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Using wearables to screen motor performance deterioration because of cancer and chemotherapy-induced peripheral neuropathy (CIPN) in adults - Toward an early diagnosis of CIPN

Mohsen Zahiri [a], Kevin M. Chen [a], He Zhou [a], Hung Nguyen [a], Biruh T. Workeneh [b], Sarvari V. Yellapragada [c,d], Yvonne H. Sada [c,d], Michael Schwenk [e,f], Bijan Najafi [a,*]

[a] Interdisciplinary Consortium on Advanced Motion Performance (iCAMP), Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX, USA
[b] Department of Nephrology, Division of Internal Medicine, MD Anderson, Houston, TX, USA.
[c] Department of Medicine, Section of Hematology and Oncology, Dan L Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA
[d] Department of Hematology and Oncology, Michael E. DeBakey VA Medical Center, Houston, TX, USA
[e] Network Aging Research (NAR), Heidelberg University, Heidelberg, Germany
[f] Department of Sports and Sports Sciences, Heidelberg University, Heidelberg, Germany

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ABSTRACT

Objective: An essential component for optimizing quality of life in adults with cancer is determining the degree to which therapy may negatively impact motor-performance, so that patients can maintain their quality of life and independence. This study examined whether instrumented gait and balance could determine the magnitude of deterioration in motor-performance from chemotherapy-induced peripheral neuropathy (CIPN).

Methods: We recruited 84 adults with cancer (age = 71.1 ± 9.7 years old, BMI = 26.8 ± 6.2 kg/m^2, gender = 56%female) and 57 age-matched non-cancer patients (age = 69.5 ± 9.8 years old, BMI = 27.1 ± 6.0 kg/m^2, gender = 79%female). Based on clinical screening, the group with cancer was classified into two groups: participants with CIPN (CIPN+) and without CIPN (CIPN-). Gait and balance were quantified using validated wearables. The Vibration Perception Threshold (VPT) test was used to stratify the CIPN+ group into mild (Mild-CIPN) and severe (Severe-CIPN) subgroups.

Results: All gait and balance parameters were deteriorated in the group with cancer compared to non-cancer group with the largest effects observed for stride-time (11%, Cohen's effect size $d = 1.00$, $p < 0.001$) and eyes-closed ankle sway (94%, $d = 0.49$, $p = 0.001$). The same trend was observed when the Severe-CIPN subgroup was compared to the Mild-CIPN. VPT correlates significantly with motor deterioration, with the largest correlation found in stride-time (Rho = 0.37, $p = 0.007$). Severe-CIPN subjects were significantly older and overall had more deterioration in the majority of motor-performance parameters after adjusting for age ($p < 0.050$).

Conclusion: These results confirmed the negative impact of CIPN on motor-performance with the largest effects on ankle stability and stride-time. VPT is a predictor of motor deterioration and may be used to determine the severity of CIPN symptom.

1. Introduction

The number of adults with cancer has steadily increased in recent years [1], accompanied by a rising interest in the timely detection of treatment-related side effects, which may have long-term consequences on quality of life [2,3]. Specifically, it is estimated that 77% of new cancer diagnoses are in adults 55 years or older [4], and it is anticipated that by 2022, eighteen million people in the United States (US) will live with cancer [1]. Given the increase of older adults with cancer, there is an increasing concern for the potential side effects of treatment on motor performance. Gait and balance are fundamental skills, and loss of these skills may lead to increased risk of falling, loss of independence, and a general deterioration in quality of life [5–7]. Thus, it is critical to

* Corresponding author at: Department of Surgery, Baylor College of Medicine, One Baylor Plaza, MS: BCM390, Houston, TX 77030, USA.
E-mail address: bijan.najafi@bcm.edu (B. Najafi).

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evaluate the consequences of cancer treatment on motor performance since early detection of changes in gait and balance during treatment may assist in timely intervention against a potentially reduced quality of life.

Although chemotherapy is used to destroy malignant cells, some chemotherapy agents cause collateral damage to normal nerve microtubules, leading to chemotherapy-induced peripheral neuropathy (CIPN) [8,9]. Additionally, CIPN is a side effect of targeted therapies, such as proteasome inhibitors and monoclonal antibodies, which have emerged over the past few decades across almost all tumor types. CIPN affects 30% to 70% of patients with cancer who report sensory deficits and increased fall frequency [9–12]. Some of the main self-reported symptoms are numbness, loss of balance, muscle weakness, tingling, and an overall decrease in quality of life [8,13–16]. Among different CIPN-related symptoms, loss of balance and difficulty walking have been identified as the leading risk factors for falls [9]. Falls may have severe and long-term consequences including increased likelihood of mortality, morbidity, costs of care, and reduction in quality of life [17,18].

While a few studies have explored how CIPN impacts gait and balance, these studies have limitations. For instance, some studies used self-reported changes to determine changes in gait and balance caused by CIPN [3,9,19]. Such subjective assessment methods could introduce bias because of their basis on the patient's ability to recall information. Few studies have used objective means to determine how CIPN impacts gait and balance [10,14,20,21]. However, self-report was used to quantify the severity of CIPN in these studies. In addition, gait was often assessed in a gait laboratory and/or over a short walking distance [10,21]. Najafi et al. have demonstrated that assessing walking over short walking distances may not represent habitual walking patterns of the geriatric population outside of the gait laboratory [22].

Our long-term goal is to present a practical solution to screen motor degradation due to CIPN, which in turn may assist with early detection of CIPN and screen its severity over time. To achieve this goal, the aims of this study were defined as follows: first, we examined the feasibility of using a wearable platform to collect the gait and balance performance of adults with cancer during routine outpatient visits. Second, we explored the degree to which CIPN and its severity impacted adults with cancer's gait and postural stability. In addition, we proposed an objective method that uses the vibration perception threshold test (VPT) [23–25] to measure the degree to which CIPN impacts plantar sensation (quantification of plantar numbness). VPT is recommended by the American Diabetes Association to determine and quantify the severity of plantar numbness in people with diabetes and peripheral neuropathy [26]. We hypothesized that VPT could be a practical tool to determine plantar numbness and its impact on motor performance among adults with cancer suffering from CIPN. Other hypotheses of this study are: 1) compared to age-matched non-cancer people, adults with cancer have deteriorated balance and gait irrespective of CIPN status, 2) CIPN+ magnifies the decline in gait and balance; 3) deteriorations in gait and balance are associated with the severity of CIPN symptoms.

2. Material and Methods

2.1. Subjects

We recruited eligible adults with cancer (aged 55 years or older) via referral from local outpatient oncology clinics. All the adults with cancer have initiated or completed chemotherapy. The age cutoff for older adults was 55 years since geriatric symptoms have been observed at an earlier age among adults with cancer [4,27]. The inclusion criteria for group of adults with cancer were as follows: age 55 years or older; ability to provide written informed consent; diagnosis of current or prior malignancy (obtained from the patient chart); neurotoxic chemotherapy or targeted therapy exposure (agents including platinums, vinca alkaloids, taxanes, proteasome inhibitors and interferons); and ability to walk with or without an assistive device for a minimum of fifteen meters. The exclusion criteria were assessed by chart review or patient self-report and included: diabetes; major known joint problems (e.g. back pain, foot problems such as active ulcers and lower extremities amputation, etc.); spinal cord injuries, neurological disorders including stroke, Parkinson's disease, multiple sclerosis, and dementia; taking medications unrelated to cancer treatment that may affect balance and gait; and severe visual, hearing, or vestibular impairment.

For the control group, we recruited adults without cancer who were age-matched to the group with cancer from outpatient clinics or community-dwelling older adults. Inclusion criteria were similar in the group with cancer except that they have not been diagnosed with a malignancy. The exclusion criteria were identical to the group with cancer. Eligible and willing participants signed a local institutional review board approved informed consent form before screening.

2.2. Measurement Procedure

2.2.1. Demographic and Clinical Characteristics

During the screening process, we recorded the participants' height, weight, and collected self-reported medical history including duration and type of cancer, history of falls in the past year, and significant comorbidities (e.g., arthritis, osteoporosis, etc.). Fall Efficacy Scale-International (FES—I) questionnaire was used to determine each subject's concern for falls [28]. Participants were asked to answer items thinking about how concerned they would be about falling in different situations such as cleaning the house or walking on uneven surfaces. Based on the cut-off points suggested by Delbaere et al. [29,30], participants were classified as having low (FES ≤ 19), moderate (20 ≤ FES-*I* ≤ 27), and high (FES-*I* ≥ 28) concern for falls.

2.2.2. Identification of CIPN and its Severity

The group with cancer was sub-categorized to those with CIPN (CIPN+) and those without a CIPN diagnosis (CIPN-). CIPN+ subjects were referred by outpatient oncology clinics. The presence of CIPN was confirmed by reviewing each patient's electronic record when it was available or by self-reported presence of clinical symptoms including numbness, tingling, or pain in the feet [31]. To determine the severity of CIPN symptoms, we used the vibration perception threshold (VPT) score. The VPT is a well-established and clinically validated protocol to determine neuropathy severity among people with diabetes [23,25]. A trained research coordinator administered VPT at the distal aspect of the great toe, 5th metatarsal head and heel using a Biothesiometer (Bio-Medical Instrument Co, Newbury, OH, USA) with the protocol described elsewhere [32,33]. A cutoff of greater or equal to 25 V [23,24] was used to distinguish between those with severe (Severe-CIPN: VPT ≥ 25 V) and mild CIPN (Mild-CIPN: VPT < 25 V).

2.3. Assessing Motor Performance

We used two validated wearable technologies for assessing gait and balance using protocols described elsewhere [34]. In summary, gait and balance were quantified using the LEGSys™ and BalanSens™ (Biosensics LLC, Watertown, MA, USA), respectively. Both platforms use the same hardware configuration of

five wearable inertial sensors attached to each subject's shins, thighs, and lower back as described elsewhere [35–37].

Gait assessment was conducted as single-task (no cognitive distraction) over fifteen meters at a self-selected speed. The LEGSys™ provides over twenty different spatiotemporal parameters of gait. For the purposes of this study, only four key gait parameters including two spatial parameter (stride velocity and stride length) and two temporal parameters (stride time and double support) were estimated. Using a validated algorithm [36–39], these parameters were averaged during the steady-state phase of walking. The steady-state point was objectively determined using a validated algorithm described elsewhere [38,39]. Balance was measured during 30 s standing still with feet close together (as close as possible without touching) during eyes-open and eyes-closed situations. Postural sway parameters were extracted from sensors data attached to each subject's shins and lower back using a two-link model [35,40]. The balance parameters of interest in this study include area of ankle sway, area of hip sway, area of center of mass (CoM) sway, and CoM sway in the medial-lateral (ML) direction. These parameters were selected based on their demonstrated association with the risk of falling as reported in prior literatures [41].

2.3.1. Statistical Analysis

Between group comparisons for parameters of interests were done using independent *t*-test, Chi-squared, or Mann Whitney *U* test as applicable. Analysis of covariance (ANCOVA) was used to evaluate the effect of cancer and CIPN on gait and balance parameters of interest, which were adjusted for age and BMI. The effect size to discriminate between groups was estimated using Cohen's d effect size [42]. Values ranging from 0.20 to 0.49 indicate small, from 0.50 to 0.79 indicate medium, from 0.80 to 1.29 indicate large, and above 1.30 indicate very large effect sizes [43]. Odds Ratio (OR) was estimated for dichotomous variables of interest. Correlations between VPT and each gait and balance parameter of interest were quantified using the Spearman correlation of coefficient and denoted as 'Rho'. The threshold of statistical significance was defined as $p = 0.050$. All statistically significant differences in variables are marked with a (*) symbol in all tables and figures. All statistical analyses were performed using SPSS statistics (Version 24; IBM, Armonk, NY, USA).

3. Result

A total of 82 adults with cancer (71.1 ± 9.7 years, 56%female) and 57 age-matched non-cancer volunteers (69.5 ± 9.8 years, 79%female) met the inclusion and exclusion criteria of this study. No significant differences were observed for age and BMI (Table 1). However, a lower percentage of the group with cancer was female compared to the control group (56% in the group with cancer versus 79% in the control group, $p = 0.004$). Concern for fall was significantly higher in the group with cancer (19.1 ± 4.5 in the control group versus 27.4 ± 8.4 in the group with cancer, $p < 0.001$). The group with cancer had on average 1.75 times more falls than the control group, which could suggest that cancer has some effect on fall rate. But the trend did not achieve statistically significant level in our sample (28% in the group with cancer versus 16% in the control group, OR = 1.75, $p = 0.131$).

3.1. Gait and Balance Comparisons between Cancer and Control Groups

All gait parameters of interest were significantly degraded in the group with cancer when compared to the control group ($p < 0.050$, Table 1). We observed no gender effect. Stride velocity was on average 16% slower ($d = 0.82$, $p < 0.001$) and stride time was on average 11% longer ($d = 1.00$, $p < 0.001$) in the group with cancer compared to the control group. Similar trends were observed for balance parameters. The largest effect size was observed for CoM sway in the medial-lateral direction ($d = 0.54$, $p = 0.009$) which was deteriorated by 32% in the eyes-open condition. Both groups had deterioration in balance with the eyes-closed compared to the eyes-open condition, but the magnitude of increase in body sway by closing eyes compared to the eyes-open condition was on average more than two-fold higher in the group with cancer compared to control group for both ankle and hip sway.

Table 1
Comparison between the group with cancer and non-cancer control group.

Variable	Non-Cancer Control (n = 57)	Cancer Survivor (n = 82)	p-value	Effect size
General characteristics				
Age, years	69.5±9.8	71.1±9.7	0.497	0.15
BMI, kg/m^2	27.1±6.0	26.8±6.2	0.838	0.05
Gender, % female	79	56	**0.004***	–
Concern for Fall (FES-I)	19.1±4.5	27.4±8.4	**<0.001***	1.23
History of fall, %	16	28	0.131	–
Gait				
Stride Velocity, m/s	1.14±0.22	0.96±0.22	**<0.001***	0.82
Stride Length, m	1.22±0.19	1.13±0.21	**0.023***	0.45
Double Support, %	21.8±4.7	26.1±4.7	**<0.001***	0.89
Stride Time, s	1.09±0.12	1.21±0.12	**<0.001***	1.00
Balance				
Double Stance – Eyes Open				
CoM Sway Area, cm^2	0.19±0.25	0.23±0.20	0.272	0.18
CoM Sway in ML Direction, cm	0.38±0.19	0.50±0.25	**0.005***	0.54
Ankle Sway, deg^2	1.00±1.31	1.21±1.09	0.373	0.17
Hip Sway, deg^2	0.93±0.75	1.23±1.27	0.163	0.29
Double Stance – Eyes Closed				
CoM Sway Area, cm^2	0.26±0.22	0.40±0.53	0.091	0.35
CoM Sway in ML Direction, cm	0.49±0.24	0.54±0.38	0.458	0.16
Ankle Sway, deg^2	1.39±1.19	2.70±3.20	**0.009***	0.54
Hip Sway, deg^2	1.34±0.86	2.56±3.08	**0.007***	0.54

BMI: Body Mass Index.
CoM: Center of Mass.
ML: Medial-Lateral.
Effect size: Cohen's d effect size.
Significant difference between groups were indicated in bold.
All gait and balance were adjusted by age and BMI; no significant gender effect was observed.

3.2. Effect of CIPN on Gait and Balance – Comparison between CIPN+ and CIPN-

Of the 58 patients who were adults with cancer, 70% of them had CIPN+. Compared to the CIPN- subgroup, the CIPN+ were on average ten years younger ($p < 0.001$) and more likely to be men (OR = 3.35, $p = 0.001$, Table 2) with no significant difference in BMI between groups. Both the CIPN- and CIPN+ had significantly higher concern of falls compared to the control group ($p \leq 0.001$). Having CIPN+ increased the OR of falls by 1.55 and 2.07, compared to CIPN- and controls, respectively. However, between groups, differences for the likelihood of falls didn't achieve statistical significance in our sample. The deterioration in gait parameters was more pronounced in the CIPN+ than the CIPN- subgroup, when compared to the control group. CIPN+ on average had 8% ($p = 0.241$) and 18% ($p < 0.001$) slower stride velocity compared to the CIPN- and control groups, respectively (Fig. 1). Stride velocity was also on average 11% slower in CIPN, when compared to control ($p = 0.024$). Similar trends were observed for other gait parameters of interest.

Results suggest high visual dependency in the CIPN+ subgroup. With eyes-closed, ankle sway in CIPN+ subgroup was greater on average by 187% ($p = 0.002$) and 146% ($p < 0.001$), compared to the CIPN-

Table 2
Comparison between adults with cancer and without Chemotherapy Induced Peripheral Neuropathy (CIPN-), adults with cancer and with CIPN (CIPN+), and controls.

Variable	Control (n = 57)	CIPN–(n = 24)	CIPN+(n = 58)	p-value		
				CIPN–Vs. Control	CIPN+Vs. Control	CIPN–Vs. CIPN+
General characteristics						
Age, years	69.5±9.8	78.33±8.45	68.03±8.60	**0.001***	0.321	**<0.001***
BMI, kg/m^2	27.1±6.0	27.4±7.3	26.9±6.1	0.515	0.495	0.310
Gender, % female	79	83	43	0.653	**<0.001***	**0.001***
Concern for Fall (FES-I)	19.1±4.5	26.5±8.2	27.8±8.5	**<0.001***	**<0.001***	0.529
History of fall, %	16	20	31	0.644	0.072	0.298
Gait						
Stride Velocity, m/s	1.14±0.22	1.01±0.25	0.93±0.20	**0.024***	**<0.001***	0.241
Stride Length, m	1.22±0.19	1.15±0.21	1.13±0.20	0.197	**0.026***	0.706
Double Support, %	21.8±4.75	25.6±4.40	26.3±4.93	**0.003***	**<0.001***	0.607
Stride Time, s	1.09±0.12	1.17±0.12	1.25±0.12	**0.013***	**<0.001***	0.073
Balance						
Double stance – Eyes open						
CoM Sway Area, cm^2	0.19±0.25	0.20±0.16	0.25±0.22	0.822	0.192	0.449
CoM Sway in ML Direction, cm	0.38±0.19	0.62±0.30	0.46±0.21	**<0.001***	0.094	**0.011***
Ankle Sway, deg^2	1.00±1.31	0.78±0.69	1.37±1.19	0.507	0.126	0.073
Hip Sway, deg^2	0.93±0.75	1.19±1.22	1.24±1.30	0.384	0.182	0.886
Double stance – Eyes closed						
CoM Sway Area, cm^2	0.26±0.22	0.36±0.25	0.42±0.62	0.390	0.084	0.627
CoM Sway in ML Direction, cm	0.49±0.24	0.62±0.25	0.50±0.41	0.153	0.904	0.199
Ankle Sway, deg^2	1.39±1.19	1.19±0.93	3.42±3.79	0.758	**<0.001***	**0.002***
Hip Sway, deg^2	1.34±0.86	1.93±2.60	2.86±3.30	0.343	**0.002***	0.155

BMI: Body Mass Index.
COM: Center of Mass.
ML: Medial-Lateral.
CIPN-: Adults with cancer without neuropathy.
CIPN+: Adults with cancer confirmed with a clinical diagnosis of CIPN.
Significant difference between groups were indicated in bold.
All gait and balance were adjusted by age and BMI. No gender significant effect was observed.

and control groups, respectively. Descriptive results revealed more deterioration in ankle and hip sway for the CIPN+ subgroup compared to the CIPN-. When compared to the eyes-open condition, the CIPN+ subgroup showed a 2.50-fold higher ankle sway with eyes-closed, whereas this ratio was 1.53 and 1.39-fold for the CIPN- and control groups, respectively.

3.3. Association between Plantar Numbness Severity and Motor Performance

According to VPT, 72% (n = 42) of CIPN+ subgroup had severe plantar numbness (Severe-CIPN) versus 28% (n = 16) with mild plantar numbness (Mild-CIPN). Participants in the Severe-CIPN were significantly older (p = 0.004) and tended to have a greater concern for falls (FES-*I* = 28.97 ± 8.57 versus 25.25 ± 8.05, p = 0.108, d = 0.45), and higher likelihood of falls (OR = 1.32, p = 0.703) compared to the Mild-CIPN subgroup (Table 3).

Overall, greater deterioration in gait parameters was observed in the Severe-CIPN compared to the Mild-CIPN (Table 3), but the trend only achieved statistically significant levels for stride time (7.8%, d = 1.109, p = 0.011). When compared to the controls, the Severe-CIPN had 21% slower gait (p < 0.001), which is 2.3-fold higher than the magnitude of deterioration in stride velocity for the Mild-CIPN subgroup.

Similarly, participants in the Severe-CIPN subgroup had overall impaired balance compared to the Mild-CIPN irrespective of test conditions. However, between group differences achieved statistical significance only during the eyes-open condition for CoM sway in the

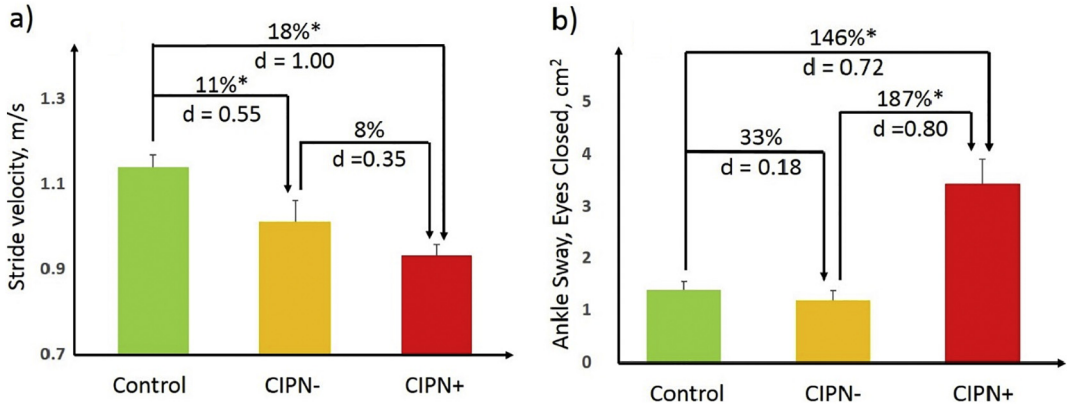

Fig. 1. (a) Stride velocity in non-cancer control (green color), patients with cancer and without chemotherapy induced peripheral neuropathy (CIPN) diagnosis, CIPN- (yellow color), and patients with cancer and with CIPN diagnosis, CIPN+ (red color) group. CIPN+ had 18% and 8% slower gait compared to controls and CIPN-, respectively. (b) Ankle sway during eyes closed for non-cancer control (green color), CIPN- (yellow), and CIPN+ (red color). '*' denotes statistical significant difference.

Table 3
Comparison between Mild-Chemotherapy Induces Peripheral Neuropathy (Mild-CIPN) and Severe- Chemotherapy Induced Peripheral Neuropathy (Severe-CIPN) groups.

Variable	Mild-CIPN (n = 16)	Severe-CIPN (n = 42)	p-value	Effect Size
General characteristics				
Age, years	62.66±5.2	70±8.8	**0.004***	1.01
BMI, kg/m^2	27.40±3.94	26.16±6.07	0.175	0.24
Gender, %	50	42	0.882	–
Concern for Fall (FES-I)	25.25±8.05	28.97±8.57	0.108	0.44
History of fall, %	25	33	0.703	–
VPT, Volt	15.84±4.57	52.17±23.26	**<0.001***	2.16
Time since diagnosis, months	32.86±20.36	66.89±70.21	0.198	0.65
Cancer type				
NSCLC (lung)	19%	40%	0.123	–
Multiple Myeloma	19%	19%	0.823	–
Colon-rectal	19%	12%	0.503	–
Breast	6%	5%	0.821	–
thers	37%	24%	0.216	–
Gait				
Stride Velocity, m/s	1.03±0.23	0.90±0.18	0.052	0.68
Stride Length, m	1.18±0.25	1.11±0.18	0.265	0.32
Double Support, %	24.6±5.0	26.8±4.8	0.111	0.51
Stride Time, s	1.16±0.09	1.25±0.12	**0.011***	1.09
Balance				
Double Stance – Eyes Open				
CoM Sway Area, cm^2	0.19±0.20	0.27±0.22	0.509	0.24
CoM Sway in ML Direction, cm	0.29±0.10	0.50±0.20	**0.012***	1.11
Ankle Sway, deg^2	0.81±0.74	1.53±1.25	0.115	0.61
Hip Sway, deg^2	0.49±0.35	1.45±1.40	**0.011***	0.92
Double Stance – Eyes Closed				
CoM Sway Area, cm^2	0.31±0.29	0.45±0.70	0.338	0.26
CoM Sway in ML Direction, cm	0.57±0.34	0.47±0.44	0.549	0.17
Ankle Sway, deg^2	2.26±1.82	3.79±4.20	0.124	0.40
Hip Sway, deg^2	1.83±1.23	3.18±3.69	0.145	0.42

BMI: Body Mass Index.
COM: Center of Mass.
VPT: Vibration Perception Threshold.
ML: Medial-Lateral.
NSCLC: Non-Small Cell Lung Cancer.
Effect size: Cohen's d effect size.
Significant difference between groups were indicated in bold.
All gait and balance were adjusted by age and Body Mass Index.

ML direction and hip sway (d = 1.11, p = 0.012). The magnitude of increase in ankle sway with the eyes-close condition was almost similar between groups (2.5-fold for severe-CIPN versus 2.8-fold for Mild-CIPN).

Results suggest that increase in VPT (lower plantar sensation) is associated with deterioration in motor performance and increase in concern for falls (Fig. 2). A significant positive correlation was observed between stride time and VPT (Rho = 0.37, p = 0.007, Fig. 2a), suggesting that a slower gait correlates with increasing plantar numbness severity. Results also suggest that increase in VPT values led to an increase in CoM sway during both the eyes-open (Rho = 0.45, p = 0.001, Fig. 2b) and eyes-closed conditions (Rho = 0.28, p = 0.045, Fig. 2c). Increase in VPT led to increased concern for falls, but this correlation did not achieve statistical significance in our sample size (Rho = 0.27, p = 0.052).

4. Discussion

To our knowledge, this is the first cohort study to objectively assess the association of a loss of plantar sensation and its severity on gait, balance, and concern for falls from CIPN. Our results suggested that adults with cancer have poorer balance, slower gait, and a higher concern for falls compared to age-matched non-cancer controls. The association of CIPN was most pronounced in ankle instability during the eyes-closed condition. While CIPN+ magnifies the deterioration in gait and balance, no significant difference was observed between CIPN+ and CIPN- for the majority of gait and balance parameters. Similarly, the likelihood of having falls and concern for falls were both increased in CIPN+ but did not achieve a statistically significant level when compared to the CIPN- subgroup. In summary, the results implied that a diagnosis of cancer irrespective of CIPN presence deteriorates gait, balance, and concerns for falling in older adults, while CIPN additionally increased vision dependency among adults with cancer.

From a gait standpoint, the present study found that patients with cancer, irrespective of CIPN condition, have slower walking speed, shorter stride length, longer stride time and double support compared to the non-cancer control group. The most significant effect size for the between-group difference was observed for stride time with 11% deterioration in patients with cancer. Slower gait has been shown to be a strong predictor of functional decline among adults with cancer [43] and is associated with a higher risk of falls for the aging population particularly among those with loss of plantar sensation [44,45]. While, both CIPN- and CIPN+ subgroups had significant gait deterioration compared to the control group, none of the gait parameters achieved significant statistical levels in our sample. Winters-Stone et al. [10] have reported significant deterioration in the CIPN+ compared to CIPN- for gait speed, stride length, and cadence (equivalent to stride time) with no difference for double support time. Although our results may contradict this, the observed effect sizes in our study (d = 0.36–0.67) were similar to Winters-Stone et al. (d = 0.32–0.5). Therefore, the lack of a statistically significant difference in our sample could be related to the smaller sample size in our study (n = 62 in our study versus n = 512 in Winters-Stone et al.). However, consistent with the Winters-Stone et al. study, we observed that increased severity of neuropathy symptoms has a significant association with poorer gait among CIPN + patients. Unlike the Winters-Stone et al. study, in which self-report values were used, we administered VPT to objectively determine CIPN severity. Interestingly, our investigation revealed a significant correlation between gait deterioration (in particular for stride time) and magnitude of plantar numbness as quantified by VPT in our study. This is consistent with reports in people with diabetes, in which it has been reported that more severity in plantar numbness because of diabetic peripheral neuropathy has been shown to be associated with poorer gait [46–48].

Results from static balance suggested that cancer negatively impacts postural control. CIPN symptoms magnify this deterioration with significant impact during eyes-closed for ankle stability. Prior literature suggested that body sway is an independent risk predictor of prospective falls in older adults [41]. Therefore, greater body sway found in CIPN could be one of the risk factors contributing to the increased likelihood of falls among adults with cancer. This was supported by our results in which a 3.3-fold higher probability of a history of falls in the group with cancer compared to age-matched control was observed. While the increase in body sway was not dependent on CIPN status, the degree of deterioration was magnified in those with more severe plantar numbness, in particular for CoM sway in the ML direction, which was 1.7 times higher than the group with Mild-CIPN. This finding is in agreement with prior research in the area of diabetic peripheral neuropathy, in which a significant correlation between the severity of plantar numbness and increase body sway has been reported [35].

Postural control depends on sensory feedback including visual, vestibular, and somatosensory feedback [49]. Plantar numbness due to CIPN may alter somatosensory feedback and thus is expected to increase body sway. However, our results suggested that body sway did not increase due to CIPN but rather due to impacted visual dependency. The result suggested that visual dependency was the most pronounced for ankle stability. For instance, ankle sway was increased by a factor of

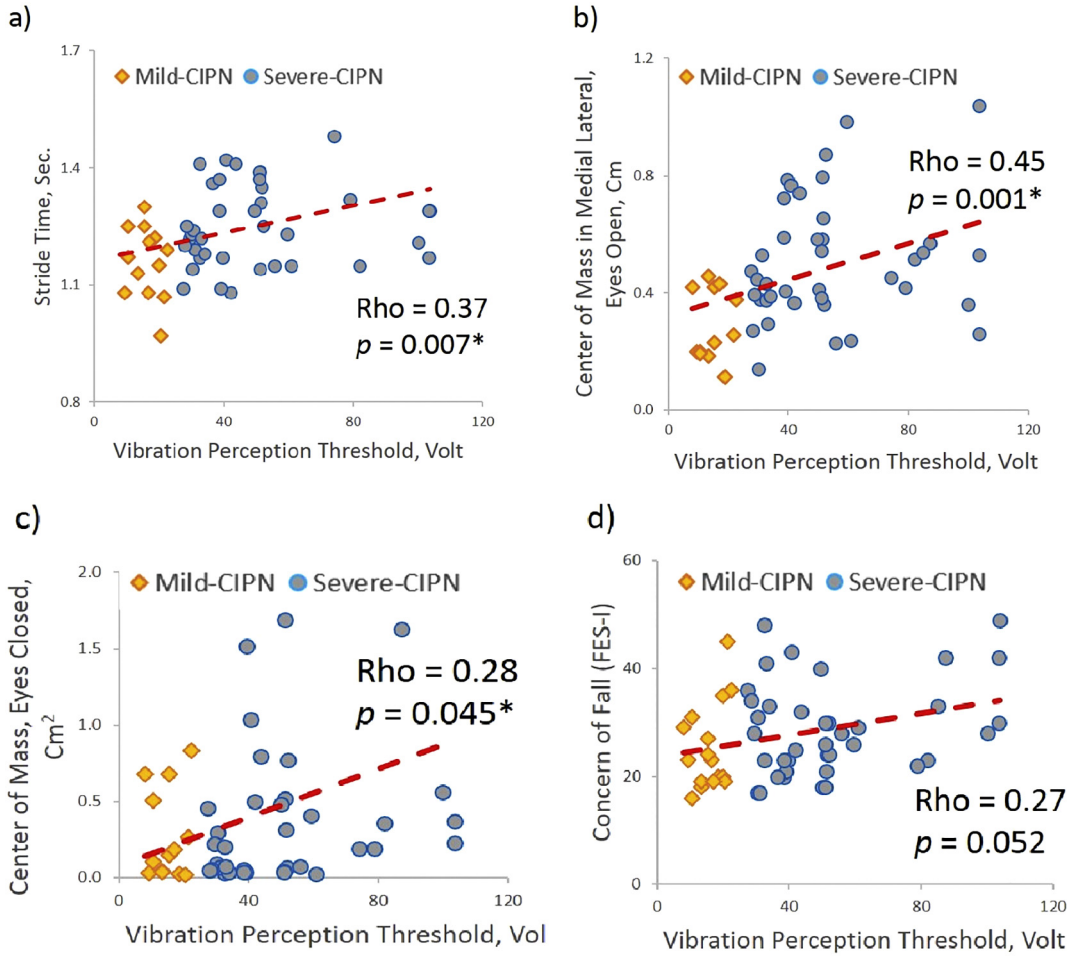

Fig. 2. Association between plantar numbness (surrogate of chemotherapy induced peripheral neuropathy (CIPN) severity) and stride time (Fig. 2a), center of mass sway during eyes-open (Fig. 2b) and eyes-closed (Fig. 2.c) conditions; and concerns for falls (Fig. 2d). Results suggest by increase in plantar numbness as quantified by vibratory perception threshold test (higher value means higher numbness), gait and balance are deteriorated and fear of fall is increasing.

2.5 in the CIPN subgroup during eyes-closed condition compared to the eyes-open condition; whereas, the magnitude of deterioration in ankle sway in the eyes-closed condition was 1.4-fold and 1.5-fold for controls and CIPN-, respectively. Prior studies have suggested that visual dependency is a key risk factor for falls in older adults including adults with cancer [50,51]. Surprisingly, CoM sway in the ML direction during the eyes-open condition was poorer in the CIPN- compared to the CIPN+ subgroup. We speculated that this is because CIPN- participants were significantly older than CIPN+. However, under the eyes-closed condition, ankle sway was markedly higher in the CIPN+ compared to the CIPN-, highlighting that the significant impact of CIPN on static balance occurred during the eyes-closed condition. Interestingly, there was an increase in ankle sway in the eyes-closed condition when compared to the eyes-open condition with a similar percentage in both the Mild-CIPN and Severe-CIPN. This may suggest that visual dependency in the CIPN population is independent of the severity of plantar numbness, a finding that should be further explored in larger sample sizes.

Our study also demonstrated that the likelihood of falls was 1.65 times greater for Severe-CIPN patients when compared to the CIPN- subgroup. This result is in line with previous research on patients with cancer that reported the risk of fall is 1.7–1.8 times greater for patients experiencing severe CIPN symptoms when compared to the fall rate of asymptomatic adults with cancer [3,10]. However, our results showed a direct association between the severity of CIPN symptoms and the risk of falling in a broader population of adults with cancer from concurrent longitudinal symptoms to CIPN symptoms that persist years beyond treatment. As expected, a higher concern for falling was observed among Severe-CIPN patients in comparison to the Mild-CIPN subgroups; however, this was not statistically significant in our sample. On average Severe-CIPN patients were classified as having high concern for fall, while the Mild-CIPN subgroup were categorized as having moderate concern.

Some limitations should be noted in this study. First, the sample size was modest, and the results need to be confirmed in a larger sample. Second, this study was cross-sectional, capturing information at one time-point for patients who were at a variety of different time points during or after their chemotherapy treatment. Because of the small sample size in the CIPN+ group, we did not distinguish between those who have completed chemotherapy and those who were still receiving therapy. This may impact the results as those who are still receiving treatment may have acute alterations in motor performance, while those who have completed therapy may have long lasting alterations. However, we believe this has little impact on our results as we assumed that initiation of CIPN symptoms may be detectable by measuring degradation in motor performance. But this assumption should be confirmed in the context of a subsequent prospective study. While the between-group comparisons were adjusted by age and BMI, several other confounding factors, which may affect the between-group comparisons such as duration, number of sessions, type of chemotherapy agent, or dose of chemotherapy; sex; level of physical

activity; etc., were not controlled. In our analysis, to examine between group differences, we used multiple comparisons, which may increase the type of errors. To limit the effect of random sampling errors, we pre-selected the most important gait and balance parameters before performing any statistical analysis instead of comparing all measurable gait and balance parameters. Finally, this study did not keep track of the CIPN symptoms based on dosage amount or specific chemotherapeutic agent. There could be different mechanisms of action in the development of CIPN symptoms based on the dosing schedule and treatment agent, leading to different responsiveness to interventions. However, this study focused on the clinical presentation and provided a useful guideline for predicting functional movement deficits based on the degree of peripheral sensation severity.

Despite these limitations, our study may encourage future research in this area by providing objective data linking CIPN and its severity to the magnitude of deterioration in gait and balance. Also, it demonstrated that measuring the extent of plantar numbness using VPT could be used to determine the magnitude of the decline in gait and balance among adults with cancer. VPT has already been frequently used in podiatry clinics to identify neuropathy and the risk of plantar ulcers among people with diabetes. This study suggested that the same test could be useful in oncology clinics and could be used to determine CIPN and its severity, when gait and balance assessments may not be practical. This, in turn, may facilitate capturing the onset of CIPN at earlier stages and empower oncologists to make more personalized decisions when deliberating on a switch to alternative, less toxic chemotherapeutic agents or a change in dose of treatment.

Conflict of Interest

None.

Authors Contributions

MZ: study concept, study design, data acquisition, quality control of data and algorithms, statistical analysis, manuscript preparation. KC: quality control of data and algorithms, manuscript preparation. HZ: quality control of data and algorithms, statistical analysis. HN: statistical analysis. BW: study concept, data acquisition, quality control of data and algorithms. SY: study concept, quality control of data and algorithms. YS: study concept, quality control of data and algorithms. MS: study design, data acquisition. BN: study concept, study design, quality control of data and algorithms, manuscript preparation. All authors contributed to interpretation of data, manuscript editing, and manuscript review.

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