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Physical activity during anthracycline chemotherapy: exploratory secondary analysis of a randomized trial of functional capacity, free-living activity, and ejection fraction

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Abstract

Background: Anthracycline-based chemotherapy produces progressive functional decline and cardiotoxicity in adults with cancer. Physical activity interventions may attenuate these effects, yet evidence across multiple domains remains limited.

Objectives: To compare trajectories of Six-Minute Walk Distance (6MWD), daily steps, weekly MVPA, and ejection fraction (EF) across six months of chemotherapy and to explore whether step-volume change showed any preliminary association with functional capacity change.

Methods: Secondary analysis of a pilot RCT (*N* = 20). Linear mixed-effects models with Kenward-Roger adjusted EMMs were fitted for each outcome, controlling for age, sex, and race.

Results: Adjusted 6MWD was higher in the PAI arm at 3 and 6 months in this pilot sample; the 6-month difference exceeded published minimally important difference estimates, but the estimate remains preliminary because of the small sample and exploratory design. Daily steps and MVPA were directionally higher in PAI. EF remained broadly within the normal range in both arms, but the sample was too small to draw safety or cardioprotection conclusions. Exploratory change-score analyses did not support step-volume change as a mediator of the functional-capacity findings.

Conclusions: In this exploratory secondary analysis, individually prescribed physical activity showed more favourable functional-capacity trajectories; cardiac findings were inconclusive and do not support safety or cardioprotection conclusions. A larger, prospectively powered trial would be needed to confirm these exploratory findings and to test cardiac outcomes and mediation prospectively.

Trial registration: Not applicable

Introduction

Cancer remains a major global health problem [1]. In 2022, an estimated 20 million new cancer cases were diagnosed worldwide, with 9.7 million deaths attributed to the disease. Projections from the International Agency for Research on Cancer indicate that the annual global cancer incidence will reach 35 million by 2050 [2], placing unprecedented demands on oncology care systems and survivorship infrastructure. Breast cancer and lymphoma collectively represent two of the most prevalent and treatment-intensive malignancies worldwide [1], and both are frequently managed with anthracycline-based chemotherapy regimens [3, 4]. While advances in oncological pharmacotherapy have substantially improved disease-free and overall survival for these patients, the systemic toxicities associated with chemotherapy, including progressive functional decline, debilitating fatigue, reduced free-living physical activity, and treatment-related cardiotoxicity, present significant challenges [5, 6] that compromise physical function, health-related quality of life, and long-term cardiovascular health.

Chemotherapy is commonly accompanied by fatigue, reduced activity, and cardiotoxicity. Cancer-related fatigue (CRF) affects approximately 52% of patients during active treatment [7], representing a common

and clinically important treatment-related symptom that may contribute to reduced activity and deconditioning during chemotherapy [8]. Concurrent with fatigue, progressive reductions in habitual physical activity and free-living step volume are commonly observed across chemotherapy cycles, reflecting a deconditioning cycle in which symptom burden reduces activity, which in turn accelerates functional impairment [9]. For patients receiving anthracycline-based regimens specifically, these activity-related declines are compounded by the cumulative cardiotoxic effects of the therapy: Anthracyclines are associated with dose-dependent cardiotoxicity, including declines in left ventricular ejection fraction in some patients [10].

Anthracycline-induced cardiotoxicity is among the most clinically significant long-term complications of breast cancer and lymphoma treatment [11, 12]. A large prospective cohort study of 2,625 patients receiving anthracycline-containing therapy reported an overall cardiotoxicity incidence of 9%, with 98% of cases occurring within the first year following chemotherapy completion [10]. A systematic review and meta-analysis of placebo arms from 19 randomized controlled trials estimated a pooled mean decline in left ventricular ejection fraction of 5.4% (95% CI [3.5%, 7.3%]) following modern anthracycline dosing [13]. Critically, anthracycline-related cardiomyopathy may be difficult to reverse once clinically established [14–16], and cardiovascular disease-related mortality in cancer patients has been shown to exceed cancer-related mortality beyond 5–7 years of diagnosis [17], underscoring the urgent need for cardioprotective strategies integrated into active treatment.

Exercise training has emerged as a promising non-pharmacological strategy for mitigating cancer treatment-induced cardiotoxicity [13, 18]. A systematic review and meta-analysis encompassing preclinical and clinical studies found that exercise interventions were associated with reduced doxorubicin accumulation in cardiac tissue, attenuated oxidative stress pathways, and measurable cardioprotection, though clinical human evidence remains sparse and underpowered [19]. A randomized controlled trial in 104 women with early-stage breast cancer receiving anthracycline-based chemotherapy found that supervised exercise training was associated with a net 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement in peak oxygen uptake and significantly greater cardiac output, stroke volume, and ventricular ejection fraction reserve compared with usual care ($p < .001$ for all), while functional disability was entirely prevented in a per-protocol analysis of adherent participants (0% vs. 20%; $p = .005$) [20]. These findings highlight the potential of exercise as a cardio-oncology intervention but also underscore the limited generalizability of supervised, facility-based programs to the broader population of patients navigating real-world treatment barriers.

Despite growing evidence for exercise as a beneficial adjunct during chemotherapy, three gaps motivate the present secondary analysis. First, the majority of existing exercise oncology trials have relied on supervised, facility-based protocols [13, 21] that may not be scalable or accessible across diverse patient populations; relatively little is known about whether scalable, individually prescribed physical activity interventions as distinct from supervised exercise programs, can equivalently preserve functional exercise capacity and free-living activity behaviour during active treatment [22]. Second, while structured exercise programs have demonstrated functional and cardiorespiratory benefits, the mechanisms by

which intervention-assigned activity changes translate into preserved functional capacity and cardiac function during chemotherapy remain poorly understood, with limited evidence examining free-living step volume as a candidate behavioural mediator of intervention effects [23]. Third, the simultaneous examination of functional capacity (six-minute walk distance [6MWD]), free-living physical activity (wearable-derived daily steps and moderate-to-vigorous physical activity [MVPA]), and cardiac function (echocardiographic EF) within a single intervention framework is rare in the existing exercise oncology literature [24], limiting the ability to characterize the multi-domain physiological response to activity-based interventions across the full chemotherapy period. Prior supervised RCTs in this population have addressed one or two of these domains, but few have examined all three within a scalable, individually prescribed intervention model.

Against this background, the present study addressed the identified evidence gaps through a secondary analysis of a publicly archived pilot randomized controlled trial (Dryad Digital Repository; [25] that assigned adults with breast cancer or lymphoma undergoing anthracycline-based chemotherapy to either a Physical Activity Intervention (PAI) arm or an attention-matched Health Literacy Intervention (HLI) control arm. The parent clinical trial has been reported in detail elsewhere as “Physical activity is associated with exercise capacity among patients undergoing chemotherapy: a pilot randomized controlled trial” [26]; PLoS ONE 20(9): e0329774; NCT01719562). The specific objectives were: (a) to characterize and compare arm-specific trajectories of 6MWD, daily steps, weekly MVPA, and EF across the six-month chemotherapy period; (b) to assess whether intervention-associated differences exceeded clinically meaningful thresholds; and (c) to explore whether changes in wearable-derived free-living step volume mediated the effect of the PAI on functional capacity and cardiac function change. By examining physical activity during active anthracycline chemotherapy across functional, behavioural, and cardiac domains, this work contributes to current efforts to position exercise as a cornerstone of integrative cancer care.

Building on the theoretical framework of exercise-induced cardioprotection and deconditioning prevention during cancer treatment, the following directional hypotheses were tested: (1) PAI participants would demonstrate significantly higher covariate-adjusted 6MWD at 3 and 6 months relative to HLI, with between-arm differences at 6 months exceeding the established minimally important difference threshold of 22–42 m; (2) PAI participants would maintain higher levels of free-living daily steps and weekly MVPA across the chemotherapy period, consistent with the expected attenuation of treatment-related activity decline; (3) EF would be preserved to a greater degree in the PAI arm, consistent with emerging evidence of exercise-mediated cardioprotection during anthracycline therapy; and (4) changes in free-living step volume would partially mediate the intervention's effect on functional capacity change, reflecting the behavioural pathway through which the physical activity prescription operates to preserve submaximal exercise capacity.

Methods

Study design and data source

This study constitutes a secondary analysis of the Physical Activity and Lymphoma Study (PALS), a two-arm pilot randomized controlled trial that evaluated a 6-month physical activity intervention versus a healthy lifestyle education control in adults with breast cancer or lymphoma receiving anthracycline-based chemotherapy. The publicly archived PALS dataset (Dryad, [25] was re-analyzed to address exploratory questions beyond the scope of the original trial report. This secondary analysis used publicly archived trial data to examine exploratory questions not addressed in the primary report as a legitimate and resource-efficient research design when conducted with full methodological transparency and clear delineation from primary hypotheses [27].

The original trial compared a Physical Activity Intervention (PAI) arm against a Health Literacy Intervention (HLI) control arm across a six-month chemotherapy period [26]. The fully de-identified dataset was publicly deposited in the Dryad Digital Repository [25] and was accessed in accordance with the repository's open-data terms of use. Ethical approval and informed consent were obtained as part of the original Physical Activity and Lymphoma Study trial protocol, which was approved by the Wake Forest University Institutional Review Board (IRB00020968) and the Virginia Commonwealth University Institutional Review Board (IRB20015233), in accordance with applicable regulations for human subjects research. The present secondary analysis used fully de-identified, publicly archived data from Dryad and did not require additional ethics review under local policies for analyses of public datasets.

Participants

The analytic sample comprised adults aged 20 to 79 years diagnosed with breast cancer or lymphoma who were enrolled in the parent RCT during active anthracycline-based chemotherapy treatment. Participants were randomized to the PAI arm, which incorporated structured and individually tailored physical activity goals, or to the HLI control arm, which delivered cancer-related health literacy education in the absence of any specific physical activity prescription. The PAI arm was designed to leverage behavioural change principles, including goal-setting and self-monitoring, to promote progressive accumulation of physical activity during treatment. The HLI arm served as an attention-matched active control to minimize performance and detection bias attributable to differential participant or assessor engagement.

Demographic and clinical characteristics collected at enrolment included age group (categorized as 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years), self-reported biological sex (male or female), and self-reported race (White or Non-White). These variables were retained in all adjusted models as a priori covariates to improve precision with exercise capacity, free-living physical activity, and cardiovascular treatment tolerance in cancer populations [10]. The total analytic dataset comprised 37 repeated observations from 20 unique participants (PAI: n = 14; HLI: n = 6) across three assessment visits.

Outcome measures

Three domains of physiological function were examined as primary outcomes of this secondary analysis, reflecting a multidimensional exercise-oncology framework encompassing functional capacity, free-living activity behavior, and cardiac safety.

Functional exercise capacity

Functional exercise capacity was assessed using the Six-Minute Walk Distance (6MWD; meters), which quantifies the total distance ambulated during a standardized six-minute walking protocol administered under resting conditions. The 6MWD is a well-validated, clinically relevant measure of submaximal cardiorespiratory fitness in patients with cancer, demonstrating high test-retest reliability (intraclass correlation coefficient = 0.93, 95% CI [0.86, 0.97]) and significant concurrent validity with peak oxygen uptake ($r = 0.67$, $p < .001$) [28]. It is widely recommended for use in exercise oncology research due to its low burden, safety, and sensitivity to clinically meaningful change [28]. A between-group difference of ≥ 30 m at six months was pre-specified as the threshold for clinical significance based on published minimally important difference (MID) estimates of 22–42 m for patients with cancer and cardiopulmonary disease [29, 30].

Habitual physical activity

Free-living physical activity was captured as mean daily step-count (steps/day) and mean weekly minutes of moderate-to-vigorous physical activity (MVPA; minutes/week), both derived from wearable activity monitors worn continuously throughout the study period. Wearable accelerometers provide objective, ecologically valid indices of daily ambulatory behavior and free-living activity intensity that are distinct from prescribed exercise dose and are validated for use in oncology patients undergoing systemic treatment [31, 32]. Daily step-count is a feasible behavioral marker in oncology studies and clinical outcomes in patients receiving chemotherapy [31, 32].

Cardiac function

Left ventricular systolic function was indexed by ejection fraction (EF; %), obtained via echocardiographic assessment at each study visit. Ejection fraction provides a continuous, validated marker of anthracycline-related subclinical and overt cardiotoxicity, and is the most commonly used clinical metric for monitoring cardiac safety during and after anthracycline-based chemotherapy regimens [33]. The normal range for left ventricular ejection fraction is defined as 55% to 70% by the American Heart Association [34].

Statistical analysis

All statistical analyses were conducted in R version 4.5.2 [35] using the tidyverse suite (version 2.0.0) for data management, wrangling, and visualization [36]. Data were imported from the archived comma-separated values file and prepared using mutate and factor functions to encode intervention arm

(reference: HLI), age group, sex, and race as appropriately ordered factors. A continuous time variable (time_num: 0, 3, 6 months) was additionally derived from the categorical visit variable to support sensitivity modelling.

Primary longitudinal models

To examine arm-specific trajectories of each outcome across the three assessment visits, separate linear mixed-effects models (LMMs) were fitted for 6MWD, daily steps, weekly MVPA, and ejection fraction using the lme4 package [37]. Statistical inference for fixed effects in the lmer() summaries was obtained using Satterthwaite's method for denominator degrees of freedom, as implemented in lmerTest; EMM-based contrasts and confidence intervals from emmeans used Kenward-Roger degrees of freedom. Satterthwaite approximation was used for denominator degrees of freedom in small-sample mixed models [38].

Each primary model was specified according to the following formula:

$$Outcome \sim visit \times arm + age + sex + race + (1 \mid pid)$$

In this specification, *visit* (Baseline, 3 months, 6 months) was treated as a three-level categorical fixed factor; *arm* (PAI vs. HLI) constituted the primary between-subjects factor; and the visit × arm interaction term captured the differential rate and pattern of change across time as a function of intervention assignment. Age group, sex, and race were included as fixed covariate adjustments to reduce residual variance and improve precision of the arm contrasts, consistent with CONSORT 2025 recommendations for covariate-adjusted analysis of randomized trial data [39]. A participant-level random intercept *(1 | pid)* was specified to account for the within-person correlation inherent in repeated-measures data. An initial random-slope specification *(1 + time_num | pid)* was explored but rendered the model non-identifiable, as the number of random-effect parameters exceeded the total number of observations (*n* = 37); the random-intercept-only structure was therefore adopted in accordance with established recommendations for parsimonious mixed-model specification in pilot samples. Models were estimated using maximum likelihood to support fixed-effect comparisons across model specifications.

Model assumptions were assessed by visual inspection of residual plots; no major departures were evident.

Estimated marginal means and pairwise contrasts

Covariate-adjusted estimated marginal means (EMMs), also referred to as least-squares means, were derived for each combination of arm and visit from each primary model using the *emmeans* package [40, 41]. EMMs were averaged over the observed joint distribution of age group, sex, and race in the analytic sample, yielding adjusted mean estimates that are interpretable as population-marginal effects. All EMMs are reported with 95% confidence intervals. Denominator degrees of freedom for EMM-based *t*-tests and confidence intervals were computed using the Kenward-Roger method, which provides a bias-

corrected covariance matrix adjustment that improves small-sample inference relative to the unadjusted Satterthwaite approach [42].

Between-arm contrasts (PAI minus HLI) at each visit were estimated using reverse pairwise comparisons (method = "revpairwise", by = "visit"). Within-arm contrasts across visits (i.e., change from Baseline to 3 and 6 months within each arm) were estimated using Tukey-adjusted pairwise comparisons (pairs(emm, by = "arm")), with the Tukey correction applied to control the familywise error rate across the three within-arm visit contrasts. The practical significance of between-arm differences in 6MWD at six months was additionally evaluated against the published MID range of 22–42 m.

Change-score regression and exploratory mediation analysis

To explore whether changes in objectively measured free-living step volume from Baseline to six months were statistically associated with intervention effects on changes in functional capacity and cardiac function over the same interval, a change-score regression approach was employed. The dataset was reshaped to wide format using pivot_wider, and Baseline-to-six-month change scores were computed for each participant with complete data at both time points: Δsteps (daily_steps_6months − daily_steps_Baseline), Δ6MWD (smwd_6months − smwd_Baseline), and ΔEF (ef_6months − ef_Baseline). This change-score approach provides a simple exploratory screen for associations among intervention assignment, step change, and outcome change, consistent with the Baron and Kenny causal steps model and its extensions for clinical trial data [43].

Three ordinary least squares regression models were fitted sequentially: (a) arm → Δsteps (*a* path), to assess whether intervention assignment was associated with changes in step volume; (b) arm + Δsteps → Δ6MWD (*b* and *c*′ paths), to test whether the arm effect on functional capacity change was attenuated after adjusting for Δsteps; and (c) arm + Δsteps → ΔEF, to test the same pathway for cardiac function change. Given the explicitly exploratory, hypothesis-generating purpose of these analyses in the context of a small pilot trial (complete-case *n* = 6), results are reported descriptively with unstandardized regression coefficients (*B*), standard errors, 95% confidence intervals, and *p*-values. Effect magnitudes and confidence interval widths are interpreted as the primary basis for inference, rather than conventional significance thresholds, in accordance with best practices for pilot trial data [44].

Sensitivity analysis

To assess the robustness of the primary visit × arm interaction findings, a sensitivity model was fitted for 6MWD using the continuous time variable (time_num: 0, 3, 6 months) in place of the categorical visit factor, yielding a linear-trajectory parameterization: $6MWD \sim time_num \times arm + age + sex + race + (1 \mid pid)$. This model tests whether the arm-by-time interaction remains evident under the simplifying assumption of a linear trajectory, and provides complementary evidence regarding the consistency of the functional capacity divergence across the chemotherapy period. Additionally, unadjusted models (visit × arm only, without covariate

adjustment) were fitted for each outcome to evaluate whether the inclusion of demographic covariates materially altered the pattern of between-arm differences and to assess robustness to model specification.

Reporting standards

This secondary analysis is reported in accordance with the CONSORT 2025 guidelines for the reporting of randomized controlled trial data and with established standards for the transparent reporting of secondary analyses of clinical study data [39, 45]. Missing data were not imputed; the longitudinal LMM framework uses all available repeated observations under a missing-at-random (MAR) assumption, which is consistent with best practice for repeated-measures clinical trial analyses with non-monotone missingness [46, 47]. A two-tailed alpha level of .05 was used as the threshold for statistical significance throughout. All analyses are fully reproducible, with R code deposited in an open repository.

Results

Participant flow and analytic sample

The analytic dataset was derived from the publicly archived dataset of a pilot randomized controlled trial. A total of 37 observations were available from 20 unique participants: 14 assigned to the Physical Activity Intervention (PAI) arm and 6 assigned to the Health Literacy Intervention (HLI) control arm. Assessments were conducted at three time points, Baseline, 3 months, and 6 months, with some participants contributing fewer than three observations due to treatment-related attrition, scheduling interruptions, or data collection gaps, a pattern consistent with the conduct of exercise trials in actively treated cancer populations [48]. Missing data were addressed using maximum likelihood estimation within the linear mixed-effects model framework, which uses all available observations under the missing-at-random assumption and does not require complete-case restriction. Inspection of residual-versus-fitted plots and quantile-quantile (Q-Q) plots of model residuals confirmed adequate normality and homoscedasticity across all three outcome models.

Baseline characteristics

Table 1 presents the observed baseline characteristics of the analytic sample, stratified by intervention arm, in accordance with CONSORT 2025 reporting guidance for baseline demographic and clinical characteristics. Participants ranged in age from 20 to 79 years. The PAI arm was predominantly female (approximately 57%) and White (approximately 79%). At Baseline, PAI participants had a mean Six-Minute Walk Distance (6MWD) of 489.7 m (*SD* = 97.3), mean daily step-count of 8,555.5 steps/day (*SD* = 2,741.6), mean weekly moderate-to-vigorous physical activity (MVPA) of 134.6 min/week (*SD* = 52.1), and mean ejection fraction (EF) of 59.7% (*SD* = 5.6). HLI participants had a mean 6MWD of 424.8 m (*SD* = 13.1), mean daily steps of 7,564.1 (*SD* = 848.0), mean MVPA of 82.0 min/week (*SD* = 74.0), and mean EF of 65.8% (*SD* = 5.2). Baseline EF values were broadly within the normal range for left ventricular systolic function.

Table 1 Baseline Demographic and clinical characteristics by intervention arm

Characteristic	PAI (n = 14)	HLI (n = 6)
Age group, n (%)		
20–29 years	2 (14.3%)	0 (0%)
30–39 years	2 (14.3%)	0 (0%)
40–49 years	3 (21.4%)	2 (33.3%)
50–59 years	3 (21.4%)	2 (33.3%)
60–69 years	2 (14.3%)	1 (16.7%)
70–79 years	2 (14.3%)	1 (16.7%)
Sex, n (%)		
Female	8 (57.1%)	3 (50.0%)
Male	6 (42.9%)	3 (50.0%)
Race, n (%)		
White	11 (78.6%)	4 (66.7%)
Non-White	3 (21.4%)	2 (33.3%)
Baseline outcome measures, M (SD)		
Six-Minute Walk Distance (m)	489.7 (97.3)	424.8 (13.1)
Daily steps (steps/day)	8,555.5 (2,741.6)	7,564.1 (848.0)
Weekly MVPA (min/week)	134.6 (52.1)	82.0 (74.0)
Ejection fraction (%)	59.7 (5.6)	65.8 (5.2)

Note. PAI = Physical Activity Intervention; HLI = Health Literacy Intervention; MVPA = moderate-to-vigorous physical activity; M = mean; SD = standard deviation. Baseline outcome means are based on participants with Baseline observations (PAI: n = 9; HLI: n = 2). All inferential results in subsequent tables are based on covariate-adjusted estimated marginal means from linear mixed-effects models.

Primary outcome: functional exercise capacity (six-minute walk distance)

Estimated marginal means and between-arm contrasts

Table 2 presents the covariate-adjusted estimated marginal means (EMMs) and 95% confidence intervals (CIs) for 6MWD at each visit, by intervention arm, and Figure 1 depicts the trajectory plots. At Baseline, the adjusted 6MWD did not differ significantly between arms (PAI: *M* = 520 m, 95% CI; HLI: *M* =

447 m, 95% CI; contrast PAI − HLI = +72.7 m, *SE* = 48.4, *t*(60.5) = 1.50, *p* = .139). By 3 months, the between-arm difference had widened substantially and achieved statistical significance (PAI: *M* = 532 m, 95% CI; HLI: *M* = 409 m, 95% CI; difference = +122.9 m, *SE* = 44.2, *t*(62.8) = 2.78, *p* = .007). At 6 months, the advantage of the PAI arm was greatest (PAI: *M* = 562 m, 95% CI; HLI: *M* = 402 m, 95% CI; difference = +159.7 m, *SE* = 43.6, *t*(62.3) = 3.67, *p* < .001). The 6-month between-arm difference was 159.7 m.

Within-arm trajectories

Within-arm contrasts, estimated via Tukey-adjusted pairwise comparisons, revealed a clinically and directionally divergent pattern across arms. In the HLI arm, 6MWD exhibited a monotonic non-significant decline from Baseline to 3 months (Δ = −38.0 m, *p* = .672) and from Baseline to 6 months (Δ = −45.2 m, *p* = .571), directionally consistent with prior reports of functional decline during chemotherapy [49]. In contrast, PAI participants demonstrated a progressive directional improvement in 6MWD over the same period (Baseline to 6 months: Δ = +41.8 m, *p* = .135), which, while not reaching statistical significance at this pilot sample size, represents a favourable directional change in this small pilot sample.

Sensitivity analysis

A sensitivity model using continuous time (months: 0, 3, 6) confirmed the robustness of the primary pattern. The time × arm (PAI) interaction term was *b* = 13.53 m/month, *SE* = 6.63, *t*(19.7) = 2.04, *p* = .055, indicating a trend toward steeper improvement in 6MWD per month in the PAI arm. The main effect of arm (PAI vs. HLI) was b = 77.87 m, SE = 33.39, t(32.9) = 2.33, p = .026, supporting the same general pattern seen in the main model. In this sample, the age 70–79 group had lower adjusted 6MWD (b = −189.1 m, SE = 42.1, t(15.3) = −4.49, p < .001), but this estimate should be interpreted cautiously because of the small sample.

Table 2 Covariate-Adjusted Estimated Marginal Means (95% CI) for Six-Minute Walk Distance (m) by Intervention Arm and Visit

Visit	PAI M	HLI M	Difference (PAI − HLI)	SE	df	t	p
Baseline	520	447	+72.7	48.4	60.5	1.50	.139
3 months	532	409	+122.9	44.2	62.8	2.78	.007
6 months	562	402	+159.7	43.6	62.3	3.67	.001

Note. Values are covariate-adjusted estimated marginal means (EMMs) from a linear mixed-effects model specified as 6MWD ~ visit × arm + age + sex + race + (1 | pid). Estimates are averaged over the observed distribution of age, sex, and race. Degrees of freedom are estimated using the Kenward-Roger method. Positive differences indicate higher adjusted 6MWD in the PAI arm relative to HLI. The minimally important difference (MID) for 6MWD in cancer and cardiopulmonary populations is 22–42 m.

Secondary Outcome: Habitual Physical Activity

Daily Step-count

Table 3 presents the EMMs for daily step-count and weekly MVPA by arm and visit. Adjusted mean daily step-counts in the PAI arm were consistently higher than in the HLI arm at all three visits (Figure 2). Although between-arm contrasts did not achieve conventional statistical significance at any single visit, consistent with the limited statistical power of the pilot sample and the high within-person variability typically observed in wearable-derived step data during cancer treatment, the directional pattern was consistent with the 6MWD findings. HLI arm participants exhibited a downward trend in daily steps from Baseline to 6 months, while PAI participants maintained or modestly increased their step volume across the chemotherapy period. These activity trajectories were directionally consistent with prior intervention studies in cancer survivors [9,50].

Weekly MVPA

A similar directional pattern was observed for weekly MVPA, with PAI participants accumulating more minutes of moderate-to-vigorous activity per week at 3 and 6 months compared to HLI controls. These findings, while not statistically significant in this underpowered pilot, suggest that the intervention may have supported activity intensity as well as total volume, an important distinction given that step intensity has been independently linked to cancer survival outcomes [51].

Table 3 Covariate-Adjusted Estimated Marginal Means (95% CI) for Daily Steps (steps/day) by Intervention Arm and Visit

Visit	PAI M [95% CI]	HLI M [95% CI]	Difference (PAI − HLI)	SE	df	t	p
Baseline	8,029	8,946	−918	2,510	54.9	−0.37	.716
3 months	8,726	6,166	+2,560	2,380	50.1	1.08	.288
6 months	9,740	7,539	+2,201	2,360	49.4	0.93	.356

Note. Values are EMMs from a model specified as daily_steps ~ visit × arm + age + sex + race + (1 | pid). Estimates are averaged over age, sex, and race. Degrees of freedom are estimated using the Kenward–Roger method. Positive differences indicate higher adjusted daily step-counts in the PAI arm relative to HLI. Weekly MVPA EMMs (if desired) can be presented in a separate table using the analogous model for weekly_mvpa.

Secondary Outcome: Cardiac Function (Left Ventricular Ejection Fraction)

Table 4 presents the covariate-adjusted EMMs for EF by arm and visit, and Figure 3 depicts the estimated trajectories. Neither the main effect of arm nor the visit × arm interaction reached statistical significance for EF over the six-month assessment period. EF values in both arms remained within or

near the normal range (55%–70%) throughout the study period, but the sample is too small to draw a cardiac safety conclusion. EF declined numerically in the HLI arm across visits, but the sample is too small to infer treatment effects on cardiac function over the course of chemotherapy [13]. The PAI arm showed a comparatively stable EF profile, which could be tested in a sufficiently powered confirmatory study.

Table 4 Covariate-Adjusted Estimated Marginal Means (95% CI) for Left Ventricular Ejection Fraction (%) by Intervention Arm and Visit

Visit	PAI M [95% CI]	HLI M [95% CI]	Difference (PAI − HLI)	SE	df	t	p
Baseline	56.9 [49.9, 63.9]	61.0 [51.9, 70.0]	−4.12	5.26	53.0	−0.78	.438
3 months	53.1 [46.0, 60.1]	61.9 [53.4, 70.3]	−8.80	5.06	48.1	−1.74	.088
6 months	53.6 [46.4, 60.7]	59.0 [50.8, 67.2]	−5.44	5.03	47.4	−1.08	.284

Note. Values are EMMs from a model specified as ef_percent ~ visit × arm + age + sex + race + (1 | pid). Estimates are averaged over age, sex, and race. Degrees of freedom are estimated using the Kenward–Roger method. Normal left ventricular ejection fraction range is approximately 55–70%. Negative differences indicate slightly lower adjusted EF in the PAI arm relative to HLI, though none of the between-arm contrasts reached statistical significance.

Exploratory Analysis: Change-Score Regression and Step-count Mediation

Table 5 presents the results of three exploratory change-score regression models examining whether changes in free-living step volume (Δsteps) from Baseline to 6 months mediated the effect of the intervention on changes in 6MWD (Δ6MWD) and EF (ΔEF). These analyses were restricted to participants with complete data at both time points (n = 6) and are treated as explicitly hypothesis-generating rather than confirmatory, consistent with methodological guidance for mediation analysis in pilot trials.

In Model 1 (arm → Δsteps), the PAI arm was associated with a directionally positive but non-significant increase in daily steps relative to HLI (b = +3,833 steps/day, SE = 2,808, 95% CI [−3,963.5, 11,629.7], $t(4)$ = 1.37, p = .244, R^2 = .318). In Model 2 (arm + Δsteps → Δ6MWD), arm assignment remained a positive predictor of improved 6MWD (b = +57.4 m, SE = 34.6, 95% CI [−52.8, 167.6], $t(3)$ = 1.66, p = .196), while the Δsteps coefficient was negligible (b = −0.001 m/step, SE = 0.005, 95% CI [−0.017, 0.015], $t(3)$ = −0.18, p = .866), with an adjusted R^2 of .24. In Model 3 (arm + Δsteps → ΔEF), neither arm (b = −3.3%, SE = 7.4, p = .685) nor Δsteps (b = +0.001%/step, SE = 0.001, p = .560) were significant predictors (R^2 = .127). In this very small complete-case analysis, step change did not explain the observed 6MWD difference. Any

mechanistic interpretation beyond that is speculative. Formal mediation testing with adequate statistical power — requiring a substantially larger sample — is warranted to test these mechanistic hypotheses.

Table 5 Exploratory Change-Score Regression Models: Effects of Arm Assignment and Change in Daily Steps on Changes in Six-Minute Walk Distance and Ejection Fraction (Baseline to 6 Months)

Model	Outcome (Δ)	Predictor	B	SE	95% CI	t	p	R^2
1	Δ Daily Steps	Intercept (HLI)	−2,539	2,564	[−9,656.2, 4,578.4]	−0.99	.378	.318
		armPAI	3,833	2,808	[−3,963.5, 11,629.7]	1.37	.244	
2	Δ 6MWD (m)	Intercept (HLI)	−39.9	29.1	[−132.6, 52.8]	−1.37	.264	.544
		armPAI	57.4	34.6	[−52.6, 167.4]	1.66	.196	
		Δ Daily Steps	−0.001	0.005	[−0.017, 0.015]	−0.18	.866	
3	Δ EF (%)	Intercept (HLI)	−1.49	6.19	[−21.17, 18.20]	−0.24	.825	.127
		armPAI	−3.29	7.35	[−26.68, 20.11]	−0.45	.685	
		Δ Daily Steps	0.00071	0.00108	[−0.00274, 0.00415]	0.65	.560	

Note. Models are ordinary least squares regressions fit in the complete-case change-score sample (n = 6). Δ Daily Steps = daily_steps_6m − daily_steps_Baseline; Δ 6MWD = smwd_6m − smwd_Baseline; Δ EF = ef_6m − ef_percent_Baseline. HLI serves as the reference arm. R^2 values are the model multiple correlation coefficients; adjusted R^2 values are reported in the text for interpretation.

Discussion

Principal findings

In this secondary analysis of a pilot randomized controlled trial, adults with breast cancer or lymphoma assigned to a Physical Activity Intervention (PAI) showed more favourable 6MWD trajectories of functional exercise capacity relative to participants in a Health Literacy Intervention (HLI) control arm across a six-month chemotherapy period. The covariate-adjusted between-arm difference in Six-Minute Walk Distance (6MWD) grew from a non-significant 72.7 m at Baseline to 122.9 m at 3 months and 159.7 m at 6 months, the latter substantially exceeding the established minimally important difference of 22–42 m for cancer and cardiopulmonary populations. HLI participants showed a monotonic, non-significant

decline in adjusted 6MWD across assessment visits, consistent with the expected trajectory of deconditioning and functional deterioration during cytotoxic treatment in the absence of structured activity support. PAI participants, by contrast, demonstrated directional preservation and modest improvement in functional capacity over the same period, suggesting a favourable trajectory for the individually prescribed physical activity arm in this pilot sample.

Functional capacity: contextualizing the between-arm differences

The magnitude of the observed 6MWD advantage in the PAI arm, approximately 160 m at 6 months, is notable, particularly given the pilot scale of the parent trial. Comparisons with clinical benchmarks are informative: breast cancer survivors who are not engaged in exercise programs have been shown to demonstrate 6MWD values approximately 103 m lower than healthy controls, and up to 46% of breast cancer survivors exhibit low cardiorespiratory fitness during or following treatment [52]. The estimated difference is larger than many published exercise-trial effects, but cross-study comparisons are imprecise [52]. Behavioral factors such as goal-setting and self-monitoring may influence response to physical activity counselling in cancer populations [53].

Free-living physical activity: directional consistency and mechanistic implications

Consistent with the 6MWD findings, PAI participants maintained higher adjusted levels of daily step-count and weekly MVPA relative to HLI controls across the chemotherapy period, with HLI participants showing a directional downward trend in free-living activity. These patterns are consistent with prior evidence demonstrating that physical activity interventions combining goal-setting and self-monitoring produce a mean improvement of approximately 526 additional steps per day in cancer survivors, relative to controls [50]. The wearable-derived activity data align with prior work suggesting that daily step-count is a useful behavioural marker during cancer treatment. Daily step-count has been proposed as a useful behavioral marker during cancer treatment and has been associated with hospitalization risk in concurrent chemoradiotherapy cohorts [31, 32, 54]. The divergence in free-living activity between arms may reflect behavioral mechanisms, but the present analysis cannot distinguish among them.

Notably, the exploratory change-score mediation analysis found that changes in step volume did not significantly mediate the intervention's effect on Δ6MWD, with the Δsteps coefficient being negligible (b = − 0.001 m/step, p = .866). This null mediation finding is inconclusive given the complete-case sample of n = 6.

Any explanation beyond that would be speculative. Some trial data suggest that higher-intensity exercise can produce larger fitness gains than walking-based programs [55].

Cardiac function: safety and preliminary cardioprotective signal

Neither arm demonstrated significant between-arm differences in ejection fraction across the six-month period, and both arms maintained EF values broadly within or proximal to the normal range throughout chemotherapy. These findings are inconclusive with respect to cardiac safety. A directional downward trend in EF was observed in the HLI arm, consistent with the pooled anthracycline-induced EF decline of 5.4% reported in a large meta-analysis of placebo-controlled trials [13], while the PAI arm exhibited a comparatively stable EF trajectory. While the present pilot data are insufficient to establish cardioprotection, and the EF trajectory should be treated as hypothesis-generating. Preclinical work has suggested that exercise may reduce doxorubicin accumulation in cardiac tissue and attenuate oxidative stress pathways underlying cardiomyocyte injury [56]. A fully powered trial designed with cardiac outcomes as co-primary endpoints, such as the ONCOR design framework, would be required to test this signal definitively [57].

Older adults: an age-stratified vulnerability

In this sample, the oldest age group had lower adjusted 6MWD, but this should be interpreted cautiously because of the small sample. This finding is consistent with the growing evidence that older cancer patients face unique vulnerabilities, including pre-existing comorbidities, age-related sarcopenia, and reduced physiological reserve, that amplify the impact of treatment-related deconditioning and fatigue [58, 59]. In this sample, the oldest age group had lower adjusted 6MWD, but the estimate is unstable and should be treated as descriptive [58, 59]. Age-tailored exercise recommendations have been proposed for older adults living with and beyond cancer [60].

Limitations

Several limitations of this secondary analysis must be acknowledged. First, the small and unbalanced sample (PAI: n = 14; HLI: n = 6; complete cases for mediation: n = 6) substantially limits statistical power, increases the risk of Type II error in null findings, and precludes definitive conclusions about mediation mechanisms or cardiac outcomes. Second, as a secondary analysis of a pilot dataset, the present study was not powered to test the objectives examined here, and the findings are appropriately interpreted as exploratory and hypothesis-generating. Third, some participants contributed fewer than three assessment visits due to treatment-related attrition, which may introduce informative missingness that the missing-at-random assumption cannot fully address. Fourth, the wearable-derived physical activity data were not collected under a standardized protocol and may be subject to device-specific measurement error. Fifth, the generalizability of findings is constrained by the predominantly White, female, and breast cancer/lymphoma composition of the analytic sample.

Conclusion

This secondary analysis provides preliminary, hypothesis-generating evidence that an individually prescribed physical activity intervention may preserve functional exercise capacity during chemotherapy over a six-month chemotherapy period in adults with breast cancer or lymphoma, while the control arm showed a directional decline in this pilot sample. Between-arm differences in 6MWD reached statistical significance at 3 and 6 months and exceeded clinically meaningful thresholds, paralleled by maintenance of higher free-living step volume and weekly MVPA in the PAI arm. Cardiac function remained broadly within the normal range in both arms, but the sample was too small to assess cardiac safety or cardioprotection. The exploratory mediation analysis did not support step volume as a mediator in this small complete-case sample; this may reflect limited power, measurement limitations, or the possibility that other pathways, including exercise intensity or symptom reduction, are more relevant. These findings support further study in a larger confirmatory trial, but they do not establish cardiovascular safety or cardioprotection. A definitive, adequately powered multi-domain RCT with wearable monitoring, echocardiography, and age-stratified analyses would be needed to confirm these exploratory observations.

Abbreviations

Abbreviation	Full term
6MWD	Six-Minute Walk Distance
AE	Adverse event
AHWFBMC	Atrium Health Wake Forest Baptist Medical Center
CI	Confidence interval
CRF	Cancer-related fatigue
EF	Ejection fraction
HLI	Health Literacy Intervention
IRB	Institutional Review Board
LMM	Linear mixed-effects model
MID	Minimally important difference
MRI	Magnetic resonance imaging
MVPA	Moderate-to-vigorous physical activity
NCT	National Clinical Trial (registry prefix)
NCI	National Cancer Institute
PAI	Physical Activity Intervention
PALS	Physical Activity and Lymphoma Study
RCT	Randomized controlled trial
R	R statistical software/environment
SD	Standard deviation

Declarations

Ethics approval and consent to participate

The parent randomized trial, Physical Activity and Lymphoma Study (PALS; NCT01719562), was approved by the Wake Forest University Institutional Review Board (IRB00020968) and the Virginia Commonwealth University Institutional Review Board (IRB20015233). All participants provided written informed consent prior to enrolment. All procedures were conducted in accordance with the ethical standards of the responsible institutional committee on human experimentation and were conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The present secondary analysis used fully de-identified, publicly archived data from Dryad and was exempt from additional review under local policies for analyses of public datasets.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is available in the Dryad repository (https://doi.org/10.5061/dryad.w6m905qzp). The reproducible analysis code and figures supporting the current study is available in the OSF project “chemotherapy-PAI-trial-secondary” (https://osf.io/2ef48).

Competing interests

The authors declare that they have no competing interests.

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Author contributions

KNA conceived and designed the secondary analysis, performed the statistical analyses, and drafted the main manuscript text. NS contributed to data curation, investigation, and critical revision of the manuscript. NA supervised the project, validated the findings, and reviewed and edited the manuscript. LRE contributed to methodological decisions, software support, and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Figures

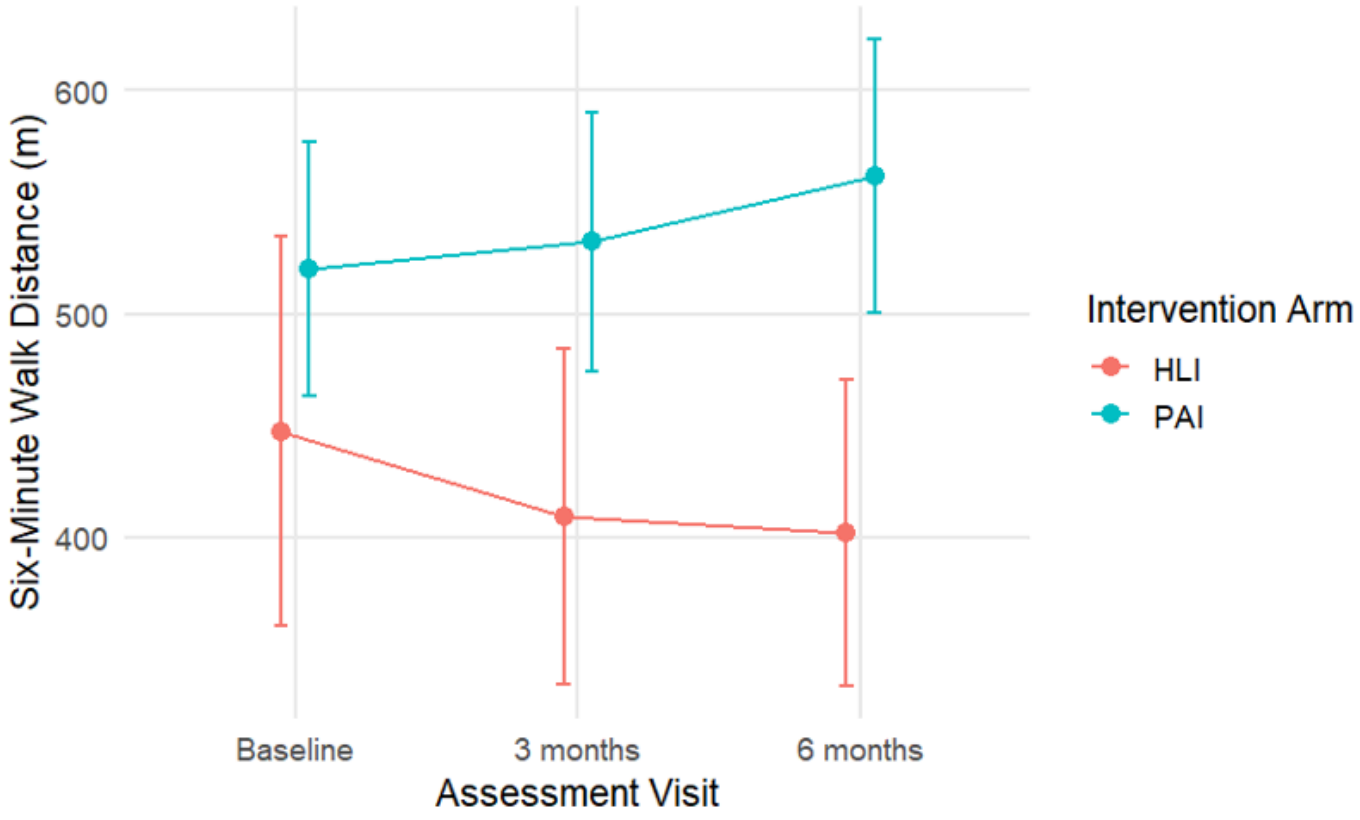

Figure 1

Covariate-Adjusted Trajectories of Six-Minute Walk Distance (m) by Intervention Arm Across the Six-Month Chemotherapy Period

Note. Points represent covariate-adjusted estimated marginal means averaged over age, sex, and race. Error bars represent 95% confidence intervals. Degrees of freedom for confidence interval calculation employed the Kenward-Roger method. The diverging trajectories show a favourable pattern for the physical activity intervention in this pilot sample. PAI = Physical Activity Intervention; HLI = Health Literacy Intervention.

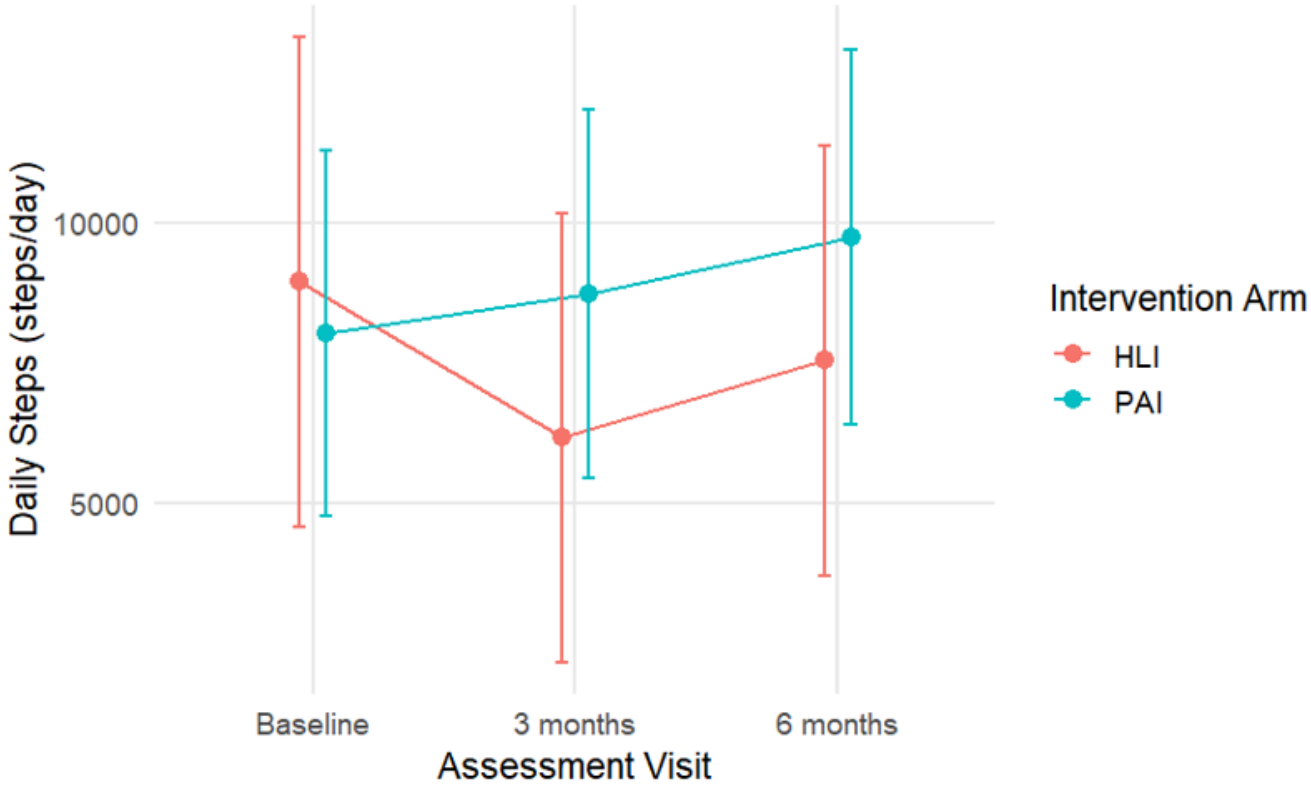

Figure 2

Covariate-adjusted trajectories of mean daily step-count (steps/day) by intervention arm across the six-month chemotherapy period

Note. Points represent covariate-adjusted estimated marginal means. Error bars represent 95% confidence intervals. Patterns paralleling those observed for 6MWD, with the PAI arm maintaining higher step volume throughout the chemotherapy period, suggest a behavioral mechanism consistent with the exercise intervention's functional benefits. PAI = Physical Activity Intervention; HLI = Health Literacy Intervention.

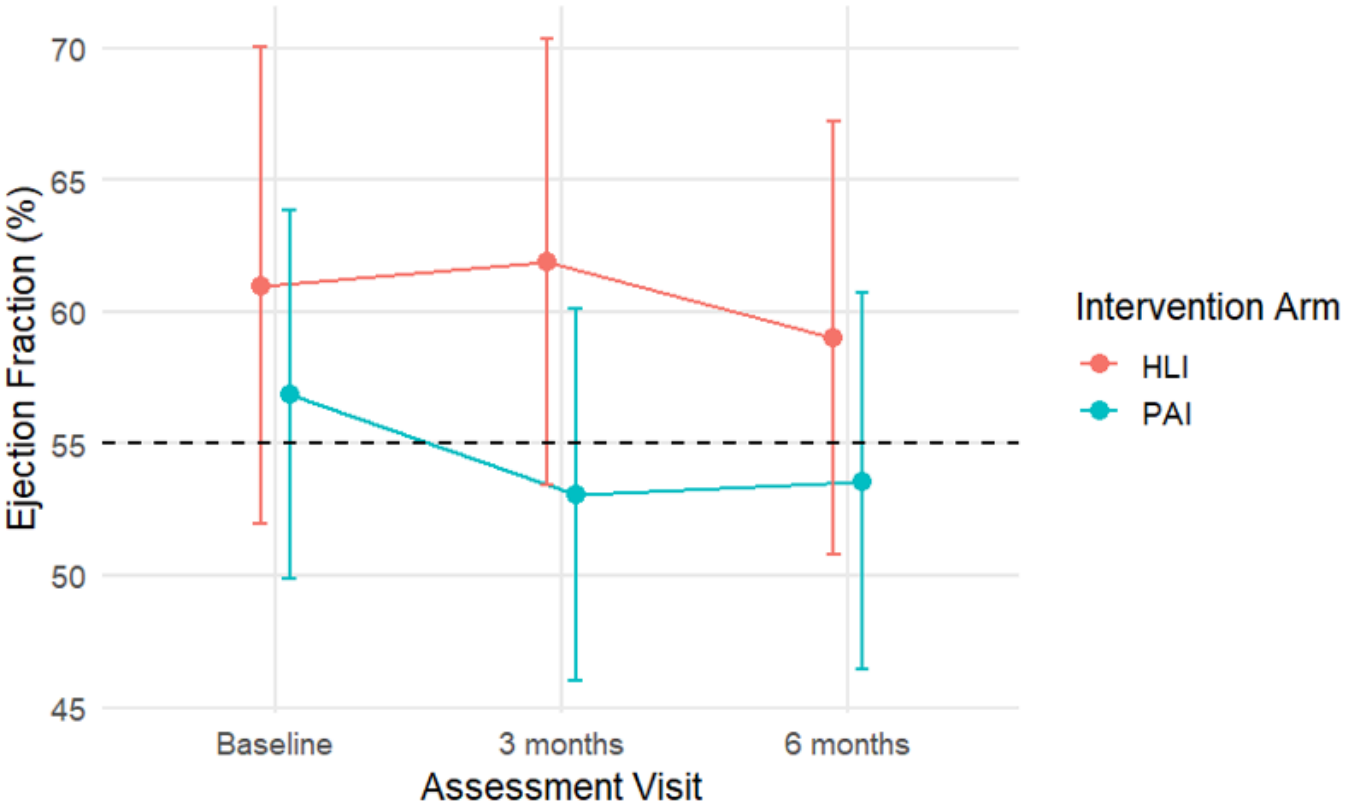

Figure 3

Covariate-Adjusted Trajectories of Left Ventricular Ejection Fraction (%) by Intervention Arm Across the Six-Month Chemotherapy Period

Note. Points represent covariate-adjusted estimated marginal means. Error bars represent 95% confidence intervals. The dashed horizontal reference line at 55% denotes the lower threshold of the normal left ventricular ejection fraction range. Both arms maintained values within or proximal to the normal range throughout the chemotherapy period. The HLI arm showed a directional decline in EF, but the study is far too small to attribute this to treatment effects.