Gait Analysis of Patients After Allogeneic Hematopoietic Cell Transplantation Reveals Impairments of Functional Performance

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Abstract
Background: After allogeneic hematopoietic cell transplantation (alloHCT), patients often report functional impairments like reduced gait speed and muscle weakness. These impairments can increase the risk of adverse health events similar to elderly populations. However, they have not been quantified in patients after alloHCT (PATs). Methods: We compared fear of falling (Falls Efficacy Scale–International) and temporal gait parameters recorded on a 10-m walkway at preferred and maximum gait speed and under dual-task walking of 16 PATs (aged 31-73 years) with 15 age-matched control participants (CONs) and 17 seniors (SEns, aged >73 years). Results: Groups’ gait parameters especially differed during the maximum speed condition: PATs walked slower and required more steps/10 m than CONs. PATs exhibited greater stride, stance, and swing times than CONs. PATs’ swing time was even longer than SENs’. The PATs’ ability to accelerate their gait speed from preferred to fast was smaller compared with CONs’. PATs reported a greater fear of falling than CONs and SENs. Conclusion: Gait analysis of alloHCT patients has revealed impairments of functional performance. Patients presented a diminished ability to accelerate gait and extending steps possibly related to a notable strength deficit that impairs power-generation abilities from lower extremities. Furthermore, patients reported a greater fear of falling than control participants and even seniors. Slowing locomotion could be a risk-preventative safety strategy. Since functional disadvantages may put alloHCT patients at a higher risk of frailty, reinforcing appropriate physical exercises already during and after alloHCT could prevent adverse health events and reduce the risk of premature functional aging.

Keywords
gait analysis, fast gait speed, fear of falling, allogeneic hematopoietic cell transplantation, cancer survivors, functional impairment

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Background
Allogeneic hematopoietic cell transplantation (alloHCT) is the most intensive treatment known for patients with hematological malignancies. It is associated with diverse procedure- and therapy-induced side effects that can limit patients’ physical and psychological functioning considerably.1,2 Patients often experience significant weight loss and a change in body composition during hospitalization,3,4 particularly muscle mass loss, resulting in substantial physical deconditioning.5,7 In addition, neurotoxic medications can compromise neuromuscular output and thus functional performance.5 Furthermore, chronic graft-versus-host disease is even known to worsen patients’ functional status.2,6 All aforementioned factors substantially increase alloHCT survivors’ frailty risk.10 This is known to be strongly

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associated with elevated risk of injury or even mortality. Despite rehabilitation programs, many patients complain about functional impairments like slowed gait speed or muscle weakness affecting their daily life and participation even in the long term. However, these reports relied on patient-reported outcomes rather than objective measures. Considering that physical function presents an acknowledged prognostic factor for the mortality of cancer survivors, it would seem worthwhile to characterize those functional impairments in greater detail. An essential everyday task of the neuromuscular and cardiopulmonary systems. Moreover, a slower preferred or maximum gait speed may predict disability and even mortality. Analizing spatiotemporal gait parameters under different walking conditions (at preferred or maximum gait speed, under dual-tasking) additionally enables to infer power-generation abilities and gait stability. Assessing variability in spatiotemporal gait parameters may suggest gait instability that is associated with a higher risk of falling. The prevalence of frailty among young alloHCT survivors corresponds to that in the elderly. We know that anticancer therapies induce degradation processes resembling normal aging mechanisms in an intensity-dependent relation: for example, patients with hematological malignancies are at particular risk for sarcopenia due to high-intensity treatment, that is, a significant loss of muscle mass and function particularly characteristic of the elderly population.

The aim of this study was to analyze alloHCT patients’ gait under 3 conditions, that is, at preferred and maximum gait speed and under dual-task walking. Preferred gait speed is a reliable sign of vitality. Maximum gait speed is known to predict disability, while the concurrent execution of a cognitive task while walking has been shown to enhance gait variability, especially in older compared with younger adults. To quantify potential functional deficits, we compared patients’ gait parameters with a group of age-matched healthy participants and normative values. We additionally aimed at comparing alloHCT patients’ gait with a group of seniors to classify potential functional deteriorations. We hypothesized that, when compared with healthy control participants, alloHCT patients would display gait alterations similar to those characteristic of seniors. It is essential to identify the relevant functional disadvantages to promote improved and effective intervention strategies to reduce the risk for disability and adverse health events.

Methods

Study Design

We applied a 3-armed cross-sectional pilot study to evaluate gait differences between cancer patients after alloHCT (PATs), matched healthy control participants (CONs), and seniors (SENs).

Ethics

Our study was approved by the Ethics Committee of the University of Freiburg (102/12_140596), conducted according to the Declaration of Helsinki, and registered in the German Register of Clinical Trials.

Participants

We recruited 16 patients at the rehabilitation center Clinic of Tumorbiology, Freiburg, Germany, and 15 CONs. We also recruited 17 SENs who regularly perform moderate physical activity at a local sports club, Freiburg. Inclusion criteria for all groups were written informed consent and >18 years of age; for PATs, being after alloHCT (that is, after hospitalization due to alloHCT procedure) and currently during inpatient rehabilitation treatment including standard sports- and physiotherapy; for CONs, matched to patients’ age, sex, weight, and height; for SENs, >70 years of age. Exclusion criteria for all groups were any neurodegenerative diseases and painful orthopedic problems, and for CONs and SENs, any cancer within the past year.

Setup and Measurements

All participants underwent detailed anamnesis including comorbidities, investigation of vibration sense, and fear of falling (Table 1). Subsequently, all participants underwent gait analysis under 3 conditions.

Vibration sense was determined on the first metacarpophalangeal joint, knuckle, and patella via the Rydel-Seiffer tuning fork with a graduating scale from 0 (no sensitivity) to 8 (highest sensitivity).

Fear of falling was evaluated by the Falls Efficacy Scale–International (FES-I), scored from 16 (no concern about falling) to 64 (very concerned about falling), showing high internal reliability and high test-retest reliability.

For gait analysis, we used the wireless insole sensor-based gait analysis system OpenGo (Moticon ReGo AG, Munich, Germany) that has been shown to be valid and reliable for the measurement of temporal gait parameters during walking. We recorded temporal gait parameters during 3 walking conditions on a 10-m walkway: (1) walking at preferred gait speed, (2) walking at maximum gait speed (fast condition: walking as fast as possible without running, meaning one or both feet always have ground contact), (3) walking at preferred gait speed while counting from 50 backward in steps of 2 (dual-task condition). Participants walked wearing their own footwear (comfortable, closed, without heels), starting 2 m before and terminating their walk at least 2 m past the 10-m walkway.
Our analysis system consists of ultrathin and flexible insoles of different sizes fitting various shoe sizes. Each insole integrates 13 capacitive pressure sensors recording at a 50-Hz sampling rate. Sensor data were downloaded for further processing. Additionally, participants were filmed while walking, and the recorded videos were synchronized with sensor data. The analysis software Beaker (Moticon ReGo AG) illustrated time-dependent ground reaction forces for each insole and displayed synchronized videos.

**Data Processing**

A custom software written in Python programming language was used to reliably identify the initial (foot-strikes) and last contacts (foot-offs) of every footfall from our gait data (see Figure 1A). Data acquired from 1 sole and 1 measurement are considered 1 data set. Each data set was analyzed independently.

To detect steps, the force values from all sensors of each sole were added together for each time point. This 1-dimensional data set (force over time) was then smoothened using a Gaussian filter of width (ie, standard deviation) $0.033 \times$ sampling rate (Hz). From the smoothened data, we identified steps via the argrelmin(. . .) function from the Scipy signal library. These minima represent the time points when the foot is lifted between 2 steps. In this analysis, 1 step is considered as the initiation of the lifted state, making a foot-strike, then taking the foot-off, and then back to the lifted

![Table 1. Patient Characteristics.](image-url)

| Variable                        | PATs (n = 16), Median (IQR) | CONs (n = 15), Median (IQR) | SENs (n = 17), Median (IQR) | P |
|----------------------------------|-----------------------------|-----------------------------|-----------------------------|---|
| Male:female (n)                  | 8:8                         | 7:8                         | 11:6                        |   |
| Age (years)                      | 56 (52-61)                  | 58 (49-62)                  | 76 (75-79) $^a$             | .000 |
| Height (cm)                      | 176 (170-182)               | 173 (168-179)               | 170 (166-177)               | NS |
| Weight (kg)                      | 83 (63-89)                  | 78 (64-90)                  | 79 (65-83)                  | NS |
| BMI (kg/m$^2$)                   | 25 (21-29)                  | 25 (22-28)                  | 27 (23-30)                  | NS |
| FES-I (points 16-64)             | 21 (18-34)                  | 16 (16-17) $^a$             | 17 (16-17) $^a$             | .001 |
| Vibration sense (score 0-8)      |                            |                            |                            |   |
| Metatarsophalangeal              | 6.2 (5.2-6.5)               | 6.5 (5.8-6.9)               | 5.8 (3.1-7.2)               | NS |
| Ankle                            | 6.0 (4.8-6.2)               | 6.4 (5.8-6.9)               | 5.8 (1.8-6.6)               | NS |
| Patella                          | 6.3 (5.3-6.7)               | 6.8 (6.3-7.0)               | 6.1 (3.1-6.9)               | NS |
| Comorbidities, n (%)             |                            |                            |                            |   |
| Orthopedic:                      |                            |                            |                            |   |
| Lower extremities                | 4 (25)                      | 2 (14)                      | 9 (53)                      |   |
| Spine                            | 2 (13)                      | 0 (0)                       | 2 (12)                      |   |
| Polyneuropathy                   | 4 (25)                      | 0 (0)                       | 0 (0)                       |   |
| Stroke                           | 0 (0)                       | 0 (0)                       | 2 (12)                      |   |
| Seizures                         | 1 (6)                       | 0 (0)                       | 0 (0)                       |   |
| Heart disease                    | 3 (19)                      | 0 (0)                       | 8 (47)                      | NS |
| PAOD                             | 1 (6)                       | 0 (0)                       | 0 (0)                       |   |
| Pulmonary disease $^b$           | 1 (6)                       | 1 (7)                       | 1 (6)                       |   |
| Diabetes mellitus                | 1 (6)                       | 0 (0)                       | 0 (0)                       |   |
| Neurotoxic agents $^c$ (n)       | 2.0 (1.0-2.8)               |                            |                            |   |
| Weeks after alloHCT              | 30.9 (11.5-61.1)            |                            |                            |   |
| GvHD grade, n (%)                |                            |                            |                            |   |
| 0                                | 5 (31)                      |                            |                            |   |
| II                               | 7 (44)                      |                            |                            |   |
| III                              | 4 (25)                      |                            |                            |   |
| Corticosteroid therapy $^c$, n (%)|                            |                            |                            |   |
| Pre alloHCT                      | 16 (100)                    |                            |                            |   |
| Post alloHCT                     | 5 (31)                      |                            |                            |   |
| Ongoing                          | 7 (44)                      |                            |                            |   |

Abbreviations: PAT, patients; IQR, interquartile range; CON, control participants; SEN, seniors; NS, not significant; BMI, body mass index; FES-I, Falls Efficacy Scale–International; PAOD, peripheral arterial occlusive disease; alloHCT, allogeneic hematopoietic cell transplantation; GvHD, graft-versus-host disease.

$^a$Indicate a significant difference to PAT.

$^b$Chronic obstructive pulmonary disease, asthma, pulmonary embolism.

$^c$Received within the alloHCT schedule.
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state. Additionally, heuristics were applied to reduce the probability of erroneous step detection.

To precisely differentiate the foot-strikes and foot-offs from the steps, we conducted the following analysis for each step: the smoothened data were linearly interpolated by a factor of 60. An individual threshold was defined at 15% from its lowest to highest load value for each interpolated step. The time points where the data passed above and below this threshold were defined as the foot-strike and foot-off, respectively. The consistency of the foot-strikes and foot-offs was checked for a pair of data sets (left and right foot) by verifying their order: foot-strike left, foot-off right, foot-strike right, foot-off left, and so forth repetitively (except at the beginning and end of the data set). Foot-strikes with missing corresponding foot-offs at the end of the measurement were ignored. The same was done for foot-offs with missing corresponding foot-strikes at the beginning of the measurement.

The step count was accumulated from the detected foot-strikes and foot-offs, and temporal gait parameters gait speed (m/s), cadence (steps/min), stride time (seconds), stance time (seconds), and swing time (seconds) were calculated subsequently. We also calculated the mean value, standard deviation (SD), and coefficients of variation (CV as SD/mean × 100) of each of these parameters (except gait speed and cadence) for each pair of data sets. Furthermore, the relative increase (%) from preferred to maximum gait speed was computed.

Velocity-dependent parameters, that is, step count, cadence, stride, stance, and swing time, were normalized to the gait speed of the appropriate walking condition for statistical analysis.

Statistics

Differences between groups were assessed by nonparametric analysis (Kruskal-Wallis analysis of variance) as the assumption of normal distribution (Shapiro-Wilk test) was not satisfied. The level of significance was set to \( P = .05 \). \( P \) values of post hoc comparisons were corrected by the Bonferroni’s procedure. Bivariate correlations were calculated according to Spearman \( \rho \) to display the relationship between gait parameters and fear of falling. All statistical analyses were conducted using IBM SPSS Version 22 software (SPSS Inc, Chicago, IL). Group data are presented as median and interquartile range (Table 2).

Graphics were created by using Prism 5 Version 5.03 (GraphPad Software, Inc, La Jolla, CA).

Results

The comparative groups PATs and age-matched CONs exhibited similar anthropometric parameters. Vibration sense did not differ between groups. Concerning FES-I, PATs reported
a significantly greater fear of falling than CONs and SENs (Table 1).

We analyzed 130 out of 141 pairs of data sets (Table 2) due to failures during recording via the soles.

### Preferred Gait Speed

All groups displayed a similar preferred gait speed and step count within the 10-m walkway. Furthermore, all temporal gait parameters were similar in all groups (Table 2).

### Fast Condition

The fast condition (Table 2) revealed greater group difference than walking at preferred gait speed (see Figure 1B). Gait speed and step count differed significantly between PATs and CONs: PATs walked slower and needed more steps to walk 10 m than CONs. PATs revealed the largest temporal gait parameters versus CONs (stride time, stance time, and swing time) and even SENs (swing time). Groups did not differ in their gait variability.

### Table 2. Gait Parameters of Patients After alloHCT (PATs), Matched Healthy Control Participants (CONs), and Seniors (SENs)*.

| Trial          | Parameter                          | PATs, Median (IQR) | CONs, Median (IQR) | SENs, Median (IQR) | Correlation ($r$)* Between Gait Parameters and FES-I |
|---------------|------------------------------------|--------------------|--------------------|--------------------|-----------------------------------------------------|
|               | n = 14                             | n = 12             | n = 16             | P                  | n = 43                                              |
| Preferred     | Gait speed (m/s)                    | 1.16 (1.03-1.27)   | 1.16 (1.11-1.50)   | 1.20 (1.10-1.30)   | ns                                                  | −.257                                              |
|               | Cadence (step/min)*                 | 103.1 (96.5-109.2) | 104.9 (97.2-110.7) | 109.0 (101.5-113.3)| ns                                                  | −.155                                              |
|               | Steps (n/10 m)*                     | 15.0 (14.0-16.0)   | 14.5 (13.0-15.0)   | 15.0 (14.0-15.8)   | ns                                                  | .301                                               |
|               | Stride time (seconds)*              | 1.14 (1.10-1.22)   | 1.12 (1.06-1.20)   | 1.09 (1.03-1.14)   | ns                                                  | .163                                               |
|               | Stance time (seconds)*              | 0.73 (0.70-0.77)   | 0.71 (0.68-0.76)   | 0.70 (0.67-0.76)   | ns                                                  | .146                                               |
|               | Swing time (seconds)*               | 0.41 (0.40-0.45)   | 0.42 (0.37-0.43)   | 0.38 (0.36-0.41)   | ns                                                  | .165                                               |
|               | Stride time (%CV)                   | 1.81 (1.34-2.12)   | 1.63 (1.40-1.81)   | 1.84 (1.55-2.61)   | ns                                                  | .151                                               |
|               | Stance time (%CV)                   | 2.04 (1.78-3.79)   | 2.60 (2.03-3.19)   | 2.71 (2.07-3.36)   | ns                                                  | .150                                               |
|               | Swing time (%CV)                    | 3.39 (3.27-5.63)   | 3.25 (2.77-4.57)   | 4.09 (3.27-5.37)   | ns                                                  | .073                                               |
|               | Gait speed increase (%)             | 31.2 (24.07-51.0)  | 57.1 (37.3-88.0)   | 51.5 (42.3-67.3)   | ns                                                  | −.423**                                             |
| Fast          | Gait speed (m/s)                    | 1.54 (1.35-1.84)   | 1.88 (1.76-2.37)   | 1.78 (1.57-2.05)   | .010                                                | −.514**                                             |
|               | Cadence (step/min)*                 | 121.1 (111.5-129.7)| 135.2 (124.7-154.9)| 131.9 (123.9-138.0)| ns                                                  | −.332**                                             |
|               | Steps (n/10 m)*                     | 12.0 (12.0-14.0)   | 11.0 (10.0-12.0)   | 12.0 (11.0-13.0)   | .018                                                | .588**                                              |
|               | Stride time (seconds)*              | 0.97 (0.91-1.05)   | 0.87 (0.76-0.93)   | 0.88 (0.85-0.94)   | .004                                                | .370*                                               |
|               | Stance time (seconds)*              | 0.61 (0.58-0.66)   | 0.54 (0.48-0.60)   | 0.58 (0.54-0.60)   | .004                                                | .371*                                               |
|               | Swing time (seconds)*               | 0.36 (0.34-0.38)   | 0.33 (0.29-0.34)   | 0.33 (0.30-0.35)   | .005                                                | .325*                                               |
|               | Stride time (%CV)                   | 1.84 (1.21-2.25)   | 1.63 (1.45-2.30)   | 1.86 (1.43-2.48)   | ns                                                  | .064                                               |
|               | Stance time (%CV)                   | 2.10 (1.78-2.82)   | 2.85 (2.10-3.19)   | 2.82 (2.41-4.06)   | ns                                                  | −.174                                              |
|               | Swing time (%CV)                    | 3.82 (2.91-4.64)   | 4.11 (2.39-4.85)   | 4.51 (3.36-6.10)   | ns                                                  | .008                                               |
| Dual task     | Gait speed (m/s)                    | 1.12 (0.93-1.29)   | 1.37 (1.23-1.61)   | 1.29 (1.05-1.50)   | .039                                                | −.504**                                             |
|               | Cadence (step/min)*                 | 104.4 (86.5-106.5) | 109.4 (98.9-114.7) | 113.7 (100.4-117.3)| ns                                                  | −.339*                                              |
|               | Steps (n/10 m)*                     | 15.0 (13.0-16.0)   | 13.0 (12.0-14.0)   | 13.0 (13.0-15.0)   | ns                                                  | .431**                                              |
|               | Stride time (seconds)*              | 1.14 (1.10-1.36)   | 1.07 (1.02-1.18)   | 1.03 (1.00-1.18)   | ns                                                  | .345*                                               |
|               | Stance time (seconds)*              | 0.72 (0.70-0.84)   | 0.68 (0.63-0.74)   | 0.66 (0.64-0.74)   | ns                                                  | .331*                                               |
|               | Swing time (seconds)*               | 0.42 (0.39-0.53)   | 0.40 (0.37-0.43)   | 0.38 (0.36-0.45)   | ns                                                  | .301                                               |
|               | Stride time (%CV)                   | 2.45 (2.08-3.44)   | 2.56 (1.25-4.54)   | 2.30 (1.85-4.25)   | ns                                                  | .069                                               |
|               | Stance time (%CV)                   | 3.63 (2.56-4.31)   | 3.15 (2.19-4.75)   | 3.57 (2.92-4.63)   | ns                                                  | .064                                               |
|               | Swing time (%CV)                    | 4.88 (3.66-6.14)   | 3.59 (3.07-7.04)   | 4.88 (3.90-6.44)   | ns                                                  | .212                                               |

*The parameters cadence, steps, stride, stance, and swing time have been normalized to gait speed of the appropriate walking condition for statistical analysis. $P$ values refer to differences of the normalized data.

**Spearman $\rho$.

*Indicate a significant difference to PAT.

**$P < .05$; ***$P < .01$. 

Abbreviations: IQR, interquartile range; $r$, correlation coefficient; FES-I, Falls Efficacy Scale–International; ns, not significant; CV, coefficient of variation.

Table 2. Gait Parameters of Patients After alloHCT (PATs), Matched Healthy Control Participants (CONs), and Seniors (SENs)*.
Furthermore, the CONs’ ability to accelerate their gait speed from preferred to fast was significantly greater compared with PATs (Table 1).

**Dual-Task Condition**

As with fast walking, during the dual-task condition (Table 2), PATs walked significantly slower than CONs. All the other temporal parameters and their variability did not differ between groups.

Correlations (Table 2) between gait parameters and reported fear of falling revealed no relationship between FES-I results and gait parameters at the preferred gait speed. However, during the fast and dual-task condition, we detected negative correlations for gait speed and cadence. The level of FES-I also correlated with step count, stride time, stance time, and swing time (only fast condition). Furthermore, we observed a negative relationship between FES-I level and the ability to increase gait speed.

**Discussion**

The present study first quantifies alloHCT patients’ gait abilities in comparison to a group of CONs and SENs. It was this study’s aim to quantify the functional deficits that may exacerbate alloHCT patients’ risk for adverse health events. Our comparison to healthy participants revealed significant differences in maximum gait speed: patients walked more slowly and took shorter steps than control participants. Furthermore, the patients’ fast gait performance more closely resembled that of seniors than of control participants. This analogy may reveal comparable alterations in joint work due to degradation processes induced by patients’ treatment or aging, respectively. These processes may result in similar compensation strategies for avoiding risk, for example, falls and injuries.

Assessing gait speed is an acknowledged method to predict health risks in terms of disability, falls, or mortality. In particular, a preferred gait speed slower than 0.8 m/s indicates a higher risk for falls, immobility, and early mortality. None of our participants walked slower than 0.8 m/s under any of the 3 test conditions. Regarding preferred gait speed, we detected no relevant group differences. The patients’ and, surprisingly, the control participants’ preferred gait speed (median 1.16 m/s) lay at the lower end of normative values (1.10-1.39 m/s). However, control participants presented a greater interquartile range than patients (0.39 m/s vs 0.24 m/s). The patients’ range was rather similar to the gait speed of individuals aged 20 years and older. Surprisingly, our seniors walked even faster than control participants, as their preferred gait speed (median 1.20 m/s) lay at the upper end of their normal age-adjusted range (1.12-1.22 m/s), assuming a healthy aging process. However, note that the seniors included in this study were physically active. Concerning the fast condition, the maximum gait speed of the control group (median = 1.88 m/s) and of seniors (median = 1.78 m/s) corresponded to reference values. In contrast, our patients walked significantly slower (median = 1.54 m/s) and took more steps, indicating shorter step length, than age-matched control participants. Furthermore, our patients exhibited longer temporal parameters, that is, stride, stance, and swing time, during fast walking. Slowing gait could be a safety strategy to compensate for reductions in muscle strength and function. Vice versa, deficits of neuromuscular function might inhibit patients’ ability to increase their gait speed to an age-appropriate maximum level.

The main differences between groups occurred during the fast walking condition. Patients did not reach the maximum speed level of control participants, which might be a result of reduced power-generation abilities. In general, walking faster requires altered joint kinetics to accelerate the body’s propulsion. Degeneration processes such as aging can modify this alteration: for example, an age-associated strength decrease may lead to a distal-to-proximal (ankle to hip) shift of joint work that can affect locomotor ability. Naturally, the neuromuscular system’s aging implies a continuous functional decline caused by time-dependent, accumulated cellular damage that results in age-related loss of muscle mass and function. This loss is strongly related to physical disability, functional impairments, and even mortality, whereby the loss of strength contributes proportionally more to predicting disability than does muscle mass. Impairment of functional performance is also prevalent in cancer survivors, depending on treatment intensity rather than age, which is why alloHCT patients carry a particularly high risk for being affected.

Generally, anticancer treatment induces degradation processes that can impair functional performance and increase the risk for premature aging. Furthermore, the lengthy therapies combined with long periods of hospitalization that often accompany alloHCT cause inactivity extending to immobility. There is ample evidence that long-term bedrest or inactivity promotes muscle mass loss, especially in the lower body’s weight-bearing, anti-gravity muscles—the more distal, the more pronounced. This degradation process can lead to considerable functional consequences. Concerning alloHCT, our patients might not have recovered from the physical decline they experienced during alloHCT, even when some of their alloHCTs dated back several months. We assume that a disease- and therapy-related change in body composition, that is, muscle mass loss, plus inactivity have impaired neuromuscular function and resulted in weaker lower body muscle strength and power output. These factors have thus quantifiably limited patients’ maximum gait speed and step length. As mentioned above, slowing locomotion can be interpreted as a risk-preventive
safety strategy, which may reflect patients’ greater fear of falling. Considering that functional impairments limit autonomy, raise the risk of adverse health events, and are associated with shorter survival in cancer survivors, improving patients’ physical capacity should be a key objective in their long-term rehabilitation. It is well known that even weak patients or frail old people can substantially enhance their physical function when they do specific exercises.

The dual-task condition revealed only group differences in gait speed as patients walked slower than control participants. Performing a cognitive task while walking may interfere with the cognitive resources needed to establish a regular gait pattern. Wide gait variability, especially under the dual-task condition, may indicate cognitive impairments, as the tasks compete with each other by challenging the cognitive system. Since our patient group did not differ from control participants and seniors, particularly in their gait variability, we assume that the alloHCT procedure did not lead to persistent considerable cognitive impairments. However, neurocognitive dysfunctions after alloHCT are known, and considering that the age of alloHCT recipients is rising, we propose focusing especially on these factors when investigating older patients. Furthermore, spatial gait parameter analyses could yield additional information about step width, a relevant parameter for interpreting gait stability. The analysis system we applied could only record temporal parameters, but the flexible and mobile use of wireless sensor–based insoles is a comfortable means of assessing gait under field conditions, for example, on an irregular surface.

Limitations and Future Perspectives
Our study implies some methodological limitations. As discussed above, the analysis system could not cover all gait dimensions. Furthermore, the seniors’ group presented a relative high performance level, patients were at various phases after alloHCT procedure, and sample size was small. For future work, a greater sample size would allow subgroup analysis in order to attribute functional deficits to specific alloHCT-related side effects. Furthermore, the comparative groups, that is, healthy control participants or seniors, should be representative for their age-appropriate cohort, and the patients’ group should be more homogeneous. Moreover, a longitudinal approach would reveal intervention effects on gait abilities of alloHCT patients and provide greater information about underlying adaptation mechanisms relevant for patients’ functional status. We propose including an exercise intervention and a long-term follow-up to detect adverse health events, as well as further physical performance tests and patient-reported outcomes in a randomized controlled trial.

Conclusions
The present study revealed functional deficits of alloHCT patients via gait analysis. While patients’ performance at preferred gait speed lay in the range of normative values, their ability to accelerate gait and extending steps was diminished. Furthermore, patients reported a greater fear of falling than control participants and even seniors. Thus, slowing locomotion could be a risk-preventive safety strategy. Furthermore, we assume that patients suffer from a notable strength deficit that may impair their power-generation abilities from lower extremities. These functional disadvantages may put alloHCT patients at a higher risk of frailty. We, therefore, strongly recommend that appropriate physical exercises be routinely integrated already during hospitalization and that the physical rehabilitation of alloHCT patients be reinforced with the goal of minimizing functional impairments and thus health risks over the long term.

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Authors’ Note
The data that support the findings of this study are available from the corresponding author on reasonable request.

Author Contributions
SK and AW designed the study and supervised the measurements. SK provided assistance in data analysis, interpreted the data, and drafted the manuscript. ES and IDW recruited participants, collected and analyzed data, and participated in data interpretation. PvO wrote the software for data processing and drafted the manuscript. AW participated in data interpretation. AG and HB participated in the study’s design and revised the manuscript. HB prepared patients’ medical history. All authors made contributions to the article, are in agreement with the content, and have read the final manuscript.

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References
1. Baker KS, Ness KK, Weisdorf D, et al. Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. Leukemia. 2010;24:2039-2047. doi:10.1038/leu.2010.210
2. Smith SR, Haig AJ, Couriel DR. Musculoskeletal, neurological, and cardiopulmonary aspects of physical rehabilitation in patients with chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2015;21:799-808. doi:10.1016/j.bbt.2014.10.019
3. Iestra JA, Fibbe WE, Zwinderman AH, van Staveren WA, Kromhout D. Body weight recovery, eating difficulties and compliance with dietary advice in the first year after stem cell transplantation: a prospective study. Bone Marrow Transplant. 2002;29:417-424.
4. Kyle UG, Chalandon Y, Miralbell R, et al. Aerobic exercise for adult patients with haematological malignancies. Cochrane Database Syst Rev. 2014;(11):CD009075. doi:10.1002/14651858.CD009075.pub2
5. Lee HJ, Oran B, Saliba RM, et al. Steroid myopathy in patients with acute graft-versus-host disease treated with high-dose steroid therapy. Bone Marrow Transplant. 2006;38:299-303. doi:10.1038/sj.bmt.1705435
6. Morishita S, Kaida K, Yamauchi S, et al. Relationship between corticosteroid dose and declines in physical function among allogeneic hematopoietic stem cell transplantation patients. Support Care Cancer. 2013;21:2161-2169. doi:10.1007/s00520-013-1778-7
7. Morishita S, Kaida K, Yamauchi S, et al. Relationship between corticosteroid dose and declines in physical function among allogeneic hematopoietic stem cell transplantation patients. Support Care Cancer. 2013;21:2161-2169. doi:10.1007/s00520-013-1778-7
8. Barba P, Piñana JL, Valcárcel D, et al. Early and late neurological complications after reduced-intensity conditioning allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2009;15:1439-1446.
9. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. Blood. 2006;108:2867-2873. doi:10.1182/blood-2006-02-03954
10. Arora M, Sun CL, Ness KK, et al. Physiologic frailty in nonelderly hematopoietic cell transplantation patients: results from the Bone Marrow Transplant Survivor Study. JAMA Oncol. 2016;2:1277-1286. doi:10.1001/jamaoncol.2016.0855
11. Khera N, Storer B, Flowers MED, et al. Nonmalignant late effects and compromised functional status in survivors of hematopoietic cell transplantation. J Clin Oncol. 2012;30:71-77. doi:10.1200/JCO.2011.38.4594
12. Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. Br J Cancer. 2015;112:194-198. doi:10.1038/bjc.2014.568
13. Liu MA, DuMontier C, Murillo A, et al. Gait speed, grip strength, and clinical outcomes in older patients with hematologic malignancies. Blood. 2019;134:374-382. doi:10.1182/blood.2019000758
14. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA. 2011;305:50-58. doi:10.1001/jama.2010.1923
15. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. J Gerontol A Biol Sci Med Sci. 2013;68:39-46. doi:10.1093/gerona/gls174
16. Cesari M, Kritchevsky SB, Newman AB, et al. Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. J Am Geriatr Soc. 2009;57:251-259. doi:10.1111/j.1532-5415.2008.02126.x
17. Cesari M, Cerullo F, Zamboni V, et al. Functional status and mortality in older women with gynecological cancer. J Gerontol A Biol Sci Med Sci. 2013;68:1129-1133. doi:10.1093/gerona/glt073
18. Artaud F, Singh-Manoux A, Dugravot A, Tzourio C, Elbaz A. Decline in fast gait speed as a predictor of disability in older adults. J Am Geriatr Soc. 2015;63:1129-1136. doi:10.1111/jgs.13442
19. Kressig RW, Beauchet O; European GAITRite Network Group. Guidelines for clinical applications of spatio-temporal gait analysis in older adults. Aging Clin Exp Res. 2006;18:174-176.
20. Hollman JH, McDade EM, Petersen RC. Normative spatiotemporal gait parameters in older adults. Gait Posture. 2011;34:111-118. doi:10.1016/j.gaitpost.2011.03.024
21. Hausdorf JM, Edelberg HK, Mitchell SL, Goldberger AL, Wei JY. Increased gait unsteadiness in community-dwelling elderly fallers. Arch Phys Med Rehabil. 1997;78:278-283.
22. HausdorfFJM. Gait variability: methods, modeling and meaning. J Neuroengineering Rehabil. 2005;2:19. doi:10.1186/1743-0003-2-19
23. Hamacher D, Singh NB, Van Dieën JH, Heller MO, Taylor WR. Kinematic measures for assessing gait stability in elderly individuals: a systematic review. J R Soc Interface. 2011;8:1682-1698. doi:10.1098/rsif.2011.0416
24. Cupit-Link MC, Kirkland JL, Ness KK, et al. Biology of premature ageing in survivors of cancer. ESMO Open. 2017;2:e000250. doi:10.1136/esmoopen-2017-000250
25. Rier HN, Jager A, Meinardi MC, et al. Severe sarcopenia might be associated with a decline of physical independence in older patients undergoing chemotherapeutic treatment. Support Care Cancer. 2018;26:1781-1789. doi:10.1007/s00520-017-4018-8
26. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: report of the
European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39:412-423. doi:10.1093/ageing/afq034
27. Fritz S, Lasardi M. White paper: “walking speed: the sixth vital sign.” *J Geriatr Phys Ther*. 2009;32:46-49.
28. Beauchet O, Dubost V, Herrmann FR, Kressig RW. Stride-to-stride variability while backward counting among healthy young adults. *J Neuroengineering Rehabil*. 2005;2:26. doi: 10.1186/1743-0003-2-26
29. Hollman JH, Kovash FM, Kubik JJ, Linbo RA. Age-related differences in spatiotemporal markers of gait stability during dual task walking. *Gait Posture*. 2007;26:113-119. doi:10.1016/j.gaitpost.2006.08.005
30. Granacher U, Bridenbaugh SA, Muehlbauer T, Wehrle A, Kressig RW. Age-related effects on postural control under multi-task conditions. *Gerontology*. 2011;57:247-255. doi: 10.1159/000322196
31. Yardley L, Beyer N, Hauer K, Kempen G, Piotz-Ziegler C, Todd C. Development and initial validation of the Falls Efficacy Scale–International (FES-I). *Age Ageing*. 2005;34:614-619. doi:10.1093/ageing/afi196
32. Dias N, Kempen GJM, Todd CJ, et al. The German version of the Falls Efficacy Scale–International Version (FES-I) [in German]. *Z Gerontol Geriatr*. 2006;39:297-300. doi:10.1007/s00391-006-0040-8
33. Oerbekke MS, Stukstette MJ, Schütte K, Linbo RA. Age-related effects on postural control under multi-task conditions. *Gerontology*. 2011;57:247-255. doi: 10.1159/000322196
34. Rathmacher J, Splinter HM, Hartenbach H, et al. Concurrent validity and reliability of gait instrumented insoles measuring postural balance and temporal gait parameters. *Gait Posture*. 2017;51:116-124. doi:10.1016/j.gaitpost.2016.10.005
35. Beauchet O, Allali G, Sekhon H, et al. Guidelines for assessment of gait and reference values for spatiotemporal gait parameters in older adults: the Biomathics and Canadian Gait Consortiums Initiative. *Front Hum Neurosci*. 2017;11:353. doi:10.3389/fnhum.2017.00353
36. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed in older people. *Age Ageing*. 2009;38:113-119. doi:10.1093/ageing/afp034
37. McKay MJ, Baldwin JN, Ferreira P, et al. Spatiotemporal and temporal gait parameters. *Gait Posture*. 2017;51:116-124. doi:10.1016/j.gaitpost.2016.10.005
38. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *J Gerontol A Biol Sci Med Sci*. 2003;58:72-77. doi:10.1093/geronj/58.1.72
39. Beijersbergen CMI, Granacher U, Gäbler M, DeVita P, Hortobágyi T. Hip mechanics underlie lower extremity power training-induced increase in old adults’ fast gait velocity: the Potsdam Gait Study (POGS). *Gait Posture*. 2017;52:338-344. doi:10.1016/j.gaitpost.2016.12.024
40. Beijersbergen CMI, Granacher U, Gäbler M, DeVita P, Hortobágyi T. Hip mechanics underlie lower extremity power training-induced increase in old adults’ fast gait velocity: the Potsdam Gait Study (POGS). *Gait Posture*. 2017;52:338-344. doi:10.1016/j.gaitpost.2016.12.024
41. Buddhadev HH, Martin PE. Effects of age and physical activity status on redistribution of joint work during walking. *Gait Posture*. 2016;50:131-136. doi:10.1016/j.gaitpost.2016.08.034
42. Delmonico MJ, Harris TB, Lee JS, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. *J Am Geriatr Soc*. 2007;55:769-774. doi:10.1111/j.1532-5415.2007.01140.x
43. Delmonico MJ, Harris TB, Lee JS, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. *J Am Geriatr Soc*. 2007;55:769-774. doi:10.1111/j.1532-5415.2007.01140.x
44. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc*. 2002;50:889-896. doi:10.1046/j.1532-5415.2002.50216.x
45. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength: a quantitative review. *Front Physiol*. 2012;3:260. doi:10.3389/fphys.2012.00260
46. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the healthy, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci*. 2006;61:72-77.
47. Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. *Am J Physiol*. 1996;270(4 pt 1):E627-E633.
48. de Boer MD, Seynnes OR, di Prampero PE, et al. Effect of 56 days of bed rest. *Eur J Appl Physiol*. 2008;104:401-407. doi:10.1007/s00421-008-0703-0
49. Branchini T, Lee SL, Nordin M, et al. Effect of 56 days of bed rest. *Eur J Appl Physiol*. 2008;104:401-407. doi:10.1007/s00421-008-0703-0
50. Buehring B, Belavý DL, Michaelis I, Gast U, Felsenberg D, Rittweger J. Changes in lower extremity muscle function after 56 days of bed rest. *J Appl Physiol*. 1985. 1996;72:1804-1811.
51. Silder A, Heiderscheit B, Thelen DG. Active and passive contributions to joint kinetics during walking in older adults. *J Biomech*. 2008;41:1520-1527. doi:10.1016/j.jbiomech.2008.02.016
52. McKay MJ, Baldwin JN, Ferreira P, et al. Spatiotemporal and temporal gait parameters. *Gait Posture*. 2017;51:116-124. doi:10.1016/j.gaitpost.2016.10.005
53. de Boer MD, Seynnes OR, di Prampero PE, et al. Effect of 56 days of bed rest. *Eur J Appl Physiol*. 2008;104:401-407. doi:10.1007/s00421-008-0703-0
54. Budhadev HH, Martin PE. Effects of age and physical activity status on redistribution of joint work during walking. *Gait Posture*. 2016;50:131-136. doi:10.1016/j.gaitpost.2016.08.034
55. Dupin P, Montoya R, Costes-Salon MC, Séverac A, Güell A. Balance and gait analysis after 30 days ~6 degrees bed rest: influence of lower-body negative-pressure sessions. *Aviat Space Environ Med*. 1992;63:1004-1010.
56. English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care*. 2010;13:34-39. doi:10.1097/MCO.0b013e328333aa66

57. Muir J, Judex S, Qin YX, Rubin C. Postural instability caused by extended bed rest is alleviated by brief daily exposure to low magnitude mechanical signals. *Gait Posture*. 2011;33:429-435. doi:10.1016/j.gaitpost.2010.12.019

58. Alexander NB. Clinical evaluation of gait disorders: no-tech and low-tech. In: Hausdorff JM, Alexander NB, eds. *Gait Disorders: Evaluation and Management*. Boca Raton, FL: CRC Press; 2005:19-30.

59. Brown JC, Harhay MO, Harhay MN. Patient-reported versus objectively-measured physical function and mortality risk among cancer survivors. *J Geriatr Oncol*. 2016;7:108-115. doi:10.1016/j.jgo.2016.01.009

60. McPhee JS, French DP, Jackson D, Nazroo J, Pendleton N, Degens H. Physical activity in older age: perspectives for healthy ageing and frailty. *Biogerontology*. 2016;17:567-580. doi:10.1007/s10522-016-9641-0

61. Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment—a systematic review. *Crit Rev Oncol Hematol*. 2013;88:573-593. doi:10.1016/j.critrevonc.2013.07.001

62. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60:2127-2136. doi:10.1111/j.1532-5415.2012.04209.x

63. Kelly DL, Buchbinder D, Duarte RF, et al. Neurocognitive dysfunction in hematopoietic cell transplant recipients: expert review from the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and Complications and Quality of Life Working Party of the European Group for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2018;24:228-241. doi:10.1016/j.bbmt.2017.09.004

64. Mortaza N, Osman NAA, Mehdikhani N. Are the spatio-temporal parameters of gait capable of distinguishing a faller from a non-faller elderly? *Eur J Phys Rehabil Med*. 2014;50:677-691.

65. DeMott TK, Richardson JK, Thies SB, Ashton-Miller JA. Falls and gait characteristics among older persons with peripheral neuropathy. *Am J Phys Med Rehabil*. 2007;86:125-132. doi:10.1097/PHM.0b013e31802ee1d1

66. Muchlauer T, Granacher U, Borde R, Hortobágyi T. Non-discriminant relationships between leg muscle strength, mass and gait performance in healthy young and old adults. *Gerontology*. 2018;64:11-18. doi:10.1159/000480150