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RESEARCH

Large fiber contribution to symptoms in chemotherapy-induced peripheral neuropathy in cancer survivors

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Abstract

Purpose Chemotherapy-induced peripheral neuropathy (CIPN) is associated with a large amount of interindividual variability in signs and symptoms. The purposes were to use latent profile analysis to identify subgroups of survivors with distinct lower extremity (LE) loss-of-function CIPN profiles; evaluate for differences in demographic, clinical, and pain characteristics between the profiles and characteristics associated with membership in the more severe profile; and examine relationships between the profiles and measures of large fiber loss and C-tactile fiber function.

Methods LE loss-of-function CIPN profiles were created using measures of worst pain, loss of light touch sensation, loss of cold sensation, loss of pain sensation, vibration threshold, and two balance measures.

Results Of the 405 survivors evaluated, two distinct profiles were identified: less severe loss of LE function (76.5%) and more severe loss of LE function (23.5%). Risk factors for membership in the more severe profile included being older, male, and having lower functional status. In terms of the loss of large fiber function, survivors in the more severe class had four more sites on average that lost light touch sensation; their vibration thresholds were 1.5 times higher; and their ratings of numbness were significantly higher. For C-tactile fiber function, significant between-group differences were found in survivors' ratings of the severity of sensitive skin and unpleasantness.

Conclusions Findings suggest that distinct "CIPN phenotypes" can be identified in cancer survivors. Detailed phenotyping and molecular characterization of various CIPN phenotypes will lead to the development and testing of targeted and personalized interventions.

Keywords Affective touch · Balance · C-Tactile afferents · Chemotherapy-induced peripheral neuropathy · Large fiber function · Numbness · Pain · Touch sensation · Vibration

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurologic complication of cancer treatment [1, 2]. CIPN results in a variable set of signs and symptoms [3, 4]. Sensorimotor complaints occur predominantly in the extremities and can include pain, numbness, tingling, and burning sensations; gait and balance disturbances; difficulty with fine motor skills; reductions in vibratory sense, touch, and proprioception; and progressive loss of deep tendon reflexes. However, a large amount of interindividual variability exists in the CIPN phenotype (i.e., both in the positive and negative expressions of signs and symptoms) [4–7].

While the etiology of neuropathic pain is the most common way to classify patients (e.g., diabetic neuropathy, post-herpetic neuralgia, and CIPN), recent work used newer analytic techniques to identify subgroups of patients with distinct neuropathic pain profiles [8–13]. For example, in one study [11], self-report and objective data from patients with polyneuropathy, peripheral nerve injury, radiculopathy, and post-herpetic neuralgia were evaluated. Using

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cluster analysis, three subgroups of patients were identified and named based on the grouping of the subjective and objective data (i.e., "sensory loss," "thermal hyperalgesia," and "mechanical hyperalgesia"). Of note, each subgroup included patients with all the pain conditions that were evaluated in the study. The authors concluded that these three subgroups or "pain profiles" that were identified using cluster analysis may be related to different underlying mechanisms and that this type of classification may be useful in the selection of patients for studies of mechanistically based interventions. However, no studies have used subjective and objective CIPN characteristics to identify distinct "CIPN profiles" in cancer survivors.

An important consideration in understanding the mechanisms of CIPN is the role of small-diameter versus large-diameter sensory neurons. In the most common classification scheme, fast conducting, large myelinated Aβ fibers (i.e., large fibers) mediate nonnociceptive sensations, and thinly myelinated A-delta and small unmyelinated C-fibers (i.e., small fibers) mediate nociceptive sensations [14, 15]. In terms of CIPN, the administration of neurotoxic chemotherapy damages both small fibers and large fibers and is associated with pain and the attenuation of light touch sensation, respectively [16–19].

However, more recent evidence suggests that damage to large fibers contributes to painful sensations associated with CIPN. For example, in our previous study of survivors with CIPN [20], average pain scores were positively correlated with subjective (severity of numbness) and objective measures of large myelinated fiber function (i.e., loss of protective sensation and increases in vibration thresholds). In terms of the patients with CIPN, these findings suggest that the symptoms and objective changes in sensation from the administration of platinum- and/or taxane-containing regimens are congruent with the loss of large fiber function and associated increases in pain. Additional support for the contribution of large fibers to CIPN comes from a recent preclinical study that used a high-frequency electrical stimulus that selectively activates large myelinated afferents as a model of large fiber CIPN [21]. In this study, that evaluated the effects of duloxetine on bortezomib and paclitaxel-induced CIPN, both neurotoxic drugs produced changes that were compatible with the loss of large fiber function. Of note, duloxetine prevented the development of CIPN.

While additional research is warranted on the relative contribution of large fiber function to CIPN, another plausible hypothesis for the development of this significant clinical problem is damage to a subgroup of C fibers known as C-tactile fibers. These slow conducting unmyelinated afferents have a low temporal and spatial resolution and are thought to contribute to the perception of pleasantness during gentle stroking of hairy skin (i.e., "affective touch") [22–24]. Evidence from preclinical models suggests that these fibers play a role in the pathophysiology of tactile allodynia [25]. Given that some patients with CIPN report tactile allodynia (e.g., burning, tender sensations from non-noxious stimuli) [26], it is plausible that the administration of neurotoxic chemotherapy damages these fibers and results in these extremely unpleasant sensations.

Given the lack of research on interindividual variability in CIPN profiles, the purpose of this study, in a sample of survivors with CIPN ($n=405$), was to use latent profile analysis (LPA) to identify subgroups of survivors with distinct lower extremity loss-of-function CIPN profiles (i.e., latent classes). Once the profiles were identified, differences in demographic, clinical, and pain characteristics between the profiles were evaluated and demographic and clinical characteristics associated with membership in the more severe profile were determined. In addition, relationships between the profiles and measures of large fiber loss and C-tactile fiber function were evaluated to determine their potential involvement in CIPN.

Methods

Survivors and settings

The current analysis is part of a larger National Cancer Institute–funded study that evaluated CIPN in cancer survivors. The methods for the larger study are described in detail elsewhere [27], and a complete description of the methods is provided in Supplemental Document 1. Of the 1450 survivors who were screened, 754 were enrolled, and 623 completed the self-report questionnaires and the study visit. Only survivors with CIPN ($n=405$) were included in this analysis.

Study procedures

Research nurses screened and consented the survivors over the phone; sent and asked them to complete the self-report questionnaires prior to their study visit; and scheduled the in-person assessment. At this assessment, written informed consent was obtained; questionnaires were reviewed for completeness; and objective measurements were done.

Study measures

Demographic and clinical characteristics

Survivors provided information on demographic characteristics and completed the Alcohol Use Disorders Identification Test [28], the Karnofsky Performance Status (KPS) scale [29], and the Self-Administered Comorbidity Questionnaire (SCQ) [30].

Pain questionnaires

A detailed history of CIPN was obtained using a questionnaire from our previous [31, 32] and ongoing studies. Information was obtained on the date of onset of pain and its level of interference with function. Average and worst pain intensity over the past 24 h were assessed using a 0 (no pain) to 10 (worst pain imaginable) numeric rating scale (NRS) [33]. The 20-item PQAS was used to assess the qualities associated with CIPN [34, 35].

Objective measures of large fiber function

Semmes–Weinstein monofilaments (SWM; North Coast Medical, Inc., Morgan Hill, CA) were used to test light touch sensation in the lower extremities [36]. Each lower extremity was evaluated at nine locations: pad of the great, third, and fifth toes; base of the heel; dorsal surface of the metacarpophalangeal joint of the great, third, and fifth toes; midway along the tibia; and the patella. The locations were tested in random order.

SWM used for the lower extremities were 4.31, 4.56, 5.07, and 6.65. Before testing began, the patient was familiarized with the filament being used and the expected sensation was demonstrated in an area of normal sensibility. Then, with the survivor's' eyes closed, starting with the smallest, filaments were applied in ascending order at each site. The filaments were applied perpendicular to the skin and pressed until the filament bowed for 1.5 s. The survivor was asked to respond to the stimulus by stating the location of the light touch sensation. In contrast to Bell-Krotoski's recommendation, two correct responses rather than one out of three at each location were considered a positive response, as a survivor could make one correct response by guessing [37]. At each location, once a positive response was identified, the next location was tested in random order. SWM measurements have good inter- and intrarater reliability and validity when calibrated and applied correctly [36, 38, 39].

Vibration threshold was tested using a biothesiometer (Bio-Medical Instrument Company; Newbury, OH). After familiarizing survivors with the sensation, vibration thresholds were tested at three sites in the lower extremities (i.e., dorsal ipsilateral joint of the great toe, medial malleolus, and patella). Following the manufacturer's instructions, the biothesiometer was placed on the skin over the bone at each location. Beginning at zero amplitude, the amplitude of the vibration was increased until the survivor reported feeling vibration (i.e., vibration perception threshold). Then, the amplitude was turned down to zero and the procedure was repeated increasing the intensity more slowly as the initial value was approached. The survivor reported the perception of the sensation of vibration by saying, "NOW." Each site was tested three times and a mean score was calculated. Loss of vibration thresholds can be categorized as follows: < 15 V is normal; 15 to 20 V is mild loss; 20 to 25 V is moderate loss; and > 25 V is severe loss of vibratory sensation [40].

Additonal measures of sensation

Cold sensation was evaluated using the Tiptherm Rod [41, 42]. Pain sensation was evaluated using the Neurotip [41]. For all of the measures of sensation, the lower extremity on the dominant side was tested.

Balance measures

The objective measures of balance were the Timed Get Up and Go test (TUG) [43] and the Fullerton Advanced Balance (FAB) test [44, 45].

Data analysis

Creation of the lower extremity loss-of-function CIPN phenotypes

The following characteristics were used to create the lower extremity loss-of-function CIPN phenotypes: rating of worst pain in the past 24 h, loss of light touch sensation, loss of cold sensation, loss of pain sensation, vibration threshold, TUG score, and FAB score. For light touch (9 sites), cold (4 sites), and pain (9 sites), the number of sites with loss of each sensation, across all the sites that were tested, was summed. For vibration, the mean score across the three sites was calculated. For the TUG and FAB, mean scores were used in the analysis.

Latent profile analysis (LPA)

Unconditional LPA was used to identify subgroups of survivors with distinct lower extremity loss-of-function CIPN profiles (i.e., latent classes). Estimation was carried out with full information maximum likelihood with standard errors and a Chi-square test that are robust to nonnormality and non-independence of observations ("estimator = MLR"). Model fit was evaluated to identify the best solution that characterized the observed latent class structure with the Bayesian Information Criterion (BIC), the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) for the K vs. $K-1$ model, entropy, and latent class percentages that were large enough to be reliable (i.e., likely to replicate in new samples) [46, 47]. Missing data were accommodated with the use of the expectation–maximization (EM) algorithm [48]. Mixture models, like LPA, are known to produce solutions at local maxima. Therefore, our models were fit with 1000 to 2400 random starts. This approach ensured that the estimated model was replicated many times and was not due to a local maximum. Estimation was done with Mplus Version 7.2 [46].

Additional analyses

Descriptive statistics and frequency distributions were calculated for survivors' demographic and clinical characteristics using IBM SPSS Statistics version 29 (IBM Corporation, Armonk, New York). Differences between the two loss of function profiles in demographic and clinical characteristics, pain characteristics, pain interference scores, and pain quality scores were evaluated using parametric and nonparametric tests. Using Stata 15.1 (StataCorp, College Station, TX), multivariable logistic regression analysis was done to assess the relationships between select demographic and clinical characteristics that differed in the bivariable analyses and CIPN profile membership. A p-value of <0.05 was considered statistically significant.

Results

Results of the LPA

As shown in Table 1, the two-class solution was selected because the BIC for that solution was lower than the BIC for the 1-class solution. In addition, the VLMR was significant for the 2-class solution, indicating that two classes fit the data better than one class. Although the BIC was smaller for the 3-class than for the 2-class solution, the VLMR was not significant for the 3-class solution, indicating that too many classes were extracted. In addition, the 3-class solution included a very small predicted class (only 27 predicted cases; 6.7% of the sample), raising the concern that the solution may not generalize to other samples. As shown in Table 2, based on the scores for the subjective and objective sensory measures, the classes were named less severe loss of LE Function (76.5%, $n=310$; less severe) and more severe loss of LE Function (23.5%, $n=95$; more severe).

Table 1 Latent profile solutions and fit indices lower extremity loss of function classes

Lower extremity loss of function latent profile analysis					
Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−5328.46	10,684.91	10,740.97	n/a	n/a
2 Class[a]	−5145.93	10,335.85	10,423.94	0.83	365.06**
3 Class	−5056.26	10,172.51	10,292.63	0.89	NS

Baseline entropy and VLMR are not applicable for the one-class solution

*$p<.01$; **$p<.001$

[a]The 2-class solution was selected because the BIC for that solution was lower than the BIC for the 1-class solution. In addition, the VLMR was significant for the 2-class solution, indicating that two classes fit the data better than one class. Although the BIC was smaller for the 3-class than for the 2-class solution, the VLMR for 3 classes was not significant, indicating that too many classes had been extracted

Abbreviations: *AIC* Akaike's Information Criterion, *BIC* Bayesian Information Criterion, *LL* log-likelihood, *n/a* not applicable, *NS* not significant, *VLMR* Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. $K-1$ model

Differences in demographic and clinical characteristics

As shown in Table 3, survivors in the more severe class were older, more likely to be male, more likely to live alone, less likely to be employed, and more likely to have a lower annual household income. In terms of clinical characteristics (Table 4), survivors in the more severe class had a lower functional status score, a higher body mass index, and a higher number of comorbidities and a worse comorbidity profile, a lower AUDIT score, a longer time since their cancer diagnosis, and were receiving fewer current cancer treatments. In addition, they were more likely to report a smoking history, less likely to exercise on a regular basis, and more likely to self-report diagnoses of depression, high blood pressure, heart disease, diabetes, lung disease, and kidney disease.

Of note, no differences were found between the two groups in types of cancer, number of prior cancer treatments, number of metastatic sites or presence of metastatic disease, doses of chemotherapy drugs received, and number of dose reductions or delays due to CIPN. In terms of the chemotherapy regimen, of the three possible pairwise contrasts, the only one that was significant was the comparison for the only platinum regimen. Survivors in the more severe class were more likely to receive an only platinum-containing regimen.

Association between demographic and clinical characteristics and membership in the more severe loss of lower extremity function class

As shown in Table 5, in the multivariable logistic regression analysis that included select demographic and clinical characteristics that differed between the two profiles (N.B., SCQ score was used instead of the number of comorbidities to account for comorbidity burden; annual income was not included in the analysis because of a large amount of missing data), age, gender, and KPS score were the only characteristics that remained significant. Patients who were older, male, and had a lower functional status score were more likely to be in the more severe class.

Differences in pain characteristics

As shown in Table 6, except for hours per day in pain, survivors in the more severe class reported higher scores for

Table 2 Sensory profile measures for the lower extremity loss of function classes

Sensory profile measure*+	Less severe loss of LE function 76.5% ($n=310$) Mean (SE)	More severe loss of LE function 23.5% ($n=95$) Mean (SE)
Worst pain (0 to 10)	5.8 (0.15)	6.9 (0.34)
Loss of light touch sensation (0 to 9)[a]	1.3 (0.15)	5.2 (0.52)
Loss of cold sensation (0 to 4)[b]	2.0 (0.08)	3.0 (0.12)
Loss of pain sensation (0 to 9)[c]	3.0 (0.13)	4.9 (0.28)
Vibration threshold (volts)[d] (normal = < 15 V, mild = 20 to 25 V, moderate = 20 to 25 V, severe ≥ 25 V)	24.0 (0.09)	37.3 (0.14)
Timed get up and go test (> 13.5 s)	7.2 (0.14)	9.3 (0.52)
Fullerton Advanced Balance test (≤ 25 is associated with a higher risk of falls)	35.0 (0.04)	27.2 (0.15)

Abbreviation: *LE* lower extremity, *SE* standard error

*When available, the clinically meaningful cut-point score is provided in parentheses next to the characteristic

+Changes in sensation are reported for the dominant extremity

[a]Lower extremity sites for light touch were as follows: pad of great toe, pad of 3rd toe, pad of 5th toe, base of heel, metocarpophalangeal (MP) joint of great toe, MP joint of 3rd toe, MP joint of 5th toe, midway along the tibia, patella

[b]Lower extremity sites for cold were as follows: top of great toe at 1 st MP joint, pad of great toe, dorsum of foot midpoint, medial malleolus

[c]Lower extremity sites for pain were as follows: pad of great toe, pad of 3rd toe, pad of 5th toe, base of heel, MP joint of great toe, MP joint of 3rd toe, MP joint of 5th toe, midway along the tibia, patella

[d]Lower extremity sites for vibration were as follows: dorsal ipsilateral joint of great toe, medial malleolus, patella

Demographic and clinical characteristics

While in the bivariable analyses, numerous demographic (Table 3) and clinical (Table 4) characteristics differed between the two classes, in the multivariable analysis (Table 5), being older, being male, and having a lower functional status were the only characteristics associated with a significant increase in the odds of being in the more severe

Table 3 Differences in demographic characteristics between the lower extremity loss-of-function classes

Characteristic	Less severe loss of LE function 76.5% (n = 310) Mean (SD)	More severe loss of LE function 23.5% ($n=95$) Mean (SD)	Test, p-value
Age (years)	59.4 (10.5)	66.1 (9.0)	$t=-5.63$, $p<0.001$
Education (years)	16.5 (2.7)	15.9 (3.0)	$t=1.86$, $p=0.064$
	% (n)	% (n)	
Female	90.0 (278)	74.7 (71)	FE, $p<0.001$
Married/partnered (% yes)	63.0 (191)	53.8 (49)	FE, $p=0.141$
Lives alone (% yes)	26.6 (81)	39.4 (37)	FE, $p=0.020$
Employed (% yes)	47.7 (148)	23.4 (22)	FE, $p<0.001$
Race or ethnicity White Asian/Pacific Islander Black Hispanic/mixed/other	76.5 (237) 8.4 (26) 4.2 (13) 11.0 (34)	80.0 (76) 2.1 (2) 8.4 (8) 9.5 (9)	$X^2=6.93$, $p=0.074$
Annual household income < $30,000 $30,000–$69,999 $70,000–$99,999 > $100,000	19.5 (57) 18.8 (55) 18.4 (54) 43.3 (127)	37.3 (31) 28.9 (24) 9.6 (8) 24.1 (20)	U, $p<0.001$
Child care responsibilities (% yes)	14.1 (43)	8.4 (8)	FE, $p=0.163$
Adult care responsibilities (% yes)	3.2 (9)	3.3 (3)	FE, $p=1.000$

Abbreviations: *FE* Fisher's exact test, *LE* lower extremity, *SD* standard deviation, *U* Mann–Whitney *U* test

Table 4 Differences in clinical characteristics between the lower extremity loss-of-function classes

Characteristic	Less severe loss of LE function (1) 76.5% ($n=310$)	More severe loss of LE function (2) 23.5% ($n=95$)	Test, p-value
	Mean (SD)	Mean (SD)	
Karnofsky performance status score	84.3 (9.7)	78.9 (11.2)	$t=4.16$, $p<0.001$
Body mass index (kg/m^2)	26.2 (5.2)	27.8 (6.5)	$t=-2.10$, $p=0.038$
Number of comorbidities	1.8 (1.4)	2.6 (1.7)	$t=-4.24$, $p<0.001$
SCQ score	3.8 (3.2)	5.5 (3.7)	$t=-3.99$, $p<0.001$
AUDIT score	2.4 (2.3)	1.9 (2.0)	$t=2.00$, $p=0.046$
Years since cancer diagnosis	4.5 (4.6)	5.8 (5.2)	$t=-2.18$, $p=0.031$
Number of prior cancer treatments	3.2 (1.0)	3.0 (1.0)	$t=1.65$, $p=0.099$
Number of current cancer treatments	0.5 (0.6)	0.3 (0.4)	$t=3.12$, $p=0.002$
Number of metastatic sites (out of 7)	0.7 (0.8)	0.8 (0.8)	$t=-0.40$, $p=0.687$
Number of metastatic sites without lymph node involvement	0.2 (0.6)	0.2 (0.5)	$t=0.07$, $p=0.944$
Only platinum			
Total dose of cisplatin (mg/m^2)	235.6 (109.0)	297.7 (155.0)	$t=-1.31$, $p=0.200$
Total dose of carboplatin (mg/m^2)	1615.0 (1037.6)	1252.3 (598.5)	$t=0.54$, $p=0.607$
Total dose of oxaliplatin (mg/m^2)	824.6 (248.8)	779.6 (237.4)	$t=0.62$, $p=0.538$
Only taxane			
Total dose of taxol (mg/m^2)	802.7 (255.1)	1060.9 (1580.0)	$t=-0.83$, $p=0.414$
Total dose of docetaxel (mg/m^2)	320.2 (135.0)	296.6 (103.5)	$t=0.44$, $p=0.665$
Total dose of abraxane (mg/m^2)	659.9 (388.9)	—	–
Both platinum and taxane			
Total dose of cisplatin (mg/m^2)	395.4 (250.5)	221.3 (300.2)	$t=1.23$ $p=0.231$
Total dose of carboplatin (mg/m^2)	1808.9 (687.2)	2052.6 (865.9)	$t=-1.41$, $p=0.160$
Total dose of oxaliplatin (mg/m^2)	74.6 (51.7)	86.1 —	–
Total dose of taxol (mg/m^2)	987.2 (378.0)	1117.8 (426.5)	$t=-1.26$, $p=0.212$
Total dose of docetaxel (mg/m^2)	417.3 (222.6)	382.7 (73.5)	$t=0.37$, $p=0.712$
Total dose of abraxane (mg/m^2)	1034.0 (594.7)	703.5 —	—
	% (n)	% (n)	
Previous or current history of smoking	35.0 (108)	48.9 (46)	FE, $p=0.016$
Exercise on a regular basis (% yes)	88.4 (274)	76.6 (72)	FE, $p=0.007$
Born prematurely (% yes)	6.7 (19)	5.7 (5)	FE, $p=1.000$
Surgery on legs (% yes)	24.4 (74)	26.6 (25)	FE, $p=0.683$
Surgery on feet (% yes)	15.7 (48)	20.4 (19)	FE, $p=0.342$
Injury to legs (% yes)	22.1 (67)	26.9 (25)	FE, $p=0.400$
Injury to feet (% yes)	26.3 (79)	32.6 (30)	FE, $p=0.287$
Comorbid conditions (% yes)			
Osteoarthritis	28.7 (89)	36.8 (35)	FE, $p=0.161$
Back pain	34.5 (107)	33.7 (32)	FE, $p=0.902$
Depression	20.3 (63)	33.7 (32)	FE, $p=0.009$
High blood pressure	22.9 (71)	37.9 (36)	FE, $p=0.005$
Heart disease	6.1 (19)	12.6 (12)	FE, $p=0.047$
Diabetes	4.5 (14)	10.5 (10)	FE, $p=0.044$
Lung disease	3.5 (11)	9.5 (9)	FE, $p=0.029$
Anemia or blood disease	4.8 (15)	8.4 (8)	FE, $p=0.206$
Ulcer or stomach disease	2.3 (7)	6.3 (6)	FE, $p=0.087$
Kidney disease	1.3 (4)	6.3 (6)	FE, $p=0.013$
Liver disease	2.3 (7)	6.3 (6)	FE, $p=0.087$
Rheumatoid arthritis	2.6 (8)	4.2 (4)	FE, $p=0.487$
Type of cancer	57.1 (177)	45.3 (43)	$X^2=4.99$, $p=0.289$
Breast	9.4 (29)	11.6 (11)	
Colon	1.6 (5)	2.1 (2)	
Lung	10.6 (33)	10.5 (10)	
Ovarian	21.3 (66)	30.5 (29)	
Other			

Table 4 (continued)

Characteristic	Less severe loss of LE function (1) 76.5% ($n=310$) Mean (SD)	More severe loss of LE function (2) 23.5% ($n=95$) Mean (SD)	Test, p-value
Any metastatic disease (% yes)	59.3 (182)	65.2 (60)	FE, $p=0.332$
Type of chemotherapy regimen			
Only platinum	19.7 (61)	33.7 (32)	$X^2=8.35$, $p=0.015$
Only taxane	49.0 (152)	37.9 (36)	1 < 2
Both platinum and taxane	31.3 (97)	28.4 (27)	NS
			NS
Patients who had a dose reduction or delay due to neuropathy	13.4 (40)	16.9 (15)	FE, $p=0.489$

Abbreviations: *AUDIT* Alcohol Use Disorders Identification Test, *FE* Fisher's exact test, *kg* kilograms, *LE* lower extremity, m^2 meters squared, *mg* milligrams, *NS* not significant, *SCQ* Self-Administered Comorbidity Questionnaire, *SD* standard deviation

all of the pain characteristics and pain interference scores. In addition, except for aching, survivors in the more severe class reported higher scores for all of the pain qualities, as well as for all of the PQAS subscale scores.

Discussion

This study is the first to use subjective and objective measures to identify two groups of survivors with distinct CIPN profiles. These survivors differed in their ratings of pain severity, as well as in their loss of primary sensations and balance problems. Of note, the more severe class, that included approximately 25% of the sample, had pain intensity scores in the severe range and clinically meaningful decrements in several measures of lower extremity function. In addition, their FAB test scores approached the cutpoint associated with an increased risk of falls. Because previous studies that used cluster analysis to identify subgroups of patients with distinct "pain profiles" used different measures and did not include patients or survivors with CIPN [11, 12], direct comparisons cannot be performed. However, the current findings suggest that different CIPN phenotypes exist and that mechanistic studies are warranted.

Table 5 Multivariable logistic regression analysis of associations among demographic and clinical characteristics and membership in the more severe loss of lower extremity function class ($n=370$)

Characteristics	Adjusted odds ratio	Standard error	95% CI	Z	p-value
Age	1.11	0.02	1.06, 1.15	5.20	< 0.001
Male gender	3.76	2.04	1.30, 10.92	2.44	0.015
Living alone	1.35	0.42	0.73, 2.49	0.96	0.337
Being employed	0.61	0.21	0.31, 1.22	−1.40	0.162
KPS score	0.94	0.02	0.91, 0.97	−3.89	< 0.001
Body mass index	1.03	0.03	0.97, 1.08	0.94	0.349
SCQ score	1.07	0.05	0.98, 1.16	1.44	0.151
AUDIT score	0.87	0.06	0.76, 1.01	−1.83	0.067
Years since cancer diagnosis	1.03	0.03	0.97, 1.09	0.88	0.378
Number of current cancer treatments	0.77	0.24	0.42, 1.43	−0.83	0.405
Previous or current history of smoking	1.20	0.36	0.67, 2.15	0.61	0.539
Exercise on a regular basis	0.70	0.26	0.33, 1.46	−0.95	0.340
Chemotherapy regimen					
Only platinum (Ref)	1.00	0.40	0.30, 2.12	−0.45	0.650
Only taxane	0.80	0.34	0.26, 1.80	−0.77	0.442
Both platinum and taxane	0.68				
Overall model fit: $X^2=104.23$; $p<0.001$; pseudo $R^2=0.2568$					

Abbreviations: *AUDIT* Alcohol Use Disorders Identification Test, *CI* confidence interval, *KPS* Karnofsky Performance Status, *SCQ* Self-Administered Comorbidity Questionnaire

Table 6 Differences in pain characteristics between the lower extremity loss-of-function classes

Characteristic	Less severe loss of LE function 76.5% (n = 310) Mean (SD)	More severe loss of LE function 23.5% (n = 95) Mean (SD)	Statistic, *p*-value
Pain characteristics			
Duration of CIPN (years)	3.6 (4.0)	5.1 (4.9)	$t = -2.81$, $p = 0.006$
Pain now	3.4 (2.2)	4.3 (2.3)	$t = -3.37$, $p = 0.001$
Average pain	3.8 (2.1)	4.7 (2.1)	$t = -3.84$, $p < 0.001$
Days per week in pain	3.3 (3.0)	4.8 (2.8)	$t = -4.74$, $p < 0.001$
Hours per day in pain	14.6 (9.6)	16.2 (8.9)	$t = -1.37$, $p = 0.171$
Pain Interference Scale			
Balance	3.2 (2.9)	4.9 (3.2)	$t = -4.71$, $p < 0.001$
Walking ability	3.0 (2.9)	4.4 (3.2)	$t = -3.76$, $p < 0.001$
Enjoyment of life	2.6 (2.6)	3.8 (3.2)	$t = -3.41$, $p < 0.001$
Normal work	2.3 (2.6)	3.9 (3.2)	$t = -4.18$, $p < 0.001$
Sleep	2.4 (2.7)	3.7 (3.2)	$t = -3.55$, $p < 0.001$
General activity	2.2 (2.4)	4.0 (3.0)	$t = -5.10$, $p < 0.001$
Mood	2.1 (2.3)	3.3 (2.8)	$t = -3.70$, $p < 0.001$
Relations with other people	1.2 (2.0)	2.5 (2.8)	$t = -4.06$, $p < 0.001$
Sexual activity	0.7 (1.8)	1.7 (3.0)	$t = -2.81$, $p = 0.006$
Mean interference score	2.2 (2.0)	3.6 (2.5)	$t = -4.73$, $p < 0.001$
Pain Qualities Assessment Scale (PQAS) Scores			
Numb	5.1 (3.0)	6.4 (2.9)	$t = -3.80$, $p < 0.001$
Unpleasant	4.2 (2.4)	5.5 (2.4)	$t = -4.82$, $p < 0.001$
Tingling	4.0 (3.0)	5.4 (2.7)	$t = -4.09$, $p < 0.001$
Intense	2.9 (2.4)	4.4 (2.6)	$t = -4.99$, $p < 0.001$
Dull	3.0 (2.7)	3.6 (2.7)	$t = -2.02$, $p = 0.044$
Cramping	2.5 (3.0)	4.0 (3.5)	$t = -3.60$, $p < 0.001$
Electrical	2.3 (2.9)	3.3 (3.5)	$t = -2.44$, $p = 0.016$
Shooting	2.3 (2.8)	3.1 (3.3)	$t = -2.30$, $p = 0.023$
Sharp	2.1 (2.7)	3.2 (3.3)	$t = -3.06$, $p = 0.003$
Aching	2.1 (2.6)	2.7 (3.1)	$t = -1.82$, $p = 0.071$
Heavy	1.8 (2.5)	3.0 (3.2)	$t = -3.10$, $p = 0.002$
Cold	1.9 (2.8)	2.8 (2.9)	$t = -2.76$, $p = 0.006$
Radiating	1.8 (2.6)	2.9 (3.0)	$t = -3.27$, $p = 0.001$
Hot	1.8 (2.5)	2.7 (3.1)	$t = -2.58$, $p = 0.011$
Tender	1.8 (2.4)	2.4 (2.8)	$t = -2.02$, $p = 0.046$
Sensitive skin	1.6 (2.1)	2.4 (2.8)	$t = -2.43$, $p = 0.016$
Throbbing	1.6 (2.4)	2.3 (3.0)	$t = -2.25$, $p = 0.026$
Itchy	0.9 (1.8)	1.6 (2.6)	$t = -2.59$, $p = 0.011$
Intense—surface pain	3.0 (2.6)	4.2 (2.8)	$t = -3.63$, $p < 0.001$
Intense—deep pain	3.1 (2.7)	4.1 (3.1)	$t = -2.90$, $p = 0.004$
PQAS subscale—paroxysmal	2.0 (2.1)	3.1 (2.6)	$t = -3.52$, $p = 0.001$
PQAS subscale—surface	2.7 (1.6)	3.7 (1.8)	$t = -5.24$, $p < 0.001$
PQAS subscale—deep	2.2 (1.9)	3.1 (2.3)	$t = -3.53$, $p = 0.001$

Abbreviations: *CIPN* chemotherapy-induced peripheral neuropathy, *LE* lower extremity, *SD* standard deviation

class. The finding of older age being associated with membership in the more severe class is consistent with previous reports [49–51]. As noted in several reviews [52–54], aging is associated with changes in organ function, body composition, significant multimorbidity, and increased use of multiple medications that can impact drug metabolism and increase the risk for adverse effects associated with the administration of chemotherapy. While controversy exists

on the magnitude of these age-related physiologic changes in pharmacokinetics and pharmacodynamics and whether dosage modifications are warranted in older adults [54], in the current study, no between-group differences were found in the doses of platinum and/or taxane compounds that the survivors received. Given the increased interest in accelerated biological aging in oncology patients [55, 56], future studies should include measures of epigenetic aging and its association with the development of CIPN.

In a recent study of risk factors for CIPN in patients with lung cancer [57], the authors noted that findings regarding sex differences in CIPN are inconclusive because most of the studies were done in patients with breast cancer. In the current study, being male was associated with a 3.76-fold increase in the odds of being in the more severe class. While additional research is warranted on sex differences in the occurrence and severity of CIPN in oncology patients and survivors, evidence from preclinical models demonstrates sexual dimorphism in the mechanisms of and treatments for CIPN [58–60]. As noted in a review of sex differences in drug effects and/or toxicity in oncology [61], these sexually dimorphic effects may be related to differences in immune function; hormonal mediators like estradiol and androgens; and social sex behaviors (e.g., smoking and alcohol use). Equally important, additional research is warranted on potential interactions between sex differences in adverse effects and perceptions and responses to pain [62].

Similar to an evaluation of sex differences, findings regarding an association with functional status and the occurrence of CIPN are limited and inconclusive [50, 51, 63]. In the current study, the differences in KPS scores between the less severe (84.3) and more severe (78.9) classes represent not only statistically significant but also clinically meaningful decrements in functional status (Cohen's $d = 0.52$ [64]) [65, 66]. While this association may be linked to older age and a higher level of multimorbidity in the more severe class, it warrants evaluation by clinicians because an increased risk of falls is associated with poorer functional status in patients with CIPN. This finding is corroborated by the lower FAB scores in this class [67].

While in the bivariable analysis, a higher percentage of patients who had received only a platinum-containing regimen were in the more severe class, type of chemotherapy regimen was not significant in the multivariable analysis. In addition, no between-group differences were found in cancer diagnoses, total doses of chemotherapy received, and dose reduction or delay due to chemotherapy. Given the inconsistent findings across studies, additional longitudinal studies are needed to assess these characteristics in patients during active treatment and into survivorship.

Loss of large fiber function and CIPN

In terms of the loss of large fiber function measures (i.e., light touch and vibration), compared to the less severe class, survivors in the more severe class had four times the number of sites that lost light touch sensation. In addition, their vibration thresholds were 1.5 times higher and were well above the severe cutoff score of > 25 V [40]. Of note, the between-class ratings of numbness (a subjective measure of loss of large fiber function) demonstrated not only a statistically significant difference but a clinically meaningful difference in its intensity (i.e., 5.1 versus 6.4, Cohen's $d = -0.42$ [64]) [65, 66]. While our previous study evaluated only simple correlations between average pain intensity scores and loss of light touch sensations, decrements in vibration thresholds, and increased severity of numbness to demonstrate the involvement of large fiber loss in patients with CIPN [20], the current study confirms this association using a more robust analytic method (i.e., latent variable modeling) that integrates the three measures of large fiber function. In addition, the FAB scale, that measures both static and dynamic balance under different sensory conditions, provides indirect information on multiple sensory and motor systems (i.e., visual, vestibular, and proprioceptive systems) [44, 45]. Given that large-diameter myelinated fibers (i.e., Aα and Aβ fibers) are involved in proprioception [68] and that the FAB test results are significantly worse in the more severe class, this provides additional support for the hypothesis that large fiber loss is involved in the CIPN phenotype.

Potential involvement of C-tactile fibers in CIPN

As noted in the Introduction, stimulation of a subgroup of C fibers known as C-tactile fibers is thought to contribute to the perception of pleasantness during gentle stroking of hairy skin (i.e., "affective touch") [22–24]. Stimulation of these fibers in humans involves the use of a soft watercolor brush made of fine smooth goat hair that is stroked at very low and uniform velocities. Germaine to this discussion, evidence from a preclinical study suggests that these fibers play a role in the pathophysiology of tactile allodynia [25]. While an objective measure of C-tactile fibers was not done in the current study, it is known that some patients with CIPN report tactile allodynia (e.g., burning, tender sensations from non-noxious stimuli) and describe the sensation as extremely unpleasant [26]. In the current study, significant between-group differences in survivors' ratings of the severity of sensitive skin (i.e., "Tell us how sensitive the skin in your feet has been to light touch or clothing rubbing against it over the past week. Words used to describe sensitive skin include 'like sunburned skin' and 'raw skin'.") and unpleasant (i.e., "Now that you have told us the different types of pain sensations you have felt, we want you to tell us overall how unpleasant your pain in your feet has

been to you in the past week, Words used to describe unpleasant pain include 'annoying,' 'bothersome,' 'miserable,' and 'intolerable'.") support the hypothesis that these fibers may be damaged by neurotoxic chemotherapy (see PQAS ratings on Table 6). To evaluate the role of C-tactile fiber activity in CIPN, future studies should incorporate an objective assessment of these fibers, as well as tactile allodynia.

Limitations

While this study describes a novel phenotypic characterization of CIPN and provides evidence to support the role of large-diameter and C-tactile fibers in CIPN, several limitations warrant consideration. While the sample size was sufficient for LPA, larger samples may reveal additional profiles and/or additional risk factors. The sample was primarily female, White, and well educated. Given that various social determinants of health may influence the stage of the disease at the time of diagnosis and associated treatments, as well as an increased likelihood of multimorbidity [69], future studies need to include survivors with more diverse backgrounds. In addition, because survivors need to attend an in-person testing session, selection bias may be present. Given that the objective measures used in this study were designed for clinical use, more detailed characterization of neural activity may provide additional insights into the role of large-diameter and C-tactile fibers in CIPN.

Conclusions and recommendations for future research

This study's findings suggest that distinct "CIPN phenotypes" can be identified in cancer survivors. The survivors in the Morse Severe class experienced CIPN for 1.5 years longer than the Less Severe class (i.e., 5.1 versus 3.6 years, respectively). While both classes had persistent pain, longitudinal studies are warranted to determine if the CIPN phenotype worsens over time. In addition, studies are warranted to determine the underlying mechanisms for a worsening phenotype (e.g., epigenetic changes). Detailed phenotyping and molecular characterization of various CIPN phenotypes will lead to the development and testing of targeted and personalized interventions.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Bruce Cooper, Steven Paul and Christine Miaskowski. The first draft of the manuscript was written by Christine Miaskowski and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Data is available from the corresponding author following the completion of a data sharing agreement with the University of California, San Francisco.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Committee on Human Research at the University of California, San Francisco and the Institutional Review Board at each of the study sites.

Consent to participate Written informed consent was obtained from the patients.

Consent to publish Not applicable.

Competing interests The authors declare no competing interests.

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