The Effects of Exercise on Patient-Reported Outcomes and Performance-Based Physical Function in Adults With Acute Leukemia Undergoing Induction Therapy: Exercise and Quality of Life in Acute Leukemia (EQUAL)

Ashley Leak Bryant, PhD, RN-BC, OCN[1], Allison M. Deal, MS[1],
Claudio L. Battaglini, PhD, FACSM[1], Brett Phillips, MA, CCRP[1],
Mackenzi Pergolotti, PhD, OTR/L[2], Erin Coffman, MA[1],
Matthew C. Foster, MD[1], William A. Wood, MD, MPH[1],
Charlotte Bailey, MA[3], Anthony C. Hackney, PhD, DSc[1],
Deborah K. Mayer, PhD, RN, AOCN, FAAN[1], Hyman B. Muss, MD[1],
and Bryce B. Reeve, PhD[1]

Abstract

Introduction. Fatigue is a distressing symptom for adults with acute leukemia, often impeding their ability to exercise. *Objectives.* 1) Examine effects of a 4-week mixed-modality supervised exercise program (4 times a week, twice a day) on fatigue in adults with acute leukemia undergoing induction chemotherapy. 2) Evaluate effects of exercise program on cognition, anxiety, depression, and sleep disturbance. 3) Evaluate effect of intervention on adherence to exercise. *Methods.* 17 adults (8 intervention, 9 control), aged 28-69 years, newly diagnosed with acute leukemia were recruited within 4 days of admission for induction treatment. Patient-reported outcomes (PROs) (fatigue, cognition, anxiety, depression, sleep disturbance, mental health, and physical health) and fitness performance-based measures (Timed Up and Go [TUG], Karnofsky Performance Status, and composite strength scoring) were assessed at baseline and at discharge. Changes in PRO and performance-based physical function measures from baseline to time of discharge were compared between groups using Wilcoxon Rank Sum tests. *Results.* With PROMIS (Patient-Reported Outcomes Measurement Information System) Fatigue, we found a median change in fatigue (−5.95) for the intervention group, which achieved a minimally important difference that is considered clinically relevant. Intervention group reduced their TUG performance by 1.73 seconds, whereas the control group remained fairly stable. A concerning finding was that cognition decreased for both groups during their hospitalization. 80% adherence of visits completed with a mean of 6 sessions attended per week. *Conclusions.* Our study provides information on the impact of exercise on symptomatology, with focus on fatigue and other psychosocial variables in acute leukemia.

Keywords

acute leukemia, exercise, quality of life, patient-reported outcomes, PROMIS, fatigue, adherence

Introduction

Acute leukemia is an aggressive disease that develops rapidly and often requires immediate hospitalization for initiation of intensive chemotherapy.[1] Intensive treatment usually consists of a 1-week chemotherapy regimen that requires a 3- to 4-week-long hospitalization for treatment-related toxicities. One persistent symptom experienced by patients with acute leukemia is cancer-related fatigue, fatigue that is

[1]University of North Carolina at Chapel Hill, NC, USA
[2]Colorado State University, Fort Collins, CO, USA
[3]Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA, USA

Corresponding Author:
Ashley Leak Bryant, School of Nursing, University of North Carolina at Chapel Hill, Carrington Hall, CB #7460, Chapel Hill, NC 27599-7460, USA.
Email: ashley_bryant@unc.edu

present during[2,3] and after treatment[4] and that is associated with decreased physical activity, directly impacting health-related quality of life (HRQOL).[2,3,5] Lower levels of physical activity contribute negatively to a downward spiral of physical deconditioning that affects physical and psychological function and promotes a debilitating state of fatigue.[5] This is evident in the nonrandomized controlled study by Baumann et al,[6] where adults with leukemia in the control group had higher rates of pneumonia ($P = .04$) compared with their intervention group. The risk of developing pneumonia and a fever were higher in the control group ($P = .06$). The study findings support the proposition that one way to combat cancer-related fatigue and other treatment-related symptoms and improve HRQOL is through consistent aerobic and endurance exercise.[7-11]

Previous research found that exercise interventions in adults with acute myeloid leukemia (AML) undergoing intensive chemotherapy[12-16] were feasible. The exercise intervention components varied from 3 to 5 days per week, 1 to 2 sessions per week, and mixed modalities of aerobic and resistance training. All the exercise studies found improvements in patient-reported fatigue and depressive symptoms, and no study reported any safety or adverse effects.[12-16] However, in those studies, participants were predominantly younger than the average age for AML, and most studies did not include a control group, with only 1 study using a randomized approach.[12] The present study differs from previous studies in the use of a Patient-Reported Outcomes Measurement Information System (PROMIS) measures, inclusion of patients with both acute lymphoblastic leukemia (ALL) and AML based on their prolonged hospitalization, format being a randomized controlled trial, and use of a variety of fitness measures. The National Institute of Health encourages the use of common data elements for clinical research and human subjects research for future comparison and combination of data.[17] PROMIS is one example of a common data element that offers opportunities to assess PROs across the acute, chronic, and general populations.

Our pilot randomized, longitudinal study was designed to test effects of a 4-week in-hospital/in-treatment progressive exercise mixed-modality program (aerobic and resistance training 4 times a week) on fatigue, HRQOL, and physical function (Timed Up and Go [TUG], 6-Minute Walk Distance [6MWD]). The secondary aim was to evaluate the effects of the exercise program on cognition, anxiety, depression, and sleep disturbance. The third aim was to evaluate the effect of the intervention on adherence to exercise.

Methods

Study Design

This randomized clinical trial (NCT 02246907) recruited patients between October 2014 and November 2015. Adults with acute leukemia were recruited at the NC Cancer Hospital (Lineberger Comprehensive Cancer Center) within 4 days of admission for induction treatment. If a patient demonstrated interest in participating, their medical oncologists were consulted and asked to evaluate the patient's eligibility to enroll in the study based on the study inclusion/exclusion criteria. Inclusion criteria consisted of the following: (1) adults ≥18 years old, newly diagnosed with AML or ALL; (2) admission to begin induction chemotherapy, with an expected hospital stay of 4 to 6 weeks; and (3) able to speak and understand English. Exclusion criteria were cardiovascular disease; acute or chronic respiratory disease; acute or chronic bone, muscle, or joint abnormalities; altered mental state, dementia, or any other psychological condition that would prevent understanding of informed consent; another active malignancy; active bleeding; acute thrombosis; ischemia; hemodynamic instability; or uncontrolled pain. Additionally, we used cardiopulmonary exercise testing (CPET) in this population. The oncologist determined if a patient would qualify for the study based on the study inclusion and exclusion criteria by reviewing the patient's medical history and through initial tests performed throughout the admissions process prior to beginning treatment. After the oncologist cleared the patient to enroll in the study, patients were asked to sign an informed consent form approved by the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center Protocol Review Board and the UNC Institutional Review Board prior to participating in any study activities.

Procedure

Intervention Components. A total of 82 patients were screened for participation in the study; 64 were excluded for various reasons, including not meeting inclusion criteria: cardiac, respiratory, joint/musculoskeletal comorbidities (n = 24), diagnosed with another cancer or leukemia (n = 12), missed recruitment window (n = 10), a hospital stay less than 3 weeks (n = 5), exercise physiologist not available for testing (n = 3), unable to speak or understand English (n = 2), VO_{2peak} testing equipment unavailable (n = 2), bleeding, thrombosis, hemodynamically unstable, uncontrolled pain (n = 2), prior malignancy (n = 2), unable to provide informed consent (n = 1), or patient discharged to hospice (n = 1; Figure 1).

In total, 18 patients were randomized to either the control or intervention group. The randomization sequence was generated by the study's statistician. The statistician and research outcome assessors were blinded to the randomization allocation. Patients randomized to the intervention received the exercise program by a certified exercise physiologist and/or exercise trainers. One person dropped out before the start of the intervention (n = 17). After randomization, demographic and clinical characteristics and
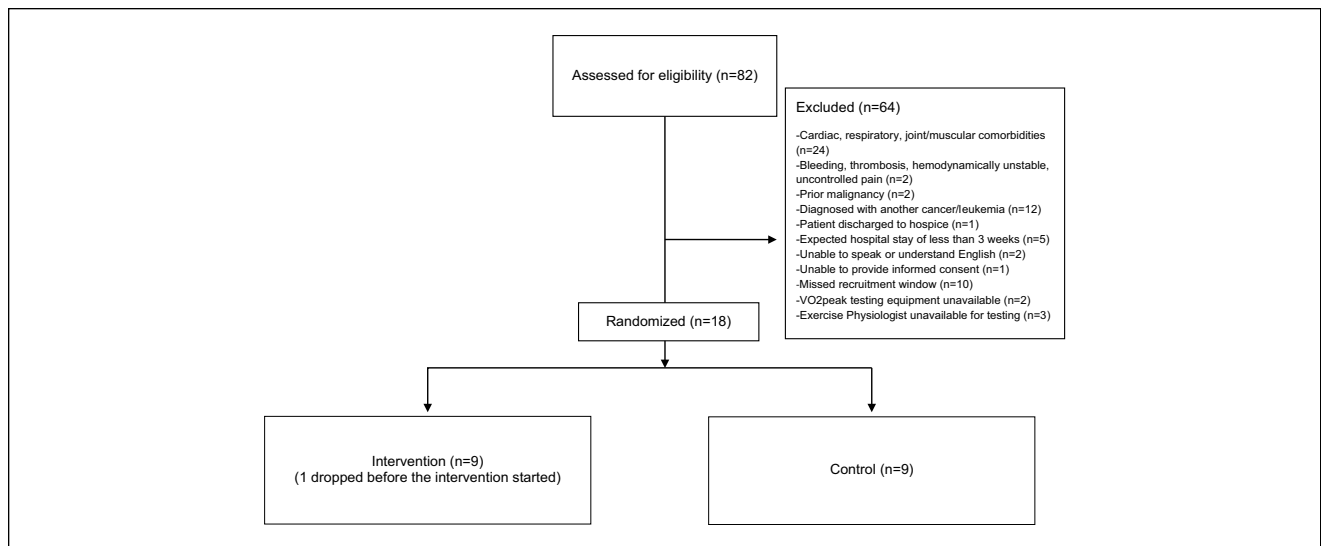
Figure 1. CONSORT diagram.

patient-reported measures were obtained. Follow-up assessments were completed for patient-reported outcomes weekly and for performance-based measures of physical function at discharge. Patients in the control arm received standard of care (no sessions with an exercise trainer) and were monitored on their activity level during the hospitalization period using self-reported activity logs.

Patients in the intervention arm participated in an individualized, mixed-modality exercise program supervised by exercise sport science specialists. Prior to the sessions, the exercise trainers would speak with the nurse about any potential exercise contraindications for that day. If a patient's platelet count was ≤10/μL, the patient would not receive the intervention on that day. This was an important safety factor and reduces any potential for spontaneous bleeding. Likewise, 2 prior AML exercise trials reported that exercise was not delivered if platelet counts were ≤10/μL.[14,18] Vital signs were collected before and after each session and reported to the nurse. The program consisted of approaching participants 4 days a week, twice a day (AM and PM sessions) for aerobic (walking or stationary bike) and resistance training (use of different strengths of resistance bands). This progressive exercise model consisted of aerobic training of 5 to 15 minutes and resistance training of 10 to 20 minutes. The aerobic exercise intensity progressed from approximately 50% to 70% of heart rate reserve, and the resistance exercise intensity increased from lighter to heavier resistance bands using a 10 Rep Max training protocol. For example, because patients were able to complete 3 sets of 10 repetitions maximum with a lighter band, a tighter band would replace the lighter band in subsequent workouts as an attempt to create a training load. The resistance exercises included lateral raises, frontal raises, chest press, low

rows, biceps curls, triceps extension, leg extension, and leg curl. In the morning session, patients would undergo upper-body exercises, and the afternoon session involved lower-body exercises. Exercises were adapted based on the patient's physical limitations. For example, if a patient was unable to participate in the above-described exercise session, trainers would walk laps with patients around the unit. A cool down session included 5 minutes of stretching at the end of each session.

Measures

Patient-Reported Measures. The PROMIS is a NIH Roadmap initiative to provide access to valid and reliable self-reported measures of HRQOL.[19] The PROMIS measures are scored on a *T*-score metric with a mean of 50 and SD of 10 in the general population in the United States. Higher PROMIS symptom scores indicate increased symptom burden, and higher PROMIS function scores indicate increased functioning. This study included PROMIS short form measures of fatigue (8 items), applied cognition-abilities (8 items), anxiety (6 items), depression (6 items), and sleep disturbance (8 items).[19] We compared mean scores using the recommended *T*-score meaningfully important differences (MIDs) ranges for 5 PROMIS scales in adults with acute leukemia undergoing induction chemotherapy: 8-item fatigue (3.0-5.0), 6-item anxiety (3.0-4.5), and 6-item depression (3.0-4.5).[20] In the absence of study-specific information on the 8-item applied cognition-abilities and 8-item sleep disturbance PROMIS measures, we estimated the MID using the 0.5 SD. The Short Form (SF-12v2) Health Survey 12-item measure was used to evaluate physical and mental health.[21] The SF-12v2 Health Survey provides Physical Component Summary and

Mental Component Summary scores, with a mean of 50 (SD = 10) in the US general population. Higher scores represent better physical and mental health scores.

Physical Function Performance–Based. Measures Physical function measures were performed to evaluate the efficacy of the exercise intervention in comparison to the control group. Baseline testing (test 1) was prior to initiation of treatment or 4 days within admission, and posttesting (test 2) was at the time of discharge. To assess functional capacity, patients participated in a 6MWD on a labeled 100-foot track in the hematology/oncology unit. Patients were instructed to wear clothing and shoes appropriate for walking exercise and were permitted to use their usual walking aids, including IV poles. They were instructed to walk as far as possible for 6 minutes back and forth in the hallway. The distance walked at the end of 6 minutes is termed the *6-minute walk distance*. To assess mobility, patients were asked to perform a TUG. To begin the test, instruction was given to sit in a standard arm chair with their back against the chair. On command, patients would stand up, walk 3 m at a comfortable pace, turn 180°, walk back to the chair, and return fully to the initial seated position. Results were measured using a stopwatch as time in seconds.[22] The Karnofsky Performance Status (KPS) tool was used for the patient and provider to self-rate performance status.[23,24] The scoring ranges from 0 to 100, and a higher score indicates better functioning.

Data Analysis

The target enrollment for this prospective study was n = 30 to allow 80% power to detect a probability of 0.795 that a change in the control group is less than a change in the intervention group, using a Wilcoxon rank sum (Mann-Whitney U) test with a 0.050 2-sided significance level. Differences in baseline measures were compared using Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables. Changes in PRO and performance-based fitness measures from baseline to time of discharge were compared between groups using Wilcoxon rank sum tests, and medians are reported. Analyses were completed using SAS 9.4 statistical software.

Results

Sample Characteristics

Patients included 17 adults (8 intervention and 9 control), 28 to 69 years old. The median age for the intervention group was 58 (range = 34-67) years and that of controls 48 (range = 28-69) years. More than half (64%) were male, 21% minority, and most had a college or advanced degree (Table

Table 1. Characteristics of the Sample.

Variable	Intervention (n = 8)	Control (n = 9)	P Value
Age (years)	52 (SD = 13), range = 34-67	49 (SD = 15), range = 28-69	.85
Gender			
Male	5 (62.5%)	7 (77.8)	.62
Female	3 (37.5)	2 (22.2)	
Race			
White	6 (75%)	7 (77.8%)	.26
African American	2 (25%)	2 (22.2)	
Education			
9th-11th Grades	1 (12.5%)	0	
High school graduate/GED	1 (12.5%)	4 (44.4%)	
Associate/Some college	0	2 (22.2%)	
College degree	3 (37.5%)	1 (11.1%)	
Advanced degree	3 (37.5%)	2 (22.2%)	
Income (household)			
>20 000	2 (25%)	2 (22.2%)	.46
20 001-40 000	1 (12.5)	4 (44.4%)	
40 001-60 000	2 (25%)	1 (11.1%)	
80 001-100 000	1 (12.5%)	2 (22.2%)	
>100 000	2 (25%)	0	
Marital status			
Single, never married	1 (12.5%)	1 (11.1%)	.57
Married/Partnered	5 (62.5%)	7 (77.8%)	
Divorced	2 (25%)	0	
Widowed	0	1 (11.1%)	
Clinical characteristics			
Type of acute leukemia			
ALL	1 (14.3%)	1 (11.1%)	.67
AML	7 (85.7%)	8 (88.9%)	
Height (cm)	168.53 (13.8)	178.88 (14.12)	.09
Weight (kg)	78.26 (19.91)	93.54 (19.52)	.36
BMI	27.09 (SD 3.4)	29.63 (SD 7.3)	.68

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMI, body mass index.

1). The median number of comorbidities was 1.5 (range = 0-5) for the intervention group and 2 (range = 0-9) for the control group. The most frequently occurring comorbidities were arthritis (82%), hypertension (68%), anxiety (58%), and depression (58%). A majority had AML. The median body mass index for the control group was 27.6 (range = 17.1-43.4) kg/m² and intervention group was 28.4 (range = 20.3-42.5) kg/m², indicating overweight status for the majority (14/16 (88%)) of the patients. Most patients had a KPS of 80 or higher at baseline; only 1 patient in each group was rated 70 at baseline. Preexisting anxiety and depression was documented in the electronic health record for many patients. Both the control and intervention groups had medians above

Table 2. Median Patient-Reported Outcomes at Baseline and Discharge and Changes Over Time.

Self-report Measures[a]	Intervention (n = 8)			Control (n = 9)			P Value for Difference in Change Between Intervention and Control Groups
	Baseline	Discharge	Change	Baseline	Discharge	Change	
SF-12							
PCS	41.2	39.2	4.4	45.5	34.7	−6.2	.29
MCS	47.29	56.99	14.96	46.92	49.66	−1.99	.15
PROMIS[b]							
Cognition	57.4	49.3	−4.2	64.8	46.7	−3.4	.49
Fatigue	57	50.4	−5.95	51.5	55.6	4.1	.11
Anxiety	58.2	48.8	−9.4	59.4	52.7	−1.3	.44
Depression	58	54	−3.0	59.5	56	−0.5	.35
Sleep disturbance	56.1	49.5	−2.8	53.6	52.3	0	.38

Abbreviations: SF-12, Short Form Health Survey 12-item; PCS, Physical Component Summary; MCS, Mental Component Summary; PROMIS, Patient-Reported Outcomes Measurement Information System.
[a]Negative change in symptoms (fatigue, anxiety, depression, sleep disturbance) indicate reduced symptom burden from baseline to discharge. Positive change in health and functioning (PCS, MCS, cognition) indicate improved health/functioning from baseline to discharge.
[b]T-scores (mean = 50; SD = 10) are presented for each PROMIS domain; higher PROMIS *T*-scores reflect a greater level of the construct measured.

50 for PROMIS anxiety and depression at baseline. There were no statistically significant differences in sample characteristics between the intervention and control arms. Although the initial recruitment plan was for 30 patients, we chose to close early because of recruitment issues—that is, identifying patients without comorbidities.

Patient-Reported Outcomes

Overall, no statistically significant differences in change scores from preintervention to postintervention were seen. The intervention group improved or remained stable in all patient-reported domains, except cognitive abilities, in which it declined (Table 2). Fatigue, the primary aim of this study, decreased for the intervention group (median = 57 to 50.4) and increased for the control group (51.5 to 55.6): a median decrease in the intervention group of −5.95 compared with the control group median increase of 4.1. Sleep disturbance did not change for the control group; however, the median sleep disturbance score for the intervention group decreased from 56.1 at baseline to 49.5 at discharge (−2.8). Physical health scores for the intervention group remained stable and decreased for the control group: 45.5 to 34.7 (−6.2). Mental health scores increased for the intervention group (14.96) and remained fairly stable for the control group (−1.99).

With regard to cognition, both groups were above the population mean of 50 at baseline, with decreases seen in both groups (intervention, −4.2; control, −3.4). For anxiety, both groups had similar median anxiety scores at baseline (58.2 and 59.4), and the median decrease was substantially larger for the intervention group compared with the controls (−9.4 vs −1.3). PROMIS depression scores decreased in the intervention group (−3.0) and the control group (−0.5).

Physical function–based measures are presented in Table 3. Participants in the intervention group shaved 1.73 s off of their TUG times, whereas the control group's times remained fairly stable. There were improvements in 6MWDs for both groups. A composite strength score combined upper- and lower-body strength measurements for an overall measure of strength. The intervention group's strength scores remained stable, whereas the control group lost strength. In our study, we had 80% adherence of visits completed, with a mean of 6 sessions attended per week.

Discussion

This is the first study to our knowledge to investigate the impact of a randomized exercise intervention for hospitalized adults with both forms of acute leukemia (AML and ALL) undergoing induction treatment, with the use of PROMIS measures. Overall, there were reductions in all symptoms (fatigue, anxiety, depression, and sleep disturbance) and improvements in physical and mental health scores in the intervention group.

Our primary aim of testing the effect of the exercise program on patient-reported fatigue was not statistically significant, but the change in fatigue (−5.95) for the intervention group achieved a minimally important difference that is considered clinically relevant. For psychosocial variables, more than half of the patients had existing anxiety and depression per their medical record when they entered our study, which might have led to non–statistical significance of these psychosocial measures. All the patient-reported measures were above the mean of 50 at both baseline and discharge, indicating a fairly healthy group.

Unfortunately, cognition decreased for the control group by almost a full SD during their hospitalization. In general,

Table 3. Median Physical Function Performance Based Capacity.

Objective Measures[a]	Intervention (n = 8)		Change Score+	Control (n = 9)		Change Score+	P Value For Difference In Change Between Intervention and Control Groups
	Baseline	Discharge		Baseline	Discharge		
Timed Up and Go (s)	8.0	6.8	−1.73	8.9	8.1	−0.6	.25
6MWD (meters)[b]	476.5	491.5	37.8	385.0	411.3	13.7	.84
Composite strength[c]	126.2	127.1	−1.7	138.6	123	−13.2	.66

[a]Negative change in strength (composite strength) indicates poorer function from baseline to discharge. Positive change in 6MWD and negative change in Timed Up and Go indicate improved function from baseline to discharge.
[b]Outlier in the intervention group: the patient walked 608.7 m at baseline and 700 m at discharge.
[c]Composite scoring of leg strength and right- and left-hand grips when patient has all 3 values.[26,27]

cognitive impairments have been reported by cancer survivors as an adverse effect of treatment[25] and warrants further assessments and research. Up to 40% of patients with AML and myelodysplastic disease have impairments in neurocognitive function (learning new information, impaired fine motor coordination, executive function, or visual-motor scanning speed) before initiation of treatment.[26] Our study finding of impaired cognition was more severe than expected. This is attributed to aggressive induction treatment alleviating distressing symptoms that also lead to other symptoms such as cognitive impairment. Future research exploring the impact of treatment on cognitive impairment over time will provide a more comprehensive picture of the barriers faced by this population.

Increases in mental health scores for the intervention group were larger than the MID, with a median change score of 14.96, whereas mental health did not change for the control group. This highlights the positive impact that the exercise intervention had on patients. Other reasons for the increase in mental health scores may be related to the constant socialization and communication between the exercise trainers and patients.

Several physical function performance-based assessments were conducted with this population during their hospitalization, but no statistically significant differences between the groups were observed. Adults with hematological cancers are found to have low physical activity levels before, during, and after chemotherapy.[27] We found no statistically significant difference in the 6MWD (meters) between the intervention and control groups (0.84, respectively). Unlike our study, Chang et al[12] reported a positive difference between groups in the 12MWD after a 3 d/wk walking intervention, and Alibhai et al[14] found significant improvements in the 6MWD using a mixed-modality exercise program 4 to 5 times a week.

Of the 5 AML studies, those by Klepin et al[15] and Alibhai et al[14] are the only 2 studies to report adherence rates. Klepin et al reported that patients attended at least 1 exercise session (70.8%), and a mean of 2.7 exercise sessions were attended per week.[15] Alibhai et al reported 94.1% adherence, with 8.1 sessions attended per week. Our study

reported 80% adherence, with an average of 6 sessions attended per week. We interviewed 6 of the intervention patients before discharge, and overall, patients were highly pleased with our exercise program. Commonly reported benefits included the structure of twice-a-day sessions and motivation from the exercise trainers. Reported barriers to exercise were symptoms such as anxiety, fatigue, and pain that interfered with their exercise participation. Overall, patients described physical and psychological benefits with the exercise intervention, with no adverse events from exercising regularly during induction chemotherapy. These findings inform the need for an intervention targeting self-management of symptoms to facilitate and support adults with acute leukemia to exercise and be physically active and maintain functional status during their hospitalization.

The mixed-modality supervised exercise program 4 times a week, twice a day plus consistent interaction with the exercise trainers might have contributed to the mental component scores being clinically significantly higher for the intervention group compared with the control group. This may be suggestive of the importance of social support during a prolonged hospitalization combined with twice-a-day exercise to help alleviate treatment-related effects. Physical health was maintained for the intervention group compared with the control group. Most likely, the exercise intervention and the interaction between patient and exercise trainers produced positive influence in the maintenance of QOL in the intervention group. During the study, we monitored the control group using self-reported activity logs. At our institution, we have a robust recreational therapy department, who assist patients with walking around the halls on the inpatient unit, use of guided imagery, and stress relieving activities. Recreational therapists interact with all patients regardless of study participation, and their level of involvement and engagement with both groups might have confounded or biased the findings.

There are several strengths of this study that contribute to the existing level of evidence, including a fairly homogeneous sample with no previous cancers; use of valid, reliable PROMIS measures to assess symptoms and the SF-12v2 to assess physical and mental changes during hospitalization;

and randomization to decrease causality bias. We stopped recruitment at n = 17 because of the large number of patients being excluded as a result of cardiac and respiratory comorbidities because it relates to feasibility of CPET. If we had achieved the full sample of 30, we might have minimized the differences at baseline between groups and seen statistically significant results between PROs and fitness performance–based measures between the groups. Our results are limited because we recruited a fairly healthy acute leukemia population during induction chemotherapy, which may not be representative of this population. We faced challenges during the study, with the primary challenge being recruitment of eligible patients because of our strict exclusion criteria related to CPET. The CPET data are to be presented in another article; therefore, no results are presented here. Furthermore, no adverse events from the exercise intervention were noted, supporting the safety of the program.

Our study provides information on the impact of exercise on symptomatology, with focus on fatigue and other psychosocial variables in acute leukemia; however, future trials must be conducted to confirm the preliminary results of this trial. Potential recommendations for future studies as they relate to recruitment would be to broaden the eligibility criteria for inclusion of adults with acute leukemia with varying health profiles (frail to healthy). This will allow increased representation of those with acute leukemia with comorbidities and not limit to relatively healthy adults. Additionally, a passive control group that would get the same amount of social attention compared with the intervention group should be considered for future studies, even though the design does not allow for detected changes by the intervention. Our end points are known to be strongly affected by social and psychological end points and may be (in part) the reason for the current results. Moderate- to high-intensity exercise training may not be appropriate for a hospitalized population; however, assisting them to maintain or improve their function while alleviating treatment-related symptoms is critical. A low-intensity intervention might be feasible, such as stretching or walking for those who are unable to engage in moderate- to high-intensity exercise. The inclusion of nursing, physical, and occupational therapy may be considered in future studies to minimize decrements in symptoms, and physical and mental health.[28]

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