Journal of Geriatric Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

journal homepage: www.elsevier.com/locate/jgo

Research Paper

Effects of high-intensity interval training on health-related quality of life in chronic lymphocytic leukemia: A pilot study

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ARTICLE INFO

Keywords:
High-intensity interval training
Resistance training
Chronic lymphocytic leukemia
Quality of life

ABSTRACT

Introduction: Chronic lymphocytic leukemia (CLL) is the most common incurable leukemia/lymphoma in the United States. Individuals with CLL are at risk for disability, frailty, and cancer-specific complications that negatively affect health-related quality of life (HRQOL). High-intensity interval training (HIIT) and resistance training (RT) are safe and feasible for individuals with chronic diseases and when combined, they may be beneficial for reducing cancer-related fatigue, symptom burden, and global quality of life. However, no studies have examined the impact of HIIT or RT on HRQOL in CLL. The purpose of this study was to investigate the effects of a 12-week HIIT and RT (HIIT+RT) intervention on HRQOL in adults with treatment naïve CLL.

Materials and Methods: Changes in HRQOL was a secondary outcome in this pilot study. Individuals with CLL (63.9 ± 8.5 yrs) were non-randomly assigned to 12 weeks of HIIT+RT or a control group. The HIIT+RT protocol consisted of three 30-min sessions/week of HIIT and two sessions/week of RT. The control group maintained usual daily activities. We assessed pre and post HRQOL using the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) questionnaire with domains of physical (PWB), social (SWB), emotional (EWB), functional (FWB), and general (FACT-G) well-being as well as a lymphoma-specific subscale (LymS). We used a two-way mixed analysis of variance to assess changes in HRQOL. We calculated effect size (ES) using Cohen's *d*.

Results: Fifteen participants (HIIT+RT: $n = 9$; Control: $n = 6$) completed the study and questionnaire. Scores for FWB improved following HIIT+RT (21.7 ± 3.4 to 23.9 ± 3.2; ES = 1.38) compared to controls (25.7 ± 2.2 to 25.7 ± 2.3). The HIIT+RT group experienced clinically meaningful improvements in total FACT-Lym, FWB, FACT-G, and LymS. The control group had clinically meaningful changes only in LymS.

Discussion: The large effect sizes and clinically meaningful improvements associated with 12 weeks of HIIT+RT support the potential benefits of this type of exercise program for FWB, lymphoma-specific symptoms, and general well-being in CLL. A future randomized trial with an adequately powered sample size is needed to evaluate these findings.

Trial Registration: NCT04950452

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia/lymphoma in the United States, with approximately 21,000

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https://doi.org/10.1016/j.jgo.2022.09.002
Received 7 February 2022; Received in revised form 24 August 2022; Accepted 2 September 2022

new cases diagnosed yearly [1]. Disease prevalence increases with age, as 67% of new cases occur in individuals who are ≥65 years [1]. Due to the intersection of age-related physiological changes and cancer-specific complications, older adults with CLL experience reduced physiological reserve and are at increased risk for infections, secondary cancers, and co-morbidities [2,3]. Impairments in physical function have been found in 56% of patients [4] and Sitlinger et al. [5] reported cardiovascular fitness levels that were 64% of normative values in those with CLL. Furthermore, reduced functional performance is associated with poorer survival, while low Instrumental Activities of Daily Living (IADL) index scores increase the risk for infection [4]. These losses in physical function along with CLL-specific side effects can negatively affect quality of life [6]. Consequently, patients with treatment naïve CLL have additional quality of life decrements as they 'watch-and-wait' for treatment to be initiated. Therefore, there is a need for interventions that minimize losses in physical function and reduce CLL-specific symptoms to improve quality of life (QOL) in this population.

The consensus statement from the American College of Sports Medicine International Roundtable suggests that twelve weeks of combined moderate-intensity aerobic activity and resistance training two to three times per week is sufficient to improve health-related quality of life (HRQOL) in cancer survivors [7]. Although findings from exercise and cancer trials are promising in regard to HRQOL [8], results may not be generalizable to CLL since most studies involved solid tumor cancers, and the interventions occurred both during and after treatment [7,8]. Compared to those with solid tumors, patients with hematologic malignancies have been found to experience higher risk for frailty, lower physical function, and greater fatigue [9], which may negatively affect HRQOL to a greater extent and alter how exercise impacts it. Since CLL side effects may differ from those in patients with solid tumor cancers and the average time from CLL diagnosis to treatment initiation is four to five years [10], there is a need for research that explicitly explores how exercise impacts HRQOL in CLL. The "watch-and-wait" period between diagnosis and treatment initiation in CLL is associated with distress, anxiety, symptom burden, and impairments in HRQOL [11,12]. Thus, the treatment naïve period may be an opportune time to introduce strategies that improve HRQOL during the "watch-and-wait" time and potentially prevent further declines that may occur after treatment initiation. While patients with other hematologic malignancies such as lymphoma were included in previous trials [13,14], to our knowledge, no study has investigated the effects of exercise on HRQOL in CLL.

One type of exercise that has been recognized as a safe and effective training mode for improving cardiovascular fitness in healthy and chronic disease populations is high-intensity interval training (HIIT). HIIT consists of repeated short bouts of exercise performed at or close to maximal levels of exertion followed by a low-intensity recovery phase [15]. It is safe and feasible for most individuals with chronic diseases [16], including cancer [17,18]. A major benefit of HIIT is that it can elicit improvements in exercise capacity comparable to moderate-intensity aerobic programs, but with a lower overall training volume [19]. Therefore, HIIT may be a practical option for improving fitness while managing training volume in patients with low function and limited training capacity, such as CLL. In addition, there is evidence supporting the benefits of HIIT alone or a combination of HIIT with resistance training on physical function and HRQOL in cancer [17,18,20]. Specifically, the combination of HIIT and resistance training may improve cancer-related fatigue and reduce symptom burden to a greater extent than HIIT alone [20]. Furthermore, findings from a recent meta-analysis suggest that programs combining aerobic and resistance exercise have a positive effect on global QOL compared to aerobic-only programs in patients with cancer [21]. The effect of a combined HIIT and resistance training program on HRQOL outcomes specifically in CLL remains unknown. We have published our findings on the safety, feasibility, and efficacy of HIIT and resistance training for improving strength and immune function in CLL [22]; however, further exploration of the effectiveness of HIIT and resistance training for enhancing HRQOL in CLL is needed.

Therefore, the purpose of this study was to determine the effects of a twelve-week HIIT intervention combined with a muscle endurance-based resistance training program (HIIT+RT) on HRQOL in adults with treatment naïve CLL. This was a secondary outcome analysis of a pilot study that examined feasibility and effects of HIIT+RT on physical fitness and immunological changes in CLL [22]. In addition to this being the first study to explore the effect of exercise on HRQOL in patients with CLL, the fact that our population is treatment naive is especially unique as treatment in other cancers often begins soon after diagnosis; thus this study offers insight into how a pre-treatment HIIT+RT impacts HRQOL in patients with CLL. We hypothesized that the twelve-week HIIT+RT intervention would improve overall HRQOL and cancer-specific symptoms compared to a usual care control group.

1. Materials and Methods

1.1. Participants

This study was a two-arm, experimental pilot study where group allocation was determined by the distance participants lived from the supervised exercise training facility (HIIT: ≤35 miles to the facility; Control >35 miles to the facility). We have published study details and findings for primary outcomes elsewhere [22]. Changes in HRQOL was a secondary outcome. The study was approved by the Duke University Medical Center Institutional Review Board, and all participants provided written informed consent.

Participants (≥18 years old) were eligible for the study based on the following criteria: (1) confirmed diagnosis of CLL as per the International Workshop on CLL Guidelines [23], (2) no prior history of CLL treatment, (3) no consideration for first-line therapy within six months due to clinical evidence of significant disease progression, (4) able to walk on a treadmill. Exclusion criteria included (1) abnormal cardiac findings observed during a maximal cardiopulmonary exercise test (CPET) that would preclude exercising safely at high intensities, (2) systemic glucocorticoid therapy within the past seven days, (3) other malignancy diagnosed within three years of study enrollment except for adequately treated basal, squamous cell carcinoma or non-melanomatous skin cancer, carcinoma in situ of the cervix, superficial bladder cancer not treated with intravesical chemotherapy or Bacillus Calmette-Guerin (BCG) within six months, localized prostate cancer, (4) absolute contraindications to exercise [24], (5) orthopedic limitations, musculoskeletal disease, and/or injury that would restrict physical activity, (6) diabetes mellitus or chronic obstructive pulmonary disease, and (7) uncontrolled hypertension (blood pressure ≥ 160/90 mmHg).

1.2. Baseline Fitness Assessments

To determine the heart rate prescription for HIIT, we assessed cardiorespiratory fitness (VO_{2peak}) using a medically supervised CPET with a 12-lead electrocardiogram assessment and breath-by-breath metabolic analysis (ParvoMedics, UT, USA) as described previously [25]. The test consisted of the Ekelund graded maximal treadmill test starting at 2.0 mph at 0% grade [26]. Speed and/or gradient were increased at an equivalent rate of approximately 3.5 mL/kg/min (1 MET) per stage, which was chosen because an incremental increase ≤1 MET per stage has been suggested for older adults, those who are deconditioned, or individuals with chronic diseases [27]. The test stages were progressed until participants reached volitional exhaustion. Briefly, speed and gradient increased from 2.0 to 3.0 mph and 0% to 2.5% over the first three minutes before speed remained constant and gradient increased by 2.5% per minute for the next seven minutes. Following this, speed increased to 3.3 mph and gradient to 19.0% over the next three minutes. No participants reached the end of peak walking intensity (3.6 mph and 23.0%) found at minute sixteen of the test. We used a respiratory exchange ratio > 1.1 or a rating of perceived exertion

≥17 as the criteria for determining a valid test. Blood pressure was recorded before the test, at the end of each stage, and following the completion of the test. The maximum heart rate achieved during the test was used to calculate the prescribed heart rates for the HIIT training. Pre and post VO_{2peak} results from the test are published elsewhere [22].

The weight used during the resistance training exercise sessions was based on results from a predicted one repetition maximum (1RM) test. We assessed upper and lower body muscle strength using three weight machines: leg press, chest, press, and seated row. Participants began with a warm-up set consisting of eight to ten repetitions at 40–50% of predicted 1RM. Next, we increased the weight to 50–60% of the predicted 1RM, and we instructed participants to complete five to seven repetitions. Following this priming set, we increased the weight to 80–85% of the predicted 1RM, and participants completed the maximum number of repetitions possible at that weight. If more than eight repetitions were performed, we increased the weight until participants reached a weight at which no more than eight repetitions could be performed. A rest period of three to five minutes was taken between sets. Following the last set, predicted 1RM was calculated [28], and that value was used to calculate weights for the resistance training sessions. Pre and post strength results are published elsewhere [22].

1.3. Intervention

We instructed participants assigned to the control group to maintain their daily activities and refrain from participating in a structured exercise program. Participants assigned to the exercise protocol completed three exercise training sessions per week for twelve weeks at the Duke Center for Living. One session consisted of a 30-min HIIT workout, while the other two sessions consisted of 30 min of HIIT followed by 30 min of resistance training. All sessions were delivered as one-on-one training sessions, supervised by a certified exercise physiologist who was trained on the study protocol and delivery of the intervention. Each HIIT workout was completed on a treadmill. Intensities for HIIT were individualized to each participant and were calculated based on the maximum heart rate achieved at VO_{2peak} on the CPET. We prescribed heart rates that corresponded to 80–90% of heart rate reserve (HRR) for the high-intensity interval and 50–60% of HRR for the active recovery interval. HRR was calculated based on the Karvonen formula: ((maximum heart rate – resting heart rate) x training intensity) + resting heart rate. Before starting the exercise intervention, participants completed 3–6 practice sessions consisting of 30- to 45-s intervals at target heart rates to familiarize themselves with the HIIT workout. For the intervention, each HIIT workout began with a five-minute warm-up, followed by 20 min of HIIT, and a five-minute cooldown. High intensity and active recovery intervals lasted 60–90 s and were achieved by adjusting treadmill speed and/or grade to allow participants to reach target heart rates while maintaining a walking pace (1–4.8 mph) throughout the session. Heart rates during the HIIT workout were recorded continuously using the Polar OH1 (Polar, USA) monitor and recorded on an exercise log. If the target heart rate was not achieved by the end of the interval, the treadmill gradient or speed was adjusted during the next interval to ensure that the participant reached the target intensities. There was no prescribed progression for HIIT intensities or time as progression is inherent to the program. As participants become fitter, the speed/grade required to meet the prescribed heart rates needs to be increased.

The resistance training protocol consisted of three exercises to target major upper and lower body muscle groups: leg press, chest press, and seated row machines. After a warm-up set of ten repetitions at 40–60% of 1RM, participants completed as many repetitions as possible at 70% of 1RM for two sets. If 20 or more repetitions were reached during a set, the weight was increased by 2–5 kg for the next training session. We chose a muscular endurance training program over strength training for two primary reasons: (1) strength training has the potential to alter body mass (i.e., increase in lean mass and decrease in fat mass) which may confound our results for immune functions [22] and (2) in untrained individuals, muscular endurance training is less likely to cause muscle damage. As people with CLL have impaired immune responses, damage will take longer to repair [29] and may negate benefits.

Adherence, compliance to the HIIT and resistance training prescriptions, and rating of perceived exertion were documented throughout the study. A flexible scheduling protocol (availability of exercise physiologist for five days per week from 6:00 am to 6:00 pm) ensured that participants could complete the three prescribed sessions per week. If participants could not attend their scheduled session time due to a time conflict or symptom-related reason, the session was rescheduled. Participants were instructed to not participate in any additional education or non-exercise components beyond the supervised sessions. Adverse events were monitored, recorded, and reported to the IRB based on Human Research Protection Program protocols.

1.4. Outcome Measures

We assessed changes in HRQOL using the Functional Assessment for Cancer Therapy – Lymphoma (FACT-Lym) [30,31], which was administered at baseline and following the twelve-week intervention. Domains assessed by the FACT-Lym include physical (PWB), social/family (SWB), emotional (EWB), and functional (FWB) well-being and an additional lymphoma subscale (LymS) section with questions specifically related to lymphoma. Since CLL is a type of lymphoma, the FACT-Lym was used instead of the FACT – Leukemia (FACT-Leu). Domain and total scores were calculated based on instrument scoring guidelines. 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 FACT-Lym score was determined by adding the FACT-G total and the lymphoma subscale score. The maximum score for the FACT-Lym is 168, with higher scores indicating greater HRQOL. Clinically meaningful changes for Fact-Lym are associated with a score change of 6.5–11.2 for the FACT-Lym and 2.9–5.4 for the LymS [32]. A score change of 5–7 for the FACT-G and 2–3 for the FWB and PWB domains are also considered clinically meaningful [33,34].

1.5. Statistical Analysis

Descriptive data are presented as means, standard deviations, and ranges. Independent *t*-tests were used to compare baseline differences between groups. To assess changes in HRQOL over the twelve-week intervention between the HIIT+RT and control groups, we used the two-way mixed analysis of variance. Group by time interactions were determined for the questionnaire subdomains and composite scores in line with recommendations from the creators, FACIT [35] and similar exercise studies in cancer [36–38]. Specifically, the FACT-Lym consists of five subdomains, four of which are independent domains assessing the quality of life where scores are used to derive the composite FACT-G and FACT-Lymphoma. Therefore, in line with recommendations and the independence of each subdomain, no adjustments for multiple comparisons between subdomains were performed. Effect size was assessed using Cohen's *d* scores, where values of 0.2, 0.5 and 0.8 are considered small, medium and large effects respectively [39]. These were calculated by subtracting the mean change score in the control group from mean change score in the HIIT+RT group, and dividing that value over the pooled standard deviation. Significance was accepted at $p \leq 0.05$. All analyses were performed using the SPSS (version 28) statistical package. We reported values as means ± standard deviations unless otherwise indicated.

2. Results

Of the 25 patients who were assessed for eligibility, nineteen consented to participate in the study. One participant was excluded prior to group allocation because of an abnormal CPET test, resulting in eighteen

participants assigned to either the HIIT ($n = 11$) or control ($n = 7$) groups. A complete diagram of the study flow has been previously published [22]. Of the eighteen participants allocated to the HIIT or control groups, sixteen completed the study; one participant in the HIIT group did not attend training sessions and did not respond to our contact attempts. One participant from the control group dropped out before the start of the intervention due to the development of a skin infection. The FACT-Lym questionnaire was completed by fifteen of the sixteen participants who completed the study. Therefore, fifteen participants were included in this analysis (9 HIIT and 6 control). Table 1 shows participant characteristics. The mean age of all participants was 63.9 ± 8.5 years, and the time since diagnosis was 6.6 ± 7.5 years.

Adherence, compliance, and safety for the study are published elsewhere [22]. Among the fifteen participants included in this analysis, adherence to the number of HIIT and resistance training sessions was 99.4% and 98.6%, respectively. All participants completed >80% of high-intensity intervals at the prescribed heart rates. The average maximum heart rate during the high-intensity intervals was equivalent to 89.7% of HRR, thus meeting the prescribed intensity for the high-intensity intervals. No adverse events were reported during any of the exercise sessions. Minor muscle soreness from the HIIT and resistance training was reported by all participants at the beginning of the study, which was determined to be a normal reaction to the exercise training. If participants were experiencing any physical concerns, training sessions were rescheduled. Reasons for rescheduling included edema in the arm ($N = 1$), knee pain (N = 1), upper respiratory infection (N = 1), groin tenderness (N = 1), and mild foot pain (N = 1). The rescheduled session was conducted at a reduced training load until the concern resolved (all resolved in <1 week). One participant experienced dizziness and nauseousness >3 h after the baseline CPET. After admission to the emergency department, it was determined that the CPET was not the cause of the symptoms, and the participant was allowed to continue to participate in the study.

Pre and post FACT-Lym scores for the HIIT+RT and control groups are presented in Table 2. The control group had significantly higher baseline scores for FWB, FACT-G, and FACT-Lym scores. A significant group x time interaction occurred for FWB, with the score increasing by 10.6% in HIIT+RT compared to no change (0%) in the control (ES = 1.38, $p = 0.021$). Similarly for the composite score FACT-G, HIIT+RT increased by 6.2% and controls by only 0.8% (ES = 1.11, $p = 0.055$). HIIT+RT also had a large non-significant effect on improvements for the composite score FACT-Lym (ES = 0.85, $p = 0.132$). The HIIT group experienced clinically meaningful improvements in the composite scores of FACT-G, LymS and total FACT-Lym scores and the FWB domain [32,34].

Table 1
Baseline participant characteristics for HIIT and control groups ($N = 15$).

	HIIT (n = 9)		*Control (n = 6)*		
Variable	*Mean ± SD*	*Range*	*Mean ± SD*	*Range*	*P value*
Age (years)	62.2 ± 9.4	49–76	66.5 ± 7.1	54–73	0.360
Sex (Male/ Female)	3/6	–	4/2	–	–
Height (cm)	169 ± 13	150–193	176 ± 8	165–187	0.317
Weight (kg)	79.3 ± 25.5	42.9–113.9	78.1 ± 10.5	65.6–93.3	0.916
BMI (kg/m^2)	27.3 ± 7.0	19.1–40.4	25.4 ± 3.1	21.8–30.8	0.530
Time since diagnosis (years)	7.9 ± 9.1	0.5–24.0	4.6 ± 4.3	0.8–10.0	0.431
Rai Stage (N, (%))	*Frequency*	*Percent*	*Frequency*	*Percent*	
0	6	66.7	4	66.7	
I	1	11.1	1	16.7	
Unknown	2	22.2	1	16.7	

Values are means ± standard deviations. HIIT: High-intensity interval training. BMI: Body mass index. RAI:

Table 2
Changes in quality of life in HIIT and control groups (N = 15).

	HIIT (n = 9)		*Control (n = 6)*			
Variable	*Baseline*	*12 weeks*	*Baseline*	*12 weeks*	*Cohen's d*	*Group x time (p value)*
Individual Domains						
Physical Well-being (PWB: 0–28)	24.9 ± 3.2	25.6 ± 2.1	27.0 ± 0.9	27.2 ± 0.8	0.28	0.611
Social Well-being (SWB: 0–28)	23.0 ± 3.2	24.6 ± 2.9	24.8 ± 2.4	25.7 ± 1.8	0.31	0.573
Emotional Well-being (EWB: 0–24)	19.6 ± 2.7	20.6 ± 2.2	20.8 ± 1.5	20.5 ± 2.3	0.49	0.372
Functional Well-being (FWB: 0–28)	21.7 ± 3.4	23.9 ± 3.2	25.7 ± 2.2*	25.7 ± 2.3	1.38	0.021¥
Lymphoma Subscale (LymS: 0–60)	49.3 ± 3.9	53.3 ± 4.2	53.2 ± 5.6	56.3 ± 3.7	0.21	0.691
Composite Scores						
FACT-G Total Score (0–108)	89.2 ± 6.6	94.6 ± 5.5	98.4 ± 5.2*	99.0 ± 4.0	1.11	0.055
FACT-Lymphoma Total Score (0–168)	138.6 ± 9.4	147.9 ± 6.7	151.5 ± 8.1*	155.4 ± 6.4	0.85	0.132

Values are means ± standard deviations.
HIIT: high-intensity interval training. PWB: physical well-being. SWB: social/ family well-being. EWB: emotional well-being. FWB: functional well-being. LymS: lymphoma subscale; FACT-G: Functional Assessment of Cancer Therapy – General; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma.
* $p \leq 0.05$; Significant difference from HIIT group for baseline values.
¥ $p \leq 0.05$; Significant group x time effect.

3. Discussion

To our knowledge, this is the first study to investigate the effects of HIIT-based exercise training on HRQOL measures in CLL. Compared to the controls, the HITT+RT group experienced significant improvements in FWB scale. In addition, the large effects observed for the composite scores of FACT-G and Fact-Lym, and the subdomain of functional well-being by HIIT+RT suggest that HIIT+RT may be beneficial for important HRQOL improvements in individuals with CLL. Furthermore, most of our participants were older, with an average age of 63.9 ± 8.5 years, and thus our findings support the value of HIIT+RT in older adults with CLL. Since older patients are often at risk for functional limitations that impede daily life activities [4], which leads to lower overall HRQOL [12], our results are promising for HIIT+RT to potentially improve these outcomes.

Although research on exercise training specifically in CLL is limited, previous studies in other patients with malignancies have investigated changes in HRQOL following exercise training, including HIIT. Systematic reviews and meta-analyses in both patients with cancer [21] and individuals with hematologic malignancies [40] have suggested that the combination of aerobic and resistance training may be ideal for favorable effects on HRQOL. This may be due to the individual effects of each mode on specific HRQOL domains. For example, while aerobic or

resistance training may improve physical and role functioning domains [21], aerobic training has been shown to specifically benefit emotional and social well-being while resistance training has been found to be superior to aerobic training for improving cancer-related fatigue and global QOL [21,41]. Results specific to HIIT alone in individuals with cancer have been mixed with some studies reporting no changes in HRQOL [18,42] and others showing improvements in domains including vitality, social functioning, role limitations due to physical health, mental health, and general health [43,44]. Differences in these findings may be attributed to the type of cancer, treatment status, differences in training volume or duration of the intervention, and adherence. Supporting the aforementioned studies on aerobic and resistance training, one study that compared a sixteen-week combined HIIT + moderate intensity aerobic intervention with a combined HIIT + resistance training intervention in patients undergoing breast cancer treatment found that the HIIT + resistance training was more beneficial for improving cancer-related fatigue and symptom burden while only the HIIT + aerobic training group improved emotional well-being. Both interventions improved physical and role functioning. Therefore, HIIT combined with resistance training may be needed for optimal HRQOL benefits, especially in those experiencing cancer-related symptoms and fatigue. Likewise, in a recent systematic review and meta-analysis, Lavín-Pérez et al. [45] concluded that high-intensity training was beneficial for HRQOL and domains for physical functioning, role functioning, social functioning, cognitive functioning, fatigue, pain, dyspnea, and insomnia in cancer patients [45]. However, they found that the combination of high-intensity training and resistance training was especially vital to maximizing improvements in physical function and global health [45].

Furthermore, Lavín-Pérez et al. [45] concluded that to achieve the greatest improvements in HRQOL, programs should last more than eight weeks and include a frequency of two times/week, total training duration of 120/min week, and contain a high-intensity component ≥fifteen minutes. Considering our program was twelve weeks and had a frequency of three sessions/week, a total training time of 150 min/week, and a HIIT component consisting of 20 min/session, our program satisfies the suggested components. As such, the HIIT+RT program was associated with clinically meaningful improvements in FWB, FACT-G, LymS and total FACT-Lym scores [32,34], while the control group experienced clinically meaningful changes in LymS [32]. Together, this suggests that participants in our study experienced a reduction in lymphoma-specific concerns regardless of the group to which they were assigned while only HIIT+RT had clinically relevant improvements in FWB, FACT-G, and FACT-Lym. Although any improvements are a positive outcome, control group contamination (e.g., unconsciously becoming more physically active) is becoming more common in exercise oncology trials, making it harder to justify the use of usual care control groups and more challenging to interpret results. This may be apparent by the lack of changes observed for the other quality of life domains such as physical well-being, social/family well-being, and emotional well-being. However, no change remains better than a worsening of these scores, and since this population generally has lower scores than healthy people, our results should be considered favorable. Furthermore, our resistance training program focused more on muscular endurance than strength and did not include exercises for all major muscle groups. A more comprehensive resistance training program focused on building strength may be needed to elicit significant improvements in FACT-Lym scores and each domain. Nevertheless, our results highlight the potential positive effects of HIIT+RT and the need for future randomized control trials focusing on the use of HIIT and resistance training on improving HRQOL outcomes in CLL.

Limitations to our study include a small sample size, lack of attention control since the RT + HIIT group had more social interaction with investigators due to supervised training, and the non-random assignment of participants, which may have introduced bias to the results. For example, the control group had higher baseline values for FWB, FACT-G, and FACT-Lym compared to the HIIT+RT. Therefore, the potential for improving scores may have been lower in the control group since they initially reported better HRQOL. Nevertheless, HIIT+RT brought the FWB, FACT-G, and FACT-Lym scores closer to the control group's baseline scores. Thus HIIT+RT may be an especially important intervention for patients with low HRQOL. In addition, the non-random assignment limits generalizability to patients who lived far from the treatment center since access to healthcare-related resources may have been different between the HIIT+RT and control groups. Strengths of this study include the individualized HIIT program that was based on resting heart rate and maximum heart rate achieved at VO_2peak during the CPET as well as our focus on treatment naïve CLL patients. Although these patients are not experiencing treatment-related side effects, this "watch-and-wait" period is associated with anxiety, distress, fatigue, and increased symptom burden [11,12]. Youron et al. [12] reported impairments in all domains of HRQOL in treatment naïve patients compared to healthy age-matched controls. Therefore, exercise training during early-stage CLL may be a useful strategy to maintain or improve HRQOL and attenuate further losses during treatment.

4. Conclusions

We demonstrate that twelve weeks of HIIT+RT had large effect sizes for improving total FACT-Lym scores and domains for Fact-G and FWB. In addition, it was associated with clinically meaningful effects on general well-being, overall quality of life, and lymphoma-specific scores in patients with treatment naïve CLL. Furthermore, reductions did not occur for physical, social/family, or emotional well-being. Our results suggest that twelve weeks of HIIT+RT may improve and maintain HRQOL components before patients require therapies that typically worsen their quality of life. However, future randomized trials with adequately powered sample sizes are needed to confirm our results and determine the long-term effects of exercise on HRQOL. In addition, more research is needed to determine the optimal mode, frequency, intensity, and duration for HIIT and resistance training for those with CLL, especially in older patients and individuals experiencing greater impairments in HRQOL.

Ethics Approval and Consent to Participate

This study was approved by the Duke University Institutional Review Board and all participants completed an informed consent form prior to participation.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated during the present study are not publicly available, owing to the risk of disclosure or deduction of private individual information, but they are available from the corresponding author on reasonable request.

Competing Interests

Danielle M. Brander has been a consultant, scientific advisory board member, and site clinical trial Principal Investigator (PI) (grant paid to institution) for AbbVie, Genentech, and Verastem; scientific advisory board member and site clinical trial PI (grant paid to institution) for ArQule and TG Therapeutics; site clinical trial PI (grant paid to institution) for Ascentage, BeiGene, DTRM, Juno/Celgene/BMS, MEI Pharma, and Tolero; consultant and site clinical trial PI (grant paid to institution) for AstraZeneca and Pharmacyclics; consultant and scientific advisory board member for Pfizer; consultant for Teva; National

Comprehensive Cancer Network panel member; and has participated in the informCLL registry steering committee (AbbVie), REAL registry steering committee (Verastem), and Biosimilars outcomes research panel (Pfizer). The remaining authors declare no competing financial interests.

Funding

This project was supported by the Duke Aging Center Postdoctoral Research Training Grant (NIA T32 AG000029), Duke Claude D. Pepper Older Americans Independence Center Pilot Study Award (National Institutes of Health, National Institute on AgingP30-AG028716), American Society of Hematology Scholars Award, National Institutes of Health, National Heart, Lung, and Blood Institute T32 grant: T32HL007057, and Durham Veterans Affairs Medical Center Research Service.

Author's Contributions

The study was conceptualized by David B. Bartlett, Danielle M. Brander and Andrea Sitlinger who developed and designed the study and experimental approach. Project administration was completeed by Grace MacDonald and Michael Deal who performed the participant fitness testing and exercise training. Grace MacDonald managed participant scheduling and data collection. Andrea Sitlinger, J. Brice Weinberg, and Danielle M. Brander provided clinical guidance and access to their patients. Components of the methodology were completed by Erik Hanson who provided guidance on the physiological assessments and exercise training. Formal analyses were provided by Carl Pieper who provided statistical guidance. Formal analyses, data curation and writing were completed by Ashley L. Artese who analyzed the questionnaire data and prepared the manuscript. All authors contributed critical revisions and approval of the final manuscript.

Acknowledgements

We acknowledge the staff members at the Duke Center for Living and the Duke Cancer Institute for their help with patient care. We appreciate the support of the Department of Medicine at Duke University and, of course, all the participants.

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