kemmler, G., Kopp, M., Nguyen-Van-Tam, D., Sperner-Unterwieser, B., & Greil, R. (2004). Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal

- investigation over 1 yr. *European Journal of Haematology*, 72(6), 381-389.
[https://doi.org/DOI 10.1111/j.1600-0609.2004.00233.x](https://doi.org/DOI%2010.1111/j.1600-0609.2004.00233.x)
- Inaba, Y., Obuchi, S., Arai, T., Satake, K., & Takahira, N. (2008). The long-term effects of progressive resistance training on health-related quality in older adults. *J Physiol Anthropol*, 27(2), 57-61.
<https://doi.org/10.2114/jpa2.27.57>
- Institute, T. N. C. (2023). *Clinical Trial Randomization Tool*. Retrieved 2023-02-24 from
<https://ctrandomization.cancer.gov>
- Kang, H. (2021). Sample size determination and power analysis using the G*Power software. *Journal of Educational Evaluation for Health Professions*, 18. [https://doi.org/ARTN 10.3352/jeehp.2021.18.17](https://doi.org/ARTN%2010.3352/jeehp.2021.18.17)
- NIH. (2022, 2023/01/12). *SEER Cancer Stat Facts: Chronic Lymphocytic Leukemia*. NIH: National Cancer Institute. Retrieved 2023/01/12 from
<https://seer.cancer.gov/statfacts/html/clyl.html>
- Noetel, M., Sanders, T., Gallardo-Gómez, D., Taylor, P., Cruz, B. D., van den Hoek, D., Smith, J. J., Mahoney, J., Spathis, J., Moresi, M., Pagano, R., Pagano, L., Vasconcellos, R., Arnott, H., Varley, B., Parker, P., Biddle, S., & Lonsdale, C. (2024). Effect of exercise for depression: systematic review and network meta-analysis of randomised controlled trials. *Bmj-British Medical Journal*, 384. [https://doi.org/ARTN e075847](https://doi.org/ARTN%20e075847)
- 10.1136/bmj-2023-075847
- Oerlemans, S., Efficace, F., Kieffer, J. M., Kyriakou, C., Xochelli, A., Levedahl, K., Petranovic, D., Borges, F. C., Bredart, A., Shamieh, O., Gziskevicius, L., Lehmann, J., Scholz, C. W., Caocci, G., Molica, S., Stamatopoulos, K., Panteliadou, A. K., Papaioannou, M., Alrjoob, W.,...Group, E. Q. o. L. (2022). International validation of the EORTC QLQ-CLL17 questionnaire for assessment of health-related quality of life for patients with chronic lymphocytic leukaemia. *Br J Haematol*, 197(4), 431-441. <https://doi.org/10.1111/bjh.18072>
- Osoba, D., Rodrigues, G., Myles, J., Zee, B., & Pater, J. (2023). Interpreting the Significance of Changes in Health-Related Quality-of-Life Scores (Reprinted from vol 16, pg 139, 1998). *Journal of Clinical Oncology*, 41(35), 5345-5350. <https://doi.org/10.1200/Jco.22.02776>
- Ou, Y., Long, Y., Ji, L., Zhan, Y., Qiao, T., Wang, X., Chen, H., & Cheng, Y. (2022). Trends in Disease Burden of Chronic Lymphocytic Leukemia at the Global, Regional, and National Levels From 1990 to 2019, and Projections Until 2030: A Population-Based Epidemiologic Study. *Front Oncol*, 12, 840616. <https://doi.org/10.3389/fonc.2022.840616>
- Parker, E. J., Riely, K. M., Ellingson, S., Modglin, C. J., & Lang, H. (2024). Effects of Cardio vs. Cardio and Resistance Training in People with Obesity. *Journal of Clinical Exercise Physiology*, 13. <https://doi.org/https://doi.org/10.31189/2165-7629-13-s1.18>
- Persoon, S., Chinapaw, M. J. M., Buffart, L. M., Liu, R. D. K., Wijermans, P., Koene, H. R., Minnema, M. C., Lugtenburg, P. J., Marijt, E. W. A., Brug, J., Nollet, F., & Kersten, M. J. (2017). Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: Results from the EXIST study. *PLoS One*, 12(7). [https://doi.org/ARTN e0181313](https://doi.org/ARTN%20e0181313)
- 10.1371/journal.pone.0181313
- Pritchard, A., Burns, P., Correia, J., Jamieson, P., Moxon, P., Purvis, J., Thomas, M., Tighe, H., & Sylvester, K. P. (2021). ARTP statement on cardiopulmonary exercise testing 2021. *Bmj Open Respiratory Research*, 8(1). [https://doi.org/ARTN e001121](https://doi.org/ARTN%20e001121)
- 10.1136/bmjresp-2021-001121
- Radtke, T., Vogiatzis, I., Urquhart, D. S., Laveneziana, P., Casaburi, R., Hebestreit, H., Crook, S., Kaltsakas, G., Louvaris, Z., Berton, D. C., Kampouras, A., Rabinovich, R. A., Verges, S., Kontopidis, D., Boyd, J., Tonia, T., Langer, D., De Brandt, J., Goërtz, Y. M. J.,...Task, E. R. S. (2019). Standardisation of cardiopulmonary exercise testing in chronic lung diseases:

summary of key findings from the ERS task force. *European Respiratory Journal*, 54(6).
<https://doi.org/Artn> 1901441

10.1183/13993003.01441-2019

Schmitz, K. (2020). *Exercise Oncology: Prescribing Physical Activity Before and After a Cancer Diagnosis*. Springer Cham. <https://doi.org/https://doi.org/10.1007/978-3-030-42011-6>

Sitlinger, A., Brander, D. M., & Bartlett, D. B. (2020). Impact of exercise on the immune system and outcomes in hematologic malignancies. *Blood Advances*, 4(8), 1801-1811.
<https://doi.org/10.1182/bloodadvances.2019001317>

Steel, J. L., Eton, D. T., Cella, D., Olek, M. C., & Carr, B. I. (2006). Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. *Annals of Oncology*, 17(2), 304-312. <https://doi.org/10.1093/annonc/mdj072>

Steele, J., Raubold, K., Kemmler, W., Fisher, J., Gentil, P., & Giessing, J. (2017). The Effects of 6 Months of Progressive High Effort Resistance Training Methods upon Strength, Body Composition, Function, and Wellbeing of Elderly Adults. *Biomed Research International*, 2017. <https://doi.org/Artn> 2541090

10.1155/2017/2541090

Van Roie, E., Bautmans, I., Coudyzer, W., Boen, F., & Delecluse, C. (2015). Low- and High-Resistance Exercise: Long-Term Adherence and Motivation among Older Adults. *Gerontology*, 61(6), 551-560. <https://doi.org/10.1159/000381473>

Webster, K., Cella, D., & Yost, K. (2003). The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes*, 1, 79. <https://doi.org/10.1186/1477-7525-1-79>

Wood, T. M., Maddalozzo, G. F., & Harter, R. A. (2002). Accuracy of Seven Equations for Predicting 1-RM Performance of Apparently Healthy, Sedentary Older Adults. *Measurement in Physical Education and Exercise Science*, 6(2), 67-94.

Yao, Y., Lin, X., Li, F., Jin, J., & Wang, H. (2022). The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. *Biomed Eng Online*, 21(1), 4.
<https://doi.org/10.1186/s12938-021-00973-6>

PAPER IV

Health Promotion Practice

Physical and Immunological Benefits of Strength Training in Older Adults with Treatment Naive Chronic Lymphocytic Leukemia: A Pilot Study.

Journal:	<i>Health Promotion Practice</i>
Manuscript ID:	HPP-25-0214
Manuscript Type:	Full Length Article
Keywords:	Aging and Older Adults, Cancer Survivorship, Disease Management, Health Care, Health Promotion, Cancer Prevention and Control, Chronic Disease, Physical Activity / Exercise
Abstract:	This pilot study explored the feasibility and potential benefits of a 16-week strength-based resistance training program for individuals diagnosed with chronic lymphocytic leukemia who had not yet received treatment. Recognizing that patients with this condition often reduce their physical activity due to disease-related symptoms, the research aimed to assess whether structured exercise could improve physical fitness and immune function. A total of eleven participants were randomly assigned to either an exercise group or a non-exercising control group. The exercise group completed two weekly sessions consisting of a brief cycling warmup, approximately 45 minutes of full-body strength training using machines at moderate to high intensity, and a short cooldown. The study employed both quantitative methods and comparative analysis of outcomes related to muscle strength, aerobic capacity, body composition, and blood-based immune markers. The findings showed that those in the exercise group experienced notable improvements in muscle strength and certain indicators of immune function compared to the control group. There was also evidence of changes in body composition and aerobic capacity. Importantly, the program was well tolerated, with high adherence among participants, suggesting that such an intervention is not only practical but potentially beneficial for this patient population. Further investigation with a larger sample is recommended to validate and expand upon these preliminary results. Trial is registered at ClinicalTrials.gov.

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Title:

Physical and Immunological Benefits of Strength Training in Older Adults with Treatment Naive Chronic Lymphocytic Leukemia: A Pilot Study.

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Abstract

This pilot study explored the feasibility and potential benefits of a 16-week strength-based resistance training program for individuals diagnosed with chronic lymphocytic leukemia who had not yet received treatment. Recognizing that patients with this condition often reduce their physical activity due to disease-related symptoms, the research aimed to assess whether structured exercise could improve physical fitness and immune function. A total of eleven participants were randomly assigned to either an exercise group or a non-exercising control group. The exercise group completed two weekly sessions consisting of a brief cycling warmup, approximately 45 minutes of full-body strength training using machines at moderate to high intensity, and a short cooldown. The study employed both quantitative methods and comparative analysis of outcomes related to muscle strength, aerobic capacity, body composition, and blood-based immune markers. The findings showed that those in the exercise group experienced notable improvements in muscle strength and certain indicators of immune function compared to the control group. There was also evidence of changes in body composition and aerobic capacity. Importantly, the program was well tolerated, with high adherence among participants, suggesting that such an intervention is not only practical but potentially beneficial for this patient population. Further investigation with a larger sample is recommended to validate and expand upon these preliminary results. Trial is registered at ClinicalTrials.gov.

Keywords: Physical Activity; Physical function; Exercise oncology; Resistance Training; Muscle strength; Quality of Life; B-Cell; Chronic lymphocytic leukemia; Immune response; Cancer Survivorship.

WORDCOUNT: 217 words.

Introduction

Chronic Lymphocytic Leukemia (CLL) is typically managed with systemic immunochemotherapy or targeted therapies (Algino et al., 1996). Despite advancements, patients often experience significantly reduced daily functioning and quality of life, even without treatment (Shanafelt et al., 2007). Most patients are asymptomatic and maintain medical follow-up until a notable decline in quality of life occurs, characterized by fatigue, increased infection susceptibility, and limitations in daily activities (Hallek et al., 2018). Social isolation, reliance on caregivers, and limited participation in meaningful activities further contribute to this decline. Additionally, the psychological impact, including anxiety and depression, exacerbates the situation.

Exercise may play a crucial role in facilitating the return to an active lifestyle post-treatment (De Backer et al., 2008). Regular physical activity is known to improve physical function, mood, self-esteem, and overall well-being in CLL patients (Campbell et al., 2019b). However, further research is needed to determine the impact of effective exercise interventions in this population. Previous studies often exhibit methodological limitations, affecting their reliability and generalizability (Cerhan et al., 2002; Courneya & Friedenreich, 2001; Walter et al., 2013). The absence of standardized protocols, control groups, and long-term follow-up makes it difficult to draw definitive conclusions about the efficacy of exercise interventions (Backer et al., 2009; De Backer et al., 2008).

It is essential to distinguish between cardiovascular and muscular exercise modalities and recognize the limitations of analyzing combined training programs (Galvao & Taaffe, 2005). Cardiovascular exercise improves fitness and endurance (Courneya et al., 2009), regulates inflammation, enhances immune function, modulates oxidative stress, and supports cellular apoptosis (Sitlinger et al., 2021). It also improves tissue perfusion, oxygenation, and reduces fatigue (Yang et al., 2019), which are particularly relevant for CLL patients. Similarly, muscular exercise targets strength, power, and muscle mass, aiding in insulin resistance management, cellular metabolism enhancement, and further fatigue reduction (MacDonald et al., 2021). Combining both modalities may yield synergistic benefits (Crane et al., 2023; MacDonald et al., 2021), but assessing each component

separately is crucial to understanding their contributions to physiological processes. Exercise in CLL remains understudied, and the effect of strength training in mitigating muscle loss is insufficiently explored (Strasser & Schobersberger, 2011). Muscle mass preservation is crucial for functional independence and mobility in CLL patients. Therefore, research should prioritize the effects of strength training on muscle hypertrophy, strength gains, and functional outcomes in this population.

This study aims to evaluate the influence of an individualized strength training program, grounded on previous pilot studies (Crane et al., 2023; MacDonald et al., 2021), which have demonstrated significant benefits from this type of exercise intervention. We seek to confirm the feasibility and effectiveness of a state-of-the-art individualized exercise program in CLL, using physical condition, fatigue, and disease-related blood markers as outcomes during clinical follow-up and free from ongoing treatment. Additionally, we aim to evaluate the influence of a strength-based training program on improved physical fitness and body composition parameters.

Methods

Study Participants

The ADRENALINE trial (randomized, controlled, and blinded) evaluated the effects of exercise in patients with chronic lymphocytic leukemia (CLL). Participants were recruited from participating University Hospital Center, Portugal, based on strict criteria. Inclusion required patients aged 45-80 years, treatment-naïve, physical capable of performing resistance and aerobic exercise, and willing to adhere to the intervention. Exclusion criteria included previous immunochemotherapy, current engagement in structured exercise, disease progression requiring treatment, other malignancies, and significant comorbidities limiting exercise.

Following consent, eligible patients underwent clinical screening, health-related quality of life assessments, body composition analysis, maximal strength testing, and cardiopulmonary exercise testing (CPET). Physical Activity levels were monitored using accelerometers over seven consecutive days (minimum 10 hours/day). The study received ethics approval and is registered at ClinicalTrials.gov.

Study Design

Patients were randomized into two groups: a resistance exercise training group (REx) and a usual care control group (CG). The intervention lasted 16 weeks with up to two sessions per week, ensuring 24-hour recovery between similar sessions. Primary and secondary outcome measures were collected pre- and post-intervention (T0 and T1). The study design followed CONSORT guidelines (Figure 1).

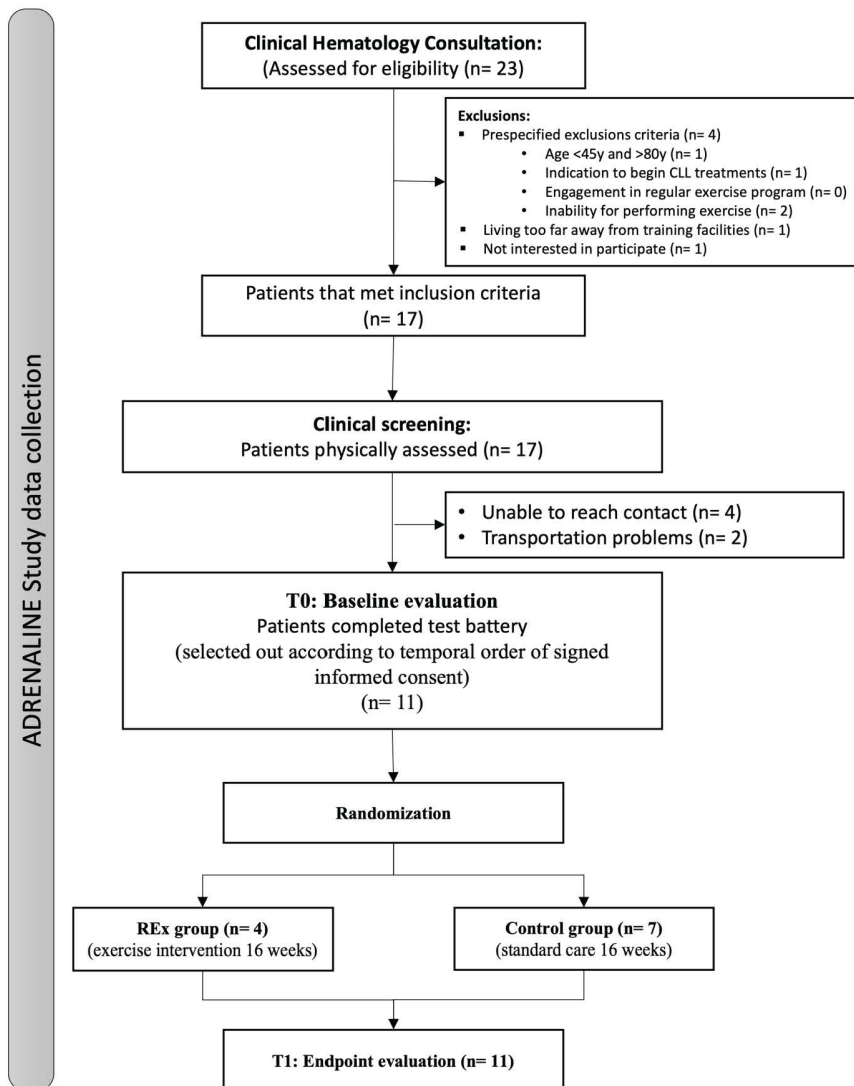


Figure 1: Consolidated standards of reporting trials (consort) diagram. REx=Resistance Exercise. CLL=Chronic Lymphocytic Leukemia.

Randomization

Randomization was performed using the Clinical Trial Randomization Tool (web application) from The National Cancer Institute's Division of Cancer Prevention (Institute, 2023), with 2 arms allocation and a maximum tolerated imbalance of three between arms, blinded for patient and laboratory staff but not for physical intervention fellows.

Evaluation

Exercise testing

At T0 and T1, assessments included anthropometry, body composition, bone mineral density (DEXA), strength (dynamometry and 1-RM estimation), CPET, and physical activity (ActiGraph GT9XLink accelerometers). CPET followed international protocols, using a Lode Corival cycle ergometer and COSMED Quark CPET system for gas exchange measurements. The protocol included a rest phase, unloaded warm-up, incremental workload increase (15 W/min), and cool-down.

Upper limb strength was measured via JAMAR dynamometer with three trials per hand. Lower limb strength was assessed with a Biodex isokinetic dynamometer at 60 °/s, evaluating dominant knee extension/flexion. Whole-body strength was indirectly estimated using the ACSM 1-RM protocol and Epley formula after a 3-week familiarization period.

For body composition assessment, weight and height were measured with standard equipment (SECA 899 and SECA 217). Body mass index was calculated (Kg/m^2), and DEXA scans evaluated fat mass, skeletal muscle mass, and bone mineral density (whole body and non-dominant hip).

Objectively physical activity was monitored via GT9XLink accelerometers (Actigraph, USA) over seven consecutive days, capturing data with a minimum of 10 hours/day validity.

Clinical, Immunologic and Inflammatory testing

Clinical evaluations at T0 and T1 included routine hematology consultations, physical exams (skin pallor, lymphadenopathy, hepatomegaly), and standard blood analyses (hemogram, liver, renal, and metabolic markers). Disease staging used RAI and BINET systems, and performance status was assessed via ECOG scale. Genetic markers were not evaluated unless treatment was indicated, per institutional practice. The protocol allowed baseline and follow-up data collection for analysis of resistance training impact across multiple domains.

Outcomes

Primary Outcomes included: Cardiorespiratory fitness, body composition, strength, and physical activity; Secondary Outcomes comprised: Disease-related symptoms, physical exam changes, and peripheral blood parameters.

Intervention

The 16-week REx protocol involved two sessions weekly with structured resistance machine exercises targeting major muscle groups. Each session included a 10-minute warm-up and 5-minute cool down (cycle ergometer). Intensity was prescribed at 60-85% of peak heart rate. The training progression followed ACSM/FITT-VP guidelines: Frequency: 2x/week; Intensity: 80% of 1-RM; Time: ~60min/session; Type: Machine-based resistance exercises; Volume: 3 sets of 8-12 repetitions after adaptation; Progression: starting at 70% 1-RM, increasing weekly by 5% until 80% was reached or until 12 repetitions were achieved twice consecutively with proper form.

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	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
	W: 80% 1RM		
	R: 60 to 90 sec passive rest		

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

Exercise order followed a structured pattern (e.g., Leg Press -> Leg Curl -> Leg Extension -> Chest Press -> Latissimus Front Row -> Shoulder Press -> Triceps Extension -> Biceps Curl -> Abdominal Crunch). Heart rate (Garmin Vivosmart 4) and rate of perceived exertion (RPE) were used for intensity monitoring. 1-RM estimates were re-evaluated every 5 weeks.

Control group participants received standard care, were encouraged to maintain normal activity levels, and were contacted bimonthly to ensure study retention.

Statistical Analysis

Sample size was calculated using G-Power software, with data from previous studies (Kang, 2021), estimating a minimum of 16 participants to detect significant differences with 95% power ($\alpha=0.05$) Due to unforeseen circumstances, only 11 participants were ultimately enrolled.

Safety, Feasibility, and Compliance: Adherence was acceptable if >75% of sessions were attended. Compliance required >80% of prescribed intensity within the 8-12 repetitions range. Retention was defined as completion of >75% of assessments at T0 and T1. Pain and injuries were recorded to monitor safety.

Risk of bias was assessed with the Cochrane Risk-of-Bias 2 tool, yielding a low overall risk.

Missing data were treated as missing completely at random (MCAR) to maximize statistical power.

Normality was assessed using Shapiro-Wilk test. Descriptive data are presented as mean and standard deviation for normally distributed variables and median (inter-quartile range) for non-normally distributed variables. Between-group differences at baseline and post-intervention were analyzed using independent t-tests for parametric variables and Mann-Whitney U tests for non-parametric variables. Within-group changes from pre- to post-intervention were assessed using paired t-tests for parametric data and Wilcoxon signed-rank tests for non-parametric data. To examine group-by-time interactions over the 16-week intervention period, a two-way mixed ANOVA was conducted for parametric variables. For non-parametric data, the Mann-Whitney U test was applied to compare delta differences between groups.

Effect sizes were calculated using Hedges' g, which was preferred over Cohen's d to mitigate overestimation in small samples). Effect sizes were interpreted as small (0.2), medium (0.5) and large (0.8).

Percentage change in variables was calculated using the formula: *Intervention Value* minus *Baseline Value*, dividing by the *Baseline Value* and Multiplying by 100 to express changes relative to baseline values. Statistical significance was set at $p < 0.05$. All analyses were conducted using IBM SPSS for Mac (version 29; Armonk, NY, United States).

Results

Twenty-three patients were assessed for eligibility (Figure 1). Six were excluded due to ineligibility or personal reasons. Four were unreachable, and two reported transportation barriers. Eleven participants (7 Control, 4 Resistance Exercise [REx]) consented and completed both baseline and 16-week evaluations.

Participant demographics and clinical characteristics are detailed in Table 2.

Variables	Control Group (n= 7)	REx Group (n= 4)	Total (n= 11)
Demographics and Body Composition			
Age (years)	66.4 (11.3)	64.0 (7.6)	65.6 (9.7)

Sex (M/F)	5/2	2/2	7/4
Height (cm)	163.0 (11.1)	163.5 (15.3)	163.2 (12.0)
Weight (kg)	70.8 (14.1)	73.9 (17.4)	71.2 (14.6)
BMI (kg/m ²)	26.4 (2.3)	27.3 (2.3)	26.7 (2.2)
Lean Mass (kg)	50.2 (11.8)	45.6 (11.7)	48.5 (11.3)
Total Fat Mass (kg)	17.2 (5.0)	26.3 (7.9)	20.5 (7.4)
Body Fat (%)	25.0 (7.5)	35.5 (6.9)	28.8 (8.7)
Whole Body BMC (kg)	2.159 (0.613)	2.182 (0.726)	2.2 (0.6)
Femur Neck BMD (g/cm ³)	0.750 (0.146)	0.743 (0.114)	0.747 (0.130)
Femur Neck BMD (T-score)	-1.257 (0.999)	-1.225 (0.699)	-1.245 (0.864)
Disease characteristics			
Time Since Diagnosis (yrs.)	4.0 (3.3)	3.0 (0.6)	3.6 (2.6)
RAI Disease Stage			
0 Low Risk	2 (28.6%)	0	2 (18.2%)
I Intermediate Risk	2 (28.6%)	4 (100%)	6 (54.5%)
II Intermediate Risk	1 (14.3%)	0	1 (11.1%)
Unknown	2 (28.6%)	0	2 (18.2%)
BINET Disease Stage			
A Low Risk	4 (57.1%)	4 (100%)	8 (72.7%)
B Intermediate	1 (14.3%)	0	1 (9.1%)
Unknown	2 (28.6%)	0	2 (18.2%)
ECOG Performance Status			
0 Fully Active	4 (57.1%)	3 (75%)	7 (63.6%)
1 Restricted Physical Strenuous Activity	2 (28.6%)	1 (25%)	3 (27.3%)
Unknown	1 (14.3%)	0	1 (9.1%)
Disease related blood markers characteristics			
WBC (x10 ⁹ /L)	18.8 (8.4)	12.4 (4.3)	16.5 (7.6)
Lymphocytes (%)	55.9 (11.9)	56.5 (16.0)	56.1 (12.7)
Monocytes (%)	3.3 (2.0)	3.4 (0.8)	3.4 (1.6)
Neutrophils (%)	28.2 (9.5)	31.4 (12.2)	29.4 (10.1)
Platelets (x10 ⁹ /L)	198.9 (75.9)	199.0 (75.6)	198.9 (71.9)
Hemoglobin (g/dL)	14.0 (1.5)	14.1 (1.1)	14.0 (1.3)
RBC (x10 ¹² /L)	4.5 (0.5)	4.9 (0.2)	4.7 (0.5)
Hematocrit (%)	42.1 (3.9)	42.6 (2.5)	42.3 (3.3)
B2-microglobulin (µg/l) ^a	1543.8 (170.5)	1866.0 (489.0)	1687.0 (364.8)

Table 2: Baseline for demographic, clinical characteristics and disease related blood markers of participants completing the intervention. Data are mean (SD). Bolded effect sizes indicate large effect sizes for mean differences between groups. a= total n=9 (REx n= 4, CG n= 5).

The cohort included 11 patients (7 men, 4 women), mean age 65.55 ± 9.73 years (range 47–78), all with treatment-naïve stable CLL. Mean time from diagnosis to intervention was 3.65 years (range 1.1–10.3). Most were RAI stage I (54.5%), BINET stage A (72.7%), and ECOG 0 (63.6%). Groups were similar in demographic and body composition at baseline, although the REx group had 42% higher body fat, potentially influencing outcomes.

Bone health assessments via DEXA indicated osteopenia in both groups (T-scores < -1 SD) without osteoporosis (T-scores < -2.5 SD). Differences with large effect sizes were noted in WBC ($g = 0.8$), RBC ($g = -0.82$), and $\beta 2$ -microglobulin ($g = -0.83$), with the REx group showing lower WBC and higher B2M values.

Table 3 summarizes physical fitness characteristics. While many between-group differences were not statistically significant, meaningful effect sizes were observed. Relative change in total fat mass showed a significant group effect ($p = 0.033$, $g = 1.573$), with a 6.02% reduction in REx vs. 3.4% increase in Control. Total mass also differed significantly ($p = 0.003$, $g = 2.48$), decreasing 1.52% in REx and increasing 1.83% in Control.

Variable	Controls (n=6)		Resistance Training (n=4)		Baseline		Post-Intervention	
	Baseline	16-week	Baseline	16-week	Mean Difference (95% C.I.)	Effect Size (g)	Mean Difference (95% C.I.)	Effect Size (g)
Fitness characteristics								
Handgrip Strength (kg)								
Left Peak	39.5 (17.9)	35.0 (16.0)	38.0 (10.1)	34.5 (7.4)	1.5 (-21.5, 24.5)	0.09	0.9 (-19.3, 20.5)	0.04
Right Peak	41.5 (19.0)	34.4 (14.5)	41.5 (19.0)	30.6 (2.9)	6.5 (-16.8, 29.8)	0.37	3.8 (-11.3, 19.0)	0.30
Left Avg	37.6 (16.9)	33.3 (16.1)	36.0 (8.8)	33.8 (7.2)	1.6 (-19.8, 23.9)	0.10	-0.5 (-20.5, 19.5)	-0.03
Right Avg	40.0 (18.0)	32.6 (14.4)	33.3 (6.1)	29.2 (3.0)	6.7 (-12.4, 25.7)	0.41	3.4 (-11.7, 18.5)	0.27
Isokinetic Strength								
Peak Torque Extension (N.m)	115.3 (69.6)	125.3 (69.2)	109.8 (27.6)	117.1 (31.5)	5.6 (-80.0, 91.2)	0.09	8.3 (-78.0, 94.6)	0.13
Peak Torque Flexion (N.m)	62.3 (24.6)	70.3 (32.5)	45.2 (11.1)	49.3 (15.7)	17.1 (-9.8, 43.9)	0.74	21.0 (-19.8, 61.9)	0.70
Peak Torque/BW Extension (%)	151.1 (69.6)	162.0 (59.7)	149.8 (26.8)	158.0 (26.4)	1.3 (-77.6, 80.3)	0.02	4.0 (-70.3, 78.2)	0.07
Peak Torque/BW Flexion (%)	83.4 (18.8)	92.3 (26.9)	62.4 (14.2)	65.2 (8.4)	21.1 (-4.5, 46.7)	1.11	27.1 (-5.5, 59.6)	1.12
Avg Power Extension (W)	72.5 (40.2)	82.3 (45.2)	67.8 (16.4)	76.1 (23.3)	4.7 (-44.8, 54.3)	0.13	6.2 (-51.1, 63.5)	0.15
Avg Power Flexion (W)	40.5 (17.6)	48.4 (22.1)	30.2 (7.5)	34.8 (12.0)	10.3 (-8.8, 29.4)	0.63	13.7 (-14.6, 41.9)	0.65
AGON/ANTAG Ratio (%)	59.9 (14.6)	59.4 (10.7)	41.5 (4.2)	41.7 (5.8)	18.5 (0.9, 36.1)	1.41	17.6 (4.0, 31.3)	1.74
Estimated 1-RM (kg)								
Leg Press			118.2 (40.8)	166.4 (37.7)				
Leg Curl			37.2 (15.2)	49.9 (15.6)				
Leg Extension			46.9 (26.2)	62.3 (18.0)				
Chest Press			34.7 (18.8)	40.3 (22.2)				
Seated Row			63.4 (20.6)	76.9 (22.3)				
Shoulder Press			17.9 (13.0)	24.3 (15.7)				
Triceps Extension			14.6 (3.7)	19.5 (4.7)				
Biceps Curl			13.6 (6.6)	16.9 (5.9)				
Aerobic Power								
Work rate Power (W)	75.0 (44.5)	92.5 (58.0)	97.5 (49.7)	112.5 (45)	-22.5 (-91.8, 46.8)	-0.44	-20 (-99.7, 59.7)	-0.34
$\dot{V}O_{2peak}$ (l/min)	1.2 (0.4)	1.4 (0.7)	1.2 (0.7)	1.6 (0.5)	32.7 (-0.8, 0.8)	0.06	-0.1 (-1.1, 0.8)	-0.18
$\dot{V}O_{2peak}$ (ml/kg/min)	16.7 (4.8)	18.9 (6.4)	15.4 (6.3)	20.8 (2.7)	1.3 (-6.7, 9.4)	0.22	-1.9 (-9.8, 6.0)	-0.32
METs	4.8 (1.3)	5.4 (1.8)	4.4 (1.8)	5.9 (0.8)	0.4 (-1.9, 2.7)	0.23	-0.5 (-2.8, 1.8)	-0.30
$\dot{V}O_2/HR$	10.4 (3.8)	11.4 (5.8)	8.9 (4.7)	11.8 (4.0)	1.5 (-4.7, 7.6)	0.33	-0.4 (-8.1, 7.4)	-0.07
PetCO ₂ (mmHg)	38.7 (5.1)	39.5 (7.0)	35.0 (7.0)	34.2 (6.0)	3.7 (-5.1, 12.4)	0.56	5.2 (-4.6, 15.1)	0.71
$\dot{V}E/\dot{V}CO_2$	31.3 (4.6)	31.0 (6.4)	33.7 (6.3)	34.8 (6.3)	-2.5 (-10.4, 5.4)	-0.42	-3.9 (-13.3, 5.6)	-0.55
Objectively assessed daily physical activity ^{1d}								
Steps per minute	75.1 (34.8)	66.2 (34.4)	44.3 (18.7)	45.5 (17.1)	30.7 (-12.3, 73.8)	0.93	20.7 (-28.6, 70.0)	0.60
Total MVPA (min)	163.6 (109.5)	161.1 (141.3)	82.5 (69.0)	76.7 (48.0)	81.1 (-57.6, 219.8)	0.76	84.5 (-54.5, 223.4)	0.61

Table 3: Baseline and Post-Intervention for physical fitness characteristics of participants completing the intervention. 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. c= control group n=7. d= 16-week REx group n=4.

Body Composition. REx reduced body fat percentage by 4.51% vs. a 1.2% increase in Control ($g = -1.00$). Lean mass increased 1.75% in REx compared to a 1.2% gain in Control, with the latter also increasing BMI more.

Blood parameters. REx induced a small effect on platelet count (+7.19%) and a large effect on neutrophils ($g = -1.28$), with moderate effects on WBC, monocytes, and RBC. WBC remained stable in REx (0.0% change) but increased 51.6% in Control. REx also improved immunologic markers: monocytes (+26.47%), neutrophils (+18.47%), and reduced lymphocytes (-1.06%). In contrast, neutrophils declined in the Control group (-13.48%), and monocytes remained unchanged.

Aerobic power. REx had a small effect on relative VO_{2peak} ($g = -0.32$) and moderate effects on $PetCO_2$ ($g = 0.71$) and VE/VCO_2 ($g = -0.55$), indicating improved respiratory efficiency. VO_{2peak} improved by 33.3% in REx vs. 16.67% in Control, with relative VO_{2peak} increasing by 35.06% and 13.17%, respectively.

Maximum strength. REx induced small improvements in dominant handgrip strength. Relative torque and power increased in both groups, although strength gains in knee flexion/extension were greater in Control, except for the Agonist/Antagonist ratio, which improved in REx ($g = 1.74$, +1.32%). Estimated 1-RM values in REx improved: Leg Press (+40.78%), Leg Curl (+34.14%), Leg Extension (+32.84%), Chest Press (+16.14%), Seated Row (+21.29%), Shoulder Press (+35.75%), Triceps Extension (+33.56%), and Biceps Curl (+24.26%).

Safety, Feasibility, Compliance and Retention. Four REx and seven CG participants completed the study. Safety was assessed by recording the incidence and severity of pain or injuries throughout the program. There were no adverse events recorded during any of the exercise sessions. All REx participants reported minor muscle soreness after exercise training. Due to population characteristics, adaptations in some patients were needed, including the substitution of Shoulder Press machine with Dumbbell Shoulder Press (due to machine limitations of positioning for best technique) and Chest Press machine with Incline Chest Press with dumbbells (due to reported dizziness when exercising in flat bench). For one patient it was needed to pause the warmup once or twice for breath during the first two weeks of the adaptation period but completed it uninterrupted by the third week.

Feasibility was assessed by the number of exercise sessions/week completed, consisting in 2 sessions/week of Resistance Training. All participants completed 100% of prescribed sessions.

Compliance was achieved, with 100% of participants completing >80% of 1-RM in resistance training within the 8-12 repetitions for all prescribed exercises, after the adaptation period.

Retention was assessed by the number of tests completed at baseline and at 16-week if values were over 75% of assessed tests completed. From the eleven patients in this study, 100% completed the tests. One patient did not complete physical capacity evaluations due to an ongoing cardiovascular assessment. Despite an uncertain condition, they met all other criteria and were included in the study, focusing on Blood Markers, Demographics, and Body Composition, as they were assigned to the Control Group.

Discussion

This pilot study is the first to show that 16-weeks of supervised Resistance Training with a Strength-based approach is feasible in older adults with treatment naïve CLL. Despite the reduced number of patients, the high adherence and compliance to REx were associated with effect sizes for differences between Controls and REx for changes in muscle strength and blood parameters. Because this intervention was made with a personal training-based approach, it was easy to control motivation and commitment to the protocol.

Patients with cancer are prone to have poor physical condition, associated with progression of symptoms and negative outcomes during and after therapy (Schmitz, 2020). Recommendations encompasses the need to avoid inactivity and encourage patients to safely engage in exercise training to prevent the decline of physiological processes and to maintain adequate daily physical activity and exercise levels (Campbell et al., 2019a; Schmitz, 2020). The treatment-naïve CLL patients in our study were a unique opportunity to explore the effects of exercise training in cancer patients without the complications of therapy-associated side effects. It is imperative to understand how immunomodulation throughout exercise training interventions impacts hematologic malignancies (Sitlinger et al., 2020),

and supports an opposed effect to the hallmarks of cancer, with myokines playing a significant role in the prevention of cancer proliferation (Ruiz-Casado et al., 2017).

Our results highlight that resistance exercise induced significant and meaningful improvements in body composition, with a large effect size for relative changes in total fat mass ($p = 0.033$, $g = 1.573$) and total mass ($p = 0.003$, $g = 2.48$). Specifically, the REx group demonstrated a reduction in total fat mass ($-6.02 \pm 5.3\%$), whereas the control group showed an increase ($+3.4 \pm 6.3\%$). Similarly, total mass significantly decreased in the REx group while increasing in the control group, reinforcing the potential role of resistance exercise in preserving lean mass while reducing fat accumulation. These findings align with previous research showing that structured resistance training can effectively reduce adiposity and preserve muscle mass in clinical populations, including cancer patients and older adults (Peterson et al., 2011; Strasser et al., 2013). Additionally, the observed large effect sizes suggest that, even in the absence of statistically significant differences in other variables due to the small sample, resistance training may exert a clinically meaningful impact on body composition, warranting further investigation in larger cohorts. One possible explanation for the significant reduction in total fat mass in the REx group is the increased metabolic demand induced by resistance training, leading to enhanced fat oxidation and energy expenditure (Hagstrom et al., 2021). Moreover, improvements in muscle mass may contribute to greater resting energy expenditure, further promoting favorable body composition adaptations (Hagstrom et al., 2021). However, the observed changes in total body mass suggest that while resistance training reduces fat mass, it does not necessarily lead to overall weight loss, reinforcing the importance of distinguishing between weight loss and body recomposition in clinical settings.

Here we show that 16 weeks of exercise training with a strength-based protocol had a small effect on aerobic power in relative $\dot{V}O_{2peak}$ and a medium effect on $P_{et}CO_2$ and $\dot{V}E/\dot{V}CO_2$, which reflects an improvement of ventilation-perfusion matching and greater respiratory efficiency. These findings indicate that less ventilation is required for the same level of oxygen uptake, suggesting improved aerobic efficiency. Given that our study was not powered to detect differences for cardiorespiratory fitness, unlike Furzer et al. (Furzer et al., 2016) or Courneya et al. (Courneya et al., 2009), we did not observe significant group differences. However, even without a structured cardiovascular training

approach, our protocol induced 33.3% improvement in $\dot{V}O_{2peak}$ in the REx group compared to 16.67% in the Control group. Past studies on CLL patients included mixed exercise types, not addressing resistance training in isolation (with muscular resistance- or strength-based approaches). Nonetheless, our results are in line with others who reached statistical significance (Courneya et al., 2009) or without statistical significance but with small-medium effect sizes (MacDonald et al., 2021; Persoon et al., 2017).

Regarding muscle function our study reports medium-to-large effects on knee flexion strength with isokinetic equipment, with an improvement in the Agonist/Antagonist muscle ratio, but with less impact on quadriceps strength. When analyzing estimated 1-RM, we observed improvements in all muscle areas, ranging from 16% to 40%. However, these results should be cautiously interpreted because they only compare baseline with post-intervention of REx group. Furzer et al. (Furzer et al., 2016) observed significant strength improvements in hematologic cancer patients recently completing treatment after 12 weeks of supervised aerobic plus resistance exercise (targeting 80% of 1-RM), and our muscle function results were consistent with these findings. Given that cancer treatments and advanced age are catabolic for lean tissue, our study adds evidence to the beneficial effects of exercise training on muscle function in cancer patients free from chemotherapy-induced muscle wasting, working with intensities near 85% of 1-RM. Future research should examine whether increasing and maintaining muscle function confers protection from CLL-related outcomes, such as frailty, time-to-relapse, and overall survival.

Since CLL is a disease mediated by the immune system, we were also interested in whether a strength-based exercise intervention could improve components of the immune system. It is well established that physical activity and structured exercise exert on immunomodulatory effects, particularly on T-cell function, natural killer (NK) cells cytotoxicity, neutrophils function, monocytes/macrophages activation, and B cell regulation (Sitlinger et al., 2020). MacDonald et al. (MacDonald et al., 2021) demonstrated that exercise training can enhance NK-cells counts and cytotoxic function, while Crane et al. (Crane et al., 2023), showed that structured training impacts T-cell phenotyping, suggesting that exercise could be a viable strategy to mitigate tumor progression. Our study also supports this concept, as we observed a large effect size on white blood cells. Notably,

neutrophils counts increased by ~18% in the REx group, whereas they decreased by 13% in the control group, despite the overall increase in total white blood cells by 51.6%. Neutrophils play a crucial role in innate immunity, mediating host defense, pathogen clearance, and cytokine release, functions that are often impaired in older adults, increasing their susceptibility to infections and poor tissue repair (Sitlinger et al., 2020).

Strengths of our study include its focus on a strength-based training approach, which is considered more intense in terms of both perceived effort and physiologic response. Additionally, our study included treatment-naïve CLL patients spanning a wide age range (47-78 years), and disease duration (1.1-10.3 years). Given that overall physical fitness is associated with better disease outcomes, these findings emphasize the importance of exercise before the onset of treatment-related toxicities, potentially improving long-term outcomes.

However, limitations must be considered, primarily the small sample size, which limited our ability to detect statistically significant differences in some outcomes. Despite randomization upon recruitment, the low number of participants may have affected group homogeneity and reduced statistical power. Therefore, generalizability should be approached with caution, as our sample included only treatment-naïve patients, not reflecting the broader CLL population, which often presents with cardiovascular and hepatic comorbidities. Future studies should recruit larger samples across multiple centers and compare different training modalities (aerobic-only vs. strength-only vs. combined training), to refine exercise guidelines for CLL patients. Moreover, research should explore specific immunological mechanisms underlying exercise-induced benefits, such as cytokines and myokines responses, and how they related to long-term outcomes in CLL, including infection rates, secondary malignancies, and time-to-treatment initiation.

Conclusions

This pilot study demonstrated the feasibility of a 16-week Resistance Training program with a Strength-based approach in treatment-naïve CLL patients. Our findings indicate that this intervention was associated with large effects on muscle strength, total fat mass reduction, and immune cell function,

highlighting the potential benefits of resistance training in improving body composition, physical function, and immunomodulation in this population. While these results are promising, further research with larger, multi-center samples is needed to confirm these effects and to better understand the long-term impact of strength-based resistance training on CLL outcomes.

Implications for Practice

- Strength-based Resistance Training at ~80% 1-RM is feasible and well-tolerated in treatment-naïve CLL patients.
- Muscle strength and immune cell function can be positively influenced by a structured Strength-based Resistance Training program.
- Strength training may contribute to improvements in aerobic power, suggesting better ventilation-perfusion matching and greater respiratory efficiency, despite not being a cardiovascular-focused intervention.
- Early implementation of exercise in CLL patients may enhance overall physical fitness, which is associated with better long-term disease outcomes and may provide benefits before undergoing treatment.

Implications for Research

Previous studies on exercise in CLL have lacked methodological rigor, with inconsistencies in standardized protocols, control groups, and long-term follow-up, limiting the reliability and generalizability of findings. This study addresses these gaps by employing a randomized controlled trial with a well-defined patient cohort, standardized outcome measures, and a resistance training program designed based on existing evidence. By systematically evaluating the effects of strength training on muscle mass, strength gains, and functional outcomes, this research contributes to the growing body of literature on exercise oncology. Future studies should build on these findings by exploring long-term adherence, immunological responses, and broader impacts on disease progression and quality of life in CLL patients.

Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

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.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of participating University's.

References

- Algino, K. M., Thomason, R. W., King, D. E., Montiel, M. M., & Craig, F. E. (1996). CD20 (Pan-B cell antigen) expression on bone marrow-derived T cells [Article]. *American Journal of Clinical Pathology*, 106(1), 78-81.
- Backer, I. C. D., Schep, G., Backx, F. J., Vreugdenhil, G., & Kuipers, H. (2009). Resistance Training in Cancer Survivors: A Systematic Review. *Int J Sports Med*, 30, 703-712. <https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0029-1225330.pdf>
- Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., Zucker, D. S., Matthews, C. E., Ligibel, J. A., Gerber, L. H., Morris, G. S., Patel, A. V., Hue, T. F., Perna, F. M., & Schmitz, K. H. (2019a). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Medicine & Science in Sports & Exercise*, 51(11), 2375-2390. <https://doi.org/10.1249/Mss.0000000000002116>
- Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., Zucker, D. S., Matthews, C. E., Ligibel, J. A., Gerber, L. H., Morris, G. S., Patel, A. V., Hue, T. F., Perna, F. M., & Schmitz, K. H. (2019b). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*, 51(11), 2375-2390. <https://doi.org/10.1249/MSS.0000000000002116>
- Cerhan, J. R., Janney, C. A., Vachon, C. M., Habermann, T. M., Kay, N. E., Potter, J. D., Sellers, T. A., & Folsom, A. R. (2002). Anthropometric characteristics, physical activity, and risk of non-Hodgkin's lymphoma subtypes and B-cell chronic lymphocytic leukemia: a prospective study. *Am J Epidemiol*, 156(6), 527-535. <https://doi.org/10.1093/aje/kwf082>
- Courneya, K. S., & Friedenreich, C. M. (2001). Framework PEACE: An organizational model for examining physical exercise across the cancer experience. *Annals of Behavioral Medicine*, 23(4), 263-272. https://doi.org/10.1207/S15324796abm2304_5
- Courneya, K. S., Sellar, C. M., Stevinson, C., McNeely, M. L., Peddle, C. J., Friedenreich, C. M., Tankel, K., Basi, S., Chua, N., Mazurek, A., & Reiman, T. (2009). Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients. *Journal of Clinical Oncology*, 27(27), 4605-4612.
- Crane, J. C., Gordon, M. J., Basen-Engquist, K., Ferrajoli, A., Markofski, M. M., Lee, C. Y., Fares, S., Simpson, R. J., & LaVoy, E. C. (2023). Relationships between T-lymphocytes and physical function in adults with chronic lymphocytic leukemia: Results from the HEALTH4CLL pilot study. *European Journal of Haematology*, 110(6), 732-742. <https://doi.org/10.1111/ejh.13958>
- De Backer, I. C., Vreugdenhil, G., Nijziel, M. R., Kester, A. D., van Breda, E., & Schep, G. (2008). Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. *Br J Cancer*, 99(1), 30-36. <https://doi.org/10.1038/sj.bjc.6604433>
- Furzer, B. J., Ackland, T. R., Wallman, K. E., Petterson, A. S., Gordon, S. M., Wright, K. E., & Joske, D. J. L. (2016). A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients. *Supportive Care in Cancer*, 24(4), 1697-1707. <https://doi.org/10.1007/s00520-015-2955-7>
- Galvao, D. A., & Taaffe, D. R. (2005). Resistance exercise dosage in older adults: Single-versus multiset effects on physical performance and body composition. *Journal of the American Geriatrics Society*, 53(12), 2090-2097. <https://doi.org/10.1111/j.1532-5415.2005.00494.x>
- Hagstrom, A. D., Koizumi, S., Wewerge, M. A., Leake, H., Ha, L., Macdonald, E., Fairman, C. M., & Clifford, B. (2021). Resistance Training And Body Composition In Cancer: A Systematic Review And Meta-analysis. *Medicine and Science in Sports and Exercise*, 53(8), 471-472. <Go to ISI>://WOS:000693955700692

- Hallek, M., Cheson, B. D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Dohner, H., Hillmen, P., Keating, M., Montserrat, E., Chiorazzi, N., Stilgenbauer, S., Rai, K. R., Byrd, J. C., Eichhorst, B., O'Brien, S., Robak, T., Seymour, J. F., & Kipps, T. J. (2018). iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*, 131(25), 2745-2760. <https://doi.org/10.1182/blood-2017-09-806398>
- Institute, T. N. C. (2023). *Clinical Trial Randomization Tool*. Retrieved 2023-02-24 from <https://ctrandomization.cancer.gov>
- Kang, H. (2021). Sample size determination and power analysis using the G*Power software. *Journal of Educational Evaluation for Health Professions*, 18. <https://doi.org/ARTN1710.3352/jeehp.2021.18.17>
- MacDonald, G., Sitlinger, A., Deal, M. A., Hanson, E. D., Ferraro, S., Pieper, C. F., Weinberg, J. B., Brander, D. M., & Bartlett, D. B. (2021). A pilot study of high-intensity interval training in older adults with treatment naïve chronic lymphocytic leukemia. *Sci Rep*, 11(1), 23137. <https://doi.org/10.1038/s41598-021-02352-6>
- Persoon, S., Chinapaw, M. J. M., Buffart, L. M., Liu, R. D. K., Wijermans, P., Koene, H. R., Minnema, M. C., Lugtenburg, P. J., Marijt, E. W. A., Brug, J., Nollet, F., & Kersten, M. J. (2017). Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: Results from the EXIST study. *PLoS One*, 12(7). <https://doi.org/ARTNe018131310.1371/journal.pone.0181313>
- Peterson, M. D., Sen, A., & Gordon, P. M. (2011). Influence of Resistance Exercise on Lean Body Mass in Aging Adults: A Meta-Analysis. *Medicine & Science in Sports & Exercise*, 43(2), 249-258. <https://doi.org/10.1249/MSS.0b013e3181eb6265>
- Ruiz-Casado, A., Martin-Ruiz, A., Perez, L. M., Provencio, M., Fiuza-Luces, C., & Lucia, A. (2017). Exercise and the Hallmarks of Cancer. *Trends Cancer*, 3(6), 423-441. <https://doi.org/10.1016/j.trecan.2017.04.007>
- Schmitz, K. (2020). *Exercise Oncology: Prescribing Physical Activity Before and After a Cancer Diagnosis*. Springer Cham. <https://doi.org/https://doi.org/10.1007/978-3-030-42011-6>
- Shanafelt, T. D., Bowen, D., Venkat, C., Slager, S. L., Zent, C. S., Kay, N. E., Reinalda, M., Sloan, J. A., & Call, T. G. (2007). Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *British Journal of Haematology*, 139(2), 255-264. <https://doi.org/10.1111/j.1365-2141.2007.06791.x>
- Sitlinger, A., Brander, D. M., & Bartlett, D. B. (2020). Impact of exercise on the immune system and outcomes in hematologic malignancies [Review]. *Blood Advances*, 4(8), 1801-1811. <https://doi.org/10.1182/bloodadvances.2019001317>
- Sitlinger, A., Deal, M. A., Garcia, E., Thompson, D. K., Stewart, T., MacDonald, G. A., Devos, N., Corcoran, D., Staats, J. S., Enzor, J., Weinhold, K. J., Brander, D. M., Weinberg, J. B., & Bartlett, D. B. (2021). Physiological Fitness and the Pathophysiology of Chronic Lymphocytic Leukemia (CLL). *Cells*, 10(5). <https://doi.org/ARTN116510.3390/cells10051165>
- Strasser, B., & Schobersberger, W. (2011). Evidence for Resistance Training as a Treatment Therapy in Obesity. *Journal of Obesity*, 2011. <https://doi.org/10.1155/2011/482564>
- Strasser, B., Steindorf, K., Wiskemann, J., & Ulrich, C. M. (2013). Impact of Resistance Training in Cancer Survivors: A Meta-Analysis. *Medicine & Science in Sports & Exercise*, 45(11), 2080-2090. <https://doi.org/10.1249/MSS.0b013e31829a3b63>
- Walter, R. B., Buckley, S. A., & White, E. (2013). Regular recreational physical activity and risk of hematologic malignancies: results from the prospective ViTamins And lifestyle (VITAL) study. *Ann Oncol*, 24(5), 1370-1377. <https://doi.org/10.1093/annonc/mds631>
- Yang, S. W., Chu, S. F., Gao, Y., Ai, Q. D., Liu, Y. J., Li, X., & Chen, N. H. (2019). A Narrative Review of Cancer-Related Fatigue (CRF) and Its Possible Pathogenesis. *Cells*, 8(7). <https://doi.org/ARTN73810.3390/cells8070738>

PAPER V

Journal of Geriatric Oncology
Age Does Not Limit Gains: A Pilot Study with Resistance Training Outcomes in
Treatment-Naïve Chronic Lymphocytic Leukemia
--Manuscript Draft--

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Response to Reviewers:	Dear Editor, We are pleased to submit our revised manuscript titled "Age Does Not Limit Gains: A Pilot Study with Resistance Training Outcomes in Treatment-Naïve Chronic Lymphocytic Leukemia" for consideration as a Research Letter in the Journal of Geriatric Oncology. In response to the editorial request, we have implemented the following substantive changes: 1. Clarified the Rationale for the Age Range (45–80 years): In the Introduction and Methods sections, we explicitly describe the rationale for selecting an age range of 45–80 years. This range was chosen to represent the clinical demographic of treatment-naïve CLL patients while ensuring both the safety and feasibility of implementing a resistance training intervention. Given the median age at CLL diagnosis (~70 years), our cohort reflects the population most likely to benefit from early, non-pharmacologic interventions before treatment initiation. 2. Addressed Age-Related Differences in Outcomes: To explore whether age influenced exercise responsiveness, we conducted two types of analyses: - Correlation analyses (Pearson's <i>r</i>) between age and changes in key outcomes (fat mass, strength, VO₂peak). - Stratified analysis comparing participants <65 years vs. ≥65 years. These findings are summarized in the Results section and interpreted in the Discussion. No significant age-related differences were observed, suggesting that the benefits of resistance training in this population are preserved across age groups, including older adults. 3. Additional Enhancements: - The manuscript was enriched with updated in-text references (APA style), integrating up to 15 key studies to support our rationale, design, and interpretations. - The content was refined for clarity, and statistical methods were explicitly aligned with the study aims, emphasizing age stratification and feasibility metrics. We believe these revisions strengthen the manuscript's relevance to the mission of the Journal of Geriatric Oncology by offering novel, practical insight into age-inclusive exercise interventions for hematologic cancer populations. We respectfully submit this

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Title: *Age Does Not Limit Gains: A Pilot Study with Resistance Training Outcomes in Treatment-Naïve Chronic Lymphocytic Leukemia*

Keywords: Chronic lymphocytic leukemia; resistance training; older adults; muscle strength; immunomodulation.

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Introduction

Chronic lymphocytic leukemia (CLL) is a neoplasm of small mature B cells that co-express CD5 and CD23, leading to a progressive accumulation of monoclonal B lymphocytes [1, 2]. CLL is the most prevalent chronic leukemia among adults in Western countries, accounting for up to 35% of leukemia cases in the U.S. [3], with a strong male predominance and frequent onset between 65–74 years—though more than 30% of new cases occur in patients aged 45–64 [1].

Global mortality from CLL is rising, particularly in low Social-Demographic Index areas, with obesity, smoking, and occupational chemical exposure noted as risk factors [4]. As CLL progresses, patients experience fatigue, reduced cardiopulmonary function, infections, and other symptoms that impair daily life and physical function [3]. These symptoms are closely linked with declining physical fitness and quality of life. Diagnostic evaluation includes blood smear analysis, flow cytometry, FISH, and evaluation of CD38, ZAP-70, and IgHV mutational status [1].

While targeted therapies such as BTK and BCL-2 inhibitors have improved outcomes, they do not offer a cure and come with significant costs and side effects [4]. Therefore, the Active Surveillance phase offers a key opportunity to implement lifestyle interventions like exercise. Prognostication in CLL has evolved from Rai and Binet staging systems to the CLL-IPI, which integrates clinical, biochemical, and genetic variables [5]. Immune dysregulation in CLL is multifaceted, involving impaired T-cell cytotoxicity and NK cell dysfunction [6], further supporting the need for immune-targeted nonpharmacologic strategies.

Regular exercise has demonstrated potential in reducing oxidative stress, modulating apoptosis pathways, and enhancing immune surveillance [7, 8]. Resistance training, in particular, induces protective antioxidant adaptations and muscle-derived cytokines (myokines), which promote anti-inflammatory responses and immune cell cytotoxicity [9]. Acute bouts of physical activity—especially involving large muscle groups—can transiently increase NK cell activity and leukocyte trafficking [10, 11].

This pilot study specifically targeted patients aged 45 to 80 years to reflect the full spectrum of clinically relevant CLL demographics. Although CLL incidence

increases with age, a substantial portion of patients are diagnosed in midlife, with more than 30% under age 65 [1]. We aimed to capture this variability to assess whether physiological benefits from resistance training are consistent across age brackets and to test the hypothesis that older adults maintain responsiveness to structured physical interventions. Understanding age-related effects is especially pertinent in oncology, where age often drives treatment decisions and health behavior recommendations. Our design allows preliminary insight into how older adults, a group often underrepresented in exercise oncology trials, respond to a feasible and clinically applicable training protocol.

Despite these promising mechanisms, resistance training remains understudied in CLL. This pilot study aimed to evaluate the feasibility, safety, and preliminary efficacy of a 16-week resistance training intervention in treatment-naïve CLL patients aged 45 to 80 years, and to explore whether age influences training responsiveness.

Methods

Participants were recruited from a university hospital hematology clinic in Portugal. Inclusion criteria were: confirmed diagnosis of stable, treatment-naïve CLL; age 45–80 years; medical clearance for exercise; and ability to participate in training and assessments. Exclusion criteria included recent cancer treatment, comorbidities limiting exercise tolerance, or enrollment in structured exercise programs. Eligible participants provided informed consent and were randomized (2:1) to a resistance exercise group (REx) or usual care control group (CG).

The REx group completed 16 weeks of supervised resistance training, consisting of two weekly sessions (60 minutes each) using commercial-grade machines. Each session began with a cycling warm-up (10 minutes) and ended with a cooldown (5 minutes). Exercises targeted major muscle groups in the following order: Leg Press -> Leg Curl -> Leg Extension -> Chest Press -> Seated Row -> Shoulder Press -> Triceps Extension -> Biceps Curl -> Curl Up Abdominal. It was implemented a progressive intensity increase from 70% to 85% of 1-repetition maximum (1-RM). Sets and

repetitions followed the American College of Sports Medicine (ACSM) guidelines (3 sets of 8–12 reps) [12].

Outcome assessments occurred at baseline and post-intervention and included: 1) body composition via dual-energy X-ray absorptiometry (DEXA); 2) cardiorespiratory fitness via VO_2peak (CPET protocol); 3) muscle strength via isokinetic (BIODEX); and 4) immune markers from routine blood tests. Physical activity levels were monitored using accelerometers (ActiGraph) worn for seven consecutive days [13].

Statistical analyses were conducted using SPSS v29. Normality was assessed with Shapiro-Wilk tests. Between-group comparisons were made using independent t-tests or Mann-Whitney U tests for non-parametric data. Within-group changes were evaluated using paired t-tests or Wilcoxon signed-rank tests. Group $\times$ time interactions were examined using two-way mixed ANOVA where assumptions were met. Hedges' g effect sizes were reported and interpreted as small (0.2), medium (0.5), or large (0.8) [14]. Age-related effects were examined using Pearson correlations and stratified analysis (≥ 65 vs. < 65 years).

Results

Eleven participants (7 CG, 4 REx) completed the study (mean age 65.6 ± 9.7 years; 64% male). All participants attended $\geq 75\%$ of assessments and REx participants completed 100% of training sessions. No adverse events were reported; mild muscle soreness was the only noted complaint. Adherence to training intensity targets was high, with all REx participants achieving $>80\%$ of prescribed 1-RM during sessions.

Significant between-group differences emerged in body composition: REx participants reduced fat mass by 6.02% ($\pm 5.3\%$), while CG increased by 3.4% ($\pm 6.3\%$) ($p = 0.033$, $g = 1.57$). Total body mass also decreased in REx ($p = 0.003$, $g = 2.48$). Lean mass increased modestly in REx and remained stable in CG. VO_2peak improved by 33.3% in REx (vs. 16.7% in CG), with relative VO_2peak increasing by 35.1% (REx)

and 13.2% (CG). Muscle strength improvements in REx ranged from +16.1% (chest press) to +40.8% (leg press).

Immunologic changes included increased neutrophils (+18.5%) and monocytes (+26.5%) in REx, while lymphocytes remained stable. In contrast, the CG showed a 13.5% decline in neutrophils and unchanged monocytes. Total white blood cells rose by 51.6% in CG but remained stable in REx. These findings align with the immunomodulatory effects of exercise reported in other cancer populations.

Exploratory analyses examined associations between age and changes in functional and immune markers. Significant negative correlations were found between age and isokinetic peak torque per body weight in extension ($r = -0.643$, $p = 0.045$) and isokinetic average power in extension ($r = -0.728$, $p = 0.017$), indicating that younger participants experienced greater improvements in these strength measures. Monocyte response showed a trend toward inverse association with age ($r = -0.563$, $p = 0.071$), while lymphocytes showed a nonsignificant positive correlation ($r = 0.441$, $p = 0.175$). Regression models showed that age alone significantly predicted improvements in isokinetic flexion strength ($R^2 = 0.413$, $p = 0.045$) and average power extension ($R^2 = 0.530$, $p = 0.017$).

When both age and group were included in linear models, group assignment significantly predicted changes in fat mass ($R^2 = 0.503$, $p = 0.022$), total body mass ($R^2 = 0.700$, $p = 0.003$), and body fat percentage ($R^2 = 0.364$, $p = 0.069$). In contrast, age did not significantly predict these body composition outcomes in adjusted models. Collectively, these findings suggest that although age was modestly associated with select strength adaptations, participation in resistance training was a stronger determinant of body composition improvements.

Discussion

This study supports the feasibility, safety, and preliminary efficacy of resistance training in treatment-naïve CLL patients aged 45–80 years. The inclusion of older adults demonstrated that age alone does not preclude benefit from structured exercise. While age was modestly associated with attenuated strength gains, resistance training yielded meaningful improvements in body composition and immune markers across the cohort. These findings support resistance training as a viable intervention during the watch-and-wait phase of CLL, especially given the non-curative nature of current treatments [4].

Exercise-induced immune modulation is particularly relevant in CLL, where immune suppression is common. In line with previous studies, resistance training improved neutrophil and monocyte levels while preserving lymphocyte stability [6, 7, 11]. These effects may reflect reduced inflammation and increased immune surveillance, both of which are critical in cancer management [8, 9]. Additionally, aerobic benefits observed in VO_2peak support complementary effects of resistance training on cardiopulmonary fitness and overall physical reserve [10].

Regression analyses underscored that group allocation—not age—was the primary determinant of fat and total body mass improvements, highlighting the intervention’s value regardless of age. The association between younger age and strength responsiveness echoes prior findings that power declines earlier than strength but remains trainable in older populations [9, 10]. Thus, exercise protocols should be adapted, not withheld, in older cancer patients.

Strengths of this study include the inclusion of older adults, the comprehensive assessment of physical and immune parameters, and the application of a safe and replicable resistance training protocol. Limitations include the small sample size, exploratory design, and lack of long-term follow-up. Future research should prioritize larger randomized trials to confirm these findings and explore mechanistic links between muscle adaptation and immune outcomes.

Resistance training should be considered an early intervention strategy for older adults with hematologic malignancies, especially during watchful waiting periods. These results add to growing evidence that age should not be a barrier to exercise prescription in oncology care.

Ethical Compliance

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

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Conflicts of Interest

All authors state that they have no conflict of interest.

Data Availability

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Hallek, M., et al., *iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL*. Blood, 2018. **131**(25): p. 2745-2760.
2. Algino, K.M., et al., *CD20 (Pan-B cell antigen) expression on bone marrow-derived T cells*. American Journal of Clinical Pathology, 1996. **106**(1): p. 78-81.
3. Shanafelt, T.D., et al., *Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients*. British Journal of Haematology, 2007. **139**(2): p. 255-264.
4. Sitlinger, A., D.M. Brander, and D.B. Bartlett, *Impact of exercise on the immune system and outcomes in hematologic malignancies*. Blood Advances, 2020. **4**(8): p. 1801-1811.
5. International, C.L.L.I.P.I.w.g., *An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data*. Lancet Oncol, 2016. **17**(6): p. 779-790.
6. Crane, J.C., et al., *Relationships between T-lymphocytes and physical function in adults with chronic lymphocytic leukemia: Results from the HEALTH4CLL pilot study*. European Journal of Haematology, 2023. **110**(6): p. 732-742.
7. MacDonald, G., et al., *A pilot study of high-intensity interval training in older adults with treatment naive chronic lymphocytic leukemia*. Sci Rep, 2021. **11**(1): p. 23137.
8. Ruiz-Casado, A., et al., *Exercise and the Hallmarks of Cancer*. Trends Cancer, 2017. **3**(6): p. 423-441.
9. Strasser, B. and W. Schobersberger, *Evidence for Resistance Training as a Treatment Therapy in Obesity*. Journal of Obesity, 2011. **2011**.
10. Bigley, A.B., et al., *Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells*. Brain Behav Immun, 2014. **39**: p. 160-71.
11. Campbell, K.L., et al., *Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable*. Med Sci Sports Exerc, 2019. **51**(11): p. 2375-2390.
12. Garber, C.E., et al., *Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise*. Medicine & Science in Sports & Exercise, 2011. **43**(7): p. 1334-1359.
13. Migueles, J.H., et al., *Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations*. Sports Medicine, 2017. **47**(9): p. 1821-1845.
14. Lakens, D., *Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs*. Frontiers in Psychology, 2013. **4**.

CHAPTER 3 – OVERALL DISCUSSION

This dissertation addresses critical gaps in the literature regarding health and immunological responses to exercise in hematological malignancies, with a particular focus on treatment-naïve patients with Chronic Lymphocytic Leukemia (CLL). Although the individual studies within this thesis pursued distinct research questions using diverse methodologies, they shared a unifying objective: to investigate the effects of individualized exercise interventions - primarily strength-based resistance training - on physical fitness, immunological function, and health-related quality of life (HRQoL).

The thesis comprises a series of studies that collectively demonstrate the feasibility and therapeutic potential of tailored exercise programs for individuals with CLL. These investigations not only advance our understanding of the role of exercise in this patient population but also expose challenges related to conceptual frameworks, assessment standardization, and methodological heterogeneity within existing research.

The central focus was on assessing the impact of resistance training on physical fitness, body composition, and disease-related hematological markers in treatment-naïve CLL patients. Special attention was given to the feasibility and efficacy of strength-based programs in mitigating fatigue, improving HRQoL, and enhancing functional capacity. Additionally, the research explored daily physical activity patterns and patients' self-perceptions of their physical condition, offering a multidimensional perspective on exercise as a supportive care strategy.

The rationale for this work stemmed from the observation that current public health recommendations - such as those by the World Health Organization, American College of Sports Medicine (ACSM), and American Heart Association - emphasize a combination of moderate-intensity aerobic activity (≥ 150 minutes/week) and muscle-strengthening exercises (≥ 2 days/week). However, awareness and adherence to these guidelines remain low. Notably, fewer than 10% of U.S. adults are aware of exercise guidelines, and only 3% correctly identify the aerobic component [66]. Awareness of strength training guidelines is even lower. Despite emerging evidence of a protective effect of pre-diagnosis physical activity in cancer patients, the American Cancer Society continues to emphasize the need for further research [67].

This gap in knowledge and adherence motivated the development of a structured strength-based resistance training protocol specifically tailored for individuals with CLL. The study began by acknowledging the lack of standardized exercise assessment protocols in CLL research, which has led to inconsistent findings and limited comparability across studies. Prior literature supports various training modalities - including aerobic training [15], high-intensity interval training [29], resistance training [68], and combined programs [34] - but methodological variability hampers evidence synthesis.

Our systematic review identified substantial inconsistencies in cardiovascular and muscular assessment protocols. Cardiovascular testing varied in terms of modality (e.g., treadmill vs. cycle ergometer), intensity markers (e.g., 90% VO_2 reserve vs. 65% maximal short exercise capacity), and session duration. Similarly, resistance training protocols differed widely in intensity (ranging from 65% to 80% 1-RM), volume, rest periods, and equipment. To address these inconsistencies, we proposed the use of gold-standard assessments such as isokinetic dynamometry, cardiopulmonary exercise testing with ECG, and dual-energy X-ray absorptiometry.

The studies comprised in this dissertation evidenced that strength-based resistance training - previously unexplored as a standalone intervention in CLL - has significant potential for improving physical function and preserving lean mass. The rationale for focusing on resistance training is grounded in prior evidence showing its benefits in other cancer populations, including improved mental health, increased self-esteem through goal-setting and physical empowerment [35, 36], and long-term behavioral changes that enhance adherence to physical activity [23].

Our randomized controlled trial was conducted among well-defined, treatment-naïve CLL patients, using standardized outcome measures and long-term follow-up. The resistance training protocol was evidence-based and individualized. Importantly, the treatment-naïve phase - characterized by stable disease without the need for pharmacological intervention - offered a unique window to assess exercise impacts without confounding effects from treatment-

induced catabolism. Insights from this phase may be transferable to other malignancies in the pre-treatment stage.

Although cancer patients are not necessarily less active than the general population, they often fall short of recommended activity levels [69]. Using accelerometry, we objectively quantified daily physical activity and found that participants averaged only 19.6 minutes/day of moderate-to-vigorous physical activity (MVPA) - well below guidelines. No significant correlations were found between MVPA and disease markers, but blood parameters were largely within normative ranges, aside from lymphocyte and neutrophil levels. These findings emphasize the relevance of early exercise interventions in hematologic malignancies.

Despite a small sample size and one exclusion due to a potential cardiac issue, all participants completed the intervention and HRQoL assessments at baseline, post-intervention, and six-month follow-up, with 8 participants retained. The program was safe and well-tolerated, with no adverse events beyond mild muscle soreness. Statistically significant improvements were observed in the resistance training group in functional well-being (FACIT-F, $p = 0.03$, $d = -1.47$), physical functioning (EORTC QLQ-C30, $p = 0.01$), and general quality of life (FACT-G, $p = 0.02$), with other domains showing clinically meaningful improvements [70, 71].

Compared to prior endurance-focused interventions (e.g., Persoon et al., 2017), our strength-based approach yielded superior gains in fatigue reduction (+37.5 points vs. -3.6) and cognitive functioning, as well as a greater decrease in symptom burden. However, these benefits were not sustained at the six-month follow-up, echoing findings on the transient nature of HRQoL gains from resistance training in older adults [72]. Long-term maintenance remains a challenge, often impeded by motivation, access, and support [73].

Physiologically, the resistance training group achieved significant reductions in fat mass (-6.02%) and body mass (-1.52%), while the control group experienced increases, with large effect sizes ($g = 1.573$ and $g = 2.48$). Muscle strength gains ranged from 16% to 40%, consistent with previous post-treatment studies [33]. Improvements in VO_{2peak} (+33.3%), $PetCO_2$, and VE/VCO_2 -

despite the absence of aerobic training - suggest enhanced cardiorespiratory efficiency. Isokinetic testing revealed significant gains in agonist/antagonist knee strength ratio ($g = 1.74$), suggesting neuromuscular adaptation.

Immunologically, resistance training resulted in increased neutrophil (+18.5%) and monocyte (+26.5%) counts, with stable white blood cell profiles, contrasting with a 51.6% WBC increase and neutrophil decline in controls. These changes align with literature indicating exercise-induced modulation of innate and adaptive immune responses, including enhanced NK cell activity and T-cell function [34, 74].

Regression analysis showed that group allocation - not age - was the strongest predictor of changes in fat and total body mass. While younger participants experienced greater strength gains, older adults also benefited substantially, reinforcing the applicability of resistance training across age groups [75].

Despite limitations - chiefly the small sample size and narrow generalizability to stable, untreated patients - this research supports resistance training as a feasible, impactful intervention to enhance physical function, body composition, and immune health in CLL. Future studies should explore larger, multicenter cohorts; compare training modalities; and investigate immunological mechanisms, including myokine and cytokine responses, to better understand long-term impacts on clinical outcomes such as frailty, infection risk, and time-to-treatment initiation.

Practice Implications and Recommendations

This dissertation supports the inclusion of structured exercise interventions in the supportive care of CLL patients. Specifically, we recommend:

- **Progressive resistance training:** Begin at 50–60% 1-RM, increasing to 70–80% as tolerated.
- **Frequency:** Two to three sessions per week, incorporating multi-joint and functional exercises.

- **Monitoring:** Continuous clinical supervision to adapt protocols based on individual needs.
- **Complementary aerobic training:** Moderate-intensity sessions (50–70% VO_2 max) to augment benefits.
- **Qualified supervision:** Exercise physiologists and physiotherapists should guide and monitor programs to ensure adherence and safety.

Exercise should be integrated across various settings - from clinical facilities to community centers and home-based programs - ensuring accessibility and sustainability. Tailored protocols supervised by trained professionals are essential to maximize benefits and minimize risks.

CHAPTER 4 – CONCLUSIONS

In summary, the current dissertation adds to a scarce field of research in oncology, the effects of an isolated strength-based resistance training, employing “gold-standard” objective methods. Considering the overall findings that emerged from the original studies, we highlight the following conclusions:

- This dissertation successfully met its primary objectives by characterizing the physical aptitude and habitual activity patterns of treatment-naïve CLL patients, demonstrating significant deficits in baseline cardiorespiratory fitness, muscular strength, and daily physical activity levels.
- Through a structured strength-based resistance training intervention, we confirmed H1, as participants in the exercise group showed statistically significant improvements in muscular strength (e.g., +40.78% in leg press) and favorable changes in body composition, including reductions in total fat mass and body fat percentage while preserving lean mass.
- H2 was also supported, with significant enhancements in overall health-related quality of life, particularly in functional well-being, physical functioning, and symptom reduction, as measured by validated instruments (FACIT-F, EORTC QLQ-C30, FACT-G).
- Regarding H3, although the intervention was associated with positive trends in daily physical activity levels, including greater engagement in moderate-to-vigorous activity, these changes did not reach statistical significance.
- Furthermore, the study confirmed the feasibility, safety, and adherence to the resistance training protocol, with a strength-based intervention, with no adverse events beyond minor muscle soreness and high retention rates, supporting its potential for clinical implementation.

Collectively, these findings reinforce the role of tailored resistance training as a feasible and effective non-pharmacological strategy to improve functional and psychosocial outcomes in early-stage CLL patients. They underscore the potential therapeutic relevance of exercise interventions within this clinical population and highlight their positive impact in a rehabilitative context. Nevertheless, given the limited sample size, future studies with larger cohorts and longitudinal designs are warranted to provide more robust evidence and to elucidate the long-term benefits and underlying mechanisms of these effects.

REFERENCES

1. Campbell, K.L., et al., *Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable*. Med Sci Sports Exerc, 2019. **51**(11): p. 2375-2390.
2. Swerdlow, S.H., et al., *WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues*. Revised 4th edition ed. 2017, Lyon: IARC Press.
3. Hallek, M., *Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment*. Am J Hematol, 2019. **94**(11): p. 1266-1287.
4. Burger, J.A. and J.G. Gribben, *The microenvironment in chronic lymphocytic leukemia (CLL) and other B cell malignancies: Insight into disease biology and new targeted therapies*. Seminars in Cancer Biology, 2014. **24**: p. 71-81.
5. Scott, D.W. and R.D. Gascoyne, *The tumour microenvironment in B cell lymphomas*. Nature Reviews Cancer, 2014.
6. Ramsay, A.G., et al., *Multiple inhibitory ligands induce impaired T-cell immunologic synapse function in chronic lymphocytic leukemia that can be blocked with lenalidomide: establishing a reversible immune evasion mechanism in human cancer*. Blood, 2012. **120**(7): p. 1412-21.
7. McTiernan, A., et al., *Physical Activity in Cancer Prevention and Survival: A Systematic Review*. Med Sci Sports Exerc, 2019. **51**(6): p. 1252-1261.
8. Walter, R.B., S.A. Buckley, and E. White, *Regular recreational physical activity and risk of hematologic malignancies: results from the prospective VITamins And lifestyle (VITAL) study*. Ann Oncol, 2013. **24**(5): p. 1370-7.
9. van Veldhoven, C.M., et al., *Physical activity and lymphoid neoplasms in the European Prospective Investigation into Cancer and nutrition (EPIC)*. Eur J Cancer, 2011. **47**(5): p. 748-60.
10. Teras, L.R., et al., *Recreational physical activity, leisure sitting time and risk of non-Hodgkin lymphoid neoplasms in the American Cancer Society Cancer Prevention Study II Cohort*. Int J Cancer, 2012. **131**(8): p. 1912-20.

11. Lu, Y., et al., *Body size, recreational physical activity, and B-cell non-Hodgkin lymphoma risk among women in the California teachers study*. Am J Epidemiol, 2009. **170**(10): p. 1231-40.
12. Courneya, K.S., et al., *Effects of supervised exercise on progression-free survival in lymphoma patients: an exploratory follow-up of the HELP Trial*. Cancer Causes Control, 2015. **26**(2): p. 269-276.
13. Streckmann, F., et al., *Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy*. Ann Oncol, 2014. **25**(2): p. 493-9.
14. Elter, T., et al., *Is physical exercise possible in patients with critical cytopenia undergoing intensive chemotherapy for acute leukaemia or aggressive lymphoma?* Int J Hematol, 2009. **90**: p. 199-204.
15. Courneya, K.S., et al., *Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients*. Journal of Clinical Oncology, 2009. **27**(27): p. 4605-4612.
16. Backer, I.C.D., et al., *Resistance Training in Cancer Survivors: A Systematic Review*. Int J Sports Med, 2009. **30**: p. 703-712.
17. NEWTON, R.U., et al., *Exercise Mode Specificity for Preserving Spine and Hip Bone Mineral Density in Prostate Cancer Patients*. Medicine & Science in Sports & Exercise, 2019.
18. De Backer, I.C., et al., *Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life*. Br J Cancer, 2008. **99**(1): p. 30-6.
19. Mugele, H., et al., *High-intensity interval training in the therapy and aftercare of cancer patients: a systematic review with meta-analysis*. J Cancer Surviv, 2019. **13**(2): p. 205-223.
20. Hallek, M., et al., *iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL*. Blood, 2018. **131**(25): p. 2745-2760.
21. Cerhan, J.R., et al., *Anthropometric characteristics, physical activity, and risk of non-Hodgkin's lymphoma subtypes and B-cell chronic lymphocytic leukemia: a prospective study*. Am J Epidemiol, 2002. **156**(6): p. 527-35.

22. Courneya, K.S. and C.M. Friedenreich, *Framework PEACE: An organizational model for examining physical exercise across the cancer experience*. Annals of Behavioral Medicine, 2001. **23**(4): p. 263-272.
23. Heywood, R., A.L. McCarthy, and T.L. Skinner, *Safety and feasibility of exercise interventions in patients with advanced cancer: a systematic review*. Supportive Care in Cancer, 2017. **25**(10): p. 3031-3050.
24. ACSM, *ACSM's Guidelines for Exercise Testing and Prescription*. Tenth ed. 2018, Philadelphia, PA: Wolters Kluwer Health.
25. Okely, A.D., et al., *2020 WHO guidelines on physical activity and sedentary behavior*. Sports Medicine and Health Science, 2021. **3**(2): p. 115-118.
26. Kim, J.S., et al., *Exercise-induced myokines and their effect on prostate cancer*. Nat Rev Urol, 2021. **18**(9): p. 519-542.
27. Stamatakis, E., et al., *Does Strength-Promoting Exercise Confer Unique Health Benefits? A Pooled Analysis of Data on 11 Population Cohorts With All-Cause, Cancer, and Cardiovascular Mortality Endpoints*. Am J Epidemiol, 2018. **187**(5): p. 1102-1112.
28. Imboden, M.T., et al., *Reference standards for lean mass measures using GE dual energy x-ray absorptiometry in Caucasian adults*. Plos One, 2017. **12**(4).
29. MacDonald, G., et al., *A pilot study of high-intensity interval training in older adults with treatment naive chronic lymphocytic leukemia*. Sci Rep, 2021. **11**(1): p. 23137.
30. Artese, A.L., et al., *Effects of high-intensity interval training on health-related quality of life in chronic lymphocytic leukemia: A pilot study*. J Geriatr Oncol, 2022.
31. Persoon, S., et al., *Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: Results from the EXIST study*. Plos One, 2017. **12**(7).
32. Galvao, D.A. and D.R. Taaffe, *Resistance exercise dosage in older adults: Single-versus multiset effects on physical performance and body*

- composition*. Journal of the American Geriatrics Society, 2005. **53**(12): p. 2090-2097.
33. Furzer, B.J., et al., *A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients*. Supportive Care in Cancer, 2016. **24**(4): p. 1697-1707.
 34. Crane, J.C., et al., *Relationships between T-lymphocytes and physical function in adults with chronic lymphocytic leukemia: Results from the HEALTH4CLL pilot study*. European Journal of Haematology, 2023. **110**(6): p. 732-742.
 35. Noetel, M., et al., *Effect of exercise for depression: systematic review and network meta-analysis of randomised controlled trials*. Bmj-British Medical Journal, 2024. **384**.
 36. Andersen, V., et al., *A Comparison of Affective Responses Between Time Efficient and Traditional Resistance Training*. Front Psychol, 2022. **13**: p. 912368.
 37. Kruger, K., et al., *Intensive resistance exercise induces lymphocyte apoptosis via cortisol and glucocorticoid receptor-dependent pathways*. J Appl Physiol (1985), 2011. **110**(5): p. 1226-32.
 38. Lee, M.K., et al., *Effects of resistance exercise on antioxidant enzyme activities and apoptosis-related protein expression of hippocampus in OLETF rats*. Technol Health Care, 2018. **26**(3): p. 457-467.
 39. Kruger, K., et al., *Apoptosis of T-Cell Subsets after Acute High-Intensity Interval Exercise*. Med Sci Sports Exerc, 2016. **48**(10): p. 2021-9.
 40. Goh, J., N. Niksirat, and K.L. Campbell, *Exercise training and immune crosstalk in breast cancer microenvironment: exploring the paradigms of exercise-induced immune modulation and exercise-induced myokines*. Am J Transl Res, 2014. **6**(5): p. 422-38.
 41. Roy, P., S. Chowdhury, and H.K. Roy, *Exercise-induced myokines as emerging therapeutic agents in colorectal cancer prevention and treatment*. Future Oncol, 2018. **14**(4): p. 309-312.

42. Barbalho, S.M., et al., *Myokines: a descriptive review*. J Sports Med Phys Fitness, 2020. **60**(12): p. 1583-1590.
43. Vasyukova, O.V., et al., *[Myokines and adipomyokines: inflammatory mediators or unique molecules of targeted therapy for obesity?]*. Probl Endokrinol (Mosk), 2021. **67**(4): p. 36-45.
44. Barbalho, S.M., et al., *Physical Exercise and Myokines: Relationships with Sarcopenia and Cardiovascular Complications*. International Journal of Molecular Sciences, 2020. **21**(10).
45. Kotani, T., et al., *Influence of physical exercise on large granular lymphocytes, Leu-7 bearing mononuclear cells and natural killer activity in peripheral blood--NK-cell and NK-activity after physical exercise*. Nihon Ketsueki Gakkai Zasshi, 1987. **50**(6): p. 1210-6.
46. Radom-Aizik, S., et al., *Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults*. J Appl Physiol (1985), 2013. **114**(5): p. 628-36.
47. Nielsen, H.B., et al., *Lymphocytes and NK cell activity during repeated bouts of maximal exercise*. Am J Physiol, 1996. **271**(1 Pt 2): p. R222-7.
48. Sitlinger, A., et al., *Exercise and Chronic Lymphocytic Leukemia (CLL) - Relationships Among Physical Activity, Fitness, & Inflammation, and Their Impacts on CLL Patients*. Blood, 2018. **132**: p. 3.
49. Chastin, S.F.M., et al., *Effects of Regular Physical Activity on the Immune System, Vaccination and Risk of Community-Acquired Infectious Disease in the General Population: Systematic Review and Meta-Analysis*. Sports Medicine, 2021. **51**(8): p. 1673-1686.
50. Krüger, K., F.C. Mooren, and C. Pilat, *The Immunomodulatory Effects of Physical Activity*. Current Pharmaceutical Design, 2016. **22**(24): p. 3730-3748.
51. Dimeo, F.C., et al., *Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation*. Cancer, 1997. **79**(9): p. 1717-1722.

52. Cramp, F. and J. Byron-Daniel, *Exercise for the management of cancer-related fatigue in adults*. Cochrane Database of Systematic Reviews, 2012(11).
53. Mustian, K.M., et al., *Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue A Meta-analysis*. Jama Oncology, 2017. **3**(7): p. 961-968.
54. Bedard, G., et al., *Meaningful change in oncology quality-of-life instruments: a systematic literature review*. Expert Review of Pharmacoeconomics & Outcomes Research, 2012. **12**(4): p. 475-483.
55. Holzner, B., et al., *Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr*. European Journal of Haematology, 2004. **72**(6): p. 381-389.
56. Youron, P., et al., *Quality of life in patients of chronic lymphocytic leukemia using the EORTC QLQ-C30 and QLQ-CLL17 questionnaire*. European Journal of Haematology, 2020. **105**(6): p. 755-762.
57. Wood, T.M., G.F. Maddalozzo, and R.A. Harter, *Accuracy of Seven Equations for Predicting 1-RM Performance of Apparently Healthy, Sedentary Older Adults*. Measurement in Physical Education and Exercise Science, 2002. **6**(2): p. 67-94.
58. Pritchard, A., et al., *ARTP statement on cardiopulmonary exercise testing 2021*. Bmj Open Respiratory Research, 2021. **8**(1).
59. Radtke, T., et al., *Standardisation of cardiopulmonary exercise testing in chronic lung diseases: summary of key findings from the ERS task force*. European Respiratory Journal, 2019. **54**(6).
60. Harkonen, R., R. Harju, and H. Alaranta, *Accuracy of the Jamar dynamometer*. J Hand Ther, 1993. **6**(4): p. 259-62.
61. Research, N.I.f.H., *Procedure for Measuring Hand Grip Strength Using The JAMAR Dynamometer*. 2014, NIHR Southampton Biomedical Research Centre: Southampton. p. 6.
62. Kannus, P., *Isokinetic evaluation of muscular performance: implications for muscle testing and rehabilitation*. Int J Sports Med, 1994. **15 Suppl 1**: p. S11-8.

63. Broderick, J.M., et al., *A guide to assessing physical activity using accelerometry in cancer patients*. Supportive Care in Cancer, 2014. **22**(4): p. 1121-1130.
64. Webster, K., D. Cella, and K. Yost, *The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation*. Health Qual Life Outcomes, 2003. **1**: p. 79.
65. Oerlemans, S., et al., *International validation of the EORTC QLQ-CLL17 questionnaire for assessment of health-related quality of life for patients with chronic lymphocytic leukaemia*. Br J Haematol, 2022. **197**(4): p. 431-441.
66. Chen, T.J., et al., *Awareness and Knowledge of the*
, *2nd Edition*. Journal of Physical Activity & Health, 2023. **20**(8): p. 742-751.
67. Rock, C.L., et al., *American Cancer Society nutrition and physical activity guideline for cancer survivors*. Ca-a Cancer Journal for Clinicians, 2022. **72**(3): p. 230-262.
68. Lee, K., et al., *Effects of high-intensity interval training on vascular function in breast cancer survivors undergoing anthracycline chemotherapy: design of a pilot study*. BMJ Open, 2018. **8**(6): p. e022622.
69. Neil, S.E., C.C. Gotay, and K.L. Campbell, *Physical activity levels of cancer survivors in Canada: findings from the Canadian Community Health Survey*. Journal of Cancer Survivorship, 2014. **8**(1): p. 143-149.
70. Cella, D., et al., *Estimating Clinically Meaningful Changes for the Functional Assessment of Cancer Therapy-Prostate: Results from a Clinical Trial of Patients with Metastatic Hormone-Refractory Prostate Cancer*. Value in Health, 2009. **12**(1): p. 124-129.
71. Clarke, N.A., et al., *A Review of Meaningful Change Thresholds for EORTC QLQ-C30 and FACT-G Within Oncology*. Value in Health, 2024. **27**(4): p. 458-468.
72. Steele, J., et al., *The Effects of 6 Months of Progressive High Effort Resistance Training Methods upon Strength, Body Composition, Function, and Wellbeing of Elderly Adults*. Biomed Research International, 2017. **2017**.

73. Van Roie, E., et al., *Low- and High-Resistance Exercise: Long-Term Adherence and Motivation among Older Adults*. Gerontology, 2015. **61**(6): p. 551-60.
74. Sitlinger, A., D.M. Brander, and D.B. Bartlett, *Impact of exercise on the immune system and outcomes in hematologic malignancies*. Blood Advances, 2020. **4**(8): p. 1801-1811.
75. Strasser, B. and W. Schobersberger, *Evidence for Resistance Training as a Treatment Therapy in Obesity*. Journal of Obesity, 2011. **2011**.

SUPPLEMENT MATERIAL

SUPPLEMENT 1 – EXAMPLE OF TRAINING PLAN FOR PATIENT

ID n°: Plano n°: 1 | Início/ Fim do Plano: 2025-01-13 / 2025-05-12 | Frequência: 2x p/ semana
Nome: | DN: | Peso: | Altura: | FCrep:

Objetivo Muscular:	Hipertrofia Personalizado	Objetivo Cardiovascular:	Melhorar Capacidade Aeróbica
Intensidade:	75 - 85 % 1RM	Intensidade:	70 - 80 % Fct máx
Modo de Aplicação:	Lento / Lento (2/2)		
Observações Gerais:			

Plano de Treino - A

	CARDIO Bicicleta Vertical Observações: Velocidade: 0 Tempo (min.): 10 Incl./Nivel: 0 FC (bpm): #VALUE!		QUADRÍCÉPES Leg Press Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!
	ISQUIOTULARES Leg Curl Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!		QUADRÍCÉPES Leg Extension Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!
	PEITORAIS Chest Press Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!		DORSAIS Seated Row Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!
	OMBROS Shoulder Press Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!		TRICÉPES Triceps Extension with High Cable Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!
	BICÍPES Biceps Curl with Low Cable Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!		ABDOMINAIS Crunch com Peso Observações: Séries: 3 Intervalo (seg.): 60-120 Repetições: 12-10-8 Carga (Kg): #REF!
	CARDIO Bicicleta Vertical Observações: Velocidade: 0 Tempo (min.): 5 Incl./Nivel: 0 FC (bpm): #VALUE!		Observações:

SUPPLEMENT 2 – INFORMATION SHEET FOR PATIENT



EFEITOS DO TREINO RESISTIDO E
DO TREINO INTERVALADO DE ALTA
INTENSIDADE NA COMPOSIÇÃO
CORPORAL, APTIDÃO FÍSICA E
QUALIDADE DE VIDA EM PACIENTES
COM LEUCEMIA LINFOCÍTICA
CRÓNICA

(FCT: 2021.07178.BD)
(COMISSÃO ÉTICA CHSJ: CE 431-19)

PROTOCOLO DE AVALIAÇÃO E INTERVENÇÃO

CRITÉRIOS DE INCLUSÃO

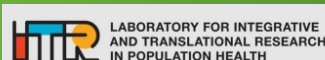
- Diagnóstico LLC confirmado;
- Idade entre os 45 e 75 anos;
- Motivação para aderir a programa de atividade física orientada;
- Sem tratamento LLC prévio;
- Sem atividade física regular atual;
- Sem indicação para iniciar tratamento LLC;
- Sem tumores primários ou incapacidade para a prática de atividade física (doença cardíaca, ou estágio avançado de doença respiratória, renal, hepática, neurológica ou osteoarticular).

BENEFÍCIOS NA PARTICIPAÇÃO

- Exames complementares gratuitos
 - Eletrocardiograma com Prova de VO2máx;
 - Avaliação da Força Muscular;
 - Avaliação da Composição Corporal (DEXA);
- Avaliação e Caracterização da Atividade Física;
- Criação de um Programa de Atividade Física personalizado;
- Acompanhamento permanente durante a intervenção;

CONTACTOS:

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912 458 876



SUPPLEMENT 3 – INFORMED CONSENT



UNIDADE LOCAL DE SAÚDE
GAIA E ESPINHO

CONSENTIMENTO INFORMADO, LIVRE E ESCLARECIDO

*Considerando a “Declaração de Helsínquia”, da Associação Médica Mundial
(Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996; Edimburgo 2000)*

*Ensaio Clínico Randomizado Controlado de Exercício Físico como Intervenção
na Leucemia Linfocítica Crónica (FCT: 2021.07178.BD)*

Eu, abaixo-assinado (nome completo do doente adulto ou do voluntário)

declaro não estar a participar em nenhum outro projeto de investigação neste momento. Recebi o texto de *Informação ao Participante* relativo ao procedimento que concordei em efetuar. Compreendi a explicação que me foi fornecida pelo investigador que assina este documento. Foi-me ainda dada oportunidade de fazer as perguntas que julguei necessárias, e de todas obtive resposta satisfatória.

Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada versou os objetivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de recusar a todo o tempo a minha participação no estudo, bem como pedir a imediata eliminação de todos os meus dados recolhidos no âmbito do estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que me é prestada.

Por isso, consinto de forma livre e esclarecida que me seja aplicado o método, o tratamento ou o inquérito proposto pelo investigador.

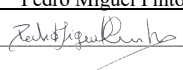
Assinatura do doente ou voluntário: _____

Data: ____/____/____

Nome do Médico responsável: _____

Data: ____/____/____ *Assinatura:* _____

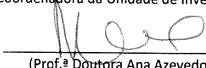
Nome do Investigador responsável: Pedro Miguel Pinto Cunha

Data: ____/____/____ *Assinatura:* 

Nota: Fornecimento obrigatório de cópia ao participante

Pedro Miguel Pinto Cunha (Investigador)
R. Dr. Plácido da Costa 91, 4200-450 Porto, Portugal
Email: pedrocunha@fade.up.pt
Telefone: 912 458 876

SUPPLEMENT 4 – ETHICS APPROVAL FROM CENTRO HOSPITALAR DE SÃO JOÃO – PORTO, PORTUGAL

Unidade de Investigação
Tomei conhecimento. Nada a opor. À DC.
12 de Maio de 2020
A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)



DIRECÇÃO CLÍNICA
93/S/2020
n.º 431/19

PEDIDO DE AUTORIZAÇÃO Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

21.4.2020

Nome do Investigador Principal:

Marta Aguiar Ferreira Gomes

Título da Investigação:

Ensaio Clínico Randomizado Controlado de Exercício Físico como
Intervenção na Leucemia Linfocítica Crónica

CONSELHO DE ADMINISTRAÇÃO - REUNIÃO DE
Presidente do Conselho de Administração
21.4.2020
(Prof. Doutor Fernando Araújo)
Vice-Presidente
Vice-Presidente
Vice-Presidente
(Prof.ª Doutora Maria João Sáez) (Prof.ª Doutora Maria João Sáez) (Prof.ª Doutora Maria João Sáez)

Pretendo realizar no(s) Serviço(s) de:

Hematologia Clínica

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

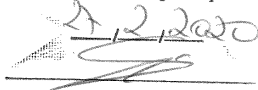
Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/Promotor

Porto, 9 de Dezembro de 2019. 
assinatura

• Centro Hospitalar São João •
Centro de Epidemiologia Hospitalar

12/12/2020


CEH-IM005-0

SUPPLEMENT 5 – ETHICS APPROVAL FROM FACULTY OF SPORT - UNIVERSITY OF PORTO



COMISSÃO DE ÉTICA

Declaração

Para os devidos efeitos declara-se que o projeto CEFAD 14_2024 "Ensaio Clínico Randomizado Controlado de Exercício Físico como Intervenção na Leucemia Linfocítica Crónica" submetido à Comissão de Ética da Faculdade de Desporto da Universidade do Porto, atende os requisitos éticos necessários.

Porto, 17 de abril de 2024

A Presidente da Comissão de Ética

Isabel Maria Ribeiro Mesquita
(Professora Catedrática)