Effects of reducing anxiety by a combinational intervention method using attention bias modification and cognitive behavioral therapy in patients with hematopoietic tumors ：a quasi-randomized controlled trial

注意偏向修正と認知行動療法の併用介入法によって造血器腫瘍患者にある不安を軽減する効果 ：準ランダム化比較試験

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Contents

Abstract

Background

Studies have suggested that anxiety is a psychological problem common in patients with cancer. In this study, we tested the hypothesis that an intervention combining attention bias modification (ABM) and cognitive behavioral therapy (CBT) in reducing anxiety and improving physical activity among patients with hematopoietic malignancies.

Methods

A total of 30 patients with hematopoietic malignancies admitted to hospital were assigned to one of the following two groups, matched according to age, sex, and type of hematopoietic malignancy: the treatment group (ABM + CBT + exercise therapy) or the control group (ABM placebo + CBT placebo + exercise therapy). The primary outcome was the change in the Profile of Mood States (POMS) score, and heart rate variability (HRV) and number of daily steps were secondary outcome measures.

Results

Posttreatment measures of the treatment group showed a decrease in the POMS (tension-anxiety) score and sympathetic nerve activity. There was no significant difference in the number of steps between the groups.

Limitations

This study did not stratify patients by cancer stage or risk of recurrence.

Conclusions

An intervention combining ABM and CBT reduced anxiety among patients with hematopoietic malignancies, likely to be mediated by attenuation of sympathetic nervous system activity, but did not the influence overall physical activity. Therefore, including a psychological component can enhance the efficacy of an exercise program.

Key words

anxiety; attention bias modification; cognitive behavioral therapy; hematologic neoplasms; sympathetic nervous system

Abbreviations

ABM, attention bias modification; ANOVA, analysis of variance; CBT, cognitive behavioral therapy; CONSORT, Consolidated Standards of Reporting Trials; dlPFC, dorsal lateral PFC; fMRI, functional magnetic resonance imaging; HF, high frequency; HRV, heart rate variability; LF, low frequency; PFC, prefrontal cortex; POMS, Profile of Mood States; QOL, quality of life; SD, standard deviation; vlPFC, ventral lateral PFC.

1. Introduction

Many patients diagnosed with cancer are psychologically distressed and some of whom require psychological support (Naughton and Weaver, 2014; Zdenkowski et al., 2016). Anxiety is recognized as a common psychological disorder among patients with cancer not only after diagnosis but also during treatment or after treatment when the side effects appear (Traeger et al., 2012; Bronner et al., 2018). The 4-week, 12-month, and lifetime prevalence of anxiety disorders in patients with cancer has been reported as 11.5%, 15.8%, and 24.1%, respectively (Mehnert et al., 2014; Kuhnt et al., 2016). Patients with hematopoietic malignancies were reported to have an incidence of anxiety disorders and depression of 27% and 17%, respectively (Clinton-McHarg et al., 2014). On an investigation of mental distress by the type of cancer, lung cancer, gynecologic cancer, and hematopoietic malignancy were found to be the highest among 12 types of cancer (Linden et al., 2012). However, the recommended psychological interventions for patients with and those receiving chemotherapy in the Guidelines for Cancer Rehabilitation in Japan (The Japanese Association of Rehabilitation Medicine, 2019) rely on weak evidence from intervention studies (e.g., psychotherapy and relaxation). Therefore, there is a need for more effective interventions to be validated.

Currently, cognitive behavioral therapy (CBT) is the preferred method for providing psychological support to patients with cancer (Jassim et al., 2015; Matthews et al., 2017). According to current cognitive theories, individuals who are anxious exhibit an attention bias toward threat-related stimuli (Bar-Haim, 2010). Attention bias is typically measured using the dot-probe task, where threat-related and neutral stimuli are displayed in pairs at two different locations on a computer screen (Macleod et al., 1986). When the stimuli are removed, a visual probe appears in one of the two locations. A short reaction time for the probe appearing in the location of threat-related stimuli is defined as an attention bias to threats. Attention bias can be modified by reducing the frequency of the probe appearing at the location of threat-related stimuli and increasing its frequency at the location of neutral stimuli. This exercise is called 'attention bias modification' (ABM) and is effective in reducing anxiety disorders (MacLeod and Clarke, 2010). Studies on patients with cancer have reported attention bias to cancer-related stimuli in patients with newly diagnosed and treated breast cancer, healthy women at a high risk of breast cancer, and breast cancer survivors with a high inflammatory status (Glinder et al., 2007; DiBonaventura et al., 2010; Boyle et al., 2017). Patients with hematopoietic malignancies are also at a risk of developing a negative attention bias (Koizumi et al., 2018). Therefore, resolution of attention bias toward threat-related stimuli in these patients may alleviate their anxiety.

Recent studies have demonstrated that CBT and ABM complement one another, each targeting different cognitive aspects of anxiety (Taylor and Amir, 2010; Shechner et al., 2014; White et al., 2017; Lazarov et al., 2018). ABM uses a bottom-up approach to control conscious behavior to address the unconscious aspects of anxiety, while

CBT uses a top-down approach. It has been reported that QOL among patients with cancer improved after participating in physical training programs, although adding CBT did not yield benefits superior to physical training alone (May et al., 2008). However, a structured program of ABM and CBT might increase compliance with physical activity and exercise programs by reducing patients' perceived barriers to physical exercise, such as cancer-related anxiety and distress.

Emotional distress (i.e., anxiety and depression) and reduced physical functioning scores are correlated in patients with hematopoietic malignancies (Nakano et al., 2019), and in the design of exercise programs for patients with chronic conditions, it is essential to listen to individuals' needs to increase uptake and adherence (Pentecost and Taket, 2011). Providing exercise with consideration of psychology is the role of cancer rehabilitation. For patients with cancer, maintaining a stable psychological state and increasing the amount of physical activity are substantial components in the secondary prevention of cancer, alleviation of complications and symptoms, improvement of QOL, and prevention of other diseases (Brown et al., 2012). However, there is a need to determine the appropriate amount of intervention for patients with cancer experiencing high levels of physical and mental stress, as it may be overdone and improperly implemented. Therefore, determining the effects of physical activity intervention on psychosocial outcomes among patients with cancer requires additional research.

In this study, we tested the hypothesis that an intervention combining ABM and CBT would reduce anxiety among patients with hematopoietic malignancies. Our secondary aim was to examine the efficacy of combined ABM and CBT to improve physical activity when combined with conventional exercise therapy.

2. Methods

2. 1. Study design

This was an interventional study of in-hospital patients with hematopoietic malignancies, primarily to assess the efficacy of psychological interventions in decreasing anxiety and improving physical activity. The study was conducted at a single facility in the form of a prospective quasi-randomized trial. With the approval of the institutional ethics committee, 30 patients with hematopoietic malignancies were enrolled. This study was designed to allocate the subjects into two groups, namely, the intervention group (electronic medical record number: odd) and control group (electronic medical record number: even), using quasi-randomized controlled trial. Participants were assigned to either the intervention (ABM + CBT + exercise therapy) or the control (ABM placebo + CBT placebo + exercise therapy) group, which were matched according to age, sex, and type of hematopoietic malignancy. The effects of ABM and CBT on anxiety have been reported (Hakamata et al., 2010; White et al., 2017; Carpenter et al., 2018). In this study, we examined the hypothesis that the combined intervention of ABM and CBT would reduce anxiety in patients with hematopoietic malignancies, so we did not include a group that underwent ABM alone. Testing an ABM-only group requires another study aimed at determining the efficacy of each treatment protocol.

2. 2. Participants

2. 2. 1. Recruitment and inclusion criteria

Consecutive patients presenting with hematopoietic malignancies at

Saitama Medical University International Medical Center, from October 2015 to May 2017, were screened for eligibility. The inclusion criteria, designed to allow continued evaluation and intervention without delaying the chemotherapy protocol, were as follows: diagnosis of hematopoietic malignancy at least two weeks prior to enrolment; scheduled to undergo chemotherapy or hematopoietic stem cell transplantation; prescribed occupational therapy; and able to maintain a sitting position for more than 40 min. Patients were excluded from the study if they were diagnosed with a central nervous system disorder; had a history of mental illness, such as depression or anxiety associated with depression, before being diagnosed with malignancy; exhibited cognitive decline (Mini Mental State Examination score <24 points); or were experiencing severe autonomic side effects due to chemotherapy. Adverse events during the intervention were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0, Japan clinical oncology group, 2009). Inclusion and exclusion criteria were assessed by a combination of interviews with patients and a review of their medical records. The reasons for ineligibility were collected for compliance with the Consolidated Standards of Reporting Trials (CONSORT) guideline (Schulz et al., 2010).

2. 3. Research ethics

This study received ethical approval from the Review Board of the Saitama Medical University International Medical Center (# 15-138, 2015) and the Saitama Prefectural University (#27506, 2015). The first author met with patients meeting our eligibility criteria to describe the study purpose and methods and to obtain informed consent. Patients were informed of their right to withdraw from the study at any time, without prejudice. Key characteristics and clinical data of patients who provided written informed consent were obtained at the time of registration. Participants included in the study were entered into the clinical trial enrollment system of the University Hospital Medical Information Network (UMIN000022141).

2. 4. Procedure

This study was conducted at the facility's hematopoietic oncology department and rehabilitation center. We explained to participants that ABM was designed to decrease their attention bias toward threat-related stimuli (Bar-Haim, 2010) as well as of our intent to evaluate the efficacy of combining ABM with CBT in reducing their state of anxiety. Finally, the patients were informed that they would be assigned to either the treatment or the control group. All participants completed two to four training sessions weekly for four weeks. Group assignments were considered appropriate when interventions were performed at least eight times for each patient. There were 113 patients with hematopoietic malignancies in the facility during the study period, among whom 32 met the inclusion criteria and consented to the study. Patients were assigned to either the treatment (ABM + CBT + exercise therapy) or control (ABM placebo + CBT placebo + exercise therapy) group, with matching to ensure an equal distribution of sex, age, and cancer type between the two groups. All patients were blinded to group assignments. Of the 32 patients, 2 dropped out as they were discharged during the study period

(Fig. 1).

2. 5. Intervention

2. 5. 1. ABM and placebo training

An ABM Trainer (Ideoquest Co., Ltd., Tokyo, Japan) was used to measure attention bias. As the visual stimuli for this assessment, we used the 'angry', 'sad', and 'neutral' expressions from the Japanese Female Facial Expression Database. Eight pairs of images were presented to participants, a mixture of "stimulus expressions" (those with high emotional value) and "neutral expressions" (those with low emotional value). Patients were instructed to select neutral expressions by pressing one of two input buttons corresponding to the two locations on the computer screen. The image presentation protocol was the same as that of a previous study (Koizumi et al., 2018; Tayama et al., 2019).

The patients were shown the image stimuli 128 times in this test. Each stimulation comprised a pair of images. A total of eight combinations of image stimuli were displayed in random combinations. The reaction time to correctly select the neutral expression was measured. Reaction times <200 ms or >2000 ms were considered as 'false' responses and excluded from the analysis (Hou et al., 2014). In the treatment group, 112 stimulus-neutral and 16 neutral-neutral pairs were displayed, with 48 stimulus-neutral and 80 neutral-neutral pairs presented to the control group.

2. 5. 2. CBT

We implemented CBT to promote cognitive and behavioral changes in cancer patients, as demonstrated in previous meta-analyses and systematic reviews (Osborn et al., 2006; Dujits et al., 2011; Fors et al., 2011; Mewes et al., 2012). CBT was implemented as one module of psychological education, four modules of cognitive reconstruction methods, and three modules of assertion training. Participants completed all eight modules in the same predetermined order over four weeks. For the placebo CBT, patients actively participated in a program of education on behavior, which did not include the cognitive or assertion training modules. (Furukawa et al., 2014). Session duration, frequency, and context were matched between CBT and control groups.

2. 5. 3. Physical therapy

Exercise therapy was provided to improve the physical activity of participants, as previously described (Hacker et al., 2011, 2017). The exercise regimen to increase physical activity was as follows: (1) warm-up, consisting of 2 min of gymnastics at an intensity of 9-10 on the 20-point Borg scale (Borg, 1998); (2) aerobic exercise, consisting of 10 min of walking, 10-12 on the Borg scale; (3) muscle strengthening exercise:, consisting of 4 min of elastic resistance exercises, 10-12 on the Borg scale; and (4) cool-down, consisting of 2 min of gymnastics, 9-10 on the Borg scale. The Borg rating of perceived exertion was low intense to decrease the risk of overload.

2. 6. Outcomes

The primary outcome measure was a change in the Profile of Mood States (POMS) questionnaire tension-anxiety score. Data were collected at three time points: pre-treatment, during treatment (after 2 weeks), and posttreatment (after 4 weeks). The Japanese version of the POMS

(Yokoyama et al., 1990) is available in the same format as the English version (McNair et al., 1992) and includes six emotion scales: tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia, and confusion–bewilderment. The raw score from the tension–anxiety subscale was used as a psychological indicator in this study.

The secondary outcome measures were heart rate variability (HRV) and the number of daily steps taken. HRV was used as an indicator of autonomic activity in this study. By analyzing sympathetic (LF/HF ratio) and parasympathetic (HF) nerve conduction, it is possible to understand the level of activation to the stress response (Geisler et al., 2013; Gillie and Thayer, 2014; Yoshihara et al., 2016). These were measured in a resting state before each exercise was performed. To measure the number of daily steps, patients were equipped with a pedometer before treatment, and data were acquired weekly.

2. 7. Sample size

G*Power 3.1 (Faul et al., 2009) was used to estimate statistical power in this study. A minimum of 15 patients per group was needed in each group to detect a difference in the anxiety score at a power level of 0.8 and an effect size of 0.25.

2. 8. Blinding

Patients were blinded to group assignment. Cognitive behavioral therapists participating in this study had all undergone CBT training and were not blinded to group assignment. Assessments were performed by a researcher who was blinded to treatment groups to reduce detection bias.

2. 9. Statistical analyses

Patient characteristics were compared at baseline between the treatment and control groups. The chi-squared test was used to compare the number of patients for the following factors: sex, age, cancer type, time since diagnosis, chemotherapy received, and performance status (a score that estimates the patient's ability to perform certain activities of daily living without the help of others, measured on a scale of 0–4, with '0' being fully functional and asymptomatic and '4' being bedridden). The number of sessions completed and body mass index (BMI) were compared between the two groups using a t-test. To examine between-group differences in the primary and secondary outcome measures, a two-factor, repeated-measures analysis of variance (ANOVA) was used, with time as the within-subject factor and intervention group as the between-subject factor. Post-hoc analyses, with Bonferroni correction, were used as needed. All evaluations were performed based on the principle of intention-to-treat, using SPSS (version 25.0; IBM Corp., Armonk, NY, USA), with the significance level set at 5%.

3. Results

3. 1. Enrollment and patient characteristics

The study protocol was completed by 30 patients (mean age = 53 years, SD = 10 years). The subjects included 10 women (mean age = 51 years, SD = 9 years) and 20 men (mean age = 53 years, SD = 12 years). During the intervention period, there were no significant adverse events (Common Terminology Criteria for Adverse Events: Grade 1 or less), no change in performance status, and no strong side effects of chemotherapy. The cancer diagnoses included non-Hodgkin lymphoma (n=13), leukemia (n=10), myelodysplastic syndrome (n=5), and multiple myeloma (n=2). There were no significant differences in demographics or baseline physical characteristics between the groups (Table 1).

Table 2 displays the mean values of the psychological index, autonomic index, ABM reaction time, and physical activity for each group. Before treatment, none of these values differed between groups (all $p > 0.05$). The number of sessions completed was also not different between the two groups, with 9-11 sessions completed by all patients in each group ($p = 0.72$, r = 0.12). No correlation was observed between patient age and ABM reaction time ($p = 0.64$, r = 0.09).

3. 2. Differences between treatment and control groups : primary outcome

3. 2. 1. Psychological index

In terms of the POMS tension-anxiety score, there was an interaction effect between intervention group and time and an association between tension-anxiety score and time. Simple main effects analysis revealed that posttreatment anxiety was significantly lower in the treatment group than in the control group ($F_{[1, 28]} = 4.51$, $p < 0.05$, partial $\eta^2 = 0.147$; Fig. 2). There was an association between time and both the depression-dejection and the fatigue-inertia score, as well as between the intervention group and the vigor-activity score (Table 2).

3. 3. Differences between treatment and control groups : secondary outcomes

3. 3. 1. Autonomic index

In terms of the LF/HF ratio, there was an interaction effect between the intervention group and time and an association between time and both the LF/HF ratio and HF (Table 2 and Fig. 3). Simple main effects analysis revealed that the post-treatment LF/HF ratio was significantly lower in the treatment group than in the control group ($F_{[1, 28]} = 5.02$, $p < 0.05$, partial $\eta^2 = 0.152$).

3. 3. 2. Physical activity

There were no significant differences in daily step counts between the two group ($F_{[1.44, 40.29]} = 0.42$, $p = 0.66$, Fig. 4). Step count was associated with time (Table 2).

4. Discussion

This study has three main findings as follows: First, after 4 weeks of intervention, anxiety in the treatment group was lower than that in the control group. Second, after 4 weeks of intervention, the sympathetic nerve activity at rest in the treatment group was lower than that in the control group, although there was no difference in the parasympathetic nerve activity between the two groups. Third, there was no difference in physical activity between the treatment and control groups, but both groups had a higher level of physical activity after 4 weeks of intervention than before the intervention. These results suggest that an intervention combining ABM and CBT improved negative emotions in patients with hematopoietic malignancies by training them to modify their attention bias and to learn adaptive behaviors, as well as by suppressing their sympathetic nerve activity at rest.

The interventions used in this study are based on most current theory of anxiety. The mechanism of emotion induction is the unconscious perception of stimuli and the processing of emotions. There are two types of control, bottom-up and top-down, through which the body recognizes external stress and processes emotions (McRae et al., 2012). Dricu and Frühholz (2020), in their meta-analysis of studies of emotion perception and neuroimaging, reported that emotion is generated via the left amygdala, in connection with multiple brain regions. Emotions are regulated on both a conscious and an unconscious level (Braunstein et al., 2017), both of which should be considered as important in an intervention targeting emotional responses.

Two reviews identified the systematic role of attention bias in threat-related information processing (Cisler and Koster, 2010; Van Bockstaele et al., 2014). In recent neuroimaging studies, attention bias toward threat-related stimuli was associated with activity in the limbic neural circuit (Shechner et al., 2012; Heeren et al., 2013). In particular, the activation of the amygdala and anterior cingulate gyrus was associated with susceptibility to threat stimuli (Carlson et al., 2012). Browning et al. (2010) reported that the attention bias to threat stimuli activates the prefrontal cortex (PFC). In another report, functional magnetic resonance imaging (fMRI) revealed that when avoiding threat stimuli, the ventral lateral prefrontal cortex (vlPFC) and amygdala were activated, with their activation being correlated. The dorsal lateral prefontal cortex (dlPFC) was activated in the process of suppressing negative emotions (Bishop, 2008, 2009; White et al., 2016). These findings suggest that the PFC regulates the amygdala and corrects attentional bias, thus suppressing negative emotions. Therefore, those with high anxiety have weak frontal-amygdala connectivity, where the amygdala cannot effectively suppress negative emotions. Repeated ABM exercises enhance the functional connectivity between the right amygdala and the emotion-driven PFC (White et al., 2017). We consider that the functional connectivity of the amygdala is enhanced as a neurological background.

The emotional control effected via CBT indicates its mechanism of action in the brain. Yang, et al. (2018) measured changes in brain activity after CBT in people with depression and anxiety and demonstrated statistically significant increases in activity in areas within the cognitive control network, including the vlPFC and dlPFC. In a study that examined changes in brain activity using a dot-probe task, subjects with generalized anxiety disorder who underwent CBT exhibited increased vlPFC and bilateral amygdala activity (Maslowsky et al., 2010). Furthermore, a combined ABM and CBT study suggested that CBT provides amygdala-based functional connectivity and ABM differentiates treatment responses (White et al., 2017). These findings suggest that the top-down CBT approach and the bottom-up ABM approach may complement one another to act on emotional processing and reduce anxiety.

In addition, results of POMS in this study showed significantly improvements on depression–dejection, vigor–activity, and fatigue–inertia, regardless of intervention. A meta-analysis showing the usefulness of aerobic exercise in patients with hematopoietic malignancies has shown that it reduces depression (low-certainty evidence) and fatigue (moderate-certainty evidence) (Knips et al., 2019). This result was similar to the effect of the exercise therapy alone group. However, as for exercises that affect psychological function, long-term aerobic exercise, muscle strengthening with moderate or higher load, and long-term intervention have been effective (DeFor et al., 2007; Wiskemann et al., 2014). The rating of perceived exertion of exercise therapy in this study was low. We speculate that the effect on the psychological aspect is limited.

In our study, resting sympathetic nerve activity was suppressed after weeks of combined CBT and ABM treatment. HRV is a marker of emotional awareness and self-regulation in healthy individuals and controls psychophysiological resources during emotion processing. It is used as an index of the autonomic nervous system (Geisler et al., 2013; Gillie et al., 2014). The autonomic nervous system attenuates parasympathetic nerve activity when psychological stress is applied (Thayer et al., 2009) and is activated in association with sympathetic nerve-related brain regions (Etkin et al., 2011). A state of high anxiety is negatively correlated with both parasympathetic and sympathetic nerve activity (Chalmers et al., 2014), resulting from an association between attention bias and emotional dysregulation (Duschek et al., 2009, 2013). ABM aims to train an individual to avoid threat stimuli instantaneously, which we achieved in this study of cancer patients. As a result, we consider that ABM suppressed patients' sympathetic nervous system activity. In contrast, there was no difference parasympathetic activity post-treatment between the treatment and control group. De Couck and Gidron (2013) investigated the cardiac vagal tone in cancer patients, using HRV as an index, and reported that it was lower than in healthy subjects. Fatigue and depression in patients with breast cancer have been demonstrated to have a strong influence on the attenuation of the cardiac vagus nerve (Arab et al., 2016). Decreased HRV is associated with elevated levels of inflammatory cytokines in the blood (Sloan et al., 2007), and inflammation is associated with elevated fatigue of cancer survivors (Bower and Lamkin, 2013). Therefore, we speculate that patients with cancer are exposed to high levels of disease-related stress, which depletes psychophysiological resources that control emotional processing. In the present study, fatigue and psychological stress associated with chemotherapy affected patients' baseline parasympathetic nerve activity, which we consider a possible reason for no change obtained in the parasympathetic nerve activity by the combination of ABM and CBT. However, we did not stratify patients by cancer type and stage, which is known to affect psychology and HRV. To account for these, we incorporated cancer type, stage, and population undergoing chemotherapy as covariates, and additional verification is required.

Increased physical activity and exercise are recommended for patients with multiple cancer types to prevent or mitigate adverse events due to cancer treatment and nutritional disorders (Rock et al., 2012). Therefore, we examined whether ABM and CBT combined with exercise therapy could increase the amount of physical activity a patient performed. As a result, both groups exhibited increased activity after 4 weeks of intervention compared with that before the intervention. In a literature review of activity monitoring during exercise programs for cancer patients, Purswani et al. (2018) revealed that such programs were associated with an improvement in physical activity, fatigue score, QOL score, self-esteem, and mood. Studies in patients with hematopoietic malignancies reported improvement in physical activity as a result of introducing resistance training after hematopoietic stem cell transplantation (Hacker et al., 2011, 2017). Patients in the current study took part in a four-week resistance training and aerobic exercise regimen. There was no difference in the amount of exercise completed between the two groups. The efficacy of exercise programs in improving physical activity can be limited by the type of cancer, whether it is conducted on an in-patient or out-patient status, and difference in the exercise environment (Granger et al., 2018; McTiernan et al., 2019). Bennett et al. (2016), in an exercise program designed for patients that received hematopoietic stem cell transplantation, reported that pain, fatigue, vomiting, tremor/chills, diarrhea, shortness of breath, and decreased social activity, physical activity, and/or overall physical health were factors causing a decrease in average daily steps. Winningham (1992) demonstrated that impaired blood biochemistry due to chemotherapy prolongs the feeling of fatigue and causes an imbalance in rest and exercise. To control for environmental factors in our study, patients were restricted within their hospital ward for all activities and had meals and baths at a set time, intended to normalize their daily routine. In addition, patients were instructed by their doctors to avoid fatigue with physical activity, thus minimizing the potential for fluctuations in blood biochemistry. For these reasons, we speculate that the physical activity of cancer patients is unlikely to increase during hospitalization. To clarify the effects of an intervention on physical activity, a future study should implement a protocol modified to control for activity-limiting factors while maintaining optimal exercise intensity.

Limitations

This study has several limitations. First, we included patients diagnosed with their first hematopoietic malignancy and did not stratify patients by cancer stage or fear of recurrence, all of which have been reported to be related to affect (Cardoso et al., 2016; Sharpe et al., 2018).

The patient group was not stratified because the classification of hematopoietic malignancy by stage is complicated, as the TNM classification does not extend to hematopoietic malignancy and, thus, would require the evaluation of lymphoma and leukemia in multiple items (Boeker et al., 2016; Leal et al., 2018). Investigation of the effects of these various factors on the outcome after combined CBT and ABM requires studies of larger sample size. Second, we did not include an ABM-alone group, which limits the interpretation of our results with combined ABM and CBT. In this study, the number of patients available to assign to each treatment component was limited. Studies are needed to examine whether ABM and CBT yield better outcomes when combined than when used in isolation (e.g., Borkovec and Costello, 1993). Patients with hematopoietic malignancies must adjust the amount of exercise they perform because of reduced motor activity and increased anxiety. Thus, even for critically ill patients and for those with limited exercise time, training may be provided if the load is appropriately adjusted. Third, we did not consider the burden of psychological tests on hematopoietic malignancy patients, as we did not measure the change in attention bias score. Attention bias may change during the cancer treatment process. Therefore, studies that incorporate changes in attention bias score to determine when the score plateaus and may be discontinued to reduce unnecessary exercises should be conducted. Fourth, this was a single-center study and our results should be verified by cluster-randomized studies. Fifth, the sample size for secondary outcomes in this study was too small to directly determine effect sizes. To test the first hypothesis, we estimated the sample size required to verify the effect size obtained using two-factor repeated-measures ANOVA in this study. For the secondary hypothesis, 54 patients per group would have been needed to reduce the type 2 error rate and demonstrate the efficacy of the intervention, as calculated by the ANOVA for Cohen's f (=0.1234035).

5. Conclusions

The results of this study indicate that the combination of ABM and CBT, aimed at reducing the negative effects in patients with hematopoietic malignancies were efficacious. This was accompanied by attenuation of the sympathetic nervous system and suggests a potential mechanism for reducing the emotional response. To enhance the effect of exercise therapy using a psychological intervention, it is necessary to conduct a study that considers the limitations posed by cancer treatment and the environment. However, the results of this study serve as a basis for psychological and exercise interventions in patients with hematopoietic malignancies.

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Figure Legends

Fig. 1 Patient recruitment and follow-up diagram.

Fig. 2 Comparison of the Profile of Mood States (POMS) tension-anxiety (T-A) score between the treatment and control groups. The posttreatment scores were lower in the treatment group than in the control group, as determined by post-hoc analysis. Error bars indicate the standard error of the mean. $*p < 0.05$.

Fig. 3 Comparison of the low frequency/high frequency (LF/HF) ratio between the treatment and control groups. The LF/HF ratio was lower in the treatment group than in the control group, as determined by post-hoc analysis. Error bars indicate the standard error of the mean. $*p < 0.05$.

Fig. 4 Comparison of the daily step count between the treatment and control groups. No significant between-group difference was observed. Error bars indicate the standard error of the mean.

Tables

Table 1. Demographic and clinical characteristics

Survey Items	Classifications	Treatment group		Control group		P-value[c]
		n	%	*n*	%	
Sex	Male	10	67	10	67	p = 1.000
	Female	5	33	5	33	
Age, years	20≦39	2	13	2	13	p = 0.993
	40≦49	4	27	3	20	
	50≦59	4	27	5	33	
	60≦69	3	20	3	20	
	70≦	2	13	2	13	
Cancer type	Non-Hodgkin lymphoma	7	47	6	40	p = 0.964
	Leukemia	5	33	5	33	
	Myelodysplastic syndromes	2	13	3	20	
	Multiple myeloma	1	7	1	7	
Time since diagnosis	≦6 months	5	33	6	40	p = 0.809
	7-12 months	8	53	8	53	
	>12 months	2	13	1	7	
Chemotherapy (first course of treatment)[a]		2	13	1	7	p = 0.543
Performance status[b]	0: Fully active	8	53	9	60	p = 0.928
	1: Restricted in physically strenuous activity	6	40	5	33	
	2: Up and about more than 50% of waking hours	1	7	1	7	
	3: Capable of only limited selfcare	0	0	0	0	
	4: Completely disabled	0	0	0	0	
		mean	SD	mean	SD	
Body mass index (kg/m^2)		20.93	1.36	21.01	1.52	p = 0.871

[a] All patients were undergoing chemotherapy. No patients received radiation therapy or hematopoietic stem cell transplantation.

[b] Performance status is a score that estimates the patient's ability to perform certain activities of daily living without the help of others.

This scale ranges from 0 to 4, with 0 being fully functional and asymptomatic, and 4 being bedridden.

[c] The P-values reflect between-group comparisons. For body mass index, this was calculated via non paired t-test; for all other survey items, it was calculated via a chi-square test.

*p < .05 **p < .01.

Table 2. Clinical variables at different time points for the treatment and control groups

Measure	interval	Treatment group n = 15		Control group n = 15		Statistics	
POMS		Mean	SD	Mean	SD	F	Partial η^2
Tension-Anxiety	Pre-treatment	16.13	6.12	15.53	6.24	$^{a}F_{[2, 56]} = 4.31^{*}$	0.133
	During treatment	16.33	5.51	15.60	5.62	$^{b}F_{[2, 56]} = 17.50^{**}$	0.385
	Post-treatment	11.87	4.55	13.87	4.34	$^{c}F_{[1, 28]} = 0.13$	0.005
Depression-Dejection	Pre-treatment	14.33	6.49	16.13	7.54	$^{a}F_{[1.36, 37.96]} = 0.29$	0.100
	During treatment	13.73	5.95	14.87	6.02	$^{b}F_{[1.36, 37.96]} = 4.08^{*}$	0.127
	Post-treatment	13.33	5.31	14.73	4.37	$^{c}F_{[1, 28]} = 0.46$	0.016
Anger-Hostility	Pre-treatment	12.07	5.95	11.53	5.66	$^{a}F_{[1.38, 38.58]} = 0.58$	0.020
	During treatment	11.13	5.60	11.33	5.29	$^{b}F_{[1.38, 38.58]} = 1.84$	0.062
	Post-treatment	11.20	4.78	11.20	4.95	$^{c}F_{[1, 28]} = 0.03$	0.000
Vigor-Activity	Pre-treatment	6.20	2.11	4.53	2.90	$^{a}F_{[2, 56]} = 0.55$	0.019
	During treatment	7.27	2.37	4.87	2.33	$^{b}F_{[2, 56]} = 2.761$	0.090
	Post-treatment	7.47	1.25	5.07	2.25	$^{c}F_{[1, 28]} = 10.04^{**}$	0.264
Fatigue-Inertia	Pre-treatment	9.60	3.27	11.07	4.33	$^{a}F_{[1.41, 39.60]} = 0.72$	0.025
	During treatment	9.40	3.44	9.73	3.20	$^{b}F_{[1.41, 39.60]} = 6.00^{*}$	0.176
	Post-treatment	8.27	2.52	9.13	2.56	$^{c}F_{[1, 28]} = 0.70$	0.024
Confusion-Bewilderment	Pre-treatment	8.60	2.72	7.93	2.19	$^{a}F_{[2, 56]} = 3.08$	0.039
	During treatment	8.80	3.45	8.93	3.10	$^{b}F_{[2, 56]} = 0.99$	0.034
	Post-treatment	8.27	2.66	8.87	3.04	$^{c}F_{[1, 28]} = 0.01$	0.000
Reaction time (ms)	Pre-treatment	879.07	74.63	883.20	81.14	$^{a}F_{[1.63, 45.75]} = 0.46$	0.016
	During treatment	828.73	60.72	846.87	83.56	$^{b}F_{[1.63, 45.75]} = 94.22^{**}$	0.771
	Post-treatment	772.93	47.18	786.07	65.13	$^{c}F_{[1, 28]} = 0.24$	0.009
LF/HF	Pre-treatment	1.74	0.77	1.85	0.59	$^{a}F_{[2, 56]} = 4.82^{*}$	0.147
	During treatment	1.69	0.66	1.92	0.57	$^{b}F_{[2, 56]} = 5.40^{**}$	0.162
	Post-treatment	1.41	0.57	1.87	0.54	$^{c}F_{[1, 28]} = 1.48$	0.050
HF	Pre-treatment	4.48	1.62	4.32	1.07	$^{a}F_{[1.40, 39.05]} = 0.65$	0.023
	During treatment	3.99	0.81	4.38	1.11	$^{b}F_{[1.40, 39.05]} = 4.80^{*}$	0.146
	Post-treatment	5.43	0.75	4.78	1.22	$^{c}F_{[1, 28]} = 1.16$	0.040
Step count (steps/D)	Pre-treatment	1616.27	624.38	1677.67	589.98	$^{a}F_{[1.44, 40.29]} = 0.42$	0.015
	During treatment	1681.67	573.96	1771.60	643.97	$^{b}F_{[1.44, 40.29]} = 4.34^{*}$	0.134
	Post-treatment	1815.60	602.83	1806.73	588.17	$^{c}F_{[1, 28]} = 0.05$	0.002
		mean	SD	mean	SD		
Intervention times		9.80	0.56	9.93	0.59	$^{d}p = 0.532$	

Statistical analysis used a two-factor repeated measures ANOVA, with time as the within-subject factor and intervention group as the between-subject factor.
a Test of interaction effect including 3 points of pretreatment, during treatment, and posttreatment between two groups.
b Test of association between the outcome measure and time (before and after treatment).
c Test of association between the outcome measure and treatment.
d For Intervention times, this was calculated via non paired t-test.
$^{*}p < .05$ $^{**}p < .01$.
POMS, Profile of Mood States; LF, low frequency; HF, high frequency; SD, standard deviation.

Figure

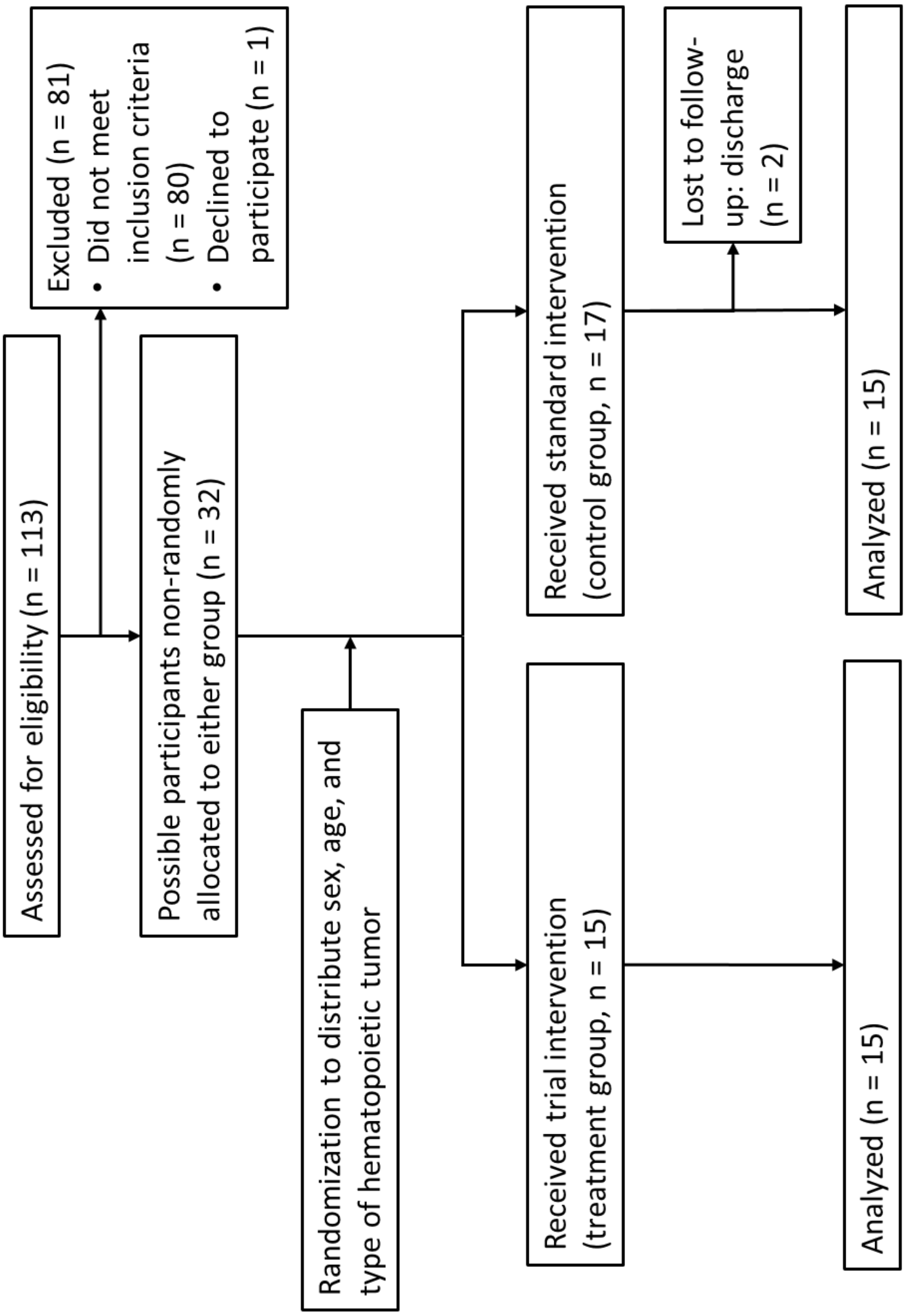

Figure 1

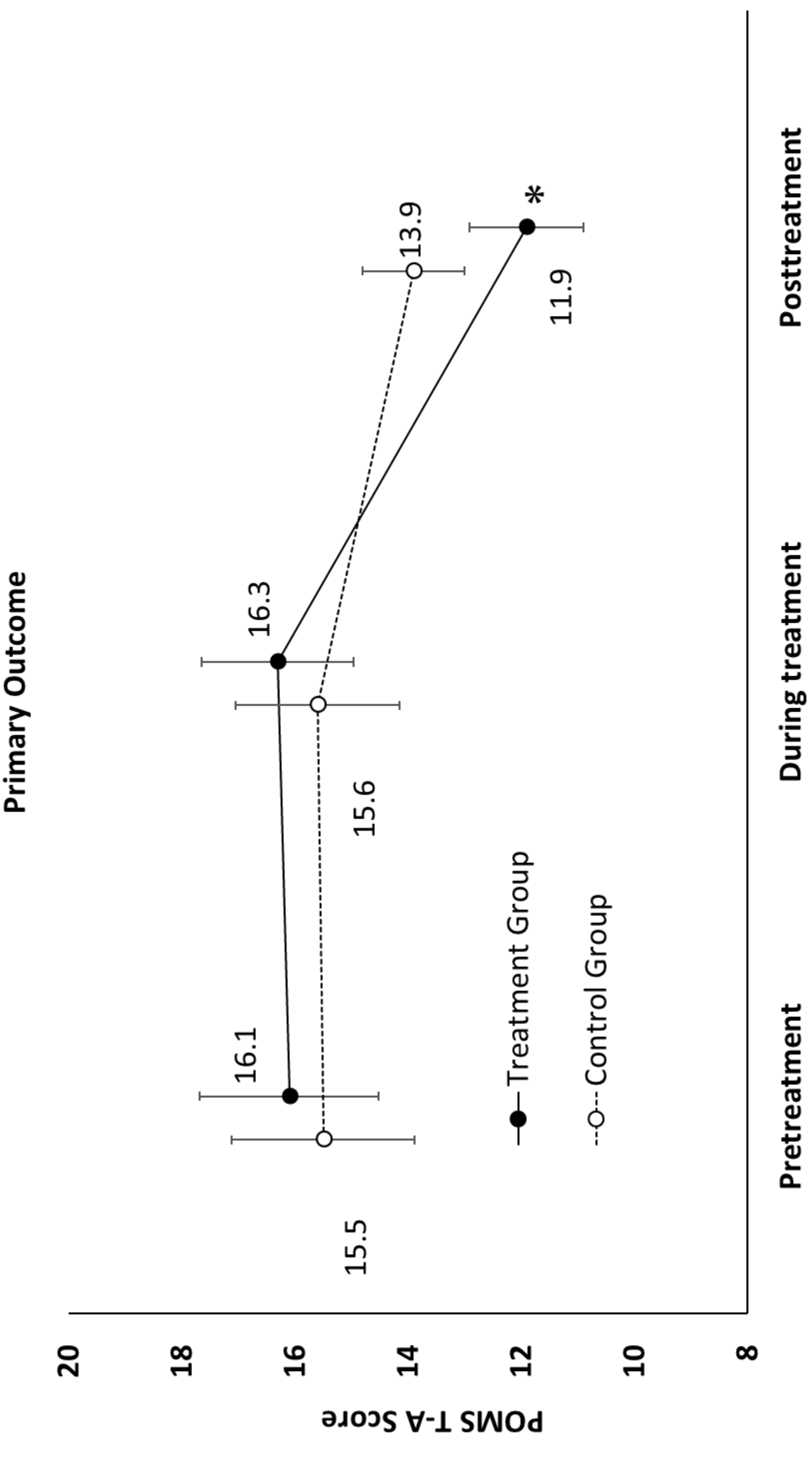
Primary Outcome
POMS T-A Score
20
18
16
14
12
10
8
Pretreatment
During treatment
Posttreatment
Treatment Group
Control Group
16.1
15.5
16.3
15.6
13.9
11.9
*

Figure 2

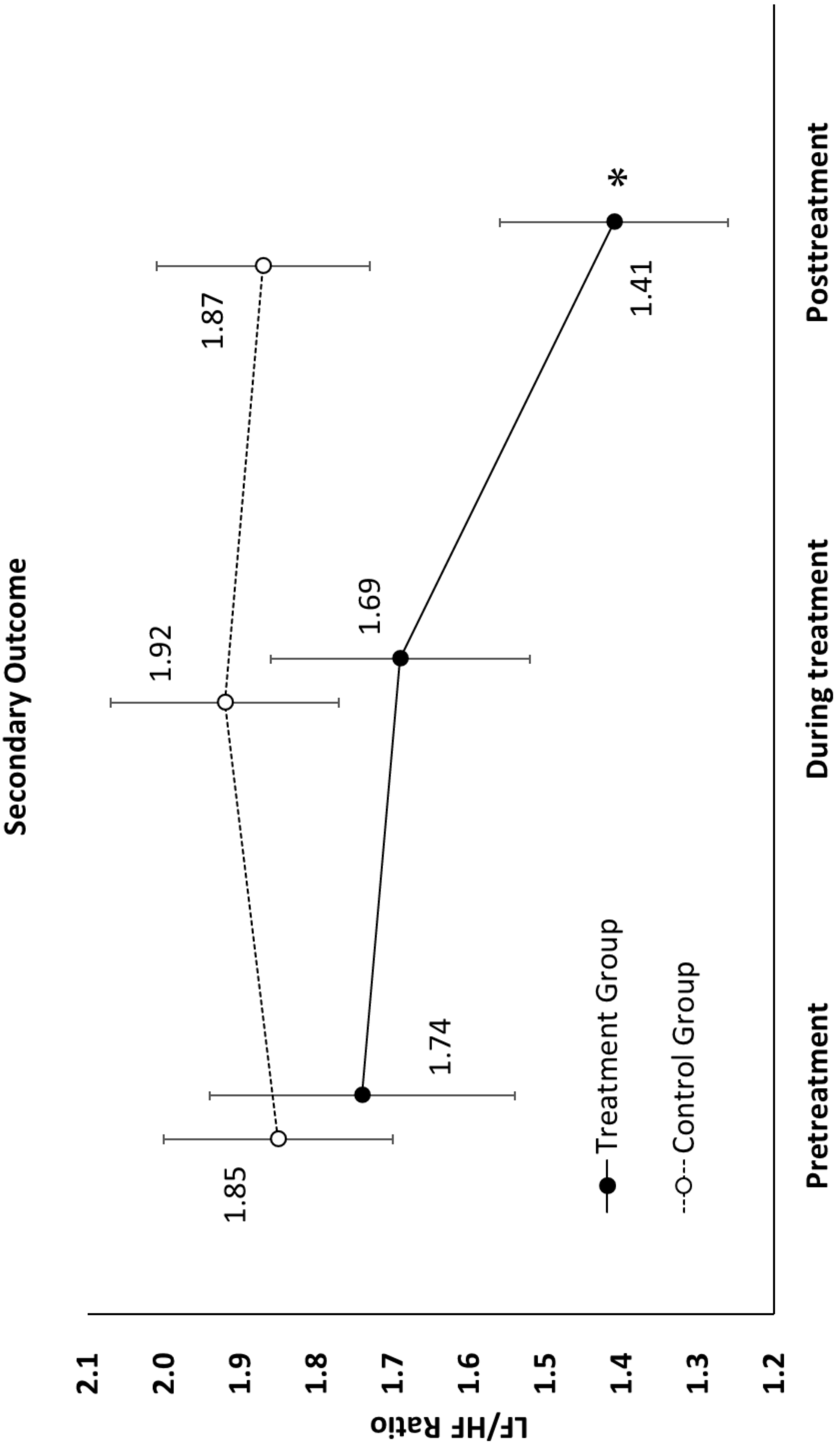
Secondary Outcome
LF/HF Ratio
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
Pretreatment
During treatment
Posttreatment
1.85
1.74
1.92
1.69
1.87
1.41
*
Treatment Group
Control Group

Figure 3

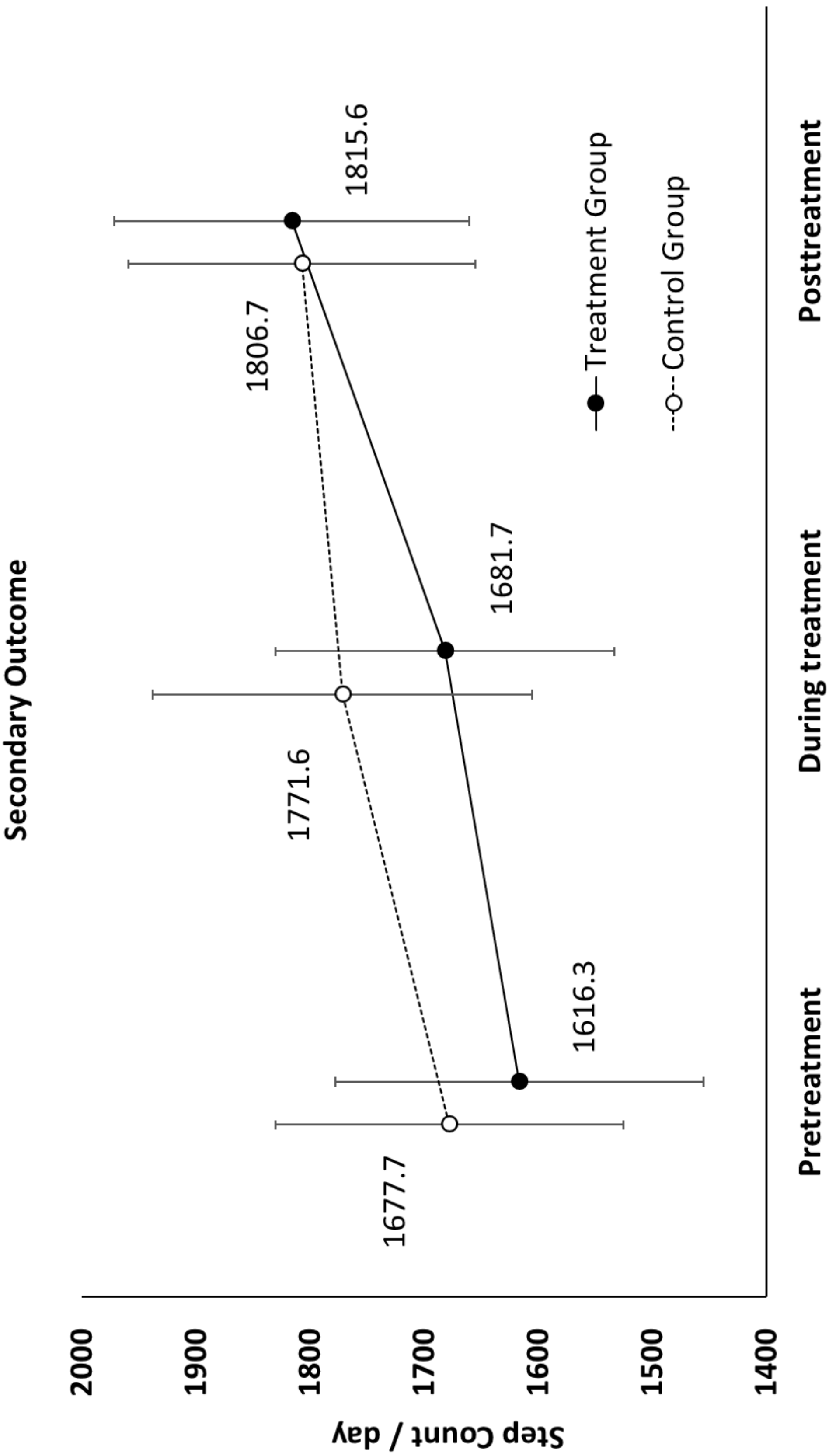
Secondary Outcome
Step Count / day
2000
1900
1800
1700
1600
1500
1400
1677.7
1616.3
1771.6
1681.7
1806.7
1815.6
Treatment Group
Control Group
Pretreatment
During treatment
Posttreatment

Figure 4