Comparison Of Physical Activity And Sedentary Behavior In Autologous And Allogeneic Hematopoietic Stem Cell Transplantation Survivors

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Abstract

Purpose: The treatment background, as well as the frequency and type of complications, in autologous (auto-) and allogeneic (allo-) hematopoietic stem cell transplantation (HSCT) survivors influence the appearance of moderate to vigorous physical activity (MVPA) or sedentary behavior. We aimed to identify differences in MVPA and sedentary behavior between auto- and allo-HSCT survivors.

Methods: We included 13 auto- and 36 allo-HSCT survivors (≈ 4 years after HSCT). MVPA and sedentary behavior were assessed using a triaxial accelerometer.

Results: There were no significant between-group differences in MVPA and sedentary behavior (p = 0.768 and 0.739, respectively). In allo-HSCT survivors, MVPA was negatively correlated with the Hospital Anxiety and Depression Scale score (r = -0.358, p = 0.032). Stepwise multiple regression analysis showed that age was a significant predictor of sedentary behavior in allo-HSCT survivors (β = 0.400, p = 0.016).

Conclusion: We observed no significant between-group differences in MVPA and sedentary behavior. Our results suggest that it may be unnecessary to change the rehabilitation program according to the donor type in interventions for promoting MVPA and reducing sedentary behavior in long-term HSCT survivors.

Introduction

There has been a recent increase in the number of hematopoietic stem cell transplantations (HSCT) in Japan [1]. Additionally, there have been improvements in conditioning, immunosuppressive drugs, and supportive care for complications, with increased long-term survival [2, 3]. However, there is a high risk of mortality from late complications during the 5 years after HSCT. The causes of late non-relapse mortality 2 years after HSCT include infectious diseases, respiratory complications, secondary malignancies, and organ disorders [4]. Late complications may reduce the quality of life (QOL) in survivors after HSCT. For cancer survivors other than HSCT survivors, there has been an annual increase in the relative 5-year survival rate due to advances in early detection and treatment of diseases, with a concomitant increase in the number of patients returning to society. A Japanese study that conducted a follow-up of cases between 2009 and 2011 reported a relative 5-year survival rate of ≥ 60% for both men and women [5]. Given the increasing number of cancer survivors, there has been extensive research on physical activity, including moderate to vigorous physical activity (MVPA) and sedentary behavior, in cancer survivors. Previous studies on cancer survivors, including survivors of breast and colorectal cancer, have reported correlations of MVPA with overall survival (OS), QOL, and treatment-related adverse effects [6–8]. Furthermore, among cancer survivors, increased sedentary behavior is associated with an increased risk of mortality [9], the development of ischemic heart disease [10], and decreased QOL [11]. Sedentary behavior is defined as waking behavior characterized by an energy expenditure of ≤ 1.5 metabolic equivalents (METs) while in a sitting or reclining posture [12]. Studies in cancer survivors have examined the correlates of MVPA and sedentary behavior assessed using an accelerometer, which can objectively measure physical activity; however, few studies have objectively measured physical activity in HSCT

survivors. Several studies have investigated physical activity using questionnaires [13–15]; however, measurement errors are likely to occur in this self-report method [16–18]. No studies have compared MVPA and sedentary behavior between autologous (auto-) and allogeneic (allo-) HSCT survivors. Differences in treatment background, as well as the frequency and type of complications, between auto- and allo-HSCT survivors may result in differences in MVPA and sedentary behavior. This study aimed to identify differences in MVPA and sedentary behavior between auto- and allo-HSCT survivors.

Methods

Study design

This prospective observational study investigated whether there were differences in MVPA and sedentary behavior between auto- and allo-HSCT survivors. Additionally, we investigated the associations of MVAP and sedentary behavior with demographic and clinical characteristics, physical function, psychological health, and QOL.

Participants

We included patients who underwent auto- or allo-HSCT (aged ≥ 18 years) at the Hamamatsu Medical Center in Japan, visited an outpatient department of hematology from March 2019 to March 2020, and were cognitively capable of handling accelerometers. We excluded patients who relapsed after HSCT or those who received treatment for recurring cancer. This study was approved by the Hamamatsu Medical Center Institutional Committee on Human Research. All the participants provided written informed consent before the study. We collected the following information from the patients' medical records: age, sex height, body weight, body mass index, hematological diagnosis, stem cell source, donor type, conditioning, comorbidity, time elapsed after HSCT, acute and chronic graft-versus-host disease (GVHD), presence of comorbidity, and corticosteroid dose. Additionally, the survivors self-reported their employment status, marital status, educational background, and smoking status.

Measurements

MVPA and sedentary behavior

We assessed MVPA and sedentary behavior using a triaxial accelerometer (HJA-750C, Active style Pro, Omron Healthcare, Kyoto, Japan). The reliability and validity of the accelerometer have been previously confirmed [19]. We investigated MVPA (≥ 3 METs) and sedentary behavior (≤ 1.5 METs); further, we calculated daily MVPA and sedentary behavior. The patients were instructed to wear the accelerometer on an elastic waistband for 7 consecutive days from their waking time in the morning to bedtime at night, with the accelerometer being removed during bathing. We used data on days when the accelerometer was worn for ≥ 10 h for ≥ 4 days. Non-wear time was defined as an interval of ≥ 60 consecutive minutes of zero counts [20]. We performed MET-based classification of physical activity using the manufacturer-provided software (HMS-HJA-IC01J; Omron Healthcare).

Physical Function

We used handgrip strength (kg) as an index of upper limb strength, which was evaluated using a standard adjustable-handle dynamometer (TKK5101; Takei Scientific Instruments Co. Ltd., Niigata, Japan). Measurements were conducted twice using both hands, with the highest value being selected for analysis. Knee extensor muscle strength (kg/ kgwt) was measured as an index of lower limb strength using handheld dynamometers (HHD; mobile MT-100; SAKAImed Co. Ltd., Tokyo, Japan). All sessions used the same HHD equipped with a stabilizing belt to facilitate resistance application by the tester. We examined the knee extension force with the patients sitting with their knee flexed to approximately 60°. We used a dynamometer to the anterior surface of the tibia proximal to the malleoli. We recorded the maximum force developed during a 10 s static effort. Triplicate measurements were bilaterally recorded, with the highest value being used for analysis. Exercise capacity was evaluated using the six-minute walking test (6 MWT) following the guidelines of the American Thoracic Society [21]. Specifically, patients walked at their own pace along a 20-m corridor for 6 min, with the distance traveled (in meters) during this period being measured.

QOL

The QOL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ C-30) version 3.0. This self-administered questionnaire incorporated five functional scales, nine symptom scales, and global health status. All item scores were transformed into values from 0 to 100. The values were positively correlated with the functional and health levels in functional scales, quality of life in the global health status, and presence of symptoms in the symptom scales. The EORTC QLQ is valid and reliable for patients with cancer worldwide [22]; moreover, the reliability and validity of the Japanese-translated questionnaire have been confirmed [23].

Psychological Health

Psychological health was assessed using the Hospital Anxiety and Depression Scale (HADS), which assesses the frequency of depressive status (7 items) and anxiety (7 items) over the past week from 0 (not at all) to 3 (most of the time). Positively worded items were reverse-scored. A higher score indicated greater symptomology. The Japanese version of the HADS has been previously validated [24].

Statistical analysis

The Shapiro-Wilk test was used to evaluate the data distribution. Between-group comparisons of continuous variables were assessed using unpaired t-tests and Mann-Whitney U tests. Between-group comparisons of categorical variables were assessed using Chi-squared tests. We calculated Pearson’s product-moment correlation coefficients and Spearman’s rank correlation coefficients to evaluate the relationships of MVPA and sedentary behavior with demographic and clinical characteristics. To identify variables independently associated with MVPA and sedentary behavior in the included patients, we

performed a stepwise multiple regression analysis. Factors correlated with MVPA and sedentary behavior were considered to be predictors of MVPA and sedentary behavior in auto- and allo-HSCT survivors. Statistical analyses were performed using SPSS 24.0 J (SPSS Japan, Tokyo, Japan). Statistical significance was set at $P \leq 0.05$.

Results

Participants

We screened 50 allo- and 16 auto-HSCT survivors (Fig. 1). Among them, 14 allo- and 3 auto-HSCT survivors dropped out of the study, with the reasons for dropping out being noted. Finally, we included and compared 36 allo- and 13 auto-HSCT patients. Table 1 shows the sample demographic and clinical characteristics. For allo- and auto-HSCT survivors, the mean ages were 49.4 and 54.8 years, respectively; moreover, 41.7% and 61.5% of the participants were men, respectively. The hematological diagnoses included acute leukemia (55.5%), myelodysplastic syndrome (25.0%), malignant lymphoma (5.6%), chronic myelogenous leukemia (2.8%), myelofibrosis (2.8%), Epstein-Barr virus-associated hemophagocytic syndrome (2.8%), aplastic anemia (2.8%), and myeloid sarcoma (2.8%). Among auto-HSCT survivors, there were seven and six patients had multiple myeloma and malignant lymphoma, respectively. In allo- and auto-HSCT survivors, the mean time elapsed after HSCT was 49.5 (4.1 years) and 43.0 (3.6 years) months, respectively. The proportion of comorbidities, including late complications, was 41.7% and 38.5% in allo- and auto-HSCT survivors, respectively. Moreover, 15 (41.7%) and 8 (22.2%) patients had a history of and current chronic GVHD, respectively. There were no significant between-group differences in demographic and clinical characteristics.

Table 1
Demographic and clinical characteristics of auto- and allo-HSCT survivors

	allo-HSCT (n = 36)	auto-HSCT (n = 13)	p
	Mean (SD)		
Age, years	49.4 (12.8)	54.8 (11.5)	0.197
Female/male, n (%)	21 (58.7%) / 15 (41.7%)	5 (38.5%) / 8 (61.5%)	0.218
Height, cm	161.4 (7.3)	163.0 (9.4)	0.532
Body weight, kg	56.1 (10.3)	63.2 (15.2)	0.054
Body mass index, kg/m^2	21.6 (3.8)	23.4 (3.9)	0.077
	Median (range)		
Time elapsed from HSCT	49.5 (8–199)	43 (1–121)	0.150
	n (%)		
Diagnosis			
Acute leukemia	20 (55.5%)	0	
Myelodysplastic syndrome	9 (25.0%)	0	
Multiple myeloma	0	7 (53.8%)	
Malignant lymphoma	2 (5.6%)	6 (46.2%)	
Chronic myelogenous leukemia	1(2.8%)	0	
Myelofibrosis	1(2.8%)	0	
EBV-AHS	1(2.8%)	0	
Aplastic anemia	1(2.8%)	0	
Myeloid sarcoma	1(2.8%)	0	
Comorbidity, n (%)			0.84
None	21 (58.3%)	8 (61.5%)	
Yes	15 (41.7%)	5 (38.5%)	
Employment status, n (%)			0.840
Not working	15 (41.7%)	5 (38.5%)	

HSCT, hematopoietic stem cell transplantation; SD, standard deviation; EBV-AHS, Epstein-Barr virus-associated hemophagocytic syndrome; NA, not applicable; HLA, human leukocyte antigen; GVHD, graft versus host disease

	allo-HSCT (n = 36)	auto-HSCT (n = 13)	p
Employed	21 (58.3%)	8 (61.5%)	
Marital status, n (%)			0.297
Not married	12 (33.3%)	2 (15.4%)	
Married	24 (66.7%)	11 (84.6%)	
Education, n (%)			1.00
Junior high school	2 (5.6%)	1 (7.7%)	
High school	15 (41.7%)	5 (38.5%)	
Technical school	7 (19.4%)	3 (23.1%)	
Junior college	4 (11.1%)	1 (7.7%)	
University/college	8 (22.2%)	3 (23.1%)	
Smoking status, n (%)			0.716
Non-smoking	33 (91.7%)	12 (92.3%)	
Current	3 (8.3%)	1 (7.7%)	
Stem cell source, n (%)			
Bone marrow	23 (63.9%)	NA	
Cord blood	9 (25.0%)	NA	
Peripheral blood stem cell	4 (11.1%)	13 (100%)	
Donor type, n (%)		NA	
HLA-mismatched/unrelated	13 (36.1%)		
HLA-matched/related	11 (30.6%)		
HLA-matched/unrelated	10 (27.8%)		
HLA-mismatched/related	1 (2.8%)		
Conditioning, n (%)		NA	
Myeloablative	28 (77.8%)		
Reduced intensity	7 (19.4%)		
Unknown	1 (2.8%)		

HSCT, hematopoietic stem cell transplantation; SD, standard deviation; EBV-AHS, Epstein-Barr virus-associated hemophagocytic syndrome; NA, not applicable; HLA, human leukocyte antigen; GVHD, graft versus host disease

	allo-HSCT (n = 36)	auto-HSCT (n = 13)	p
Steroid dose at survey, (n %)		NA	
Yes	8 (22.2%)		
No	28 (77.8%)		
History of aGVHD, n (%)		NA	
Yes	26 (72.2%)		
No	10 (27.8%)		
cGVHD at survey, n (%)		NA	
Yes	8 (22.2%)		
No	28 (77.8%)		
History of cGVHD, n (%)			
Yes	15 (41.7%)		
No	21 (58.3%)		

HSCT, hematopoietic stem cell transplantation; SD, standard deviation; EBV-AHS, Epstein-Barr virus-associated hemophagocytic syndrome; NA, not applicable; HLA, human leukocyte antigen; GVHD, graft versus host disease

Between-group comparisons of MVPA, sedentary behavior, physical function, psychological health, and QOL

Table 2 shows the between-group comparison of MVPA, sedentary behavior, physical function, psychological health, and QOL. There were no significant between-group differences in MVPA and sedentary behavior ($p = 0.768$ and 0.739, respectively). The mean duration of accelerometer wear time in allo- and auto-HSCT survivors was 903.2 and 870.8 min/day, respectively. Allo-HSCT survivors had 539.1 min of sedentary behavior per day (9.0 h; standard deviation [SD] = 106.9 min) and performed 40.4 min of MVPA per day (SD = 32.8 min). Contrastingly, auto-HSCT survivors had 526.7 min of sedentary behavior per day (8.8 h; SD = 123.0 min) and performed 34.9 min of MVPA per day. There was a significant between-group difference in dyspnea, which is the symptom scale of the EORTC QLQ C-30 ($p = 0.011$). There were no significant between-group differences in the other measurements.

Table 2
Between-group comparison of MVPA, sedentary behavior, physical function, psychological health, and QOL

	Allo-HSCT	**Auto-HSCT**	
Variables	Mean (SD)		p
Accelerometer wear time, minutes/day	903.2 ± 79.5	870.8 ± 97.7	0.254
MVPA, minutes/day	40.4 (32.8)	34.9 (26.5)	0.768
Sedentary behavior, minutes/day	539.1 (106.9)	526.7 (123.0)	0.739
Handgrip, kg	29.7 (9.5)	33.0 (8.9)	0.262
Knee extension force, kgf/kgw	0.53 (0.16)	0.58 (0.18)	0.460
6MWT, m	481.7 (60.7)	457.9 (73.4)	0.270
HADS			
Anxiety	3.2 (2.9)	3.9 (3.6)	0.521
Depression	4.3 (3.0)	5 (2.2)	0.264
EORTC QLQ C-30			
Global health status	78.9 (15.7)	69.1 (20.3)	0.208
Physical function	87.8 (14.5)	86.2 (12.5)	0.473
Role function	88.5 (22.4)	88.5 (17.7)	0.798
Emotional function	90.6 (13.1)	90.6 (11.4)	0.718
Cognitive function	82.9 (19.7)	85.8 (8.9)	0.838
Social function	87.2 (24.1)	89.7 (19.2)	0.977
Fatigue	27.7 (19.7)	27.8 (21.3)	0.898
Nausea/vomiting	2.8 (7.4)	0	0.161
Pain	15.3 (20.1)	16.6 (27.7)	0.738
Dyspnea	7.4 (19.4)	20.4 (20.8)	0.011*
Insomnia	14.7 (21.3)	10.2 (15.2)	0.571
Appetite loss	12.0 (19.5)	12.8 ± 20.8	0.955

MVPA, moderate-to-vigorous intensity physical activity; *6 MWT*, six minutes walking test; HADS, Hospital Anxiety and Depression Scale; *EORTC QLQ C-30*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30

*$p < 0.05$

	Allo-HSCT	Auto-HSCT	
Constipation	10.1 (17.2)	23 ± 30.3	0.164
Diarrhea	13.8 (21.2)	10.2 ± 15.2	0.692
Financial difficulties	19.4 (31.8)	12.7 ± 16.1	0.936

MVPA, moderate-to-vigorous intensity physical activity; *6 MWT*, six minutes walking test; HADS, Hospital Anxiety and Depression Scale; *EORTC QLQ C-30*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30

*$p < 0.05$

Table 3
Associations of MVAP and sedentary behavior with demographic and clinical characteristics, physical function, psychological health, and QOL in allo-HSCT survivors.

	MVPA		**sedentary behavior**	
Variables	correlation coefficient (*r*)	*p*	correlation coefficient (*r*)	*p*
Age	-0.194	0.099	0.400	0.016*
Height	-0.110	0.353	0.268	0.114
Body weight	-0.018	0.881	0.231	0.175
BMI	0.035	0.764	0.212	0.214
Highest education level	-0.047	0.733	0.084	0.626
Comorbidity	-0.051	0.707	0.211	0.217
Time elapsed from HSCT	0.166	0.156	-0.160	0.352
Handgrip	0.025	0.827	0.205	0.230
Knee extension force	0.035	0.764	0.269	0.112
6MWT	0.013	0.913	-0.16	0.927
HADS (anxiety)	0.084	0.490	-0.408	0.014*
HADS (depression)	-0.358	0.032*	0.071	0.680
EORTC QLQ-C30				
Global health status	0.053	0.667	0.075	0.665
Physical function	0.079	0.529	0.055	0.749
Role function	0.042	0.755	-0.171	0.319
Emotional function	-0.057	0.661	0.356	0.033
Cognitive function	0.079	0.544	0.110	0.521
Social function	-0.021	0.876	-0.106	0.539
Fatigue	-0.062	0.621	-0.301	0.075
Nausea/vomiting	0.022	0.873	-0.173	0.314

MVPA, moderate-to-vigorous intensity physical activity; BMI, body mass index; HSCT, hematopoietic stem cell transplantation; *6 MWT*, six minutes walking test; HADS, Hospital Anxiety and Depression Scale; *EORTC QLQ C-30*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30

*$p < 0.05$

	MVPA		sedentary behavior	
Pain	-0.066	0.615	0.018	0.919
Dyspnea	0.059	0.672	0.278	0.100
Insomnia	0.040	0.772	-0.277	0.102
Appetite loss	-0.226	0.099	0.327	0.052
Constipation	-0.112	0.419	0.025	0.886
Diarrhea	-0.177	0.202	0.165	0.355
Financial difficulties	-0.037	0.781	0.148	0.388

MVPA, moderate-to-vigorous intensity physical activity; BMI, body mass index; HSCT, hematopoietic stem cell transplantation; *6 MWT*, six minutes walking test; HADS, Hospital Anxiety and Depression Scale; *EORTC QLQ C-30*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30

*p < 0.05

Associations of MVAP and sedentary behavior with demographic and clinical characteristics, physical function, psychological health, and QOL among auto- and allo-HSCT survivors

Table 2 shows the associations of MVAP and sedentary behavior with demographic and clinical characteristics, physical function, psychological health, and QOL in allo-HSCT survivors. There was a negative correlation between MVPA and HADS (depression) in allo-HSCT survivors (r = -0.358, p = 0.032). Similarly, there was a negative correlation of sedentary behavior with HADS (anxiety) (r = -0.408, p = 0.014), age (r = 0.400, p = 0.016), and EORTC QLQ-C30 (emotion) (r = 0.356, p = 0.033) in allo-HSCT survivors. Contrastingly, MVPA and sedentary behavior were not associated with demographic and clinical characteristics as well as measurements in auto-HSCT survivors (results not shown). Stepwise multiple regression analysis revealed that age was a significant predictor of sedentary behavior (β = 0.400, p = 0.016, Table 4).

Table 4
Stepwise multiple regression analysis of predictive factors for sedentary behavior in allo-HSCT survivors

Variables	β	95%CI	*p*
Age	0.400	0.673–6.023	0.016*
HADS (anxiety)	-0.311	-22.828-0.201	0.054

CI, confidence interval; *HADS*, Hospital Anxiety and Depression Scale,

*p < 0.05

Discussion

This is the first study to compare objectively measured MVPA and sedentary behavior among auto- and allo-HSCT survivors. We observed no significant between-group differences in MVPA and sedentary behavior. Additionally, we found that depression and age were associated with MVPA and sedentary behavior, respectively, in allo-HSCT survivors. The lack of a between-group difference in MVPA and sedentary behavior could be attributed to the low prevalence of chronic GVHD among allo-HSCT survivors, as well as the lack of a between-group difference in the prevalence of complications. The cumulative incidence of chronic GVHD among allo-HSCT survivors was reported to be 47% [25]; additionally, the incidence of chronic GVHD at 2 years after allo-HSCT in Japan is 37% [26]. Furthermore, HSCT survivors with chronic GVHD have lower physical and social functioning than those without chronic GVHD [27]. Consistent with previous findings, physical function could decrease due to the effects of chronic GVHD and late complications, with an increase and decrease in sedentary behavior and MVPA, respectively. The incidence of chronic GVHD was 41.7%, which was consistent with previous findings; however, there was a low prevalence during the survey. In our study, the mean time elapsed after HSCT was approximately 4 years; moreover, the population was considered to have a low risk of developing chronic GVHD. Contrastingly, a previous study found that HSCT survivors with three or more late complications had reduced physical function, restricted daily activities, and decreased full-time employment compared with HSCT survivors without late complications [28]. The cumulative incidence of late complications without malignancies at 5 years after HSCT was 44.8% and 79% among auto- and allo-HSCT patients, respectively [28]. A previous study on chronic health disorders in survivors about 7 years after HSCT reported that the proportion of survivors with health disorders was 71% and 61% after allo-HSCT and auto-HSCT, respectively. Moreover, allo-HSCT survivors had a significantly higher rate of health problems than auto-HSCT survivors [29]. In our study, the proportion of complications, including late complications, was 38.5% and 41.7% among auto- and allo-HSCT survivors, respectively, with no significant between-group difference in the proportion of comorbidities.

We observed a negative correlation between MVPA and depression in allo-HSCT survivors. Similarly, previous studies on breast and colorectal cancer survivors reported a negative correlation between MVPA and depression [30, 31]. Additionally, approximately 15% of auto- and allo-HSCT survivors have moderate-to-severe depression [32]. Depression is associated with the severity of chronic GVHD in allo-HSCT survivors [33]. Therefore, it is important to examine for depression in the long-term follow-up of HSCT survivors. Depression should be considered when applying interventions for promoting MVPA in HSCT survivors who have returned to daily activities and work. Age was significantly associated with sedentary behavior in allo-HSCT survivors. Previous studies on cancer survivors have reported a positive correlation between age and sedentary behavior [34, 35]. Similarly, a previous study on healthy adults reported that sedentary behavior tended to increase with age [36]. This suggests that age should be considered when developing effective interventions for reducing sedentary behavior.

This study has several limitations. First, the sample size was small; specifically, there was a small number of auto-HSCT survivors. The small number of auto-HSCT survivors could be attributed to some

auto-HSCT survivors being classified as recurrent or intractable cases. Second, there was a large variation in the time elapsed after HSCT. This is because this was a cross-sectional study and there was no opportunity for outpatient visits during this study period given the decreased frequency of outpatient visits upon stabilization of medical conditions after a long period following HSCT. Third, although we used the accelerometer to objectively measure physical activity, it cannot detect non-walking physical activity (e.g., swimming and cycling), which may have affected the results. However, in Japan, where medical fees are not granted for outpatient rehabilitation after HSCT, our findings may facilitate the introduction of outpatient rehabilitation after HSCT.

In conclusion, we observed no significant between-group differences in MVPA and sedentary behavior. Our results suggest that it may be unnecessary to change the rehabilitation program according to the donor type in interventions for promoting MVPA and reducing sedentary behavior in long-term survivors of HSCT.

Declarations

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Competing interest: The authors declare that they have no conflicts of interest.

Authors' contributions: TN, the corresponding author, designed the study and prepared the draft of manuscript. YT, designed the study and revised the draft of the manuscript. JS, revised the draft of the manuscript. KN recruited the patients, collected clinical data and revised the draft of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material: All data generated or analysed during this study are included in this article.
Code availability: Not applicable

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Figures

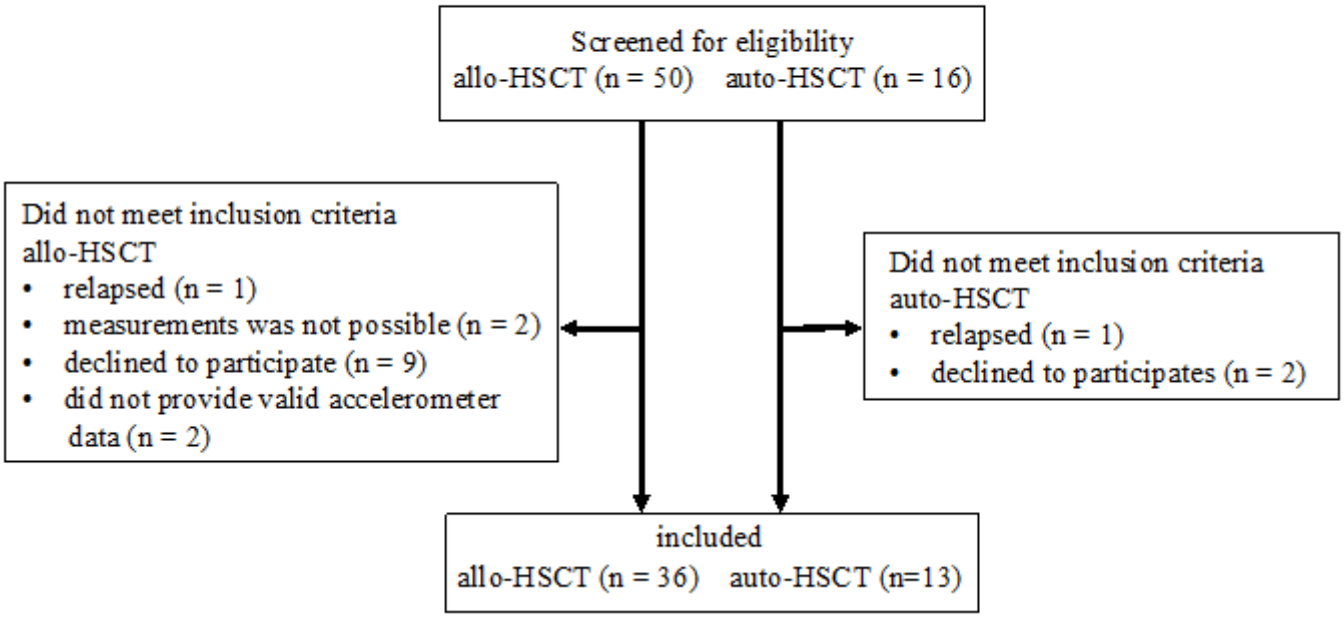

Figure 1

Study flow diagram.